Motivation in motor and cognitive control

Effects of dopamine and monetary reward and penalty

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I, Stephanie Theresa Hirschbichler, 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.

Abstract

Dopamine has been identified as a key player in reward signalling and motivational processes and has been linked to apathy in Parkinson's disease (PD), its hallmark being dopamine depletion. Direct characterisation of how dopamine modulates reward sensitivity especially in the presence of aversive stimuli is, however, still a matter of controversy. Saccadic eye movements have long been considered reward insensitive due to their high level of stereotypy, but in recent years have been recognised as a precise tool to study motor and cognitive control processes and measure reward sensitivity.

This thesis investigates how oculomotor properties are influenced by different dopamine levels and motivation through both reward anticipation and penalty avoidance. Thereby I seek to shed light on the underlying pathomechanisms responsible for motor and non-motor symptoms in diseases characterized by dopamine depletion (e.g., PD). Data from the first experimental chapter suggest a common "net-value" for both incentive valences and confirms similar effects of both incentives on saccadic properties in healthy participants. The second part investigates the role of dopamine in signalling incentive values, which indicates a similar role of dopamine in both rewarding and aversive incentives. Both drugs (haloperidol and levodopa) decreased motor vigour, while having different effects on preparatory and inhibitory processes, which ultimately led to antagonistic effects on precision. Most intriguingly we also found increased reward sensitivity after a single dose of levodopa independent of incentive valence.

As some of these effects might reflect motor effects of dopamine, I next examined the high-level cognitive effects using a visual working memory task. This was assessed in health as well as in a cohort of patients who had undergone VTA DBS surgery. No effect of Madopar or motivation was found on working memory in a tablet-based task, while haloperidol was detrimental to memory precision. DBS stimulation in the VTA improved performance potentially by increasing dopamine levels in the mesocorticolimbic pathway.

In conclusion, this thesis aims provide a comprehensive picture of the role of nigrostriatal as well as mesolimibic dopamine on motor and cognitive control potentially aiding early diagnosis and optimising treatment strategies in disease.

Impact statement

Parkinson's disease, a movement disorder which is amongst the most common neurodegenerative diseases, poses many challenges in terms of treatment strategies, not only with regards to its motor symptoms. Although often underdiagnosed, PD patients often suffer from non-motor symptoms including apathy, depression, anxiety, or executive dysfunction. They, however, represent a significant burden on patient's quality of life and healthcare systems as they often proof difficult to treat. Dopamine, amongst others, has been identified as key neuromodulator involved in a variety of cognitive processes, yet, studying these in humans poses difficulties. In order to optimise tailored therapy, it is of utmost importance to understand the multitude of mechanisms dopamine is involved in, in both motor and cognitive control. Saccadic data collected in my experiments **(1)** show how motivation through incentives of both valence (reward anticipation, penalty avoidance) influences goal-directed behaviour and **(2)** assess the effect of changes in tonic dopamine on motor behaviour and cognitive control. **(3)** Pupillometry, a rather novel measure of reward sensitivity will allow to link motivational effects on motor vigour with those on attention. By recording data from healthy participants, with and without dopaminergic drug manipulations as well as from patients who have undergone VTA DBS surgery, this thesis aims to provide a comprehensive account of the roles of nigrostriatal and mesolimbic dopaminergic pathways in goal-directed behaviour. Bridging the gap between animal and human literature in this field may have important implications on patients' quality of life by opening avenues for reliable diagnostic tools potentially aiding early diagnosis on the one hand and optimising treatment strategies on the other hand.

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List of Abbreviations

a.u.	arbitrary units
AMI	Apathy Motivation Index
DBS	deep brain stimulation
EBR	eye blink rate
GPi	globus pallidus internus
HD	Huntington's disease
ICD	impulse control disorders
MGS	memory-guided saccades
NAcc	nucleus accumbens
NHNN	National Hospital for Neurology and Neurosurgery
OMT	Oxford memory test
PD	Parkinson's disease
PFC	prefrontal cortex
px	pixel
RA	response alternatives
RT	reaction time
SN	substantia nigra
SNr	substantia nigra pars reticulata
UPPS-P	Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behaviour scale
Vel	velocity
VTA	ventral tegmental area
WM	working memory

Statement of contributions

Sanjay Manohar supervised the project throughout and was, therefore, involved in all steps from idea development to the final version of the manuscript. He also provided Matlab scripts for the saccadic “Task 1” including scripts for further data analysis. He helped develop the idea for the novel tasks and provided support with task design, coding, and analysis.

William De Doncker helped setting up the SR Eyelink and provided advice with coding issues throughout the project. He also provided initial help with statistical analysis with R.

Jaime Ibáñez provided his Matlab coding expertise for the novel tasks and helped devising as well as adapting scripts for data analysis and filtering.

Susie Lagrata recruited patients for data collection in Chapter 4 and performed adjustments of DBS settings for the experiment as well as supplied clinical information about this cohort.

Nicholas Shedd helped with part of the data collection during the drug study.

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I am immensely thankful for all the volunteers who participated in my studies and especially for the patients from Dr. Matharu's clinic, who went to great lengths and were very patient with me along our journey together. In this context I would also like to thank Susie Lagrata and Dr. Matharu. Without them a very interesting part of this work would not have been possible.

My time at Queen Square has been enriched by a number of kind and inspiring people a few of which I would like to mention here: William De Doncker, who was never tired of providing help and advice, Jaime Ibáñez, who shared his coding expertise with me, and Nicholas Shedd, who was a huge help during parts of the data collection.

Finally, I want to thank my parents, who have remained greatly supportive of me throughout my entire life and my sister Elisabeth for her unwavering belief in me. Last but not least, I want to thank my partner Sebastian, who has been an indispensable support over the last months and has pushed me beyond my limits while never failing to put a smile on my face.

1. General Introduction

Choosing beneficial actions and learning from previous experiences is key for survival and improves reward outcome (Hikos*aka et* al., 2013). It guides every-day human behaviour and involves two main processes, action selection "what" and action execution "how" (Chen, Holland and Galea, 2018). Optimising behaviour requires both cognitive and motor control mechanisms similarly. Indeed, choosing the "what" may again consist of two distinct but interacting processes, namely, decision-making and action selection. The former can be described as the slower process in which relevant information is gathered and alternative options are weighed and filtered to assess their value (Gold and Shadlen, 2007). They are made in order to maximise reward or minimise harm and are usually slower than action selection processes, which are fast and more intuitive, automatic responses to an unpredictable environment according to the "Two Minds Theory" (Kahneman, 2003). In the presence of an advantageous goal, we are motivated to reach reward as soon as possible, potentially prompting improvement in both motor and cognitive performance (Duka and Lupp, 1997; Chiew and Braver, 2013; Manohar *et al.*, 2015, 2018; Muhammed *et al.*, 2018; Yee and Braver, 2018; Codol *et al.*, 2020). Salience is a property that drives perception, which in turn enables (an advantageous) stimulus to attract attention. When it drives behaviour (Kno*lle et* al., 2018), it is referred to as motivation (Manohar, 2014).

Dopamine has amongst others been identified in a number of human and animal studies to be a key player in reward signalling and motivational processes within the brain, by shifting attention towards seemingly "attractive" or beneficial stimuli (Assad, 2003; Small, Jones-Gotman and Dagher, 2003; Ernst *et* al., 2004; Maunsell, 2004; Bendiksby and Platt, 2006; Louie, Grattan and Glimcher, 2011; Malhotra *et* al., 2013). As such it is tightly linked to action selection, memory, and learning and has been considered as the "link between the memory of the past and future actions" (Wag*ner et* al., 1998; Fellows, 2018). The exact underlying mechanisms remain unclear, however, as studying neurotransmitters in humans poses significant challenges. Since disruptions in these processes have been associated with

a variety of movement disorders (e.g., Parkinson disease) and are believed, amongst others, to be responsible for a number of often underdiagnosed non-motor symptoms like depression, apathy, and executive dysfunction in the context of degenerative disease (Chaudhuri and Schapira, 2009; Schaeffer and Berg, 2017), bridging the gap between animal and human literature remains a pressing issue. Understanding mechanisms underlying both motor and cognitive control and the link between them is of utmost importance as it could help identify new treatment avenues for these, often debilitating, symptoms and may be key to help improve patients' quality of life.

1.1. Theoretical framework of goal-directed behaviour and the basal ganglia

Body movements are controlled by the basal ganglia and dysfunction of and lesions therein clinically present with movement disorders. The immense variety of movement disorders linked to basal ganglia dysfunction, ranging from hypokinetic to hyperkinetic movements, point towards the involvement of rather complex mechanisms, however. Indeed, it has long been established that focal lesions to the basal ganglia in humans can cause a number of symptoms beyond movement disorders such as abulia, a disorder of diminished motivation (Denny-Brown, 1968; Albin, Young and Penney, 1989; Bhatia and Marsden, 1994).

An extensive body of evidence found the basal ganglia also involved in cognitive and motivational processes (Graybiel, 1997; Casey, Durston and Fossella, 2001; van Schouwenburg, Aarts and Cools, 2010; Wylie *et al.*, 2010; Shine *et al.*, 2013; Tremblay *et al.*, 2015; Misiura *et al.*, 2017). In this context they play a key role in action selection and learning (Gurney, Prescott and Redgrave, 2001; Kravitz and Kreitzer, 2012). By inhibiting movements or removing inhibition on others based on inputs from cortical areas or other basal ganglia nuclei (Friend and Kravitz, 2014), they form the anatomical correlate for action selection and learning of optimal behaviours.

Among other examples, clinically this is underpinned by emerging knowledge about the frequent occurrence of non-motor symptoms in patients suffering from movement disorders such as Parkinson disease (PD), its hallmark being dopaminergic depletion. A great number of lesion studies on animals also support a role of dopamine and the basal ganglia in both motor and cognitive control processes (Mavridis *et al.*, 1991; Carman and Schneider, 1992; Bhatia and Marsden, 1994; Gasbarri *et al.*, 1996; Schwabe *et al.*, 2004). Bridging the gap between animal work and patient studies by conducting drug studies on healthy participants is crucial because it allows to further complement the available knowledge on goal-directed behaviour in humans without having to account for potentially confounding effects of disease pathologies.

1.2. Dopamine and its pathways

1.2.1. The multiple roles of dopamine

The catecholamine dopamine influences how we behave towards incentives and is important in motivated behaviour (Schultz, 2002, 2016b). It also plays, amongst other neurotransmitters, a central role in motor control (Crocker, 1997). Parkinson disease, e.g., its hallmark being a loss of dopaminergic neurons, is defined by a significant impairment of motor function. As mentioned above, patients suffering from PD can also present with a variety of non-motor symptoms including depression, abulia, executive dysfunction or difficulties with memory or sustaining attention. Both motor and non-motor symptoms could be the result of dopamine depletion leading to a shift in the cost/benefit ratio and, therefore, to slower movements and less reward sensitivity (Matsumoto and Hikosaka, 2007; Mazzoni, Hristova and Krakauer, 2007; Manohar *et al.*, 2015).

Through phasic responses to rewards, the midbrain dopamine neurons encode prediction error signals (difference between expected reward and actually received reward). Positive prediction errors (reward bigger than anticipated) lead to a phasic *activation*, a negative prediction error (reward

smaller than anticipated) to a *depression* of these signals and reward as predicted to no response (Schultz, 2016c). A recent model of reinforcement learning suggests that in response to positive prediction errors dopamine release in the frontal cortex and the basal ganglia strengthens synapses that are currently active (Montague, Dayan and Sejnowski, 1996; Glimcher, 2011). The prediction error theory also held true for trials where penalty had to be avoided representing a "better than expected" outcome scenario (Bromberg-Martin, Matsumoto and Hikosaka, 2010). In support of above, there is evidence in rats that intracranial electrical self-stimulation of the substantia nigra (SN) induces positive reinforcement learning through the potentiation of cortical inputs to the striatum (Reynolds, Hyland and Wickens, 2001). Behaviour-related activity would, hence, be activated favourably in the presence of a positive prediction error and would be supressed with negative prediction errors. Indeed, there is a growing body of evidence that patients with dopaminergic depletion are more likely to choose low effort/low reward options and take longer to exert effort (Le Bouc *et al.*, 2016), in other words, show diminished reward sensitivity (Manohar *et al.*, 2015). As a result, dopamine replacement therapy has been shown to improve several aspects of goal-directed behaviour while also impairing others (further details, see **section 1.7**). Some PD patients for that matter have been found to develop impulse control disorders as a result of the treatment with dopamine agonist (Voon *et al.*, 2010; Weintraub *et al.*, 2010), the reason of why this occurs in some and not others still remains to be fully understood.

1.2.2. Different dopaminergic pathways and their roles

In the human brain the main sources of dopamine are to be found within the midbrain, more specifically, the substantia nigra pars compacta, the ventral tegmental area (VTA) and the retrorubral field (RRF) (Taber *et al.*, 2012). It is then transmitted to other brain areas, among others via two major dopaminergic pathways: The basal ganglia, mainly the striatum, receive dopaminergic input from the substantia nigra pars compacta forming the nigrostriatal dopaminergic pathway. Dopamine neurons within the VTA and

the RRF of the midbrain reticular formation on the other hand build the mesocorticolimbic projections (**Figure 1.1**).

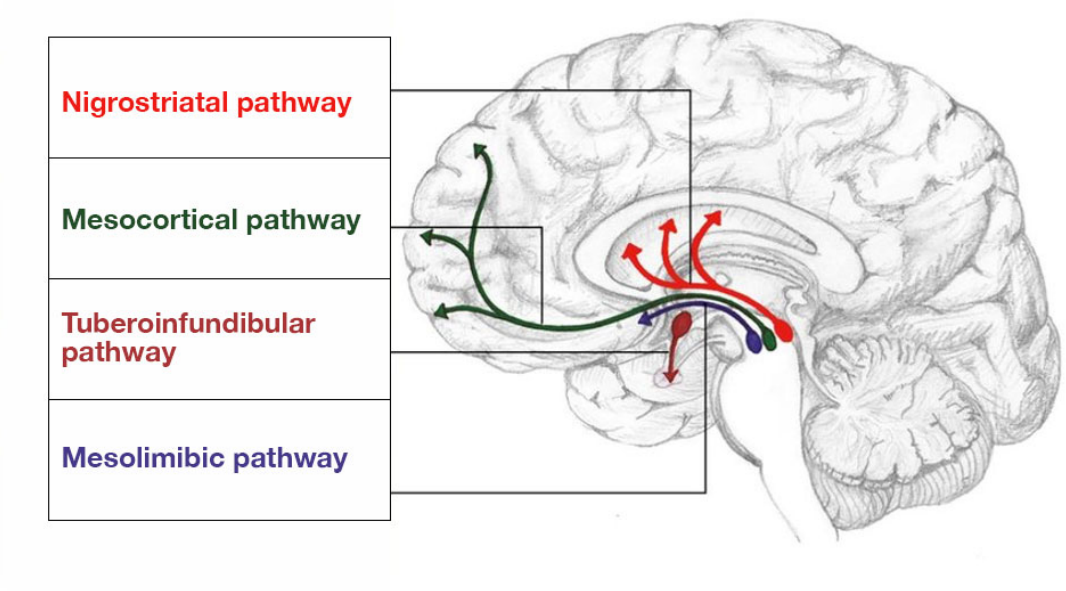

Figure 1.1 Different dopamine pathways in the brain: The nigrostriatal pathway plays an important role in motor control. The mesocorticolimbic pathway, comprising of mesocortical and mesolimbic pathways, is crucial for cognitive functions (figure adapted from Tarland 2018).

Nigrostriatal projections play an essential role in voluntary movements by modulating the corticostriatal transmission in medium spiny neurons expressing dopamine D1 (direct pathway) and D2 receptors (indirect pathway), which leads to movement activation or suppression, respectively (Prensa *et al.*, 2009). The second major dopaminergic pathway is the mesocorticolimbic circuit (comprising of the mesolimbic and the mesocortical pathway) (Hollerman, Tremblay and Schultz, 2000). Originating from the VTA (Yokochi, 2007) it is involved in reward and aversion signal processing (Gardner, 2011) as well as attention, inhibitory control (Floresco and Magyar, 2006) and working memory (Ott and Nieder, 2016). The main projections originating in the VTA are directed towards the nucleus accumbens (NAcc) and the olfactory tubercle and innervate vast parts of the prefrontal motor and cingulate cortices (Woodward *et al.*, 2009; Zald *et al.*, 2010). Animal studies investigating the consequences of damage to the mesolimibic dopaminergic

pathway showed a bias towards low effort/low reward options (Walton, Bannerman and Rushworth, 2002) and resulted in attenuating effects on behaviour in rats (Koob, Stinus and Le Moal, 1981; Hand and Franklin, 1985; French, 1986; Shimura, Kamada and Yamamoto, 2002) or depressive symptoms, which were alleviated by bilateral deep brain stimulation of the medial forebundle (Furlanetti, Coenen and Döbrössy, 2016).

Evidently, those types of lesion data on humans are lacking. Therefore, assessing the effect of deep brain stimulation in humans in general, and more specifically within the VTA, might offer a unique opportunity to aid further understanding of the exact function of the different dopaminergic pathways and the consequences of disruptions therein. PET studies have shown direct evidence of changes in dopamine activity within the NAcc and prefrontal cortex (PFC) as a result of drug -related or gambling-related rewarding stimuli (Koepp *et al.*, 1998; Volkow *et al.*, 2004). In fact, it is believed that the VTA serves as neural interface between the limbic and the motor system translating “motivation into action” (Mogenson, Jones and Yim, 1980). Assessing the effect of VTA-DBS on goal-directed behaviour and working memory will, hence, be of special interest in **Chapters 4 & 5.**

Although this anatomical dissection between the two pathways has long been established, findings indicate that there is no distinct functional boundary between the two (Dahlstroem and Fuxe, 1964). Both SN and VTA dopamine neurons project to overlapping areas (Fallon and Loughlin, 1995) and even the PFC, initially thought to get projections from the VTA exclusively (mesocortical pathway), has been found to receive projections also from the medial SN (Loughlin and Fallon, 1984). Furthermore, the SN can be subdivided into two parts, the ventral projecting to the ventral striatum and the dorsal projecting to both striatal and limbic areas (Gerfen, Herkenham and Thibault, 1987; Fallon, 1988). These findings and others from more recent behavioural studies imply an involvement of both pathways in reward signalling, potentially making distinct functional subdivisions obsolete (Wise, 2009).

1.3. Dopamine and cognitive control

Cognitive control is defined as the *"allocation of mental resources"* in the service of goal maintenance, attentional selection, and inhibition of automatic/inappropriate responses in order to facilitate optimal goal-directed behaviour (Chiew and Braver, 2013). It was recently proposed that dopamine has three distinct roles in these cognitive processes within the PFC: "**(1)** Gating sensory input, **(2)** maintaining and manipulating working memory contents, and **(3)** relaying motor commands" to the striatum (Ott and Nieder, 2019). There is a close link between motivation and cognitive control as competing options require cognitive control to facilitate optimal choice outcome. In this context incentives of both positive and negative valence have been shown to improve specific cognitive functions (Engelmann and Pessoa, 2007; Fröber and Dreisbach, 2014; Umem*oto et* al., 2015; Libera and Chelazzi, 2016).

Dopamine has been identified in a number of human and animal studies to be crucially involved in reward signalling by shifting attention towards seemingly "attractive" or beneficial stimuli (Assad, 2003; Ernst *et al.*, 2004; Maunsell, 2004; Sugrue, 2004; Small *et al.*, 2005; Bendiksby and Platt, 2006; Peck *et al.*, 2009; Louie, Grattan and Glimcher, 2011; Malhotra *et al.*, 2013; Husain and Roiser, 2018). This makes dopamine a potent link between motivation and attention. The effects of dopamine on task performance may, however, depend on a multitude of factors and contradictory results have been reported. PD patients are, e.g., known to show an increase latency on antisaccades as well as decreased accuracy on memory-guided saccades, which does not improve on dopaminergic treatment suggesting additional, potentially non-dopaminergic, pathomechanisms (Vermersch *et al.*, 1994). It, however, suggests deficits in preparatory/inhibitory processes in the former and impaired memory precision in the latter. The correlation between performance and dopamine levels are felt to be best described by an "inverted-U-shaped" function (Cools and D'Esposito, 2011; Meder *et al.*, 2019) (**Figure 1.2**).

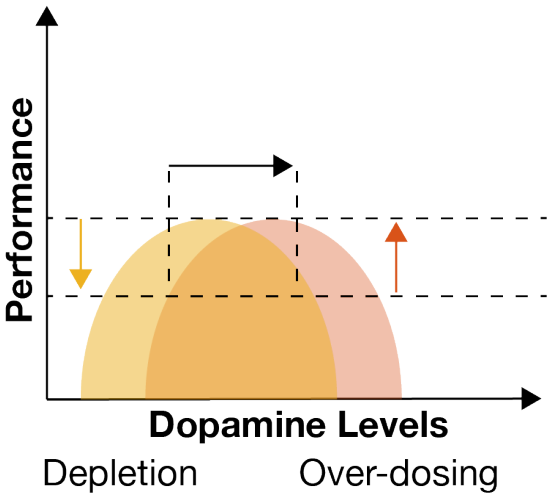

Figure 1.2 Adapted from Cools and Esposito 2011 this figure shows the relationship of dopamine levels and cognitive performance. If more/less dopamine is beneficial or detrimental to performance may depend not only on baseline dopamine levels but also on specific task requirements.

This could lead to detrimental effects on performance in the presence of "higher or lower" (compared to baseline) dopamine levels, while it may enable optimal performance in between. This theory is supported when observing patients with PD where treatment with dopamine agonists is found to interfere with some aspects of cognitive performance, e.g., shown by a 2.5-3-fold likelihood of developing impulse control disorders (ICD) (Weintraub *et* al., 2010). The exact mechanisms of why some develop ICDs and others don't have not yet been fully understood.

The effect of dopamine on cognitive control is controversial as it was also found to both impair and improve performance in different domains (Cools and D'Esposito, 2011; Schneider *et al.*, 2013). While it is believed that dopamine enhances preparatory control processes and optimises signal-to-noise ratio (Gruber *et al.*, 2006; Yee and Braver, 2018), increased levels of dopamine were found to impair working memory (Cools and D'Esposito, 2011). To explain both the beneficial and detrimental effect of motivation on cognitive control found in previous studies, Yee et al. introduced the idea of two separate dopaminergic pathways (DA-PFC loop and DA-striatal loop) (Yee and Braver, 2018). Hereby it is thought that tonic release of dopamine into the PFC may assist the precision and persistence of current task goal representations (i.e., cognitive stability), while phasic dopamine in the

striatum enables cognitive flexibility through shifting and updating of task goal representations (Yee and Braver, 2018). Taking a closer look, dopamine excess has been associated with increased oculomotor distractibility (Crawford *et al.*, 1995; Duka and Lupp, 1997; Hutton *et al.*, 2002), while dopamine depletion has been found to improve performance by filtering/blocking irrelevant stimuli and reducing distractibility (Mehta *et al.*, 2004). However, a recent paper suggests that both excess and reduced dopamine activity in the PFC may lead to a variety of different effects in different cognitive domains (Floresco and Costa, 2013). Rodent studies have also reported increases in motor behaviour after dopamine agonists administration (Ross, Jackson and Edwards, 1989). There is, furthermore, evidence of cross-species differences, necessitating translation into human studies (Ralph and Caine, 2005; Broos *et al.*, 2012). In contrast to this, D2 agonists have also been linked to a reduction of impulsivity in a cohort of pre-selected impulsive rats (Weintraub *et al.*, 2006). The latter effect of dopamine replacement has also been clinically observed when patients with ADHD improve their symptoms under treatment with methylphenidate. Methylphenidate, better known as Ritalin, is believed to alleviate symptoms through blocking the dopamine re-uptake in patients with attention deficit hyperactivity disorder (ADHD) (Fernando *et al.*, 2012), who have been found to have dopamine and noradrenalin dysfunction on functional brain imaging.

The detrimental effects of dopamine therapy on certain cognitive functions were discovered a decade ago and have since sparked more research leading to the "overdose hypothesis" (**Figure 1.3**). The overdose hypothesis seeks to provide a framework to explain the complex relationship between dopamine levels and performance and suggests that increased levels of dopamine in the ventral striatum (nucleus accumbens) hampers top-down inhibitory control while increasing bottom-up appetitive drive areas leading to changes in behaviour (Cilia and van Eimeren, 2011).

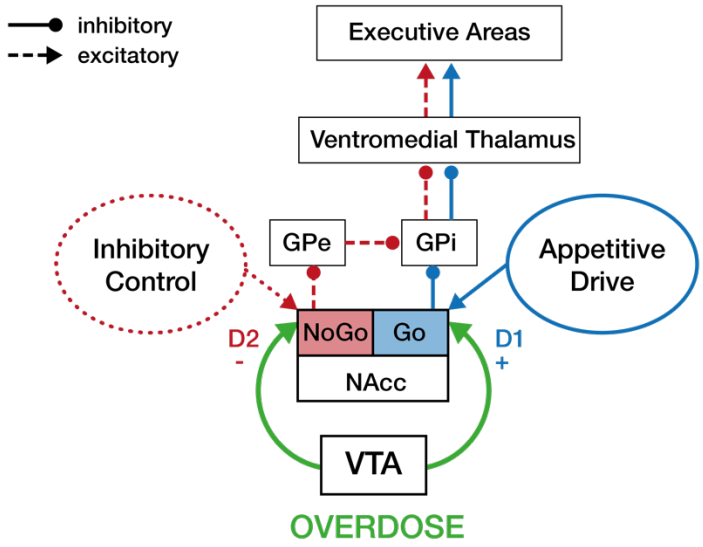

Figure 1.3 Simplified illustration explaining the "overdose hypothesis": Increased levels of tonic dopamine may lead to a decrease in top-down inhibitory influences on the NAcc while increasing bottom-up appetitive drive areas (adapted from Cilia and van Eimeren, 2011).

Why additional dopamine hampers performance in some but improves it in others, may be determined by a number of different factors in disease and in health. These include gene polymorphisms in connection to the specific type of pharmacotherapy (e.g., COMT), regional differences in (nigrostriatal) denervation due to the underlying disease pathology, or an individual's genotype influencing the relative baseline position on the "inverted-U-curve" (Vaillancourt *et al.*, 2013), which are just a few to be found in the literature. Another explanatory model for seemingly very different effects of dopamine treatment on cognitive performance of patients is the "Dopamine denervation model". While treatment naïve patients seem to benefit from levodopa treatment, some effects seem to wear off over time. In a study following initially treatment naïve PD patients for 24 months after levodopa introduction, improvements in both motor and cognitive domains were observed directly after treatment introduction. Only motor benefits, however, persisted after 24 months when patients were assessed again (Kulisev*sky et* al., 2000). Moreover, patients experiencing motor fluctuation usually show detrimental effects of a levodopa challenge on their cognitive abilities (Kulisevsky *et al.*,

2000). It is thought that this stems from striatal neurons developing a super-sensitivity to alterations of levodopa plasma concentrations after long-term therapy. Cognitive effects of levodopa may also vary in an individual patient over time with disease progression (Williams-Gray *et al.*, 2009) and receptor changes due to prolonged drug therapy (Antonini *et al.*, 1997). Further evidence gathered showed levodopa to improve working memory, but to have a detrimental effect on other domains such as motor sequence learning and probabilistic reversal learning (Cools *et al.*, 2001; Ghilardi *et al.*, 2006; Graef *et al.*, 2010; Kwak *et al.*, 2010; Beigi *et al.*, 2016). Models on working memory and dopamine found D1 mediated modulation to improve robustness of memory via reduced distractibility and noise attenuation in the PFC (Durstewitz and Seamans, 2002). It is suggested that external dopamine replacement could lead to excessive amounts of dopamine in areas relatively spared from dopaminergic degeneration, e.g., the VTA output areas in disease models, although the latter being disputed (Phani, Gonye and Iacovitti, 2010). Understanding the mechanisms underlying this huge variety of effects of dopaminergic treatment on patients is of utmost importance in order to provide optimal therapy and improve patients' quality of life.

In summary these findings suggest an interaction of a multitude of factors predicting an individual's reaction to dopaminergic manipulation, e.g., **(1)** performance may depend on the individual's baseline dopamine level and may follow an "inverted-U-shaped" function. **(2)** It may not be a simple question of avoiding "too much" or "too little" dopamine, but the effect may also be task-specific and depend on the exact location of degeneration in the brain (**Figure 1.2**). Different tasks may require different dopamine levels to optimise outcome (Gotham, Brown and Marsden, 1988; Swainson *et al.*, 2000; Cools *et al.*, 2001). **(3)** There may be additional factors like gender, age and DAT1 gene polymorphisms (Cools and D'Esposito, 2011) contributing to the great variety of findings.

1.4. The speed-accuracy trade-off and motivation

Internal or external incentives can alter the behaviour of a biological system by creating a "motivated state" (Yee and Braver, 2018). Higher order decisions are made based on the expected value (reward probability x reward magnitude) and aim to maximise reward or minimise harm respectively (Yee and Braver, 2018). This behaviour was described as early as 1954 by Olds and Milner in their paper on self-stimulation and reward in rats (Olds and Milner, 1954). Motivation through reward, however, influences not only the decision to make a movement ("if/what") but can also change movement properties ("how") (e.g., response time, accuracy) (Leon and Shadlen, 1999). Similar to the speed-accuracy trade-off in motor control, models of decision-making predict a speed-accuracy trade-off, showing that faster reactions imply less time to weigh up evidence and consequently lead to erroneous choices (Spieser *et al.*, 2017). Ultimately, this should lead to fast but inaccurate movements/choices considering it is a limited capacity system – and does not explain the violation of the speed-accuracy in producing both faster and more accurate movements/decision when rewarded (Manohar *et al.*, 2015). This holds true for both motor and cognitive performance: While motivation by reward can lead to faster and more precise movements, it also leads to shorter reaction times and reduces errors (Edwards, 1965). Individuals are driven to obtain reward sooner and will, accordingly, increase their movement speed or vigour in order to do so. If the task does not favour velocity *or* accuracy, decisions are made to maximise reward. This has been demonstrated by improved motor and cognitive performance resulting in both faster and more accurate movements/decisions simultaneously, depending on the expected value of the outcome (Juras, Slomka and Latash, 2009).

