Role of reward and punishment in motor learning in health and after stroke

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Declaration

I, Graziella Quattrocchi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: _Graziella Quattrocchi_

Date: 27/02/2018

Abstract

Is the carrot more effective than the stick? Through a combination of behavioural experiments, pharmacological manipulations and computational modelling, this thesis investigates the effects of reward and punishment feedback on adaptive motor learning, in both healthy subjects and stroke survivors.

The role of error-based motor learning in neurorehabilitation is still unclear partly because, although it leads to fast and large changes in behaviour, these changes are often short-lived once the perturbation is removed. Nevertheless, recent evidence shows that motivational feedback can increase adaptation to a perturbation and retention of the motor memory in healthy subjects. In the first study presented in this thesis I show that these effects partially apply also to stroke survivors. In particular, reward or punishment-based feedback enhance error-correction during adaptation, and reward increases the retention of the new motor memory in stroke survivors.

I then moved to investigate the role of dopamine in error-based motor learning under reward or punishment in healthy young subjects. Consistently with results in stroke patients, reward increased motor memory retention. In addition, I show here that this effect of reward on retention is mediated by dopaminergic pathways.

Finally, I investigated if pharmacologic dopaminergic stimulation can potentiate the positive effect of reward on retention in dopamine-deficient subjects, such as older adults. Unfortunately, likely due to the dopaminergic deficit, reward had no effect on elderly participants, and this study failed to show a benefit of dopaminergic

stimulation in the elderly. However, this evidence is not sufficient to rule out possible positive effects of pharmacologic dopaminergic stimulation on motor learning in brain injured patients, such as stroke survivors.

Taken together, these results represent a step further toward the combined use of reward feedback, pharmacological stimulation and motor learning paradigms in clinical rehabilitation. Indeed, as shown by the qualitative survey presented at the beginning of this thesis, an evidence-based guide to the use of reward and punishment feedback during rehabilitation would be welcome by stroke professionals.

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Four years have quickly gone by and a number of people are, less or more directly, less or more unwillingly, involved in this thesis… may they like this or not. ☺

First and foremost, I would like to thank all patients who took part in my research. Their stories and their strength have been an invaluable source of inspiration during the first years of my PhD. This work would have not existed without them. Alongside patients and all participants, the Stroke Association and Different Strokes deserve special thanks for the precious help they gave me with subjects' recruitment.

I started my PhD by telling my German supervisor, Prof Sven Bestmann, that I would have written my thesis while travelling around South America. I remember him getting quite anxious and replying seriously that what I was starting was a P-H-D, no time for relaxation… Well, it is also thanks to his help and guidance that I have been able to suppress my Southern Italian genes and sit still in front of a screen long enough to finish this thesis… so thank you Sven!

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Table of contents

List of tables

List of figures

Abbreviations

AD Angular Reach Direction

AI Adaptation Index

ANCOVA Analysis of Covariance

ANOVA Analysis of Variance

CW Clockwise

CCW Counter-clockwise

CIMT Constraint-Induced Movement Therapy

DA Dopamine

DRN Dorsal Raphe Nuclei

FF Force-field

GPe Globus Pallidus Pars Externa

GPi Globus Pallidus Pars Interna

Halo Haloperidol

LD Levodopa

M1 Primary motor cortex

MRN Median Raphe Nuclei

MT Movement Time

N Neutral

P Punishment

PCA Principal Component Analysis

PD Parkinson's disease

Pl Placebo

R Reward

RT Reaction Time

SD Standard Deviation

SEM Standard Error of the Mean

SNc Substantia Nigra Pars Compacta

SNr Substantia Nigra Pars Reticulata

STN Subthalamic Nucleus

tDCS Transcranial Direct Current Stimulation

TMS Transcranial Magnetic Stimulation

UDP Use-Dependent Plasticity

Var Variability

VTA Ventral Tegmental Area

Chapter 1.

Motor Learning principles in healthy humans and stroke survivors
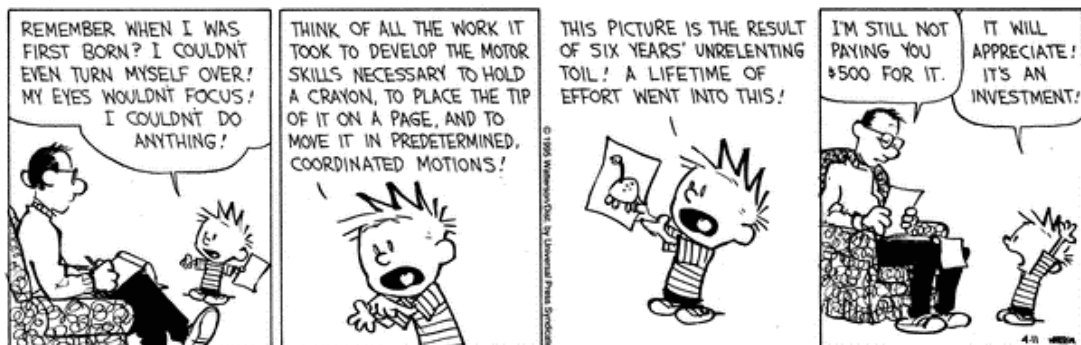
Calvin & Hobbes by Bill Watterson, Permission granted by Andrews McMeel Syndication

1.1   Introduction

"What is more important for us, at an elemental level, than the control, the owning and operation, of our own physical selves? And yet it is so automatic, so familiar, we never give it a thought." — Oliver Sacks, The Man Who Mistook His Wife for a Hat

"Life is never stagnation. It is constant movement, un-rhythmic movement, as we as constant change. Things live by moving and gain strength as they go" – Bruce Lee

Life is constant motion. Try to sit still and quiet as you read this thesis and you will realize that…nothing will really stay the same. Your lungs will constantly change dimension through the breathing cycles, your muscles will relax (or get more tense) as long as this reading will make you the more and more interested (or sleepy?), and even your weight will slightly change. You are actually changing now. And so it is the world around you. And maybe it is raining out there and the usual path you take to work will be unusually slippery and muddy today. Or maybe you have new shoes you have to adapt to... Yes, life is constant change.

How do we cope with this? And, specifically, how do we manage to accomplish successful movements in such constantly changing conditions without committing massive errors? Adaptation, the specific form of learning that refers to error reduction in response to a novel perturbation (Shadmehr and Mussa-Ivaldi, 1994), is one mechanism developed by our brain to cope with changes. In particular, adaptation permits to quickly adjust our behaviour in order to minimize any mismatch between actual and expected outcomes. While we can easily appreciate the vital importance of this process, we are often not even aware of it happening.

1.1.1   Aims and questions of this thesis

How does our brain learn new movements? And how does it adapt the learnt movements to the new conditions? Learning (or failing) to accurately perform certain movements can also bring us rewards or punishments, both explicit and implicit. Is learning to adapt to new situations influenced by positive or negative feedback, or are the underlying processes independent and do not interact? And, finally, if they interact in healthy subjects, do the same mechanisms apply in brain-injured patients?

This thesis seeks to give an answer to these questions. In particular, this thesis focuses on the mechanisms through which we adapt motor commands to our changing environment. Through a combination of behavioural tasks and pharmacological interventions, during my PhD I have investigated whether the mechanisms underlying motor adaptation can be influenced, and even facilitated, through the use of positive/negative feedback and pharmacological stimulation. Specifically, I based my experiments on the following hypotheses:

1. Reward and punishment have differential effects on motor adaptation tasks, in healthy subjects and in stroke patients
2. Reward increases the retention of a newly acquired motor behaviour
3. The positive effects of reward on motor memory retention are mediated by dopaminergic pathways
4. Pharmacologic dopaminergic stimulation can increase further the positive effect of reward on retention in dopamine-deficient subjects, such as elderly subjects and, potentially, stroke survivors.

For the reasons extensively outlined in Paragraph 1.5, I have focused on both healthy subjects and stroke survivors. The central idea is that the same mechanisms underpinning motor learning in the healthy brain are, at least partially, still used by brain-injured patients. My premise is that taking a closer look at how motor learning is accomplished in the healthy brain permits insights into how motor learning

paradigms could be used in clinical neurorehabilitation, and to thereby improve the way patients train to re-gain their lost motor abilities.

In this introductory chapter, I will introduce the mechanisms of motor learning (and their known interactions with rewarding and punishing feedback). I will review the functional neuroanatomy underlying these mechanisms, and I will briefly discuss the applicability of motor learning paradigms in stroke rehabilitation. This will lead to the questions addressed in this thesis.

1.2 Motor learning: background and general framework

1.2.1 General concepts and definitions

This thesis investigates *motor learning*. The term motor learning broadly refers to improvement, through practice, in the performance of motor behaviours (Krakauer and Mazzoni, 2011). Motor learning processes have been traditionally distinguished by the type of information that the motor system uses as a learning signal. We can broadly differentiate *skill learning*, *motor adaptation*, and *reinforcement learning*, or, more simply, learning features and representations, learning from errors, and learning from reinforcements (Wolpert et al., 2011). These forms of learning have been associated with different biological substrates (Wolpert et al., 2011). Nonetheless, to acquire a complex motor task almost certainly requires that instruction and knowledge are combined with adaptation and reinforcement, and all forms of learning are therefore often involved, in various combinations, in everyday life.

However, acquisition is not of great use if what is learned is not retained. For example, a person who is disabled after stroke may successfully perform a task at the end of a rehabilitation session, but critical is the ability to perform it again once

leaving the rehabilitation environment. Therefore, effective motor learning can be seen as a dynamic process that evolves along two main behavioural stages: *online learning* and *retention*. Online learning, i.e. the acquisition of a certain motor behaviour during the performance of a task, can be related to at least two different effects of practice: persistent effects (representing the actual learning), and temporary effects, such as changes in mood or attention (Kantak and Winstein, 2012). Retention, by contrast, consists of the strength of the new motor memory representation over time. This is ensured by an interaction of the initial on-line learning with subsequent off-line consolidation, i.e. a process which enhances memories, integrates them with other memories, and makes them resistant to interference (Breton and Robertson, 2014).

Once the new motor behaviour, learnt in specific settings, is retained, it is crucial that this can be applied and used in novel conditions. This process, called *generalization* (or transfer) is critical in daily life, as it permits to perform in a post-acquisition situation that is different from the acquisition phase, without the need to invest time and energy in a new learning process.

Keeping these broad concepts in mind, we will explore in the next paragraphs the three main types of motor learning: skill learning, motor adaptation and reinforcement learning.

1.2.2 Skill learning

1.2.2.1 Defining motor skills and skill acquisition

A motor skill is defined as the "*ability to reliably deliver accurate execution*" (Kitago and Krakauer, 2013). One characteristic of skills is their flexibility. From this perspective, then, a skill can be also defined as the capacity to execute an "intentional action" (i.e. a voluntary movement to achieve a goal) reliably with a broad range of parameters defining its execution (Dudman and Krakauer, 2016). Skill learning consists of the changes that lead to these performance improvement and is "*the product of both learning actions and the capacity to flexibly parameterize their execution*" (Dudman and Krakauer, 2016). Examples are learning to ride a bicycle or to play the piano: they require repeated and extended practice, which can take days to months, depending on the complexity of the task.

Of note, an increase in accuracy alone does not indicate improved skill, as subjects tend to make less errors as movement speed decreases. Thus, true skill acquisition involves acquiring new patterns of muscle activation and achieving a higher level of performance by reducing errors without a decrease in movement speed, i.e. it requires a systematic change in the learner's *speed-accuracy trade-off* (Heitz, 2014; Kitago and Krakauer, 2013).

A key parameter of movement is its *vigor*, that is, its speed, amplitude, or frequency. The ability to act over a range of vigor can be considered an essential aspect of skill (Dudman and Krakauer, 2016).

An interesting point in the motor skill literature, which I will only cite here, is the debate around the traditional distinction between knowledge and skill, and therefore between declarative and procedural memory. Indeed, the traditional view that being skilled at an activity is independent of knowing facts about that activity, has been recently questioned and it has been argued that improvements in skills require not

only increased precision in selected action, but also knowledge-based selections of the right actions (Stanley and Krakauer, 2013).

1.2.2.2   Skill learning in the lab

Many skilled motor behaviours, such as playing the piano, consist of a sequence of movements. Therefore, the classical, and extensively used, experimental paradigm of skill learning is the serial reaction time task (SRTT), in which subjects are unaware of a repeating sequence embedded within the task and learning is measured as a reduction in response time (Goedert and Willingham, 2002; Nissen and Bullemer, 1987). Another commonly used paradigm requires subjects to learn a short sequence of movements, and learning is measured as an increase in speed and accuracy (Karni et al., 1998). A third approach combines the two components of sequence learning (i.e. the effector-independent acquisition of the order of elements in the sequence, and the effector-dependent performance of each element in the sequence). In this case, subjects are asked to explicitly learn a sequence of movements, thus allowing for separate quantification of both the explicit acquisition of sequence order and performance (speed/accuracy) measures (Hikosaka et al., 1995).

1.2.2.3   Influencing skill learning: from practice to reward and punishment feedback

According to the *power law of practice,* acquisition of a skill is determined solely by the number of times that a task is practiced (Newell and Rosenbloom, 1980). Nevertheless, numerous studies have proposed that acquisition and retention of motor skills can be influenced by a variety of factors, such as *task variability* and *contextual interference* (i.e. random schedule of several tasks within the same training session). Rest, in the form of a *distributed practice* with long inter-training intervals, can also increase learning, a phenomenon called "the spacing effect" (Cepeda et al., 2009). Specifically, relatively long periods of rest and sleep between training sessions would act by facilitating motor consolidation (Al-Sharman and Siengsukon, 2013; Kwon et al., 2015). Recent studies also support the idea that

aerobic exercise can improve both learning and retention of motor skills (Roig et al., 2012; Statton et al., 2015). Even much simpler exercises involving the *modulation of breathing patterns,* such as deep alternate-nostril breathing can have a positive impact on retention of the newly learned skill (Yadav and Mutha, 2016).

Moreover, skill learning can be modulated by a variety of informational or motivational feedbacks. These can be intrinsic, i.e. provided through the sensory system, or extrinsic, i.e. given by an external source, such as knowledge of performance or knowledge of results (Kitago and Krakauer, 2013). Considering the central role they have in this thesis, I will focus here on reward and punishment-based feedback.

The past ten years have seen a rapid expansion in our understanding of the role of reward and punishment feedback in motor learning. In animal models, learning under conditions in which good performance is rewarded or bad performance punished can transiently improve formation of new associations between events (Nakatani et al., 2009; Tempel et al., 1983). In humans, the effect of reward and punishment on motor learning has been recently investigated. Combining the classical serial reaction time task with monetary incentives, Wätcher and colleagues found that reward, but not punishment, had some benefits on procedural learning, the process by which skills are acquired by practice (Wächter et al., 2009). This suggests that reward and punishment likely engage qualitatively different motivational systems, partially in agreement with other evidence on various motor learning paradigms, which I will briefly review in the next sections, and with the results discussed in this thesis. Indeed, the positive effect of monetary reward feedback on skill learning, measured as improved reaction times in sequential key presses, was subsequently confirmed (Palminteri et al., 2011). Monetary reward was also shown to have long-term positive effects on retention of a motor skill in humans (Abe et al., 2011). Moreover, other kinds of reinforcement, such as social rewards (in the form of praise) could benefit offline consolidation of motor memories (Sugawara et al., 2012). Indeed, learning on

the serial reaction times task is impaired in patients affected by Parkinson's disease (Doyon et al., 1997; Jackson et al., 1995; Muslimovic et al., 2007; Wilkinson et al., 2009; Wilkinson and Jahanshahi, 2007), Huntington disease (Knopman and Nissen, 1991), focal lesions of the basal ganglia (Obeso et al., 2009), traumatic brain injury (De Beaumont et al., 2012; Mutter et al., 1994), and animal models of dopamine depletion (Matsumoto et al., 1999), thus supporting the hypothesis of an involvement of the reward system networks in procedural motor sequence learning.

Based on these findings, Wilkinson and colleagues tested the possibility to restore skill learning deficits through the use of reward or punishment feedback after disruptive transcranial magnetic stimulation (TMS) (Wilkinson et al., 2015). Inhibitory TMS, in the form of continuous theta burst stimulation (cTBS), or sham, were delivered to the primary motor cortex (M1) of healthy volunteers, as this is known to create a temporary impairment of motor sequence learning (Rosenthal et al., 2009; Wilkinson et al., 2010). Subjects were then tested in a probabilistic version of the serial reaction time task (pSRTT) with and without monetary reward/punishment feedback in separate sessions at least one week apart. Counter to some (Wächter et al., 2009), but in agreement with other (Abe et al., 2011) evidence, feedback did not affect online learning. However, and consistently with the time course observed by Abe and colleagues (Abe et al., 2011), incentive feedback improved sequence knowledge from the learning to the recall phase in both sham and cTBS groups. Unfortunately, the task used in this study did not allow for disentangling the specific roles of reward and punishment, because subjects were rewarded or punished within each feedback block. Nevertheless, these results support the hypothesis that reward or punishment feedback may benefit consolidation of motor memories (Wilkinson et al., 2015). However, one should always be cautious in extrapolating from a single experiment in a specific context to a more general account, as the effect of feedback could be task specific (Steel et al., 2016). When comparing different studies, we should indeed consider not only the task used, but also other factors, such as the

differential motivational valence of punishment versus reward, the potential effect of reward on motor noise (Galea et al., 2013), and the influence of different reinforcement schedules (Dayan et al., 2014).

1.2.3   Motor adaptation

1.2.3.1   *Defining motor adaptation*

Motor adaptation is a specific form of motor learning which refers to error reduction in response to a novel *perturbation*. The perturbation can be internal, such as fatigue, or external, such as a force-field (Shadmehr and Mussa-Ivaldi, 1994). Unlike learning a new skill, motor adaptation doesn't require the acquisition of a new pattern of muscle activations, but a new mapping between well-learned movements and a novel spatial goal (Krakauer, 2009). Adaptive motor learning occurs daily and permits to rapidly adjust already learned skills to a changing environment. Examples are walking on a slippery surface, using a new tool, wearing new shoes, driving a new car or playing a sport in variable weather conditions (Figure 1-1). These adjustments occur rapidly but are also quickly washed-out. This has some advantages in everyday life, where the adapted behaviour may be needed just temporarily, but represents a limitation to the use of motor adaptation-based paradigms in clinical settings such as motor neurorehabilitation.

Figure 1-1 Motor adaptation

From the left: when a perturbation occurs (e.g. we lift a weight for the first time), we rapidly adjust the motor output to the new circumstances (adaptation). If the perturbation is removed, the motor output will manifest an error in the opposite direction (after-effects). These after-effects indicate that the forward model has been updated. Readaptation can be investigated after some time to evaluate the strength of the new motor memory. Figure adapted from Blam Lab, Johns Hopkins University, http://blam-lab.org/

Early theories relied on closed-loop control in which ongoing movements are continuously updated by sensory feedback (Kawato, 1999; Shadmehr et al., 2010; Wolpert and Ghahramani, 2000; Wolpert and Miall, 1996). However, sensory feedback is subject to significant delays, rendering a simple close-loop control scheme inadequate (Kawato, 1999; Shadmehr et al., 2010; Wolpert and Ghahramani, 2000; Wolpert and Miall, 1996). The sensory delay constraint can be resolved by assuming that the central nervous system implements *forward internal models* that predict the sensory consequences of motor commands. Extensive evidence supports this hypothesis (Diedrichsen et al., 2005; Flanagan and Wing, 1997; Imamizu et al., 2000; Maschke et al., 2004; Morton and Bastian, 2006; Wolpert et al., 1995; Xu-Wilson et al., 2009). Specifically, the perturbation induces a *sensory prediction error*, i.e. a mismatch between the actual and the expected sensory feedback (Shadmehr and Krakauer, 2008). This prediction error informs the brain of a movement error. To return to accurate performance the brain gradually updates its forward internal model, and the resulting motor behaviour, so that it accounts for the new

environment conditions (Shadmehr and Krakauer, 2008). *Error-based learning* is therefore the driving force behind motor adaptation, which involves updating the forward model to minimize systematic error. As shown in Paragraph 1.3.2, this process particularly relies on the cerebellum (Galea et al., 2011). When the perturbation is removed, an *after-effect* is observed as a movement error in the opposite direction to that seen during initial adaptation (Figure 1-2). This suggests that participants have not simply reacted to the perturbation but have learned to alter their planned movements in the new environment (Kawato, 1999; Kitago et al., 2013). The recall of previous learning manifests as *savings*: adaptation is faster and greater when subjects are re-exposed to the same perturbation after a time interval (Krakauer, 2009). Evidence supports the involvement of the primary motor cortex in the retention of the newly learnt transformation (Galea et al., 2011). Therefore, *acquisition* and *retention* are likely distinct processes with different neural correlates (Shadmehr and Krakauer, 2008).
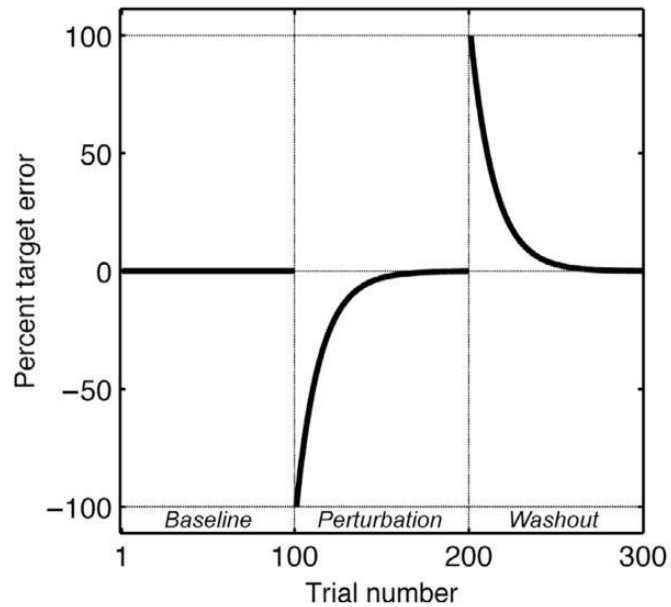
Figure 1-2 Stereotypical learning curve during adaptation to an arbitrary visuomotor perturbation

The perturbation is imposed during trials 100 to 200. Target errors are initially in the direction of the perturbation, but, with training, adaptation occurs. The perturbation is removed on trial 201 and an after-effect is observed in which target errors are in the direction opposite to the perturbation (adapted from Taylor and Ivry, 2014 with permission from Elsevier).

1.2.3.2 Motor adaptation in the lab

In what is probably the first documented version of visuomotor adaptation, conducted at UC Berkley, Stratton used inverting spectacles for 8 consecutive days to assess the impact on daily behaviour of perturbing the visual field. He claimed to have adapted by the seventh day (Stratton, 1897).[1] Nowadays, experimental paradigms of motor adaptation include prisms (Martin et al., 1996), saccade adaptation (Pélisson et al., 2010), visuomotor adaptation (Krakauer et al., 2000), reaching in force-fields (Shadmehr and Mussa-Ivaldi, 1994), grip force adaptation (Flanagan and Wing, 1997) and the split-belt treadmill for gait (Reisman et al., 2007). In all these paradigms, subjects gradually adjust their motor output in order to improve their performance in response to a perturbation. Performance errors induced by the perturbation are used to maintain the accuracy of current movements.

Based on the limited time for a PhD and on the relatively limited space for a thesis, here I will focus primarily on *motor adaptation of goal-directed upper limb movements.* This raises a question that is rarely mentioned in the field of motor neuroscience: how to choose which body part, or task, to study? In this case, I am aware of the obvious limitations of this reductive approach, but I also acknowledge the need, common to all scientific fields, to study reduced systems and then build up from the simple to the complex. Based on this, I decided to focus on *upper limb* movements as I think they represent an intermediate level of behaviour embodying both low-level motor execution and higher-level cognition, but also because of the availability of well-studied reaching tasks permitting to acquire objective and accurate measures of learning. I decided to focus on *motor adaptation* as this permits to observe learning within a session in the lab setting, and because the potential of this motor learning paradigm in rehabilitation has still not been sufficiently

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[1] A video of subsequent studies using inverted prisms in real-life settings, carried out by Erismann and Kohler at the University of Innsbruck, can be found here https://www.youtube.com/watch?v=X5mjU3_vuvM .

investigated. One of the central questions I ask is whether adaptation can be optimized with appropriate combination of feedback and/or pharmacologic stimulation.

In this thesis I use two experimental tasks to investigate motor adaptation: *force-field* (Shadmehr and Mussa-Ivaldi, 1994*)* and *visuomotor* (Krakauer et al., 2000) *adaptation reaching tasks.* In both cases participants grasp the handle of a robotic manipulandum. A horizontal mirror, suspended above the hand, prevents direct vision of the arm and hand, but shows a reflection of a computer monitor mounted above it. Visual feedback regarding hand position is provided by a cursor projected onto the screen (Figure 1-3). The paradigm consists of centre-out fast shooting movements to selected visual targets. In the force-field adaptation reaching task, perturbation consists of a velocity-dependent force-field, whereas in the visuomotor adaptation paradigm perturbation consists of a screen cursor rotation with respect to the actual hand position. In both cases subjects experience a sensory prediction error, which drives learning (Tseng et al., 2007). Indeed, the addition of online motor corrections to the prediction error, as in pointing movements, doesn't benefit motor adaptation compared to shooting movements (Tseng et al., 2007). In all tasks I used an abrupt, rather than a gradual, perturbation. This for two main reasons: firstly, from an ecological point of view, many errors experienced in daily life are typically abrupt, and not gradual. Secondly, evidence shows that that the level of cerebellar inhibition increases when the perturbation is abrupt, rather than gradual, thus supporting the idea that abrupt perturbations require more error-based learning than gradual perturbations (Schlerf et al., 2012). The perturbation (force-field or cursor rotation) is then suddenly removed, and this produces after-effects, i.e. movement errors in the opposite direction to that seen during initial adaptation (Figure 1-2). After-effects are used as proxy of learning.
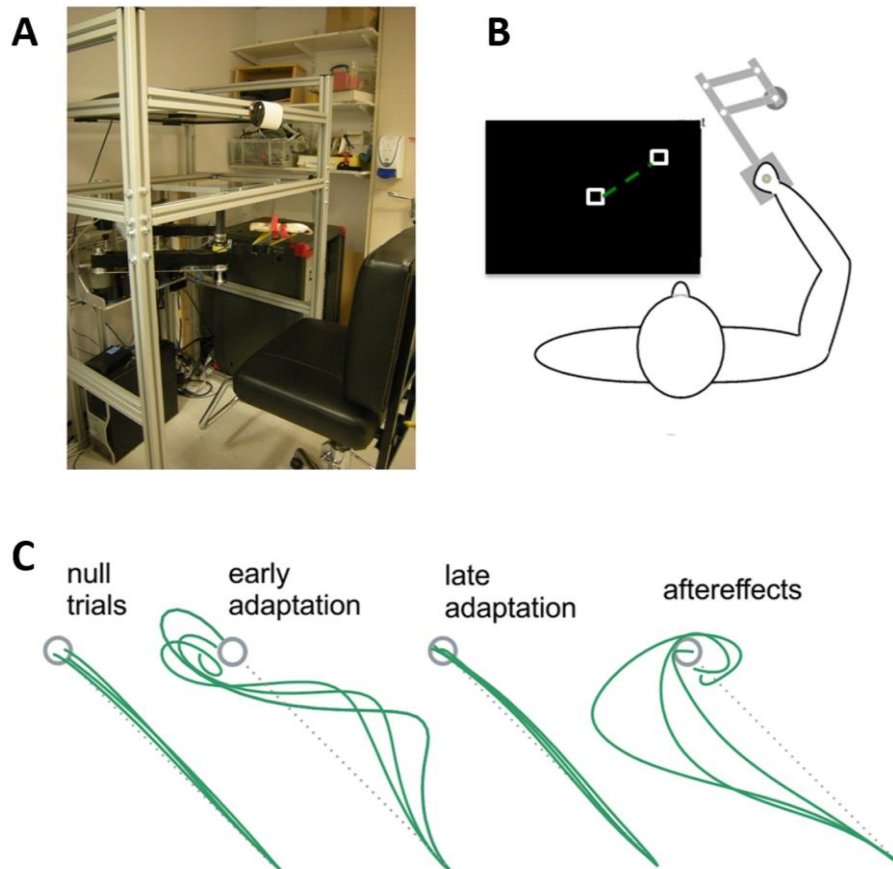
Figure 1-3 Reaching task: experimental set-up

A) Photo of the robotic manipulandum used for the experiments in this thesis (Sobell Department or Motor Neuroscience, UCL, London). B) Schematic of the experimental set-up. Participants had to grasp the handle of the manipulandum while sitting in front of it. A horizontal mirror, suspended above the hand, prevented direct vision of the hand, but showed a reflection of screen mounted above it. Visual feedback regarding hand position was provided by a cursor projected onto the screen. The paradigm consisted of centre-out fast shooting movements to selected visual targets. C) Examples of hand trajectories during a force-field motor adaptation reaching task. Hand paths are initially straight in the baseline period, in the absence of perturbation (null trials). During early stages of adaptation they become deviated in the direction of the force. With practice, subject learn to compensate to the force-field. After-effects occur when the force-field is removed. (Partially adapted from Della-Maggiore et al., 2015a with permission granted by SAGE Publishing).

1.2.3.3   Not-so-simple as it seemed: multiple learning processes during adaptation tasks

The concept of motor adaptation considered so far is based on the traditional vision of motor adaptation as a unique, *implicit,* learning process, that occurs through the updating of an internal forward model based on sensory-prediction errors (Synofzik et al., 2008; Tseng et al., 2007; Wolpert and Kawato, 1998). However, it is now known that things are more complex than this. In fact, at least two processes with different timescales operate during adaptation: a *fast* one, which learns but also forgets rapidly, and a *slow* one, which learns and forgets slowly (Huberdeau et al., 2015; Smith et al., 2006). Furthermore, *explicit*, along with *implicit*, learning, plays a role in motor adaptation (Bond and Taylor, 2015; Mazzoni and Krakauer, 2006; Taylor et al., 2014; Taylor and Ivry, 2011). Explicit knowledge can rapidly compensate for a perturbation (Mazzoni and Krakauer, 2006) and operates in a dynamic interplay with implicit learning (Taylor and Ivry, 2011). According to this model, explicit and implicit processes would work in parallel, with explicit contributions large, flexible, and exploratory early in training, and implicit learning slower, gradual throughout adaptation, and relatively rigid (Bond and Taylor, 2015; Taylor et al., 2014). Thus, explicit and implicit learning seem to correspond to the fast and slow processes (McDougle et al., 2015; Smith et al., 2006) (Figure 1-4). The fast, explicit, process probably relies on a network including attentional, executive and motor areas (McDougle et al., 2015), whereas the implicit, slow, process, in origin thought as exquisitely cerebellar (Medina et al., 2001; Smith et al., 2006), could be more complex and likely involves both subcortical and neocortical areas (McDougle et al., 2015).
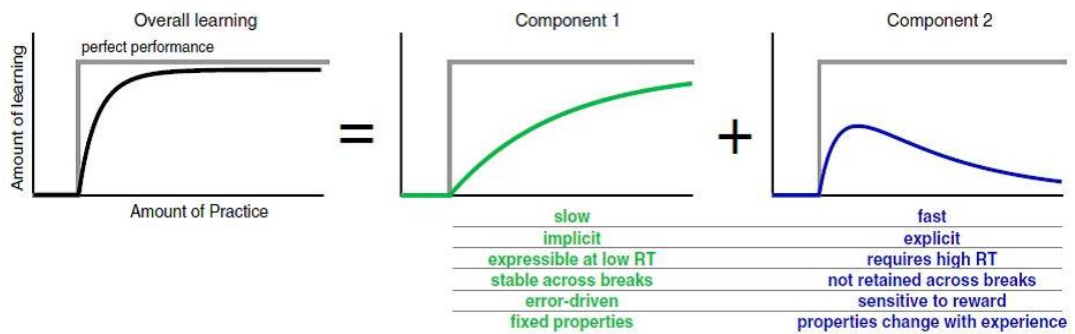
Figure 1-4 Components underlying learning in motor adaptation tasks

(Adapted from Huberdeau et al., 2015, permission granted).

1.2.3.4   *Motor adaptation and reward/punishment feedback: evidence so far*

Experiments using a visuomotor adaptation reaching paradigm show that the various learning mechanisms underlying adaptation could be differently influenced by reward and target angular errors (i.e. deviation between the movement outcome and the target). In particular, angular errors provide input to a system that learns the mapping between visual targets and motor output. Reward, on the other hand, provides input to a learning mechanism that reinforces successful movements and learns slowly but has good retention (Huang et al., 2011; Izawa and Shadmehr, 2011; Therrien et al., 2016). The reward- and error-based systems were initially considered to be independent (Huang et al., 2011; Izawa and Shadmehr, 2011; Shmuelof et al., 2012). In particular, Shmuelof et al. (2012) suggested that adaptation occurs through an error-based learning mechanism, but that an additional success-based reinforcement process could be responsible for longer-term retention of the new adapted behaviour. In this study, retention was better when binary reinforcement feedback (in terms of success or not) was not accompanied by error feedback, thus supporting the idea of two independent systems competing with each other (Shmuelof et al., 2012). Nevertheless, recent results indicate that the combination of positive (rewarding) or negative (punishing) feedback and sensory feedback could

enhance motor adaptation (Galea et al., 2015). Specifically, using a visuomotor adaptation reaching task, Galea and colleagues found a differential effect of monetary reward and punishment on motor adaptation, with punishment increasing online adaptation and reward increasing retention (Galea et al., 2015). This finding has been recently, at least partially, replicated (Song and Smiley-Oyen 2017). In particular, the delivery of punishment in 100% of the trials accelerated adaptation compared to reward or punishment given in 50% of the trials (Song and Smiley-Oyen 2017). The positive effect of reward on retention is consistent with evidence on skill learning (Abe et al., 2011; Sugawara et al., 2012; Wilkinson et al., 2015) and on adaptation of gait (Hasson et al., 2015). Conversely, Nikooyan and Ahmed found a positive effect of reward on online adaptation rather than retention (Nikooyan and Ahmed, 2015).

Thus, results are still partially contradictory, likely due to subtle methodological differences between studies. Despite this, the existing evidence largely points toward dissociable roles played by reward and punishment on motor adaptation. Though, this literature did not clearly discriminate between the various learning processes underlying the observed behaviour, and in particular the use of a cognitive strategy versus cerebellar error-based motor learning. Taylor and colleagues designed a paradigm which permits to measure strategy use in a sensorimotor adaptation task by asking participants to explicitly report their aim location before each trial (Taylor et al., 2014). This gives an estimate of the magnitude of implicit learning by subtracting the aiming angle from the measured movement angle (Figure 1-5).
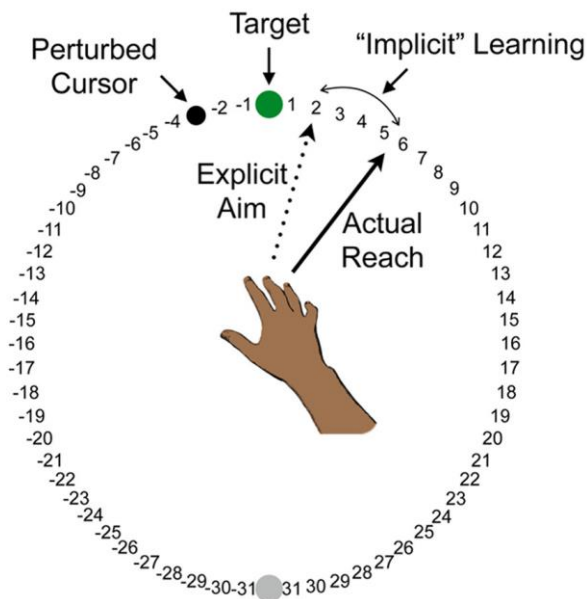
Figure 1-5 Experimental task to disentangle explicit strategy and implicit learning

Subjects are requested to declare their aiming direction prior to each reach. The difference between the explicit aiming direction and the actual reach is a measure of the implicit learning. (Adapted from McDougle et al., 2015 with permission from JoN/SfN).

This task was developed when the experiments presented in this thesis were already ongoing. Therefore, at the moment of writing, we can't yet discriminate whether the observed effects of reward and punishment on motor adaptation tasks influence the use of a cognitive strategy, or whether they directly modulate error-based learning. The use of tasks permitting to disentangle the various processes underlying the observed behaviour, combined with the delivery of reward and punishment feedback, is needed in future studies to solve this debate. This issue may seem irrelevant, but it is actually crucial also in the context of a possible clinical translation. Indeed, the differential effect of reward and punishment observed by Galea and colleagues (Galea et al., 2015) suggests that alternative forms of feedback could recruit different mechanisms, and maybe different learning processes. Identifying

these mechanisms could enable therapies that are potentially suitable for alternative groups of patients, with distinct underlying pathological neuroanatomy. The experiments presented in this thesis represent a first, crucial, step in examining the overall effect of feedback on motor adaptation tasks, and future investigations on the specific learning processes would therefore be a logic step further.

Another issue to be taken into account in view of a possible clinical translation is which type of positive or negative feedback would be the most effective and feasible in a clinical rehabilitation setting. Indeed, financial incentives, the most common form of reward or punishment used in neuroscience, would be not applicable to clinical settings. However, the effect of punishment may not depend on the financial losses associated with the performance scores (Galea et al., 2015) and a reward could be beneficial even when not associated to monetary gains (Nikooyan and Ahmed, 2015). Financial incentives could therefore be not so necessary to elicit the effects of reward and punishment feedback. Of note, other forms of positive feedback, even though still poorly investigated in the field of motor learning, have been suggested in other fields, and span from social rewards (Sugawara et al., 2012), to enjoyable music, or angry and happy faces (Russell et al., 2013).

In the next paragraph I will introduce the third category of motor learning, i.e. reinforcement learning, as classified in paragraph 1.2.1. As for the case of skill learning, also reinforcement learning will be presented as a category *per se*, isolated from the context of motor adaptation.

1.2.4   Reinforcement learning

1.2.4.1   Defining reinforcement learning

In the motor learning context, there is a broader category of learning that is more difficult to characterize, but which can be captured by the idea of *action selection*. *Reinforcement learning* refers to selecting particular actions or behaviours to maximize reward or avoid negative outcomes based on past experiences. This is considered different from skill learning as the quality of the motor performance itself is not the metric of interest, and the motor system is used just to read out whether learning has occurred. As with error-based learning, reinforcement learning operates by comparing an expected and realized outcome. However, in this case the expectation is on anticipated reward (Sutton and Barto, 1998). *Reward* is an operational term, which refers to something (a stimulus or an object) that the subject wants to obtain (Schultz et al., 1997). Reward can be *extrinsic*, i.e. based on external stimuli such as objects, money, or the performance of a certain act, or *intrinsic*, i.e. based on an internal state such as the self-perceived success. Reward has three main functions: it can act as positive reinforcer that promotes learning, it prompts movement towards the desired outcome, and it can be associated with emotions, such as pleasure and desire. The value of a reward for the individual is subjective and can be formalized as *economic utility* (Schultz, 2016a). If the outcome produces a greater than expected reward, the likelihood of repeating the action is increased; whereas if the outcome is less than the expected reward, the likelihood of repeating that action is decreased (Schultz, 1998). The difference between the reward the subject gets and the one that was predicted represents the *reward prediction error* (Hollerman and Schultz, 1998). The information content of the error signal represents a crucial difference between error-based learning and reinforcement learning. In fact, in error-based learning, the sensory prediction error is vectorial, i.e. it provides information on how the movement should be modified to be successful. In reinforcement learning, instead, the reward prediction error is either categorical, i.e.

reward obtained or not, or metrical, i.e. it indicates the difference in the value of the reward (Taylor and Ivry, 2014). This difference can be *positive,* i.e. the obtained reward is better than what predicted, or *negative*, i.e. the reward is worse than expected. The learning mechanism works because we all want to obtain positive prediction errors and avoid negative prediction errors. This is a mechanism built in by evolution that pushes us to always want more (Schultz, 2016b). At the neural level, both rewards and rewards predictors cause a firing of midbrain dopamine neurons. However, the response disappears when the reward is predicted: any reward we receive automatically updates our predictions and the previously larger-than-predicted reward becomes the norm and no longer triggers a dopamine neurons firing. This explains why we always want higher rewards and we are never satisfied with what we have (Schultz, 2016b).

1.2.4.2   Reinforcement learning and other motor learning mechanisms

Reinforcement learning paradigms include the delivery of reward or punishment in learning tasks. The interaction between reinforcement learning and other motor learning mechanisms has been studied in the context of both motor skills (Abe et al., 2011; Steel et al., 2016; Sugawara et al., 2012; Wächter et al., 2009; Wilkinson et al., 2015) and adaptation tasks (Gajda et al., 2016; Galea et al., 2015; Nikooyan and Ahmed, 2015; Shmuelof et al., 2012; van der Kooij and Overvliet, 2016). Thierren and colleagues, in particular, recently investigated reinforcement learning and motor adaptation in a group of patients affected by ataxia (Therrien et al., 2016). Patients with cerebellar damage showed normal levels of exploration variability and were able to learn through reinforcement, but their high levels of motor noise limited the extent of this learning. Thus, reinforcement learning seems to depend on a balance between exploration variability and motor noise (Therrien et al., 2016). In addition, and in agreement with previous findings (Shmuelof et al., 2012), while reward feedback led to near perfect retention of the learned behaviour, error feedback learning was not retained and decayed. In line with this evidence, several studies

support the hypothesis that reward increases retention of motor memories, whereas the effect of punishment is more controversial. Back in 1953, Skinner, who regarded punishment as a "questionable technique", speculated as to whether it actually worked, and stressed the fact that even when it did, its effects tended to be short lived (Skinner, 1965). Indeed, studies in various species of insects found that punishment memory is relatively short-lived compared to reward memory in various learning tasks, ranging from olfactory (Honjo and Furukubo-Tokunaga, 2009; Tempel et al., 1983; Unoki et al., 2005) to visual pattern (Unoki et al., 2006) and colour learning (Nakatani et al., 2009). In humans, punishment is effective for producing immediate termination of undesirable behaviour but effects tend to be short-lived compared to those of reward (Gershoff, 2002).

But, if that is the case that reward and punishment have differential effects on motor learning, what would be, from an evolutionary perspective, the benefit of this? An intriguing explanation is provided by Nakatani et al. (2009). According to these Authors, in our changing environment stimuli that once predicted punishment may change to reward predictors or *vice versa*. In this context, long-term retention of avoidance for once-punished stimuli (with the exception of extremely intense punishments, causing physical injury) could have a high cost, as this would reduce the opportunity to obtain useful resources in the future. On the other hand, long-term retention of preference for once-rewarded stimuli would not have such cost. An example is an inedible food item in one season, which may become profitable in the next season. This would explain the convenience, from the adaptive point of view, of having differential behavioural and learning effects as well as differential neural correlates at the basis of reward and punishment learning.

Although the cognitive neuroscience literature has focused on behavioural evidence for different learning mechanisms, brain-imaging and neurostimulation studies have also investigated the neural correlates of these mechanisms. In the next section, I will briefly discuss the main findings from these studies.

1.3 The functional neuroanatomy of motor learning

Motor learning is a complex process relying on multiple brain areas to properly happen. In this section I will focus on the functional neuroanatomy of the primary motor cortex, the cerebellum and the basal ganglia, which are the major nodes in the motor network, and have unique cytoarchitectural properties, reciprocal connectivity, and plasticity mechanisms that allow efficient communication among them (Figure 1-6).
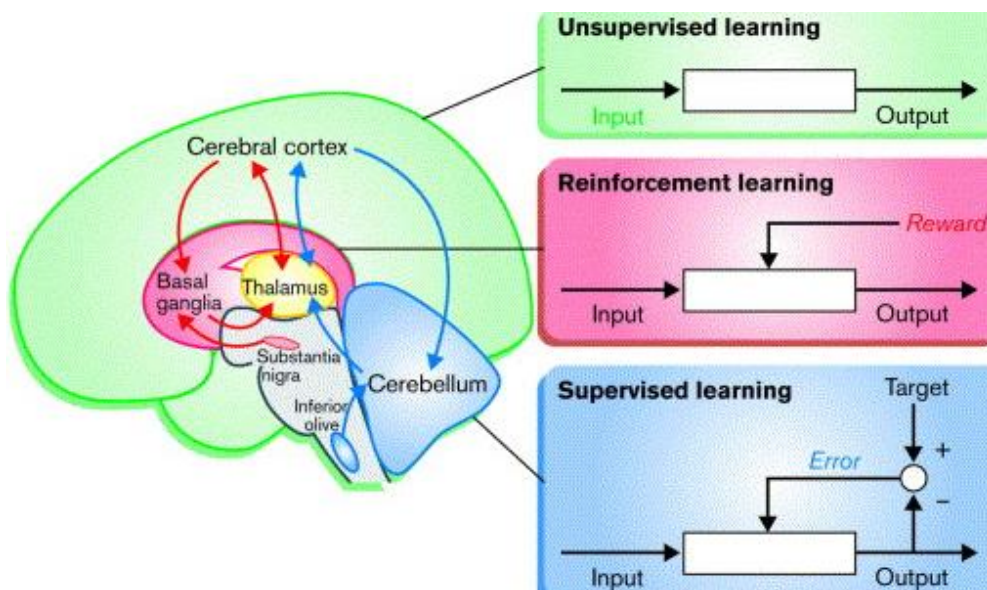
Figure 1-6 Schematic representation of the specialization of the cerebellum, basal ganglia and motor cortex for different types of motor learning

The cerebellum (blue) is specialized for supervised error-based learning. The basal ganglia are specialized for reinforcement learning, which is guided by the reward signal. The cerebral cortex is specialized for unsupervised skill learning. (Adapted from Doya, 2000 with permission from Elsevier).

I will adopt here a "decomposition strategy", often used in cognitive neuroscience to describe each structure separately (Sternberg, 2011). This has to be considered as a starting point, with the underlying assumption that it is the combination of single anatomical structures that generates the behaviour as seen in real life, and that new

behaviours, which no single structure can individually process, can arise through their interactions (Shmuelof and Krakauer, 2011).

Interestingly, from an evolutionary perspective, the cerebellum and the basal ganglia have been structurally highly conserved among vertebrates, which suggests that their computational role may not have substantially changed, and may suffice for the vast majority of animals. Conversely, some of the functions mediated by the motor cortex may be a late evolutionary development, particularly advanced in humans (Shmuelof and Krakauer, 2011).

1.3.1   Control and retention of motor memories: the primary motor cortex

The primary motor cortex, or M1, is the major cortical output to the descending motor system and generates the neural commands that result in voluntary movement. M1 is strongly interconnected with somatosensory and spatial processing regions in the parietal lobe, the premotor cortex and supplementary motor area, as well as both the basal ganglia and cerebellum. M1 is organized as a motor map with a globally somatotopic organization (Penhune and Steele, 2012). Importantly, M1 is not just a static motor control structure, but it is a dynamic substrate with a central role in motor learning (Sanes and Donoghue, 2000).

A large amount of evidence suggests that improvements in motor skills, in terms of faster and more accurate performance, are accompanied by plasticity in M1 (Shmuelof and Krakauer, 2011). Specifically, both animal and human research has shown that motor learning elicits long-term potentiation (LTP) changes in M1 (Kleim et al., 1998, 2002; Nudo et al., 1996; Rioult-Pedotti et al., 1998, 2000; Rosenkranz et al., 2007; Ziemann et al., 2004). Repetitions of simple motor actions, in particular, lead to plastic reorganizational changes in the primary motor cortex, a phenomenon known as use-dependent plasticity (UDP) (Mawase et al., 2017). Indeed,

improvement in the speed and accuracy of sequential finger movements correlates with increased local blood oxygenation level-dependent (BOLD) signal in M1 (Karni et al., 1995; Stagg et al., 2011), is enhanced by transcranial direct current stimulation (tDCS) (Classen et al., 1998; Reis et al., 2009; Stagg et al., 2011) and is inhibited by repetitive TMS over M1 (Muellbacher et al., 2002). Similarly, behavioural investigations have shown that consistent repetition of movements induces directional biases toward the repeated direction (Diedrichsen et al., 2010; Huang et al., 2011; Verstynen and Sabes, 2011). Furthermore, small strokes in the motor cortex lead to significant recovery of premorbid prehension kinematics (Gonzalez and Kolb, 2003), which seems to be mediated by plasticity in the peri-infarct cortex, with structural changes very similar to those described after reach training in healthy rats. Similar findings have been made in the squirrel monkey (Nudo et al., 1996). Thus M1 is necessary for recovery of previously acquired skills after small cortical lesions and acquisition of new skills, likely using very similar plasticity mechanisms.

Although UDP has been interpreted as the result of Hebbian changes in the motor cortex (Huang et al., 2011; Orban de Xivry et al., 2011; Verstynen and Sabes, 2011), i.e. induced by and further amplifying correlations in neuron activities, this form of plasticity seems to be sensitive to inputs from the basal ganglia. This is supported by the presence of dopamine receptors on cells in M1 (Huntley et al., 1992; Luft and Schwarz, 2009), by the fact that dopaminergic medication leads to increased UDP (Flöel et al., 2008a), and by the deficit of motor cortex plasticity in Parkinson's disease patients under off-medication condition (Morgante et al., 2006).

In the specific context of motor adaptation, early neuroimaging studies showed a shift in in brain activity and functional connectivity before and after adaptation, with greater activity in sensorimotor areas, including M1, in the later stages of adaptation, rather than in the early phases (Della-Maggiore et al., 2015a, 2015b). These findings were corroborated by a tDCS study showing that 15 minutes of anodal (i.e. excitatory) stimulation over M1 during a sensorimotor adaptation task had no effect on learning

but increased memory retention (Galea et al., 2011). Thus, M1 appears to intervene during late stages of motor adaptation tasks and seems to have a role in the establishment and expression of long-term memories (Della-Maggiore et al., 2015a).

In summary, M1 is the likely site of storage of new motor memories, probably as part of a network including also the premotor and parietal cortex, and seems to have a key role in the retention of motor memories. The strength of cortical plasticity associated with retention could be modulated by reward signals, likely through dopaminergic pathways (as partially supported by the experiments described in Chapter 4), and the motor cortex might therefore be able to integrate reward prediction errors (Mawase et al., 2016).

1.3.2 Integration of information to update predictions: the cerebellum

The cerebellum is one of the most fascinating and deeply studied structures of the central nervous system, and the fact that it contains about 50 billion neurons, i.e. roughly half of all the neurons in the brain, gives an idea of its powerful processing capacity (Zagon et al., 1977). The cerebellar cortex has the unique characteristic to be structurally uniform, with the same basic neuronal circuitry throughout its surface (despite this having recently been questioned (Cerminara et al., 2015)), and yet, thanks to its global connections (Ramnani, 2006), this structure is capable of a range of functional roles, from purely motor to cognitive (Schmahmann and Sherman, 1998).

In 1967 John Eccles, Masao Ito and John Szentagothau were the first to investigate the cerebellar microcircuitry, and to show that the Purkinje cells, the only efferent cerebellar cells, are inhibitory in nature (Eccles et al., 1967). Their studies were expanded further by David Marr (Marr, 1969) and James Albus (Albus, 1971), who inspired the so called *Albus-Marr hypothesis.* The main core of this hypothesis is that

the cerebellar cortex has the role of learning motor skills and the climbing fibres act as an error-detecting device.

It may be useful, at this point, to briefly explore the anatomy of the cerebellar cortex.

As already mentioned, the cerebellar cortex presents a uniform structure, composed of three layers throughout its surface: the granular layer (the deepest one), containing the granule cells; the Purkinje cells layer (intermediate) and the molecular layer (on the surface) (Figure 1-7). The *Purkinje cells* represent the *only efferent cells* of the cerebellar cortex, and therefore they have a central role in the cerebellar information processing. They send their projections to the deep cerebellar nuclei, subcortical structures deep inside the cerebellar white matter, which form the outputs from the cerebellum to other main areas (Figure 1-7).

The two main classes of *afferent fibres* are represented by the mossy fibres and the climbing fibres.

The *mossy fibres,* coming from the motor cortex, the brainstem (mainly pontine) nuclei and the spine, bring information about fine skilled movements and motor planning (cortico-ponto-cerebellar system), proprioception (spino-cerebellar system), and position of the head (vestibule-cerebellar system). These fibres target the granule cells, whose axons bifurcate in the molecular layer to become the *parallel fibres*. Each Purkinje cell can receive up to 200.000 afferent parallel fibres (Fox and Barnard, 1957). Through the granule cell-parallel fibre pathway, mossy fibres indirectly excite the Purkinje cells, causing these to discharge "simple spikes" (conventional action potential). In addition, mossy fibres also contact various interneurons in the cerebellar cortex, both directly and indirectly.

The other main class of afferent fibres are the *climbing fibres*, which arise exclusively from the inferior olive, a well-defined complex of nuclei in the ventral part of the caudal brainstem. Each Purkinje cell receives direct contact from just one climbing

fibre. Nevertheless, the contact with the Purkinje cell's dendritic tree is so extensive that climbing fibres generate the largest depolarizing event seen in any neuron: a highly characteristic burst of impulses known as "complex spike" (Apps and Garwicz, 2005). Climbing fibres have been suggested to play a range of roles, but overall their main function seems to be mediating error signals and driving the synaptic plasticity underlying error-based learning (Gilbert and Thach, 1977). It is therefore not surprising that the integrity of the climbing fibres is vital to the cerebellar contributions to movement control.
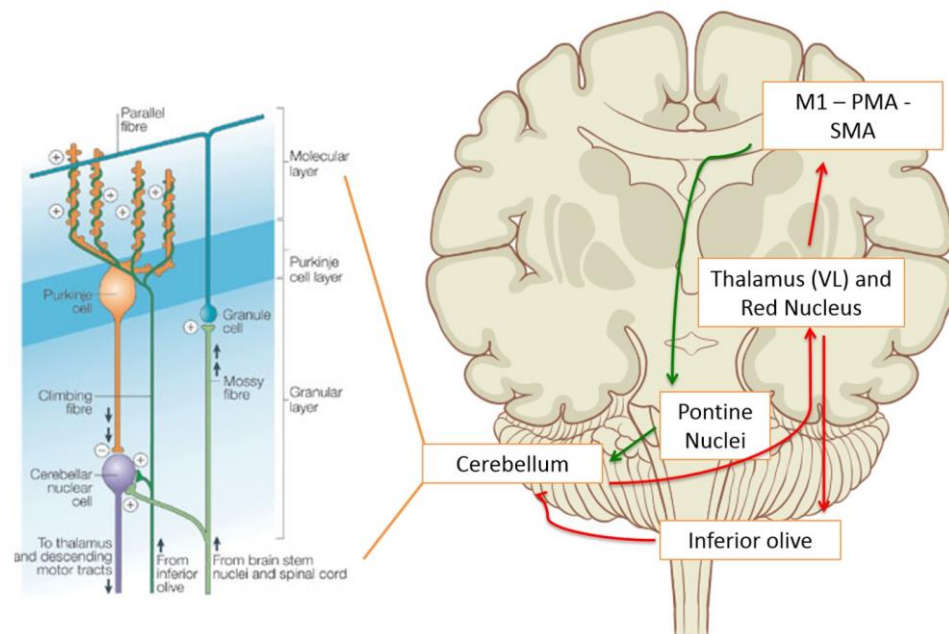
Figure 1-7 Basic structure of the cerebellar cortex and of the main cerebellar connections relevant for motor learning

See main text for details. (Adapted from Apps and Garwicz, 2005 with permission from Macmillan Publishers Ltd: Nature Rev Neurosci, copyright 2005)

In the Marr-Albus-Ito hypothesis, long term depression of parallel fibre-Purkinje cell synapses resulting from co-activation of parallel and climbing fibre inputs underlies motor learning (Albus, 1971; Ito, 2001; Marr, 1969). In this context, complex spikes are evoked by errors and provide a teaching signal that modifies subsequent simple spike activity to correct the behaviour (Gilbert and Thach, 1977; Kitazawa et al., 1998; Medina and Lisberger, 2008; Yang and Lisberger, 2014). This hypothesis has been elaborated and modified over the past 40 years, but the core idea of the cerebellum as a system for supervised, error-based, learning remains one of the central tenants of cerebellar control theory (Ito, 2005, 2006; Miall et al., 1993; Wolpert and Kawato, 1998). In particular, it has been suggested that the cerebellar cortex could be the site of motor memories in the form of *forward internal models*. Motor commands generated in M1 are sent to lower motor control centres in the brainstem and spinal cord (Dum and Strick, 1996; Georgopoulos, 1991; He et al., 1993, 1995). Fibres on their way to the spinal cord collateralize, and synapse with neurons in the pontine nuclei: thus, the cortico-ponto-cerebellar system, through the mossy fibres, would bring an *efferent copy* of the motor command to the forward model. This is used by the forward model to predict the ideal new state, and the related sensory consequences, of the body after the movement. Evidence suggests that the inferior olive serves as comparator of these *predicted sensory feedback*, conveyed from the cerebellum to the inferior olive either directly or through the red nucleus (Courville and Otabe, 1974), with *the actual sensory feedback,* i.e. reafferent sensory and proprioceptive signals conveyed from the spinal cord to the inferior olive (Armstrong and Schild, 1979). Therefore, the inferior olive would "detect" the unexpected sensory consequences of movements (sensory prediction error) and the climbing fibres would cause the complex spike in the Purkinje cells, thus causing long term depression of the cells which were activated by the motor command. This would update the forward model as well as influencing directly the motor commands through projections back to the motor cortex via the thalamus (Dum et al., 2002; Dum and Strick, 2003) (Figure 1-8).This theory has been, at least partially, tested in a

TMS study, assessing cerebellar excitability during locomotor adaptation in a split-belt treadmill task (Jayaram et al., 2011). Interestingly, the authors found a strong correlation between adaptation and cerebellar excitability depression, which supports the idea that adaptive learning is mediated, at least in part, by long-term depression in Purkinje cells. The interposed deep cerebellar nuclei would be important to consolidate procedural memory (Monaco et al., 2014; Okamoto et al., 2011). Indeed, neuroimaging studies reveal activity in the human cerebellum related to error signals (Diedrichsen et al., 2005; Imamizu et al., 2000; Ramnani et al., 2000), and the main symptoms shown by patients with cerebellar ataxias can be framed in the context of malformation or mis-selection of internal models (Tada et al., 2015).
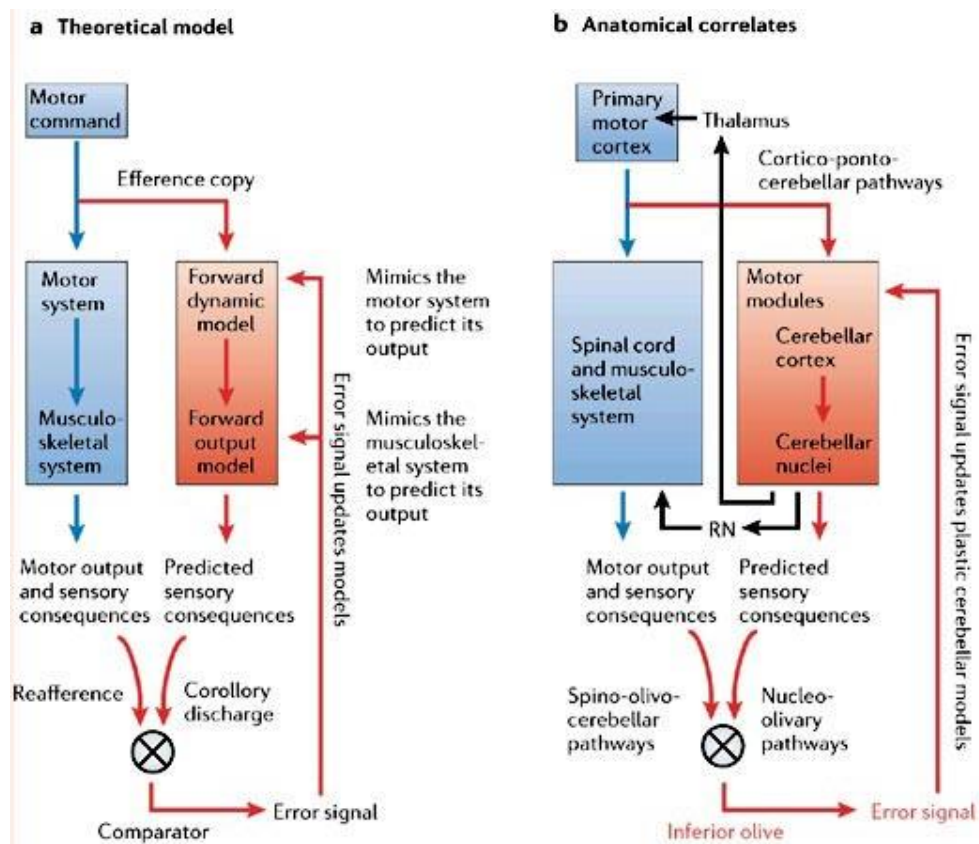
Figure 1-8 Theoretical and neural organization of cerebellar error-based learning

A) Theoretical organization of error-based cerebellar learning (see text for details). B) Anatomical correlates of this theoretical organization (see text for details). RN, red nucleus. (Adapted from Ramnani, 2006 with permission from Macmillan Publishers Ltd: Nature Rev Neurosci, Copyright 2006).

This hypothesis, despite its elegance, still needs to be refined. For example, although substantial evidence supports a role for climbing fibres in error signalling and motor learning, complex spikes are not invariably activated by errors (Popa et al., 2016) and are not essential for cerebellar motor learning (Hewitt et al., 2015; Ke et al., 2009; Nguyen-Vu et al., 2013).

Nevertheless, the notion of two systems, the cerebral and the cerebellar one, working in parallel, provides a possible explanation of how our brain manages to overcome some of the main limitations of motor control.

Indeed, the process of motor control can be theoretically described in terms of lower centres (such as those in the spinal cord) translating motor commands from higher centres (such as the cerebral cortical motor areas) into movements. The resulting movement is accompanied by a set of sensory consequences; such as proprioceptive and sensory feedback. However, before such feedback can be usefully implemented, three problems have to be solved. First, inherent delays in the transmission of this data back to the brain mean that the sensory feedback arrives when it would be too late to influence the ongoing movement. Second, the sensory consequences of action indicate the extent to which movement deviates from an ideal performance only if compared with an appropriate reference. Third, the sensory information fed back to the brain cannot be directly decoded by systems that normally generate information for the motor system (Ramnani, 2006). The cerebellar control theory, despite still partially debated, provides an elegant solution to all these issues, and offers an ideal framework for supervised, error-based learning. Accordingly, patients with cerebellar pathology show a marked impairment in adapting to sensorimotor perturbations (Criscimagna-Hemminger et al., 2010; Gibo et al., 2013; Izawa and Shadmehr, 2011; Morton and Bastian, 2006; Rabe et al., 2009; Smith and Shadmehr, 2005).

The structural uniformity of the cerebellar cortex implies also functional uniformity. It can therefore be argued that the diverse information processing in the cerebellar cortex arises not from local differences in information processing, but from the diverse nature of its connections, in particular with the cerebral cortex (Ramnani, 2006). Some dissociations within the cerebellum seem to exist even within adaptation tasks, with force-field adaptation associated with more superior aspects of the cerebellum relative to visuomotor adaptation (Donchin et al., 2012; Rabe et al., 2009).

There is nowadays growing evidence that the cerebellum is involved also in motor learning processes others than adaptation (Taylor and Ivry, 2014). For example, it could play a role in explicit strategic learning, through cerebellar–prefrontal loops that may be part of a working memory system, helping maintain action plans such as the current strategy (Spencer and Ivry, 2009), or simulating outcomes for different aiming locations (Strick et al., 2009). The cerebellum may also be involved in reinforcement learning, as suggested by the observed correlation between the cerebellar BOLD response and reward prediction error (O'Doherty et al., 2003).

Whereas the computational roles of the cerebellum in these processes remain unclear, recent studies have identified anatomical projections between the cerebellum and the basal ganglia which could partially support these roles (Bostan et al., 2010; Hoshi et al., 2005). One hypothesis could be that the cerebellar projections to the basal ganglia, and probably also to the prefrontal cortex, allow the reward prediction system to differentiate between errors in selection (i.e. the selected object was erroneously valued) and errors in execution (i.e. the required action was not properly executed). This means that the cerebellar output could modulate reward prediction errors, with the occurrence of a sensory prediction error providing a signal to deemphasize a reward prediction error (Taylor and Ivry, 2014). In this context, the recent observation that the granule cells encode the expectation of reward (Wagner et al., 2017) represents a departure point from the classical, and likely simplistic, understanding of cerebellar circuits as represented above. Indeed, the great number of granule cells, as well as the pontine input from highly diverse regions of the neocortex, suggests that the cerebellum is designed to integrate more information than the delayed sensory feedback and the motor efferent copy. Reward expectation, for example, could be a useful contextual cue to improve predictive cerebellar computations in the motor, but also in the cognitive, forward models.

1.3.3 Optimizing behaviour in pursuit of reward: the basal ganglia

The basal ganglia are a group of nuclei at the base of the brain strongly connected to the cortex. They include the striatum (caudate, putamen and nucleus accumbens), globus pallidus (GP), subthalamic nucleus (STN), substantia nigra (pars compacta, SNc, and pars reticulata, SNr) and the ventral tegmental area (VTA) (Figure 1-9). Based on both structural and functional evidence, the striatum is often divided into a ventral (nucleus accumbens and ventromedial portions of the caudate and putamen) and a dorsal part (the remainder of the caudate and putamen).
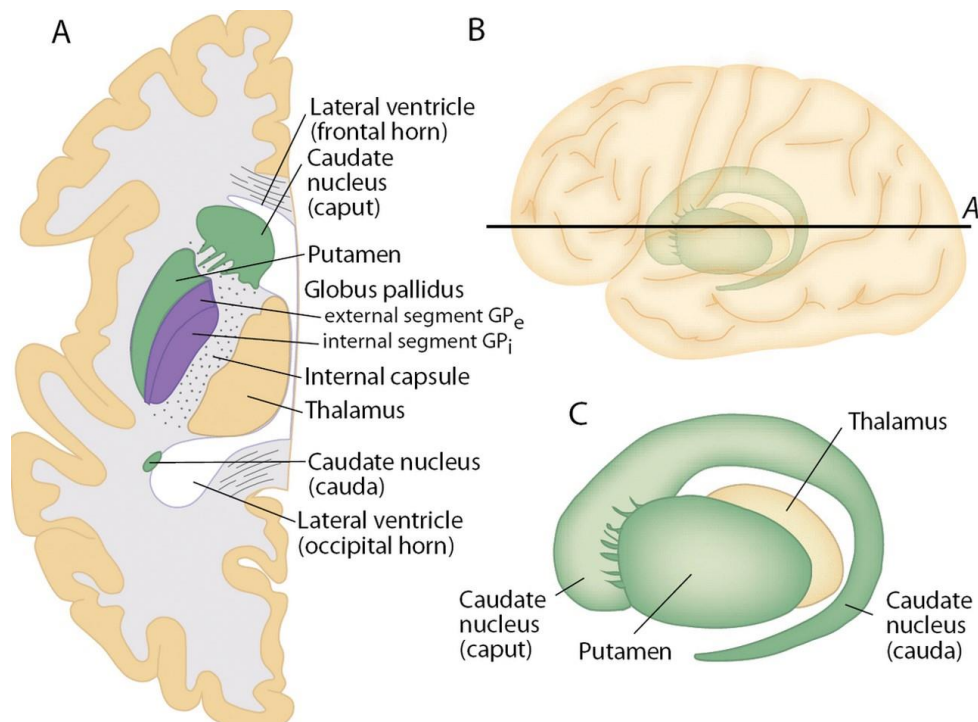
Figure 1-9 The basal ganglia

A) Part of a horizontal section through the hemisphere, as shown B) with a line in drawing of the hemisphere. C) Left putamen and caudate nucleus; lateral aspect. (Adapted from Brodal, 2016)

The striatum receives the majority of afferent inputs from three major sources: a) the cerebral cortex (virtually all the neocortex sends excitatory projections to the striatum, in a fairly strict spatial topography, Reiner et al., 2010); b) the thalamus; c) the brainstem (primarily dopaminergic projections from the SNc and the VTA, projecting respectively to the dorsal and ventral striatum). The ventral striatum receives an additional subcortical input from the amygdala and the hippocampus (Fudge et al., 2002; Russchen et al., 1985). These inputs are processed via the so called direct and indirect pathways, pass through the globus pallidus pars externa (GPe), the STN and the SNc, and leave through the pars interna of the globus pallidus (GPi) and SNr to go to the thalamus (Figure 1-10). The GPi and SNr are therefore the sources of the majority of efferent connections that target cortical regions via the thalamus, thus creating a closed frontal-subcortical feedback loop. Thanks to this organization, the basal ganglia are able to integrate and feedback information from large cortical regions.
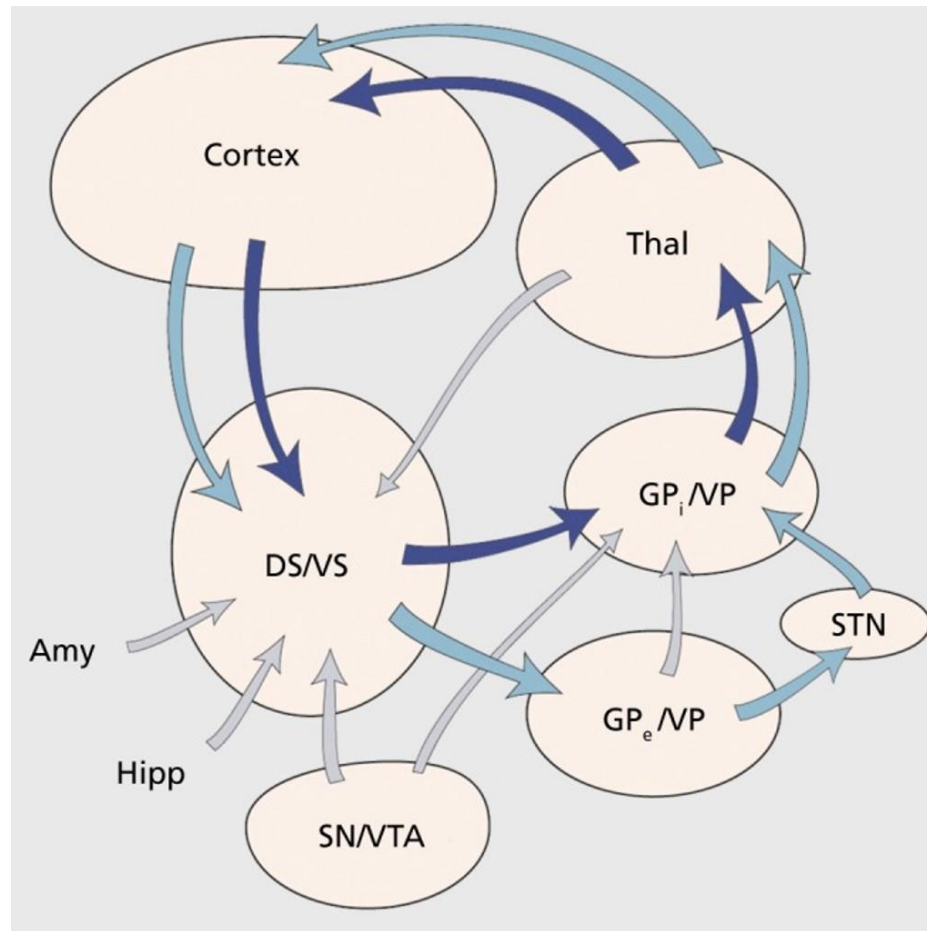
Figure 1-10 Schematic illustration indicating pathways and connections of the basal ganglia

Dark blue arrows represent the direct pathway; light blue arrows represent the indirect pathway. Amy, amygdala; DS, dorsal striatum; GPi, globus pallidus, internal segment; GPe, globus pallidus, external segment; Hipp, hippocampus; SN, substantia nigra STN, subthalamic nucleus; Thal, thalamus; VP, ventral pallidum; VS, ventral striatum; VTA, ventral tegmental area. (Adapted from Haber, 2016, permission granted under Creative Commons Attribution License).

Via these cortico-subcortical networks, the basal ganglia work in tandem with the cortex to develop and play complex motor and non-motor functions. In particular, they are involved not only in goal-directed motor behaviours, but also in the processes and the elements that drive actions, such as emotions, motivation and

cognition (Haber, 2016). These processes all share the common aim of optimising behaviour in pursuit of reward. Overall, the ventral regions of the basal ganglia play a key role in reward and reinforcement; more central areas are involved in cognitive functions, such as procedural learning and working memory; while the dorsal areas are involved in motor functions, such as the selection of parameterizable action (Dudman and Krakauer, 2016). Accordingly, the inputs from the cortex and the thalamus to the striatum are organized in a topographic manner, such that the ventromedial striatum receives inputs from the limbic areas, the central striatum from the associative cortical areas, and the dorsolateral striatum from the sensory-motor areas (Haber, 2016).

Compared to the cerebellum, the precise role of the basal ganglia in motor learning remains less clear (Shmuelof and Krakauer, 2011). Review of the literature across species suggests that the basal ganglia are critical for early learning of sequential actions through trial and errors. In particular, at early stages of learning, the basal ganglia seem to increase movement variability, and therefore aid trial and error learning. Variability in motor output can be beneficial early in learning as it allows the motor system to explore a range of actions and selectively reinforce the ones that improve performance (Sutton and Barto, 1998; Tumer and Brainard, 2007; Wu et al., 2014). In this view, motor variability has been defined as being to skill learning what genetic variation is to evolution: an essential component of a process that, through trials and errors, shapes behaviour (Dhawale et al., 2017). As viable solutions are found, variability in motor output can become detrimental for expert performance and is often reduced. Therefore variability progressively decreases as the chosen successful action automatizes, thus improving action selection (Figure 1-11). This role of variability has been suggested to be broad, i.e. not just limited to skill learning, but also extending to error-based paradigms (Dhawale et al., 2017; Wu et al., 2014). At later stages of training, instead, basal ganglia connections to the motor cortex could enhance selection of better muscle combinations (Shmuelof and Krakauer, 2011).
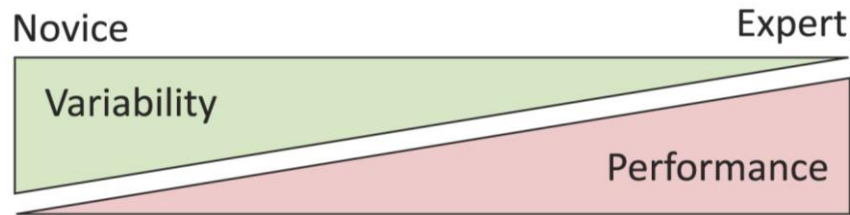
Figure 1-11 Variability and performance in motor skill learning

A strong coupling between performance improvement and variability reduction is a characteristic of most forms of motor skill learning. (Adapted from Garst-Orozco et al., 2014, permission granted under Creative Commons Attributions License, CC-BY).

In other words, the basal ganglia optimize motor (and non-motor) behaviour by implementing reinforcement-based feedback to allow the effective combination of motor elements. The reinforcement learning theory describes three major classes of algorithms for action selection and learning: exploratory (i.e. generate variability in action), model-based (i.e. evaluate the results of those actions), and motor-memory (i.e. modify future behaviour accordingly) strategies (Sutton and Barto, 1998). The exploratory strategy updates values of states and actions to efficiently utilize experiences resulting from exploratory actions and acquired rewards. The model-based strategy employs an internal model that enables simulation of the future state reached by a hypothetical action, or multiple actions. As mentioned above, Schultz and colleagues (Schultz, 2016b) have demonstrated the role of midbrain dopaminergic neurons in encoding the evaluative signal at the basis of this mechanism. Indeed, these neurons fire in proportion to the difference between expected and actual reward, generating the reward prediction error (O'Doherty et al., 2003). This error signal, along with environmental cues from the cortex (Haber, 2011; Matsumoto et al., 2001), is coincident upon the striatum, whose neurons modify their activity based on this convergent information (Kawagoe et al., 2004; Lauwereyns et al., 2002; Samejima et al., 2005). The motor-memory strategy

reinforces the sequence of states and actions that led to successful results in the past. This is simple, but requires many trials before finding an optimal sequence, unless there are clues to minimize exploration. The neural substrates of these algorithms are different: the ventromedial prefrontal cortex and ventral striatum would increase activity in the exploratory condition; whereas the dorsolateral prefrontal cortex, dorsomedial striatum, and lateral cerebellum in the model-based condition; and the supplementary motor area, putamen, and anterior cerebellum in the motor-memory condition (Fermin et al., 2016). In particular, a decrease in the GABAergic GPi inhibitory activity in the early phases of learning, as observed in associative learning tasks (Sheth et al., 2011), would release downstream thalamo-cortical circuits from inhibitory tone, thus facilitating the initial exploratory behaviour.