Recent theories that try to explain why people exert effort and when they choose to do so often include the factor of "proximity of the reward" (Juras, Slomka and Latash, 2009). Then not only the timing of reward, but also more economical considerations, such as the balance between the value of the

outcome vs. cost of exerting cognitive control, are critical considering a potentially limited capacity of the latter (Westbrook and Frank, 2018). The ego depletion phenomenon delineating these limitations has, however, been recently challenged by the observation that these can be overcome by motivation (Muraven and Baumeister, 2000). There might, consequently, be a value assigned to the effort exerted itself, independently of the value of the outcome (Hagger *et* al., 2010; Inzlicht, Shenhav and Olivola, 2018). The quantification of "mental effort", thus, is complex, and reaction times as well as pupillometry have been amongst the tools most commonly used for it (for pupillometry review, see Eckstein *et* al., 2017). A growing number of computational models seek to describe the relationship between cognitive control and motivation and the associated costs of allocating resources (Shenhav *et* al., 2017) although a number of question still remain unanswered.

1.5. Saccades and motivation

Raymond Dodge first described the function of saccades as "to move the eyes so that the point of interest will be seen with the visual centre of the retina" (Dodge, 1903). Saccades are voluntary, rapid, accurate and brief eye movements, made to foveate the object of interest without interfering with vision (Leigh and Zee, 1999). They were long believed to be highly stereotyped and follow the "main sequence" (**Figure 1.4**), which describes a rigid relationship between peak velocity and amplitude of a saccade (Bahill, Clark and Stark, 1975; Leigh and Zee, 1999). This was felt to be the case to optimise the trade-off between the duration of an eye movement (time during which vision is blurred) and its accuracy (Harris and Wolpert, 1998).

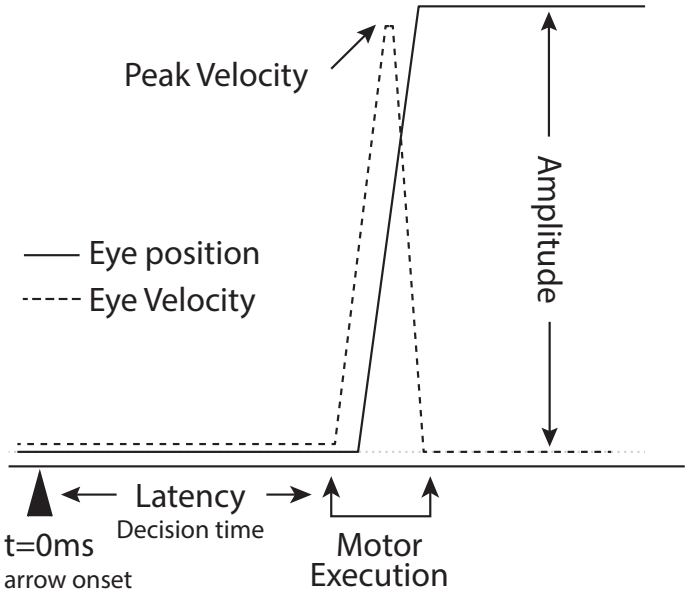

Figure 1.4 Saccadic parameter and the main sequence (figure adapted from www.liverpool.ac.uk/~pcknox/teaching).

There is, however, growing evidence that saccadic parameters can, indeed, be modulated by reward, violating the speed-accuracy trade-off (Takikawa *et al.*, 2002; Chen *et al.*, 2013; Manohar *et al.*, 2015). Saccades allow a fairly direct interpretation of behavioural findings due to relatively few degrees of freedom (Fuchs, Kaneko and Scudder, 1985; Scudder, Kaneko and Fuchs, 2002), which make them the method of choice when recording behavioural data. In fact, the number of studies using eye movements and especially saccades to address question in the field of behavioural neuroscience has dramatically increased in the last decades, proving eye tracking to be a sophisticated tool to assess specific areas of brain function. But where is the link between reward and saccadic eye movements? For an amplitude of a given size, saccadic peak velocity can be increased through incentives (Chen *et al.*, 2013). Moving the gaze towards an object of value/interest by eliciting saccades has been linked to the basal ganglia via heavy connection of the superior colliculus known to be involved in orienting responses and saccadic eye movement generation (Ingle, 1973; Carman and Schneider, 1992). The superior colliculus, however, is targeted by the substantia nigra pars reticulata not the globus pallidus internus, indicating a crucial role of the basal ganglia

in orienting processes (Takikawa *et al.*, 2002; Chen *et al.*, 2013; Manohar *et al.*, 2015). The caudate nucleus, involved in cognitive functions, also controls saccadic eye movement and encodes reward values for visual targets via dopaminergic inputs (Kim and Hikosaka, 2015). Neurophysiologically, saccades follow a pause in tonic firing of a group of neurons in the substantia nigra pars reticulata (SNr), thus removing inhibition on the superior colliculus (Hikosaka, 1989). Saccades are faster towards objects of greater value and their directions highly influenced by the location of rewarding stimuli (Takikawa *et al.*, 2002; Hayhoe and Ballard, 2005; Nakamura and Hikosaka, 2006; Hikosaka, Nakamura and Nakahara, 2019). Evidence from animal studies suggest a role of the caudate nucleus- SNr- superior colliculus-pathway in orienting the eyes towards reward (Lauwereyns *et al.*, 2002; Sato and Hikosaka, 2002; Takikawa *et al.*, 2002). In the presence of an advantageous/rewarded goal, we aim to reach reward as soon as possible, leading to an improvement in saccadic performance when incentives are offered (Duka and Lupp, 1997; Manohar *et al.*, 2015, 2018; Muhammed *et al.*, 2018). While this is the case for healthy people, disorders that alter reward processing (e.g., PD, ADHD, schizophrenia) produce altered saccadic patterns and may show slower saccades and diminished reward sensitivity (Michell *et al.*, 2006; Reilly *et al.*, 2008; Fried *et al.*, 2014; Manohar *et al.*, 2015). These were fairly surprising findings, given saccades were thought to be following the “main sequence” describing a rigid relationship between peak velocity and amplitude (Bahill, Clark and Stark, 1975). A recent study looking into saccade trajectories has found that one of the reasons that the speed-accuracy trade-off can be overcome might be an improved signal-to-noise ratio through strengthening negative feedback mechanisms, thus, increasing robustness of the neural signal through reward (Manohar *et al.*, 2018). This effect is diminished in PD patients, who showed less reward sensitivity on the same task which may be linked to dopamine dysregulation (Manohar *et al.*, 2015).

As a consequence, saccades can, indeed, provide an important insight into the mechanisms behind these observations and have been used to

investigate reward-related behaviour for decades (Leigh and Zee, 1999). Human and animal research using saccades has demonstrated that oculomotor properties such as saccadic velocity, accuracy and reaction time can be modulated by incentives (Sato and Hikosaka, 2002; Takikawa et al., 2002; Nakamura and Hikosaka, 2006; Hickey and van Zoest, 2012; Tachibana and Hikosaka, 2012; Chen et al., 2013, 2014) and allow to indirectly quantify processes of motor and cognitive control. Saccadic latency, e.g., does not only reflect visual processing but also decision-making processes and is, therefore, highly dependent on the task properties (e.g., prosaccades vs. antisaccades).

Patients with certain diseases can show saccades that differ from the normal main-sequence plots in a specific way, making them a useful diagnostic tool (Jazbec *et al.*, 2005). PD, e.g., has been repeatedly reported to show hypometric saccades, especially when made to remembered targets (Shaunak *et al.*, 1999; Armstrong *et al.*, 2002; Fried *et al.*, 2014). The observed hypometria and reduction in peak velocity in PD patients was also shown to improve on dopaminergic therapy (Anderson and MacAskill, 2013) confirming a dopaminergic mechanism. Pharmacological studies using haloperidol in healthy controls showed a slowing of saccades (velocity) after haloperidol, they did not comment on amplitude size, though (Lynch *et al.*, 1997). In unpublished data on the effect of cabergoline on saccadic amplitudes in healthy volunteers, there was no effect of drug on amplitude size. Cabergoline increased reward sensitivity while decreasing motor vigour (velocity) specifically in low/no-reward conditions (Manohar, 2014).

In summary, eye tracking data including saccades, eye blink rates (EBR) and pupillometry have been used to assess brain function and cognition for many years (Montastruc *et al.*, 1989). Recently the extent of pupil modulation has also been used to quantify reward sensitivity (Manohar and Husain, 2015; Muhammed, Manohar and Husain, 2015). This indicates that eye tracking in combination with EBR and pupillometry may aid to assess processes underlying motivation and cognitive control.

1.6. Reward and reward valence

Goal-directed behaviour is guided by the possibility of obtaining reward or avoiding negative outcomes respectively. This means, we adapt our behaviour in order to receive reward *or* avoid punishment. Successful punishment avoidance can, depending on the context, similar to reward, acquire an absolute "positive value", thus, reinforce a response (Palminteri *et al.*, 2015). Significant research efforts have focused on the effect of incentives of positive valence on behaviour, less on penalty avoidance, and even fewer have examined both conditions together in the same task. As reviewed by Bissonnette et al., anatomical correlates for both appetitive and aversive stimuli have been identified in both human and animal literature (Bissonette *et al.*, 2014). Here midbrain dopaminergic neurons projecting to the striatum and the orbitofrontal cortex have been implicated in signalling incentives of positive valence (Hollerman, Tremblay and Schultz, 2000; O'Doherty, 2004; Delgado, 2007; Haber and Knutson, 2010), while amygdala and anterior insula are activated during the processing of aversive stimuli (LeDoux, 2000; Craig, 2002, 2009; Davis *et al.*, 2010). Reflected by the big variety of results in behavioural data, both incentive types have, however, also been linked to activity in the regions implicated in processing of incentives of the opposite valence (Everitt *et al.*, 2003; Jensen *et al.*, 2003; Delgado *et al.*, 2008; Liu *et al.*, 2011). In addition to those areas, the VTA was also found to be involved in the signalling of incentives of both valences (Carter *et al.*, 2009).

Behavioural data have shown that motivation through reward was found to improve saccadic performance (accuracy and velocity) (Takikawa *et al.*, 2002; Chen *et al.*, 2014; Manohar *et al.*, 2015; Reppert *et al.*, 2015). This effect was also observed for both appetitive and aversive incentives (Jazbec *et al.*, 2005, 2006). Indeed, penalty and reward conditions were both shown to increase motor vigour when reward outcome was contingent (performance dependent) (Manohar *et al.*, 2017). There is an extensive body of evidence for the role of dopamine in reward-related behaviour and positive motivation (Griffiths, Lieder and Goodman, 2015; Holroyd and McClure, 2015; Verguts, 2017).

However, less is still known about the role of dopamine in signalling aversive stimuli and the available findings are inconsistent (Kim and Hikosaka, 2015), sparking a discussion about the mechanisms behind motivation through incentives of different valence. In fact, investigating incentives of different valence using saccades has just recently received more attention.
Clinical observations in this context go back to the loss aversion theory (Kahneman and Tversky, 1979) many years ago, suggesting stronger reactions to losses than gains. Even further back, the report of "kinesia paradoxa" by Souques (1921) showed that PD patients seemed to be able to improve motor performance dramatically when "motivated sufficiently", a phenomenon that has been reported repeatedly since. Often these incentives were of aversive value and patients would exert effort in order to avoid harm or danger. A more recent observation was that PD patients "OFF" their medication were more likely to learn from negative reinforcement than from positive (Frank, Seeberger and O'Reilly, 2004) pointing towards a link between incentives and dopamine which seems to be stronger for appetitive stimuli.

Task designs, where three conditions were used, e.g., "loss", "nil" and "win", allowed to investigate whether activation signals in specific brain regions were likely to represent "value" (which would be biggest for win and smallest for loss trials) or, indeed, "salience", for which both "loss" and "win" trials would elicit a greater activation than neutral trials (Bissonette *et al.*, 2014). The value based cognitive control (VBCC) framework leads to the expectation that while appetitive incentives increase *cognitive* control, aversive incentives should decrease it (Galea *et al.*, 2015). This theory contrasts with more recent findings showing either stronger effects of monetary reward when compared to loss on both reaction time and accuracy or reports of no difference between the two at all (Camerer and Hogarth, 1999; Richter *et al.*, 2013; Carsten *et al.*, 2019). This was also supported by evidence of increased effort for incentives of both valences, as measured by fMRI and EEG (Dambacher, Hübner and Schlösser, 2011; Potts, 2011), although even functional imaging did not show uniform results. Some fMRI studies found that reward and loss

anticipation have common neural substrates (striatum, thalamus, insula and amygdala) (Braem, Duthoo and Notebaert, 2013; Makwana, Cubillo and Hare, 2019), while others point to different brain regions being involved in reward signalling for incentives of different valence (Hikida *et al.*, 2010; Krawczyk and D'Esposito, 2013; Jiang, Kim and Bong, 2014; Kim *et al.*, 2016). Effects might also be specific to task complexity, where reward seems to increase brain activity in task-relevant regions during highly demanding attention trials, while aversive stimuli did so across all trial types, shown by shorter reaction times on gain trials than on loss trials pointing towards increased allocation of resources for the duration of the entire block of trials rather than for a single trial in the presence of aversive stimuli (Oldham *et al.*, 2018). Similar behavioural findings on incentives of both valences would be in favour of theories suggesting that both appetitive and aversive stimuli have a comparable motivational salience (Paschke *et al.*, 2015), thus, enhancing performance independent of their value. This was also suggested by Bissonette et al. proposing that incentives of different valence are translated into a net motivational value influencing cognitive control (Bissonette *et al.*, 2014). In contrast, data have been published where reward improved motor and cognitive performance in a learning task, but punishment only showed an enhancement in motor performance (Yee *et al.*, 2015), while others reported accelerated learning in order to avoid punishment (Galea *et al.*, 2015). Similarly, reward has been associated with increased activity in dopaminergic frontostriatal circuits (O'Doherty, 2004; Shiner *et al.*, 2012), while punishment led to changes in activity in both the striatum and the insula (Jensen *et al.*, 2003; Tom *et al.*, 2007; Palminteri *et al.*, 2012).

The great variety of findings might be explained in parts by the individual sensitivity to incentive values (Yee and Braver, 2018), personality traits (e.g., anxious, confident) as well as affect and gender on performance outcome under aversive stimuli (Galea *et al.*, 2015). To account for these individual differences and their potential effects on overall performance in general and reward sensitivity more specifically, two questionnaires will be used later in this thesis. Firstly, the apathy motivation index (AMI), adapted from the Lille

Apathy Rating Scale (LARS), was found to be a reliable tool to assess apathy in PD (Ang *et al.*, 2017) and has also been used to measure intrinsic motivation in otherwise healthy controls. Since some of the tasks in this thesis require inhibitory processes, the second questionnaire included was the UPPS-P rating scale, a measure for an individual's impulsivity trait (full questionnaires see appendix).

The idea that different subgroups of dopamine neurons signal motivational *value*, while another population encodes motivational *salience,* however, has recently been introduced and could also account for the inconsistent findings (Sakuragi and Sugiyama, 2009; Robinson *et al.*, 2010; Chiew and Braver, 2011). The exact mechanisms underlying reward and punishment anticipation and processing, ultimately, remain to be further investigated and might carry critical therapeutic implications for patients with dopamine dysregulation.

1.7. Drug effects in disease and in health

1.7.1. Dopamine depletion and PD

PD, probably the most thoroughly studied movement disorder, is characterised by nigrostriatal degeneration. It is associated with a variety of motor and non-motor symptoms that have mainly been associated with dopaminergic dysregulation, although other neurotransmitters, e.g., acetylcholine, noradrenaline and serotonin are also thought to be involved (Baloyannis, Vassiliki and Baloyannis, 2005; Remy *et al.*, 2005; Bohnen *et al.*, 2006; Guttman *et al.*, 2007; Delaville, De Deurwaerdère and Benazzouz, 2011). Whilst it is long known that dopamine replacement therapy improves motor performance in PD (Cotzias, Van Woert and Schiffer, 1967; Cotzias, Papavasiliou and Gellene, 1969), psychiatric comorbidities such as anxiety and depression have also been linked to dopamine depletion in the limbic system (Remy *et al.*, 2005). Dopaminergic treatment strategies are in fact suggested for the treatment of depression in PD (for review, see Chaudhuri and Schapira, 2009; Leentjens, 2011). This also led to the observation that

dopaminergic therapy could at least partially restore reduced reward sensitivity and apathy in a patient with bilateral globus pallidus lesions (Adam *et al.*, 2013). In contrast, dopamine has also been found to have somewhat detrimental effects on cognitive control on some patients (for details, see **section 1.3**). Pharmacologically, drugs like levodopa and dopamine agonists have been found to increase receptor stimulation in the dorsal striatum (Connolly and Lang, 2014).

Different effects of dopamine replacement therapy in the context of learning from reward and penalty have been reported. Patients "ON" dopamine agonists were better in choosing symbols associated with a high probability of reward but worse in avoiding those with low probability. "OFF" medication, however, they showed the opposite pattern. This led to the interpretation that learning by reward is enhanced "ON" medication, while learning by penalty is better "OFF" (Frank, Seeberger and O'Reilly, 2004). Similarly, dopamine agonists were found to enhance novelty seeking and reward processing, while it disrupted punishment processing in a cohort of young PD patients (Bódi *et al.*, 2009). However, these findings were not reliably reproduced (Grogan *et al.*, 2017; Manohar, 2020). Saccadic amplitudes known to be hypometric in PD, improved with a single dose of levodopa (Montastruc *et al.*, 1989), prosaccades were, however, slowed down by it, when compared to the same cohort "OFF" drugs (Michell *et al.*, 2006a). Another cohort was found to improve accuracy of antisaccades when "ON" their usual levodopa treatment dose (Hood *et al.*, 2007). Parkinsonism induced by neuroleptic treatment in some patients with no previous history of movement disorders have been reported, suggesting a potential role of genetic susceptibility (Erro, Bhatia and Tinazzi, 2015).

But how could we predict an individual patient's reaction to dopaminergic replacement therapy? In order to dissect the role of dopamine in different domains of motor and cognitive control without having to account for confounding effects driven by disease pathologies, healthy controls seem to be a promising avenue to investigate the effects of (anti-) dopaminergic drug

manipulation. These studies allow to further dissect the huge variety of findings in both motor and cognitive control processes.

1.7.2. Pharmacological manipulation in health- what is already known?

Administration of (anti-)dopaminergic drugs to young, healthy participants allows to assess the effect of exogenous dopamine and how it improves/disrupts specific brain functions in a cohort, presumably dopamine replete. Results are, therefore, expected to be less confounded by ageing, comorbidities and previous dopaminergic therapy or regional pathological differences in dopamine relative to normal state (e.g., nigrostriatal vs. mesolimibic dopamine depletion in PD). There have been a number of studies using different dopaminergic and antidopaminergic drugs investigating their effect on behaviour in healthy controls, however, fewer are available comparing the effects of dopaminergic and antidopaminergic medication in a within-subject design. Since our study discussed in **Chapter 3** will use levodopa and haloperidol the main focus here will be to summarise findings from these two drug manipulations (for review, see Reilly *et al*., 2008). Levodopa increased the speed of button press responses (reaction time) towards reward but not when avoiding punishment trials (Guitart-masip *et al.*, 2012). It also increased learning speed, retention (Knecht *et al*., 2004) and restored decision-making processes of older adults to the level of young adults (Chowdhury *et* al., 2013). A higher proportion of risky choices for potential gains but not losses in an economic risk-taking task, which they described as “increased Pavlovian approach” (Rutledge *et* al., 2015) were reported. Of special interest for this thesis, healthy participants on levodopa showed an increased frequency of high probability gain but not loss choices when compared to haloperidol in an instrumental learning task (Pessiglione *et* al., 2006). In terms of studies on saccades, levodopa was found to decrease the number of correct antisaccades (Duka and Lupp, 1997). The absence of an effect of haloperidol on saccadic peak velocity was reported by King et al. (King and Bell, 1990), while the presence thereof in form of a

dose-dependent slowing of prosaccades after higher doses of haloperidol (4mg and 6mg) was found by others (Lynch *et al.*, 1997). Haloperidol was surprisingly not shown to increase saccadic latency in the same study. It was, however, found to increase go learning from positive reinforcement through postsynaptic action (Frank and O'Reilly, 2006) but decrease correct somatosensory judgements (Pleger *et al.*, 2009).

1.7.3. Pupillometry

"Attention is the process of optimising precision" (Friston, 2010). Eye tracking data including measuring saccades but also EBR and pupil size have been used to assess brain functions like attention and cognitive load in the past (van Reekum, Stuss and Ostrander, 2005; Fried *et al.*, 2014; Eckstein *et al.*, 2017). Previous evidence also suggests that pupillometry may be a helpful tool to objectively measure reward-processing and the influence of reward-related motivation on attention and cognitive control (Chiew and Braver, 2013). Reward as well as reward expectation have been shown to modulate pupil size (Delaville, De Deurwaerdère and Benazzouz, 2011; Manohar and Husain, 2015; Manohar *et al.*, 2017), showing that changes in pupil size are greater in response to incentives than in unrewarded conditions. Changes in pupil diameter following incentives might help to understand goal-directed behaviour and has recently been used to explore motivation and reward sensitivity in pathologies such as PD. Patients diagnosed with PD showed reduced pupil response to reward when "OFF" medication, while dopaminergic medication restored their reward sensitivity (Manohar and Husain, 2015). Pupil size also provides important insights into cognitive processes and arousal and how they may influence pupil diameter (Lehmann and Corneil, 2016). The exact mechanisms in which both dopamine and noradrenalin are involved in controlling pupillary and cognitive processes, however, remain elusive. The suggested anatomical correlate may be noradrenergic locus coeruleus projections originating in the pons (Aston-Jones and Cohen, 2005).

The identified relationship between pupil size, attention and reward sensitivity opens a unique avenue for objectively measuring non-motor symptoms like apathy in patients suffering from dopamine depletion, e.g., and may allow to identify patients more vulnerable to developing ICDs on dopamine agonists by potentially using it as a proxy for "baseline" dopamine levels. Due to the lack of available biomarkers, clinicians currently need to rely on binary, subjective questionnaire scores for this that do not reflect the dynamic processes during reward anticipation and decision-making.

1.8. Conclusion

In summary, apart from the basal ganglia's well-studied role in musculoskeletal movements, they are of key importance in cognitive processes and are involved in the suppression or initiation of saccadic eye movements (Hikosaka 1989). The planning and execution of purposeful movements are dependent on a number of behavioural inputs (e.g., working memory, learning, attention, and motivation and reward expectation) which influence basal ganglia signalling (Hikosaka, Takikawa and Kawagoe, 2000). This makes eye movements a powerful tool to investigate basal ganglia mechanisms involved in motor and cognitive control in the context of motivation.

By exploring how oculomotor properties are influenced by dopamine and motivation, I seek to shed light on the underlying neural pathways responsible for motor and non-motor symptoms in diseases characterised by dopaminergic imbalance. To further investigate the role of dopamine in motor control and action selection/decision making, a number of novel and established tasks will be used in this thesis. This involves assessing the influence of incentives of different valence (reward, penalty) on motivation, saccadic eye movements and working memory, as well as the impact of sub/supra-normal dopamine levels on the two. In the third part of the thesis,

I will investigate the role of mesocorticolimibic dopamergic pathways in reward-related behaviour and working memory more specifically.

1.9. Outline of study

1.9.1. Chapter 2

In the first experimental chapter I investigated how saccadic properties of healthy volunteers are influenced by incentives in three different saccadic paradigms of which two are novel. For the first paradigm the expectation was to replicate Manohar's findings of improved saccadic performance in a task requiring avoiding an early distractor in unrewarded trials as well as in the presence of two different levels of monetary reward. Pupil response to anticipated reward was also recorded as an additional measure of reward sensitivity. The second paradigm assessed the effect of a varying number of choice alternatives on internally triggered saccades and the effect of reward anticipation and penalty avoidance on performance therein. This allows to infer what effect increasing uncertainty has on the costs of cognitive control, potentially shifting the cost/benefit ratio. The third paradigm assessed different levels of memory load and recall delay on memory-guided saccades in the presence of reward and penalty. This paradigm was designed to assess the effect of a shift in signal-to-noise ratio (delay, memory load) on motivational control of motor vigour and memory precision.

1.9.2. Chapter 3

As dopamine has been found to modulate the desirability of a goal and reduce the amount of effort perceived, in the following chapter I repeated all three saccadic paradigms described above and investigated the effect of different dopaminergic levels on task performance. This was done by adding external pharmacological manipulation (levodopa, haloperidol). The placebo-controlled, within-subject study design allowed the interpretation of higher and lower than normal dopaminergic levels and their effects on saccadic performance. A special focus was given on the effects of different dopamine

levels on motivational processes driven by both appetitive and aversive incentives. This may possibly allow to dissect the mechanisms of dopamine and serotonin in different reward valences. At the end of this chapter, I also discussed additional measures of reward sensitivity recorded during this study, namely, pupillometry data and spontaneous eye blink rate and match saccadic results with self-reported measures of personality traits.

1.9.3. Chapter 4

Eleven patients with ventral tegmental area deep brain stimulation (VTA) were recruited at the National Hospital for Neurology and Neurosurgery (NHNN) for this study and completed the saccadic double-step paradigm (previously introduced in **section 2.1**). This allowed for the modulation of mesocorticolimbic dopamine specifically and aimed to answer whether DBS stimulation ("ON" vs. "OFF") within the VTA has an effect on oculomotor properties, distractibility and reward sensitivity assuming it may potentially alter (increase?) dopamine activity therein.

1.9.4. Chapter 5

In the final experimental chapter, the link between dopamine and working memory, being a key component of goal -behaviour, was further explored. Using a tablet-based working memory task, localisation and identification performance was examined in, firstly, the same group of healthy volunteers described in **Chapter 3**, on either placebo or a single dose of Madopar and haloperidol and, secondly, in the cohort of VTA-DBS patients described in **Chapter 4** "ON" and "OFF" their stimulation. This paradigm was chosen to shed light on the effect of sub/supra-normal dopamine in the striatum and prefrontal cortex on working memory precision.

2. Influence of motivation on saccadic performance in healthy volunteers

2.1. Task I: Effect of incentives on avoiding an early distractor

2.1.1. Background and hypothesis

Distraction can be both beneficial and detrimental depending on the circumstances. Evolutionarily, reacting to prey or predators fast was of great importance for survival (Shelley-Tremblay and Rosén, 1996). More generally, orienting to a distractor is only beneficial if the danger of ignoring it is greater than the gains from continuing with the current goal. This is because distraction comes at the cost of neglecting an ongoing task in a limited capacity system. This limitation may be due to different ongoing tasks sharing the same pathways within the network, necessitating control mechanisms to operate (Shenhav *et al.*, 2017). It is, however, discussed whether the limited capacity for control mechanisms may actually reflect the purpose of control itself rather than a disadvantageous limitation (Shenhav *et al.*, 2017). Optimising this trade-off may, hence, be critical for survival depending on the circumstances.

Cognitive control processes can be measured by involuntarily evoked saccades to a distractor termed “oculomotor capture errors” (Ding and Hikosaka, 2007; Milstein and Dorris, 2007; Anderson, Laurent and Yantis, 2012; Theeuwes and Belopolsky, 2012). A recent paper by Manohar et al. (Manohar et al., 2015) revealed the effect of motivation on saccades and distractor avoidance using an incentivised variant of the double-step paradigm. Due to the paradigm’s setup it allows to assess saccadic curvature towards the distractor location as a measure of distractor pull and its reward sensitivity to low and high monetary reward incentives (Hickey and van Zoest, 2012; Schütz, Trommershäuser and Gegenfurtner, 2012; Theeuwes *et al.*, 2016). Collecting data from healthy controls they found an increase in

saccadic peak velocity, a decrease in reaction time as well as reduced distractibility (distractor pull) when reward was on offer (Manohar et al., 2015). These findings were intriguing in a few ways. **(1)** It challenged the long-established speed-accuracy trade-off, **(2)** underpinned the sensitivity of attention towards rewards and **(3)** found saccades, traditionally thought of as ballistic movements and, therefore, not susceptible to feedback signals, to be modulated by reward. To explain these findings, they introduced a "cost for controlling intrinsic neuronal noise" into the standard optimal control theory, which they hypothesised is reduced by reward and thereby leads to an improvement in performance across apparent limits (speed-accuracy trade-off) (Salamone, 2002). These effects, likely mediated by dopamine, had been shown to increase response vigour (Niv *et al.*, 2006; Beierholm *et al.*, 2013) and were also looked at in PD, a condition well-known to involve dopaminergic deficits. In this cohort reduced reward sensitivity of motor vigour but maintained levels of accuracy were found (Manohar *et al.*, 2015). These findings were in line with previous research which had shown diminished accuracy and increased errors for matched velocities in PD (Rand *et al.*, 2000; Joti *et al.*, 2007; Mazzoni, Hristova and Krakauer, 2007) supporting their theory. It is hypothesised that dopamine depletion spares the "liking" of rewards while reducing the willingness to exert effort in order to reach them (Salamone, 2002), potentially due to a higher "energetic cost" of the movement (Mazzoni, Hristova and Krakauer, 2007). More recently pupillometry has been suggested as an additional tool to, objectively, but more importantly dynamically, measure reward processing and the influence of reward-related motivation on attention and cognitive control (Chiew and Braver, 2013). Reward as well as reward expectation have been shown to modulate pupil size (Delaville, De Deurwaerdère and Benazzouz, 2011; Manohar and Husain, 2015; Manohar *et al.*, 2017), showing that changes in pupil size are greater in response to or expectation of rewards when compared to unrewarded conditions.