Thus, the basal ganglia are a learning machine dedicated to achieving success in behaviour (Graybiel and Grafton, 2015), and variability is, at least partially, a form of exploration driven by the recent history of rewards. Indeed, when the function of the basal ganglia is compromised, such as in patients affected by Parkinson's disease, the reward-dependent control of movement variability is impaired, particularly affecting the ability to increase variability after unsuccessful outcomes (Pekny et al., 2015).

Another role of the basal ganglia is the control of vigor, i.e. the movement speed, amplitude and frequency (Dudman and Krakauer, 2016). Movement vigor is influenced by prior experience, explicit instruction, expected outcomes and implicit motivational state. Indeed, basal ganglia deficits such as in Parkinson's disease produce movements of reduced vigor (Baraduc et al., 2013; Mazzoni et al., 2007). Of note, these deficits can be partially ameliorated by deep brain stimulation (Baraduc et al., 2013). Thus, the basal ganglia seem to have also a role in implicit motivation operating through the control of vigor.

1.3.4 The interplay between motor cortex, cerebellum and basal ganglia

As anticipated above, the structures described don't work in isolation and, not only their interaction influences and generates each motor behaviour, but, also, new behaviours, which no individual structure can individually process, can arise through their combination. However, although we know that these structures are interconnected, less is known regarding the neural basis of the interaction between cerebellar-dependent motor adaptation and frontal/basal ganglia-dependent learning (explicit strategies/reinforcement learning). A possible framework could be to see motor learning as underwritten by parallel, interacting processes that are instantiated in specific cerebellar, striatal or M1 mechanisms. Based on this, the ensemble of regions that are engaged at a particular phase of learning will depend on task demands that tap each specific mechanism. However, much still needs to be known, and this thesis partially represents also an attempt toward a better knowledge on the interaction between the different motor learning systems.

During my PhD I have used a pharmacological approach with the aim to modulate the effect of reward and punishment on a motor adaptation task. Therefore, in the next section I will briefly introduce the basis of the neuropharmacology of motor learning processes. Once again, I have to point out that this has to be seen as an introduction to the intricate world of motor learning. I will focus here on dopamine, which is the neurotransmitter I have manipulated in some of the experiments presented in this thesis. However, for its putative role in punishment processing, I will also give a brief outline of serotonin.

1.4 The neuropharmacology of motor learning: dopamine and serotonin

Dopamine, one of the main protagonists of motor learning processes, is a neurotransmitter belonging to the catecholamine family, which includes also norepinephrine and epinephrine. Dopamine is formed from levodopa (LD) by the enzyme dopa-decarboxylase (Stahl, 2008). The main sources of dopamine are the lateral SNc, the medial VTA, and the retrorubral area. Dopamine is transmitted via three major brain pathways: the first one, nigro-striatal pathway, extends from the SN to the striatum and is concerned with the control of voluntary movement; the second one, the meso-cortico-limbic pathway, projects from the VTA to the ventral striatum and the prefrontal cortex and is involved in the regulation of emotions and reward, but also of the executive functions (i.e. working memory, selective attention, cognitive flexibility, behavioural inhibition, and rule-based reasoning); the third one, known as tubero-infundibular pathway, is concerned with neuronal control of the hypothalamic-pituitary endocrine system (Figure 1-12).
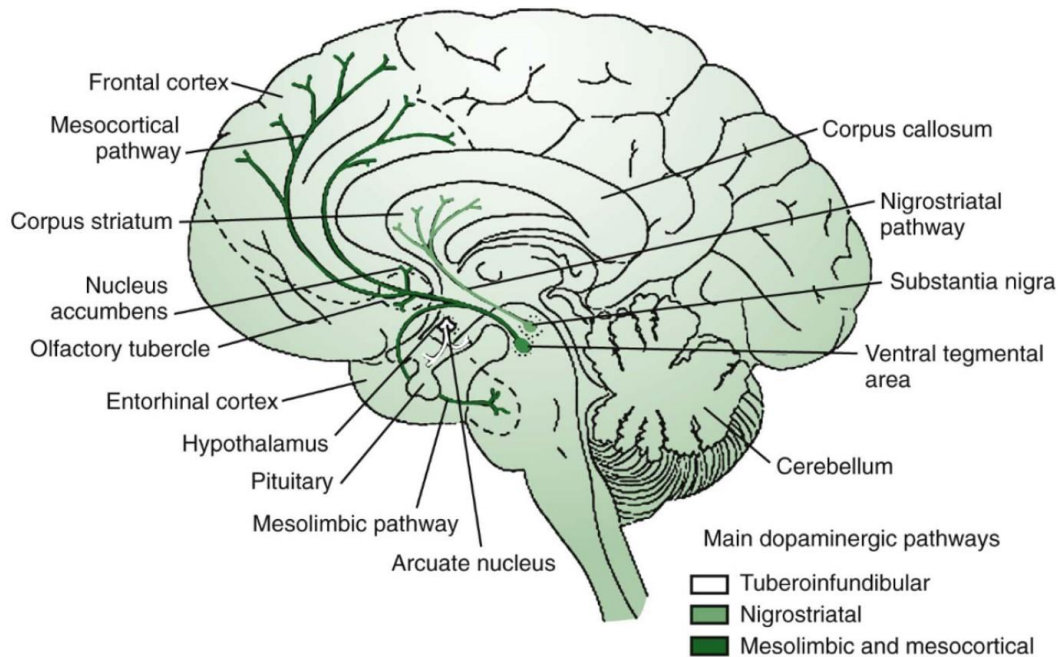
Figure 1-12 The dopamine projection systems in the brain

Adapted from www.australianprescriber.com

Dopamine is a key neurotransmitter in reinforcement learning processes. The dopamine neurons in the midbrain (SNc and VTA) show fast, phasic, responses to rewards and reward-predicting stimuli. These signals, are likely generated from the convergence on dopaminergic neurons of information regarding the predicted reward (afferences from the striatum, which encodes the learned values of actions) and the sensory feedback (from sensory areas, i.e. the received reward), and they code the reward prediction error (Glimcher, 2011). A reward that is better than predicted at a given moment in time (positive reward prediction error) elicits a phasic activation, a reward that occurs exactly as predicted in value and time (no prediction error) elicits no phasic change in dopamine neurons, and a reward that is worse than predicted at the predicted time (negative reward prediction error) induces a phasic depression in activity (Schultz, 2016a). This signal leads to locally varied dopamine

63

release that acts on heterogeneous postsynaptic structures and thus results in diverse dopamine functions. Specifically, whenever a positive prediction error occurs and dopamine is released throughout the frontal cortices and the basal ganglia, any segment of the frontocortical–basal ganglia loop that is already active will have its synapses strengthened, thus representing the basis for reinforcement learning mechanisms (Glimcher, 2011). Thus, through dopaminergic pathways, positive dopamine prediction error activation would enhance behaviour-related neuronal activity and thus favour behaviour that leads to increased reward. Indeed, dopamine enhances the propensity to select high reward/high effort options and at the same time it increases the energy actually invested in the behaviour (Le Bouc et al., 2016). On the other hand, negative dopamine prediction error would reduce neuronal activity and thus disfavour behaviour resulting in diminished reward.

Interestingly, brainstem dopaminergic neurons from the VTA and SN also send direct projections to M1 (Albanese and Bentivoglio, 1982; Descarries et al., 1987). However, whereas the direct dopaminergic projections to the prefrontal cortex are well characterized, the anatomy and function of the dopaminergic innervation to M1 remain poorly understood. It has been hypothesized that, in analogy with the projections from VTA to the prefrontal cortex, dopamine release in M1 is triggered by reward-related signals (Luft and Schwarz, 2009). Dopamine can cause various effects in M1 (as evidenced in rodents): it can have a more immediate effect by enhancing cortical excitability (Hosp et al., 2009), but it also can have longer-term effects such as an increase in the expression of learning-related genes (Hosp et al., 2011) and the formation of long-term potentiation (Jonas A. Hosp and Luft, 2013). These effects can be driven by interaction of dopamine with pyramidal cells, with inhibitory interneurons or with both, thus making it difficult to predict the net dopaminergic effect on the network level (Luft and Schwarz, 2009). From the behavioural point of view, dopaminergic projections to M1 have been hypothesized to play a role in the retention of motor memories. Indeed, in rodents, the integrity of

these projections is essential for long-lasting storage of motor memories (Hosp et al., 2011; Jonas A. Hosp and Luft, 2013; Molina-Luna et al., 2009). In humans, the administration of the dopamine precursor levodopa or the D2-receptor agonist cabergoline facilitated practice-dependent plasticity in M1 (Flöel et al., 2005; Meintzschel and Ziemann, 2006) and improved motor learning in elderly and in stroke patients (Flöel et al., 2005; Flöel et al., 2008a; Flöel et al., 2008b; Rösser et al., 2008).

While the effects of dopamine in learning from rewards have been extensively investigated, the neuromodulator has a more complex association with punishment. We can identify two main currents: the "single dimension" hypothesis proposes that dopamine (but also any other reward-sensitive circuit) is also sensitive to punishment (Wang and Tsien, 2011), whereas the second one, or "two dimensions" hypothesis, suggests that some dopaminergic neurons are sensitive just to rewards and others just to punishments (Fiorillo, 2013; Matsumoto and Hikosaka, 2009; Mirenowicz and Schultz, 1996).

The neurobiology of punishment has also been linked to serotonin, which appears closely related to behavioural inhibition in aversive contexts (Crockett et al., 2009; Dayan and Huys, 2009; Soubrié, 1986). Serotonin (or 5-hydroxythryptamine, 5HT) is synthesized from the amino acid tryptophan. Evidence point towards functional opponency between dopamine and serotonin, even if the roles of these two neurotransmitters and their relationship seem nowadays much more complex than a simple opponency (Boureau and Dayan, 2011; Guitart-Masip et al., 2014). Interestingly, the cell bodies and terminal regions of all three dopaminergic pathways shown above are innervated by serotoninergic neurons originating from the median (MRN) and the dorsal raphe nuclei (DRN) in the midbrain (Beart and McDonald, 1982; Geyer et al., 1976; Nedergaard et al., 1988; Parent, 1981). Neurons in the DRN make connections with areas innervated by the dopaminergic system (amygdala, striatum and prefrontal cortex), which implicates a close interaction between the dopamine

and serotonin system at several network levels. In particular, it has been hypothesized that DRN might be a reward hotspot (Luo et al., 2015) and that serotonin mediates the behavioural responses to punishment by antagonizing the action of dopamine (Daw and Touretzky, 2002; Dayan and Huys, 2009; Soubrié, 1986), but also that serotonin mediates behavioural inhibition and promotes patience while waiting for reward (K. Miyazaki et al., 2011; K. W. Miyazaki et al., 2011; Soubrié, 1986). Conversely, MRN neurons make connections to the hippocampus and septal nuclei, which are not major dopaminergic targets. A large serotoninergic projection from the medullary and pontine reticular formation is also present in the cerebellar cortex and nuclei (Bishop and Ho, 1985; Chan-Palay, 1975). Indeed, the involvement of serotonin in cerebellar-based motor learning has been observed in several cerebellar-dependent paradigms. For example, depletion of brain serotonin has been shown to impair the horizontal vestibule-ocular reflex adaptation in rabbits (Miyashita and Watanabe, 1984). In addition, chronic treatment with buspirone, a 5-HT1AR partial agonist, improves the motor coordination deficits in a mouse model of cerebellar neurodegeneration (Le Marec et al., 2001). Given the widespread distribution of serotonergic innervation and the richness of signals evoked by different receptor subtypes, serotonin has the potential to modulate both excitatory and inhibitory synaptic signals throughout the cerebellar network (Hoxha et al., 2016). In conclusion, while the effects of dopamine are well known, the role of serotonin still has to be better investigated, but it looks like this neurotransmitter may be related to aversive learning and to cerebellar-based learning.

1.5 Bridging the gap between research and clinical practice: motor learning in stroke

The work undertaken during my PhD, which I present in this thesis, focuses not only on healthy humans, but also on brain injured patients, and in particular stroke survivors. In this section I will show the reasons, apart than my personal interest in clinical neurology, which brought me to focus on this condition. In particular I will show the high impact of long term disabilities on the global burden of stroke, thus highlighting the need for more effective restorative therapeutic strategies. I will then move on to evaluate the general principles of motor recovery after stroke, and the applicability and possible benefits of motor learning paradigms in neurorehabilitation. In this thesis I will focus mainly on rehabilitation of upper limb paresis after stroke. This narrower focus is essential to remain within the bounds of a PhD. That said, my hope is that the general principles introduced here could be broadly applicable across the range of post-stroke impairments and to other neurological conditions.

1.5.1 The burden of stroke: the case for improving long-term support

Stroke is defined by the World Health Organization as "*rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin*" ("The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease)", 1988). The underlying pathology is infarction (about 85% of cases in Caucasian populations), intracerebral haemorrhage (about 10% of cases), or subarachnoid haemorrhage (about 5% of cases).

Stroke is a major public health problem, being the second most common cause of death worldwide after ischaemic heart disease (World Health Organization, 2017).

With an age-standardized worldwide prevalence in people aged > 65 years of 46-72 per 1000 (Feigin et al., 2003), and with more than half of all survivors suffering from long-term sensory and motor deficits (Anderson et al., 1995), stroke is also one of the leading causes of adult disability worldwide, and the leading cause of adult disability in both the UK and the USA (Gallacher et al., 2013). Reduction in mortality rates (declined by 21.0% between 2005 and 2015), together with longer survival, population growth and ageing, led to a rise of the global burden of stroke (Feigin et al., 2016). In particular, stroke went from fifth worldwide cause of lost disability-adjusted life-years[2] in 1990 (Feigin et al., 2014), to third cause in 2010 (Murray et al., 2012b), reflecting an increase of almost 20% during the past two decades (Figure 1-13). Global projections to the year 2020 indicate that this will rise even further, in both western and resource-poor countries (Gallacher et al., 2013). In England and Wales, every year about 110,000 people have their first stroke and around half of all survivors are left dependent on others for everyday activities. As of 2013, there were more than 25 million stroke survivors worldwide (Feigin et al., 2015), and this population is predicted to reach 70 million by 2030 (Feigin et al., 2014). Up to 85% of these have hemiparesis that affects their upper limb (Mayo et al., 1999).

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[2] DALYs (disability-adjusted life-years), including years of life lost (YLL) because of death and years lived with disability (YLD). To calculate YLL, the age at death for each fatality is subtracted from the reference life expectancy at that age. YLD represent healthy life-years lost in survivors, and are calculated from the number of patients living with stroke sequelae, the number of years living with disability due to the disease, and the disability weight (i.e., its severity). Disability weights range between 0 (no disability) and 1 (a life value equal to death). The methodology for calculation of DALYs has been described elsewhere (Murray et al., 2012a).
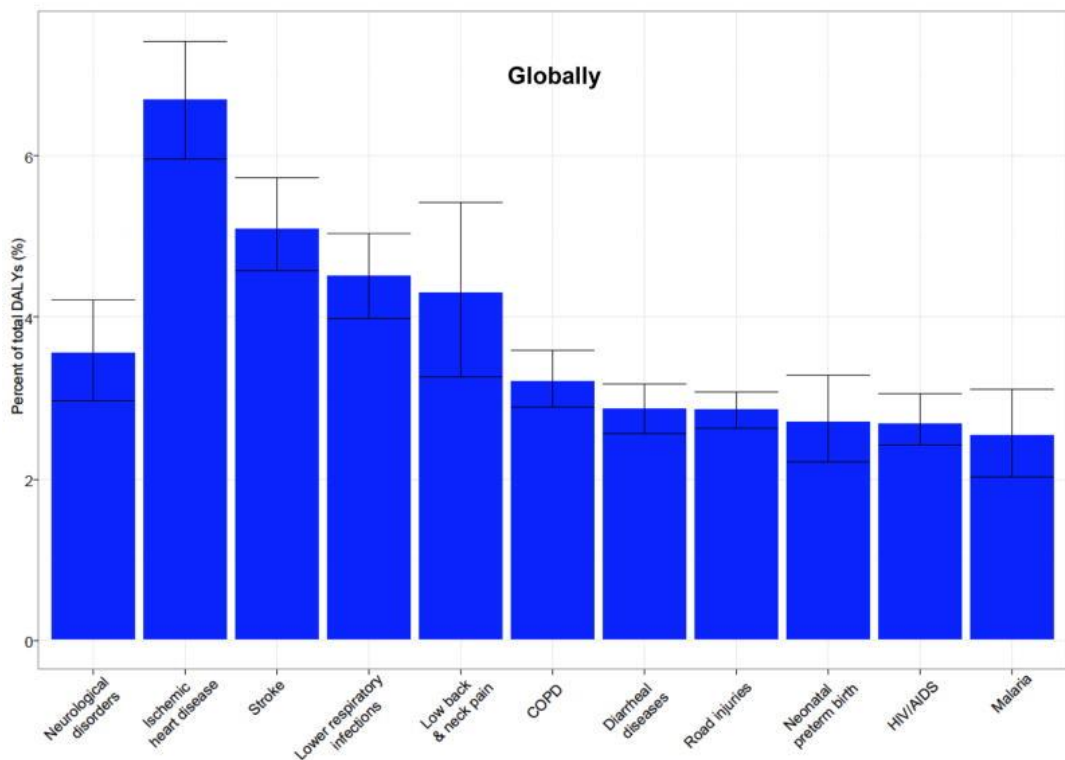
Figure 1-13 Proportion contribution of age-standardised DALYs from stroke in comparison to 10 other leading causes of DALYs, Global, 2003.

Stroke represents the third cause of DALYs worldwide, after all neurological conditions and ischemic heart disease. (Adapted from Feigin et al., 2015, permission granted by S. Karger AG, Basel).

From these data it is clear how the economic burden of stroke, estimated at over £9 billion a year in the UK (Ward, 2017), is impacted not only by initial hospitalization and medications, but also by continuing medical care and work limitations. On this basis, cost-effective neurorehabilitation interventions become a key tool to improve patients' quality of life and at the same time to decrease the global burden of stroke. Indeed, at the time of writing, the release of a new report on the burden of stroke in Europe, a comprehensive analysis of 35 European countries carried out by King's College London and published by the Stroke Alliance for Europe and the Stroke Association, highlights the need for policy makers and researchers to focus not only

on acute treatment and prevention of stroke, but also on long-term support of stroke survivors (Stevens et al., 2017).

Although traditional rehabilitation helps patients, a better understanding of its scientific basis could increase further its impact. Insights from neuroscience are nowadays providing a new foundation for rehabilitation outcomes that could prove useful in this sense. Basic and translational research could help determine the effects of different rehabilitation therapies on recovery both as isolated interventions as well as in various combinations. Detailed, standardized therapy protocols need to be developed based on scientific results (Hachinski et al., 2010). A brief exploratory survey carried on at the beginning of my PhD, which I will present in Chapter 2, shows that stroke professionals are open to such changes, and would be willing to implement standardized evidence-based approaches in their everyday practice. One example of basic research with quite promising clinical applications is the case of visuospatial neglect, a post-stroke syndrome predictor of prolonged hospital stay, worse recovery of motor and sensory function, and greater dependence for the activities of daily living (Li and Malhotra, 2015). Indeed, despite the need of larger-scale and better-conducted randomised controlled trials (Azouvi et al., 2016), rehabilitation of spatial neglect includes nowadays various promising techniques derived from basic neuroscience research. Without going into the details (see Li and Malhotra, 2015 for a brief review), it is interesting to notice how some of these techniques, such as prism adaptation (Frassinetti et al., 2002; Rossetti et al., 1998), motivational stimulation (Russell et al., 2013) and pharmacological dopaminergic stimulation (Gorgoraptis et al., 2012) share some common grounds with the ones proposed in the field of motor rehabilitation, which I will partially present and investigate in this thesis.

1.5.2 Motor recovery after stroke: restitution versus compensation

Recovery is generally defined as the improvement in movement ability over time. Improvement after stroke encompasses two distinct processes: a) restitution of normal biological structure and functions, i.e. the reappearance of the same end effectors during task performance (true recovery) (Krakauer et al., 2012); b) compensation, i.e. the use of biological structures and/or function different from those originally used before the injury to achieve a movement goal (Reinkensmeyer et al., 2016). These would respectively represent recovery of body functions and recovery of activities as defined by the International Classification of Function, Disability and Health (ICF) (Levin et al., 2009) (Figure 1-14).

Commonly used human and animal behavioural assessment protocols can rarely differentiate between the two processes, and it remains unclear from the current literature to what extent improvements in motor performance are caused by true neurological repair, by learning compensatory strategies or by a combination of both (Buma et al., 2013). Indeed, most neuroscientists would argue that there is never true recovery because once neural tissue is gone, it does not return, and therefore any functional improvement is accomplished through compensation. On the other hand, many therapists argue that functional improvement represents recovery because the patient can now perform tasks that he could not perform immediately after injury.

Accordingly, in this thesis when I use the term "recovery" I mean "improved performance", without a formal distinction between the degree of compensation and restitution.

Ischaemic stroke (about 80%)
Syndrome classified according to the Oxfordshire Community Stroke Project classification

Haemorrhagic stroke (about 15%)
• Intracerebral (about 10%)
• Subarachnoid (about 5%)

Not otherwise specified (about 5%)

Most relevant body functions affected
• Consciousness orientation and intellectual
• Temperament and personality
• Energy and drive
• Sleep, attention, and memory
• Psychomotor and perceptual
• Cognitive and seeing
• Proprioception and touch
• Voice and articulation
• Ingestion, defecation, urinary, and sexual
• Mobility and stability of joints
• Muscle power, tone, and reflexes
• Muscle endurance
• Control of (in)voluntary movement
• Gait pattern functions

Most relevant structures affected
• Brain
• Cardiovascular system
• Leg and arm
• Shoulder region

Most relevant activities affected
• Communicating with and speaking
• Reading, writing, and calculating
• Solving problems
• Undertake single and multiple tasks
• Transferring oneself
• Maintaining body position
• Walking
• Mobility
• Toileting
• Dressing
• Moving around, driving, and transportation
• Washing and self-care
• Hand and arm use
• Eating and drinking
• Preparation of meals
• Use of transportation
• Recreation and leisure
• Doing housework

Most relevant restrictions in participation
• Acquisition of goods and services
• Doing housework
• Preparation of meals
• Basic interpersonal
• Recreation and leisure activities
• Remunerative employment

Figure 1-14 The international classification of function, disability and health (ICF) for the effect of stroke on an individual

The ICF describes three levels of recovery: body function and structure, activities and participation. The main relative relevant impairments are shown below each one. (Adapted from Langhorne et al., 2011, The Lancet, with permission from Elsevier).

72

1.5.3   The applicability of motor learning to rehabilitation

Neurorehabilitation is often defined as a form of learning or relearning (Kleim, 2011). However, just because training is happening this doesn't mean that anything is being learned. Learning implies either improving motor control or finding alternative compensatory strategies with effectors/joints/muscles in which motor control remained relatively intact. The learning premise of rehabilitation is based on the assumptions that the nature of the deficit to be rehabilitated is known and that patients have an intact capacity of learning despite impaired performance. While it is known that localized strokes, such as cerebellar or parietal ones, can cause learning deficits, a general impairment of motor learning processes in patients with infarcts of motor cortical areas and/or their output pathways has not been clearly demonstrated (Krakauer, 2015). To date, only a few studies have investigated the effect of stroke-related brain injury on motor learning processes, with contrasting results (Bondi et al., 1993; Haaland and Harrington, 1994; Patton et al., 2006; Platz et al., 1994; Scheidt and Stoeckmann, 2007; Takahashi and Reinkensmeyer, 2003; Winstein et al., 1999). This could be partly due to methodological issues (different experimental designs and tasks) but also to the heterogeneity of the stroke population (Winstein et al., 1999). In fact, different elements of motor learning processes could be impaired depending on the lesion location and/or extension. In addition, patients' movements are often more variable than controls', and this could have limited the expression of learning. In particular, no learning was found by Platz and colleagues (Platz et al., 1994) in a one-day retention test of a simple spatial motor task in a group of 20 functionally recovered hemiparetic stroke patients. In this case, anyway, the low number of trials used could have affected the results, permitting to elicit only the initial phases of skill acquisition, but not its consolidation. Accordingly, a subsequent research, using a larger number of trials of an elbow flexion-reversal task, found no significant differences between stroke patients and controls in acquisition, offline forgetting, and one day retention, suggesting a preservation of

73

motor skill learning in unilateral stroke damage affecting the sensorimotor areas (Winstein et al., 1999). However, in this study patients performed the task with the ipsilateral, unaffected, arm. On one hand, this permits to disentangle motor learning capability from motor control deficits strictly related to paresis or sensory impairment. However, on the other hand, studying the ipsilateral arm doesn't permit to investigate possible learning deficits specific for the affected side.

Specifically, regarding motor adaptation, evidence shows that stroke survivors retain a certain ability to adapt, even if at a lower level than controls (Patton et al., 2006; Takahashi and Reinkensmeyer, 2003), with some exceptions for the most severely impaired individuals (Scheidt and Stoeckmann, 2007).

In conclusion, stroke patients retain, at least partially, both the ability to adapt to a perturbation (Patton et al., 2006; Scheidt and Stoeckmann, 2007; Takahashi and Reinkensmeyer, 2003), and to learn a new skill (Hardwick et al., 2017; Hatem et al., 2016; Winstein et al., 1999). Nevertheless, some issues are still controversial and need to be investigated further in order to allow the translation of motor learning paradigms into clinical practice. In the following sections I will discuss some of these issues.

1.5.3.1   Is there an optimal time window for rehabilitation?

Almost all patients show a certain degree of spontaneous neurological recovery in the first few months after stroke. This peaks approximately in the first 4-5 weeks (Cortes et al., 2017; Li, 2017) and then tapers off over about 6 months (Ward, 2017). Evidence suggests that most recovery occurs within this sensitive period because of a unique plasticity environment that is initiated by ischaemia and falls off as a function of time and distance from the infarct. This environment is characterized by unique changes in genes expression, in the structure and physiology of synapses, and

in excitatory/inhibitory balance (Murphy and Corbett, 2009). Spontaneous biological recovery is not motor learning per se but an endogenous repair process that presumably relies on residual intact neural architecture as a template for reorganization (Krakauer, 2015). However this period is also characterized by a heightened responsiveness to motor training, and research is focusing on exploiting this to achieve better outcomes (Krakauer, 2015).

Although some aspects of neural reorganization involved in spontaneous recovery arise because of the unique biological state caused by injury, other aspects of neural reorganization that contribute to recovery relate to normal motor learning mechanisms. Therefore, in the acute and subacute phase, motor rehabilitation relies on a combination of recovery and compensation through spontaneous recovery and motor learning during rehabilitation (Li, 2017).

The presence of spontaneous recovery does not necessarily impose physiological limits to improvement. Indeed, through novel rehabilitation protocols and mass practice, considerable motor improvement has been achieved also in the chronic stages post-stroke (Page et al., 2004). Such motor rehabilitation programs should include repetitive and task-specific practice at high intensity in a multidisciplinary environment to promote neural plasticity for motor recovery (Langhorne et al., 2009; Takeuchi and Izumi, 2013). This could be realized through a number of novel neurorehabilitation methods, such as constraint-induced movement therapy (Wolf et al., 2006), robotic training (Krebs et al., 2008), and body weight-supported treadmill training (Hesse et al., 2001; Høyer et al., 2012).

Accumulated evidence has supported the idea that the recovery-related cortical plastic reorganization and activation changes after the above training methods are used in chronic stroke (Levy et al., 2001; Liepert et al., 2000; Miyai et al., 2006; Takahashi et al., 2008; Ward et al., 2003). Pharmacological agents, such as amphetamines, levodopa, or fluoxetine have shown to enhance motor recovery after

stroke via modulation of spontaneous neural plasticity, even if more studies are needed to support their use in clinical practice (Perez et al., 2014). On the other hand, more recent evidence supports the hypothesis that the treatment effects on impairment in the chronic stages are minimal and that meaningful motor improvements are just due to compensatory mechanisms (Krakauer, 2015). This is, at present, still a controversial and debated issue.

In the work shown in Chapter 3, I have included patients in the chronic phase after stroke. This not only for obvious logistic issues (i.e. higher compliance to research studies in the chronic phases after stroke), but also to avoid any confounding effect due to spontaneous recovery rather than the training itself. I tried to focus on true recovery by minimizing the possibility of compensatory movements to occur (using in particular belts and straps to limit trunk movements during the reaching). Despite all this, I am aware that a certain degree of compensation can't be completely ruled out, and that further research is needed to evaluate the applicability of my findings to acute and subacute phases after stroke.

1.5.3.2   *Which motor learning paradigm is the best for stroke recovery?*

Patients might be capable to learn certain tasks but not others, and the best motor learning paradigm for promoting post-stroke motor recovery has not yet been identified.

During my PhD I have particularly focused on error-enhancement motor adaptation paradigms. Indeed, they are learned rapidly, and can be used to induce after-effects that follow a "normal" movement pattern (Bastian, 2008). The idea is that repeated adaptations might result in learning a more permanent motor pattern. In other words, hypothetically, if subjects adapt and de-adapt certain movement patterns repeatedly over days or weeks, they can develop a new learned calibration for the

context that initially drove adaptation. That is, they would no longer have to adapt from one behavior to the other but instead they would have two learned behaviors that they could switch between, without practice, immediately upon introduction of the different context. (Figure 1-15) (Reisman et al., 2010).
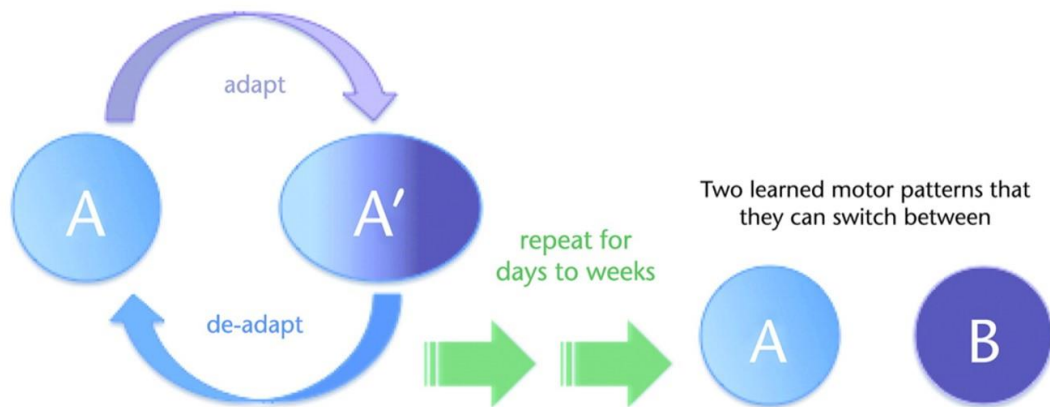
Figure 1-15 The process of motor adaptation and the transition to longer term learning

The typical motor behaviour (A) is adapted through practice to accommodate a change in task demands, and this adaptation results in a modified pattern (A'). After the new demands are removed, the adapted pattern continues, and practice under the original task demands is required in order to return to the typical pattern (A). After days to weeks of practicing both the original pattern (A) and the adapted pattern (A'), people may be able to produce two patterns (A and B) that they can switch between, given the appropriate task demands. (Adapted from Reisman et al., 2010, with permission from Oxford University Press)

One innovative paradigm inspired by motor adaptation tasks is the split-belt treadmill for rehabilitation of gait (Reisman et al., 2007). Through this, the walking pattern can be altered so that the two legs (positioned on two separate belts) move at different speeds and sometimes in different directions. This enables a controlled disruption of the normal walking pattern and produces asymmetrical walking. In adults with unilateral stroke who show step length asymmetry during unperturbed walking, the

after-effects can result in improved symmetry[3] (Reisman et al., 2007). This paradigm is promising as it may provide insight into the control of normal gait, but it may also be used to change walking patterns.

However, the applicability of motor adaptation paradigms in clinical practice is still limited, and this for two main reasons: the after-effects are short-lived, and their degree of generalization to other contexts may be limited. It is partially with the aim to overcome the first of these limitations, that during my PhD I have investigated possible ways to optimize motor adaptation and retention, through the use of feedback and/or pharmacologic stimulation.

1.5.3.3 *Would training with the unaffected side benefit recovery and better functional outcome of the paretic side?*

Another issue which would merit further investigation is whether training with the unaffected side may improve task performance with the affected side (Kitago and Krakauer, 2013).

Back in 1998, Gazzaniga proposed hemispheric lateralization as a neural optimization process (Gazzaniga, 1998). The role of hemispheric lateralization for motor control and motor learning mechanisms has been particularly investigated by Sainburg and colleagues, who showed that, after stroke, the non-paretic arm presents motor deficits resulting from a loss of the specific contributions of the ipsilateral hemisphere to motor control (Sainburg et al., 2016). Despite this, motor rehabilitation protocols continue to either completely focus on the paretic arm, or employ bilateral movements. Training of the non-paretic arm is so novel that little empirical evidence

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[3] A simple explicative video of this paradigm can be seen here https://youtu.be/N23QHGSijGo .

exists as to whether such intervention could affect non-paretic arm control. On this note, a recent pilot study suggests that intense non-paretic arm training not only improves motor performance in the trained arm, but also functional independence and performance in the paretic arm (Sainburg et al., 2016). These findings are consistent with another pilot study which showed that the speed and accuracy of the non-paretic arm, and the impairment level of the paretic arm, improved when non-paretic arm intervention was combined with paretic arm training (Pandian et al., 2015). Thus, non-paretic upper limb training might produce improvements in both upper limbs function.

Further studies on the lateralization of motor learning mechanisms and on ipsilesional arm intervention in stroke survivors are warranted to determine whether rehabilitation protocols of the non-paretic arm based on specific motor learning paradigms can positively affect motor outcomes.

1.5.3.4 Is more better?

Whether intensive rehabilitation is more effective than conventional treatment after stroke is still controversial. Unfortunately, till now, rehabilitation in published studies in humans has not been intense. Interest so far has been mainly focused on constraint-induced movement therapy (CIMT), and robot-assisted therapy. Higher-intensity upper- and lower-limb physiotherapy, but not higher-intensity general physiotherapy, seem to result in significantly greater improvement in motor function (Sehatzadeh, 2015) and, overall, greater intensity in rehabilitation seems to be associated with improved outcome (Teasell et al., 2005).

However, results regarding upper limb functional rehabilitation are controversial. Data from the Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS) trial, a study of the amount of therapy and motor improvement after

stroke, suggest that more therapy does not always result in significantly better outcomes (Dromerick et al., 2009). However, it should be stated that here "intense" meant 3 hours of CIMT. Similarly, animal models have demonstrated enlargement in areas of ischemia correlating with poor function when CIMT is applied early after a stroke (Kozlowski et al., 1996). This could be due to the increased ischemic demand, which could cause neurologic injury (Belagaje, 2017). The issue of rehabilitation dose and intensity is therefore at present still controversial and more studies, using the various motor learning paradigms, are needed to allow an optimal translation of motor neuroscience research to clinical practice.

1.6   Hypotheses and predictions of this thesis

We have now covered the relevant background to arrive at a testable framework for investigating the mechanisms behind reward/punishment feedback and motor adaptation. In summary the most important hypotheses of this thesis are:

5. Reward and punishment have differential effects on motor adaptation tasks, in healthy subjects and in stroke patients
6. Reward increases the retention of a newly acquired motor behaviour
7. The positive effects of reward on motor memory retention are mediated by dopaminergic pathways
8. Pharmacologic dopaminergic stimulation can increase further the positive effect of reward on retention in dopamine-deficient subjects, such as elderly subjects and, potentially, stroke survivors.

Chapter 2 is a short qualitative investigative survey on the attitude of stroke professionals toward the use of reward and punishment in stroke rehabilitation.

Chapter 3 scrutinizes hypothesis 1 and 2 by investigating the role of reward and punishment in a motor adaptation task in stroke survivors. I show that stroke patients can adapt and that reward or punishment feedback can increase online learning. Furthermore, consistently with previous evidence in healthy subjects, reward increases the retention of the newly acquired motor behaviour in stroke patients.

Chapter 4 explores hypothesis 2 and 3 through the combination of pharmacologic dopaminergic manipulation and reward/punishment feedback in young healthy subjects performing a visuomotor adaptation reaching task. The results, consistently with results in stroke patients, show that reward increases motor

memory retention. Importantly, I directly show for the first time that this effect is mediated by dopamine.

Chapter 5 tests the possibility to increase further the effect of reward on retention through pharmacological stimulation in dopamine-deficient subjects. To test this idea, healthy elderly participants performed a visuomotor adaptation reaching task under reward feedback and under placebo or levodopa. Unfortunately, likely due to dopaminergic function deficit, reward had no effect on retention and, thus, the potential effect of levodopa was missing as well.

Chapter 6 contains some of the thoughts and reflections which came to my mind during these years, and a general discussion about the main factors which still need to be investigated in order to permit a translation of motor neuroscience principles to motor rehabilitation.

Chapter 2.

Reward and punishment feedback in stroke rehabilitation - an exploratory survey of healthcare professionals' views
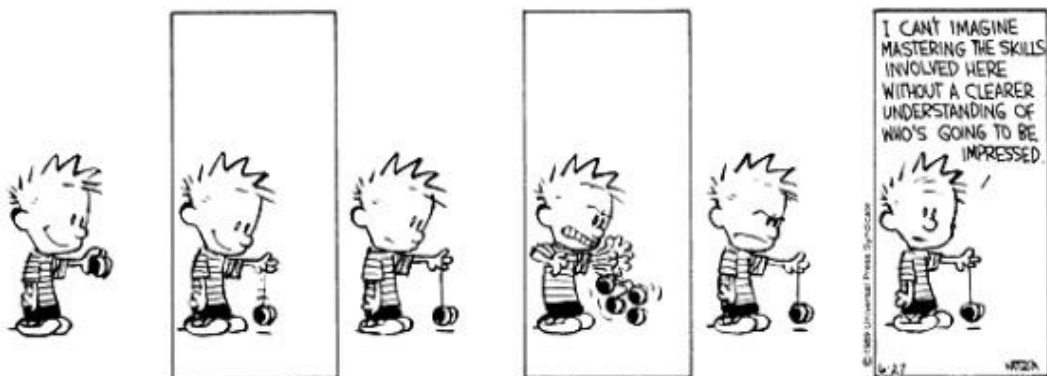
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2.1   Introduction

During my PhD I have investigated possible ways to optimize motor learning, with a particular focus on the role of reward and punishment feedback, in healthy subjects and stroke survivors. Reward and punishment are generally viewed as "motivational" feedbacks. Motivation, defined as the energizing of behavior in pursuit of a goal, is a fundamental element of our interaction with the world and with each other. However, quantifying the positive or negative motivational valence of a feedback is challenging, and, this is why, personally, I have generally tried to avoid the term "motivation" in this thesis. Despite these considerations, this term is commonly used among stroke professionals and in rehabilitation settings, the common belief being that patients' motivation has an important role in stroke recovery (Maclean et al., 2002). However, there is still a lack of consensus on the nature and determinants of motivation in stroke survivors (Maclean et al., 2000, 2002), and on the possible ways to increase motivation during rehabilitation. If we take into account the evidence from the field of motor neuroscience, showing positive effects of reward- and punishment-based feedback on motor learning (Abe et al., 2011; Galea et al., 2015; Goodman et al., 2014; Nikooyan and Ahmed, 2015; Wächter et al., 2009), the lack of correspondent clinical studies is rather surprising. This even more when considering the current attempts to develop rehabilitative interventions based on motor learning paradigms (Kitago and Krakauer, 2013), as they clearly could represent the ideal framework to implement the delivery of feedbacks.

Based on these considerations, at the beginning of my PhD I carried out an exploratory survey among a group of stroke professionals in order to investigate their attitude towards the use of reward and punishment feedback in rehabilitation, their opinion on the potential roles of these feedbacks in motor learning mechanisms, and their knowledge in the field. I carried on this short survey mainly to satisfy a personal curiosity about the interest of clinical staff on the themes related to my PhD research. Despite its limitations, which I will discuss later, I have included this survey in the

present thesis as I think it is somehow interesting to show, at this point, the views of the professionals fighting in first line with stroke survivors their everyday "battle for recovery". This could be seen also as a reminder, addressed to myself in first instance and to any scientists involved in translational research in second instance, to keep clinicians' opinions always in mind, and to proactively search for these, when planning a new study with translational potential. Indeed, an active and bilateral collaboration between clinical staff and basic researchers is, from my point of view, essential for the design of good quality translational studies.

2.2 Methods

2.2.1 Instrument

For this survey I designed ad hoc a semi-structured self-administered questionnaire and I distributed it to stroke professionals participating to the third annual Queen Square Upper Limb Neurorehabilitation Course, held at the National Hospital of Neurology and Neurosurgery, UCLH NHS Trust, London, in July 2015. I stressed that filling in the questionnaire was voluntary and that all the information would have been kept confidential. All the forms were anonymous.

The 24 items questionnaire covered the following topics: respondent's socio-demographics, determinants of motor outcome after stroke, role of positive or negative feedback in clinical practice, knowledge about research on reward and punishment in motor learning. Participants were also asked their opinion about the utility of recommendations on the use of reward or punishment feedback in rehabilitation. A mix of dichotomous (yes/no), multiple-choice, ranking and open-ended questions was used. Subjects were encouraged to write any additional comments at the end of the questionnaire.

2.2.2 Analysis

All coded, checked and cleaned data were stored in an ad-hoc created database and were processed using IBM SPSS version 21.0. Quantitative variables were expressed as means $\pm$ SD (standard deviation), qualitative variables as frequencies and percentages (%). Ranked data (determinants of motor outcome after stroke) were analysed using Friedman test. Post hoc analysis with Wilcoxon signed-rank tests with a Bonferroni correction was then conducted.

2.3 Results

2.3.1 Socio-demographic characteristics of the sample

Thirty-six stroke professionals (n = 31 women, 86.1%) participated in the survey. As shown in Table 2.1, 14 were physiotherapists, 21 occupational therapists and one neuropsychologist. Each professional used on average two rehabilitation techniques. In particular, 97.2% used traditional one-to-one physical therapy, followed by group therapy (63.9%), robotics (16.7%), and virtual reality (11.1%). Mirror box, cognitive rehabilitation, and functional electrical stimulation were also used.

Table 2.1 Socio-demographic characteristics of the respondents

	Age	Sex, female	Years' experience
PT (n = 14)	33.8 $\pm$ 6.4	11 (78.6)	7.6 $\pm$ 4.7
OT (n = 21)	35.8 $\pm$ 8.6	20 (95.2)	9.1 $\pm$ 7.1
NPS (n = 1)	38	-	11

PT = physiotherapist; OT = occupational therapist; NPS = neuropsychologist, Years' experience = number of years working in the field of stroke rehabilitation. Quantitative variables (age, years) are expressed as mean $\pm$ SD, qualitative variables (sex) as count and %.

As shown in Figure 2-1 and in Figure 2-2 the respondents came from a variety of work settings and they were looking after patients at various phases post-stroke (acute/subacute/chronic).
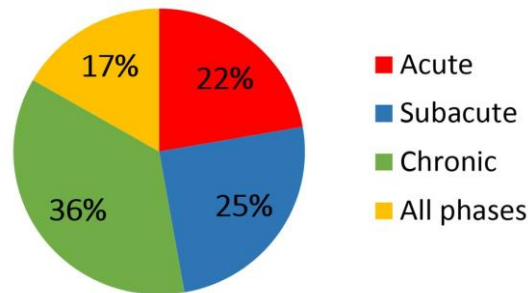
Figure 2-1 "Which patients (acute/subacute/chronic/all) do you deal with in your practice?"

Participants were allowed to tick more than one answer.
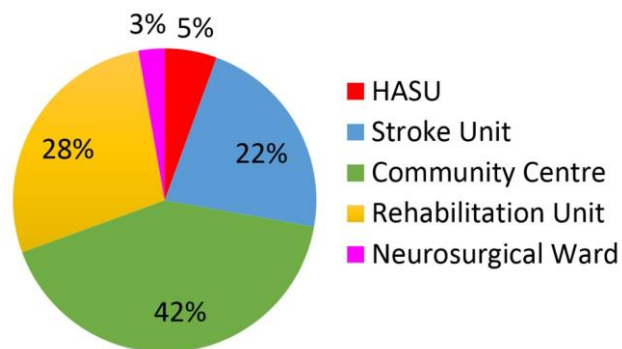
Figure 2-2 "Where do you work?"

Participants were allowed to tick more than one answer. HASU = hyper-acute stroke unit (including patients within 72 hours post-stroke).

2.3.2 Determinants of motor outcome after stroke

In order to indirectly investigate the perceived role of motivation in motor recovery, the respondents were required to rank a set of factors that, according to them,

influence motor outcome after stroke. These included motor impairment, cognitive deficits, patient's personality, patient's motivation, social support, familial support, rehabilitation team support and support from other patients. Subjects were invited to add to this list, and to rank accordingly, any additional factor, if there was, that they thought could be relevant. There was a statistically significant difference between the influence that each factor has, according to the respondents, on motor outcome after stroke [$\chi^2_{(8)}$ = 229.65, p < 0.001]. Post hoc analysis with Wilcoxon signed-rank tests was conducted and a Bonferroni correction was applied, resulting in a significance level set at p < 0.001. Motivation was scored as one of the most important determinants of motor recovery after stroke, and in particular it was ranked as important as motor impairment (Z = -3.128, p = 0.002) and patient's personality (Z = -2.972, p = 0.003), less influential than cognitive impairment (Z = -3.526, p < 0.001), and more influential than social (Z = -5.020, p < 0.001), familial (Z = -5.064, p < 0.001), team (Z = -5.197, p < 0.001), or other patients' support (Z = -5.302, p < 0.001).

2.3.3   Role of motivation in stroke recovery

When asked directly ("*do you think that motivation has a key role in stroke recovery?*"), all subjects indicated patients' motivation as a key determinant to recovery. Despite this, there was no consensus on how to assess motivation in everyday clinical practice. The majority of respondents mainly based their judgment on an open discussion with the patient himself (91.7% of the professionals) and/or through a close observation of the patient's behaviour (77.8%). 52.8% also took into account the patient's family opinion, whereas just 16.7% relied on formal cognitive tests or scales.

2.3.4 Use of reward and punishment-based feedback in stroke rehabilitation

Figure 2-3 illustrates the use of reward and punishment feedback in clinical practice. Four (11.1%) of the responded had never used reward feedback, while 17 (47.2%) and 15 (41.7%) stated to use reward, respectively occasionally and often. The large majority of stroke professionals delivered rewards in the form of verbal praise (80.6%) or "social reward" (19.4%), followed by favourite food and/or favourite music (11.1%). 13.9% also used other rewards, such as outings, preferred activities and permission to use social networks. Interestingly, the survey outlined an opposite situation regarding the use of punishing feedback. In particular, just one (2.8%) respondent stated to use punishment-based feedback often, and 3 (8.3%) to use it occasionally. Punishment was delivered mainly in the form of negative verbal feedback or, in one case, as "additional physical exercise".

When asked about the timing of feedback delivery (i.e. before/during/after the session), the opinions were quite divergent. Specifically, reward feedback tended to be used during (84.4% of the professionals using reward feedback), and/or at the end of the session (56.3%), whereas less professionals (34.4%) tended to reward patients at the beginning of the session, with the aim to increase their participation. Considering the four professionals using punishment-feedback, two of them used it during the session and the other two at the end of it. The delivery of reward/punishment feedback was individually tailored, based on subjective impressions about patient's motivation and personality.
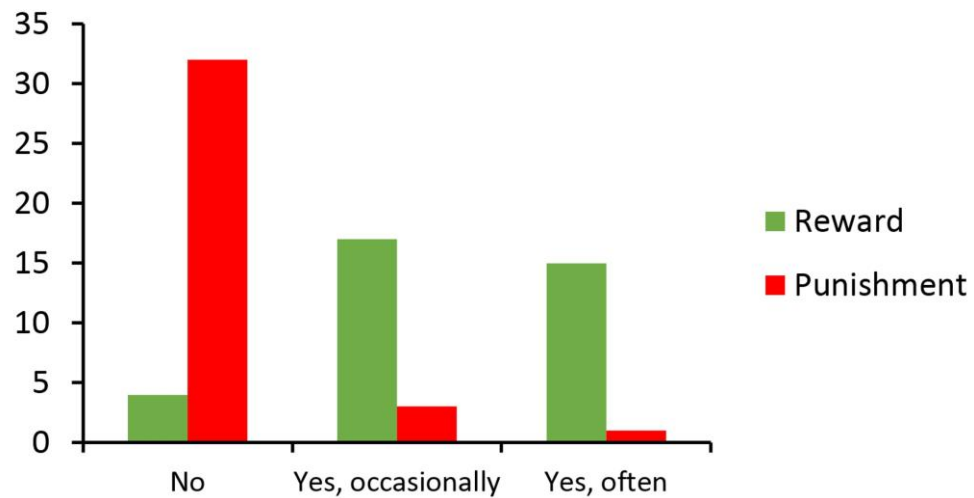
Figure 2-3 "Do you use reward/punishment feedback in your clinical practice?"

Y-axis indicates the number of respondents.

2.3.5 Role of reward and punishment in motor learning

When directly asked about the possible role of reward in motor learning, 61.1% of the respondents stated that reward could increase learning. However, a third of them (33.3%) didn't have any strong opinion on this topic, and 2 (5.6%) thought reward had not effects on motor learning. Conversely, 44.4% of the interviewed professionals thought that punishment does not increase motor learning, and 50% didn't know, while just 2 respondents believed in a positive effect of punishment (Figure 2-4).
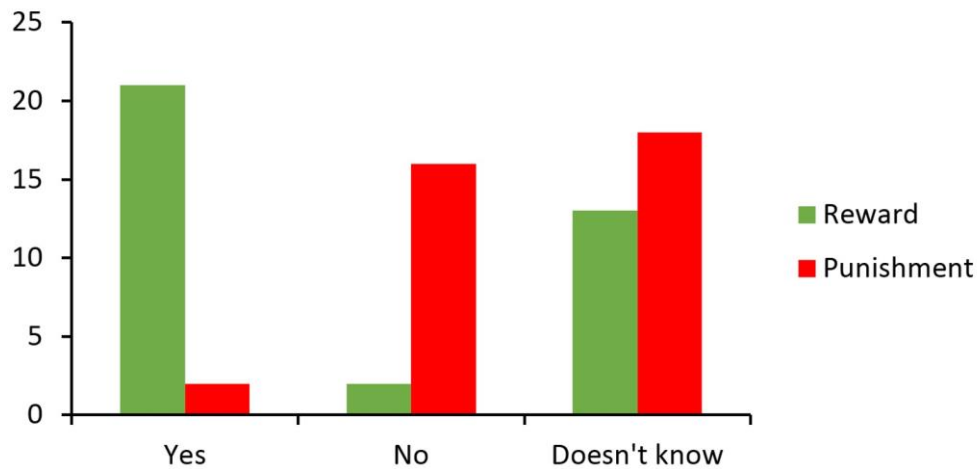
Figure 2-4 "Do you think that reward/punishment can increase motor learning?"

Y-axis indicates number of respondents.

Despite these divergent opinions on reward and punishment-feedback, when asked about potential differential effects of these two feedbacks on motor learning, 61.1% of the respondents didn't have any opinion, and, remarkably, just one replied yes. Indeed, 69.4% of the respondents had never overtly discussed with their colleagues about the role of reward/punishment-feedback in rehabilitation, and 83.3% of them was not aware of any research on the role of these in motor learning. Of note, more than half (58.3%) of the respondents stated that they would welcome the introduction of evidence-based recommendations on the use of motivational feedback in their practice.

2.4   Discussion

I used a semi-structured questionnaire to investigate professionals' views on the role of motivation and of reward and punishment-based feedback on rehabilitation and recovery after stroke. I chose to deliver the questionnaire in a course setting, rather than in a selected clinical ward, with the intent of enrolling participants from across the whole health service and therefore representative of the general population of stroke professionals. Indeed, the variety of work settings the responders were coming from shows that this has been, at least partially, achieved. Nevertheless, I am aware that the results of this survey could be affected by a certain degree of selection bias (Delgado-Rodríguez and Llorca, 2004), as course attendants are usually the most interested and up to date with research, and the most open to its translational applications. Accordingly, respondents in this sample were on average in their thirties, an age when one is generally more open to changes in his practice. In addition, I am aware that, being the research carried on in a single Country, the interviewed will have particular cultural beliefs, including beliefs about the nature of health care and motivation. Therefore, further research would help to find out whether these findings could be generalized. Despite these limitations, however, some of the results of this survey are interesting and deserve some thoughts.

First of all, this survey confirms that stroke professionals consider motivation as one of the key elements of recovery. However, there is still a lack of consensus about how to assess patients' motivation. Already back in 1989, King and Barrowclough had flagged up the inconsistencies in what rehabilitation professionals identified as motivated and unmotivated behaviour, thus suggesting to remove the term "motivation" from the lexicon of physical rehabilitation (King and Barrowclough, 1989). Despite this, as also confirmed here, the concept of motivation has remained deeply ingrained in stroke professionals' beliefs. At present, rehabilitation teams still mainly rely on subjective judgments to "quantify" patients' motivation. As previously pointed out (Maclean et al., 2000, 2002), this reliance on subjective impressions

could put patients at risk of being erroneously "labelled" and treated. Indeed, some rehabilitation professionals have admitted that they tend to put less efforts in the rehabilitation of what are considered "unmotivated" patients compared to the "motivated" ones (Maclean et al., 2002). A higher use of clinical scales, which could be included in a formal post-stroke neuropsychological assessment, would in this context represent a more objective assessment, useful also for serial follow-ups, of patients' motivation. One example of useful scale, which I have extensively used during my PhD, is the Apathy Evaluation scale (Marin et al., 1991). Interestingly, this scale can be at the same time filled in by the patient himself, the caregiver and/or the stroke physician. In a clinical setting, using the three versions of this scale could help to identify erroneous "labelling" of patients who, despite feeling motivated, may be perceived (and treated) as "apathetic" by caregivers or clinical staff. However, this scale is not specific for post-stroke apathy, and the development of novel tools targeted to stroke survivors may be useful.

Interestingly, the majority of stroke professionals already use reward feedback in their practice, with the belief that this can increase motor learning. Conversely, punishment is poorly used and considered unhelpful. However, all these practices are based on subjective opinions and experiences, as confirmed by the fact that the actual knowledge about research on this topic was very limited across the whole sample. Indeed, feedbacks are individually tailored based on subjective clinical judgement, and no attempt to standardize their use was mentioned. On this point, it is important to highlight that stroke patients may differ in their sensitivity to rewards also based on the neural structures disrupted by the stroke itself. Indeed, Rochat and colleagues, in their study published in 2013 (Rochat et al., 2013), which I discussed in a subsequent journal club (Quattrocchi and Bestmann, 2014) showed that low sensitivity to reward can contribute to post-stroke apathy and lack of motivation, and that the prefrontal cortex-basal ganglia circuits, as well as the insula, may be part of the underlying network. Apathy, a disturbance of goal directed behaviour, it's in fact

a multidimensional disorder (Figure 2-5), and a score of its global severity could not be sufficient to predict the response to reward feedback. This is why, in addition to the Apathy Evaluation scale (Marin et al., 1991), during my PhD I have also scored participants' sensitivity to reward and punishment, using the questionnaire by Torrubia and colleagues (Torrubia et al., 2001). Despite the obvious limitations of using a scale, in my opinion, an attempt at considering the individual sensitivity to reward/punishment should always been done when conducting between-subjects studies using positive or negative feedback. In the specific case of stroke patients, ideally, in the future, relating the pattern of brain lesions to the specific disrupted processes leading to apathy (and reward insensitivity) might permit individualized pharmacologic and behavioural management in stroke and in other neurologic disorders (Quattrocchi and Bestmann, 2014).
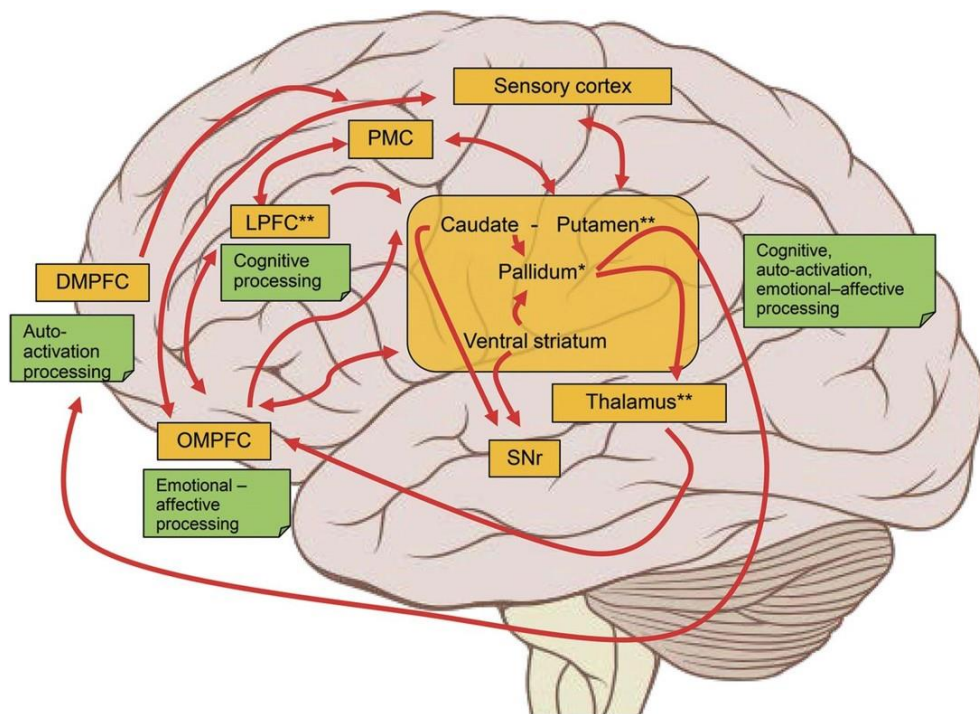
Figure 2-5 Main prefrontal-basal ganglia circuits and relative apathy dimensions

*Lesions associated with poor reward sensitivity. **Lesions associated with poor reward sensitivity and apathy in the study by Rochat (Rochat et al., 2013). (Adapted from Quattrocchi and Bestmann, 2014, no formal permission required. Previously adapted from Patrick Lynch, medical illustrator, Creative Commons License, CC-BY-2.5).

In summary, this exploratory survey highlights the misalignment between the high importance given to the role of reward feedback in stroke recovery and the poor knowledge about it. However, it was encouraging, at the beginning of my PhD, to know that stroke professionals would largely be interested in evidence-based recommendations on the use of reward/punishment feedback in their practice, and in particular in motor rehabilitation.

In the following chapter, I will illustrate the first experiment of my PhD, a personal attempt toward a better understanding of the role of positive/negative feedback in motor learning after stroke.

Chapter 3.

Reward and punishment enhance motor adaptation in stroke

The work presented in this chapter is object of the following publication:
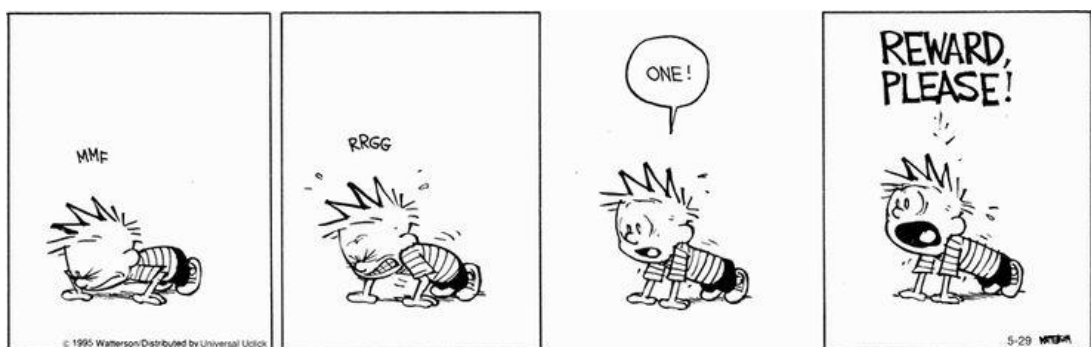
Calvin & Hobbes by Bill Watterson, Permission granted by Andrews McMeel Syndication

3.1   Introduction

Upper limb paresis is a common post-stroke outcome and it has a great influence on the ability to live independently after the stroke itself (Veerbeek et al., 2011). Although rehabilitation can lead to improvements, the benefits are often inconsistent (Pollock et al., 2014). As outlined in Chapter 1, principles of motor learning may offer ways to increase the efficacy of rehabilitation. This is underpinned by two assumptions: these principles apply to motor recovery, and patients retain the ability to learn (Kitago and Krakauer, 2013). To date, only a few studies have investigated the effect of stroke on motor learning, with mixed outcomes (Haaland and Harrington, 1994; Patton et al., 2006; Platz et al., 1994; Scheidt and Stoeckmann, 2007; Takahashi and Reinkensmeyer, 2003; Winstein et al., 1999), and interventions based on motor learning principles are often no more effective than conventional rehabilitation (Chang and Kim, 2013).

Motor adaptation tasks permit to investigate learning in a standardized way within a single session. Previous studies show that stroke patients retain the ability to adapt to perturbations, even if at a slower rate than healthy individuals (Patton et al., 2006; Scheidt and Stoeckmann, 2007; Takahashi and Reinkensmeyer, 2003). In particular, error-enhancing perturbations, i.e. magnifying movement error, appear more beneficial than error-reducing ones, as they lead to after-effects which compensate for the original error (Patton et al., 2006; Reisman et al., 2007).

Reward and punishment-based feedback are candidate mechanisms to optimize online learning and retention in motor adaptation tasks (Abe et al., 2011; Galea et al., 2015; Sugawara et al., 2012). In particular, in young healthy participants, punishment was associated with faster online learning, and reward with greater memory retention (Galea et al., 2015). These results point to dissociable effects of reward and punishment in motor adaptation tasks. If these findings generalised to patients, they would provide a principled way for enhancing motor adaptation and

retention in stroke survivors. This would be in line with previous research showing the benefits of rewards during ankle boot training in stroke survivors (Goodman et al., 2014). In the present experiment I tested the effects of reward- or punishment-based feedback in 45 chronic stroke patients performing a force-field (FF) adaptation reaching task. I will show here that these feedbacks enhance online error-correction in the motor adaptation task, and that reward increases the retention of the newly acquired motor behaviour in stroke survivors.

3.2 Materials and methods

3.2.1 Study population

I included in this study all patients meeting the following criteria: (1) first-ever unilateral chronic (> 6 months) stroke; (2) Mini Mental Scale Examination (MMSE) > 24 (Folstein et al., 1975); (3) ability to perform 45° shoulder flexion while upper limb supported against gravity; (4) ability to be active for an hour; (5) no upper limb therapy during the study duration; (6) ability to understand the task and to give written informed consent. I excluded all patients who met any of the followings: (1) ataxia and/or cerebellar stroke; (2) alcohol and/or drug abuse; (3) peripheral motor problems; (4) major psychiatric/other neurological disorders; (5) vision/hearing impairment; (6) neglect (as assessed with the Bells test) (Gauthier et al., 1989); (7) shoulder pain and/or musculoskeletal impairment preventing passive ranging to the workspace; (8) aged less than 18 years old.

Figure 3-1 shows the CONSORT diagram of recruitment (Begg et al., 1996). I screened 75 stroke survivors, recruited via the Thames Stroke Research Network and via local community stroke groups. 45 of these were included in the study. Patients were randomly allocated to one of three groups, according to the feedback given during adaptation (reward/punishment/neutral). To control for confounding effects,
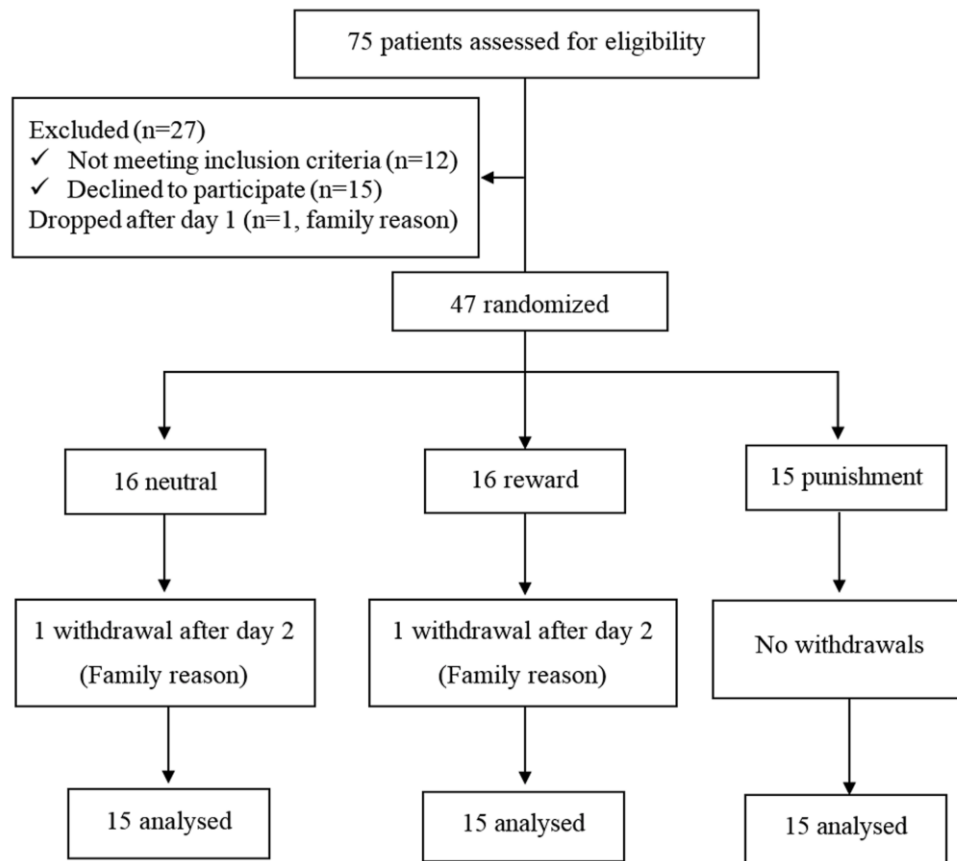
Figure 3-1 Patients' enrolment

The reasons for exclusion of patients from the study were: incapability to perform the task due to excessive weakness (n = 5 patients); cardiorespiratory impairment (n = 3); cerebellar stroke (n = 2); significant peripheral motor problems (n = 1); significant sleep disturbance (n = 1). (Reproduced from Quattrocchi et al., 2017, with permission from BMJ Publishing Group Ltd).

randomization was stratified for age and time post-stroke. Fifteen healthy controls, with no history of neurological, psychiatric or general medical diseases, were also included. To account for the effect of aging and hand asymmetries, controls (n = 10, 66.6% men) were matched to the neutral stroke group for age and performing arm. No adverse events were reported.

All participants gave written informed consent. The study was approved by the Joint Ethics Committee of the Institute of Neurology, UCL and the National Hospital for

Neurology and Neurosurgery, and was conducted in accordance with the Declaration of Helsinki.

3.2.2   Experimental task

In this study I used a force-field adaptation paradigm, as described in Chapter 1 (Shadmehr and Mussa-Ivaldi, 1994). Participants sat in front of a workstation, with their forehead supported on a headrest, and held a cylindrical handle of a two-joint robotic manipulandum with their semi-pronated paretic arm. To avoid compensatory movements, the forearm was stabilized by straps to a moulded cast and the trunk was belted to a high-backed chair. A horizontal mirror, suspended approximately 2 cm above the hand, prevented direct vision of the arm and hand, but showed a reflection of a screen mounted above. Visual feedback regarding hand position was provided by a small white cursor (0.3 cm diameter) continuously projected onto the screen (Figure 3-2, A).

The task consisted of centre-out fast ballistic movements to visual targets. Subjects had to initially bring the cursor within a 1-cm^2 starting box in front of the body's midline. Once the cursor was within the starting point, a white 1-cm^2 target box appeared 6 cm from the starting position. Subjects were instructed that, when ready, they should make a fast, accurate, "shooting" movement through the target, avoiding online corrections. As the cursor crossed an imaginary 6 cm radius circle centred at the starting position, a green endpoint dot appeared at the crossing point. After 500 ms, the manipulandum returned the hand back to the starting position. For the main experiment, subjects were exposed to two targets positions chosen as described below (see *Day 1: individual calibration of targets and perturbation*). To encourage constant speed, the target turned red or blue if the movement was > 500 ms or < 100 ms, respectively (Figure 3-2, B).

For force-field trials, the manipulandum produced a force proportional to the hand velocity. For a clockwise (CW) curl-field (pushing to the right) the force was:

$$\begin{matrix} f_x \\ f_y \end{matrix} = \begin{bmatrix} 0 & 4 \\ -4 & 0 \end{bmatrix} N/(m/s) \begin{matrix} v_x \\ v_y \end{matrix}$$

For counter-clockwise (CCW) curl-fields, the force direction was mirrored (Shadmehr and Mussa-Ivaldi, 1994).

3.2.3 Reward and punishment feedback

To assess the influence of reward and punishment, participants began each block with 0 points and accumulated points across the block. The reward group accumulated positive points, the punishment group accumulated negative points and the neutral group received zero points regardless of performance. Points were calculated based on angular endpoint error as follows:

Reward: 4 points: < 1º; 3 points: 1-5º; 2 points: 5-10º; 1 point: 10-15º; 0 points: ≥ 15º.

Punishment: 0 points: < 1º; −1 point: 1-5º; −2 points: 5-10º; −3 points: 10-15º; −4 points: ≥ 15º.

Neutral: points were replaced by two uninformative zeros.

Both the points received on a trial-by-trial basis and the cumulative score of the block were shown on the screen (Figure 3-2, B). To ensure participants paid attention to this feedback, the score turned yellow at the end of each trial for 300 ms. Subjects were explicitly informed that points had monetary value (3.57 pence/point) and depended on performance. Participants in the reward group started from £0 and earned money based on the accumulated points (average sum won £24.7 ± 2), while

patients in the punishment group were initially given £50 and lost money based on the cumulative negative points (average sum lost £24.5 ± 1.7). The neutral group simply received £25 at the end of the study on day 3.

3.2.4   Experimental protocol

I tested all subjects across three consecutive days, and I carefully provided the same amount of social interaction to each of them (Figure 3-2, C). Each session lasted around 2.5 hours. As sleep can enhance off-line consolidation of motor memories (Al-Sharman and Siengsukon, 2013), participants were encouraged to sleep at least 6 hours every night, and sleep was assessed with a questionnaire (Ellis et al., 1981).

Day 1 (D1): Individual calibration of targets and perturbation

Goal of this study was to examine whether reward and punishment influenced motor adaptation in stroke patients, not to specifically treat individual motor deficits. As such, I required relatively accurate behaviour across patients during baseline and a force-field which enhanced movement error. Therefore, on day 1 I exposed participants to six blocks (1 block = 80 trials) of null trials (no force-field) towards eight target locations (25, 65, 115, 155, 205, 245, 295 or 335º CW from 0º, with 0º representing 12 on a clock face). This allowed participants to familiarize themselves with the task, and enabled me to analyse each individual's baseline direction bias. Based on this, I then individually tailored the task for the main experimental sessions. Specifically, based on performance, I selected for each subject the two targets in the same quadrant with the smallest average error and the force-field direction (CW or CCW) enhancing this baseline error.

Day 2 (D2): Adaptation under reward, punishment or neutral feedback

On day 2, participants were randomly allocated to the reward, punishment or neutral group (between-subject design) and performed 12 blocks (50 trials each) of reaching movements towards the two selected targets (25 trials to each target). After two baseline unperturbed blocks (*D2 baseline*), the perturbation (CW or CCW FF) was introduced for 7 blocks (*D2 adaptation* phase). During this phase, subjects received reward, punishment or neutral feedback according to their group allocation. The force-field (as well as the reward, punishment or neutral feedback) was then removed and subjects performed three additional blocks. This phase (*D2 washout*) served to remove the after-effects and return performance back to baseline levels (Figure 3-2, C).

Participants were informed before beginning that they should expect the manipulandum to interfere with their performance, and that they should perform as accurately as possible whilst maintaining a constant speed. No further description of the perturbation was given. Short breaks during which the participants released the handle were given after the second, fifth and tenth block. In addition, participants were allowed to rest for a few minutes in between the other blocks if necessary.

Day 3 (D3): readaptation at 24 hours

On day 3, participants were exposed to the same blocks with the same targets and force-field direction as day 2 (*D3 baseline, D3 readaptation, D3 washout*), the only difference being that they all received neutral feedback (Figure 3-2, C).
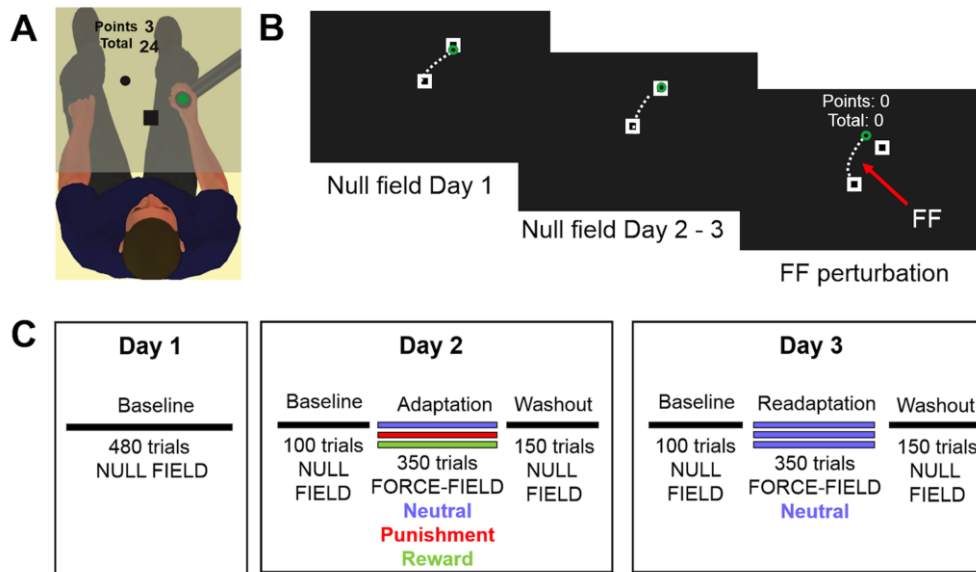
Figure 3-2 Task and protocol overview

(A) Experimental setup. (B) Experimental task. Participants moved the cursor from the starting point (central square) to a target on the screen. On Day 1, they had to reach towards one of eight targets, appearing in a pseudorandom order (null field day 1). On day 2 and 3, participants reached towards two selected targets, which were chosen based on minimising baseline error (null field day 2 and 3). The perturbation consisted of a velocity-dependent force-field (red arrow) in the direction increasing baseline error (clockwise or counter-clockwise). Positive and negative points, given on the basis of on movement error, represented reward and punishment feedback. Two uninformative zeros, instead of points, appeared on the screen for the neutral group. (C) Experimental protocol. Participants were tested across three consecutive days. On day 1, they performed unperturbed reaching movements towards 8 targets (baseline: 6 blocks of 80 trials). Day 2 began with unperturbed reaching movements towards 2 targets (baseline: 2 block x 50 trials). This was followed by movements that were perturbed by a force-field (adaptation: 7 blocks x 50 trials). During this phase, subjects received neutral, punishment or reward feedback according to their group. Finally, participants experienced another set of unperturbed trials (washout: 3 blocks x 50 trials). Day 3 was identical to day 2, except that all groups received neutral feedback during the readaptation phase. (Reproduced from Quattrocchi et al., 2017, with permission from BMJ Publishing Group Ltd).

3.2.5   Cognitive tests and functional scales

In order to take into account any between-group cognitive or motor difference that may have influenced the results, all subjects underwent an extensive battery of validated tests and scales according to a fixed study calendar, as outlined below.

Functional scales

The following functional scales were administered on day 1:

- Barthel Index (Mahoney and Barthel, 1965), measuring activities of daily living. Scores range zero (totally dependent) to 100 (completely independent);
- Fugl Meyer Assessment – Upper limb subset (Fugl-Meyer et al., 1975), assessing motor performance of the paretic upper limb. Scores range zero to 66. Four broad categories of impairment can be distinguished: severely impaired (FM-UL $\leq$ 30), moderately impaired (30 < FM-UL $\leq$ 50), mildly impaired (50 < FM-UL $\leq$ 65), and unimpaired (FM-UL = 66) (Scheidt and Stoeckmann, 2007);
- Modified Ashworth scale (Bohannon and Smith, 1987), used to evaluate spasticity. Scores range 0 (no increase in tone) to 4 (affected parts rigid in one position). To obtain an overall estimate of the upper limb spasticity, I averaged the scores across the shoulder, elbow and wrist joints (Scheidt and Stoeckmann, 2007; Zackowski et al., 2004);
- Medical Research Council scale for muscle strength (Medical Research Council (Great Britain), 1975), to assess power in shoulder flexors, elbow flexors and wrist extensors muscles. These muscles were chosen as they resist gravity in a reaching-out movement (Zackowski et al., 2004). Scores range 0 to 5, with higher scores indicating higher muscle strength. To obtain an overall estimate of power of the upper limb, scores were averaged across the muscles (Scheidt and Stoeckmann, 2007).