In the first part of this experimental chapter, I will repeat the same experiment published by Manohar et al. with a cohort of young healthy volunteers collecting data on saccadic properties and subsequently matching them with their pupillometry data on reward sensitivity. These data will serve as baseline data for a later study (**Chapter 3**), which will explore the role of pharmacologically altered dopamine levels in healthy volunteers on the same task.

2.1.2. Demographics

Sixteen healthy volunteers, of which 7 were female and 9 were male, were recruited through a departmental online recruitment pool (Demographics, see **Table 2.1**). All participants were right-handed. Pre-screening was conducted via telephone or email. Exclusion criteria for participation were as follows: **(1)** Age <18 years or >60, **(2)** significant cognitive impairment (MMST <22/30), **(3)** pre-existing psychiatric illnesses or **(4)** neurological conditions, **(5)** concurrent treatment with centrally acting drugs or use of recreational drugs in the last month (self-reported).

The study was approved by the local Research Ethics Committee at University College London (project ID number: 9125/001) and conducted at the UCL Institute of Neurology. All participants gave written informed consent in accordance with the Declaration of Helsinki. Eligible subjects were asked to attend on one occasion to complete one eye tracking paradigm.

Demographic data	
age	28.67 years
SD	± 5.94 years
female	7
male	9

Table 2.1 Demographics – Double-step paradigm

2.1.3. Eye tracking setup

Participants were seated in front of an LCD monitor (resolution 1280 x 800 pixels, 75Hz), their heads positioned in a head and chin rest at a distance of 60 cm from the screen (**Figure 2.1**). Stimuli appeared on the screen, controlled by MATLAB and Psychophysics Toolbox while eye movements and pupil size were recorded by the SR Eyelink 1000 Hz infrared eye tracker. Eye movements were parsed online by the Eyelink PC and these data sent to the presentation PC to provide trial-by-trial feedback to the participant. Randomised 9-point calibration was performed at the beginning of each experiment. Auditory cues were played over speakers attached to the monitor. This general setup remained unchanged and will apply to all other eye tracking paradigms discussed in this and the next chapters.

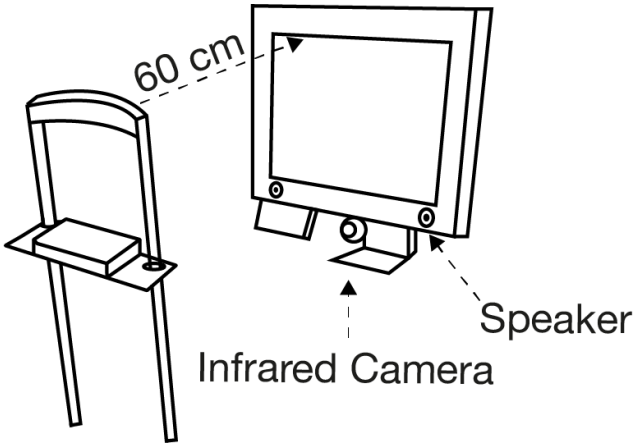

Figure 2.1 Eye tracker setup: The head and chin rest (on the left) was placed 60 cm away from the computer monitor (on the right) which was equipped with an infrared eye tracking camera (SR Eyelink 1000). Speakers were attached to the bottom of the monitor displaying auditory cues.

2.1.4. Eye tracking paradigm

Three equidistant grey circles were displayed in front of a black background on the monitor and participants were asked to fixate on the disc lighting up white (= fixation point) **(Figure 2.2)**. Once fixation on the initial disc was confirmed by the eye tracker, an auditory cue announced the maximum

monetary reward on offer for each trial ("0p, 10p or 50p maximum"). Participants were instructed to look from the fixation point to a subsequently illuminated target disc (yellow) as fast and accurate as possible while ignoring the distractor disc which was illuminated shortly before the onset of the target disc. The distractor appeared following a random foreperiod of 1400, 1500 or 1600 ms after fixation on starting point was confirmed. The distractor-target interval varied between 40 and 120 ms. After the gaze reached the target, participants received feedback on how much reward they earned (details on reward calculation, see **section 2.1.6**). The task consisted of 2 blocks with each 54 trials plus 10 practice trials at the beginning, the latter having been excluded from the analysis.

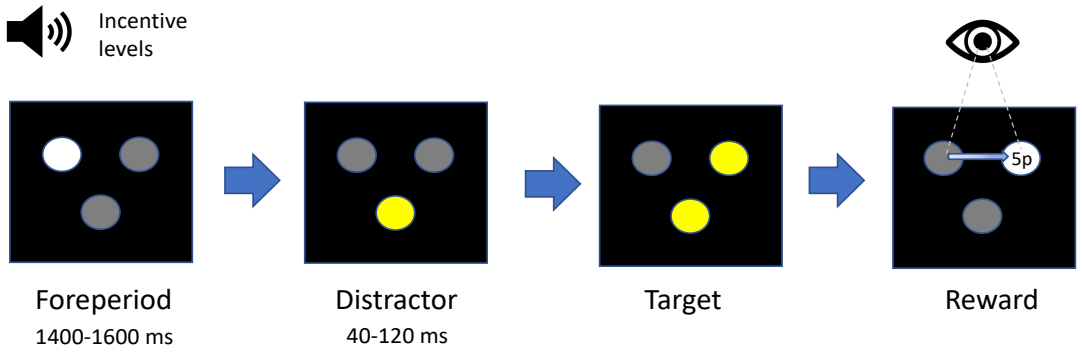

Figure 2.2 Double-step paradigm- experimental setup: At the beginning of each trial 3 discs (two grey, one white) were displayed on a black screen, each 4° in diameter (visual angle). The white disc represented the initial fixation point. An auditory cue announcing the reward level (0p, 10p or 50p maximum) was followed by a variable foreperiod of 1400-1600ms. A distractor lightened up first and after 40-120ms was followed by the illumination of the final target. The distance between the discs was 11.4° (visual angle). The participants were asked to ignore the distractor and elicit a saccade from the fixation point to the final target as fast as they could. On reaching the target they received feedback on how much reward they earned.

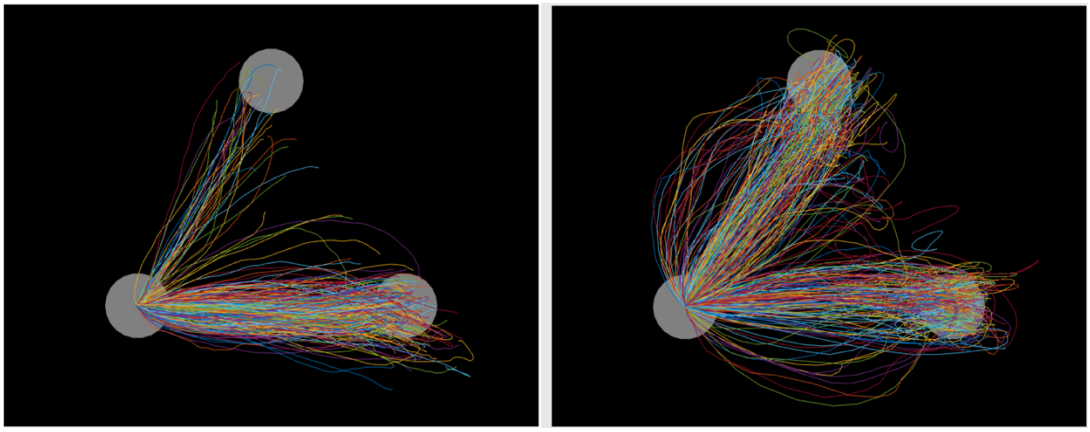

Figure 2.3 Double-step paradigm: Example of eye movements of two subjects completing the task (left: ~10% of trials incorrect; right: ~50% of trials incorrect); On both illustrations the right bottom circle represents the target, the top circle the distractor. For the graphical illustration saccadic directions have been rotated resulting in the fixation point being at the left bottom circle for all trials on this figure.

2.1.5. Eye tracker data handling

The data extracted were parsed into saccades using criteria on velocity of $30°s^{-1}$, and acceleration > $8000°s^{-2}$ (**Figure 2.3**). Saccadic reaction times were calculated as the time from distractor onset until the threshold defined above was exceeded. Saccades were classified as correct if the saccadic endpoint of the first saccade complying with above criteria was closer to the target than the distractor. The proportion of oculomotor capture errors, saccades that landed closer to the distractor location than the target, was used as an index of distractibility. For correct trials (endpoint closer to target than distractor), the peak velocity was calculated using 4ms windows from saccade onset to termination, discarding any speeds greater than 900°/s and smaller than 100°/s and any saccades during which tracking was lost. To factor out the effect of amplitude size on saccadic peak velocity (main sequence), a linear regression between amplitude size and peak velocity was performed and statistical analysis was subsequently carried out on the calculated peak velocity residuals. Saccadic amplitudes were defined as the distance (visual angle in degrees) between fixation point and the endpoint of the first saccade registered fulfilling above criteria. Amplitudes smaller than

1° and bigger than 20° were discarded. Amplitude variability was calculated as the standard deviation of saccade amplitudes and used as a measure of endpoint variability. The departure angle of the saccade, defined as the direction the saccade is heading in at the start of its trajectory (when it leaves the 0.83° (= 30 px) radius of the starting point), was used to assess distractor pull, indicating the level of distractibility on this trial. Its unit is a number between 0 and π/3 where 0 represents the direction towards the target and π/3 is the direction pointing towards the distractor. A summary of the units and calculation of all variables used in this chapter can be found in **Table 2.2**.

Measures	**Units/Description**
Peak Velocity	Degrees/second (°/s); 4ms windows from saccade onset to termination
Residual Peak Velocity	Degrees/second (°/s); Velocity residuals after regressing out amplitude size
Amplitude	Degrees (°); Distance (visual angle) from saccade onset to termination
Amplitude Variability	Degrees (°); Standard deviation of amplitude
Reaction Time	Milliseconds (ms); time between distractor onset and reaching saccadic threshold (velocity of 30°/s, acceleration > 8000°s^{-2} and amplitude >1°)
Proportion of Oculomotor Capture	Percentage (%) of trials where endpoint was closer to distractor than target
Departure Angle	Angle measured in a frame where angle of zero is correct (towards target), and positive values are increasingly toward the distractor; a value of π/3 represents the direction of the distractor

Table 2.2 Double-step paradigm: Overview of parameters used to assess saccadic properties in the next chapters and their units.

Pupil size was recorded from all participants throughout this task by the SR Eyelink 1000 and was measured in arbitrary eye tracker units. Pupillary

change was calculated as the mean proportional change of pupil size between the time 1200-1400ms after auditory cue onset relative to pupil size before cue onset. Pupillary reward sensitivity was defined as the mean pupillary diameter change as a response to rewarded trials versus unrewarded conditions and which set pupil change at 0p to zero (0p-0p; 10p-0p; 50-0p). Greater change in diameter indicated higher reward sensitivity.

2.1.6. Reward calculation and feedback

Participants received feedback on how much money they earned at the end of each trial. The reward amount was displayed in p (pence) inside the target disc after the target was reached. This was accompanied by a bell sound if the reward earned was higher than 10p and a cash register sound if it was higher than 30p. The reward was calculated as a proportion of the maximum amount announced at the beginning of the trial and was dependent on the participants' performance. It was calculated according to the reaction times of the participants' 20 previous trials using an exponential fall-off function (**Figure 2.4**). This ensured all participants experienced similar reward feedbacks and aimed to allow for potential fatigue effects during the task. Reward was calculated as below:

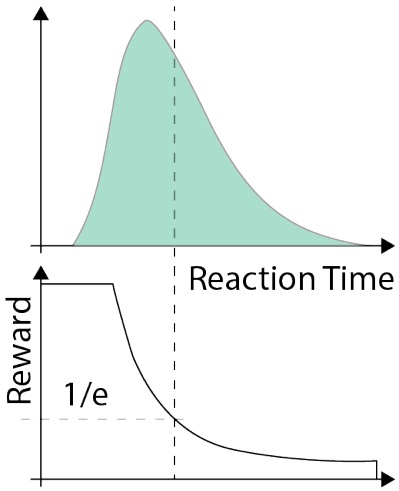

Figure 2.4 Reward calculation-exponential fall-off (adapted from Manohar et al 2015)

$$R(t) = R_{\max} \cdot \min\left(1 - e^{\frac{t-\tau_2}{\tau_1}}\right)$$

Where R is reward for the current trial, t is the time taken to reach the target, R_{max} is the maximum reward available on the specific trial, and τ1 and τ2 are adaptive reward criteria. These were adjusted using the last 20 trials of the participant keeping 10% of trials faster than τ1 and 30% of trials slower than

τ2. This was done to ensure that each participant experienced the full range of reward feedback independent of their baseline performance. This reward calculation also remains valid for all further incentivised tasks in this thesis.

2.1.7. Statistical analysis

A mixed linear model was used to analyse the effect of reward on the variables listed above (**Table 2.2**). This was done with R's nlme package as well as SPSS using a restricted maximum likelihood ratio (general linear model, see **Table 2.3**). Comparing different models using the Chi-square test and taking our research questions into account, data analysis was eventually performed using a random intercept model to account for each participant's individual baseline performance. Reward was used as a linear within-subject factor. Residual plots were plotted to check for normal distribution. The alpha level was set at 0.05.

R	lmer (*var* ~ reward + (1 | ID), data)
SPSS	MIXED *var* BY reward /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE) /FIXED= reward | SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC).

Table 2.3 Double-step paradigm: Model used for statistical analysis in R and SPSS respectively. The placeholder "var" represents the variable of interest in the analysis (i.e., peak velocity).

Statistical analysis for pupil reward sensitivity was performed using the same mixed linear model (see **Table 2.3**). Reward was again defined as a linear factor (0p -10p -50p) and means of proportional pupil change per subject per reward condition were used. Results reported were retrieved from the R analysis.

2.1.8. Results

2.1.8.1. Reward improved accuracy and distractibility

Participants showed a reduced proportion of oculomotor capture errors when they were incentivised (**Figure 2.5 (A)**). The proportion of trials where saccadic endpoints were closer to the distractor than the target was significantly smaller on rewarded trials (F (1, 31.00) = 7.45 p= .005, β= -8.6% (2.92)). Improved distractibility, reflected by the departure angle of saccades as a measure of distractor pull, was also noted. Significantly fewer saccades were initiated heading in the direction of the distractor on rewarded trials when compared to the "0p- conditions" (F (1, 1876.4) = 5.97 p= .015, β= -0.08 (0.032). These findings may suggest improved cognitive control through motivation (**Figure 2.5 (B)**).

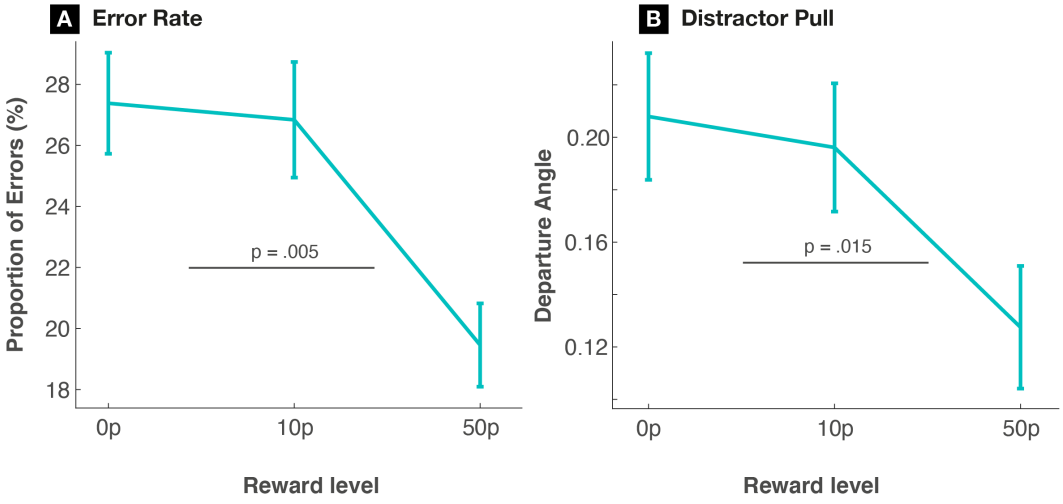

Figure 2.5 Double-step paradigm: (A) Proportion of trials with saccadic endpoint closer to the distractor than the target (= oculomotor capture). (B) Departure angle: Saccadic trajectory at beginning of the saccade (target (= 0), distractor (= π/3)). There was a significant main effect of reward on both parameters improving overall performance.

2.1.8.2. Reward increased peak velocity

Although, following the speed-accuracy trade-off, the assumption could have been to find slower saccades in the presence of greater accuracy, as

previously reported by Manohar et al. (Manohar *et al.*, 2015), my findings also reflected that motivation increased saccadic peak velocity (F(1, 1352.2) = 43.57, p< .001; β= 29.78°/s (4.52), **Figure 2.6 (A)**). This also held true after regressing out the effect of amplitude size according to the main sequence (**Figure 2.6 (B)**). Residual peak velocity remained reward sensitive resulting in faster saccades on rewarded trials (F (1, 1371.0) = 28.58, p< .001; β= 32.24°/s (6.04)).

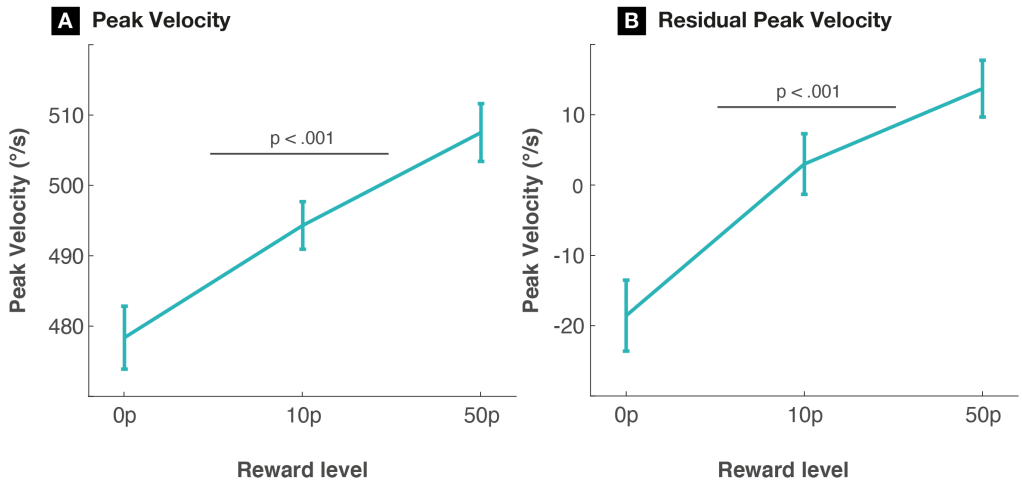

Figure 2.6 Double-step paradigm: (A) Saccadic peak velocity as well as (B) residual peak velocity were reward sensitive in this cohort. Participants were faster when rewarded (p< .001).

2.1.8.3. Amplitude size did not change with incentives

There was no main effect of reward on amplitude size (F (1, 1356.0) = 0.37, p= .54) and despite amplitude variability being slightly reduced on rewarded trials, this did not reach significance (F (1, 31.16) = 2.89 p= .099).

2.1.8.4. Reward decreased reaction time

Participants had significantly reduced reaction times on rewarded trials when compared to unrewarded trials (F (1, 1351.5) = 7.34 p= .006; β= -13.24ms (4.88) (**Figure 2.7 (A)**). Conditional accuracy plots (**Figure 2.7 (B-C)**) showed that, while reaction time and distractor pull improved significantly, especially

in high reward conditions, this did not lead to a speed-accuracy trade-off. Participants were more accurate when rewarded at *comparable* reaction times for both measures.

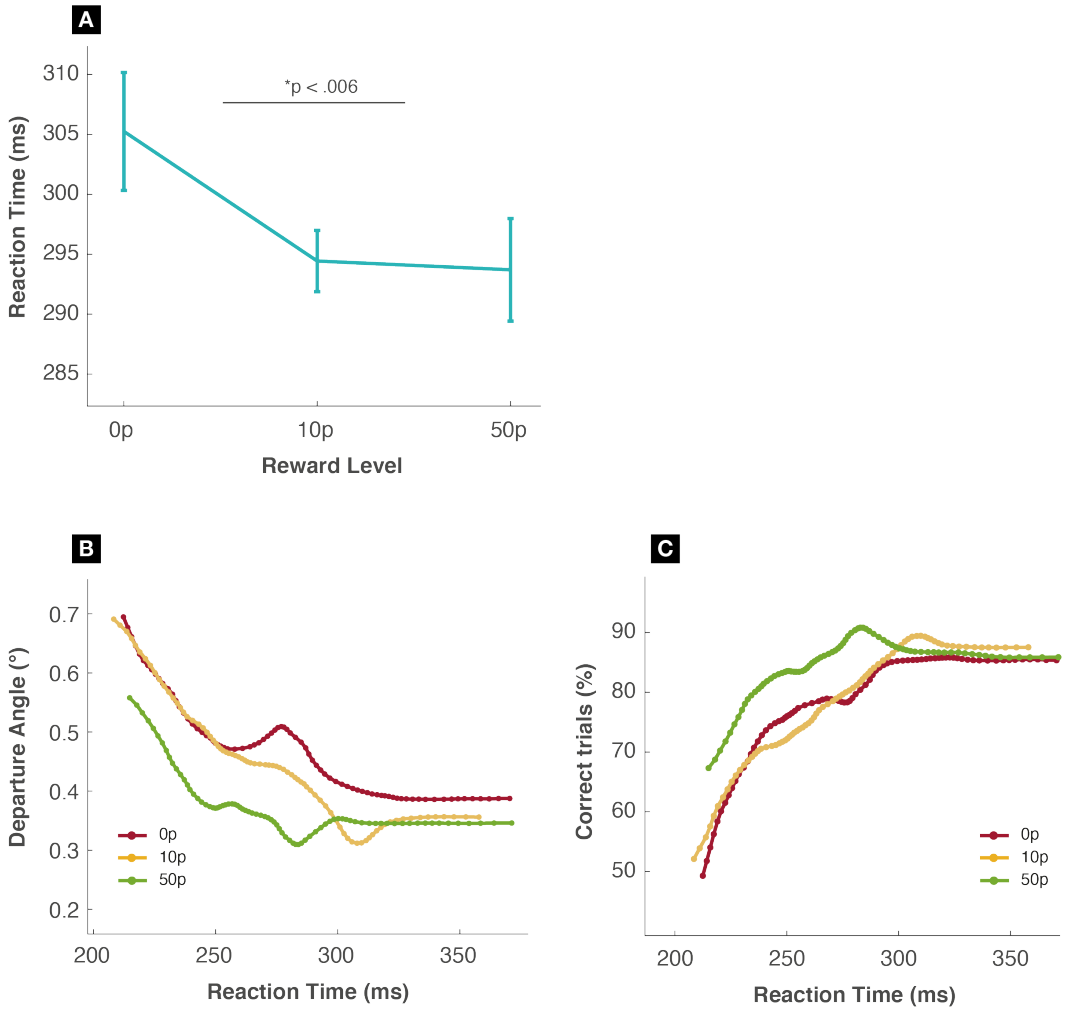

Figure 2.7 Double-step paradigm: (A) Reward shortened reaction time. (B) Conditional accuracy plot showing the relationship between reaction times and distractor pull, (C) as well as between the proportion of correct trials and reaction times. The gradient shown in both figures (B+C) points towards a preserved speed-accuracy trade-off within each reward condition. Participants were more accurate on trials with longer reaction times and in high reward conditions.

2.1.8.5. Pupil size changed significantly with motivation

Pupil modulation in anticipation of reward has more recently been used as a measure of reward sensitivity. In this cohort, pupil size changed significantly

with reward (F (1, 31) = 12.36, p= .001, **Figure 2.8**) in keeping with the findings of improved saccadic properties by reward in the same cohort.

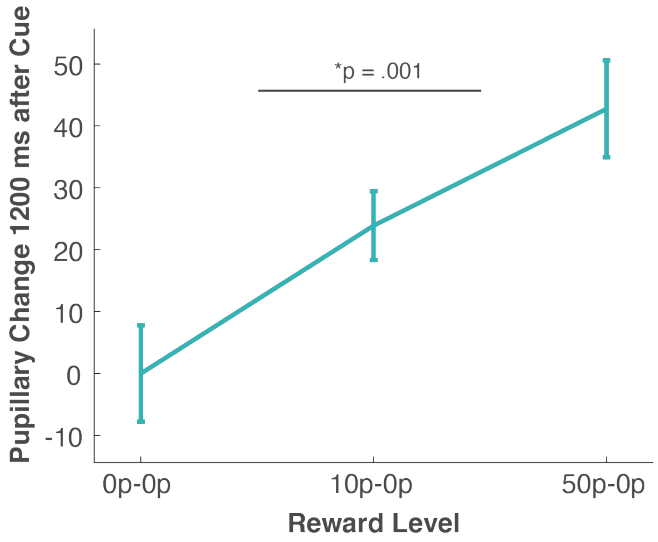

Figure 2.8 Double-step paradigm-pupillometry: Pupil size increased significantly more in the anticipation of reward. Data in the graph reflect the relative pupil change compared to unrewarded conditions (0p conditions set to zero).

2.1.9. Discussion

Above findings are in line with published data of improved saccadic performance in the presence of incentives in both human and animal studies (Takikawa *et al.*, 2002; Tachibana and Hikosaka, 2012; Chen *et al.*, 2013; Bissonette *et al.*, 2014). More specifically, I was able to replicate Manohar's findings on the same task including motivation to increase *speed* (peak velocity) *and accuracy* (decrease the number of oculomotor capture trials) despite a concurrent decrease of reaction times (Manohar *et al.*, 2015). Diminished endpoint variability on incentives reported by them (p= .003) did not reach significance in this cohort (p= .099) although one could argue for a trend. As a measure of distractibility, the amount of distractor pull was assessed, which also showed improved cognitive control as a result of reward sensitivity. In summary this means that both motor and cognitive control were found to improve simultaneously in the presence of reward overcoming well-

established limits described in the speed-accuracy trade-off. Moreover, pupil modulation, as an additional measure of reward sensitivity, was found to be greater in the anticipation of reward.

But how can the speed-accuracy trade-off be overcome by motivation? Manohar et al. (Manohar *et al.*, 2015) here introduced a precision command in addition to the force command in order to explain the apparent violation of the speed-accuracy trade-off in human saccades. The precision command could, hence, account for the increased amount of noise created by the recruitment of larger forces in order to increase movement speed. These improvements are, however, costly and would only seem attractive if the additional cost is covered by a reward of some kind. Seemingly more "attractive" choices could, thus, allow greater exertion of the precision command and lead to an overall improvement of performance. While greater precision is needed to obtain reward, reward discounting might also make it more attractive to obtain reward sooner rather than later (Green and Myerson, 2004; Kable and Glimcher, 2007), which may explain greater precision *and* speed in these trials.

And what are the underlying physiological mechanisms of these findings?

The PFC plays a central role in both action selection and the suppression/inhibition of unwanted movements, building the front end of the cortical-basal ganglia-thalamo-cortical loop (Seo, Lee and Averbeck, 2012). In this context cortical inputs represent a variety of different options, upon which the striatum needs to select one and inhibit the rest based on each option's "value" (Mink, 1996; Humphries, Stewart and Gurney, 2006; Houk *et al.*, 2007). The superior colliculus, situated on the surface of the midbrain, plays a principal role in orienting the eyes toward a target of interest and also receives inhibitory projections from the PFC. Similarly, it serves as a relay transforming sensory input into movement output or the paucity of the same. These signals subsequently lead to high-frequency bursts of spikes in medium-lead burst neurons and long-lead burst neurons in the paramedian

pontine reticular formation or the superior colliculus (Van Gisbergen, Robinson and Gielen, 1981; Opstal and Goossens, 2008; Walton and Freedman, 2014) eventually leading to saccades being elicited. These areas also receive inputs from the caudate nucleus via the substantia nigra pars reticulata, likely to be involved in reward signalling and also cognitive control (Kawagoe, Takikawa and Hikosaka, 1998). Consequently, the basal ganglia, indeed, are thought not to be responsible for the initiation of eye movements but rather for selecting or gating appropriate movements by suppressing unwanted saccades and removing suppression on others through dopaminergic projections (Chevalier *et al.*, 1985; Deniau and Chevalier, 1985). A computational model suggests that the functional basal ganglia anatomy, in fact, can be split into "selection" and "control" pathways, with the former performing the selection as such and the latter controlling the selection process complemented by dopamine (Gurney, Prescott and Redgrave, 2001).

And how do we choose the appropriate action?

Reward-oriented behaviour is driven by a number of factors including attention, motivation and context uncertainty (Dayan and Balleine, 2002; Doya, 2008; Gottlieb, 2012; Kim and Hikosaka, 2015). Competing options are thought to be represented and signalled broadly throughout the neuronal networks (Gurney, Prescott and Redgrave, 2001). Information signals about these actions arise mainly in the cerebral cortex and are relayed to specific subregions of the striatum (Kim and Hikosaka, 2015), the exact location depending on their function (e.g., limbic more medial and sensorimotor information lateral) (Parent, 1990; Brown, Smith and Goldbloom, 1998; Haber, Fudge and McFarland, 2000). The level of activity in those regions depend on the potential action's salience and the propensity of the action to be selected for execution (Koechlin and Burnod, 1996). More salient distractors will require the exertion of more extensive cognitive control processes in order to withstand the distraction which will in turn need to be accounted for by the "benefit" of the goal (Gurney, Prescott and Redgrave, 2001).

The novel paradigm used in the next section was devised to answer the question if and in which way greater distractor salience could be compared with increased entropy created by greater uncertainty in decision-making (higher number of choice alternatives) and if the latter influences saccadic performance and reward sensitivity through a shift in the cost/benefit ratio. To answer this question data were collected from healthy controls completing internally triggered saccades in different levels of decision uncertainty (Hick's law). We hypothesise that the costs of the precision command may correlate positively with an increase in distraction/entropy and negatively with the enhancing effect of incentives. Additionally, we introduce incentives of different valence (reward anticipation vs. penalty avoidance) to probe if these may have differential effects on different saccadic outcome measures.