Cognitive tests

- Mini Mental State Examination (Folstein et al., 1975), the most common psychometric screening assessment of cognitive functioning, was administered on day 1 to assess eligibility. Scores range 0 (worse performance) to 30 (no cognitive deficit). Subjects had to score more than 24 (i.e. no major cognitive impairment) to be included in the study;

- Bells test (Gauthier et al., 1989), a cancellation task evaluating visual neglect, was used on day 1 to assess eligibility. Subjects omitting six bells or more in the contralateral half of the test were not included in the study;

- Frontal Assessment Battery (Dubois et al., 2000), was administered on day 1 to assess executive functions. These were assessed for two main reasons: they are not tested by the MMSE, and they are known to have a role in motor control (Gentili et al., 2015). Scores range 0 (worst performance) to 18 (no deficit);

- Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) – short version (Aluja and Blanch, 2011) This is a 20-items version of the SPSRQ (Torrubia et al., 2001), and assesses individual trait differences in the sensitivity to punishment and sensitivity to reward dimensions. Subjects filled in this self-administered yes/no questionnaire on day 1. Scores range 0 (low sensitivity) to 10 (high sensitivity) for each one of the two dimensions (sensitivity to punishment and sensitivity to reward);

- Stroop test (Stroop, 1935), measuring executive selective attention. As I was more interested in between-groups differences than in the absolute scores, I programmed (using Matlab and Cogent programming), and administered an *ad hoc* computerized version of this test. This was administered to all subjects on day 2. Both the number of errors and the time (seconds) were recorded for each subjects;

- Apathy Evaluation scale (Marin et al., 1991). Both the clinician (AES-C) and the self-administered (AES-S) versions were used, respectively on day 2 and 3. Scores range 18 to 72, with higher scores indicating more apathy. I assessed apathy as this is a frequent complication of stroke and it is, at least partially, related to reward insensitivity (Adam et al., 2013; Levy and Dubois, 2006; Quattrocchi and Bestmann, 2014; Rochat et al., 2013);

- Fatigue Severity scale (Krupp LB et al., 1989), was administered on day 2. Scores range 9 to 63, with higher scores indicating more fatigue;

- Beck Depression Inventory (day 3) (Beck et al., 1961), measuring characteristic attitudes and symptoms of depression;

- St Mary's sleep questionnaire (Ellis et al., 1981), administered every day to assess the previous night's sleep;

- Visual analogue scale for alertness (A-VAS) and fatigue (F-VAS), 10-point self-administered scales delivered at the end of each study visit (A-VAS: higher scores indicating higher alertness; F-VAS: higher scores indicating lower tiredness).

Handedness was evaluated on day 1 using the Edinburgh Inventory (Oldfield, 1971).

3.2.6   Data collection and analysis

The 2D (x, y) position of the hand was collected through custom C++ code (sampling rate=100 Hz). Data and statistical analysis were performed using Matlab (MathWorks, USA, version R2013a) and SPSS (IBM, USA, version 21.0). Movement onset was defined as the point at which velocity crossed 10% of peak velocity. Movement endpoint was defined as the position where the cursor breached the 6-cm target perimeter. To compare between subjects, errors of subjects receiving the CW force-field were flipped.

Performance was quantified using angular error at peak velocity (AE_{maxV}), i.e. the difference between the target angle and the angular hand position at the peak outward velocity (^{o}). This has been used as a measure of feedforward control whilst excluding feedback processes (Galea and Miall, 2006). To adjust for between-subjects baseline directional biases, AE_{maxV} on day 2 and day 3 were corrected by subtracting the average baseline AE_{maxV} of the corresponding day (Ghilardi et al., 1995; Krakauer et al., 2005). Reaction time (RT, time between target appearance and movement onset, ms); movement time (MT, time between movement onset and movement end, ms); peak velocity (MaxV); maximum velocity percentage (MaxV%, time point in movement when MaxV occurred); within subject variability (SD of AE_{maxV}); and online corrections (difference between AE_{maxV} and angular endpoint error), were calculated for each trial. Trials in which angular error exceeded 60° (Galea et al., 2015) or MT or RT exceeded 1150 ms (representing the mean + 2.5 SD for both MT and RT) were removed (6.8% of trials). Epochs of all kinematics were created by averaging across 10 consecutive movements (Galea et al., 2011; Krakauer et al., 2005).

Difference between demographics, cognitive and functional scores were evaluated by one-way ANOVA (quantitative data) or Chi-square or Fisher exact test (proportions). Repeated-measures ANOVAs were used to compare MT, RT, MaxV,

MaxV% and online corrections between groups (neutral, reward, punishment) and phases (baseline, adaptation/readaptation, washout).

Due to the unfamiliarity with the manipulandum, unperturbed trials during day 1 were also subject to a process of correction (Smith and Shadmehr, 2005; van Beers, 2009). To evaluate this, I computed average sum of squared AE_{maxV} during the first and last block of day 1, and performed a repeated-measures ANOVA with group (N, R, P) and block (first, last). I used sum of square as I was interested in the absolute magnitude of the error, irrespective of direction.

To assess the amount of learning/adaptation independently from the co-contraction (i.e. stiffening) of the arm, I computed an adaptation index (AI) which took into account both the error in the force-field and after-effect trials (Criscimagna-Hemminger et al., 2003; Maschke et al., 2004; Rabe et al., 2009; Smith and Shadmehr, 2005):

$$AI = \frac{|Error\ aftereffect|}{|Error\ aftereffect| + |Error\ FF|}$$

I considered as "after-effect trials" the ones representing the initial error after the removal of the force-field. To select these, I performed an ANOVA across the average of every 2 trials for the first 10 trials (5 levels). On both days, I found a significant difference between trials 1-2 and 3-4 (Day 2: $p = 0.004$; Day 3: $p < 0.001$), and 3-4 and 5-6 (Day 2: $p < 0.001$, Day 3: $p = 0.033$). Based on this, I selected as "after-effect trials" the first six trials after force-field removal. Results were qualitatively similar by using an average between 2 and 6 trials. I defined as "force-field trials" the last block of the adaptation or readaptation. The adaptation index could range zero, indicating no learning (but possibly co-contraction), to one, indicating complete learning (Criscimagna-Hemminger et al., 2003; Maschke et al., 2004; Rabe et al., 2009; Smith and Shadmehr, 2005). This is based on the premise that learning is represented by zero error for force-field trials but a large error in aftereffect trials (AI = 1); no learning

will lead to a large error in force-field but zero error in the aftereffect trials (AI = 0); and arm stiffening would cause zero error in both (AI = 0).

To assess retention, i.e. the strength of the new motor memory, I calculated the average AE_{maxV} across the last two washout blocks for day 2 and day 3 ($AE_{retention}$) (Galea et al., 2015).

To account for differences in motor and cognitive functions, a principal component analysis (PCA) was conducted on the functional and cognitive scores, with varimax orthogonal rotation. The Kaiser-Meyer-Olkin (KMO = 0.72) measure verified the sampling adequacy, and all KMO values were > 0.6, which is above the acceptable limit of 0.5 (Kaiser, 1974). Bartlett's test indicated that correlations between items were sufficiently large for PCA ($\chi^2_{(45)}$ = 136.36, p < 0.001). Three components had eigenvalue over Kaiser's criterion of 1 and explained 71% of the variance. I interpreted the first component as the motor level, the second as the psychomotor level and the third as the cognitive level (Table 3.1). I used these components as covariates in independent one-way ANCOVAs to compare groups for AI day 2, AI day 3, $AE_{retention}$ day 2 and $AE_{retention}$ day 3.

To assess savings, i.e. the presence of faster readaptation when re-exposed to the same perturbation (Kojima et al., 2004), I calculated an average AE_{maxV} for the first two perturbation blocks and performed a repeated measure ANOVA with groups (N, R, P) and days (day 2, day 3) (Krakauer, 2009).

No statistical methods were used to predetermine the sample size, but this is in line with similar studies on motor learning in stroke (Haaland and Harrington, 1994; Patton et al., 2006; Platz et al., 1994; Scheidt and Stoeckmann, 2007; Takahashi and Reinkensmeyer, 2003; Winstein et al., 1999). Data were tested for normality using the Shapiro-Wilk test. Homogeneity of variance was evaluated using Mauchly's or Levene tests. When sphericity was violated, Greenhouse-Geisser (epsilon, ϵ < 0.75)/Huynh-Feldt (ϵ > 0.75) corrections or Brown-Forsythe tests were used.

Significance level was set at $p < 0.05$. LSD post-hoc tests were conducted when warranted. Effect size was provided by partial eta (η^2).

Table 3.1 Factor loadings after varimax rotation for principal component analysis

	Component		
	1	**2**	**3**
Muscle strength	0.878		
FMA-UL	0.847		
Spasticity	-0.824		
Barthel Index	0.603		
BDI		0.835	
FSS		0.830	
AES-S		0.576	
FAB			0.803
MMSE			0.737
AES-C		0.423	-0.595

We can interpret the three components as (1) patients' motor functional level (muscle strength, FMA-UL, spasticity, Barthel index), (2) psychomotor functional level (BDI, FSS, AES-S, AES-C) and (3) cognitive functional level (FAB and MMSE).

Muscle strength = average Medical Research Council score measured from the shoulder flexors, elbow flexors and wrist extensors muscles; FMA-UL = Fugl-Meyer Assessment Upper-Limb score; Spasticity = averaged modified Ashworth scale score from the shoulder, elbow and wrist joints; BDI = Beck Depression Inventory; FSS = Fatigue Severity Scale; FAB = Frontal Assessment Battery; MMSE = Mini Mental State Examination; AES-S = Apathy Evaluation Scale self-administered version; AES-C = Apathy Evaluation Scale clinician version.

Table 3.2 Demographics and clinical characteristics of participants

	N (n = 15)	R (n = 15)	P (n = 15)	$\lambda^2_{(2)}$ or $F_{(2,42)}$	p	Effect size
Sex (male)	9 (60)	10 (66.7)	7 (46.7)	1.27	0.529	0.168
Age (years)	58.5+3.6	58.9+3.1	56.3+3.4	0.17	0.846	0.008
Education (years)	14+0.8	14.9+0.9	13.1+0.8	1.13	0.333	0.051
Stroke type (ischemic)	10 (66.7)	13 (86.7)	11 (73.3)	3.21	0.66	0.267
Paretic limb (left)	9 (60)	8 (53.3)	9 (60)	0.18	0.913	0.064
Dominant affected	3 (20)	6 (40)	6 (40)	1.8	0.407	0.200
Post-stroke (months)	58.3+13.2	41.5+5.4	45+13.7	0.6	0.552	0.028
Stroke site*						
Cortical	7 (46.7)	9 (60)	8 (53.3)	0.07	0.966	0.046
Subcortical	3 (20)	3 (20)	3 (20)	0.07	0.966	0.046
Functional scores						
FMA-UL	41.8+3.4	49.8+3.3	45.6+3.5	1.39	0.26	0.062
Barthel Index	90.3+3.6	95+1.4	94+1.5	1.05	0.360	0.047
Spasticity	0.9+0.2	0.5+0.1	1+0.2	2.12	0.122	0.095
Muscle strength	2.8+0.4	3.8+0.4	3.4+0.3	2.42	0.101	0.103
Psychoactive drugs						
Antidepressants	2 (13.3)	1 (6.7)	2 (13.3)	0.45	0.799	0.1
Antianxiety	2 (13.3)	0 (0)	1 (6.7)	2.14	0.762	0.218
Muscle relaxants	1 (6.7)	1 (6.7)	2 (13.3)	0.55	1.000	0.110

Categorical values are indicated as number of patients (n) and the percentage this relates to in terms of each group (%), numeric values as mean $\pm$ SEM. Comparison between proportions is made with Chi-square test, comparison between means with one-way ANOVA test. Effect sizes are φ (phi) for chi-square test and η^2 (eta squared) for one-way ANOVA.

N = neutral; R = reward; P = punishment; FMA-UL = Fugl-Meyer Assessment Upper-Limb, measuring UL motor and sensory impairment. Scores range 0 to 66 with higher scores indicating better functioning; Barthel Index measures activities of daily living, scores range from 0 (totally dependent) to 100 (completely independent); Spasticity = averaged Modified Ashworth Scale (MAS) score from the shoulder, elbow and wrist joints. The MAS measures ranges 0 to 5, with higher scores indicating more spasticity; muscle strength = average Medical Research Council score measured from the shoulder flexors, elbow flexors and wrist extensor muscles, scores range 0 to 5, with higher scores indicating higher muscle strength. These muscles were chosen as they resist gravity in a reaching-out movement.

*Stroke site was not known in 12 patients (5 neutral, 3 reward and 4 punishment group).

Table 3.3 Patients' cognitive tests

	N (n = 15)	R (n = 15)	P (n = 15)	$F_{(2,42)}$	p	Effect Size
MMSE	27.5±0.7	28.4±0.5	28.1±0.4	0.77	0.468	0.036
FAB	14.3±0.7	15.1±0.5	15.1±0.5	0.74	0.485	0.034
Stroop Errors	1.3±0.4	2.3±0.7	2±0.6	0.66	0.521	0.031
Stroop time (s)	15.9±2.8	28.7±10.1	16.1±2.4	1.41	0.255	0.063
BDI	11.7±2	7.3±1.5	13.6±3	2.28	0.114	0.098
FSS	36.1±3.3	30±3.1	35.8±4.1	0.95	0.394	0.043
AES-C	32.5±1.8	27.1±2	29.7±2	1.83	0.172	0.08
AES-S	31.8±1.4	28.3±1.9	33±1.4	2.39	0.104	0.102
SP	5.1±0.6	3.3±0.5	5±0.6	2.76	0.075	0.116
SR	3.7±0.6	3.6±0.6	3.9±0.7	0.07	0.929	0.003
A-VAS Day 1	7.2±0.6	7.7±0.6	6.7±0.6	0.77	0.466	0.036
A-VAS Day 2	5.8±0.6	7.1±0.6	6.5±0.6	1.11	0.337	0.050
A-VAS Day 3	6.6±0.5	7.5±0.5	6.7±0.5	0.81	0.454	0.037
F-VAS Day 1	6.7±0.6	6.7±0.7	6.5±0.4	0.03	0.968	0.002
F-VAS Day 2	5.7±0.4	6.5±0.8	7±0.5	1.22	0.306	0.055
F-VAS Day 3	5.6±0.7	6.9±0.5	6.9±0.5	1.32	0.279	0.059
Sleep hours day 1	7.9±0.3	7.7±0.3	7.5±0.3	0.34	0.717	0.016
Sleep hours day 2	7.7±0.2	8±0.4	7.9±0.3	0.28	0.757	0.013
Sleep hours day 3	7.6±0.2	7.9±0.3	8.1±0.3	0.64	0.532	0.030

Values are mean $\pm$ SEM. N = neutral; R = reward; P = punishment; MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; BDI = Beck Depression Inventory; FSS = Fatigue Severity Scale; AES-C = Apathy Evaluation Scale clinician version; AES-S = Apathy Evaluation Scale, self-administered version; SP = sensitivity to punishment; SR = sensitivity to reward; A-VAS = alertness visual analogue scale; F-VAS = fatigue visual analogue scale; Sleep hours = overnight sleep prior each study day.

Table 3.4 Healthy controls' cognitive tests

	Controls (n = 15)
Mini Mental State Examination	29.1 $\pm$ 0.3
Frontal Assessment Battery	18 $\pm$ 0.8
Stroop errors	1.6 $\pm$ 0.6
Stroop time (s)	11 $\pm$ 1.8
Beck Depression Inventory	7.3 $\pm$ 1.9
Fatigue Severity Scale	23.1 $\pm$ 3.6
AES-Clinician version	27.7 $\pm$ 1.6
AES-Self-administered version	29.4 $\pm$ 2
Sensitivity to Punishment	3.4 $\pm$ 0.7
Sensitivity to Reward	3.8 $\pm$ 0.5
Alertness-VAS day 1	7.3 $\pm$ 0.4
Alertness-VAS day 2	7.5 $\pm$ 0.4
Alertness-VAS day 3	7.1 $\pm$ 0.6
Fatigue-VAS day 1	7.5 $\pm$ 0.4
Fatigue-VAS day 2	7.3 $\pm$ 0.4
Fatigue-VAS day 3	7.2 $\pm$ 0.5
Sleep hours day 1	6.8 $\pm$ 0.1
Sleep hours day 2	6.9 $\pm$ 0.2
Sleep hours day 3	6.7 $\pm$ 0.3
Values are depicted as mean $\pm$ SEM. AES-C = Apathy Evaluation Scale; VAS = visual analogue scale.	

3.3   Results

3.3.1   Demographic and cognitive functions were similar between groups

Demographic and cognitive parameters were similar between groups (Table 3.3 and Table 3.3). Healthy controls (n = 10, 66.7% males) were similar to patients for age (mean + SEM, 62.5 + 3.7 years), dominant side (n = 14, 93.3% right handed), education (mean + SEM, 17.5 + 0.7 years) and main cognitive tests (Table 3.4).

3.3.2   Day 1: baseline performance was similar across groups

MT, RT, MaxV, online corrections and variability on day 1 were not significantly different across the patients groups (Table 3.5 and Table 3.6). The average sum of squared AE_{maxV} in the first and last block of day 1 was different across blocks [$F_{(1,42)}$ = 17.57, $p < 0.001$, η^2 = 0.295], but not between groups [$F_{(1,42)}$ = 0.62, p = 0.541, η^2 = 0.029], with no group*block interaction [$F_{(2,42)}$ = 0.695, p = 0.505, η^2 = 0.032]. This indicates similar baseline capability to correct for error across groups (Ghilardi et al., 1995; Krakauer et al., 2005).

For each participant I then selected the target quadrant with the least amount of error, and the force-field direction (CW versus CCW) that enhanced this error. The target quadrants and the FF direction chosen are reported in Table 3.7.

Table 3.5 Patients' movement times and reaction times

	Movement Time (ms)			Reaction Time (ms)		
	Neutral	**Reward**	**Punish**	**Neutral**	**Reward**	**Punish**
Day 1	408$\pm$25	482$\pm$37	472$\pm$30	569$\pm$36	465$\pm$36	514$\pm$41
ANOVA	$F_{(2,42)}$ = 1.6, p = 0.204, η^2 = 0.073			$F_{(2,42)}$ = 1.9, p = 0.161, η^2 = 0.083		
Day 2						
Baseline	362$\pm$18	447$\pm$40	401$\pm$24	545$\pm$39	428$\pm$37	480$\pm$37
Adaptation	400$\pm$35	472$\pm$44	436$\pm$36	495$\pm$32	406$\pm$36	470$\pm$33
Washout	386$\pm$24	450$\pm$41	414$\pm$25	539$\pm$26	419$\pm$36	490$\pm$40
ANOVA	G: $F_{(2,42)}$ = 1.4, p = 0.255, η^2 = 0.063 **Ph: $F_{(2,84)}$ = 3.9, p = 0.025, η^2 = 0.084** G*Ph: $F_{(4,84)}$ = 0.1, p = 0.964, η^2=0.007			G: $F_{(2,42)}$ = 2.7, p = 0.081, η^2 = -0.113 **Ph: $F_{(2,84)}$ = 3.5, p = 0.033, η^2 = 0.078** G*Ph: $F_{(4,84)}$ = 0.6, p = 0.633, η^2 = 0.03		
Day 3						
Baseline	332$\pm$23	425$\pm$42	393$\pm$20	502$\pm$33	409$\pm$34	508$\pm$37
Readaptation	395$\pm$40	453$\pm$34	390$\pm$29	494$\pm$32	406$\pm$36	470$\pm$33
Washout	371$\pm$23	412$\pm$29	368$\pm$26	519$\pm$29	409$\pm$30	472$\pm$31
ANOVA	G: $F_{(2,42)}$ = 1.4, p = 0.246, η^2 = 0.065 **Ph: $F_{(2,84)}$ = 3.2, p = 0.045, η^2 = 0.071** G*Ph: $F_{(4,84)}$=1.5, p = 0.206, η^2 = 0.067			G: $F_{(2,42)}$ = 2.6, p = 0.084, η^2 = 0.111 Ph: $F_{(1.7,73.8)}$ = 1.5, p = 0.237, η^2 = 0.034 G*Ph: $F_{(3.5,73.8)}$ = 1.4, p=0.234, η^2=0.064		

Values are mean $\pm$ SEM for each subject by averaging over consecutive epochs. For each parameter, a mixed ANOVA compared group (G: N, R, P) and phase (Ph: Baseline, Adaptation/Readaption, Washout) for each day. Greenhouse-Geisser or Huynh-Feldt corrections are shown when sphericity was violated.

Table 3.6 Patients' velocity and online corrections

	Max V (cm/s)			Max V %			Online corrections		
	N	**R**	**P**	**N**	**R**	**P**	**N**	**R**	**P**
Day 1	27 ± 2	24 ± 2	24 ± 1	82 ± 3	70 ± 4	74 ± 2	-0.1 ± 0.3	-1 ± 0.3	-0.1 ± 0.3
ANOVA	$F_{(2,42)} = 1.3$, $p = 0.276$, $\eta^2 = 0.059$			**$F_{(2,42)} = 3.5$, $p = 0.04$, $\eta^2 = 0.142$**			$F_{(2,42)} = 2.8$, $p = 0.071$, $\eta^2 = 0.118$		
Day 2									
Baseline	29 ± 2	26 ± 3	27 ± 2	86 ± 3	75 ± 4	82 ± 2	0.3 ± 0.02	0.05 ± 0.04	0.04 ± 0.04
Adaptation	29 ± 3	25 ± 3	26 ± 2	79 ± 4	68 ± 5	76 ± 3	1.8 ± 0.5	2.8 ± 0.8	2.6 ± 1.1
Washout	28 ± 2	26 ± 2	26 ± 2	86 ± 3	78 ± 5	84 ± 3	-0.2 ± 0.4	2.2 ± 0.6	0.3 ± 0.5
ANOVA	G: $F_{(2,42)} = 1.6$, $p = 0.564$, $\eta^2 = 0.027$ Ph: $F_{(1.7,71)} = 0.3$, $p = 0.694$, $\eta^2 = 0.007$ G*Ph: $F_{(3.4,71)} = 0.7$, $p = 0.982$, $\eta^2 = 0.003$			G: $F_{(2,42)} = 2$, $p = 0.146$, $\eta^2 = 0.088$ **Ph: $F_{(1.8,74.8)} = 29$, $p < 0.001$, $\eta^2 = 0.408$** G*Ph: $F_{(3.6,74.8)} = 0.3$, $p = 0.849$, $\eta^2 = 0.015$			G: $F_{(2,42)} = 2.3$, $p = 0.114$, $\eta^2 = 0.098$ **Ph: $F_{(1.7,73.3)} = 15.8$, $p < 0.001$, $\eta^2 = 0.273$** G*Ph: $F_{(3.5,73.3)} = 1.5$, $p = 0.2$, $\eta^2 = 0.069$		
Day 3									
Baseline	32 ± 2	27 ± 3	27 ± 2	87 ± 3	78 ± 4	83 ± 3	0.01 ± 0.0	-0.03 ± 0.03	0.02 ± 0.01
Readaptation	31 ± 3	25 ± 2	29 ± 2	80 ± 4	70 ± 5	79 ± 3	1.7 ± 0.8	2.7 ± 0.8	2.8 ± 0.9
Washout	30 ± 2	27 ± 2	30 ± 2	86 ± 3	81 ± 5	86 ± 3	-0.1 ± 0.3	0.6 ± 0.6	-0.1 ± 0.5
ANOVA	G: $F_{(2,42)} = 1.2$, $p = 0.319$, $\eta^2 = 0.053$ Ph: $F_{(2,84)} = 0.2$, $p = 0.791$, $\eta^2 = 0.006$ G*Ph: $F_{(4,84)} = 1.7$, $p = 0.153$, $\eta^2 = 0.076$			G: $F_{(2,42)} = 1.5$, $p = 0.241$, $\eta^2 = 0.065$ **Ph: $F_{(1.8,77.6)} = 22.7$, $p < 0.001$, $\eta^2 = 0.351$** G*Ph: $F_{(3.7,77.6)} = 0.9$, $p = 0.418$, $\eta^2 = 0.045$			G: $F_{(2,42)} = 0.9$, $p = 0.427$, $\eta^2 = 0.04$ **Ph: $F_{(1.4,60)} = 17.8$, $p < 0.001$, $\eta^2 = 0.298$** G*Ph: $F_{(2.8,60)} = 0.5$, $p = 0.681$, $\eta^2 = 0.023$		

Values depict the mean $\pm$ SEM for each subject by averaging over consecutive epochs. For each parameter, a mixed ANOVA compared group (G: N, R, P) and phase (Ph: Baseline, Adaptation/Readaptation, Washout) for each day. Greenhouse-Geisser or Huynh-Feldt corrections are shown when assumption of sphericity was violated. Max V = peak velocity; Max V%, time point in movement (%) when peak velocity occurred; Online corrections = difference between angular error at peak velocity and angular endpoint error. N = neutral; R = reward; P = punishment.

Table 3.7 Targets and force-field directions selected after day 1

	N (n = 15)	R (n = 15)	P (n = 15)
Targets			
25° and 65°	2 (13.3)	2 (13.3)	1 (6.7)
115° and 155°	8 (53.3)	6 (40)	2 (13.3)
205° and 245°	4 (26.7)	3 (20)	5 (33.3)
295° and 335°	1 (6.7)	4 (26.7)	7 (46.7)
Force-field direction (CW)	3 (20)	2 (13.3)	10 (66.7)

Values are depicted as number of patients and the percentage this relates to in terms of each group (%). N = neutral; R = reward; P = punishment; CW = clockwise.

Table 3.8 Within-subject variability across the patients groups

	N	R	P	$F_{(2,42)}$	p	η^2
Day 1	12.7+1	13.7+0.7	12.8+0.9	0.33	0.717	0.016
Day 2-3	9.4+1	9.8+0.6	9+0.6	0.30	0.733	0.015
Early adaptation	9.4 +1	11.4+0.7	9+0.5	3.03	0.059	0.126
Late adaptation	9.4+1	9.1+0.7	9.2+0.7	0.03	0.968	0.002
Early readaptation	9.6+0.9	11.1+0.7	10+0.9	0.78	0.462	0.036
Late readaptation	9.4+1.6	9.1+0.6	8.2+0.5	0.39	0.678	0.018

Values are mean + SEM. N = neutral; R = reward; P = punishment; Day 1 = overall variability during the baseline day; Day 2-3 = overall variability during day 2 and 3; Early adaptation = variability first block of adaptation on day 2; Late adaptation = variability last block of adaptation day 2; Early readaptation = variability first block of adaptation day 3; Late readaptation = variability last block of adaptation day 3.

3.3.3 Day 2 and 3: reward and punishment effects on adaptation and retention

3.3.3.1 Kinematics, baseline performance and initial perturbation were similar across groups

Movement kinematics were similar across groups (Table 3.5 and Table 3.6). As expected, following target selection, variability was lower on day 2 and day 3 than day 1 [$F_{(1,42)}$ = 101.7, $p < 0.001$, η^2 = 0.708], but there were no differences between groups [$F_{(2,42)}$ = 0.34, p = 0.715, η^2 = 0.016] (Table 3.8).
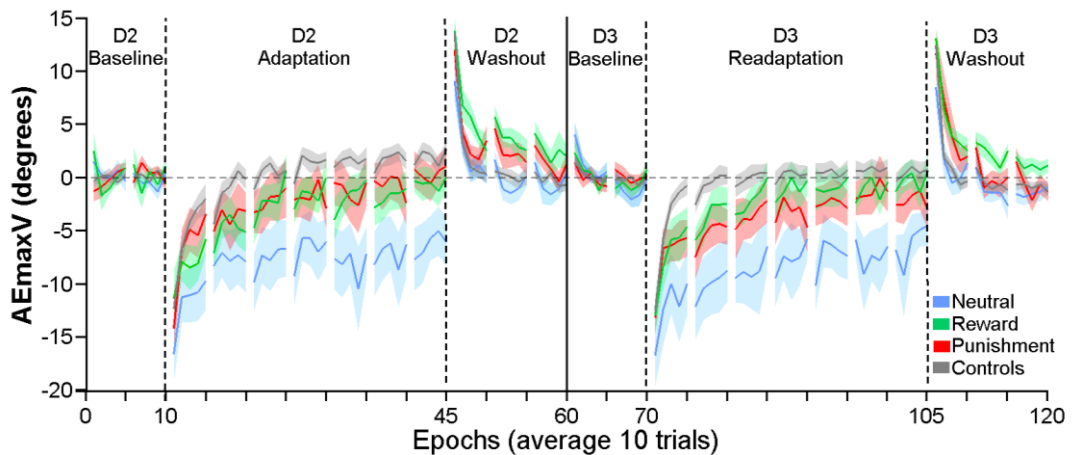
Figure 3-3 Average group data for day 2 and day 3

Day 2 (D2) and day 3 (D3) angular error (degrees) at max velocity is shown during baseline, (re)adaptation and washout for the neutral stroke (blue), punishment stroke (red), reward stroke (green) and neutral healthy control (grey) groups. Values are mean (line) ± SEM (shaded area) across epochs (average of 10 trials). (Reproduced from Quattrocchi et al., 2017, with permission from BMJ Publishing Group Ltd).

Baseline AE_{maxV} was similar across patients groups on both day 2 [N: 0.46 $\pm$ 0.81°, R: -1.6 $\pm$ 1°, P:-0.96 $\pm$ 0.65°, $F_{(2,42)}$ = 1.5, p = 0.235, η^2 = 0.067] and day 3 [N: 0.13 $\pm$ 0.67°, R: -0.2 $\pm$ 0.74°, P: 1.1 $\pm$ 0.94°, $F_{(2,42)}$ = 0.7, p = 0.497, η^2 = 0.033; Figure 3-3]. The force-field caused a similar initial perturbation across the three groups on both day 2 [average AE_{maxV} across first two trials of force-field, $F_{(2,42)}$ = 0.5, p = 0.577, η^2 = 0.026; Figure 3-4, A] and day 3 [$F_{(2,42)}$ = 0.6, p = 0.551, η^2 = 0.028; Figure 3-4, B].
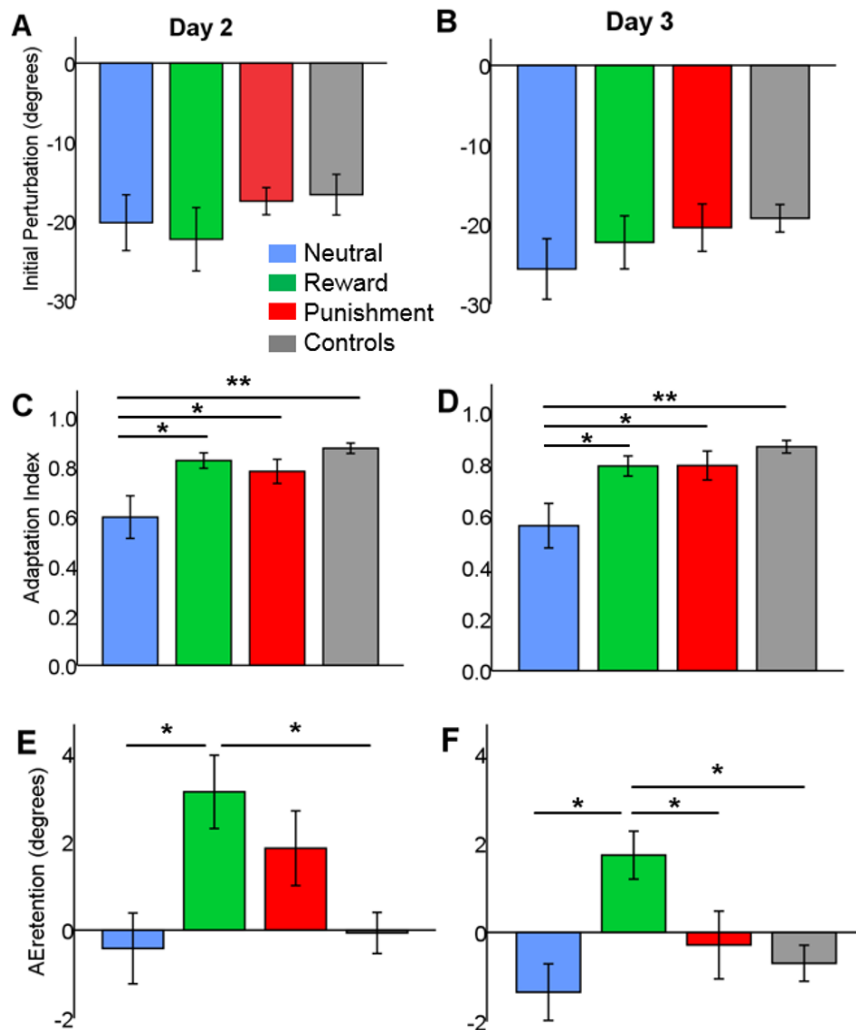
Figure 3-4 The initial perturbation (average AE_{maxV} across the first two FF trials) was similar across groups on A) day 2 (adaptation) and B) Day 3 (readaptation). C) Adaptation index on day 2 was significantly lower in the neutral stroke group compared to the punishment stroke, the reward stroke and the neutral healthy controls groups. D) AI on day 3 (readaptation) was significantly lower in the neutral stroke group relative to the punishment, reward stroke, and neutral healthy control groups. E) $AE_{retention}$ on day 2 –i.e. average AE_{maxV} across last two washout blocks- was higher in the reward group than in the neutral stroke group and the neutral healthy control group. No significant difference was found between the reward and punishment stroke groups. F) $AE_{retention}$ on day 3 was significantly higher in the reward stroke group vs. the neutral stroke, punishment stroke and neutral healthy control groups. $*p < 0.05$, $**p < 0.001$. (Reproduced from Quattrocchi et al., 2017, with permission from BMJ Publishing Group Ltd).

3.3.3.2 Reward and punishment were associated with greater error-reduction during the adaptation and readaptation phases

Although all groups adapted, the reward and punishment group did to a greater extent (Figure 3-3). After controlling for motor, psychomotor and cognitive functions, I found a significant effect of group on day 2 AI [$F_{(2,39)}$ = 3.422, p = 0.043, η^2 = 0.149; Figure 3-4, C], with lower adaptation in the neutral versus the reward (p = 0.019) or punishment (p = 0.050) groups.

Despite reward or punishment only being provided on day 2, the improvements were maintained 24 hours later. Specifically, after controlling for the covariates, there was a main effect of group on day 3 AI [$F_{(2,39)}$ = 3.271, p = 0.049, η^2 = 0.144; Figure 3-4, D], once again with lower readaptation in neutral than either the reward (p = 0.038) or punishment (p = 0.029) groups.

3.3.3.3 Reward was associated with higher retention

All groups displayed substantial after-effects during washout on both day 2 and day 3 (Figure 3-3), but the retention of this aftereffect was different across patient groups [D2 AE$_{retention}$; $F_{(2,42)}$ = 3.425, p = 0.043, η^2 = 0.149; Figure 3-4, E], with the neutral retaining less than the reward group (p = 0.016). Interestingly on day 3 [$F_{(2,42)}$ = 7.102, p = 0.002, η^2 = 0.267; Figure 3-4, F], the reward group displayed a greater amount of retention than either the neutral (p = 0.001) or punishment (p = 0.008) groups.

No savings were observed across the groups, with no effect of group [$F_{(2,42)}$ = 1.8, p = 0.179, η^2 = 0.079] nor day [$F_{(1,42)}$ = 0.37, p = 0.544, η^2 = 0.009].

3.3.3.4 Healthy controls adapted similarly to the reward and punishment groups but retained less

Although my focus was on patient groups, I also tested a group of age-matched healthy controls under neutral feedback. These showed less variability than patients [one-way ANOVA between the three stroke groups and the healthy controls: overall variability (6.1 ± 0.2 in healthy controls): $F_{(3,56)}$ = 7.17, p < 0.001, η^2 = 0.278; day 1: $F_{(3,56)}$ = 8.43 p < 0.001, η^2 = 0.311; day 2-3: $F_{(3,56)}$ = 7.17, p < 0.001, η^2 = 0.278; early adaptation: $F_{(3,56)}$ = 4.04, p = 0.011, η^2 = 0.178; late adaptation: $F_{(3,56)}$ = 6.5, p = 0.001, η^2 = 0.257; early readaptation: $F_{(3,56)}$ = 2.3, p = 0.085, η^2 = 0.110; late readaptation: $F_{(3,56)}$ = 4.2, p = 0.010, η^2 = 0.183] (Table 3.9). Healthy controls also showed faster RTs than patients [day 1: $F_{(3,56)}$ = 8.42, p < 0.001, η^2 = 0.311; baseline day 2: $F_{(3,56)}$ = 7.7, p < 0.001, η^2 = 0.291; adaptation: $F_{(3,56)}$ = 6.9, p < 0.001, η^2 = 0.271; washout day 2: $F_{(3,56)}$ = 7.7, p < 0.001, η^2 = 0.294; baseline day 3: $F_{(3,56)}$ = 7.6, p < 0.001, η^2 = 0.289; readaptation: $F_{(3,56)}$ = 6.5, p = 0.001, η^2 = 0.258; washout day 3: $F_{(3,56)}$ = 9.2, p < 0.001, η^2 = 0.331] (Table 3.10). There were no differences between healthy controls and stroke patients in other kinematic parameters (Table 3.10), with the exception of MaxV% on day 1 [$F_{(3,56)}$ = 3.16, p = 0.032, η^2 = 0.145] and online corrections on day 2 washout [$F_{(3,56)}$ = 5.2, p = 0.003, η^2 = 0.036]. Baseline AE_{maxV} [D2: $F_{(3,56)}$ = 1.3, p = 0.284, η^2 = 0.065; D3: $F_{(3,56)}$ = 0.67, p = 0.575, η^2 = 0.035] and initial perturbation [D2: $F_{(3,56)}$ = 0.7, p = 0.556, η^2 = 0.036; D3: $F_{(3,56)}$ = 0.82, p = 0.485, η^2 = 0.042] were similar between healthy controls and stroke patients.

Healthy controls adapted and readapted. Adaptation was significantly different across groups [D2 AI: Brown-Forsythe $F_{(3,28.5)}$ = 5.3, p = 0.005; Figure 3-4, C], with controls performing similar to the reward (p = 0.51) and punishment (p = 0.217) groups but significantly better than the neutral stroke (p < 0.001) group. The same was observed for readaptation [D3 AI: Brown-Forsythe $F_{(3,33.2)}$ = 5.6, p = 0.003, Figure 3-4, D], with controls adapting more than the neutral (p < 0.001), but similarly to the reward (p = 0.353) and punishment (p = 0.365) stroke groups.

Table 3.9 Within-subjects variability in healthy controls

Variability	Controls (n = 15)
Variability during day 1	8.3 $\pm$ 1.5
Variability during day 2 and 3	6.1 $\pm$ 0.2
Early adaptation	8.2 $\pm$ 0.4
Late adaptation	5.7 $\pm$ 0.4
Early readaptation	8.2 $\pm$ 0.5
Late readaptation	5.3 $\pm$ 0.3

Values are mean $\pm$ SEM. Early adaptation = variability first block of adaptation on day 2; Late adaptation = variability last block of adaptation day 2; Early readaptation = variability first block of adaptation day 3; Late readaptation = variability last block of adaptation day 3.

Table 3.10 Kinematic parameters for healthy controls

	MT (ms)	RT (ms)	Max V	Max V %	Online corrections
Day 1	411 $\pm$ 13	342 $\pm$ 12	23 $\pm$ 0.7	71 $\pm$ 2	-0.3 $\pm$ 0.3
Day 2					
Baseline	358 $\pm$ 17	327 $\pm$ 11	27 $\pm$ 2	78 $\pm$ 3	0 $\pm$ 0.01
Adaptation	365 $\pm$ 19	319 $\pm$ 12	28 $\pm$ 2	71 $\pm$ 3	2.8 $\pm$ 0.5
Washout	363 $\pm$ 15	343 $\pm$ 13	26 $\pm$ 2	78 $\pm$ 2	0.5 $\pm$ 0.3
Day 3					
Baseline	353 $\pm$ 16	331 $\pm$ 11	27 $\pm$ 2	81 $\pm$ 3	0.002 $\pm$ 0.01
Readaptation	371 $\pm$ 18	326 $\pm$ 10	26 $\pm$ 2	73 $\pm$ 3	2.2 $\pm$ 0.6
Washout	371 $\pm$ 15	331 $\pm$ 9	26 $\pm$ 1	79 $\pm$ 2	-0.2 $\pm$ 0.3

Values depict the mean $\pm$ SEM determined for each subject by averaging over consecutive epochs. MT = movement time; RT = reaction time; Max V = peak velocity; Max V % = time point in movement (%) when peak velocity occurred; Online corrections = difference between angular error at peak velocity and angular endpoint error.

3.4   Discussion

In this study I showed for the first time that providing reward or punishment-based feedback to stroke patients during a motor adaptation task can bring their performances to the levels of healthy subjects of the same age range. More strikingly, reward increases the retention of the new motor behaviour to a level even higher than healthy subjects.

3.4.1   Reward and punishment increased error-correction during the adaptation (and readaptation) phase

Although experiencing 350 trials, patients within the neutral group were unable to fully adapt. Remarkably, by simply providing reward or punishment, patients showed nearly complete error-correction, similar to healthy age-matched controls. In fact, across the reward and punishment groups, patients were able to return to baseline levels of performance.

This result, according to me, is not simply due to cognitive or motor differences between groups. In fact, cognitive and functional motor scores were statistically similar across groups. In addition, I entered these scores into a principal component analysis which revealed three main components that represented each patient's motor, psychomotor and cognitive levels. I then used these parameters as covariates within the group analysis to ensure that the results were not simply due to non-experimental group differences.

Another possibility could be that the groups simply differed in terms of their baseline motor performance. First, all three patient groups improved their reaching accuracy similarly across day 1. This suggests that when these groups experienced similar task feedback, their ability to correct for error was comparable. Second, by individually tailoring the task on day 2 and 3, I was able to limit baseline between-subject

differences that may have exaggerated or cancelled any difference across groups. Therefore, I believe that these results are not due to simple differences between groups in cognitive or functional status, nor to baseline differences in motor performance.

Previous evidence in young healthy subjects showed that punishment led to faster adaptation, whereas reward caused greater retention (Galea et al., 2015). Here I partially replicated these results, but I found an association with increased adaptation for both punishment and reward. One could argue that this effect may have been partially triggered by the knowledge of results provided by the feedback. In fact, there is a suggestion that explicit feedback can increase motor learning in stroke patients (van Vliet and Wulf, 2006). Nevertheless, the points system adopted here was unlikely to provide substantial amount of information in comparison to the visual feedback itself (i.e. 1 point represented a range of at least 5°). Secondly, patients' sensitivity to feedback could be different to young healthy subjects. However, although aging is associated with reduced sensitivity to reward and punishment, the relative difference indicates an age-related hypersensitivity to reward (Bauer et al., 2013). In other words, the decrease in reward sensitivity is less than with punishment sensitivity. Therefore, if we assume that younger adults' greater sensitivity to punishment during adaptation represents the expected difference (loss aversion), then the stroke patients' (older adults) results could demonstrate a hypersensitivity to reward (Bauer et al., 2013). This also suggests that the specific effect of punishment on adaptation found in the previous work by Galea and colleagues may be explained through loss aversion, rather than the hypothesised effect on cerebellar activity (Galea et al., 2015).

The improvements observed in the reward and punishment groups were maintained 24 hours later despite no further motivational feedback being provided. However, across all groups, there were no savings. This is most likely due to the 250 washout trials and the 24 hour gap between adaptation blocks, both of which are known to

significantly impair savings (Criscimagna-Hemminger and Shadmehr, 2008). These results indicate that reward and/or punishment not only can enhance within-session adaptation in stroke patients, but, by making them learn better in the first place, could have long lasting benefits even when the feedback is no longer provided.

3.4.2   Reward increased motor memory retention

As discussed in Chapter 1, motor adaptation paradigms are already being implemented in some rehabilitation settings, such as gait rehabilitation (Reisman et al., 2007). Nevertheless the acquired motor behaviour is quickly forgotten, thus limiting the use of these paradigms in clinical practice. I found here that rewarding patients during adaptation increased retention. Most importantly, this effect was still present after 24 hours, with patients who had been rewarded retaining even more than controls. This result is in line with previous evidence (Abe et al., 2011; Galea et al., 2015; Goodman et al., 2014), and represents a promising step toward the use of reward and motor learning paradigms in rehabilitation.

One caveat of using after-effects as measure of retention is that this is influenced by the forgetting of what has been previously learnt (true retention), but also by simultaneous learning from movement errors (Hadipour-Niktarash et al., 2007). Retention can be assessed using error-clamp trials (Scheidt et al., 2000), but I preferred to avoid them as I was concerned that these may provide additional reward because patients are always successful in these trials. Nevertheless, the size and persistence of an after-effect during washout trials with vision has been used numerous times as a proxy of retention (Patton et al., 2006; Reisman et al., 2007).

3.4.3   Implications

Despite the existing controversies highlighted in Paragraph 1.5.3, clinically meaningful motor improvements in chronic stroke patients generally appear possible only with a large amount of contact hours (Cauraugh et al., 2011). Therefore, developing interventions that reduce the amount of hours required is crucial. This exploratory study highlights for the first time the potential of targeted motivational feedback as a tool to enhance the amount of learning and retention within and between sessions. Motor adaptation was used here as a model process, and further investigations on the effects of reward/punishment feedback over long-term training regimes are warranted. Robotic devices already in use in clinical rehabilitation could produce error-enhancing force-fields although improvements from robot-assisted therapy may not generalize to everyday life activities (Mehrholz et al., 2015). Therefore, how the improvements seen with motivational feedback could be administered within a setting where more practical behaviours are learnt remains a relevant question.

3.4.4   Conclusions

In this study I showed for the first time that reward and punishment enhance motor adaptation in stroke patients to similar level as controls. These improvements are maintained across 24 hours. These findings suggest that the engagement of motivational processes during motor learning-based therapies could be a promising adjunct to rehabilitation. This will motivate further investigation about the long-term effects of motivational feedback, and thus avenues for translating these promising results into rehabilitation.

Chapter 4.

Reward increases memory retention in motor adaptation tasks through dopaminergic pathways – a pharmacological study in healthy young participants

Calvin & Hobbes by Bill Watterson, Permission granted by Andrews McMeel Syndication

4.1 Introduction

Motor adaptation tasks have traditionally been considered as investigating an exclusively implicit mechanism, driven by sensory prediction errors (Tseng et al., 2007) and unaffected by motivational feedback (Mazzoni and Krakauer, 2006). Contrary to this assumption, and as outlined in Chapter 1, the beneficial effects of reward and punishment during motor adaptation paradigms have recently been shown (Gajda et al., 2016; Galea et al., 2015; Nikooyan and Ahmed, 2015; Shmuelof et al., 2012; Song and Smiley-Oyen, 2017). Specifically, by using reward- or punishment-based monetary feedback, Galea and colleagues previously showed that the latter accelerated error reduction during adaptation, while the former increased retention of the newly acquired motor behaviour (Galea et al., 2015), findings that have been, at least partially, replicated recently (Song and Smiley-Oyen, 2017). These results point towards the existence of independent mechanisms underpinning learning and retention, but also towards differential neural processes driving the effects of reward and punishment during motor adaptation tasks.

The reward system relies heavily on dopamine, with dopamine neurons firing in response to reward and reward predictors (Schultz, 2016a; Volman et al., 2013). In rodents, dopaminergic projections to M1 are required for successful motor skill learning, and in particular for long-lasting storage of motor memories (Hosp et al., 2011; Jonas A. Hosp and Luft, 2013; Molina-Luna et al., 2009). These projections originate mainly from the rostro-lateral VTA and the rostro-medial portion of the substantia nigra and thus form part of the reward meso-cortico-limbic system (Hosp et al., 2011). On this bases, it has been hypothesized that reward may improve motor memory retention by promoting plastic changes in M1 through the release of dopamine (Jonas A. Hosp and Luft, 2013). In addition, administration of levodopa (LD), a precursor of dopamine, improves motor learning in elderly healthy adults (Flöel et al., 2008a; Flöel et al., 2008b; Flöel et al., 2005) and in stroke patients (Flöel et al., 2005; Rösser et al., 2008). Indeed, dopaminergic stimulation coupled with

motor rehabilitation has been proposed as a possible tool for improving motor recovery after stroke (Scheidtmann et al., 2001).

While dopamine is important to learn from rewards, its role in mediating the effect of punishment on adaptation is unclear. Indeed, the "single-dimension" hypothesis proposes that dopamine (but also any other reward-sensitive circuit) is also sensitive to punishment (Wang and Tsien, 2011), whereas the "two-dimension" hypothesis suggests that some dopaminergic neurons are sensitive only to reward, and others only to punishment (Fiorillo, 2013; Matsumoto and Hikosaka, 2009; Mirenowicz and Schultz, 1996). Moreover, serotonin has also been associated with the anticipation and/or the delivery of punishment (Amo et al., 2014; Dayan and Huys, 2015; Deakin and Graeff, 1991), thus making the study of punishment-related effects even more complex (see also Chapter 1, paragraph 1.4).

A deeper understanding of the neural mechanisms underpinning the effect of reward and punishment during motor adaptation tasks could inform attempts to further potentiate the beneficial impact of motivational feedback for optimization of motor learning in health and in clinical rehabilitation settings. Indeed, the need to target motor recovery at multiple sites along the motor learning network by combining motor robotic therapy with pharmacotherapy and reward learning has already been pointed out (Tran et al., 2016).

Thus, in the present study I sought to investigate the role of dopamine during a motor adaptation task under reward or punishment conditions. To this end, I tested young healthy participants in the presence of reward- or punishment-based monetary feedback. In a placebo-controlled double-blind design, I examined the role of dopamine by either increasing dopamine availability with levodopa (dopamine precursor; experiment 1) or decreasing dopamine effects with haloperidol (dopamine antagonist; experiment 2).

My prediction was that manipulating the dopaminergic system would specifically alter the impact of reward-based feedback on motor memory retention.

4.2 Materials and methods

4.2.1 Study population

For this study I recruited from the University College London Psychology pool 110 participants fulfilling the following criteria: (a) right-handed (as assessed with the Edinburg handedness inventory) (Oldfield, 1971); (b) 18-45 years old; (c) no self-reported history of major medical disorders or drug abuse; (d) normal or corrected-to-normal vision; (e) no drug allergies; (f) not currently taking any medication that would affect the central nervous system or interfere with the absorption of levodopa; (g) not pregnant (self-report). As a medical doctor, I personally evaluated the suitability of the participants for the pharmacological protocol based on a review of their clinical history. A total of 64 participants were tested in experiment 1 [aged 18-40 years, 23.34 ± 4.02 years (mean $\pm$ SD), n = 38 females], and 46 participants in experiment 2 (age 19-39, 24.63 ± 5, n = 32 females). All participants were naïve to the experimental aims and provided written informed consent. The experiments were approved by the UCL Research Ethics Committee and were conducted in accordance with the principles expressed in the Declaration of Helsinki.

4.2.2 Experimental task

I used here a standard visuomotor adaptation reaching task (Krakauer et al., 2000; Taylor and Ivry, 2014). Participants sat with their forehead supported in front of a workstation whilst holding the handle of a two-joint robotic manipulandum with their dominant right arm. The forearm was stabilized by straps to a moulded cast. A

horizontal mirror, suspended 2 cm above the hand, prevented direct vision of the arm, but showed a reflection of a screen mounted above. Online visual feedback regarding hand position was provided by a white cursor (0.3 cm diameter) projected onto the screen. In some blocks (no vision) the online visual feedback of the cursor was removed.

The task consisted of centre-out fast ballistic movements to visual targets. Participants had to initially bring the cursor within a 1 cm^2 starting box located in front of the body's midline. Once the cursor was within the starting point, a white 0.5 cm^2 target appeared pseudo-randomly in one of six positions arrayed radially at 6 cm from the start (15, 75, 135, 195, 255 and 315° clockwise, with 0° representing 12 on a clock). Participants were instructed that, when ready, they should make a fast, accurate, 'shooting' movement through the target, avoiding corrections. As the cursor crossed an imaginary 6 cm radius circle centred at the starting position, a green dot appeared at the endpoint. After 500 ms, the manipulandum returned the hand back to the start. Participants were instructed that they had to try to maintain a constant and relatively fast speed across the whole experiment. To encourage this, the target turned red or blue if the movement was > 300 ms or < 100 ms, respectively. In the adaptation trials, the manipulandum introduced a visuomotor perturbation, in which the cursor position was rotated 40° clockwise from the actual hand position (Figure 4-1, A).
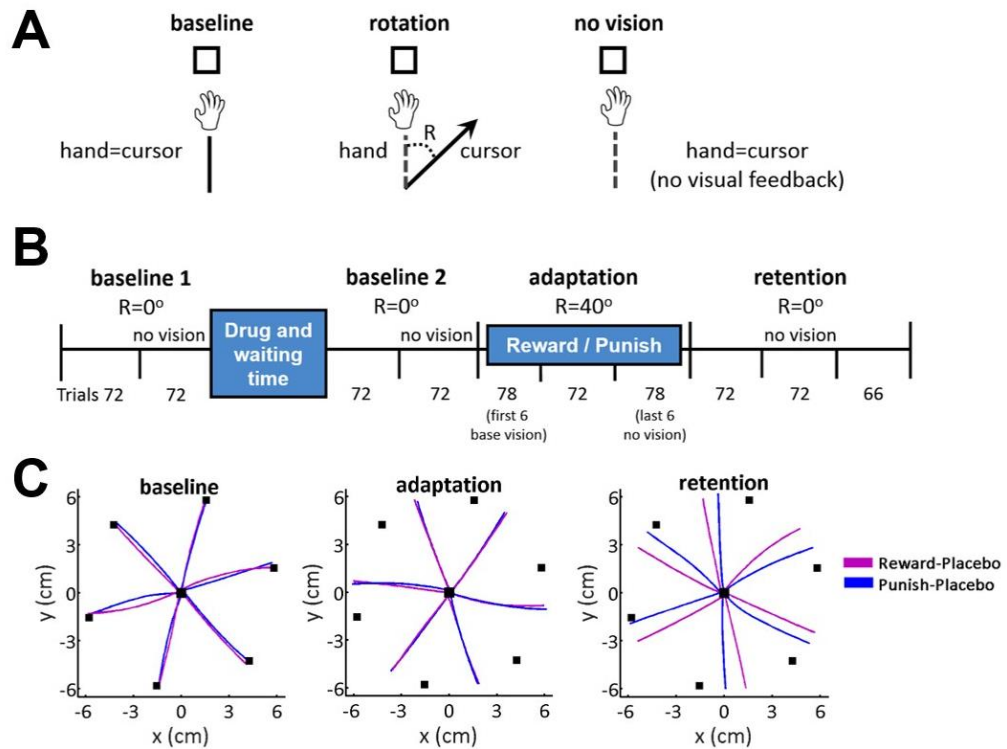
Figure 4-1 Experimental task and paradigm

A) Task. Participants made 6 cm reaching movements to a target. Visual feedback was perturbed by a 40° clockwise rotation (R) in adaptation phase (rotation). In "no vision" trials, the cursor and the hand position corresponded but there was no visual feedback. B) Study protocol. Participants completed 72 trials of baseline training with veridical visual feedback, followed by 72 trails with no visual feedback (no vision). Drug (levodopa/placebo in experiment 1 or haloperidol/placebo in experiment 2) was then administered and participants waited the corresponding waiting time (60 min in experiment 1, 120 min in experiment 2). After that, the two baseline blocks were repeated (baseline 2). During adaptation, visual feedback was perturbed 40° clockwise for 216 trials (3 blocks). In order to avoid this starting abruptly at the beginning of a block, the first adaptation block started with 6 baseline trials with veridical visual feedback, followed by 72 trials with the perturbation. Then, participants were exposed to 216 (retention, 3 blocks) trials with no perturbation and no visual feedback. Again, in order to avoid a context change at the beginning of a block, the last adaptation block finished with 6 retention trials. C) Hand trajectories toward each target of one representative subject in the reward-placebo (violet) and punish-placebo (blue) group. From left to right: last trial toward each target of baseline 1, last trial toward each target of adaptation, last trial toward each target of retention.

4.2.3 Reward and punishment feedback

During the adaptation phase, the reward groups accumulated positive points, the punishment groups accumulated negative points and the neutral group received no points. Points were calculated based on endpoint angular error, i.e. the difference between the cursor endpoint angle and the target angle, as follows:

Reward: 4 points: < 1°; 3 points: 1-5°; 2 points: 5-15°; 1 point: 15-25°; 0 points: ≥ 25°.

Punishment: 0 points: < 1°; −1 point: 1-5°; −2 points: 5-15°; −3 points: 15-25°; −4 points: ≥ 25°.

Neutral: points were replaced by two uninformative zeros.

Both the points received on a trial-by-trial basis and the cumulative score of the block were shown. Participants were informed that points had a monetary value (3.47 pence/point) and depended on performance. Participants in the reward groups started with £0 and could earn up to £30 based on the accumulated points, while those in the punishment groups were given an initial amount of £30 and lost money based on the cumulative negative points. The neutral group received £20 at the end of the study, irrespective of performance.

4.2.4 Experimental protocol

The study was composed of four phases (Figure 4-1, B). Participants initially performed a baseline (baseline 1) composed of one block (72 trials) with visual feedback and one with no visual feedback (no vision) of the cursor. After the drug/placebo administration and the correspondent waiting time, a second equivalent baseline (baseline 2) was performed. The cursor was then rotated 40° clockwise and reward or punishment feedback was provided as described above for 3 blocks (adaptation). In order to avoid the perturbation beginning at the start of a

block, the first adaptation block started with 6 baseline trials with veridical visual feedback and no reward/punishment feedback, followed by 72 trials with the perturbation. Finally, participants were exposed to 216 trials (3 blocks) with no perturbation and no visual feedback (retention). Again, in order to avoid this change in context starting at the beginning of a block, the last adaptation block finished with 6 retention trials (i.e. there were 78 trials in the last adaptation block, followed by two retention blocks of 72 trials and 66 trials). The removal of visual feedback of the cursor restricts re-learning and therefore the observed gradual drift back to baseline performance represents memory retention (Galea et al., 2011; Kitago et al., 2013). Each block was separated by a short (< 1 min) rest period.

4.2.4.1 Experiment 1: the effect of levodopa on a motor adaptation paradigm under reward or punishment feedback

In experiment 1, participants (n = 64) were randomly allocated to one of four groups (16 participants per group): reward-levodopa (R-LD), punishment-levodopa (P-LD), reward-placebo (R-Pl), and punishment-placebo (P-Pl). After baseline 1, subjects received either 100 mg of the dopamine precursor levodopa (plus 25 mg of carbidopa) or placebo. To coincide with the peak plasma concentration of levodopa (Nutt and Fellman, 1984), the task was restarted after a 60 minute wait period, during which participants sat quietly in the laboratory.

4.2.4.2 Experiment 2: the effect of haloperidol on a motor adaptation paradigm under reward or punishment feedback

In experiment 2, participants (n = 46) were randomly allocated to one of three groups: reward-haloperidol (R-Halo, n = 16 participants), punishment-haloperidol (P-Halo, n = 16) and neutral-placebo (N-Pl, n = 14). After baseline 1, participants received either 2.5 mg of the D1/D2-antagonist haloperidol or a placebo. To coincide with the peak plasma concentration of haloperidol (Tomassini et al., 2016), the task was

restarted after a 120 minute wait period, during which participants sat quietly in the laboratory.

4.2.5   Blinding procedure

In both experiments, a medical doctor performed the randomization and administration of the drug, while the examiner and the participants were naïve to the aim of the experiment and blinded to the drug/placebo status. The doses and administration times were similar to previous studies that have shown clear behavioural and neurophysiological effects for levodopa and haloperidol (Bestmann et al., 2015). All participants fasted for at least 2 hours preceding drug/placebo intake to prevent interference with drug absorption (Nutt and Fellman, 1984). No adverse events were reported.

4.2.6   Cognitive tests

To take into account possible confounding cognitive factors, all participants underwent a battery of validated neuropsychological tests. The Mini Mental State Examination (Folstein et al., 1975) was used as a general cognitive screening tool, while the Frontal Assessment Battery (Dubois et al., 2000) and the Stroop test (Stroop, 1935) assessed executive function. I also evaluated apathy (Apathy Evaluation Scale) (Marin et al., 1991), depression (Beck Depression Inventory) (Beck et al., 1961), and sensitivity to punishment and reward (SPSRQ-20) (Aluja and Blanch, 2011). To control for the effect of sleep on motor learning, participants were asked to sleep at least 6.5 hours the night before the study day (Al-Sharman and Siengsukon, 2013). After completion of the session, participants reported whether they thought they had taken the active drug or placebo, and scored their levels of alertness on a 10-point visual analogue scale (0 = very sleepy, 10 = fully alert).

4.2.7 Data analysis

The 2D (x, y) position of the hand was collected through a custom C++ code at a sampling rate of 100 Hz. Movement onset was defined as the point at which radial velocity crossed 10% of peak velocity. Movements were considered terminated when the cursor breached the 6-cm target perimeter. Performance was quantified using angular reach direction (AD, ^{o}), i.e. the difference between the target angle and the angular hand position at the end of the movement (Hadipour-Niktarash et al., 2007). During veridical feedback, the goal was for reach direction to be 0°. However, with the visuomotor perturbation, reach direction had to compensate; i.e. for a $+40^o$ (clockwise) visuomotor rotation, a reach direction of -40° (counter-clockwise) was required. To adjust for between-subject baseline directional biases in the vision and no vision conditions (Ghilardi et al., 1995), AD was corrected by subtracting the average AD of the first baseline 1 block from the trials with cursor vision, and the average AD of the second baseline 1 block ("no vision") to the trials with no visual feedback of the cursor (Krakauer et al., 2005).

Reaction time (RT, time between target appearance and movement onset, ms) and movement time (MT, time between movement onset and movement end, ms) were calculated for each trial. Trials in which AD exceeded 20° or was less than -60° (Galea et al., 2015; Tanaka et al., 2009), or MT or RT exceeded 1000 ms or were less than 100 ms, were removed. This accounted for 1.58% of trials. Epochs of all kinematics were created by averaging across 6 consecutive trials (Galea et al., 2011; Krakauer et al., 2005). For the purpose of analysis, the first six trials of the first adaptation block (which were still without perturbation, as described in "Experimental protocol") were annexed to baseline 2, while the final six trials of the last adaptation block (without vision and no perturbation, see "Experimental protocol") were considered as retention.

Data and statistical analysis were performed using Matlab (version R2013a, The MathWorks, Natick, MA, USA) and IBM SPSS (version 21.0). Differences between demographics, cognitive scores, MT, RT and baseline AD were evaluated by one-way ANOVA (quantitative data) or Chi-square or Fisher exact test (proportions).

In experiment 1, I first performed repeated-measure ANOVAs for each study phase (i.e. adaptation, retention) by comparing AD with drugs (placebo x levodopa) and feedback (reward x punishment) as between-subject factors, and blocks as a within-subject factor (3 blocks in adaptation, 3 blocks in retention). For experiment 2, I performed a similar analysis comparing, for each phase, AD between the three groups with blocks as a within-subject factor.

A model-based analysis was also performed. Specifically, I applied a single-rate state-space model (SSM) (Donchin et al., 2003; Galea et al., 2015; Tanaka et al., 2009; Thoroughman and Shadmehr, 2000) to each participant's entire data set. This has the advantage of estimating learning and retention rates from all available data, with no arbitrary selection of time points or trials of interest. The SSM took the following form:

$$y_n = -z_n^t$$

$$z_{n+1}^t = A z_n^t + B(r_n - z_n^t)$$

y_n represents the angular direction (relative to target) on trial n; z_n^t is the state of the learner, i.e. the current estimated visuomotor mapping (rotation) with the target t; r_n represents the visuomotor rotation that was imposed on trial n; $r_n - z_n^t$ is the error in the visuomotor mapping (i.e., cursor error). The learning rate (B) determines how much of the cursor error ($r_n - z_n^t$) is adapted for. In addition, the visuomotor mapping slowly forgets at a rate determined by the scalar parameter A (decay rate). During blocks with no visual feedback (no vision, retention phase) one can assume that B = 0. Therefore, in this case, the system forgets with constant A (with larger values signifying increased retention). Using the Matlab function *fmincon*, for each

subject I estimated A and B to minimize the squared error between trial-by-trial predicted hand direction and actual trial-by-trial hand direction, subject to constraints (0 < A < 1) and (-1 < B < 1).

As the assumption of normality was violated, in experiment 1 I examined between-groups differences for the A and B parameters using an adjusted rank transform (ART) test (Leys and Schumann, 2010), with feedback (reward x punishment) and drugs (placebo x levodopa) as independent variables[4]. In experiment 2, I compared A and B between-groups using a one-way ANOVA. The model's goodness of fit was determined using R-squared.

Finally, I also assessed performance across groups when splitting trials based on fast versus slow reaction time (Haith et al., 2015; Leow et al., 2017). I defined the fast versus slow RT cut-off as the median reaction time for all trials across both experiments. Based on this criteria, RTs > 326 ms were defined as slow, while RTs < 326 ms were considered as fast. I then repeated the same model-free analysis described above in both experiments separately for fast and slow reaction time trials.

All data was tested for normality using the Shapiro-Wilk test and, in case of data that did not follow a normal distribution, the correspondent non-parametric test was used, as indicated in the tables and text. Homogeneity of variance was evaluated with Levene test, and Welch test was used when this assumption was violated. Greenhouse-Geisser (if epsilon, $\varepsilon < 0.75$) or Huynh-Feldt (if $\varepsilon > 0.75$) corrections were applied when sphericity was violated (Mauchly's test). Tukey post-hoc test was used when warranted. I used no statistical methods to predetermine sample sizes, but the sample sizes of this study are similar to those reported in previous studies (Galea et al., 2011, 2015). Significance level was set at $p < 0.05$. Effect sizes are provided by phi

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[4] For more information about adjusted rank test, and an easy tool to calculate it, see https://sites.google.com/site/derwinkcchan/software/art-anova , Chan 2014.

for Chi-square test, Cohen's *d* for t-tests or r score for Mann-Whitney test, partial eta (η^2) for ANOVA, and epsilon-squared (ε^2) for Kruskal-Wallis H test.

4.3 Results

4.3.1 Experiment 1

4.3.1.1 Demographics, cognitive and kinematic parameters were similar across groups

In experiment 1, I investigated the effect of levodopa on a motor adaptation task under reward or punishment conditions in four groups (n = 16 each): reward-levodopa (age 19-40 years, 23.4 $\pm$ 5 years, n = 8 females), punishment-levodopa (age 18-28, 22.4 $\pm$ 2.8, n = 10 females), reward-placebo (age 20-40, 25 $\pm$ 4.7, n = 10 females), and punishment-placebo (age 19-28, 22.5 $\pm$ 2.2, n = 10 females). As shown in Table 4.1, all groups were comparable for Body Mass Index, education level, cognitive scores, amount of money received at the end of the session, and success rate, defined as number of times each subject received the maximum points (i.e. 4 points in the reward groups and 0 points in the punishment groups). Participants' alertness at the end of the session was similar across groups [R-LD = 7.6 $\pm$ 0.3, mean $\pm$ SEM, P-LD = 7.1 $\pm$ 0.3, R-Pl = 7.2 $\pm$ 0.4, P-Pl = 7 $\pm$ 0.2; $F_{(3,60)}$ = 0.7, *p* = 0.577, η^2 = 0.032]. Thirteen of the 32 (41%) participants in the placebo groups believed they had received levodopa, while 18 of 32 (56%) in the levodopa groups believed they had received placebo, thus showing that the blinding protocol was effective.

Table 4.1 Participants' characteristics (experiment 1)

	R-LD	P-LD	R-Pl	P-Pl	$\lambda^2_{(3)}$ / $F_{(3,60)}$	*p*	Effect size
BMI	21.9 ± 0.7	23.4 ± 0.9	22.3 ± 0.7	21.5 ± 0.5	1.31	0.280	0.066
High education	13 (81.3)	11 (68.7)	15 (93.7)	12 (75)	4.39	0.212	0.169
MMSE	29.7 ± 0.1	29.4 ± 0.3	29.5 ± 0.2	29.7 ± 0.1	0.07	0.995	0.001
FAB	17.6 ± 0.2	17.6 ± 0.1	17.6 ± 0.1	17.7 ± 0.1	0.36	0.948	0.006
Stroop Errors	0.4 ± 0.2	0.7 ± 0.3	0.4 ± 0.2	1 ± 0.3	5.10	0.167	0.081
Stroop Time (s)	4.6 ± 0.9	4.2 ± 1.3	5.5 ± 0.7	5 ± 2.1	5.09	0.166	0.081
AES-S	28.4 ± 1.3	26 ± 1.5	28.7 ± 1.5	30 ± 1.6	1.41	0.247	0.066
BDI	3.3 ± 0.9	2.9 ± 1	3.7 ± 1.1	5.2 ± 1.3	3.54	0.315	0.056
SP	3.7 ± 0.7	3.4 ± 0.5	3.8 ± 0.7	3.7 ± 0.7	0.06	0.981	0.003
SR	4.8 ± 0.6	3.7 ± 0.5	4.4 ± 0.6	3.8 ± 0.7	0.82	0.487	0.040
Money received	18.3 ± 0.4	18.1 ± 0.6	18 ± 0.4	18.9 ± 0.3	0.73	0.537	0.035
Success rate	435 (12.6)	454 (13.1)	454 (13.1)	463 (13.4)	1.06	0.786	0.130

Categorical values are indicated as number and percentages (%), numeric values as mean ± SEM. Comparison between proportions is made with Chi-square test, comparison between means with one-way ANOVA or Kruskal-Wallis (MMSE, FAB, Stroop, BDI) test. Effect size is provided as phi for Chi-square test, partial eta for ANOVA and epsilon-squared for Kruskal-Wallis.

R-LD = reward-levodopa (n = 16); P-LD = punishment-levodopa (n = 16); R-Pl = reward-placebo (n = 16); P-Pl = punishment-placebo (n = 16); High education = participants with ≥15 years of education; BMI = body mass index (Kg/m^2); MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; AES-S = Apathy Evaluation scale, self-administered version; BDI = Beck depression inventory; SP = sensitivity to punishment; SR = sensitivity to reward; Money received = GBP (£) received at the end of the session; Success rate = number of trials in which the maximum amount of points was received (i.e. 4 points in the reward groups and 0 points in the punishment groups).

Angular reach direction was similar across groups during baseline 1 and baseline 2 (Table 4.2, Figure 4-2, A). Despite the reward-placebo group showing slower RTs than the punish-placebo group during baseline 2 (p = 0.031, Tukey post-hoc test), MTs and RTs were similar for all other phases (Table 4.2).

Table 4.2 Reaction times, movement times and baseline angular reach direction across groups (experiment 1)

		R-LD	P-LD	R-Pl	P-Pl	ANOVA
Baseline 1	RT	317 ± 14	333 ± 17	387 ± 29	333 ± 13	$F_{(3,60)} = 2.48$, $p = 0.070$, $\eta^2 = 0.110$
	MT	286 ± 14	$261 + 10$	278 ± 13	278 ± 11	$F_{(3,60)} = 0.74$, $p = 0.533$, $\eta^2 = 0.036$
	AD	-0.7 ± 0.3	-1.5 ± 0.5	-1.2 ± 0.5	-0.9 ± 0.2	$F_{(3,60)} = 0.91$, $p = 0.440$, $\eta^2 = 0.044$
Baseline 2	RT	305 ± 22	318 ± 18	374 ± 30	287 ± 14	$\mathbf{F_{(3,60)} = 2.99}$, $\mathbf{p = 0.038}$, $\mathbf{\eta^2 = 0.130}$
	MT	249 ± 8	259 ± 14	255 ± 11	237 ± 7	$F_{(3,60)} = 0.72$, $p = 0.545$, $\eta^2 = 0.035$
	AD	-0.7 ± 0.3	-0.4 ± 0.5	-1.2 ± 0.2	-0.9 ± 0.3	$F_{(3,60)} = 0.89$, $p = 0.454$, $\eta^2 = 0.042$
Adaptation	RT	298 ± 21	327 ± 17	371 ± 25	321 ± 23	$F_{(3,60)} = 1.95$, $p = 0.131$, $\eta^2 = 0.089$
	MT	243 ± 6	264 ± 15	270 ± 15	264 ± 13	$F_{(3,60)} = 1.56$, $p = 0.219$, $\eta^2 = 0.041$
Retention	RT	292 ± 24	288 ± 14	338 ± 23	289 ± 12	$F_{(3,60)} = 1.68$, $p = 0.180$, $\eta^2 = 0.078$
	MT	227 ± 8	232 ± 14	245 ± 10	231 ± 9	$F_{(3,60)} = 0.50$, $p = 0.686$, $\eta^2 = 0.024$

Values depict the mean $\pm$ SEM by averaging over consecutive epochs for each participant and group. One-way ANOVA was used to compare mean values across groups. R-LD = reward-levodopa; P-LD = punishment-levodopa; R-Pl = reward-placebo; P-Pl = punishment-placebo; RT = reaction time (ms); MT = movement time (ms); AD = angular reach direction (º).
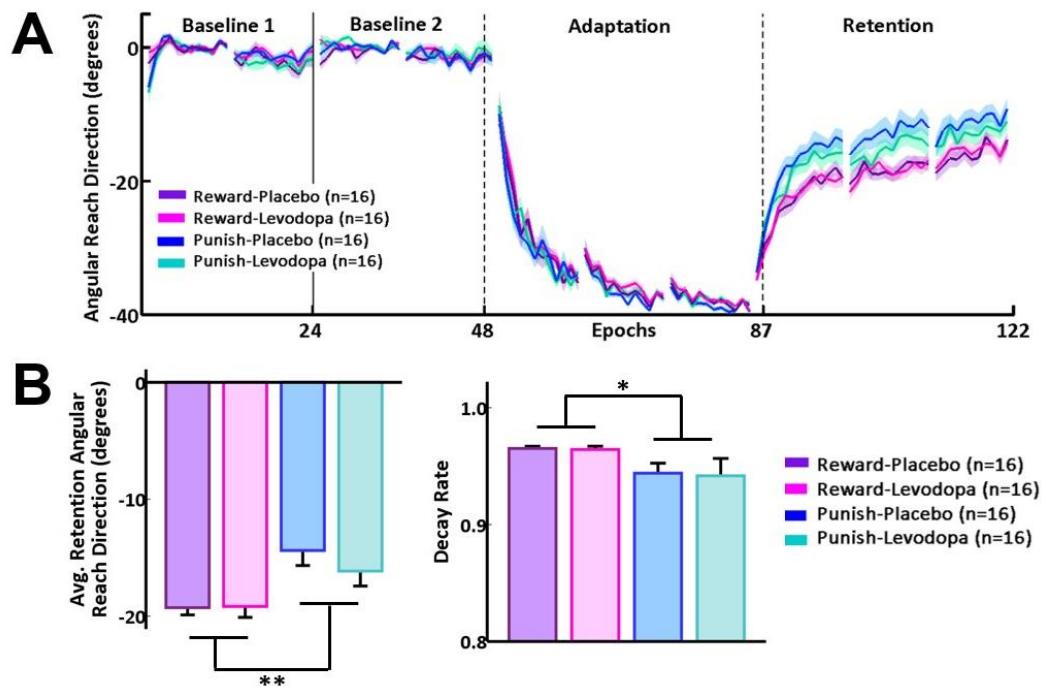
Figure 4-2 Experiment 1: reward was associated with greater retention than punishment, independently of levodopa or placebo

A) Angular reach direction (°) during baseline, adaptation and retention for the four groups (n = 16 each). The x-axis indicates the number of epochs (average across six trials). The plots represent mean $\pm$ standard error of the mean (SEM). The solid vertical line indicates the 60 minutes wait period after the administration of levodopa or placebo. The dashed vertical lines indicate the actual beginning and end of first and last adaptation blocks (i.e. the first adaptation block started with 6 baseline "vision" trials, and the last adaptation block finished with 6 retention "no vision" trials). B) Bar graph on the left: average ($\pm$ SEM) angular reach direction (°) for each group during the retention phase. The reward groups retained significantly more than the punishment groups [$F_{(1,60)}$ = 13.78, $p < 0.001$, η^2 = 0.187] irrespective of levodopa or placebo status. Bar graph on the right: model parameter A (decay rate, higher values signifying larger retention, average $\pm$ SEM) across groups. *$p < 0.05$, **$p < 0.001$

4.3.1.2 Feedback and Levodopa did not influence online error-reduction during visuomotor adaptation

Figure 4-2, A, shows the angular reach direction across epochs in the four groups. As expected, all groups showed clear error-reduction in response to the visuomotor perturbation with a main effect of block [$F_{(1.1,68.8)}$ = 403.3, $p < 0.001$, η^2 = 0.87, Greenhouse-Geisser corrected]. However, contrary to the expectations, adaptation was not differentially affected by punishment versus reward [$F_{(1,60)}$ = 1.36, $p = 0.247$, η^2 = 0.022], or by levodopa versus placebo [$F_{(1,60)}$ = 0.74, $p = 0.393$, η^2 = 0.012; Figure 4-2, A].