2.2. Task II: The effect of incentives on multi-alternative decision-making

2.2.1. Background and hypothesis

"Higher levels of environmental uncertainty (quantified as risk, or variance in outcome) should breed (…) higher levels of distractibility (Hick, 1952)".

This well-established law governing cognitive information capacity in the presence of different response alternatives states that increasing the number of options increases the decision time/reaction time logarithmically (Hick, 1952). This is the case because decisions are not made one by one, but after grouping options into subcategories, eliminating one category (half of the options) at a time in order to speed the overall decision process (Proctor and Schneider, 2018). Similarly, higher uncertainty measured by entropy according to the information theory (Shannon, 1949), can prolong decision time. Cognitive control is crucial for optimal behaviour especially in conditions of higher uncertainty (Wu *et al.*, 2017) and consists of two processes:

Uncertainty representation and response generation (Miller and Cohen, 2001; Fan, 2014). Functional imaging studies showed a positive relationship between activity in the cognitive control network including frontoparietal network and amongst others the basal ganglia and entropy (Lucetti *et al.*, 2010; Fan, 2014; Koziol, 2014), pointing to the fact that greater uncertainty requires a higher level of engagement in control networks, which in turns may be costly.

Hick's law has since its discovery in 1952 been replicated in numerous behavioural studies, with many more examples having recently been published (Usher, Olami and McClelland, 2002; Fan *et al.*, 2008; Hawkins *et al.*, 2012). It has, however, long been unclear whether saccades also follow the same relationship. In the last two decades studies on saccades have found mixed results. Internally triggered saccades to remembered colour-coded locations obeyed the law and showed longer reaction times when higher numbers of choice alternatives were presented (Keller and Heinen, 2005; Hill and Keller, 2008). The absence of an effect in prosaccades was found, while antisaccades followed Hick's law (Kveraga, Boucher and Hughes, 2002) and even reports of a negative relationship for externally triggered saccades were published, termed the "anti-Hick's" effect (Lawrence *et al.*, 2008; Lawrence and Gardella, 2009). The violation of Hick's law in prosaccades/externally triggered saccades is thought to be due to visually guided saccades being an "overlearned" operation, that reaches a degree of automisation and, therefore, would be less sensitive to uncertainty and less burdening for cognitive control processes. It has been hypothesised that this is due to a greater level of movement planning involved in internally triggered rather than externally triggered saccades. This is supported by the finding that internally triggered saccades show a greater activation of the frontal eye field, involved in the preparation and triggering of saccades than internally triggered saccades do, indicating a higher complexity of preparational processes (Schall, 1995). In contrast, activation of short loops in the parietal lobe through the posterior part of the internal capsule may be sufficient to

elicit reflexive saccades (Pouget, 2015). Evidence from non-saccadic data supports this idea by showing a greater peak of the "bereitschaftspotential", reflecting motor preparation in internally triggered movement (Obhi and Haggard, 2004) as well as greater activation in medial frontal areas for internally generated actions in neuroimaging studies (e.g., Jenkins *et al.*, 2000; Cunnington *et al.*, 2002) when compared to externally driven actions. In other words, if behaviour follows Hick's law or not may, indeed, depend on the degree of complexity of the task used (Bibi and Edelman, 2009).

We know from the previous task that distractor effects are attenuated by reward-induced motivation (Manohar *et al.*, 2015). Applying this idea to the current task, an open question may be if motivation also decreases response time in a multi-alternative response task and if reward and penalty may play different roles in controlling those cognitive control processes, potentially having different neural correlates all together (Hübner and Schlösser, 2010; Krebs *et al.*, 2011; Manohar *et al.*, 2015). Cognitive control can be improved by allocating internal resources to the task and improving the signal-to-noise ratio by shielding the system from irrelevant external stimuli (Lu, 2008; Manohar, 2014). Both desiring a positive outcome or avoiding an unfavourable outcome could, hence, improve performance through motivational processes. Reward-guided behaviour could in this context be the process of improving outcome via both loss avoidance and reward anticipation, irrespective of the valence (Dolan, Singer and Seymour, 2007).

These findings led me to hypothesise that both reward and penalty could improve saccadic performance in this task similarly. However, differential effects on procedural learning and distinct neural correlates have been reported in a serial reaction time task for incentives of different valence (Wächter *et al.*, 2009). Although penalty led to improved task performance measured by RT gain, it did not show an effect on sequence learning, which was improved in the rewarded block. In contrast to this, improved learning was also found in punishment when compared to reward in another study (Galea *et al.*, 2015).

To answer these questions, a novel incentivised task was devised assessing Hick's law using internally triggered saccades to a varying number of response alternatives/targets. Given internally triggered saccades may represent a higher degree of complexity than externally triggered saccades, I expected to find an increase in choice RTs with a higher amount of response alternatives in this task, where saccades were to be made to either two, four or eight placeholders (experimental paradigm, see **section 2.2.3**.). Based on above discussion, I hypothesise that reward enhances performance regardless of incentive valence but that the extent may be diminished by the higher cost of the control demand in conditions in higher entropy conditions.

2.2.2. Demographics

A total of twenty participants completed the task of which eighteen datasets were included in the analysis below due to eye tracking/data quality issues of the remaining two datasets (**Table 2.4**). The study was approved by the local Research Ethics Committee at University College London (project ID number: 9125/001) and conducted at the UCL Institute of Neurology. All participants gave written informed consent in accordance with the Declaration of Helsinki. Exclusion criteria remained unchanged from those listed in **section 2.1.2**.

Demographic data	
age	30.83 years
SD	± 5.01 years
female	13
male	5

Table 2.4 Demographics -multi-alternative decision-making task

2.2.3. Eye tracking setup and paradigm

The eye tracker setup was unchanged to the previous section (details, see **section 2.1.3**).

Either two, four or eight circular placeholders (grey, 1.4° in diameter) were displayed on a black screen around a central fixation point (=white) **(Figure**

2.9). After fixation on the latter was confirmed, an auditory cue indicated the incentive levels ("lose", "nil" or "win"). Nil trials were not incentivised, win trials had a potential maximum reward of 50p, lose trials a maximum loss of 50p depending on the participants' performance. The auditory cue was followed by a random foreperiod between 0.5-1.7 s. Subsequently, the central fixation disc was replaced by an arrow pointing towards one of the placeholders on offer on the trial, and participants were instructed to look at the indicated placeholder as quickly and accurately as they could in order to get reward or avoid penalty. The location of the placeholders was randomised. Two possible targets could, hence, take any locations opposite of each other surrounding the central fixation point, while 4 possible targets could be arranged either square- or diamond-shaped (with constant distances between each other). Once the target was reached, participants received visual feedback as the target turned yellow and the amount of money earned/lost was printed in the centre of the target. Participants were then to return to the central fixation point to start the next trial. Reward/penalty feedback was accompanied by different bell/cash register sounds for wins and horn sounds for penalty of different magnitudes. Reward/penalty calculation was unchanged to the previous chapter and calculated as a function of the reaction time (detailed information, see **section 2.1.6**). "Reward" calculation for "lose" trials was mirrored from that for "win" trials where optimal performance meant not losing any money.

The task consisted of 8 blocks of each 72 trials amounting to a total of 576 trials per participant. Ten practice trials were made at the beginning of the first block, they were not included in the analysis. **Figure 2.10** shows all 576 eye movements made by one participant during this task.

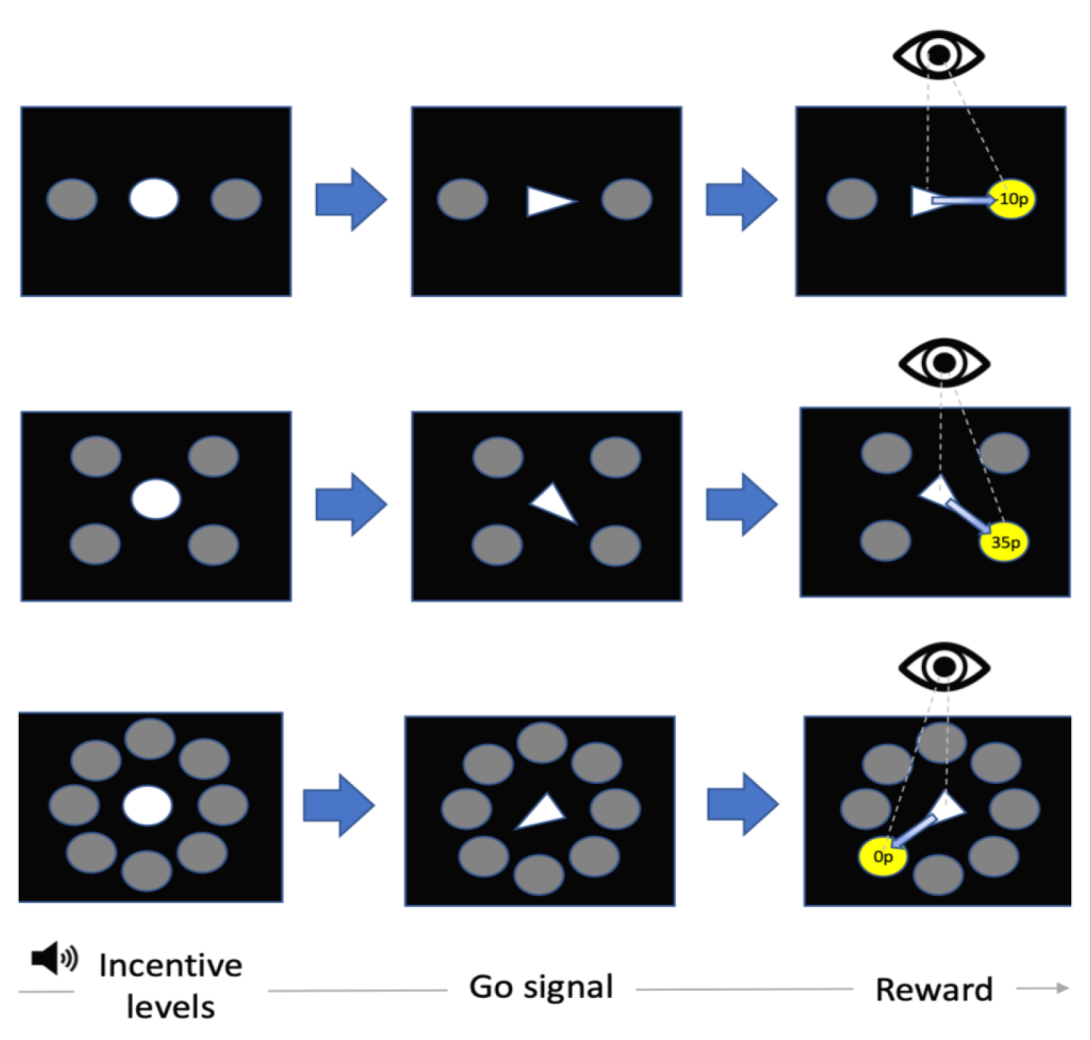

Figure 2.9 Multi-alternative decision-making- Internally triggered saccades in conditions of varying uncertainty: Participants were presented with either two (top row), four (middle row) or 8 (bottom row) possible targets for each trial. After the central disc was fixated by the participant, it was replaced by an arrow (second column) pointing towards one of the placeholders. A saccade then had to be made from the fixation point (replaced by the arrow) to the target indicated as fast and accurate as possible. Incentive levels were announced at the beginning of each trial. The amount of reward (0p - 50p) or penalty (-50p - 0p) earned/lost was displayed in the centre of the target after the target was reached. The position of targets in row one and two of the graph are examples for possible locations and were randomly rotated around the fixation point during the task.

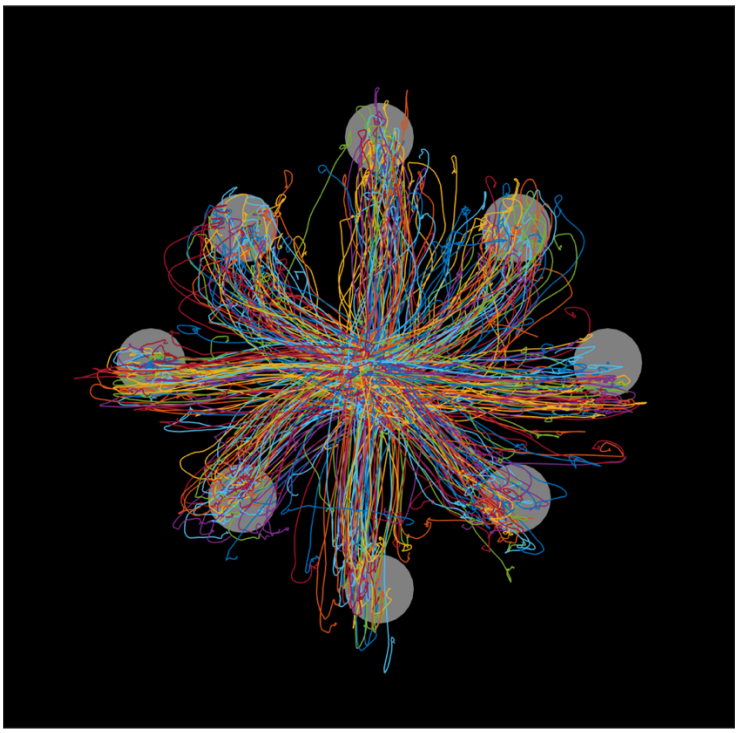

Figure 2.10 Multi-alternative decision-making: Example graphic of all saccades (= 576) made by one subject during the task before filters for analysis were applied. All trials started from the central fixation point and ended at one of the targets indicated by the arrow.

2.2.4. Statistical analysis

Analysis was performed using a mixed linear model with “incentive” as a 3-level factor (-50p, 0p, 50p) and uncertainty (number of possible targets 2, 4 and 8) as a linear covariate (**Table 2.5**). Due to a slightly varying number of trials the z-score for the uncertainty-factor was calculated for each subject and analysis was performed using z-scored values. While in the previous chapter reward was also used as a linear factor, the presence of an incentive with negative valence and the hypothesis that penalty trials would show similar effects on saccadic properties as win trials warranted an analysis defining incentive as a 3-level factor with 0p being used as baseline reference. The analysis was again performed in R and SPSS using a compound symmetry covariance matrix and was fitted using the restricted maximum likelihood method (REML). Post-hoc comparisons for the different incentive levels were performed using Bonferroni correction. Results reported in the section below are from the SPSS analysis.

R	lmer (*var* ~ incentive*number of targets + (1 | ID), data)
SPSS	MIXED *var* BY incentive WITH number of targets /CRITERIA=DFMETHOD (SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE) /FIXED= incentive number of targets incentive * number of targets | SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC)

Table 2.5 Multi-alternative decision-making: Model used for statistical analysis in R and SPSS. The placeholder "var" represents the variable of interest in the analysis (i.e., peak velocity). "number of targets" represents the linear uncertainty factor (2, 4 and 8 possible targets computed as z-scored values), "incentive" represents the three different incentive conditions ("lose", "nil", "win").

2.2.5. Results

2.2.5.1. Both incentives decreased reaction times of internally triggered saccades

Remarkably, in this task reaction times were not found to be significantly slower when more placeholders were on display. In fact, there was no main effect of uncertainty on saccadic latencies ($F(1, 9404.03) = 0.017$, $p = .897$. Given the non-linearity of the uncertainty factor (**Figure 2.11**), I repeated the analysis using uncertainty as a 3-level within-subject factor, which resulted in a smaller p, but eventually did not reach significance ($F(2,9401.01) = 1.99$, $p = .137$). Analysis showed, however, that the reaction time of internally triggered saccades decreased when participants were incentivised ($F(2, 9404.01) = 7.51$, $p<.001$). More interestingly, there was no statistical difference ($p = .81$) between avoiding monetary loss (ß= - 4.3 ms (1.14), $p< .001$) and anticipating reward (ß= - 3.05 ms (1.14) $p = .023$). Furthermore, the incentive effect was

not modulated by uncertainty (interaction between incentive and uncertainty interaction F (2, 9404.02) = 1.41, p= .25).

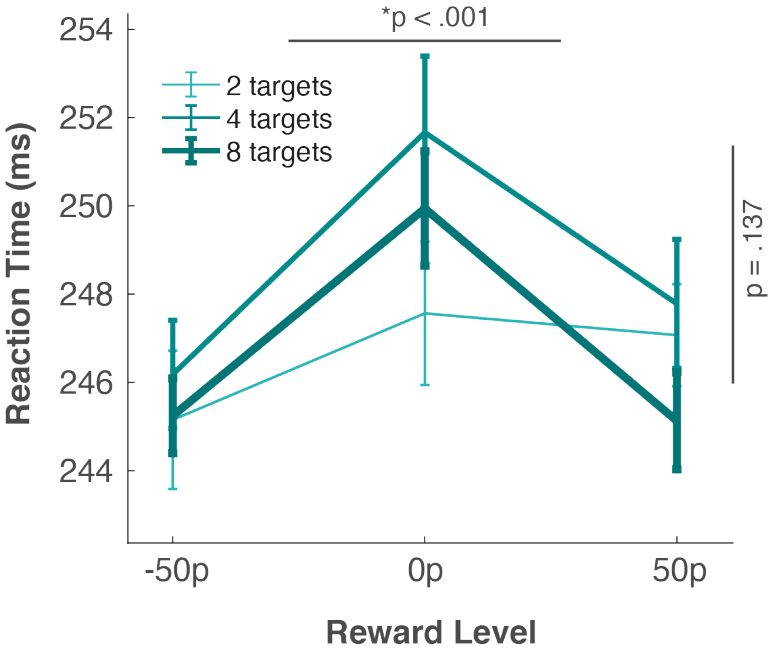

Figure 2.11 Multi-alternative decision-making: Reaction time did not change with increasing uncertainty. The lack of statistical significance may be due to quite large standard errors or the filter criteria used. Running the model with a 3-level factor of uncertainty resulted in a p= .15 (n.s.) for uncertainty.

2.2.5.2. Greater uncertainty reduces motor vigour

Saccades were faster when incentivised (F (2, 9411.0) = 12.68, p<.001) and slower with greater uncertainty (F (1, 9411.0) = 6.99, p= .008; **Figure 2.12 (A)**). The latter was due to smaller amplitude size caused by greater uncertainty (F (1, 9423.99) = 59.46, p<.001). Win trials led to an increase in speed (ß= 8.89°/s (1.77), p<.001), while avoiding penalty, although speeding participants up, did not *significantly* improve speed (ß= 4.15°/s (1.76), p= .057). This led to significantly faster saccades when rewarded compared to penalty trials (reward vs. penalty ß= 4.75°/s (1.76), p= .021). There was no interaction found indicating that incentives and uncertainty had parallel additive effects on vigour (F (2, 9411.01) = 0.267, p= .77).

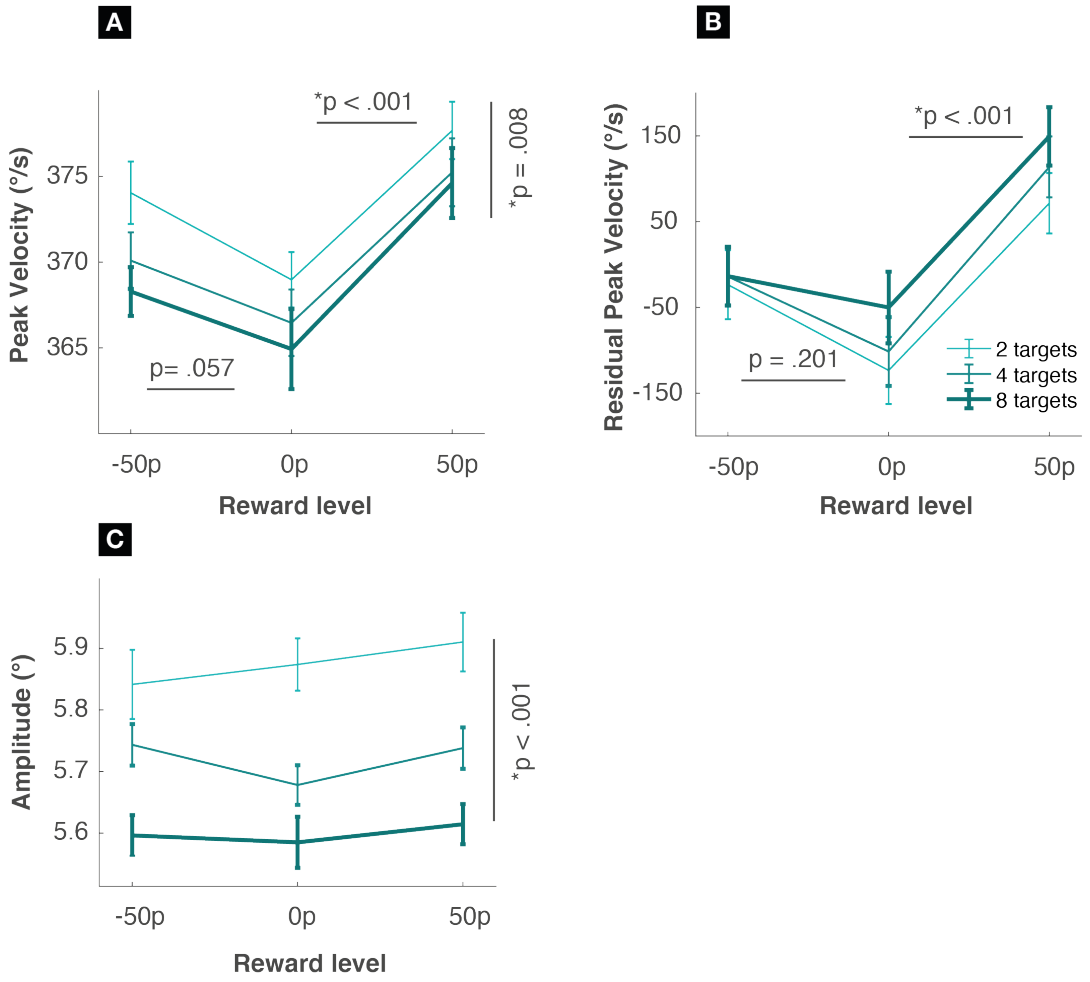

Figure 2.12 Multi-alternative decision-making: (A) An initial effect of uncertainty on peak velocity disappeared after factoring out amplitude size. (B) Participants were faster on win trials but not on loss trials when looking at velocity residuals. (C) Greater uncertainty led to significantly smaller amplitudes.

Saccadic residual velocity remained reward-sensitive even after factoring out amplitude size (F (2, 9428.0) = 12.36, p<.001; **Figure 2.12 (B)**). Here the difference between positive and negative valence was even more pronounced, showing no effect of penalty (win: ß= 202.22°/s (41.16), p< .001; loss: ß= 75.39°/s (41.15), p= .201). Indeed, there was a significant difference between loss and win trials (ß= 127°/s (41.09), p= .006). The main effect of uncertainty vanished in this variable (F (1, 9428.0) = 0.75, p= .386), indicating that the decrease in peak velocity when facing greater uncertainty is mainly driven by hypometric amplitudes, **Figure 2.13 (A-B)**. Reward sensitivity of

residual peak velocity was again not influenced by uncertainty (F (2, 9428.0) = 0.42, p= .66). Amplitude size was not affected significantly by either incentive (F (2, 9424.0) = 0.98, p= .375) and no interaction between incentives and uncertainty was found (F (2, 9424.02) = 0.009, p= .99; **Figure 2.12 (C)**).

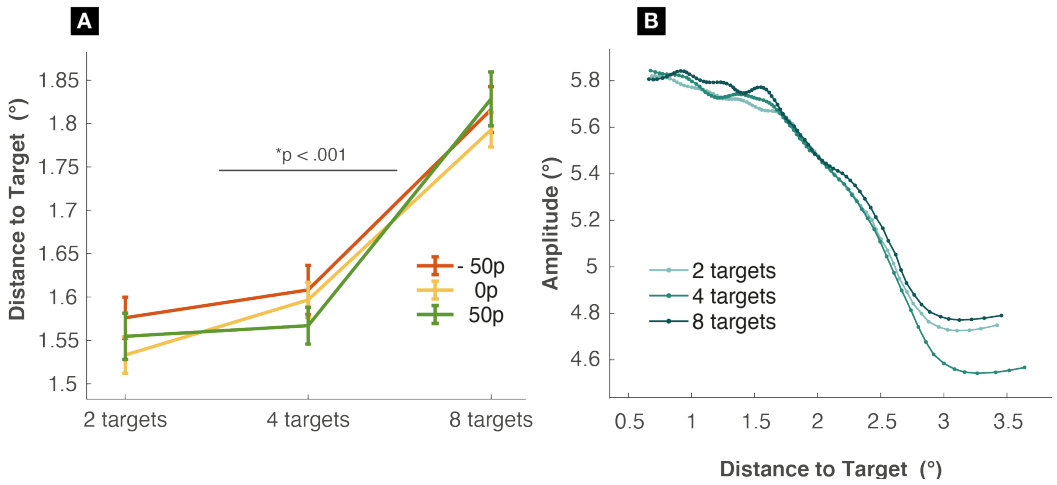

Figure 2.13 Multi-alternative decision-making: (A) Greater uncertainty led to hypometric saccades shown by the distance between saccadic endpoint and target location, (B) conditional plot confirming the relationship between amplitude size and distance to target.

2.2.5.3. Absent correlation between reward and penalty sensitivity and BIS/BAS sensitivity scores

In light of the above findings especially with regards to reward sensitivity of residual peak velocity and the knowledge that movement vigour in this context may be closely linked to an individual's personality and their willingness to exert effort (Reppert *et al.*, 2015), participants were asked to complete the BIS/BAS questionnaire (behavioural inhibition/activation sensitivities). This is of interest because motivated behaviour was previously found to be influenced by two systems (behavioural inhibition/activation system), whose sensitivities may vary among individuals depending on their disposition (Carver and White, 1994). BIS/BAS scores were correlated to saccadic parameter and no interaction between reward sensitivity and questionnaire scores was found. Looking at residual peak velocity specifically, there was no main effect of BIS/BAS (F (1, 9422.0) = 0.00, p= .99)

and no interactions between BIS/BAS scores and incentives (F (1, 9422.0) = 0.06, p= 95) or uncertainty (F (1, 9422.0) = 0.034, p= .85).

2.2.6. Discussion

The recorded data from this paradigm did not reveal a significant effect of uncertainty on reaction times. This may be explained by the higher degree of "learned" behaviour in this paradigm due to its design showing a central arrow. Indeed, remembering a colour code and matching it to the target in question may require a higher degree of movement planning. This idea would also be supported by evidence that arrow cues elicit a type of automatic oculomotor response, which may require less motor planning than an internally triggered saccade in the absence of an arrow cue (Juras, Slomka and Latash, 2009), although this was not reported by Lawrence also using a central arrow cue (Lawrence, 2010). Another reason for this finding could be the failure to split saccades according to their direction, which is known to influence reaction time (Heywood and Churcher, 1980) with Lawrence, e.g., not having used vertical saccade directions in their paradigm (Lawrence, 2010). Finally, it is also possible that the study was simply underpowered to answer this question, which I aim to clarify in the next chapter repeating the paradigm with larger sample size.

2.2.6.1. Uncertainty reduced motor vigour

Another interesting finding from the data was that saccadic amplitudes were significantly smaller when uncertainty was high, which correlated negatively with the Euclidian distance to target. Uncertainty, hence, led to hypometric saccades. This phenomenon was observed previously (Keller and Heinen, 2005), where saccades to 4 and 8 possible targets were shown to be hypometric, followed by a second corrective saccade towards the target. It was hypothesised that correcting the direction of saccades within a sequence (corrective saccades back to the target after hypermetric saccade) may be costlier than opting for rather hypometric saccades and correcting into the same direction (Kuhn and Kingstone, 2009; Hermens and Walker, 2010) while

it also minimises the period of visual blur. Hypometric saccades could, consequently, occur with increasing uncertainty in the oculomotor system optimising cost/benefit ratio. In this context it may also be of interest that amplitude size was found to correlate positively with reaction times (smaller movements require shorter planning times) (Fuller, 1996), which may also be a possible explanation for the lack of effect of uncertainty on saccadic reaction times in this cohort. The prolongation of reaction times may well be masked by smaller amplitudes in higher uncertainty conditions.

2.2.6.2. Incentives of both valences improved reaction times

Looking at the effect of incentives and incentive valence I found that both incentives led to faster reaction times. This was previously predominantly found to be the case for incentives of positive valence (Guitart-masip *et al.*, 2011). Motivation-driven reaction time improvements for both incentive valences, thus, seem to be a novel finding. In the case of saccadic velocity, however, penalty avoidance just about missed significance (p= .057), while reward speeded participants up. It was, indeed, reported that in a task with contingent incentives the effect of penalty trials on saccadic velocity was weaker (but present) than that of reward, which again raises the possibility that this study could have simply been underpowered. Another aspect to be addressed when repeating this paradigm in the next chapter, is to control for participants' intrinsic motivation levels. The above findings indicate a similar motivational net value for both penalty and reward trials for cognitive control (reaction time) and a weaker effect of penalty on motor control (velocity). These observations will be reviewed again in the next chapter when this task will be repeated by thirty healthy controls, revisiting the questions above and investigating the effects of dopaminergic drug effects on the underlying mechanisms.

In summary, the cost of "uncertainty" led to a decrease in motor vigour, but reward sensitivity was not altered by increased entropy in either of the variables in this task. Another way of thinking about varying amounts of

entropy in goal-directed behaviour and cognitive control may be different amounts of memory load stored in short-term memory. For the third part of this chapter, a novel task was thus devised, requiring participants to store varying numbers of target locations and to, subsequently, elicit saccades towards them after short or long delay periods. With this paradigm we seek to answer the following questions: **(1)** Are higher memory load and longer delay periods detrimental to working memory precision? **(2)** Will movement preparation for higher memory load increase reaction times and, **(3)** could incentives of either valence pay for the higher costs of cognitive and motor control in those conditions?