4.3.1.3 Reward enhanced retention but was not affected by levodopa

In the retention phase, there was a main effect of block [$F_{(1.9,116.5)}$ = 374.1, $p < 0.001$, η^2 = 0.862, Huynh-Feldt corrected] suggesting participants gradually returned towards baseline performance (Figure 4-2, A). As predicted, there was a main effect of feedback [$F_{(1,60)}$ = 13.78, $p < 0.001$, η^2 = 0.187] with reward leading to greater retention than punishment (Figure 4-2, B and C). However, levodopa had no effect on retention [$F_{(1,60)}$ = 0.60, $p = 0.440$, η^2 = 0.010]. The lack of block*feedback [$F_{(1.9,116.5)}$ = 0.71, $p = 0.489$, η^2 = 0.012, Huynh-Feldt corrected], feedback*drug [$F_{(1,60)}$ = 0.76, p = 0.385, η^2 = 0.013], or block*feedback*drug [$F_{(1.9,116.5)}$ = 0.38, $p = 0.679$, η^2 = 0.006, Huynh-Feldt corrected] interaction, suggests that the effect of feedback was independent of block and drug status.

4.3.1.4 Model-based analysis confirmed model-free results

In order to estimate learning and retention rates from all available data, I also performed a model-based analysis by applying a single-rate state-space model to each participant's entire data set (Donchin et al., 2003; Galea et al., 2015; Tanaka et al., 2009; Thoroughman and Shadmehr, 2000). The model was able to explain a substantial amount of variance (R^2: 0.79: reward-placebo, 0.80: reward-levodopa,

0.79: punishment-placebo, 0.78: punishment-levodopa), with a similar goodness of fit across groups [$F_{(3,60)}$ = 1.02, p = 0.388, η^2 = 0.049].

The SSM confirmed that error-reduction during adaptation phase (learning parameter B, mean $\pm$ SEM 0.32 $\pm$ 0.04, median 0.31: reward-placebo; 0.31 $\pm$ 0.03, median 0.34: reward-levodopa; 0.41 $\pm$ 0.04, median 0.29: punishment-placebo; 0.40 $\pm$ 0.06, median 0.34: punishment-levodopa) was not was not differentially affected by punishment versus reward [ART test, $F_{(1,60)}$ = 0.32, p = 0.574, η^2 = 0.005], or by levodopa versus placebo [ART test, $F_{(1,60)}$ = 0.05, p = 0.824, η^2 = 0.001]. In addition, there was no correlation across participants between executive functions (FAB, Stroop time and Stroop error scores) and the learning parameter B (FAB: Spearman rho, ρ = -0.002, p = 0.984; Stroop time: ρ = -0.199, p = 0.131; Stroop errors: ρ = -0.052, p = 0.694).

Retention, represented by the decay parameter A (mean $\pm$ SEM 0.96 $\pm$ 0.002, median 0.97: reward-placebo; 0.96 $\pm$ 0.003, median 0.97: reward-levodopa; 0.94 $\pm$ 0.008, median 0.95: punishment-placebo; 0.94 $\pm$ 0.01, median 0.95: punishment-levodopa), was not affected by levodopa [ART test, $F_{(1,60)}$ = 0.90, p = 0.346, η^2 = 0.015] but was influenced by feedback [ART test, $F_{(1,60)}$ = 9.20, p = 0.004, η^2 = 0.015], with reward leading to greater retention than punishment (Figure 4-2, B). Similarly to the learning parameter B, the decay parameter A was also not correlated with executive functions scores (FAB: Spearman rho, ρ = -0.054, p = 0.670; Stroop time: ρ = -0.227, p = 0.084; Stroop errors: ρ = 0.069, p = 0.603).

In summary, experiment 1 showed that reward caused higher retention of the newly acquired motor memory than punishment, but levodopa showed no effects on either error-reduction or retention.

4.3.2 Experiment 2

4.3.2.1 Demographics, cognitive and kinematic parameters were similar across groups

In experiment 2, I investigated the effect of haloperidol during motor adaptation under reward or punishment conditions by comparing three groups: reward-haloperidol (n = 16, age 21-39 years, 26.1 $\pm$ 5, n = 13 females), punishment-haloperidol (n = 16, age 19-37, 23.1 $\pm$ 4.6, n = 9 females), and neutral-placebo (n = 14, age 19-32, 24.6 $\pm$ 3.5, n = 10 females). As shown in Table 4.3, the groups were similar for demographics and cognitive scores. The two haloperidol groups received a similar amount of money at the end of the session [R-Halo = £17.7 $\pm$ 0.6, mean $\pm$ SEM; P-Halo = £18 $\pm$ 0.2; $t_{(30)}$ = -0.53, p = 0.605, η^2 = 0.009], while the neutral group received £20 at the end of the study, irrespective of performance. The success rate was similar between the two groups [R-Halo = 419 (12.1), number (%), P-Halo = 407 (11.8), $\lambda^2_{(1)}$ = 0.19, p = 0.656, phi = 0.308]. Participants' alertness at the end of the session was similar between groups [R-Halo = 7.1 $\pm$ 0.6, mean $\pm$ SEM, P-Halo = 5.6 $\pm$ 0.4, N-Pl = 6.9 $\pm$ 0.7; $F_{(2,43)}$ = 2.14, p = 0.130, η^2 = 0.090]. Furthermore, 19 (59.4%) of the participants in the haloperidol groups believed they had received placebo, thus showing that the blinding protocol was effective.

Table 4.3 Participants' characteristics (experiment 2)

	R-Halo	P-Halo	N-Pl	$\lambda^2_{(2)}$ / $F_{(2,43)}$	p	Effect size
BMI	23.5 ± 1.4	21.8 ± 1.1	22.1 ± 0.8	0.96	0.619	0.021
High education	15 (93.8)	13 (81.3)	13 (92.9)	1.42	0.598	0.185
MMSE	29.4 ± 0.3	29.7 ± 0.1	29.7 ± 0.2	2.22	0.330	0.049
FAB	17.1 ± 0.4	17.6 ± 0.1	17.6 ± 0.2	1.04	0.593	0.023
Stroop Errors	0.5 ± 0.2	1.5 ± 0.5	0.7 ± 0.2	0.71	0.701	0.016
Stroop Time	3.9 ± 0.9	5.5 ± 1.7	4.6 ± 1.1	0.35	0.841	0.008
AES-S	27.9 ± 1.5	31 ± 1.6	28.6 ± 1.9	5.06	0.080	0.112
BDI	3.3 ± 1.1	6 ± 1.7	3.1 ± 1	2.85	0.240	0.063
SP	4.8 ± 0.6	4.1 ± 0.6	3.0 ± 0.8	2.04	0.142	0.087
SR	5.2 ± 0.6	5.3 ± 0.5	5.0 ± 0.5	0.08	0.924	0.004

Categorical values are indicated as number and percentages (%), numeric values as mean ± SEM. Comparison between proportions (education) is made with Chi-square test, comparison between means with one-way ANOVA or Kruskal-Wallis (BMI, MMSE, FAB, Stroop, AES-S, BDI). Effect size is provided as phi for Chi-square test, partial eta for ANOVA and epsilon-squared for Kruskal-Wallis.

R-Halo = reward-haloperidol (n = 16); P-Halo = punishment-haloperidol (n = 16); N-Pl = neutral-placebo (n = 14); High education = participants with ≥ 15 years of education; BMI = body mass index (Kg/m²); MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; AES-S = Apathy Evaluation scale, self-administered version; BDI = Beck depression inventory; SP = sensitivity to punishment; SR = sensitivity to reward.

Angular reach direction was similar across the two haloperidol groups during baseline 1 and baseline 2 (Table 4.4, Figure 4-3, A). Apart from baseline 1, where R-Halo had slower MT than P-Halo (p = 0.006, post-hoc Tukey test), MTs and RTs were similar between groups for all other phases (Table 4.4).

Table 4.4 Reaction times, movement times and baseline angular reach direction across groups (experiment 2)

		R-Halo	P-Halo	N-Pl	ANOVA
Baseline 1	**RT**	352$\pm$10	350$\pm$11	362$\pm$18	$F_{(2,43)}$ = 0.2, p = 0.799, η^2 = 0.010
	MT	303$\pm$6	269$\pm$8	293$\pm$8	**$F_{(2,43)}$ = 5.5, p = 0.007, η^2 = 0.205**
	AD	-0.9$\pm$0.4	-1.2$\pm$0.3	-0.8$\pm$0.5	$F_{(2,43)}$ = 0.35, p = 0.705, η^2 = 0.016
Baseline 2	**RT**	346$\pm$9	353$\pm$10	346$\pm$13	$F_{(2,43)}$ = 0.14, p = 0.868, η^2 = 0.007
	MT	269$\pm$7	269$\pm$6	277$\pm$7	$F_{(2,43)}$ = 0.39, p = 0.677, η^2 = 0.018
	AD	-0.3$\pm$0.5	-0.9$\pm$0.3	-0.6$\pm$0.3	$F_{(2,43)}$ = 0.60, p = 0.552, η^2 = 0.027
Adaptation	**RT**	343$\pm$8	368$\pm$15	354$\pm$15	$F_{(2,43)}$ = 0.97, p = 0.388, η^2 = 0.043
	MT	277$\pm$11	279$\pm$7	277$\pm$9	$F_{(2,43)}$ = 0.01, p = 0.990, η^2 = 0.000
Retention	**RT**	351$\pm$8	348$\pm$10	353$\pm$18	$F_{(2,43)}$ = 0.04, p = 0.958, η^2 = 0.002
	MT	262$\pm$7	250$\pm$6	267$\pm$9	$F_{(2,43)}$ = 1.49, p = 0.236, η^2 = 0.065

Values depict the mean $\pm$ SEM by averaging over consecutive epochs for each participant and group. A one-way ANOVA was used to compare mean values across groups.

R-Halo = reward-haloperidol (n = 16); P-Halo = punishment-haloperidol (n = 16); N-Pl = neutral-placebo (n = 14); RT = reaction time (ms); MT = movement time (ms); AD = angular reach direction (°).

4.3.2.2 Feedback and haloperidol did not influence error-reduction during visuomotor adaptation

Figure 4-3, A, shows the angular reach direction across epochs in the three groups. All groups showed a similar degree of error-reduction in response to the visuomotor perturbation [$F_{(2,43)}$ = 0.219, p = 0.805, η^2 = 0.930], with a main effect of block reflecting the progressive improvement [$F_{(2.1,47.1)}$ = 567.79, p < 0.001, η^2 = 0.930, Greenhouse-Geisser corrected].
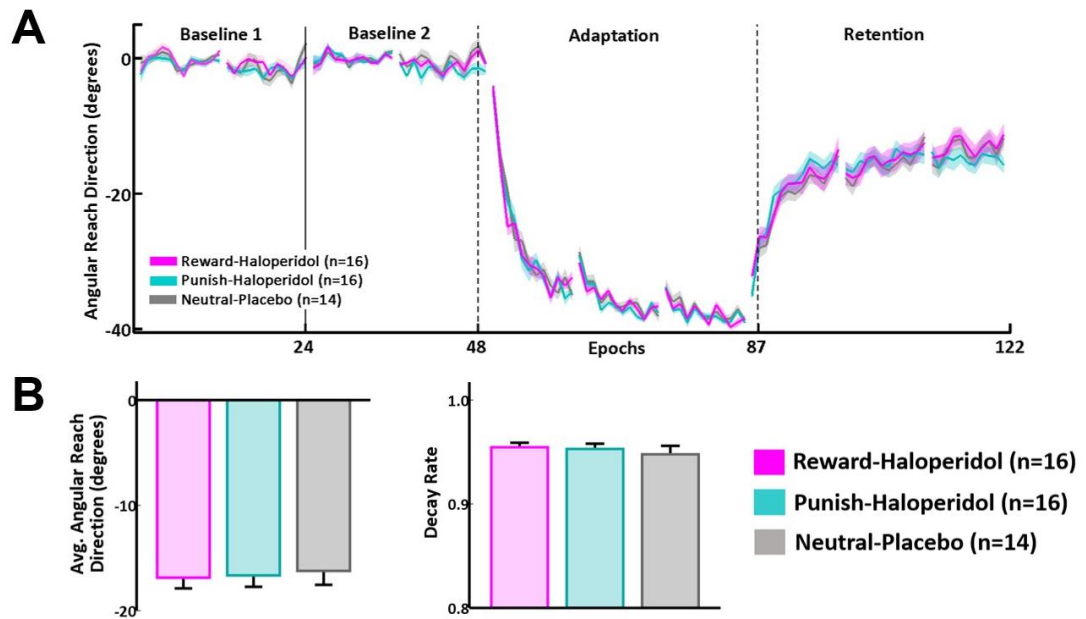
Figure 4-3 Experiment 2: reward was not associated with greater retention in participants who had received haloperidol.

A) Angular reach direction (^{o}) during baseline, adaptation and retention for the three groups. The x-axis indicates the number of epochs (average across six trials). The plots represent mean $\pm$ SEM. The solid vertical line indicates the 120 minutes wait period after the administration of haloperidol or placebo. The dashed vertical lines indicate the actual beginning and end of first and last adaptation block (i.e. the first adaptation block started with 6 baseline "vision" trials, and the last adaptation block finished with 6 retention trials). B) Bar graph on the left: average ($\pm$ SEM) angular reach direction (^{o}) for each group during the retention phase. Bar graph on the right: model parameter A (decay rate, higher values signifying larger retention, average $\pm$ SEM) across groups. The three groups presented a similar amount of retention.

4.3.2.3 Retention under haloperidol was similar for reward and punishment, and comparable to the neutral-placebo condition

Similarly to experiment 1, during the retention phase there was a main effect of block suggesting all participants gradually returned towards baseline performance [$F_{(1.6,67.8)}$ = 206.85, $p < 0.001$, $\eta^2 = 0.828$, Huynh-Feldt corrected, Figure 4-3, A]. Crucially, all the three groups displayed a similar level of memory retention [$F_{(2,43)} = 0.08$, $p = 0.922$, $\eta^2 = 0.004$; Figure 4-3, A and B]. In other words, the beneficial effect of reward versus punishment on retention was no longer observed under haloperidol, and the haloperidol groups displayed a similar level of memory retention to the neutral-placebo group, thus suggesting that haloperidol disrupted the effect of reward on retention.

4.3.2.4 The reward-haloperidol group retained less than the reward-placebo/levodopa groups

To further explore this result, I compared retention (average AD across the three retention blocks) in the reward-haloperidol group (experiment 2) with a combined reward-placebo/levodopa group (experiment 1). I found that the reward-placebo/levodopa group retained significantly more than the reward-haloperidol group [R-Pl/LD = -19.2 $\pm$ 0.5º, mean $\pm$ SEM; R-Halo = -16.9 $\pm$ 1º; independent t-test: $t_{(46)} = -2.22$, $p = 0.031$ 2-tailed, $d = 0.649$], thus further supporting the hypothesis that haloperidol disrupted the positive effects of reward on retention.

4.3.2.5 Model-based analysis confirmed model-free results

To estimate learning and retention rates in the three groups, I also performed a model-based analysis. The SSM was able to explain a substantial amount of variance (R^2: 0.80: reward-haloperidol; 0.80: punish-placebo; 0.81: neutral-placebo), with a similar goodness of fit across groups [$F_{(2,45)} = 0.26$, $p = 0.773$, $\eta^2 = 0.012$].

The model estimates confirmed the model-free results. Specifically, both the learning [parameter B, mean $\pm$ SEM 0.32 $\pm$ 0.03 reward-haloperidol; 0.34 $\pm$ 0.04 punishment-haloperidol; 0.35 $\pm$ 0.05 neutral-placebo; $F_{(2,45)}$ = 0.22, p = 0.800, η^2 = 0.010] and decay rate [parameter A, reflecting retention, mean $\pm$ SEM 0.95 $\pm$ 0.02 reward-haloperidol; 0.95 $\pm$ 0.005 punishment-haloperidol; 0.95 $\pm$ 0.008 neutral placebo; $F_{(2,45)}$ = 0.35, p = 0.709, η^2 = 0.016, Figure 4-3, B] were similar across groups.

No correlation was found between executive functions scores and either the learning parameter B (FAB: Pearson r = 0.201, p = 0.181; Stroop time: r = -0.007, p = 0.964; Stroop errors: r = -0.026, p = 0.866) or retention parameter A (FAB: Pearson r = -0.181, p = 0.229; Stroop time: r = -0.095, p = 0.531; Stroop errors: r = -0.149, p = 0.324).

In line with the model-free analysis results, the reward-placebo/levodopa group showed a significantly higher decay rate (i.e. higher retention, mean $\pm$ SEM 0.96 $\pm$ 0.01, median 0.97) than the reward-haloperidol group [Mann-Whitney: U = 157, p = 0.030 2-tailed, r = -0.311].

In summary, experiment 2 showed that, in participants who received the dopamine-antagonist haloperidol, the positive effect of reward versus punishment on motor memory retention was disrupted.

4.3.2.6 Reward under placebo or levodopa enhanced retention specifically during trials with a fast reaction time

As reaction times in experiment 2 were generally slower than in experiment 1, I reasoned that the non-significant difference between reward and punishment within experiment 2 could have been simply a result of a shift in the underlying mechanism driving adaptation (Haith et al., 2015; Leow et al., 2017). To address this possibility, I performed an additional analysis in which I compared groups separately for trials with either fast (< 326 ms) or slow (> 326ms) reaction times (Figure 4-4).

Slow RTs

Fast RTs

A Exp 1

Baseline 1 | Baseline 2 | Adaptation | Retention

Angular Reach Direction (degrees)

Reward-Placebo (n=16)
Reward-Levodopa (n=16)
Punish-Placebo (n=16)
Punish-Levodopa (n=16)

Epochs

B

Baseline 1 | Baseline 2 | Adaptation | Retention

Angular Reach Direction (degrees)

Reward-Placebo (n=16)
Reward-Levodopa (n=16)
Punish-Placebo (n=16)
Punish-Levodopa (n=16)

Epochs

C Exp 2

Baseline 1 | Baseline 2 | Adaptation | Retention

Angular Reach Direction (degrees)

Reward-Haloperidol (n=16)
Punish-Haloperidol (n=16)
Neutral-Placebo (n=14)

Epochs

D

Baseline 1 | Baseline 2 | Adaptation | Retention

Angular Reach Direction (degrees)

Reward-Haloperidol (n=16)
Punish-Haloperidol (n=16)
Neutral-Placebo (n=14)

Epochs

161

Figure 4-4 Angular reach direction in trials with slow (> 326ms) versus fast (< 326) reaction times (RTs, ms).

The plots represent mean ± SEM. The solid vertical line indicates the wait period after the administration of drug or placebo. The dashed vertical lines indicate the actual beginning and end of first and last adaptation block (i.e. the first adaptation block started with 6 baseline "vision" trials, and the last adaptation block finished with 6 retention trials). A) Experiment 1, slow RTs (> 326 ms). Performance was similar across groups. B) Experiment 1, fast RTs (< 326 ms). Reward was associated with greater retention than punishment, independently of levodopa or placebo. C) Experiment 2, slow RTs (> 326 ms). Performance was similar across groups. D) Experiment 2, fast RTs (< 326 ms). Performance was similar across groups.

In experiment 1, AD during baseline 1 and baseline 2 was similar between groups for slow [respectively, baseline 1: $F_{(3,36)}$ = 0.99, p = 0.406, η^2 = 0.083; baseline 2: $F_{(3,31)}$ = 0.34, p = 0.868, η^2 = 0.025] and fast [baseline 1: $F_{(3,33)}$ = 2.19, p = 0.111, η^2 = 0.185; baseline 2: $F_{(3,42)}$ = 0.43, p = 0.730, η^2 = 0.033] reaction time trials.

All groups in experiment 1 showed error-reduction in response to the perturbation with a main effect of block, both in the slow [$F_{(1.2,30)}$ = 111.7, p < 0.001, η^2 = 0.82, Greenhouse-Geisser corrected; Figure 4-4, A] and in the fast [$F_{(1.1,40)}$ = 108.5, p < 0.001, η^2 = 0.76, Greenhouse-Geisser corrected; Figure 4-4, B] reaction time trials. This was not differentially affected by punishment versus reward in either the slow [$F_{(1,25)}$ = 0.31, p = 0.862, η^2 = 0.001] or the fast [$F_{(1,25)}$ = 0.31, p = 0.862, η^2 = 0.001] reaction time trials. Similarly, error-reduction under the perturbation was not affected by levodopa versus placebo in the slow [$F_{(1,25)}$ = 0.38, p = 0.542, η^2 = 0.015; Figure 4-4, A] or in the fast [$F_{(1,35)}$ = 0.54, p = 0.467, η^2 = 0.015; Figure 4-4, B] RT trials.

In the retention phase, we found a main effect of block for both slow [$F_{(2,36)}$ = 35.8, p < 0.001, η^2 = 0.665] and fast [$F_{(1.3, 64.6)}$ = 131, p < 0.001, η^2 = 0.732, Greenhouse-Geisser corrected] reaction time trials. Levodopa had no effect on retention in either slow [$F_{(1,18)}$ = 2.58, p = 0.126, η^2 = 0.125] or fast [$F_{(1,48)}$ = 0.15, p = 0.697, η^2 = 0.003] reaction time trials. Interestingly, the positive effect of reward on retention was not present in slow reaction time trials [$F_{(1,18)}$ = 1.62, p = 0.219, η^2 = 0.083], but was present in fast reaction time trials [$F_{(1,48)}$ = 11.34, p = 0.002, η^2 = 0.191] (Figure 4-4, A, B). There was no interaction of feedback*drug in slow [$F_{(1,18)}$ = 4.36, p = 0.051, η^2 = 0.195] and in fast [$F_{(1,48)}$ = 0.23, p = 0.634, η^2 = 0.005] reaction time trials.

In summary, the analysis of slow versus fast reaction time trials revealed that the positive effect of reward versus punishment on motor memory retention observed in experiment 1 was mainly present during trials with fast reaction times.

4.3.2.7 Under haloperidol, adaptation and retention were unaffected by feedback, either for slow or fast reaction time trials

In experiment 2, AD during baseline 1 and baseline 2 was similar between groups for slow [respectively, baseline 1: $F_{(2,36)}$ = 1.58, p = 0.221, η^2 = 0.085; baseline 2: $F_{(3,41)}$ = 0.58, p = 0.565, η^2=0.029 ; Figure 4-4, C] and fast [baseline 1: $F_{(2,24)}$ = 2.1, p = 0.148, η^2 = 0.160; baseline 2: $F_{(2,22)}$ = 0.30, p = 0.742, η^2 = 0.029 ; Figure 4-4, D] reaction time trials.

All groups showed a similar degree of error-reduction in response to the visuomotor perturbation, both for slow [$F_{(2,32)}$ = 0.236, p = 0.791, η^2 = 0.015] and fast [$F_{(2,19)}$ = 0.178, p = 0.838, η^2 = 0.018] reaction time trials. In addition, all the three groups displayed a similar level of memory retention for both slow [$F_{(2,35)}$ = 0.07, p = 0.930, η^2 = 0.004] and fast [$F_{(2,17)}$ = 1.23, p = 0.317, η^2 = 0.126] reaction time trials.

In summary, there was no significant difference between reward and punishment under haloperidol irrespective of reaction time speed.

4.4 Discussion

Aim of this study was to investigate the role of dopamine during a motor adaptation task under reward or punishment conditions. In experiment 1, reward enhanced motor memory retention relative to punishment. Surprisingly, this was not affected by levodopa. I hypothesized that this was due to young healthy participants already exhibiting optimal dopamine levels. In support of this, experiment 2 showed that the effect of reward on retention was disrupted by the dopamine-antagonist haloperidol.

4.4.1 Reward led to higher memory retention than punishment

Experiment 1 showed that reward delivered during adaptation phase led to higher motor memory retention. This is in line with previous research on healthy participants (Abe et al., 2011; Galea et al., 2015; Wächter et al., 2009), as well as with my data in stroke patients showed in Chapter 3 (Quattrocchi et al., 2017). Reward has been associated with increased retention across multiple motor learning tasks, ranging from sequence learning (Wächter et al., 2009; Wilkinson et al., 2015), to skill learning (Abe et al., 2011), visuomotor adaptation (Galea et al., 2015; Shmuelof et al., 2012) and force-field adaptation tasks (Quattrocchi et al., 2017). Interestingly, here the effect of reward on retention was mainly observed during fast reaction time trials. This may suggest that reward doesn't lead to an increased use of explicit strategies which are only expressible during slow reaction time trials, but rather to a greater engagement of a reinforcement-based process that is expressible at fast reaction times (Haith et al., 2015; Haith and Krakauer, 2013; Leow et al., 2017; Wong et al., 2017).

Dopaminergic neurons in VTA increase their firing in response to the presentation of rewards and to conditioned stimuli predicting reward (Schultz, 2016a; Volman et al.,

2013). At the same time, dopaminergic neurons from the rostro-lateral VTA, and, to a lesser extent from the rostro-medial substantia nigra, project to M1 (Hosp et al., 2011). The integrity of these projections is necessary for retention of new skills (Jonas A. Hosp and Luft, 2013). On this basis, I hypothesized that reward increases motor memory retention through the release of dopamine on M1. Therefore, my prediction was that the levodopa would potentiate the beneficial effect of reward on retention.

4.4.2 Levodopa had no effect on error-reduction or on retention

Surprisingly, levodopa did not influence neither error-reduction during adaptation nor the effect of reward on retention. Levodopa, the most widely and effective treatment used in Parkinson's disease (PD), is converted to dopamine in the brain. Although motor and some cognitive symptoms in PD are improved by levodopa, others, such as motor sequence learning and probabilistic reversal learning, appear to be worsened (Cools et al., 2001; A. Feigin et al., 2003; Ghilardi et al., 2007; Graef et al., 2010; Kwak et al., 2010; Swainson et al., 2000). This paradoxical effect has been explained by the "dopamine overdose hypothesis", suggesting that the effect of dopaminergic therapy on a given function is determined by the baseline dopamine levels in the brain regions mediating that function (Vaillancourt et al., 2013). Specifically, cognitive functions attributed to VTA-innervated regions, relatively spared in PD, are theorized to be normal at baseline and to worsen with dopamine replacement, as this causes excessive levels of dopamine in these regions. Young healthy participants are presumed to have optimal endogenous baseline dopamine levels. Consequently, I reasoned that the lack of effect of levodopa observed here could be due to the already optimal dopaminergic levels in young healthy participants, rather than to the non-involvement of dopaminergic pathways. This hypothesis would be in agreement with evidence showing that premedication with levodopa leads to improved motor skill functions in elderly but not in young

individuals (Flöel et al., 2008b). Similarly, in a reinforcement-learning task, older adults with lower levels of performance at baseline improved following levodopa administration (Chowdhury et al., 2013). Healthy aging, in fact, is associated with diminished dopaminergic function (Karrer et al., 2017), and levodopa effects on motor memory in the elderly have been correlated to the increase of dopamine release in the striatum (Flöel et al., 2008a). One could object that, in disagreement with these results, the dopamine overdose hypothesis would predict a deterioration of performance under levodopa compared to placebo. However, factors such as optimal levels of dopamine transporters (DAT), a membrane protein which clears dopamine from the synapse; a normal cognitive reserve; and the lack of dopamine receptor sensitization through chronic dopaminergic therapy, may play a role in safeguarding young healthy participants against dopamine oversaturation (Vo et al., 2016). On this basis, I hypothesized that, if reward increases retention through dopaminergic mechanisms, then by antagonizing dopamine function we should observe a deterioration of this effect.

4.4.3   Haloperidol reduced the effect of reward on motor memory retention

To investigate further this hypothesis, I performed a second experiment with the same paradigm under the D1/D2-antagonist haloperidol. I used a non-selective dopamine-receptor antagonist as motor learning depends on both D1- and D2-receptors mechanisms (Molina-Luna et al., 2009), probably through the activation of the intracellular phospholipase-C pathway in M1 (Rioult-Pedotti et al., 2015).

Under haloperidol, the reward group showed similar retention not only to the punishment, but also to the neutral-placebo group. Importantly, this was significantly less than the retention of the reward-levodopa/placebo group from experiment 1, thus supporting the hypothesis of a role of dopamine in mediating the positive effects of reward on motor memory retention.

4.4.4 Through which dopaminergic pathways does reward increase retention?

This study shows that reward increases retention through dopaminergic pathways. But which pathways are involved? Multiple reports suggest a role of M1 in motor memories retention (Galea and Celnik, 2009; Hadipour-Niktarash et al., 2007; Muellbacher et al., 2002; Reis et al., 2009; Richardson et al., 2006). Anodal M1 tDCS, a non-invasive form of brain stimulation known to increase excitability, improved retention in a visuomotor rotation reaching task (Galea et al., 2011). M1 may store new visuomotor mappings, reflected by increased activity of neurons in motor areas whose preferred direction in hand space matches the required trajectory (Tanaka et al., 2009). Studies in rats showed that motor memory consolidation requires the integrity of dopaminergic meso-cortical projections to M1 (Hosp and Luft, 2013). Dopamine has multiple effects on rodents' M1: it stabilizes motor representations and enhances cortical excitability (Hosp et al., 2009); increases the expression of learning-related genes (Hosp et al., 2011); and induces long-term potentiation (Hosp and Luft, 2013). Dopaminergic projections to M1 come mainly from the rostro-lateral VTA and the rostro-medial portion of the substantia nigra, i.e. they are part of the meso-cortico-limbic system, evaluating the value and behavioural significance of environmental stimuli (Hosp and Luft, 2013). Cortically projecting dopaminergic neurons are much more abundant in humans/primates than in rodents (German and Manaye, 1993), and can be found also beyond the VTA and the substantia nigra (Berger et al., 1991; Williams and Goldman-Rakic, 1998). This reflects an increase in complexity of cortical dopaminergic innervation during phylogeny. However, dopaminergic signalling in humans seems to have similar motor learning functions to rodents (Hosp and Luft, 2013). In particular, in humans, single doses of levodopa or the D2-receptor agonist cabergoline facilitated practice-dependent plasticity in M1 (Flöel et al., 2005; Meintzschel and Ziemann, 2006), whereas haloperidol decreased it (Meintzschel and Ziemann, 2006). Therefore, dopaminergic projections to M1 seem to play a role in motor memory retention.

Yet, it is known that reward not only modulates activity in various local regions other than M1 (such as the prefrontal and the orbitofrontal cortex) (Bissonette and Roesch, 2015), but also alters the interactions between widespread regions that form task-specific networks. Alternative hypotheses could be, for example, that reward potentiates the use of strategies through the release of dopamine on the prefrontal cortex, or that it increases valence of action outcomes through the orbitofrontal cortex (O'Doherty, 2007). However, this would have likely reflected in altered reward-based performance also during the adaptation phase, which was not the case here. Furthermore, the higher retention for rewarded trials with fast but not slow reaction time supports the role of non-explicit learning mechanisms. On this bases, my hypothesis is that dopaminergic projections to M1 act by facilitating the occurrence of plastic changes in response to rewarding stimuli.

4.4.5 Punishment showed no effect on error-reduction during visuomotor adaptation

Contrary to previous findings (Galea et al., 2015), I found no benefit of punishment versus reward on error-reduction in response to the perturbation. Both studies used a visuomotor perturbation, but the magnitude of the perturbation was larger here than in the cited previous study (respectively 40° versus 30° in Galea et al., 2015). As the degree of explicit awareness is known to increase as a function of perturbation size (Werner et al., 2015), error-reduction here may have involved a greater use of explicit strategies than in the study by Galea (Galea et al., 2015). With smaller perturbations, the motivational salience of punishment (loss aversion) (De Martino et al., 2010) may motivate participants to utilise a strategy (and thus show faster error-reduction) in circumstances in which they are more difficult to develop. Conversely, in the present study punishment may have been unable to potentiate further an already well-represented explicit strategy. Therefore, my hypothesis is

that punishment may enhance performance during adaptation paradigms by increasing participants' use of a cognitive strategy, and that this becomes overtly beneficial in cases where this strategy is not yet optimally implemented. However, I am aware that this would not explain all the literature results, and other mechanisms, such as increased motor noise (Steel et al., 2016) or cerebellar mechanisms (Galea et al., 2015) could play a role. Additionally, the lack of effect makes it hard to evaluate the role of dopamine in motor learning under punishment.

4.4.6 Strengths and limitations

The between-subjects pharmacological approach adopted in this study has the advantage of directly manipulating the dopaminergic system. Furthermore, the debriefing scores, and the lack of adverse events, confirmed that blinding was maintained. Nevertheless, I am aware of the limitations of this study.

In particular, I acknowledge that pharmacological manipulations are non-specific and have widespread effects (Crockett and Fehr, 2014). Therefore, as discussed above, the role of dopaminergic pathways to M1 in motor memory retention, despite plausible, remains at this stage speculative, and more studies are needed to directly investigate the dopaminergic circuitry in motor learning. Moreover, the genetic variability of dopamine receptor isoforms and dopamine cleaving or metabolizing enzymes could influence the effect of exogenous dopaminergic stimulation (Pearson-Fuhrhop et al., 2013). This confounder could have been ruled out by using a within-subjects design, however this is not advisable in learning tasks as it introduces the problem of carry-over effects (Crockett and Fehr, 2014).

The adaptation task used here does not disentangle the differential effects of positive or negative reinforcement on the multiple learning processes now known to influence performance (Bond and Taylor, 2015; Huberdeau et al., 2015; McDougle et

170

al., 2015; Smith et al., 2006; Taylor et al., 2014). For example, when participants made no vision reaching movements they were simply instructed to "reach towards the target even without vision". As this instruction was relatively ambiguous, the observed dopamine-dependent effect of reward on retention could either be due to participants maintaining the use of an explicit cognitive strategy or reflecting a highly stable reinforcement-based learning process (Bond and Taylor, 2015; Huberdeau et al., 2015; McDougle et al., 2015; Smith et al., 2006; Taylor et al., 2014). However, the fact that higher retention was observed for rewarded trials with fast rather than slow reaction times is against the increased use of an explicit strategy (Haith et al., 2015; Haith and Krakauer, 2013; Leow et al., 2017; Wong et al., 2017). I provide here evidence for a role of dopamine in reward-based adaptation tasks, but future work is needed to decompose the role of reward and dopamine in the various subprocesses playing a role in these tasks.

4.4.7 Implications and conclusions

This is the first direct pharmacological investigation on the role of dopamine in motor adaptation tasks under reward or punishment conditions. The results support the hypothesis that reward increases motor retention through dopaminergic pathways. Despite the lack of effect on young healthy participants, a beneficial effect of external dopaminergic stimulation could be possible when the dopaminergic system is challenged by aging or pathological conditions, such as stroke. This could have possible applications in potentiating the effect of reward on motor memory retention in elderly or stroke patients through exogenous dopaminergic stimulation, thus increasing the potential benefit of using motor adaptation paradigms in neurorehabilitation (Quattrocchi et al., 2017).

Chapter 5.

Reward and levodopa in motor adaptation tasks in healthy elderly – a pharmacological study

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5.1   Introduction

As shown in the previous chapters, reward-based feedback has been suggested to increase the retention of a new motor behaviour in a series of motor learning tasks (Abe et al., 2011; Galea et al., 2015; Wächter et al., 2009; Wilkinson et al., 2015), not only in healthy young adults (Chapter 4) but also in chronic stroke survivors (Chapter 3). This effect has been hypothesized to be mediated by dopaminergic mechanisms, likely through the release of dopamine on M1 (Chapter 4). However, the administration of the dopamine precursor levodopa failed to enhance motor memory retention in young healthy participants (Chapter 4). I attributed this to the already optimal levels of dopamine in participants of this age group, which would make any pharmacological stimulation ineffective. On these premises, a beneficial effect of external dopaminergic stimulation would then be possible in cases where the dopaminergic system is challenged.

A physiological example of dopaminergic degeneration is given by healthy aging. The dopaminergic system declines at around 5% to 10% per decade across adulthood (Karrer et al., 2017). The decline of the dopaminergic function has been related to the worsening, with age, of a range of cognitive functions, such as decision making, learning, and attentional control, probably through the decrease of reward-based learning (Vink et al., 2015).

The effects of aging on adaptive motor learning are still controversial (Buch et al., 2003). In particular, some studies found no age-related adaptation deficits (Bock and Schneider, 2002; Buch et al., 2003; Etnier and Landers, 1998; Roller et al., 2002), while others suggest that aging results in slower and decreased adaptation (Fernandez-Ruiz et al., 2003; McNay and Willingham, 1998; Nemanich and Earhart, 2015; Teulings et al., 2002). Interestingly, experiments which yielded adaptation deficits in elderly found no corresponding decrease of after-effects (Buch et al., 2003; Fernandez-Ruiz et al., 2003; McNay and Willingham, 1998). One hypothesis is that elderly are

impaired at using cognitive strategies, due to the reduced dopaminergic activity in the prefrontal cortex, and that, therefore, the explicit component of adaptation may be more impaired than the implicit one, leaving after-effects unaffected (Bock, 2005; Heuer and Hegele, 2014). In addition, a decline of reward-based reinforcement learning has also been suggested to contribute to the worsened performance in visuomotor adaptation tasks in elderly subjects (Heuer and Hegele, 2014). Thus, age-related decline of the dopaminergic system may also account, at least partially, for a decline in visuomotor adaptation.

On this basis, in the present study I sought to investigate error-reduction and memory retention in a visuomotor adaptation task in elderly subjects, and in particular I focused here on the role of reward feedback and of dopaminergic stimulation. My prediction was that reward would have an effect on retention, even if less obvious than the one observed young healthy subjects. Also, I expected that, differently than what observed in young participants, levodopa, through the increase of dopamine levels, would have enhanced the effect of reward on retention in elderly participants.

To this end, I tested healthy participants aged 55 to 80 years old in the presence of reward-based monetary feedback. In a placebo-controlled double-blind design, I examined whether reward affects error correction and/or motor memory retention in elderly adults and whether the dopamine precursor levodopa has any influence on its effects.