2.3. Task III: Effect of incentives, memory load, and delay on memory-guided saccades

2.3.1. Background and hypothesis

Memory-guided saccades are saccades that are made in response to previously memorised targets. The need to hold information for short periods of time (seconds to minutes) makes memory-guided saccades a precise tool to assess short-term memory capacities. Short-term memory capacities have been extensively studied in both humans and animals for many decades and have been found to correlate with an individual's cognitive ability (Kyllonen and Christal, 1990). Visual working memory has hitherto been classified as a limited capacity system (Miller, 1956), with declining precision if more than 3 to 4 items are to be remembered (Luck and Vogel, 1997; Vogel, Woodman and Luck, 2001). Attention can, yet, be shifted to objects of greater interest or higher reward, dynamically allocating resources within a scene or task (Bays and Husain, 2008). While many studies looked into mechanism underlying working memory, the nature of allocating attention resources in working memory is to date not well understood. Berg et al. argued that the limitations of working memory may stem from rational cost minimisation

rather than from capacity constraints (Berg and Ma, 2018). This again raises the question whether motivation through incentives could account for part of these costs and, consequently, improve performance across apparent limits. In this context a study using monetary reward found no improvements of working memory capacity (Berg, Zou and Ma, 2020) and others argue that improvements observed should be interpreted merely as resource trade-offs (Morey *et al.*, 2011a; Atkinson *et al.*, 2018). Nonetheless, there is evidence suggesting that reward can improve working memory capacity (Kawasaki and Yamaguchi, 2013; Gong and Li, 2014).

While digit spans are a well-established tool to assess working memory in clinical practice, visual working memory has more recently come into focus. The physiological correlate of spatial working memory is thought to be persistent neural firing in the prefrontal cortex *after* stimulus presentation, which subsides once the remembered stimulus is no longer needed (Fuster, 1973; Compte *et al.*, 2000). Recurrent pattern of neural firing can form attractor networks with stable states called “bump attractors” (Compte *et al.*, 2000). If connections are strong, it can persist even if the stimulus is removed, therefore, storing information in working memory (Compte *et al.*, 2000). Neural noise, which can even seem probabilistic, is defined as the variability of neuronal spikes. It can affect attractor networks to jump from a low energy “stable” state into a decision state (Webb *et al.*, 2011). Fiete et al. devised a model to predict the interaction between build-up of neural noise, delay time of presented stimuli, and error in the saccade endpoint (Burak and Fiete, 2012).

If reward has the ability to improve endpoint accuracy in both arm movements (Codol *et al.*, 2020) and saccades as shown in the first task of this chapter and other studies (Manohar and Husain, 2015), I may hypothesise that this could be the case for working memory precision similarly. While saccades to single remembered targets have been studied in detail (Pierrot-Deseilligny *et al.*, 1991; Rivaud-Pechoux *et al.*, 2000; Brown *et al.*, 2004), the mechanisms underlying visual working memory in the control of saccadic sequences is not

well understood (Mcsorley, Gilchrist and Mccloy, 2019). A close relationship between set size, target order and clustering effects has, however, been reported (Müri *et al.*, 2009). Based on the findings above, I devised a novel incentivised task in which participants were required to memorise either a single target location or a random sequence of 4 locations. The target location display was followed by two delay periods of different length before saccades were to be recalled, namely, either 1s or 4s. The aim was to investigate how incentives of both valences (reward and penalty), different memory load (single and sequence of saccades) and built-up noise during delay periods (1s or 4s) influence overall memory recall time and precision. This may enable direct calculation of maintenance and noise reduction costs (Westbrook and Frank, 2018; Yee and Braver, 2018). I hypothesise that greater memory load and longer delay periods lead to a decline in precision through a decay effect. Both of those measures may be sensitive to incentives and may improve in their presence differently depending on the cost of the control demand.

2.3.2. Demographics

Twenty participants were recruited within the department and through the departmental subject pool (**Table 2.6**). The study was approved by the local Research Ethics Committee at University College London (project ID number: 9125/001) and conducted at the UCL Institute of Neurology. All participants gave written informed consent in accordance with the Declaration of Helsinki. Exclusion criteria remained unchanged from those listed in **section 2.1.2**.

Demographic data	
age	29.36 years
SD	±14.05 years
female	12
male	8

Table 2.6 Demographics- Memory-guided saccades.

2.3.3. Eye tracking paradigm

The eye tracker setup was unchanged to the previous section (details, see **section 2.1.3**). Participants were presented with a central fixation point (white) and 8 placeholders (grey) on a black screen (**Figure 2.14**). Both, the central fixation point and the target placeholders were circular and 1.4° in diameter. The position of the placeholders varied across three different allocation templates. An auditory cue indicated the incentive level ("lose", "nil" or "win") at the beginning of each trial. Nil trials were not incentivised, win trials had a maximum reward of 50p, lose trials a maximum loss of 50p. The auditory cue was followed by a 1200ms foreperiod. After fixation on the central fixation point had been confirmed, either one or a sequence of four of the placeholders flashed for 200ms each. The go-signal (black screen after placeholders and central fixation point vanished) appeared after a delay period of either 1s or 4s. During the presentation of the targets and the delay period the participants were requested to hold their gaze on the central fixation point. With the go-signal, they were required to look towards the remembered target(s) as fast and accurately as possible. As soon as the participants reached the target in question (fixation tolerance 80px/ ~2.2°) they received visual feedback (disc illuminated again, **Figure 2.15**). The same applied to target two, three and four in a sequence. On reaching the last target the amount of money lost/won was displayed as a function of the reaction time of the first saccade (details about reward/penalty calculation, see **section 2.1.6**).

Each participant completed 9 blocks of each 36 trials amounting to a total of 324 trials per participant. Ten practice trials completed at the beginning of the first block were excluded from the analysis.

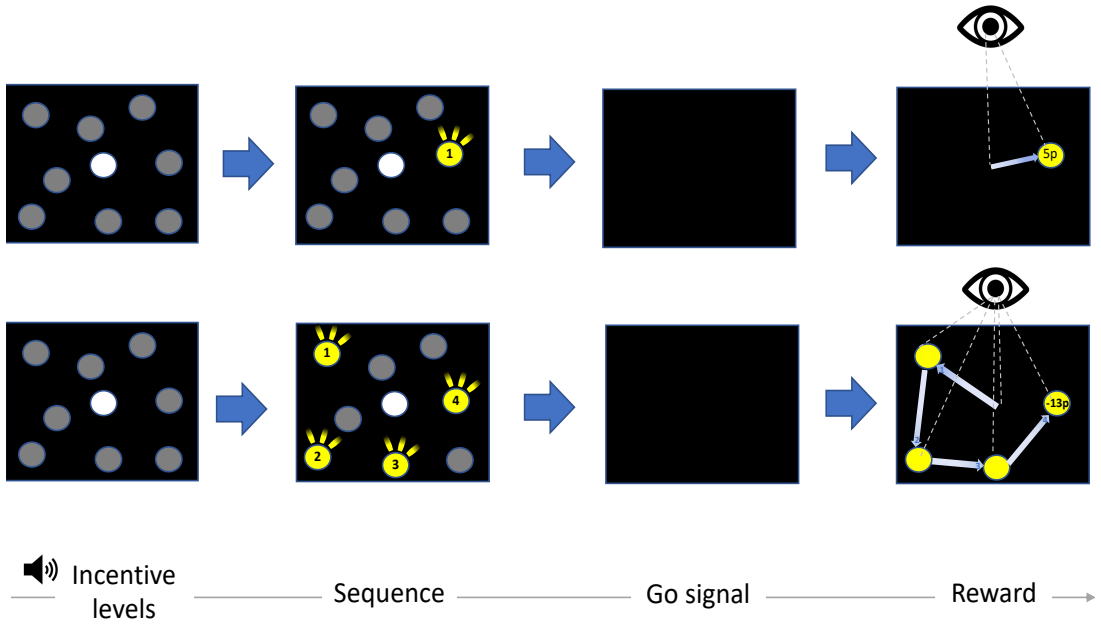

Figure 2.14 Memory-guided saccades-experimental setup: Either a single target (top row) or a sequence of 4 targets (bottom row) had to be remembered in this paradigm. After a variable delay of either 1s or 4s a black screen represented the go-signal for participants to look at the remembered target location(s). Incentive conditions included rewarded, penalised, and unrewarded trials. On arrival at the last target, feedback about the amount lost/won was displayed in the centre of the final target.

2.3.4. Data handling

The data extracted were parsed into saccades as described in **section 2.1.5**. Three parameters were looked at in this paradigm, namely, saccadic velocity, response time and memory precision. Due to the markedly different distances between the randomly displayed targets (~5-20°), residual peak velocity was used instead of peak velocity, factoring out the effect of amplitude size on velocity first. Peak velocity was calculated using 4ms windows from saccade onset to termination, discarding any speeds greater than 900°/s and smaller than 100°/s and any saccades during which tracking was lost. For each target

location, the first saccade made by the participant of which the amplitude was greater than 2° (excluding microsaccades and small corrective saccades) landing closer to the target in question than 8° was considered the saccade of interest (**Figure 2.16**).

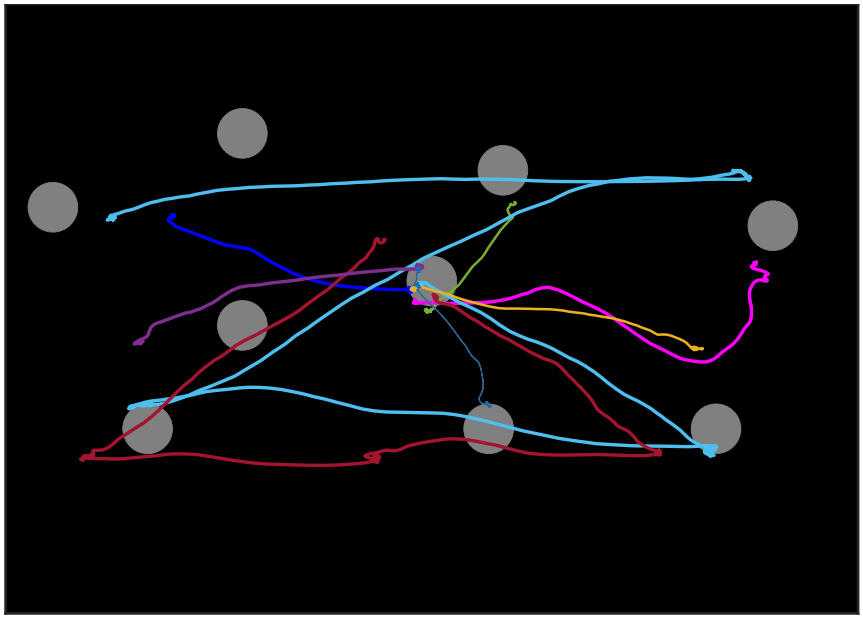

Figure 2.15 Memory-guided saccades: Example of 8 trials of either a single or sequences of memory-guided saccade(s) completed by one participant during the paradigm. Each colour represents one separate trial.

This threshold for the latter was chosen according to the histogram of endpoint errors of all saccades and participants in this task (**Figure 2.17**). Errors larger than 8° were considered errors, where the target position was forgotten, and the participant was guessing. Reaction time was only analysed for the initial saccades (single and first of sequence) to assess preparatory processes and was defined as the time between the go-signal (black screen) and when the criteria on velocity of $30°s^{-1}$ and acceleration > $8000°s^{-2}$ were fulfilled. Reaction times faster than 80ms were discarded (express saccades). In order to assess endpoint accuracy Euclidian distance between saccadic endpoint and the targets was calculated.

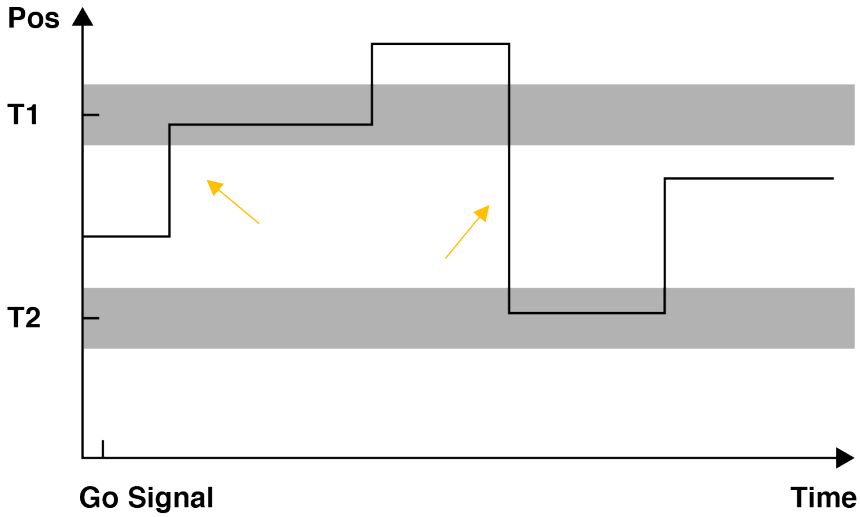

Figure 2.16 Memory-guided saccade filter criteria: Schematic illustration of the x and y position of saccades made within a trial, where the first saccade landing close to the target (grey area: 8° around the centre of the target) was chosen for analysis, while others were discarded (T1 = first target, T2= second target). Saccades fulfilling these criteria in this example are marked with yellow arrows (above).

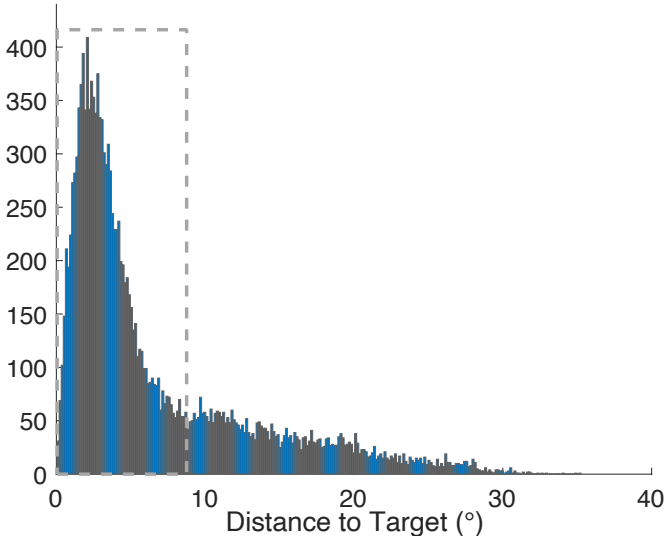

Figure 2.17 Memory-guided saccades: Histogram of all endpoint errors (distance between saccadic endpoints and target locations in degrees) of all participants on all trials made during the task. Data within grey dashed box were used for endpoint accuracy calculation.

2.3.5. Statistical analysis

A mixed linear model with random intercept was used for the analysis of these data (**Table 2.7**). Given the research question a separate analysis was performed assessing the effect of memory load, which included only data from the single and the first remembered saccades made within the sequence of four. The model was run for all three variables (memory precision, reaction time and peak velocity). A separate analysis was performed looking at the data of all four saccades made when a sequence of targets had to be remembered, assessing the effect of "serial position" on the parameter of interest. Within-subject factors included in the model were "incentives" (3 levels: -50, 0 and 50p, using 0p as a reference), "delay" (2 levels: 1s vs. 4s delay) and either "memory load" (2 levels: "high" vs. "low") for the first analysis or serial position (4 levels: saccade 1-4) for the second.

R	lmer (var ~ incentives * saccade number *delay+ (1 | ID), data)
SPSS	MIXED *var* BY incentives saccade number delay /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE) /FIXED=incentives delay saccade number incentives* delay incentives* saccade number delay * saccade number incentives* delay * saccade number | SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC)

Table 2.7 Memory-guided saccades: Model used for statistical analysis in R and SPSS. Var = variable of interest (i.e., reaction time), "incentives" represents the three different incentive conditions (3-level within-subject factor: "lose", "nil", "win"), "saccade number" = either "memory load" (2-level factor: single vs. first saccade of sequence) in the first analysis or serial position (4 levels: saccade number 1-4 in sequence) in the second.

2.3.6. Results

2.3.6.1. Memory precision was not reward-sensitive and worsened by higher memory load

Comparing data of a single saccade to that of the first remembered saccade of a sequence of four, endpoint accuracy deteriorated with higher memory load (F (1, 5855.14) = 159.81, ß= 0.53° (0.04), p< .001**, Figure 2.18**) and surprisingly improved with longer delays (F (1, 5855.73) = 7.44, p= .006, ß= -0.11° (0.04)). There was no main effect of incentives of either valence on memory recall precision in these data (p= .913, F- statistics, see **Table 2.8**). No interaction between memory load and incentives (p= .116) or delay and incentives (p= .449) was present, in keeping with an absent effect of motivation on memory precision. No other interactions were found.

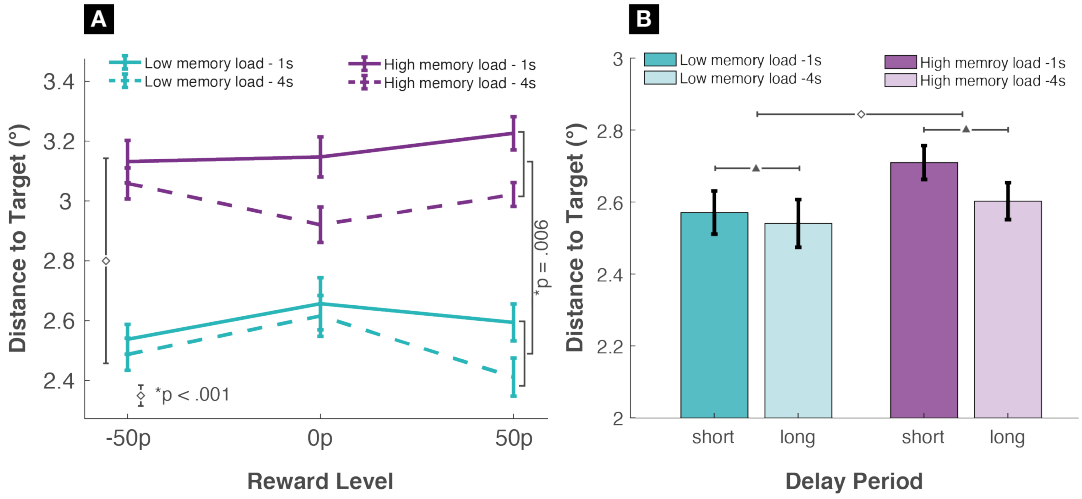

Figure 2.18 Memory-guided saccades: Euclidean distance to target showed two main effects – shorter delays and higher memory load were, therefore, detrimental for endpoint accuracy (Figure includes data from the single and the first saccades of the sequence, ◇ p<.001; ▲p= .006).

In the second analysis (involving data from all saccades made within the remembered sequence) there was only one main effect on endpoint accuracy, that is serial position (p< .001, F-statistics, see **Table 2.8**) showing that the second saccade of a sequence was significantly more accurate than the others within a sequence (ß= -0.17° (0.004), p<.001). There was also a trend

towards an interaction between delay and serial position (p= .054). Interestingly this was driven by delay having a positive effect on accuracy in the first saccade only (**Figure 2.18**, ß= -0.15° (0.06), p= .014) and no effect on the other saccades within the sequence (2-4). An absence of an incentive effect on memory precision was also confirmed for the remaining saccades of a sequence (p= .110). No other interactions were present.

		F_A	p
Initial saccades			
	incentives	(2, 5854.11) = 0.091	= .913
	delay	(1, 5854.99) = 7.44	= .006
	memory load (1/4)	(1, 5855.14) = 159.81	< .001
	memory load* incentives	(2, 5854.09) = 2.15	= .116
	delay* incentives	(2, 5854.14) = .80	= .449
	delay * memory load	(1, 5854.63) = 1.05	= .305
	incentives*delay*memory load	(2, 5854.08) = 0.92	= .400
Sequence			
	incentives	(2, 11954.22) = 2.21	= .110
	delay	(1, 11954.19) = 1.39	= .237
	serial position	(3, 11954.13) = 10.98	< .001
	incentives * serial position	(6, 11954.01) = 0.58	= .749
	incentives *delay	(2, 11954.26) = 1.65	= .193
	delay*serial position	(3, 11954.01) = 2.55	= .054
	incentives*delay*memory load	(6, 11954.01) = 0.37	= .902

Table 2.8 Memory-guided saccades-F-statistics: Distance from saccadic endpoint to target.

2.3.6.2. Saccadic peak velocity remains sensitive to incentives also in memorised saccades

Due to variable distances between saccade starting point and target locations in this task (random target sequence), analysis of peak velocity was only performed after accounting for different saccadic amplitudes. The first analysis (first vs. single saccade) resulted in two significant main effects. Participants were faster when incentivised (F (2, 5873.00) = 6.43, p= .002) and

slower in higher memory load conditions (F (1, 5873.0) = 4.08, p= .042, **Figure 2.19**), the latter reflected by a weak main effect of memory load (ß= -104.19°/s (51.56)) which was mainly driven by a slowing in unrewarded trials (interaction between memory load and incentives: p= 093 n.s.). Both incentive conditions increased peak velocity (win: ß= 208°/s (63.07), p= .003; win: ß= 180°/s (63.09), p= .013)) with no difference between them (p= 1.0).

The analysis including all four saccades of the remembered sequence resulted in one main effect, despite a number of trends that did not reach significance (**Table 2.9**). The effect of incentives (F (2, 11973.00) = 8.77, p< .001) was consistently present in all saccades (win: ß= 141.11°/s (49.43), p= .013; loss: ß= 201.52°/s (49.43), p< .001, see **Figure 2.20** for data from all saccades shown together) and was not altered by serial position (interaction between serial position and reward p= .725 n.s.). There was no significant difference between the two incentive conditions (p= 1.0). There was, however, a trend for an interaction between incentives and delay (p= .064) indicating higher reward sensitivity in longer delay conditions (**Figure 2.20**). No other significant main effects or delays were found.

		F_A	p
Initial saccades			
	incentives	(2, 5873.00) = 6.43	= .002
	delay	(1, 5873.00) = 0.44	= .509
	memory load (1/4)	(1, 5873.00) = 4.08	= .042
	incentives *memory load	(2, 5873.00) = 2.37	= .093
	incentives *delay	(2, 5873.00) = 0.99	= .370
	delay* memory load	(1, 5873.00) = 0.67	= .412
	incentives*delay*memory load	(2, 5873.00) = 0.82	= .441
Sequence			
	incentives	(2, 11973.00) = 8.77	< .001
	delay	(1, 11973.00) = 3.69	= .055
	serial position	(3, 11973.00) = 0.37	= .779
	incentives *delay	(2, 11973.00) = 2.75	= .064
	incentives*serial position	(6, 11973.00) = 0.61	= .725
	delay* serial position	(3, 11973.00) = 2.33	= .072
	incentives*delay*memory load	(6, 11973.00) = 0.36	= .903

Table 2.9 Memory-guided saccades - F-statistics: Residual velocity.

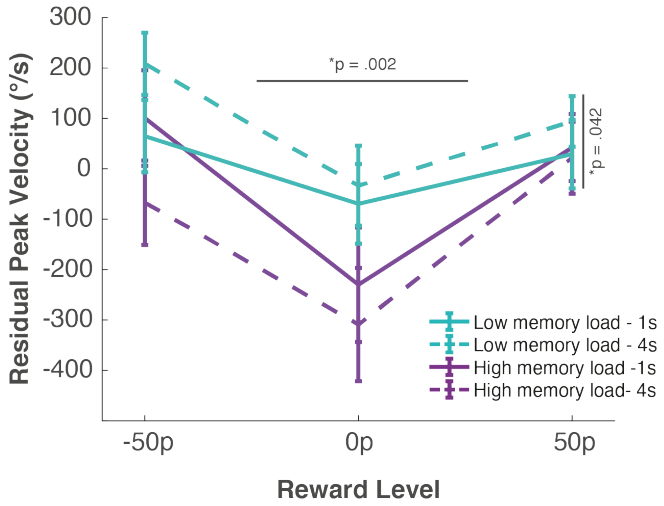

Figure 2.19 Memory-guided saccades: Residual peak velocity. Participants were faster when incentivised (on both incentives) and when memory load was low.

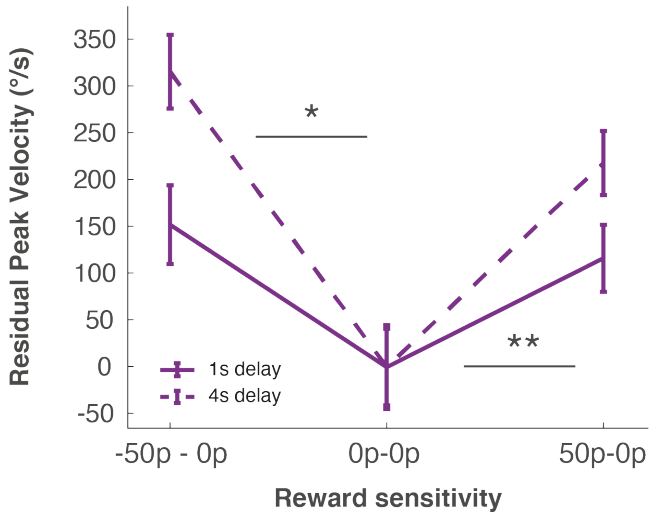

Figure 2.20 Memory-guided saccades: Differences in reward sensitivity of residual peak velocity of all saccades reflected on this figure, independent of serial position, in both incentive conditions vs. unrewarded trials: * p< .001, ** p= .013; no statistical difference was found between the two incentive conditions. This figure also illustrates the trend towards higher reward sensitivity in longer delay conditions (p= .064 n.s.).

2.3.6.3. Faster reaction times were observed when memory load was low, but only in long delay conditions

For the analysis of reaction times in this paradigm I exclusively looked at the initial saccades made in both low and high memory conditions, meaning both the single remembered saccade and the first saccade in a sequence of four remembered saccades. Since sequences of saccades are believed to be prepared in parallel ahead of eliciting the first saccade (Mcsorley, Gilchrist and Mccloy, 2019), this measure allows us to quantify the time taken for memory recall and saccade generation in conditions with different memory load.

While the expectation was to find longer reaction times when memory load was high, this only partly held true. Greater memory load led to longer reaction times in the long delay conditions only (interaction between memory load and delay: (F (1, 5810.44) = 20.35, p< .001). Pairwise comparison showed that reaction times were slower in high memory when delay was 4 s (ß= 44.87 ms (7.49), p< .001), while there was no difference in reaction times with memory load in the short delay condition (p= .63, **Figure 2.21**).

A main effect of motivation was shown (F (2, 5810.08) = 3.27, p= .038). Speedier reaction times were the result of both incentive types (loss: ß= -12.27 ms (4.79), p= .032; win: ß= -13.0 3 ms (4.77), p= .019). There was no difference between the two incentive valences and no other significant interactions (detailed statistics **Table 2.10**).

		F_A	p
Initial saccades			
	incentives	(2, 5810.07) = 3.27	= .038
	delay	(1, 5810.51) = 101.93	<. 001
	memory load (1/4)	(1, 5811.33) = 14.55	<. 001
	delay* memory load	(1, 5810.44) = 20.35	< .001
	memory load*incentives	(2, 5810.06) = .426	= .653
	delay*incentives	(2, 5810.08) = .699	= .497
	incentives*delay*memory load	(2, 5810.04) = 0.85	= .427

Table 2.10 Memory-guided saccades - F-statistics: Reaction time.

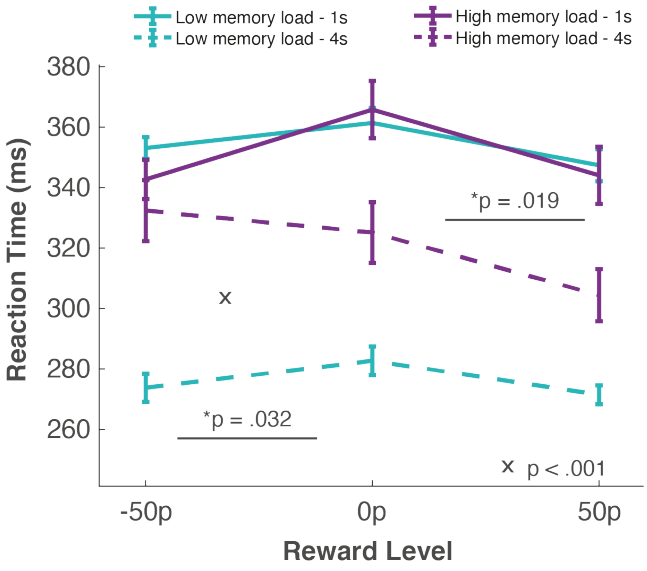

Figure 2.21 Memory-guided saccades: Difference of reaction time and reward effect between low and high memory load conditions (x = interaction between delay and memory load: p< .001).

2.3.7. Discussion

2.3.7.1. Similar effects of appetitive and aversive incentives

The most consistent finding in this data was the effect of incentives. Similar to the previous task, motivation through incentives improved reaction time and saccadic velocity. This effect was present in all saccades analysed. Especially noteworthy, there was no difference between the effect of appetitive versus aversive incentives on the two variables. This was specifically the case for saccadic peak velocity.

2.3.7.2. Motivation did not affect working memory precision

Endpoint accuracy as a measure of memory recall precision, on the other hand side, was not reward sensitive. This is in line with published data about an absent effect of monetary reward on working memory (Berg, Zou and Ma, 2020). My results now additionally provide evidence that working memory precision in a saccadic task is similarly not modulated by monetary incentives

of either valence (e.g., not improved by penalty avoidance). These data adhere to the theory of an overall limited capacity system in which resources can be shifted, though its limits can ultimately not be overcome (Morey *et al.*, 2011b; Wallis *et al.*, 2015; Allen, 2019). Indeed, this is underpinned by the finding that motor vigour and reaction time were found to be reward sensitive in the same cohort, reflecting a shift in resources by motivation.

Another factor to be considered though, is that precision was calculated as Euclidean distance to target, which is heavily dependent on saccadic amplitude size. Indeed, while it is well known that amplitude variability decreases with incentives, mixed findings were reported about the effect of motivation on amplitudes sizes, indicating the possibility of a lack of reward sensitivity of this parameter (Takikawa *et al.*, 2002). This was also the case in our own data in the previous section **Figure 2.12(C)**. It may point towards amplitude size being a fairly rigid parameter for a given distance (e.g., potentially due to economical considerations) and, therefore, being reward insensitive.

Higher memory load had a detrimental effect on endpoint accuracy, which is very well described in the literature and was in line with what had been expected, considering that a higher amount of memory load may lead to greater neuronal noise (Bays, 2014), which is in turn detrimental for precision. Memory precision was interestingly significantly reduced in the first saccade shown by a greater Euclidean distance between saccadic endpoint and target location. One interpretation of this finding could be the decay effect (Brown, 1958), which states that memory fades with time if it is not updated. If sequences of saccades are planned ahead of the first saccade, time passed since presentation of target number one is longer than for the other targets, which may explain the inaccuracy.

Previous studies looking at the execution of sequences of saccades found that the reaction time of the first saccade increases with sequence length (Carolina and Kowler, 1987). This held true for visible targets as well as remembered targets, which gave rise to the hypothesis that sequences of

saccades are planned before they are executed as “pre-established” motor programmes (Carolina and Kowler, 1987). As a result, I would have expected that higher memory load leads to longer reaction times. This was surprisingly only the case for long delay condition, while no difference was found within the short delay condition. This is surely surprising given a multitude of studies have found longer latencies, reflecting memory recall processes when more items were stored. One of the reasons for this observation could be the varying delay/foreperiod (1s vs. 4s) in this task. It has been found that uncertainty of the length of a foreperiod could lead to an overall increase in reaction times (Klemmer, 1956). This effect was even found to correlate not only with the foreperiod of the current trials but might also be influenced by the foreperiod of the last and second last trial (Klemmer, 1956), which could have potentially confounded the results.

Working memory and sustained activity in PFC activity has been found to heavily depend on dopaminergic modulation (Brozoski et al., 1979). Deficits are recognised in PD, especially in the sub-domain of short-term memory. Although it is believed they stem from dopamine degeneration within the basal ganglia, increased levels of dopamine have also been found to impair working memory (Cools and D’Esposito, 2011), with conflicting results having been published. In the next chapter I, therefore, aim to investigate the influence different drug-induced dopamine levels have on working memory performance and reward sensitivity in the same task. In order to exclude the confounding factor of delay period uncertainty on reaction times, a fixed delay period (1s) will be used in in this task in the next chapter.

2.4. Brief summary of findings in Chapter 2

The main findings in this chapter were:

- Motivation improved velocity and reaction times of internally triggered, externally triggered, as well as remembered saccades of healthy controls. In the first task this was also accompanied by improved distractibility and in the latter two with an absence of a negative effect on endpoint precision (absent speed-accuracy trade-off). No effect of incentives on amplitude or Euclidean distance to target was found in any of the tasks. Findings regarding reward sensitivity of saccadic amplitudes are mixed in the literature being present in some (Manohar, 2014) and absent in other (Muhammed, 2018) and our own data. This has led to the discussion whether for given distance between saccadic start point and target location amplitude size may be fixed and whether additional increases may potentially be uneconomical if extra costs are not covered by incentives. It raises the question whether again this depends on the task and the individual's reward sensitivity.

- Win trials showed a slightly stronger effect on saccadic velocity of internally triggered saccades than penalty trials did. This was, however, the only measure where a significant difference was found between the two incentive conditions. Furthermore, did the improvement of reaction time in both memory-guided and internally triggered saccades not significantly differ between the two incentive conditions, suggesting both incentives may represent the same net value in goal-directed behaviour. Indeed, this is in line with findings from an fMRI study, showing similar activation pattern in the nucleus accumbens for both appetitive and aversive stimuli if incentives were contingent, which was the case for all paradigms in this chapter (Kawasaki and Yamaguchi, 2013). The findings reported would certainly be in favour of a similar motivational salience or "net value" of both incentive types and would be in line with the expected value of

control (EVC) framework (Shenhav *et al.*, 2017), suggesting the optimal control to depend on the value of the gain discounting the cost of control. It will be a question to answer in the next chapter, whether dopamine may be capable of shifting this cost-benefit ratio leading to stronger effect of incentives on supra-normal dopamine levels.

- Increasing memory load slowed saccadic velocity, which was previously described (Di Stasi *et al.*, 2010; Luigi *et al.*, 2011), and increased distance to target as did higher uncertainty, most likely due to smaller amplitudes. The effect incentives had on saccadic properties was, however, not influenced or attenuated by a higher degree of entropy, uncertainty, or memory load in any of the tasks. This points to a fixed optimal balance between speed and accuracy for a certain entropy level in unrewarded trials. This balance may be shifted by incentives, with costs for these improvements remaining constant across the different entropy levels in keeping with the EVC framework.

3. Investigating the influence of haloperidol and levodopa on saccadic performance in health

3.1. Background and hypothesis

Dopaminergic pathways are crucially involved in reward signalling, and disruptions have been associated with symptoms like impulsivity, addiction, depression, and apathy. PD, a disorder characterised by dopamine depletion, often presents not only as a movement disorder, but is accompanied by non-motor symptoms including apathy. Apathy is defined as "reduced motivation" and a link between dopamine depletion and apathy has been proposed (Chong *et al.*, 2015; Muhammed, Manohar and Husain, 2015). Impulsivity and addiction on the other hand have been linked to hyperdopaminergic states (Pine *et al.*, 2010; Voon *et al.*, 2010; Sinha, Manohar and Husain, 2013; du Hoffmann and Nicola, 2014).

Oculomotor deficits have been characterised in a number of pathologies linked to dopaminergic imbalances including PD, schizophrenia, Huntington disease (HD) and ADHD, showing specific patterns depending on the type of dopaminergic imbalance, sometimes even aiding diagnosis. It is well known that PD, as a hypokinetic movement disorder, causes hypometric saccades, while HD belonging to the spectrum of hyperkinetic movement disorders can lead to slower reaction times and saccadic velocities (Rubin *et al.*, 1993; Termsarasab *et al.*, 2015). Recent work on PD has also found a tendency for slower saccades (reaction time and velocity) and furthermore decreased reward sensitivity (Manohar *et al.*, 2015), which could be restored by dopamine replacement therapy (Manohar *et al.*, 2015). Interestingly, saccadic performance was also found to correlate with clinical symptoms (e.g., freezing of gate) in PD (Nemanich and Earhart, 2016) again supporting its dependency on treatment status (Crevits *et al.*, 2000). These observations suggest a common mechanism, likely to be at least in part dopaminergic and could make saccades an interesting tool for tracking disease progression and treatment monitoring. The fact that impaired oculomotor performance can be

observed in both, pathologies linked to dopamine excess and depletion, may instinctively be surprising, but may be in line with the previously mentioned hypothesis of the "inverted-U-shaped" relationship between dopamine levels and performance in goal-directed behaviour (Cools and D'Esposito, 2011). To further dissect symptoms and observations caused by dopamine imbalance directly and those related to additional non-dopaminergic disease pathologies, we need to look at data from pharmacological studies in disease but more importantly in health.

Levodopa was found to increase prosaccadic latency but decrease oculomotor errors in PD patients (Hood *et al.*, 2007; Lu *et al.*, 2019) while also improving accuracy and amplitude (Gibson, Pimlott and Kennard, 1987; Montastruc *et al.*, 1989). Others found no effect of dopaminergic replacement in PD (Gibson, Pimlott and Kennard, 1987; Nakamura *et al.*, 1991). Antisaccadic errors were reduced in PD patients on levodopa treatment (Hood *et al.*, 2007) and paradoxically *increased* in healthy controls after a single dose of levodopa (Duka and Lupp, 1997). Since antisaccades are saccades elicited away (opposite direction) from a target and, hence, require not only the inhibition of a reflexive saccade but the inversion of a visual signal, these results may indicate a detrimental effect of dopamine in some of these inhibitory processes. In terms of animal studies, MPTP-monkeys were found to have hypometric saccades, which improved when given levodopa (Brooks, Fuchs and Finocchio, 1986; Schultz *et al.*, 1989). Non-saccadic data showed that levodopa improved reinforcement learning in the presence of reward, while haloperidol impaired overall task performance (Pleger *et al.*, 2009). Levodopa was also found to enhance reward expectation, e.g., (Sharot *et al.*, 2009) and to restore reward prediction errors, which were found to decline with age (Chowdhury *et al.*, 2013). Additionally, levodopa was found to increase temporal discounting, leading to the desire to reach reward sooner (Pine *et al.*, 2010).

These findings might point towards impaired motor and cognitive control in the presence of dopaminergic imbalances and increased reward seeking

behaviour after dopaminergic stimulation, which, however, may be detrimental to inhibitory processes clinically observed in patients developing impulse control disorders following treatment with dopamine agonists. But why are findings of pharmacological studies partially inconsistent? This could be due to studies differing in drug formulations and doses used, the population tested, age, gender and most importantly also in the individuals' baseline dopamine levels (e.g., COMT polymorphism), which all may influence the effect dopamine shows on each individual. In clinical studies, patients in different stages of disease with different spectrums of cognitive and motor features may have a range of dopaminergic tone in different brain areas. This further complicates interpretation, suggesting preclinical work in healthy participants may be crucial.

For this thesis, I, hence, conducted a placebo-controlled, cross-over study, involving healthy volunteers, who received a single dose of Madopar (containing the dopamine precursor levodopa) and the D2 receptor antagonist haloperidol. Very few studies have adopted this within-subject method (Frank and O'Reilly, 2006; Pleger *et al.*, 2009), which is more powerful and allows for a better interpretation of the findings and changes in behaviour relative to participants' "normal" dopamine baseline levels. By collecting saccadic data but also additional measures of reward sensitivity and baseline motivation (e.g., pupillometry, spontaneous EBR and self-reported assessments of intrinsic motivation), I aim to provide a clearer characterisation of the effects both drugs have on goal-directed behaviour. For one it will be interesting to see whether any of the non-saccadic measures recorded could potentially serve as a non-invasive dopamine proxy. Additionally, I aim to answer some of the questions arising about if and how different dopamine levels alter reward signalling in conditions of different incentive valence, and whether different dopamine levels alter reward sensitivity in conditions of different entropy (e.g., uncertainty, memory load), which may represent higher levels of cognitive load.

3.2. Methods

3.2.1. Demographics

Thirty healthy participants were recruited through a departmental online recruitment pool (**Table 3.1**). Pre-screening was conducted via telephone and email. Exclusion criteria for participation were as follows: **(1)** Age <18 years or >80, **(2)** significant cognitive impairment (MMST <22/30), **(3)** severe clinical depression or other psychiatric illnesses, **(4)** other neurological conditions, **(5)** concurrent treatment with centrally acting drugs/use of recreational drugs in the last month, **(6)** a known allergy and/or a contraindication to one of the drugs used (e.g., hypotension), **(7)** a history of cardiovascular disease (esp. long QT-syndrome). All participants were right-handed.

Demographic data	
age	31.67 years
SD	±12.34 years
female	16
male	14

Table 3.1 Demographics – Drug study.

3.2.2. Consent

This study was approved by the local Research Ethics Committee at University College London (project ID number: 9125/001) and conducted at the UCL Institute of Neurology. All participants gave written informed consent in accordance with the Declaration of Helsinki.

3.2.3. Study timeline

Eligible subjects were invited to participate in 3 sessions, with a minimum interval of 7 days in between each session. After obtaining consent, a blood pressure measurement was taken (to exclude hypotension) and a fruit-flavoured drink containing either Madopar® dispersible (100/25mg), haloperidol oral solution (2.5mg) or no additive drug (placebo) was dispensed. Participants were blinded for the order of the administration and the order

was randomised across participants. To ensure appropriate plasma drug concentration the administration of the drink was followed by a variable waiting period of 1 hour in Madopar® and placebo sessions and 2 hours in haloperidol sessions (detailed schedule, see **Figure 3.1)**. Participants completed a number of different tasks and attended on three occasions of which all three followed the same schedule. In order to account for physiological fluctuations in dopamine levels over the course of a day, all sessions started between 9 and 10am. Questionnaires to assess intrinsic motivation (Apathy Motivation Index) and impulsivity (short UPPS-P) were completed once at the beginning of the first session by every participant.

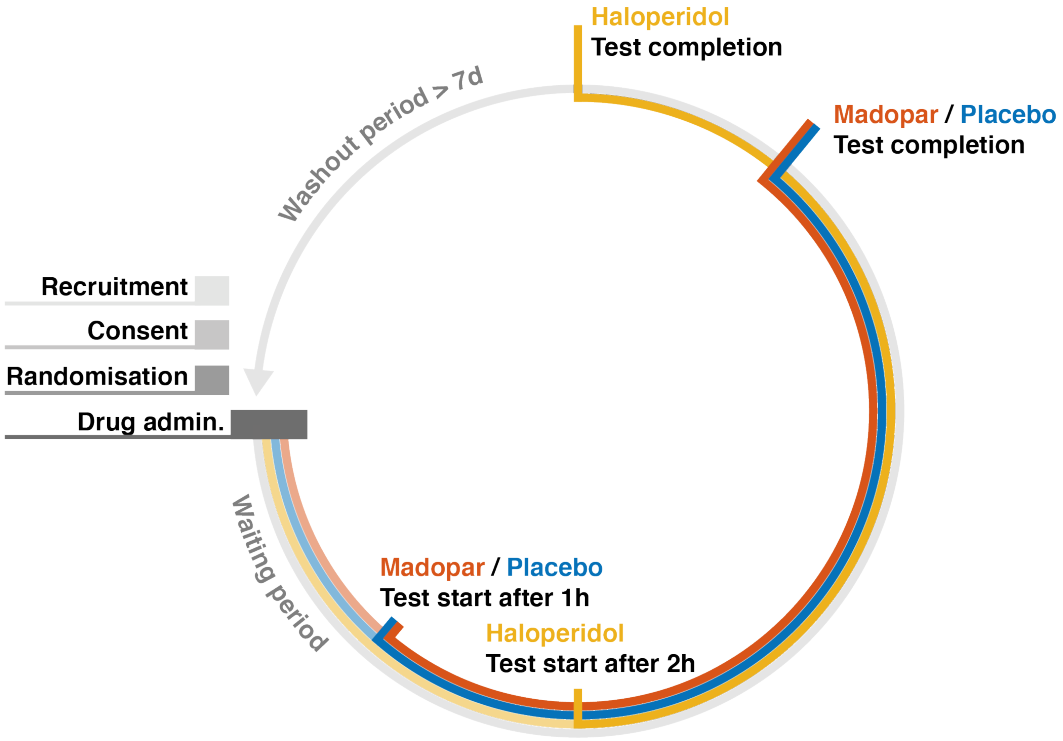

Figure 3.1 Timeline drug study: After the participants gave written informed consent, they were randomly assigned to one of the three study arms and received a fruit juice containing either no additive drug (= placebo), Madopar or haloperidol following a within-subject design. After a waiting period of either 1h (placebo and Madopar) or 2h (haloperidol) participants completed the same tasks on all three testing days. A washout period of > 7days was required in between each session.

3.2.4. Drugs dose and rationale

Madopar dispersible consisting of 100mg levodopa and 25mg Benserazide was used to *increase* participants' dopamine levels in the study. Levodopa is an amino-acid and precursor to dopamine in the brain and as such can pass the blood brain barrier. It is clinically used for the treatment of motor symptoms in PD and has also been used in a multitude of behavioural studies involving healthy controls. While higher doses reportedly led to side effects such as sedation or nausea, a dose of 100/25mg was reported to generate behavioural changes without causing side effects in a large number of studies.

Dopamine antagonist: Haloperidol is a dopamine antagonist mainly acting on dopamine D2 receptors (D2, D3 and D4), with a much smaller affinity to D1 and D5 receptors and was used in this study to *decrease* participants' dopamine levels. It is clinically used for the treatment of schizophrenia, psychosis, and delirium. The dose of 2.5mg was used in previous human studies of cognitive control showing effects without causing side effects such as sedation (Norbury *et al.*, 2015). The potential effect of increasing dopamine levels via presynaptic receptors, however, yields caution when interpreting results (Richfield, Penney and Young, 1989).

In conclusion, levodopa and haloperidol have been previously used in research and have shown to alter goal-directed behaviour, also proven by altered activation pattern on functional imaging (Pleger *et al.*, 2009) without causing side effects. Madopar (levodopa) is also the most commonly used drug in the treatment of motor symptoms in PD and its additional effects on other domains are, hence, of special interest.

3.3. Effect of drug manipulation on avoiding an early distractor

3.3.1. Background and hypothesis

The same task described in **section 2.1.4** was repeated in this drug study (study timeline, see **section 3.2.3**). While healthy controls completing this task were found to improve both saccadic velocity and accuracy when rewarded, a number of questions regarding the role of dopamine in these reward signalling processes have emerged: **(1)** How would pharmacological manipulation of dopamine levels influence saccadic parameters especially in light of the presumed "inverted-U-shaped" relationship between tonic dopamine and performance? **(2)** Will drugs have different effects on motor vs. cognitive control? **(3)** Will higher dopamine levels increase reward sensitivity, potentially also leading to greater distractibility?

Published data from the same task revealed reduced reward sensitivity in dopamine deplete PD patients with slower saccadic velocities but preserved accuracy when compared to age-matched controls. In order to explain these findings a cost of noise control was introduced in their model and it was hypothesised that the cost of control may be higher in PD patients than in healthy controls due to the underlying dopaminergic deficit (Manohar *et al.*, 2015). On cabergoline, a D2 dopamine agonist, healthy controls completing this task were found to have slower saccadic velocity in low reward conditions only, but increased reward sensitivity shown by an interaction between drug and reward. Despite the prediction that activation of the D2-pathways could lead to slower RTs, cabergoline did not show an effect on reaction times or accuracy (Manohar, 2014). This indicates a generally lower motivational state only for smaller rewards on cabergoline.

In order to further dissect the effects of dopamine on reward sensitivity and potential differences in dopamine receptor subtypes, the same paradigm was used in healthy volunteers pharmacologically altering their dopamine levels

by administering Madopar and haloperidol. Haloperidol, acting as a dopamine antagonist, mainly on D2 receptors, may show an opposite pattern of effects than seen after cabergoline. And with Madopar, acting on both the direct and the indirect pathways, different roles in the initiation of action and desisting from less valuable actions have been suggested (Manohar, 2014).

I, therefore, hypothesise that haloperidol may reduce reward sensitivity and increase overall oculomotor capture while Madopar may increase reward sensitivity but also increase distractibility, which may lead to a greater proportion of erroneous trials. The within-subject design of the study allows to account for individual dopamine baseline levels by measuring the "more" and "less" than normal dopamine effect. Results will also be matched with questionnaire-based assessments of intrinsic motivation impulsivity trait.

3.3.2. Statistical analysis

Data handling was identical to that described in **section 2.1.5**. Participants completed 7 blocks of each 54 trials (total of 378 saccades) with 5 minutes breaks in between the blocks and 10 practice trials at the beginning of the first block which were excluded from the subsequent analysis. From the total of 90 recorded datasets (30 participants each completing 3 sessions), 4 datasets had to be excluded/are missing from the analysis, due to participants' time constraints or technical issues. This concerned one dataset within the placebo cohort and 3 datasets in the haloperidol arm.

In order to account for different baseline performance between subjects as well as for the four missing datasets, a mixed linear model with random intercept, using the restricted maximum likelihood method, was used to analyse the data using SPSS (mixed linear models) and R (nlme package) (**Table 3.2**). The model fit was assessed using the chi square test.

R	lmer (var ~ reward * drug + (1 | ID), data)

SPSS	MIXED var BY drug WITH reward /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE) /FIXED=drug reward drug*reward | SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC).

Table 3.2 Double- step paradigm- Model used for statistical analysis in R and SPSS. The placeholder "var" represents the variable of interest in the analysis (i.e., peak velocity).

Groups were split comparing the effect of dopamine vs. placebo and haloperidol vs. placebo separately, using drug as a one level within-subject factor each time (**Figure 3.2**). Reward was used as a linear covariate. Interaction terms were performed for within-subject factors. Results reported are from the R analysis. Where only p-values were reported in the text, F-statistics of all results are to be found in the table at the bottom of each subsection. The alpha level was set at .05.

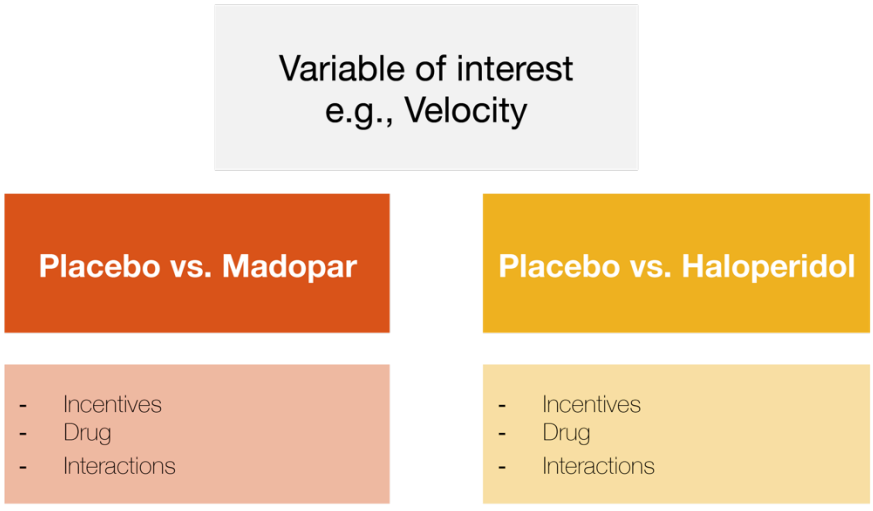

Figure 3.2 Double-step paradigm- drug study: Hierarchical structure of statistical analyses: Two separate analyses were performed with data comparing Madopar (red) and haloperidol (yellow) to placebo data separately. In each analysis the following factors were included: (1) Incentives (linear factor 0-10-50p), (2) drug (2 levels) and their (3) interaction terms.

3.3.3. Results

3.3.3.1. Fewer oculomotor capture errors on Madopar, more on haloperidol

Looking at the proportion of oculomotor capture errors (proportion of saccades landing closer to the distractor than the target), participants on haloperidol performed worse than those on placebo (p<.001), while Madopar improved performance (p= .040, **Table 3.3** & **Figure 3.3(B)).** There was no main effect of reward on this variable and no interaction between reward and drug.

		F_A	p	ß (%) ± SE
MADOPAR				
	reward	(1, 143.93) = 0.989	= .321	
	drug	(2, 144.26) = 4.287	= .040	-1.95 ± .94
	reward*drug	(1, 143.93) = 0.202	= .654	
HALOPERIDOL				
	reward	(1, 135.91) = 0.382	= .537	
	drug	(2, 136.89) = 14.299	< .001	4.06± 1.07
	reward*drug	(1, 135.12) = 0.016	= .898	

Table 3.3 Double-step paradigm - drug study, F-statistics: Proportion of erroneous trials.

Using saccadic departure angle as a measure of distractor pull, I found a similar pattern as described above. Haloperidol increased distractor pull significantly (p< .001, **Figure 3.3(A)**, F-statistics, see **Table 3.4**), while Madopar on the other hand improved inhibitory control and led to a decrease in the distractor pull (p= .049, **Table 3.4)**. A noteworthy difference between the two parameters was that reward seemed to have a beneficial effect on distractor pull in the placebo vs. Madopar data (p= .005). The analysis haloperidol vs. placebo did not lead to a significant main effect of reward (p= .194). Although the effect of incentives was strongest in the Madopar data, the interaction between drug and reward for placebo vs. Madopar did not reach significance (p= .158, **Figure 3.4**). Taken together, this means that reward sensitivity of both these parameters were not significantly altered by

either of the two drugs. Overall distractibility was, however, improved by Madopar and worsened by haloperidol.

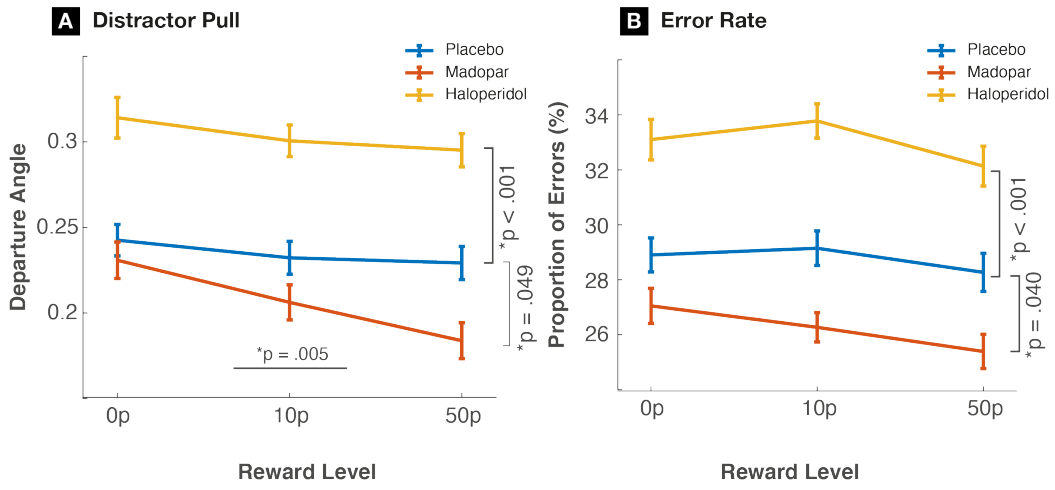

Figure 3.3 Double-step paradigm- drug study: (A) Distractor pull: Direction of saccade, where π/3 is the distractor and 0 is direction target (B) Error Rate: Proportion of erroneous trials (%). Both measures show performance improved on Madopar and worsened on haloperidol.

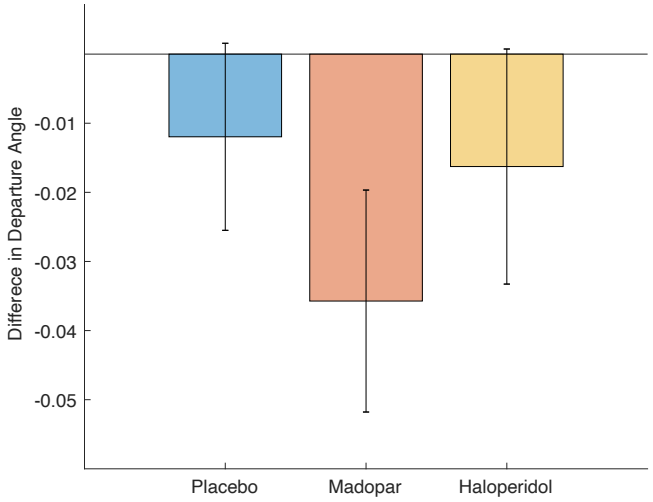

Figure 3.4 Double -step paradigm- drug-study: Reward sensitivity measured by the difference of departure angle between rewarded (50p) and unrewarded trials; Madopar showed greatest reward sensitivity (placebo vs. Madopar p= .158, n.s.).

		F_A	p	ß (a.u.) ± SE
MADOPAR				
	reward	(1, 22308.03) = 7.87	= .005	-0.03 ± 0.01
	drug	(1, 22327.06) = 3.87	= .049	-0.02 ± 0.01
	reward*drug	(1, 22308.01) = 1.99	= .158	
HALOPERIDOL				
	reward	(1, 20731.08) = 1.68	= .194	
	drug	(1, 20746.50) = 45.35	< .001	-0.08± 0.01
	reward*drug	(1, 20731.01) = 0.011	= .916	

Table 3.4 Double-step paradigm- drug study, F-statistics: Departure angle. Saccadic trajectory where π/3 is towards distractor and 0 towards target [arbitrary units])

3.3.3.2. Both drugs reduced peak velocity

Peak velocity was reduced by both drugs (p< .001, **Table 3.5**). This is in line with previous findings of the effect of a single dose of haloperidol on healthy volunteers (Lynch *et al.*, 1997; Visser *et al.*, 2001). Intriguingly cabergoline was found to selectively slow unrewarded (0p) trials (Manohar, 2014), while in the current data Madopar caused an overall slowing of all reward conditions. There was a main effect of reward in both drug arms showing participants to be faster on rewarded trials (p< .001, **Table 3.5; Figure 3.5(A)**). Neither of the drugs influenced reward sensitivity of saccadic velocity (interaction between reward and drug: Madopar p= .213 and haloperidol p= .501).

		F_A	p	ß (°/s) ± SE
MADOPAR				
	reward	(1, 15187.27) = 205.47	< .001	25.08 ±1.74
	drug	(1, 15193.99) = 197.69	< .001	-20.33 ±1.45
	reward*drug	(1, 15190.27) = 1.55	= .213	
HALOPERIDOL				
	reward	(1, 13129.21) = 149.63	< .001	24.56 ± 2.01
	drug	(1, 13142,23) = 134.73	< .001	-30.35 ±2.64
	reward*drug	(1, 13129.27) = .454	= .501	

Table 3.5 Double-step paradigm- drug study, F-statistics: Peak velocity.

These findings confirmed previously published data as well as my own findings (see **section 2.1.8**) about the effect of reward on saccadic peak velocity (Lynch *et al.*, 1997; Visser *et al.*, 2001; Manohar *et al.*, 2015).