5.2 Materials and methods

5.2.1 Study population

For this study I recruited 30 participants fulfilling the following criteria: (a) right-handed (as assessed with the Edinburgh handedness inventory) (Oldfield, 1971); (b) aged 55 to 80 years old; (c) no self-reported history of major medical disorders or drug abuse; (d) normal or corrected-to-normal vision; (e) no drug allergies; (f) not currently taking any medication that would affect the central nervous system or interfere with the absorption of levodopa. As a medical doctor, I personally evaluated the suitability of the participants for the pharmacological protocol based on a review of their clinical history (self-reported). After recruitment, subjects were randomly assigned to one of three groups: reward-levodopa (R-LD), reward-placebo (R-Pl), and neutral (N). All participants were naïve to the experimental aims and provided written informed consent. The experiment was approved by the UCL Research Ethics Committee and was conducted in accordance with the principles expressed in the Declaration of Helsinki.

5.2.2 Experimental task

I used here a standard visuomotor adaptation reaching task (Krakauer et al., 2000), as described in Chapter 4 (paragraph 4.2.2).

5.2.3 Reward and punishment feedback

During the adaptation phase, the two reward groups accumulated positive points, while the neutral group received no points, i.e. two uninformative zeros appeared on the screen instead than points. Points were calculated based on endpoint angular

error, i.e. the difference between the cursor endpoint angle and the target angle, as follows:

4 points: < 1º endpoint angular error; 3 points: 1-5º; 2 points: 5-15º; 1 point: 15-25º; 0 points: ≥ 25º.

Both the points received on a trial-by-trial basis and the cumulative score of the block were shown on the screen. Participants were informed that points had a monetary value (i.e., 3.472 pence/point) and depended on performance. Participants started with £0 and could earn up to £40 based on the accumulated points. The neutral group received £20 at the end of the study, irrespective of performance.

5.2.4 Experimental protocol

The study was composed of four phases (Figure 5-1). Participants initially performed a baseline (baseline 1) composed of one block (72 trials) with visual feedback and one block with no visual feedback (no vision) of the cursor. After baseline 1, subjects received either 100 mg of the dopamine precursor levodopa (plus 25 mg of carbidopa, reward-levodopa group) or placebo (reward-placebo group), in a double blinded manner, or nothing (neutral group). To coincide with the peak plasma concentration of levodopa (Nutt and Fellman, 1984), the task was restarted after a 60 minute waiting period during which participants sat quietly in the laboratory. After the levodopa/placebo administration and the waiting time, a second equivalent baseline (baseline 2) was performed. Participants in the neutral group did not receive any levodopa or placebo but, nevertheless, they had to wait 60 minutes after baseline 1, i.e. the same than the other two groups. The cursor was then rotated 40º clockwise and reward feedback (or no feedback in the neutral group) was provided for 4 blocks (adaptation), as described above. Finally, participants were exposed to 5 blocks with no perturbation and no visual feedback of the cursor (retention). The removal of

visual feedback restricts re-learning and therefore the observed gradual drift back to baseline performance represents memory retention (Galea et al., 2011; Kitago et al., 2013). Each block was separated by a short (< 1 min) rest period.
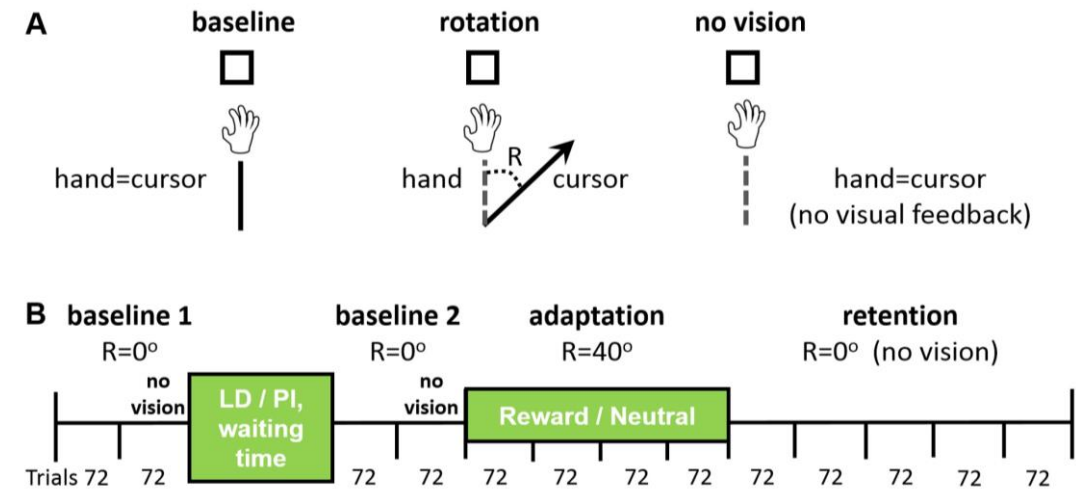
Figure 5-1 Experimental task and paradigm

A) Task. Participants made 6 cm reaching movements to a target. Visual feedback was perturbed by a 40° clockwise rotation (R) in adaptation phase (rotation). In "no vision" trials, the cursor and the hand position corresponded but there was no visual feedback. B) Study protocol. Participants completed 72 trials of baseline training with veridical visual feedback, followed by 72 trails with no visual feedback (no vision). Drug (levodopa/placebo) was then administered (in reward groups) and participants waited the corresponding waiting time (60 min). After that, the two baseline blocks were repeated (baseline 2). During adaptation, visual feedback was perturbed 40° clockwise for 288 trials (4 blocks). Finally, participants were exposed to 360 (retention, 5 blocks) trials with no perturbation and no visual feedback.

5.2.5   Blinding procedure

A medical doctor (i.e. myself) performed the randomization and administration of the drug or placebo, while the examiner and the participants were naïve to the aim of the experiment and blinded to the levodopa/placebo status (R-LD and R-Pl groups). The doses and administration times were similar to previous studies that have shown clear behavioural and neurophysiological effects for levodopa and haloperidol (Bestmann et al., 2015). All participants (including the ones in the neutral group) were asked to fast for at least 2 hours preceding the study to prevent interference with drug absorption (Nutt and Fellman, 1984). No adverse events were reported.

5.2.6   Cognitive tests

To take into account possible confounding cognitive factors, all participants underwent a battery of validated neuropsychological tests. These, apart than the Stroop test (not performed here), were the same than the ones described in Chapter 4 (paragraph 4.2.6). Subjects were also asked to score the length (in hours) and the quality (on a 7-point scale, from 0 = poor to 7 = excellent) of the previous night's sleep. After completion of the session, participants filled in a debriefing questionnaire where they reported whether they thought they had taken the active drug or placebo, and scored their levels of attention and fatigue on a 7-point scale (from 0 = poor/least, to 7 = maximal).

5.2.7 Data analysis

The 2D (x, y) position of the hand was collected through a custom C++ code at a sampling rate of 100 Hz. Movement onset was defined as the point at which radial velocity crossed 10% of peak velocity. Movements were considered terminated when the cursor breached the 6-cm target perimeter. Performance was quantified using angular reach direction (AD, ^{o}), i.e. the difference between the target angle and the angular hand position at the end of the movement (Hadipour-Niktarash et al., 2007). During veridical feedback, the goal was for reach direction to be 0°. However, with the visuomotor perturbation, reach direction had to compensate; i.e. for a $+40^o$ (clockwise) visuomotor rotation, a reach direction of -40° (counter-clockwise) was required. To adjust for between-subject baseline directional biases in the vision and no vision conditions (Ghilardi et al., 1995), AD was corrected by subtracting the average AD of the first baseline 1 block from the trials with cursor vision, and the average AD of the second baseline 1 block ("no vision") to the trials with no visual feedback of the cursor (Krakauer et al., 2005).

Reaction time (RT, time between target appearance and movement onset, ms), movement time (MT, time between movement onset and movement end, ms) and within subject variability (Var, SD of AD) were calculated for each trial. Trials in which AD exceeded 20° or was less than -60° (Galea et al., 2015; Tanaka et al., 2009), or MT or RT exceeded 1000 ms or were less than 100 ms, were removed. This accounted for 4.6% of trials. Epochs of all kinematics were created by averaging across 6 consecutive trials (Galea et al., 2011; Krakauer et al., 2005).

Data and statistical analysis were performed using Matlab (version R2013a, The MathWorks, Natick, MA, USA) and IBM SPSS (version 21.0). Differences between demographics, cognitive scores, MT, RT and baseline AD were evaluated by one-way ANOVA (quantitative data) or Chi-square or Fisher exact test (proportions).

Differences in the AD between groups were evaluated with repeated-measures ANOVAs for each study phase (adaptation and retention), with blocks as within-subject factor.

All data were tested for normality using the Shapiro-Wilk test and, in case of data that did not follow a normal distribution, the correspondent non-parametric tests were used, as indicated in the tables and text. Homogeneity of variance was evaluated with Levene test, and Welch test was used when this assumption was violated. Greenhouse-Geisser (if epsilon, $\varepsilon < 0.75$) or Huynh-Feldt (if $\varepsilon > 0.75$) corrections were applied when sphericity was violated (Mauchly's test), as indicated in text and tables. Tukey post-hoc test was used when warranted. Significance level was set at $p < 0.05$. Effect sizes are provided by phi for Chi-square test or partial eta (η^2) for ANOVA.

5.3 Results

5.3.1 Demographics, cognitive and kinematic parameters were similar across groups

Participants were randomly allocated in three groups as follows: reward-levodopa, n = 9 (n = 5, 55.6%, women), age (mean $\pm$ SD) 68.9 $\pm$ 7.6 years; reward-placebo, n = 10 (n = 6, 60%, women), age 69.1 $\pm$ 6.7 years; neutral-placebo, n = 11 (n = 9, 81.8%, women), age 69.4 $\pm$ 8.9 years. The three groups were similar for age [$F_{(2, 27)}$ = 0.013, p=0.987, η^2=0.001] and sex distribution [$\lambda^2_{(2)}$ = 1.8, p = 0.390, phi = 0.247].

As shown in Table 5.1, all groups were also comparable for Body Mass Index, educational level, hours and quality of previous night's sleep, and cognitive scores. The two reward groups received a similar amount of money at the end of the session, while the neutral group received £20 after the study, independently of performance.

Participants' attention and fatigue at the end of the session were similar across groups [respectively, quite high levels of attention: R-LD = 6.5 $\pm$ 0.2, mean $\pm$ SEM, R-Pl = 5.9 $\pm$ 0.3, N = 6.1 $\pm$ 0.2; $F_{(2,27)}$ = 2.05, p = 0.148, η^2 = 0.132; and an intermediate level of fatigue: R-LD = 3.7 $\pm$ 0.7, R-Pl = 3.3 $\pm$ 0.6, N = 3.6 $\pm$ 0.5; $F_{(2,27)}$ = 0.16, p = 0.853, η^2 = 0.012]. Four of the 10 (40%) participants in the reward-placebo group believed they had received levodopa, while 5 of 9 (55.6%) in the levodopa group believed they had received placebo, thus showing that the blinding protocol was effective.

Additionally, as shown in Table 5.2, angular reach direction was similar across groups during baseline 1 and baseline 2; and movement times, reaction times and variability were similar between the three groups during all the study phases.

Table 5.1 Participants' characteristics

	R-LD	R-Pl	N	$\lambda^2_{(2)}$ / $F_{(2,27)}$	p	Effect size
BMI	24.5 ± 1.3	23.2 ± 1.2	23.6 ± 1.4	0.23	0.797	0.019
High education	4 (44.4)	4 (40)	8 (72.7)	2.62	0.281	0.298
Sleep hours	6.8 ± 0.3	6.8 ± 0.4	6.9 ± 0.2	0.05	0.948	0.004
Sleep quality	5 ± 0.5	4.6 ± 0.7	4.9 ± 0.4	0.14	0.868	0.010
MMSE	29.8 ± 0.5	28.7 ± 0.5	29.5 ± 0.2	2.99	0.067	0.181
FAB	17.6 ± 0.2	17.3 ± 0.4	17.2 ± 0.3	0.32	0.730	0.023
AES-S	31 ± 3.1	28.2 ± 1.8	27.8 ± 1.1	0.69	0.510	0.049
BDI	4.9 ± 1.2	5.5 ± 1.3	6.8 ± 1.4	0.55	0.583	0.041
SP	3.2 ± 0.9	1.9 ± 0.9	4.3 ± 0.9	1.99	0.155	0.129
SR	3.2 ± 0.5	2.6 ± 0.6	2.4 ± 0.5	0.52	0.600	0.037
Money received	23.3 ± 0.8	22.3 ± 0.9	20	0.79	0.385	0.045

Categorical values are indicated as number and percentages (%), numeric values as mean ± SEM. Comparison between proportions is made with Chi-square test, comparison between means with one-way ANOVA. Effect size is provided as phi for Chi-square test and partial eta for ANOVA.

R-LD = reward-levodopa (n = 9); R-Pl = reward-placebo (n = 10); N = neutral (n = 11); High education = participants with ≥ 15 years of education; BMI = body mass index (Kg/m^2); MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; AES-S = Apathy Evaluation scale, self-administered version; BDI = Beck depression inventory; SP = sensitivity to punishment; SR = sensitivity to reward; Money received = GBP (£) received at the end of the session.

Table 5.2 Reaction time, movement time, variability and baseline angular reach direction across groups

		R-LD	R-Pl	N	ANOVA
Baseline 1	RT	363 $\pm$ 22	380 $\pm$ 20	404 $\pm$ 28	$F_{(2,27)}$=0.74, p=0.487, η^2=0.052
	MT	359 $\pm$ 15	341 $\pm$ 15	340 $\pm$ 12	$F_{(2,27)}$=0.64, p=0.534, η^2=0.045
	AD	-0.2 $\pm$ 0.2	-0.02 $\pm$ 0.08	0.002 $\pm$ 0.03	$F_{(2,27)}$=0.74, p=0.488, η^2=0.052
	Var	5.5 $\pm$ 0.3	5.7 $\pm$ 0.4	5.8 $\pm$ 0.3	$F_{(2,27)}$=0.21, p=0.812, η^2=0.015
Baseline 2	RT	365 $\pm$ 12	356 $\pm$ 17	391 $\pm$ 19	$F_{(2,27)}$=1.28, p=0.295, η^2=0.087
	MT	301 $\pm$ 12	273 $\pm$ 13	295 $\pm$ 8	$F_{(2,27)}$=1.53, p=0.235, η^2=0.102
	AD	0.8 $\pm$ 0.7	1.2 $\pm$ 0.4	0.05 $\pm$ 0.9	$F_{(2,27)}$=0.66, p=0.524, η^2=0.047
	Var	5.7 $\pm$ 0.4	5.9 $\pm$ 0.3	5.7 $\pm$ 0.4	$F_{(2,27)}$=0.12, p=0.891, η^2=0.009
Adaptation	RT	352 $\pm$ 15	358 $\pm$ 23	403 $\pm$ 24	$F_{(2,27)}$=1.71, p=0.200, η^2=0.112
	MT	294 $\pm$ 16	283 $\pm$ 14	298 $\pm$ 11	$F_{(2.27)}$=0.35, p=0.708, η^2=0.025
	Var	6.3 $\pm$ 0.2	7.2 $\pm$ 0.4	7.2 $\pm$ 0.4	$F_{(2,27)}$=2.21, p=0.129, η^2=0.141
Retention	RT	346 $\pm$ 8	387 $\pm$ 26	390 $\pm$ 20	$F_{(2,27)}$=1.37, p=0.271, η^2=0.092
	MT	298 $\pm$ 19	274 $\pm$ 12	288 $\pm$ 10	$F_{(2,27)}$=0.77, p=0.474, η^2=0.054
	Var	6.5 $\pm$ 0.3	7.3 $\pm$ 0.6	6.8 $\pm$ 0.3	$F_{(2,27)}$=0.85, p=0.440, η^2=0.059

Values depict the mean $\pm$ SEM by averaging over consecutive epochs for each participant and group. One-way ANOVA was used to compare mean values across groups. R-LD = reward-levodopa (n = 9); R-Pl = reward-placebo (n = 10); N = neutral (n = 11); RT = reaction time (ms); MT = movement time (ms); AD = angular reach direction (º), Var = variability.

5.3.2 Online error-reduction during visuomotor adaptation was similar across groups

Figure 5-2 shows the angular reach direction across epochs in the three groups. All groups showed clear error-reduction in response to the visuomotor perturbation, and this was similar between groups [$F_{(2,27)}$ = 0.66, p = 0.524, η^2 = 0.047, Figure 5-2].

5.3.3 Motor memory retention was similar across groups

During the retention phase there was a main effect of block suggesting all participants gradually returned towards baseline performance [$F_{(2.1,59.5)}$ = 115.70, $p <$ 0.001, η^2 = 0.879, Greenhouse-Geisser corrected, Figure 5-2]. Crucially, all the three groups displayed a similar level of memory retention [$F_{(2,27)}$ = 1.31, p = 0.287, η^2 = 0.088; Figure 5-2], with no effects of reward or levodopa.
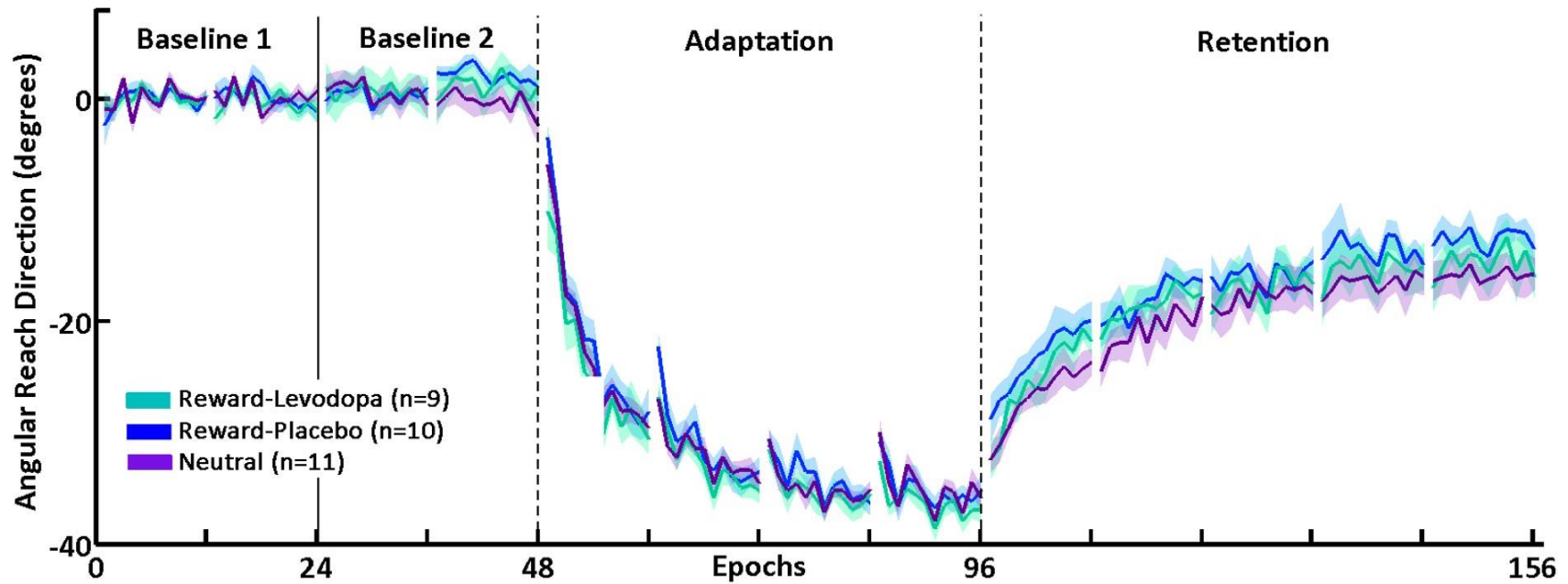
Figure 5-2 Error-reduction and memory retention were similar across groups, and not affected by levodopa or reward

Epoch (average across six trials, x-axis) angular reach direction (^{o}) during baseline, adaptation and retention for the three groups. The plots represent mean $\pm$ SEM. The solid vertical line indicates the 60 minutes waiting period after baseline 1. The dashed vertical lines indicate the beginning and end of adaptation phase.

5.4   Discussion

Aim of this study was to investigate the role of reward and dopamine during a visuomotor adaptation task in healthy elderly participants. Surprisingly, I found not effect of reward, isolated or under levodopa, on both error-reduction during adaptation and motor memory retention.

5.4.1   Reward had no effect on error-reduction or on retention in elderly

Reward delivered during adaptation phase in healthy elderly participants did not lead to higher error-reduction or motor memory retention. In particular, there was no difference between the reward-placebo and the neutral group, in disagreement with previous research on young healthy participants (Abe et al., 2011; Galea et al., 2015; Wächter et al., 2009), as well as with the experiments shown in Chapter 4.

Reaction time, movement time, or variability, as shown above, remained similar across groups in all the experimental phases, thus ruling out a confounding effect. However, I acknowledge that other factors could, at least partially, have influenced these results. In particular, the sample size may be too small. Indeed, an a posteriori exploratory power analysis showed a power of 42% (two-tailed t-test between average AD of whole retention phase), and a sample of 26 subjects per group would have been needed to have an 80% power. Indeed, we have to notice from Figure 5-2 that the neutral group seems to trend toward retaining more than the reward-placebo group, as if reward tended to actually worsen motor memory retention. However, this trend is already visible in the second block of baseline 2 (no vision). A careful review of the raw data, however, shows a group bias toward the opposite direction in the "no vision" block of baseline 1, with no different trends observed between groups in adaptation or retention. Thus, I would be careful in considering

the trend as a true one, and, also in view of the small sample size, I would rather interpret it as an artefact introduced by the data normalization. Indeed, being the bias in baseline 1, this cannot be attributed to different drug status and it is maybe just a random difference due to small sample size.

Reward likely acts through both a reinforcement learning process, impaired in elderly adults (Mell et al., 2005; Vink et al., 2015), and an explicit strategy mechanism, which as well is impaired in the elderly (Bock, 2005; Heuer and Hegele, 2014). Thus, reward may have failed to cause any effect as the mechanisms through which it acts are impaired in the elderly. In addition, literature suggests that the combination of cognitive (such as reward-feedback processing) and motor tasks causes in elderly performance deficits which are disproportionately greater than the additive age-related costs of performing the two tasks independently (Seidler et al., 2010). In fact, in order to perform a motor task elderly subjects recruit larger regions of various cortical areas (compared to young), such as the prefrontal cortex, thus leading to a reduction in neural resources available for performance of a concurrent task.

Considering that these mechanisms are dopamine-driven, my hypothesis was that the dopamine precursor levodopa could have potentiated the effects of reward. For this reason, I tested a group of elderly subject under reward and levodopa or placebo.

5.4.2 Levodopa associated to reward had no effect on error-reduction or on retention

Contrary to my predictions, levodopa had no effect on either error reduction or memory retention in elderly under reward. Again, this may reflect small sample sizes. Alternatively, the external dopaminergic stimulation may be not sufficient to show an effect of reward, also in light of the fact that this was not evident at all under placebo.

Of note, a recent meta-analysis (Karrer et al., 2017) has shown that older adults, compared to young adults, exhibit a decrease in the number of dopamine receptors (Inoue et al., 2001; Kaasinen et al., 2000; Suhara et al., 1991), and in the amount of dopamine transporters (Rinne et al., 1998; van Dyck et al., 1995; Volkow et al., 1994), but a spared level of dopamine synthesis. Indeed, as a compensatory mechanisms, dopamine synthesis could even be higher in elderly compared to young subjects (Karrer et al., 2017). Thus, one can hypothesize that increasing dopamine levels through external dopaminergic stimulation may be in this case ineffective.

However, this would be in contrast with previous evidence showing that increasing dopamine levels through administration of levodopa or dopamine agonists improves both cognitive (Gierski et al., 2007) and motor (Flöel et al., 2008a; Flöel et al., 2008b) functions in the elderly. In addition, some studies, in disagreement with the cited meta-analysis (Karrer et al., 2017), suggest that the dopaminergic presynaptic stores decrease with aging (Fearnley and Lees, 1991; Jay, 2003).

An alternative hypothesis could also be that the dose of levodopa used here may have been insufficient to potentiate an effect which was already non-existent (or not detectable) under placebo. Indeed, previous evidence has suggested a dose-response effect to levodopa in regard to learning enhancement (Knecht et al., 2004).

Further research with a larger sample and larger (repeated) doses of levodopa could help to solve this issues, which at the moment remain speculative.

### 5.4.3 Implications and conclusions

In this experiment I did not confirm the effect of reward on retention which I had found in young healthy subjects (Chapter 4) and in stroke patients (Chapter 3). However, it is interesting to note that the sample in this study was on average 10 years older than the stroke patients group (respectively 69.2 $\pm$ 7.6 years old and 59.1

$\pm$ 13.3, mean $\pm$ SD). Thus, it could be that older stroke patients, similarly to healthy adults, don't benefit from reward and levodopa, but, conversely, younger ones could benefit from adding levodopa to reward. If that was the case, it could be useful, in clinical practice, to stratify stroke survivors by age and to use feedback and pharmacologic stimulation accordingly. In addition, it would be useful to profile the dopaminergic balance of each individual and to tailor dopaminergic stimulation accordingly. This, as previously suggested, could be achieved through physical examination, neuropsychiatric testing, radiographic imaging, genetic polymorphisms, biomarkers, or TMS (Tran et al., 2016).

Further studies, possibly with bigger sample sizes, are needed to clarify the role of dopamine in motor learning under reward in stroke patients, as well as in middle aged elderly adults.

Chapter 6.

General discussion
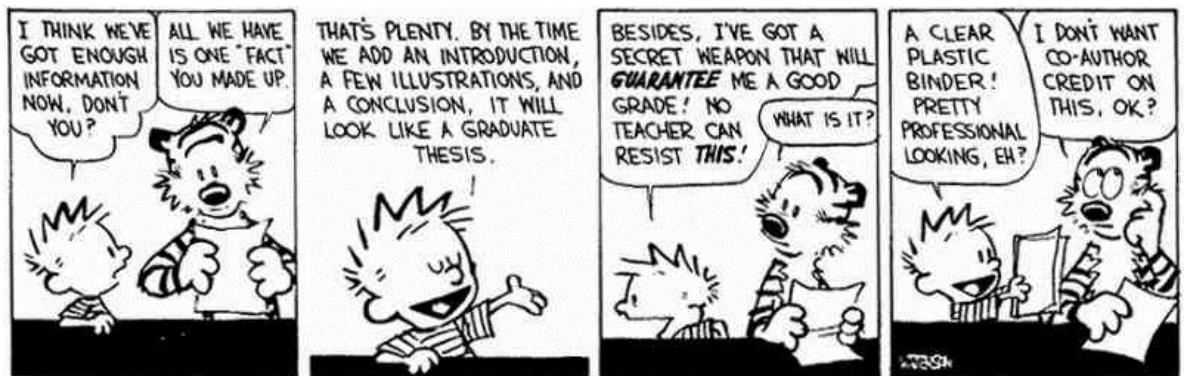
Calvin & Hobbes by Bill Watterson, Permission granted by Andrews McMeel Syndication

6.1 The journey so far: general considerations

I have displayed in this thesis my PhD journey, exploring possible ways to enhance error-correction and motor memory retention with the use of reward and punishment feedback, in both healthy participants and stroke survivors. The journey started from the clinical ground, with an exploratory survey on the views of stroke professionals (Chapter 2). This represented an encouraging basis for the following steps. Indeed, reward feedback is already used in clinical practice, although with an empirical and unstructured approach, and professionals would welcome evidence-based recommendations on the use of reward/punishment feedback in rehabilitation. On this basis, I moved to investigate the effects of reward/punishment feedback on chronic stroke survivors performing a motor adaptation tasks (Chapter 3). The results were quite promising: not only reward/punishment increased online learning, but also reward feedback enhanced retention of the new motor memory. I subsequently partially replicated these results in young healthy subjects, and proved that the positive effect of reward on motor memory retention is likely dopamine-driven, thus opening the door to a possible use of pharmacologic stimulation in adjunct to reward feedback in rehabilitation (Chapter 4). Unfortunately, in life as in research, expectations are not always encountered, and the last study of my PhD failed to confirm my predictions, i.e. reward and levodopa didn't have any effect on motor adaptation tasks in elderly healthy subjects (chapter 5). However, for a series of reasons already discussed above, this study doesn't rule out a possible role of pharmacologic dopaminergic stimulation in enhancing reward effects in brain injured patients, and in particular in stroke survivors. A subsequent step could be, therefore, to investigate the effect of coupled reward feedback and dopaminergic stimulation in patients.

As each chapter already contains a quite extensive discussion on the issues pertinent to the relative study, in this summary I will take a step back and give a look at the whole picture. In particular, I will discuss the main issues that, according to me, still

limit the translation of the discussed motor neuroscience findings to clinical practice. This also in light of the personal experience acquired by direct observation of healthy subjects and stroke patients performing the tasks.

6.2 Feedback: type and valence

One of the first challenges of using reward/punishment feedback, in research as in clinical practice, is to ensure a similar feedback valence across participants. In the studies presented in this thesis I tried my best to overcome this limitation, by scoring factors such apathy, depression and sensitivity to punishment and reward, which could influence the value given by each individuals to incentives. Nevertheless, the valence of reward and punishment remains specific, and difficult to quantify, to each participant, based also on the baseline physical and, in the case of monetary incentives, financial conditions, and of expectations regarding the own performance. Predictions (and therefore prediction-errors) regarding performance and reward are of central importance, as they are the basis of error-based and reinforcement learning. In my personal experience, during my PhD, I noted a substantial difference in predictions and expectations (i.e. prior beliefs) between stroke survivors and healthy subjects. Indeed, healthy subjects had quite clear expectations regarding the task, i.e. they expected to do well and their prediction was to gain a good amount of money from the study. On the contrary, stroke survivors, who were motivated by their own improvement in performance more than by the monetary gains, tended to have less clear predictions regarding their performance. In fact, it struck me that patients tended to ask frequently how "patients like them", i.e. with their similar level of impairment, had done in the same task. This made me reflect about the fact that reward prediction error needs a prediction itself to be generated, and I reasoned that the lack of a clear prior belief in stroke survivors could in some way alter (in both a negative or positive direction, depending on the degree of "optimism" or

"pessimism") the valence of reward. That is the case, to a minor degree, also for healthy subjects, as each subject will have different expectations regarding oneself performance, but it is, according to me, even more striking for stroke survivors. It is maybe to create a "prior belief" that patients continuously ask how people like them have done previously.

For this reason, my opinion is that comparison with peers could be a good feedback to be used in stroke patients. This has been previously named as "normative feedback", and involves information about others' performance, such as a peer group's average performance scores, provided in addition to the learner's personal scores (Wulf et al., 2010b). Normative feedback could be manipulated to lead each individual to believe that one's own performance is above (reward) or below (punishment) average. Previous research showed that positive normative feedback increases learning of a new motor skill in healthy subjects (Lewthwaite and Wulf, 2010; Wulf et al., 2010a). Considering what discussed above, normative feedback could be particularly useful in the case of stroke survivors. However, leading a stroke survivor to believe he is performing below the average raises some obvious ethical issues. In particular, we could wonder if that is acceptable for us to "cheat" by giving stroke patients "fake scores" and what would be patients' reaction (in terms of mood and motivation) to a negative normative feedback. For these reasons, as my aim was to investigate the effects of punishment feedback as well as reward, during my PhD I decided to stick to the classical monetary incentives. Nevertheless, my personal opinion is that normative rewarding or punishing feedback combined to motor learning tasks could be particularly effective in accelerating motor learning and/or retention in stroke survivors and could be reasonably easier to implement in clinical practice compared to monetary incentives. In addition, using the most appropriate feedback could also increase therapy "enjoyment" and engagement, which have been shown to optimize outcomes in chronic stroke survivors (Putrino et al., 2017), and which at present are poor in the average rehabilitation ward, with a perceived

lack of empathy from professionals and a shortage of stimulating activities (Gallacher et al., 2013).

6.3   Generalization: the need for more studies

In this thesis we have investigated possible ways to enhance motor learning, with the final aim to apply these paradigms to motor rehabilitation. However, as previously mentioned, it is crucial that what is learnt can be applied and used in novel conditions, i.e. that it generalizes. In the case of stroke survivors, this is particular important, as the newly acquired motor memory would be relevant for patients just if it transfers to daily life activities.

In my opinion, the relatively poor knowledge of generalization processes, and how to enhance them, is one of the main factors hindering the use of motor learning paradigms in rehabilitation.

In the field of visuomotor adaptation, in particular, generalization has been defined as transfer of the adapted movement (i.e. counteracting the perturbation) from the trained direction to other, untrained, adjacent directions (Poggio and Bizzi, 2004; Thoroughman and Shadmehr, 2000). Recent evidence suggests that generalization is centred on the explicit movement plan, i.e. on the aiming trajectory, and not on the target (Day et al., 2016; McDougle et al., 2017). In particular, it has been suggested that the limited direction-specific generalization observed in motor adaptation tasks could be eliminated by priming an explicit learning process (McDougle et al., 2017; Yin et al., 2016). In agreement with these observations, another form of generalization, the interlimb transfer (i.e. the transfer of learning across limbs) (Sainburg and Wang, 2002), has also been recently shown to occur for explicit more that for implicit learning (Poh et al., 2016). In light of the reasoning shown in this thesis, if punishment feedback, as hypothesized, enhances adaptation through an

increase in the use of an explicit strategy, then it could have a positive effect also on generalization, at least in young healthy subjects. Generalization, indeed, is a process as central as learning itself, and further studies on the effect of reward and punishment feedback on generalization should be encouraged, both in healthy subjects and in stroke survivors.

6.4 Technology and neuroscience: towards a bright future?

Technology supported training is emerging as a critical strategy to help therapists in the delivery of more extensive repetitive training. In particular, robotic-assisted therapy is a novel and rapidly expanding technology in rehabilitation that can enhance the recovery process and facilitate the restoration of physical function. A recent systematic review showed that motor recovery of the paretic upper limb is significantly higher in stroke survivors who underwent robotic therapy versus the ones who underwent conventional physical therapy (Zhang et al., 2017). At the same time, robotics can be combined with specially designed virtual-reality games, thus providing a more entertaining therapy environment to interest patients to participate in treatment. Finally, protocols with robotics are easier to standardize across multiple centres when compared with conventional therapy.

All these characteristics make of robotic rehabilitation the ideal candidate to implement the delivery of reward/punishment feedback. In particular, patients could train and receive "fake" normative feedback showing peers' scores at the same time than their own scores. The belief to perform better than others, acting as a reward, could increase the retention of the new motor memory, thus improving the subsequent performance. Finally, the training could be combined with pharmacologic dopaminergic stimulation, in order to increase recovery even further.

6.5 Everyone is unique: the need to individualize therapy

As we go through life, we get to learn, and deeply experience, the fascinating and powerful variety of nature that makes each individual unique. This is a central fact to take into account whenever planning a research study, as well as a rehabilitation programme with patients such as stroke survivors. Indeed, from the very beginning of my PhD, when piloting for the experiment presented in chapter 3, I had to acknowledge that stroke survivors' baseline directional bias was very different from one individual to the other, and that without taking this into account the subsequent perturbation would have been error-enhancing in some cases and error-reducing in others. For this reason, I decided to individually tailor the task to each patient, in terms of FF direction and targets. I also tried my best to allow for cognitive and functional between-subjects differences, by scoring them with the use of standardized scales and questionnaires. However, variety is not restricted to these few characteristics, and includes a number of other factors. An improved understanding of these individual factors, and of how they interact between themselves and with the key motor learning processes, would permit to individually tailor rehabilitation interventions in order to obtain the best outcomes from each patient.

Genetic variation is one of the several factors that may impact an individual's response to an intervention. In particular, some genetic polymorphisms[5], such as for dopamine, BDNF or Apolipoprotein E have been shown to impact neuroplasticity and motor learning (Stewart and Cramer, 2017). In addition, as briefly mentioned in chapter 4, the genetic variability of dopamine receptor isoforms and dopamine cleaving and metabolizing enzymes can influence the response to external

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[5] Genetic polymorphisms are defined as relatively frequent variations in DNA among individuals within a population (>1%) that are not directly disease-causing but that can impact underlying systems, especially when interacting with certain other genetic variants or environmental factors (Stewart and Cramer, 2017).

dopaminergic stimulation, and should be taken into account in future research/interventions using pharmacologic stimulation (Pearson-Fuhrhop et al., 2013). Stroke patients, also, have heterogeneous lesions in terms of locations and size, which can affect not only the actual degree of impairment but also the future recovery and the response to motor learning paradigms and to reward/punishment feedback. On this topic, I just mention here the invaluable amount of work carried on by Cathy Stinear and her research group on identifying biomarkers of recovery in stroke patients, which I think should be taken into account when planning future research on motor learning in stroke (for a review see Stinear, 2017). Finally, recovery may change also accordingly to the time after stroke, and, even if I for the already mentioned reasons I have focused here on chronic stroke survivors, further research on acute patients should be carried on to be able to generalize what found here also to the early phases post-stroke.

6.6 The big picture: relations between this research and neuro-rehabilitation and recovery

As outlined above, many are still the issues to solve to permit the use of the above findings in clinical practice. Motor adaptation has been used here as a model process, and further studies are needed to evaluate its applicability in stroke patients, in particular in the acute phase. More importantly, the generalization of what learnt to everyday life. Indeed, the applicability of motor adaptation paradigms in clinical practice is still limited, and this for two main reasons: the after-effects are short-lived, and their degree of generalization to other contexts may be limited. It is partially with the aim to overcome the first of these limitations, that during my PhD I have investigated possible ways to optimize motor adaptation and retention, through the use of feedback and/or pharmacologic stimulation.

A combination of various motor learning mechanisms, such as adaptation and skill learning, could be a good option in clinical practice, as we could, for example, guide stroke patients in learning a new skill, and then improve it through adaptation. Investigating the neural correlates of each one of these mechanisms is thus important, as ideally in the future various combinations of learning mechanisms could be adapted to the specific brain damage. In addition, despite the promising results showed in this thesis, further investigations on the effects of reward/punishment feedback over long-term training regimes are warranted.

Thus, work is needed to directly apply the current research in clinical practice. However, being rehabilitation a form of motor re-learning, a deeper knowledge of the various processes involved is of central importance to guide clinicians in the use of a more scientific approach in such a – still – empirical area.

6.7   Concluding remarks

The picture that this thesis paints is just a part of the vast picture of motor learning mechanisms in health and in stroke survivors. Although I focused on the role of reward and punishment feedback in motor adaptation tasks, my hope is that future work develops more sophisticated models, combining the various forms of motor learning, and ways to enhance performance, that may help stroke survivors in their daily struggle to regain their lost motor functions. In particular, the future of motor rehabilitation needs to target multiple sites along the motor learning network, by combining robotic therapy with pharmacotherapy and reward learning. In addition, therapies need to be tailored and individualized to each individual's degree of impairment and dopaminergic levels. Finally, further research should investigate the effects of reward/punishment feedback and pharmacologic stimulation in the acute phase post-stroke.

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