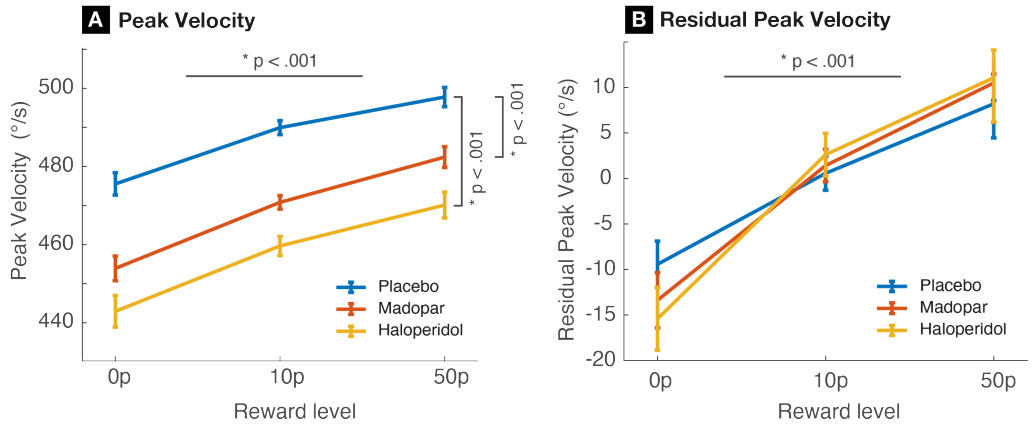

Figure 3.5 Double-step paradigm- drug study: (A) Peak velocity, (B) residual peak velocity

3.3.3.3. Both drugs reduced motor vigour

In order to exclude the effect of saccade amplitude as a contributor to higher peak velocities, in the context of the well-known principle of the main sequence, a linear regression between amplitude size and peak velocity was performed. Velocity residuals were calculated for each subject and each drug arm separately and a main effect of reward on residual peak velocity was confirmed (p<.001, F-statistics, see **Table 3.6**) making saccades faster on rewarded trials in both comparisons Madopar vs. placebo and haloperidol vs. placebo (**Figure 3.5 (B)**).

		F_A	p	ß (°/s) ± SE
MADOPAR				
	reward	(1, 15275.0) = 113.73	< .001	20.44 ± 1.94
	drug	(1, 15275.0) = 0.00	= .996	
	reward*drug	(1, 15275.0) = 1.41	= .236	
HALOPERIDOL				
	reward	(1, 13209.0) = 102.27	< .001	22.32 ± 2.22
	drug	(1, 13209.0) = 0.00	= .966	
	reward*drug	(1, 13209.0) = 3.49	= .061	

Table 3.6 Double-step paradigm- drug study, F-statistics: Residual Peak velocity.

There was no statistically significant interaction between drug and reward in either of the analyses (Madopar p= .236, haloperidol p= .061), although there was a trend towards an interaction between drug and reward in the haloperidol vs. placebo cohort, intriguingly showing a steeper slope of reward effect on residual peak velocity on haloperidol (**Figure 3.6** & **Table 3.6**). This trend was, however, not significant and no interaction was present for Madopar (p= .236). The previously found main effect of drug on residual peak velocity, however, vanished (Madopar p= .978, haloperidol p= .953), which can be explained by significantly smaller amplitudes in both drug groups when compared to placebo (p< .001, F-statistics, see **Table 3.7** below). Smallest amplitudes were found in the haloperidol group, but amplitudes were also significantly smaller in the Madopar group when compared to placebo.

		F_A	p	ß (°) ± SE
MADOPAR				
	reward	(1, 15250.53) = 22.41	< .001	0.14 ± 0.03
	drug	(1, 15263.07) = 18.89	< .001	-0.11± 0.02
	reward*drug	(1, 15250.52) = 0.001	= .969	
HALOPERIDOL				
	reward	(1, 13183.53) = 8.01	= .004	0.09 ± 0.03
	drug	(1, 13209.31) = 58.15	< .001	-0.22± 0.03
	reward*drug	(1, 13183.74) = 1.46	= .228	

Table 3.7 Double-step paradigm- drug study, F-statistics: Amplitude size.

While PD patients are well known to have hypometric saccades, levodopa therapy has been shown to improve this (Montastruc *et al.*, 1989). Little, however, is known about the effect of levodopa on saccades in healthy controls. Our findings may suggest that (too) high *and* (too) low levels of dopamine may decrease motor vigour of saccades following an "inverted-U-shaped" relationship. Reward increased amplitude size in both the Madopar data (p<.001) and the haloperidol data (p= .005) showing that, indeed, amplitudes can be modulated even when saccadic distance is fixed (**Figure 3.7**), which our data on a smaller cohort in the previous section did not reflect.

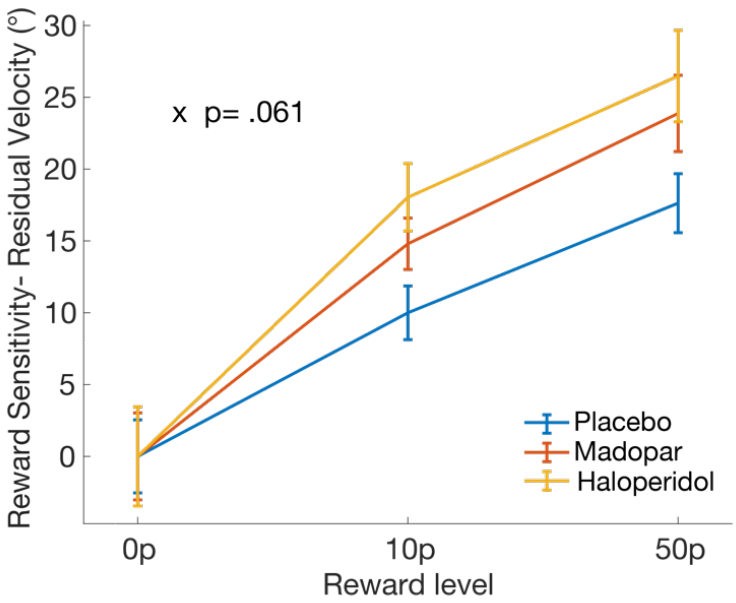

Figure 3.6 Double-step paradigm- drug study: Reward sensitivity. Difference in residual peak velocity per reward level. Velocity at 0p was subtracted from the other two reward levels. There was a trend towards greater reward sensitivity on haloperidol (p= .061 n.s.) but not on Madopar.

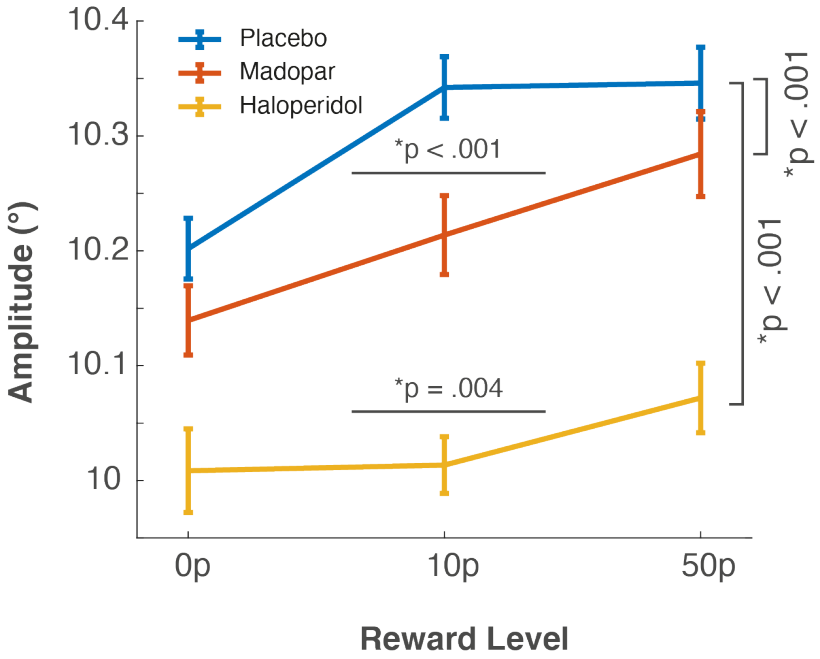

Figure 3.7 Double-step paradigm- drug study: Amplitude size.

3.3.3.4. Haloperidol decreased inhibitory control

Reaction times were significantly faster on rewarded trials (p<.001, F-statistics, see **Table 3.8**). Saccadic latencies were, in fact, also shorter in the haloperidol group when compared to placebo (**Figure 3.9 (A)**).

To understand why this might arise, I examined the correlation between amplitude size and reaction times across trials, analysed per condition and per participant. Amplitude size correlated positively with reaction times in both the placebo and the Madopar but not in the haloperidol data (**Figure 3.8**), where amplitudes remained hypometric throughout.

Shorter reaction times may, therefore, be explained by the known trade-off for planning time previously termed "amplitude latency relation" in the literature (Fuller, 1996). It states that smaller movements require shorter preparation time. Linear regression between amplitude and reaction time confirmed that there was no main effect of haloperidol on residual reaction times (p= .999, p= .971, F-statistics see, **Table 3.9**, **Figure 3.9 (B)**).

		F_A	p	ß (ms)± SE
MADOPAR				
	reward	(1, 15170.42) = 44.94	< .001	15.08± 2.26
	drug	(1, 15181.03) = 0.092	= .726	
	reward*drug	(1, 15170.42) = 0.054	= .817	
HALOPERIDOL				
	reward	(1, 13040.29) = 29.23	< .001	12.43± 2.28
	drug	(1, 13069.34) = 4.67	= .031	-6.44 ± 2.98
	reward*drug	(1, 13037.38) = 0.71	= .398	

Table 3.8 Double-step paradigm- drug study, F-statistics: Reaction time.

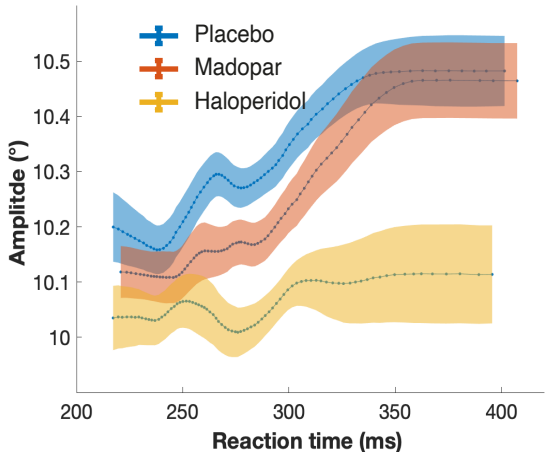

Figure 3.8 Double-step paradigm- drug study: Correlation plot between saccadic reaction times and amplitude sizes. Amplitudes of greater size correlated with longer reaction times in the placebo und Madopar group. This was not the case in the haloperidol group where amplitude size was reduced overall.

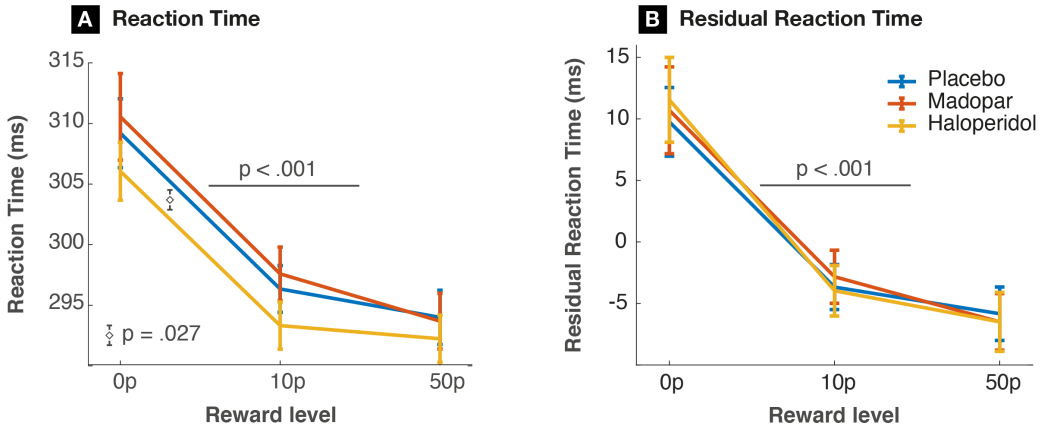

Figure 3.9 Double-step paradigm- drug study: (A) Saccadic reaction times seemed to be significantly faster in the haloperidol group. (B) This effect was absent after accounting for smaller amplitude sizes in the haloperidol group by performing a linear regression on data of all three groups.

An alternative interpretation of these findings may, however, be that they reflect reduced inhibitory control caused by haloperidol, indicated by the observation that faster reaction times were also accompanied by a higher

proportion of erroneous saccades (**Figure 3.10**), potentially reflecting a reduced ability to inhibit early saccades towards the distractor. Residual reaction time remained reward sensitive (p< .001) with no interaction between drug and reward (**Table 3.9**).

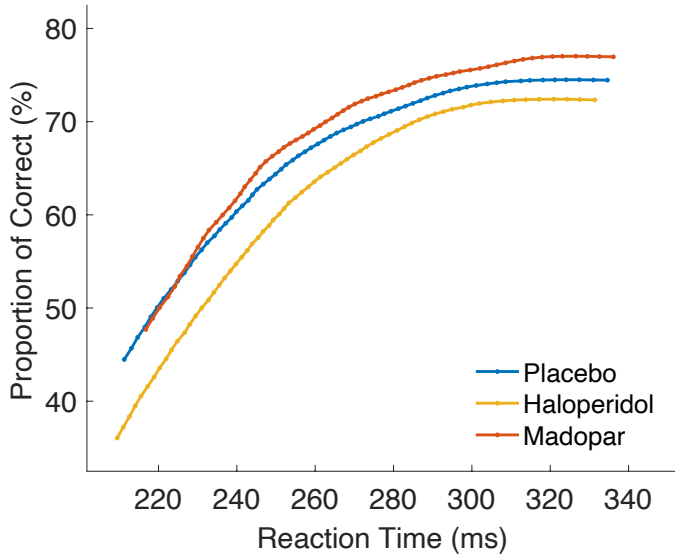

Figure 3.10 Double-step paradigm- drug-study: Conditional plot showing that for comparable reaction times haloperidol increased and Madopar decreased the proportion of erroneous trials.

		F_A	p	ß (ms) ± SE
MADOPAR				
	reward	(1, 15199.18) = 64.64	< .001	-15.15 ± 1.87
	drug	(1, 15199.77) = 0.001	= .999	
	reward*drug	(1, 15199.79) = 0.005	= .941	
HALOPERIDOL				
	reward	(1, 13830.64) = 60.14	< .001	-15.22 ± 1.95
	drug	(1, 13830.12) = 0.001	= .982	
	reward*drug	(1, 13830.04) = 0.001	= .977	

Table 3.9 Double-step paradigm- drug study, F-statistics: Residual reaction time.

3.3.3.5. Haloperidol caused greater endpoint variability, Madopar did not

Haloperidol led to greater endpoint variability measured by the standard deviation of saccadic amplitudes (p< .001, F- statistics, see **Table 3.10**). This was not the case for Madopar, where no significant drug effect was found (p=

.231, **Table 3.10**). While the placebo cohort itself showed a main effect of reward, improving endpoint variability when rewarded (F (1, 55) = 4.56, p= .037), this effect was attenuated in both drug arms (p= .294, p= .130), however, not ultimately leading to an interaction between drug and reward. In summary, haloperidol increased variability, while there was no conclusive evidence that this was related to reduced motivation.

		F_A	p	ß (°) ± SE
MADOPAR				
	reward	(1, 139.04) = 1.11	= .294	
	drug	(1, 139.22) = 1.14	= .231	
	drug*reward	(1, 139.04) = 2.02	= .158	
HALOPERIDOL				
	reward	(1, 133.22) = 2.32	= .130	
	drug	(1, 135.11) = 23.31	< .001	0.20 ± 0.05
	reward*drug	(1, 133.22) = 0.50	= .823	

Table 3.10 Double-step paradigm- drug study, F-statistics: Amplitude variability.

3.3.3.6. People with low intrinsic motivation are more likely to improve inhibitory control on Madopar

Could someone's intrinsic motivation tell us something about their dopamine levels? To clarify in which situations dopamine could have beneficial and in which detrimental effects on cognitive control, intrinsic motivation was assessed as a potential proxy for dopamine baseline activity. I included the self-reported Apathy Motivation Index score (median split low vs. high) into the mixed linear model and repeated analysis on the mean values per subject. This questionnaire was previously found to be a sensitive tool to assess intrinsic motivation in otherwise healthy controls (Ang *et al.*, 2017). Intriguingly, I found interactions between AMI scores and Madopar manipulation on two variables of accuracy/inhibitory control when comparing placebo data to data retrieved after a single dose of Madopar. Interactions were found in the variables of departure angle (F (1, 138.87) = 8.82, p= .004) and proportion of erroneous trials (F (1, 138.64) = 6.65, p= .011, **Figure 3.11**). The most consistent finding across these variables was that participants with

low AMI scores showed an improvement of inhibitory control after a single dose of Madopar, while this effect was absent in high AMI score participants, where there was no drug effect to be found. A main effect of AMI scores interestingly also showed that low AMI scores led to better inhibitory control overall when compared to highly motivated participants (departure angle: F (1, 27.05) = 4.53, p= .042, proportion of errors: F (1, 27.01) = 6.22, p= .023). No main effect of AMI scores or interactions between drug and AMI scores were found in other variables including velocity, reaction time or amplitude size. In the analysis including haloperidol and placebo, there was no main effect of AMI scores on performance (departure angle: p= .19, proportion of errors: p= .07) and no interactions between AMI and drug (departure angle: p= .45, proportion of errors: p= .41) cohort.

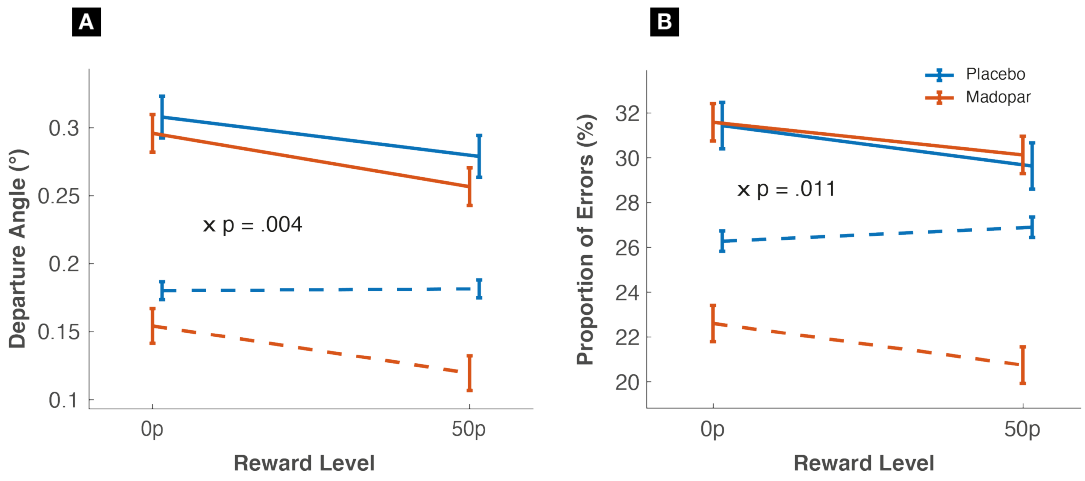

Figure 3.11 Double-step paradigm- drug study: Interaction between drug and AMI scores show (A) improved inhibitory control and (B) a decreased proportion of erroneous trials after a single dose of Madopar *if* intrinsic motivation was low to start with. No difference was found in the "high" motivation group (dashed lines= low AMI score, solid lines= high AMI score).

3.3.4. Discussion

3.3.4.1. Distractor inhibition and proportion of errors improved by Madopar and worsened by haloperidol

Haloperidol was detrimental to performance in two ways. It led to greater distractibility and worsened endpoint accuracy. The proportion of saccadic endpoints being located closer to the distractor than the target was higher and distractor pull was increased, resulting in saccadic curvature pointing increasingly into the direction of the distractor. This is in line with a rise in antisaccadic errors through heightened distractibility reported in healthy volunteers after a dose of intravenous 1mg of haloperidol (McCartan *et al.*, 2001) pointing towards impaired cognitive control on haloperidol, which may also be reflected by the decrease of reaction time in my data leading to early more erroneous saccades. Madopar, on the other hand, improved the proportion of errors. Evidence from predictive coding models suggested that dopamine increases the confidence of actions by increasing the precision signal but promoting distractibility (Dreisbach *et al.*, 2005; Galea *et al.*, 2012; Rawji, 2019), which is supported by clinical studies (MacDonald *et al.*, 2016) but not entirely in line with my findings. In this task I found higher dopaminergic levels to coincide with improved distractibility when compared to placebo. In order to explain this finding and to account for participants' intrinsic motivation, I subsequently added AMI score results to the model ("high" vs. "low"). Performance improvements after Madopar, in this case, only held true in participants with low intrinsic baseline motivation, suggesting that Madopar improves performance in low dopamine baseline individuals only. These findings are very interesting especially in light of the hypothesis that "optimal" dopamine levels may be embedded in the centre between "too much" and "too little" dopamine. If low AMI scores, therefore, indicate low-normal dopamine levels, adding Madopar could potentially improve performance without creating an "overdose", whereas in high AMI scores could potentially worsen it (Floresco and Costa, 2013). It, however, remains unclear why no correlation was found between haloperidol and AMI scores.

It may be possible that self-reported motivation tracks D1-receptor occupancy and the selective D2-effects are not modulated by this. These findings are of special interest due to the neat within-subject design of this study, which allows for a better interpretation of results even without having invasive dopamine measures.

3.3.4.2. Both drugs caused a significant decrease in motor vigour

Significantly smaller amplitudes were found in both drug groups compared to placebo. This in consequence led to slower peak velocities in both cohorts reflecting decreased motor vigour on both drugs. The drug effects on velocity and reaction time did, however, not survive regression with amplitude sizes. Neither of the residual variables was, therefore, significantly altered by either drug. There might be two possible explanations for the reduced reaction times on haloperidol: They could either be the result of smaller amplitude sizes in the haloperidol group (smaller movements require shorter planning times) or reflect reduced cognitive (inhibitory) control as a higher proportion of erroneous trials was observed concurrently. Due to the task's setup, reaction times represent two different processes: The speed of inhibition of the first saccade (towards the distractor) and the reaction time taken to elicit the saccade to the (correct) target. Haloperidol was overall rather detrimental to participants' performance, which makes it more likely that the reduced reaction time in this paradigm reflects reduced inhibitory control or the relationship between amplitude size and preparatory processes rather than an improvement of the motor preparation processes itself.

Data suggest that tonic dopamine controls motor vigour and is tightly connected to an individual's motivational state (Niv, 2007). This would promote the idea that increased dopamine levels (Madopar) increase motor vigour, while haloperidol decreased it, which was not the case in these data. Hypometric saccades are well documented in patients with PD and have been reported in MTPT induced parkinsonism (Poletti and Bonuccelli, 2013). They have, thus, also been reported in Huntington disease and schizophrenia,

indicating hypometric saccades might not only be a *hypo*-dopaminergic phenomenon (Hotson, Langston and Langston, 1986; Kato *et al.*, 1995; Winograd-Gurvich *et al.*, 2003). This is supported by data from DAT scans, showing a correlation between DAT binding activity and the severity of hypometric saccades (Railo, Olkoniemi and Eeronheimo, 2018). Although there are studies investigating the effect of dopaminergic drug manipulation on saccades of healthy controls, most of these studies assessed saccadic velocity and reaction time, while data on the drug effect on amplitudes remain scarce.

The available data may point towards a “too high”- “too low” hypothesis for saccadic amplitude as well. Nevertheless, it is important to mention that the interaction found between drug and AMI scores was present only in variables of accuracy in this paradigm, which suggests an interdependence between baseline dopamine levels and the impact of additional dopaminergic manipulation. This effect was absent when measuring motor vigour (amplitude, velocity) as the drug effect was not dependent on intrinsic motivation scores (no interaction between AMI and drug).

It is believed that the main sequence, being the relationship between amplitude size and velocity, optimises the trade-off between the accuracy of an eye movement and its movement duration (Harris and Wolpert, 2006). Faster movements result in increased noise in the motor command and, hence, in less accurate movements. While it was shown that this observation can be violated by motivation through reward, both drugs also seemed to shift this relationship, causing participants to elicit slower saccades also in unrewarded trials. Whereas this led to greater level of accuracy on Madopar, haloperidol caused accuracy to deteriorate, potentially due to a disruption of inhibitory processes also reflected by shorter reaction times.

Since saccade circuits are well-studied, the exact patterns of oculomotor parameters allow us to infer the locus of the effect these two drugs may have on them. Saccadic velocity and amplitude have, e.g., been reported to be

diminished in monkeys with local dopamine depletion within the caudate nucleus (Kato *et al.*, 1995). This is thought to be the case because the local dopamine depletion in the caudate causes increased inhibitory activity in the SNr towards the superior colliculus and, consequently, to reduced saccadic vigour. Primate studies have also shown that electrical stimulation of the SNr, too, inhibits the superior colliculus leading to a similar saccadic pattern (Basso and Liu, 2007).

3.3.4.3. Reward sensitivity was not significantly altered by either of the drugs

Due to previous findings of cabergoline increasing reward sensitivity in the same task, we assumed higher levels of dopamine could coincide with greater willingness to exert effort. Motivation, here, was found to improve saccadic performance when reward was on offer, namely, leading to greater saccadic peak velocity and shorter reaction times as well as amplitude size and amplitude variability in the placebo group. Neither of the drugs, however, significantly altered reward sensitivity in this paradigm, with only one trend to be reported. In fact, haloperidol surprisingly led to the numerically biggest increase in residual peak velocity on rewarded trials (drug x reward p= .061, n.s.). There has been controversy around the effect of a (small) single dose of haloperidol, where pharmacological studies yielded contradicting results. While haloperidol is believed to act mainly on post-synaptical D2 receptors and, hence, should lead to a decrease in dopamine, animal studies suggested that, indeed, haloperidol administered in small doses (as 2.5mg is considered to be) could act on pre-synaptical receptors and eventually lead to an increase in dopamine release (Richfield, Penney and Young, 1989), which could explain my results. Another interesting finding in this context was that in monkeys D2 blockade increased reward sensitivity of saccadic RT, as measured in a simple saccadic paradigm, suggesting a more complex underlying mechanism (Nakamura and Hikosaka, 2006).

Figure 3.12 illustrates the simplified drug effects I found in this task assuming participants had an “optimal baseline dopamine” to start with and haloperidol

would, in fact, decrease dopamine levels. Saccadic amplitude (grey) was diminished by both drug manipulations, while reward sensitivity (dashed blue) was not significantly altered by either drug in this task. Inhibitory control interestingly was overall improved by Madopar (green), although considering intrinsic motivation scores it remains to be clarified whether this green line may flatten for higher-than-normal dopamine levels.

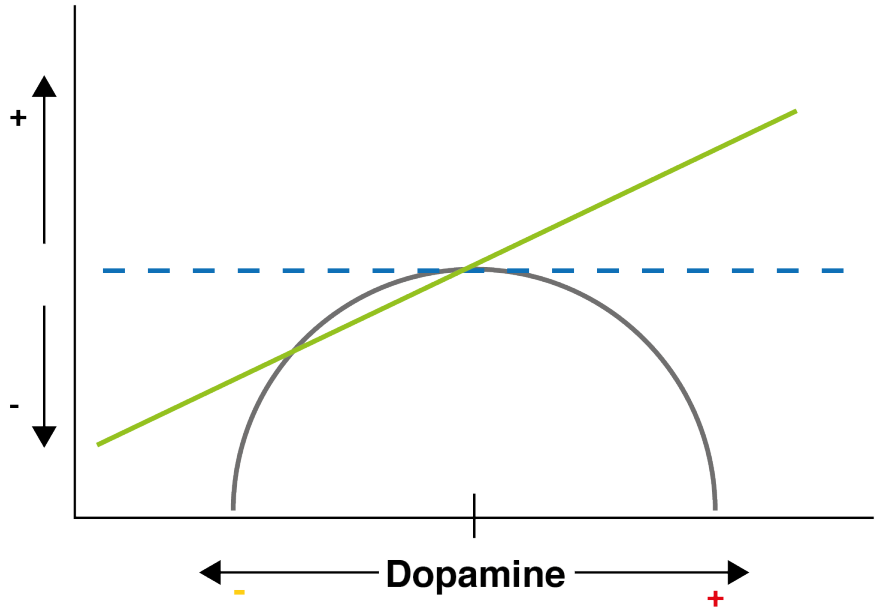

Figure 3.12 Double-step paradigm- drug study: Illustration of the relationship between dopamine levels (x-axis), saccadic amplitude sizes (grey), reward sensitivity (blue) and inhibitory processes (green). While amplitude size diminished on both drug manipulations, inhibitory processes seemed improved on Madopar and worsened on haloperidol, reflected by accuracy measures. Reward sensitivity did not, as expected, increase with higher dopamine levels significantly.

3.4. Effect of dopamine on reward sensitivity in multi-alternative decision-making

3.4.1. Background and hypothesis

In order to make a saccade to a target we first need to choose "the right" target from a number of alternatives. Dopamine is thought to be closely involved in this process via the basal ganglia, specifically in the filtering of irrelevant stimuli, which in turn is a key skill in reinforcement learning (Frank and O'Reilly, 2006). A disruption in these mechanisms could, hence, lead to delayed, on the one hand, or premature and erroneous decisions on the other hand side. Apathy and impulsivity could be considered clinical syndromes reflecting those two types of choices, both linked to decreased and increased levels of dopamine respectively. If those conditions, indeed, represented two syndromes on a dopamine-dependent spectrum of goal-directed behaviour (Sinha, Manohar and Husain, 2013), one could expect to find a specific pattern of saccadic changes in this multi-alternative choice paradigm after drug administration.

It, however, remains a matter of controversy if pharmacologically altered dopamine levels impair the timing of (Soares, Atallah and Paton, 2016; Mitchell *et al.*, 2018) or disrupt the action selection process as such. Brown et al. found an impairment of choice reaction time rather than simple reaction time in dopamine deplete rats and interpreted these findings as "impaired motor readiness but preserved response preparation" (Brown and Robbins, 1991), which was in line with findings from other studies involving PD patients (Rafal *et al.*, 1984; Pullman *et al.*, 1988). Animal work on dopamine-depleted rats confirmed these findings and showed motor impairments probably as a result of disrupted response initiation rather than selection (Carli, Evenden and Robbins, 1985).

These findings have led to the first question to be addressed by this paradigm as to if/how altered levels of dopamine will influence choice reaction time and

accuracy. Based on previous findings, the expectation may be to observe longer reaction times but preserved accuracy, although the former was not reflected by our data in the previous chapter.

The second crucial question is the role of dopamine in signalling incentives of different valence. While dopamine's role in reward signalling is well established, also the degeneration of serotonergic pathways within the caudate nucleus has been found to correlate with the severity of apathy in a PET-study involving PD patients (Maillet *et al.*, 2016). These pathways have previously been found to encode aversive stimuli and punishment avoidance rather than rewards (Daw, Kakade and Dayan, 2002; Denk *et al.*, 2004; Guitart-Masip *et al.*, 2014; Hu, 2016). More recent evidence, however, points towards the involvement of serotonin and its 5-HT neuronal receptors in reward encoding in mice studies (Miyazaki *et al.*, 2014; Li *et al.*, 2016). The question to be answered here is whether pharmacologically altered dopamine levels induce different motivation-related changes in saccadic performance depending on the incentive valence.

A rather unexpected finding from the previous chapter was the absence of an increase in choice RTs with a higher amount of response alternatives. The level of uncertainty in the task did not significantly alter choice reaction times of healthy participants. It is unclear whether this was due to the experimental setup of my task (central arrow, number of choice alternatives, position of targets including vertical saccades) or if there might have been additional factors contributing to the results (e.g., cohort tested, sample size).

I, therefore, repeat the same task with a larger sample size and aim to answer the following questions: **(1)** Do internally triggered saccades follow Hick's law, **(2)** does dopaminergic manipulation have a detrimental effect on cognitive control as described by the "inverted-U-shaped" relationship, potentially leading to longer reaction times, **(3)** how do incentives of different valence affect motor control of internally triggered saccades and **(4)** could there be an

interaction between reward sensitivity and drug manipulation in internally triggered saccades?

3.4.2. Eye tracking paradigm

The eye tracker setup described in **section 2.1.3** remained unchanged, and more detailed task instructions can be found in **section 2.2.3**. Thirty participants completed 5 blocks of each 72 saccades (total 360 saccades) in each of the three drug conditions. Breaks were taken in between each block and 10 practice trials at the beginning of the first block were not included in the analysis. From the total of 90 recorded datasets (30 participants each completing 3 sessions), 5 datasets had to be excluded/are missing from the analysis, due to participants' time constraints or technical issues. This concerned one dataset within the placebo cohort and 4 datasets in the haloperidol arm.

3.4.3. Statistical analysis

A random intercept model was used to perform statistical analysis using incentives, number of possible targets and drug as within-subject factors (**Table 3.11**). Incentives were defined as a factor with 3 levels (-50, 0 and 50p) with the reference level being 0p. To investigate the effect both drugs have in comparison to placebo performance, two separate analyses were conducted using placebo as the reference level (**Figure 3.13**). The number of response alternatives/targets was defined as linear factor and the z-scored values of it were used in the model due to slightly varying number of trials for each participant.

The analysis was performed in R and SPSS. Post-hoc comparisons were conducted using Bonferroni correction. The following codes were used, and SPSS results were reported in the results section below:

R	lmer (var ~ incentives * number of targets * drug + (1 | ID), data)
SPSS	MIXED *var* BY drug incentives WITH number of targets /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE) /FIXED= incentives drug number of targets incentives * drug incentives * number of targets drug * number of targets incentives * drug * number of targets | SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC)

Table 3.11 Multi-alternative decision-making- drug study: Model used for statistical analysis in R and SPSS: "Var" represents the variable of interest in the analysis (i.e., peak velocity). "Number of targets" represents the linear factor of uncertainty (1-level factor: 2, 4 and 8 possible targets computed as z-scores), "incentives" represent the three different incentive conditions (3-level within-subject factor: "lose", "nil", "win").

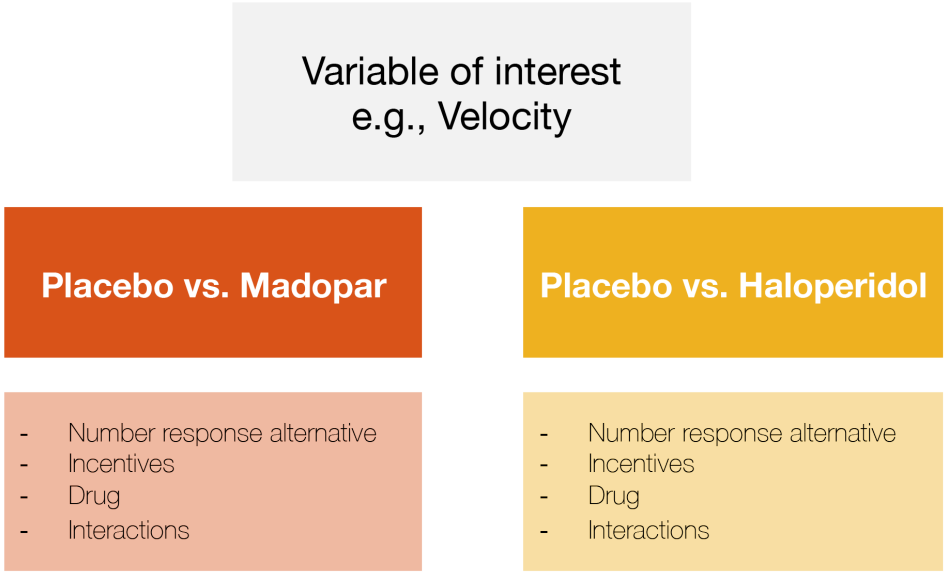

Figure 3.13 Multi-alternative decision-making- drug study; hierarchical structure of statistical analysis: Two separate analyses were performed with data comparing Madopar and haloperidol to placebo data separately. In each analysis the following factors were included: (1) Uncertainty/number of alternatives (z-scored linear factor), (2) incentives (3 levels with 0p as reference), (3) drug (2 levels) and their (4) interaction terms.

3.4.4. Results

3.4.4.1. Hick's law was obeyed in both placebo and Madopar but not haloperidol data

Greater uncertainty led to longer reaction times in both Madopar and placebo groups (p< .001, **Table 3.12**) and, hence, confirmed Hick's law for internally triggered saccades in this cohort (**Figure 3.14**). This effect was, however, diminished on haloperidol, which led to a weak but significant interaction between drug and uncertainty in the placebo vs. haloperidol analysis (p= .047). Although none of the post-hocs within the placebo vs. haloperidol group nor the separate analysis of the effect of uncertainty in the haloperidol data reached significance, it seems that haloperidol blocked the slowing of reaction times driven by uncertainty. This was accompanied by overall prolonged reaction times in the haloperidol arm (ß= 17.07 ms (1.29), p< 001)

when compared to placebo. Madopar did not have a main effect on reaction times (p= .129).

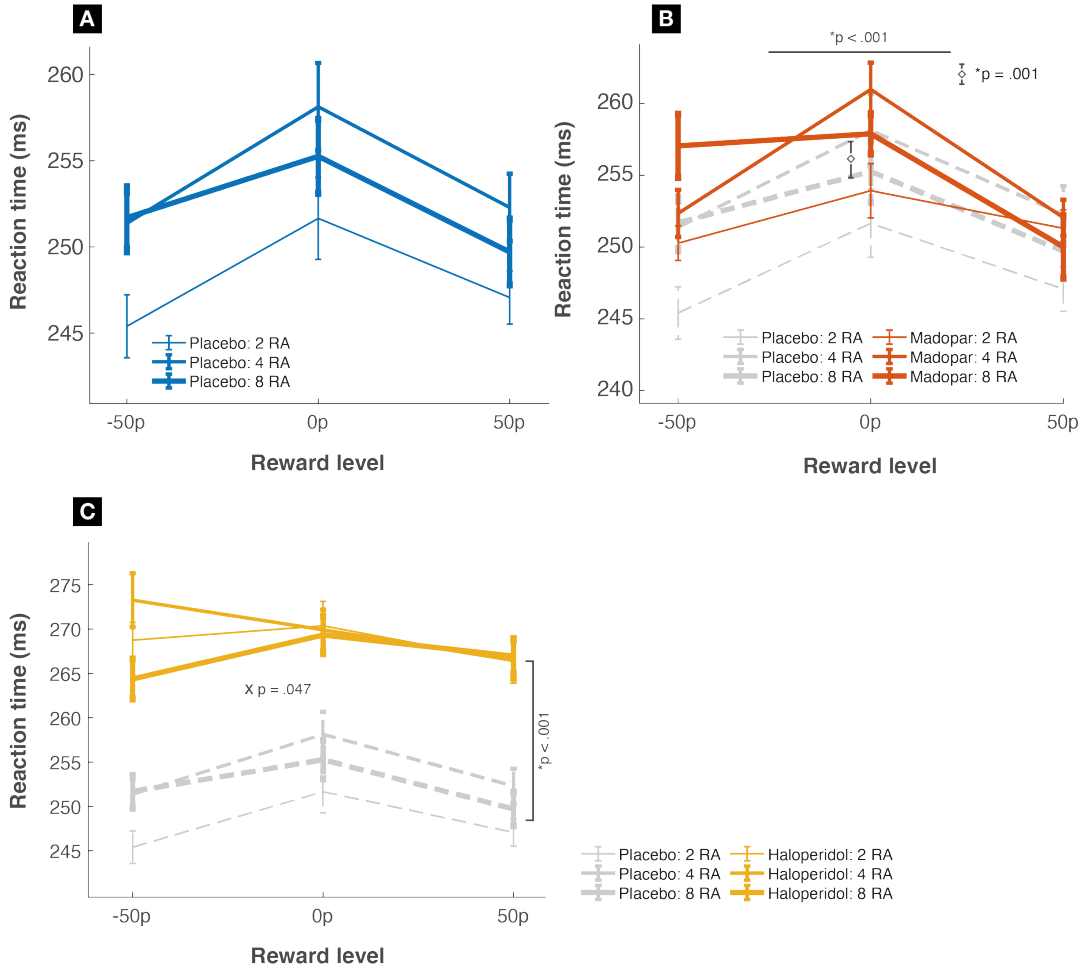

Figure 3.14 Multi-alternative decision-making- drug study, reaction time: RA= response alternative/number of targets. (A) Placebo data confirmed Hick's effect on reaction times. (B) Statistics including Madopar data show a main effect of uncertainty as well as a main effect of incentives. (C) Haloperidol, however, attenuated the effect of uncertainty shown by an interaction between drug and uncertainty and showed overall slower performance independent of the uncertainty level.

Participants' reaction times showed a main effect of incentives in both comparisons (haloperidol vs. placebo and Madopar vs. placebo, F-statistics, see **Table 3.12)**. They were faster when incentivised. Comparing Madopar with placebo, both loss and win trials resulted in faster reaction time (win: ß= -5.54 ms (1.30), p<.001; loss: ß= -4.84 ms (1.30), p= .001) with no difference between them (p= 1.0). The main effect of incentives was also present in the

haloperidol-placebo comparison (p= .031). In this analysis only win trials sparked improved performance (ß= 3.82 ms (1.54), p= .039), while there was no significant difference for loss trials compared to unrewarded trials (p= .14). Although this might be an interesting observation leading to the interpretation that haloperidol attenuates the motivating effect of aversive stimuli, there was no significant difference between win and loss trials (p= 1.0) leading to the conclusion that overall reward sensitivity in haloperidol was low.

		F_A	p
MADOPAR			
	incentives	(2, 22244.01) = 10.74	< .001
	drug	(1, 22257.66) = 2.41	= .129
	number of targets	(1, 22244.00) = 8.33	< .001
	incentives *drug	(2, 22244.01) = 0.728	= .485
	incentives* number of targets	(2, 22244.06) = 1.38	= .252
	drug*number of targets	(1, 22243.02) = 0.553	= .575
	incentives*drug*number of targets	(2, 22244.04) = 0.47	= .627
HALOPERIDOL			
	incentives	(2, 20223.18) = 3.47	= .031
	drug	(1, 20249.70) = 175.49	< .001
	number of targets	(1, 20223.18) = 0.40	= .525
	incentives *drug	(2, 20223.18) = 1.03	= .365
	incentives* number of targets	(2, 20223.16) = 0.03	= .970
	drug*number of targets	(1, 20223.12) = 3.96	= .047
	incentives*drug*number of targets	(2, 20223.15) = 1.61	= .186

Table 3.12 Multi-alternative decision-making- drug study, F- statistics: Reaction time.

3.4.4.2. Madopar increased reward sensitivity of peak velocity

There were three main effects found in both drug comparisons when looking at saccadic velocity: Participants were faster when they were incentivised, slower with greater uncertainty and slower when on drugs vs. placebo (F-statistics, see **Table 3.13**). Most interestingly, I found an interaction between drug and incentives (p= .020, see **Figure 3.15)**, whereby Madopar increased

reward sensitivity in both incentive conditions compared to placebo. This was not the case for haloperidol.

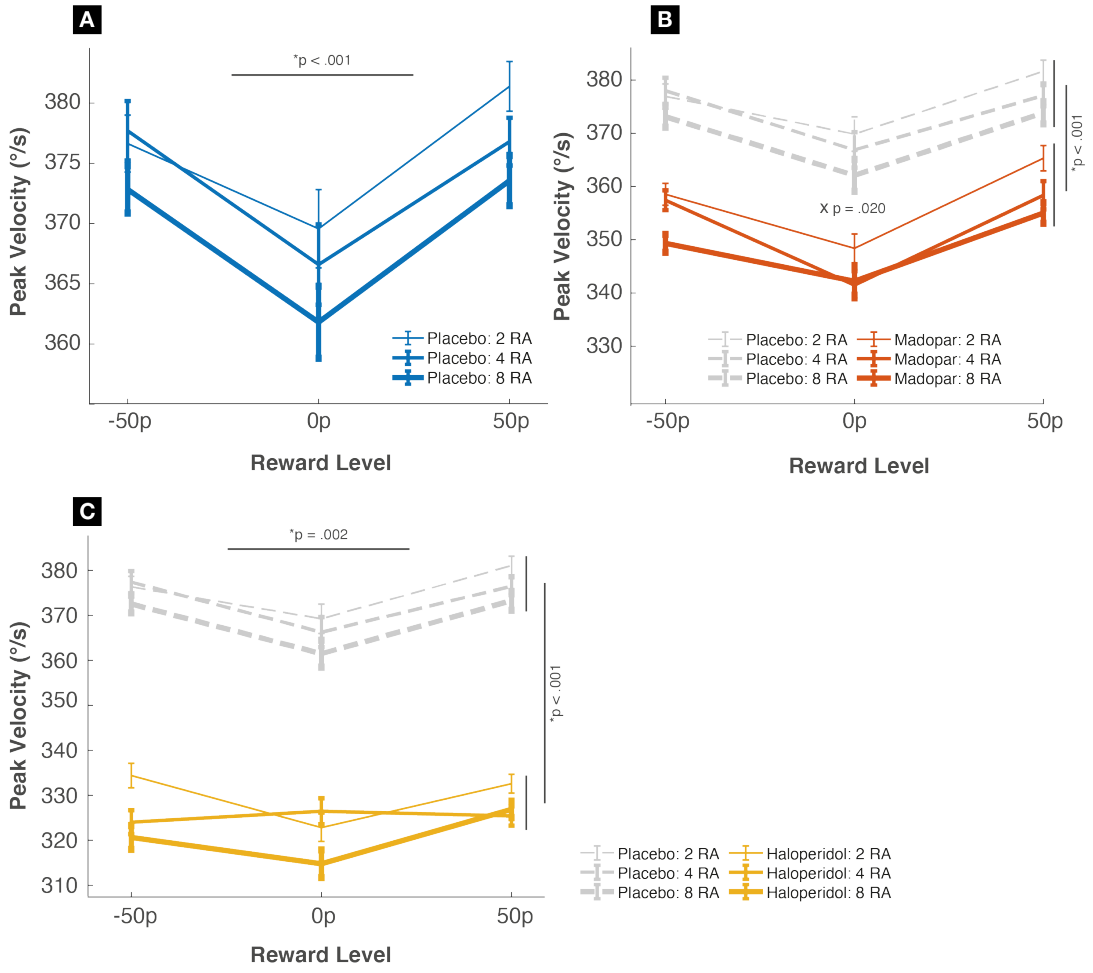

Figure 3.15 Multi-alternative decision-making- drug study: Peak saccadic velocity. Reward had an effect on both drug arms, and Madopar increased overall reward sensitivity. Greater uncertainty led to slower saccades in all three study arms.

Pairwise comparisons in the placebo vs. Madopar analysis showed that participants, when on placebo, increased their velocity in both win (ß= 7.79°/s (2.19), p= .001) and loss conditions (ß= 6.1°/s (2.19), p= .016) equally. As reflected by the interaction between drug and reward in the same analysis, this effect was also present but stronger in the Madopar group than for placebo for both incentives (win: ß= 16.34°/s (2.18), p< .001, loss: (ß=

11.42°/s (2.18), p< .001, **Figure 3.16**), again with no difference between the two (p= 1.0). Similarly, within the haloperidol vs. placebo data, participants were significantly faster when motivated (p= .002; win: ß= 6.33°/s (1.90), p= .002; loss: ß= 4.93°/s (1.90) p= .029) when compared to unrewarded trials. There was no difference between the effect of both incentive conditions in either of the two drugs nor placebo (p= 1.0).

There was a main effect of drug in the Madopar data (F (1, 22247.53) = 59.86, p< .001). As previously shown to be the case for saccades in the double-step paradigm, internally triggered saccades were also slowed by Madopar when compared to placebo (ß= -9.85°/s (1.27), p< .001) as they were on haloperidol (ß= -41.06°/s (1.59), p<.001), with a much bigger difference for the latter. A higher number of choice alternatives led to slower peak velocities in both drug comparisons (p< .001, see **Table 3.13**), probably driven by smaller amplitudes (see next section). For a full list of main effects and interaction terms please refer to **Table 3.13.**

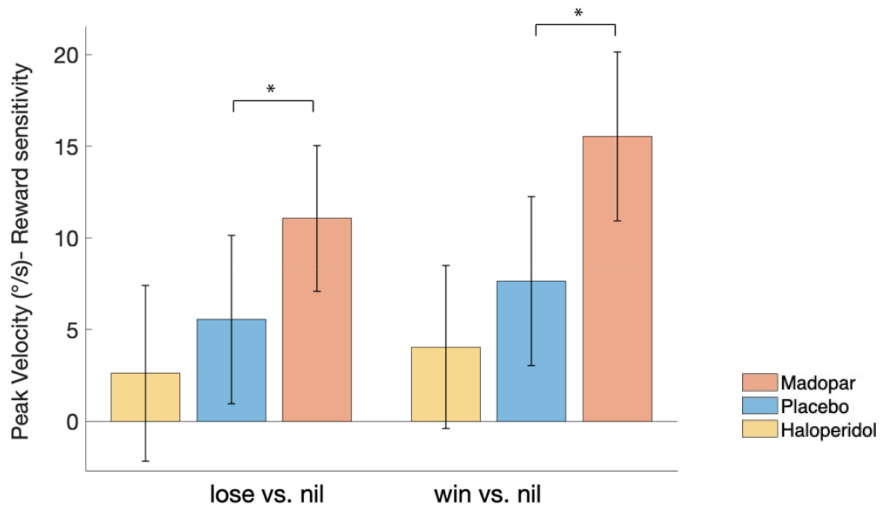

Figure 3.16 Multi-alternative decision-making- drug study: Reward sensitivity of peak velocity on haloperidol, placebo and Madopar. Participants were more willing to increase peak velocity when on Madopar compared to placebo (* interaction between reward and drug p= .020); haloperidol caused an overall slowing of peak velocity with no effect on reward sensitivity.

		F_A	p
MADOPAR			
	incentives	(2, 22244.01) = 32.60	< .001
	drug	(1, 22247.53) = 59.86	< .001
	number of targets	(1, 22244.02) = 17.18	< .001
	incentives *drug	(2, 22244.01) = 3.89	= .020
	incentives* number of targets	(2, 22244.00) = 0.63	= .531
	drug*number of targets	(1, 22243.99) = 1.18	= .278
	incentives*drug*number of targets	(2, 22243.99) = 0.16	= .852
HALOPERIDOL			
	incentives	(2, 20223.00) = 6.09	= .002
	drug	(1, 20241.89) = 662.38	< .001
	number of targets	(1, 20222.99) = 12.42	< .001
	incentives *drug	(2, 20223.00) = 0.24	= .783
	incentives* number of targets	(2, 20223.00) = 0.122	= .885
	drug*number of targets	(1, 20223.01) = 1.03	= .311
	incentives*drug*number of targets	(2, 20223.01) = 0.35	= .705

Table 3.13 Multi-alternative decision-making- drug study; F- statistics: Peak velocity

After factoring out amplitude size, the only remaining main effect on residual peak velocity was the one of incentives (Madopar: p< .001, haloperidol p= .008, see further **Table 3.14)**. Participants on Madopar were significantly faster in both incentive conditions (win: ß= 207.82°/s (33.69), p<.001, lose: ß= 119.31°/s (33.71), p= .001). There was a stronger effect of reward than penalty, however, (win vs. lose: ß= 88.52°/s (33.67), p= .026) which resulted in greater velocities when reward was on offer when compared to trials of loss avoidance.

This confirms the findings from the same paradigm discussed in **section 2.2.** The latter was even more exaggerated after haloperidol, where participants were still faster for win trials (ß= 112.21°/s (36.9), p= .007) but there was no effect of loss (p= .11). In fact, dissecting whether this could be the effect of one of the drugs alone, I looked at the effect of incentives on the haloperidol

data separately, where no main effect of incentives was present at all (F (2, 9171.0) = 1.34, p= .263). This was the case with no significant interactions between drug and reward being present.

		F_A	p
MADOPAR			
	incentives	(2, 22273.00) = 19.15	< .001
	drug	(1, 22273.00) = 0.00	= .998
	number of targets	(1, 22273.00) = 1.98	= .160
	incentives *drug	(2, 22273.00) = 2.14	= .117
	incentives* number of targets	(2, 22273.00) = 0.25	= .777
	drug*number of targets	(1, 22273.00) = 0.68	= .409
	incentives*drug*number of targets	(2, 22273.00) = 1.62	= .198
HALOPERIDOL			
	incentives	(2, 20251.00) = 4.84	= .008
	drug	(1, 20251.00) = 0.00	= .993
	number of targets	(1, 20251.00) = 2.73	= .099
	incentives *drug	(2, 20251.00) = 0.27	= .763
	incentives* number of targets	(2, 20251.00) = 0.46	= .629
	drug*number of targets	(1, 20251.00) = 0.15	= .698
	incentives*drug*number of targets	(2, 20251.00) = 0.83	= .438

Table 3.14 Multi-alternative decision-making- drug study, F-statistics: Residual peak velocity.

3.4.4.3. Both drugs caused smaller amplitudes

Amplitude sizes changed significantly with uncertainty (as observed before) and drugs in both drug comparisons (for F-statistics, see **Table 3.15**). Greater uncertainty led to smaller amplitudes as did both drugs (Madopar (ß= -0.149° (0.023), p<.001); haloperidol (ß= -0.388° (0.027), p< .001, **Figure 3.17**)). Amplitudes were greater for both incentives in placebo vs. Madopar with no significant difference in between both incentive conditions (win: ß= 0.12° (0.028), p= .001; loss: ß= 0.11° (0.032), p= .001), which was not the case for the haloperidol comparison (main effect of incentives p= .090). Assessing whether this is the effect of haloperidol alone, I conducted an analysis for the

effect of incentive on the placebo data separately, which confirmed the absence of reward sensitivity (F (2; 11052.01) =2.39, p= .091). There was, however, no significant interaction between incentives and drug in the Madopar vs. placebo analysis (p= .243). This is in line with data from this paradigm in the previous chapter where saccadic amplitudes were not modulated by motivation.

		F_A	p
MADOPAR			
	incentives	(2, 22243.95) = 11.31	< .001
	drug	(1, 22256.84) = 41.74	< .001
	number of targets	(1, 22243.95) = 101.62	< .001
	incentives *drug	(2, 22243.95) = 1.49	= .243
	incentives* number of targets	(2, 22243.96) = 1.55	= .212
	drug*number of targets	(1, 22243.96) = 0.19	= .660
	incentives*drug*number of targets	(2, 22243.96) = 0.69	= .498
HALOPERIDOL			
	incentives	(2, 20222.81) = 2.41	= .090
	drug	(1, 20250.94) = 214.66	< .001
	number of targets	(1, 20222.79) = 84.92	< .001
	incentives *drug	(2, 20222.81) = 0.27	= .764
	incentives* number of targets	(2, 20222.82) = 0.01	= .987
	drug*number of targets	(1, 20222.82) = 0.43	= .513
	incentives*drug*number of targets	(2, 20222.82) = 0.57	= .567

Table 3.15 Multi-alternative decision-making- drug study, F- statistics: Amplitude.

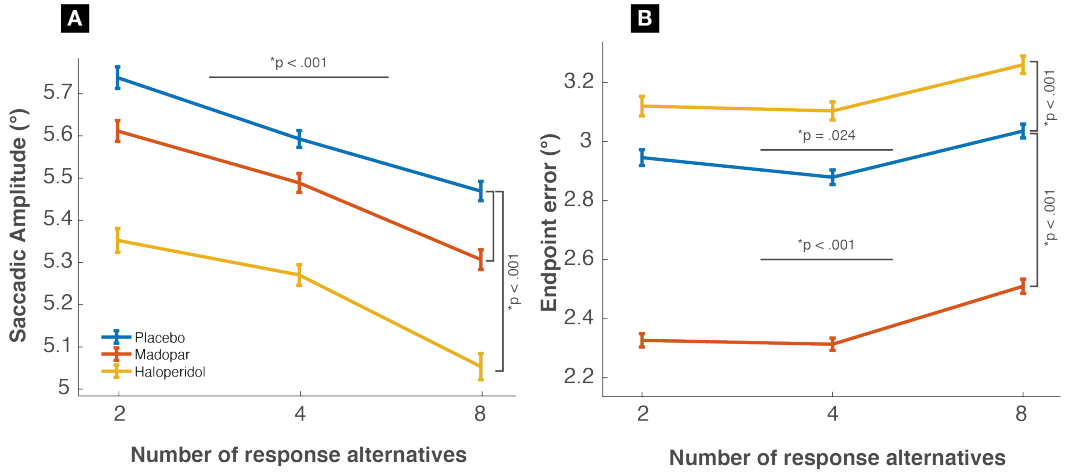

Figure 3.17 Multi-alternative decision-making- drug study: (A) Amplitudes decreased with uncertainty and both drug manipulations. (B) Despite this, saccades landed closest to target on Madopar followed by placebo. Haloperidol led to greater inaccuracy most likely due to hypometric saccades.

3.4.4.4. Madopar prompted participants to act faster and more accurately

Madopar caused participants' saccades to become more accurate (p< .001). The endpoint of saccades was significantly closer to the target on Madopar (ß= -0.56° (0.03), p<.001) than placebo. The opposite was the case for haloperidol which had a detrimental effect on accuracy (p< .001). Greater uncertainty also led to greater Euclidean distance to target, as reflected previously in my data (Madopar: p< .001, haloperidol p= .024). Endpoint accuracy was not influenced by motivation (F-statistics, see **Table 3.16)**.

		F_A	p
MADOPAR			
	incentives	(2, 22243.99) = 0.49	= .612
	drug	(1, 22252.37) = 385.19	< .001
	number of targets	(1, 22243.99) = 14.21	< .001
	incentives *drug	(2, 22243.99) = 0.006	= .994
	incentives* number of targets	(2, 22244.00) = 2.51	= .081
	drug*number of targets	(1, 22243.99) = 1.61	= .204
	incentives*drug*number of targets	(2, 22244.00) = 0.77	= .462

HALOPERIDOL			
	incentives	(2, 20223.07) = 1.69	= .844
	drug	(1, 20223.96) = 47.46	< .001
	number of targets	(1, 20223.06) = 5.08	= .024
	incentives *drug	(2, 20223.07) = 0.06	= .939
	incentives* number of targets	(2, 20223.07) = 1.77	= .171
	drug*number of targets	(1, 20223.07) = 0.19	= .661
	incentives*drug*number of targets	(2, 20223.07) = 0.01	= .994

Table 3.16 Multi-alternative decision-making- drug study, F- statistics: Euclidean distance to target.

3.4.5. Discussion

3.4.5.1. Internally triggered saccades obey Hick's law

Internally triggered saccades were found to obey Hick's law in both the placebo and the Madopar data. Participants showed longer reaction times in the presence of a higher number of choice alternatives. This was, however, not the case for haloperidol, which blocked the slowing of reaction times by uncertainty and showed overall prolonged reaction times. Hick's law was not obeyed in the cohort of healthy controls completing the same paradigm in the previous chapter (see **section 2.2**).

One explanation for this could be the increased level of practice in the second study (3 sessions vs. 1 session), potentially improving reaction times predominantly in the low uncertainty conditions. This hypothesis would, however, warrant further data analyses looking at the effects of practice over time during the task. Although no significant increase in reaction times with uncertainty has been found in the previous data (p= .14), one could still argue for the tendency towards longer reaction times, especially in unrewarded conditions. This could also give rise to the possibility that the first study was simply not sufficiently powered to detect the effect of uncertainty in all three incentive conditions. The overall slowing of reaction times on haloperidol was also a new finding, compared to the speeding effect of it in the previous task. Given the different nature of the tasks (inhibitory control vs. choice reaction

time), this may be in line with the finding of impaired choice reaction time but normal simple reaction time in both dopamine-depleted animals and human studies on PD (Rafal *et al.*, 1984; Pullman *et al.*, 1988; Brown and Robbins, 1991).

3.4.5.2. Both drugs reduced motor vigour

While the role of dopamine in action selection and initiation is well established, its function in movement timing and velocity also provides interesting research avenues (Beradelli *et al.*, 2001; Buhusi and Meck, 2005; Turner and Desmurget, 2010). Lesions within the basal ganglia, e.g., have been shown to cause isolated slowing of saccades (Horak and Anderson, 1984; Desmurget and Turner, 2010). In PD reduced motor vigour has been a widely studied phenomenon, not exclusively observed in saccades, and was shown to be a primary deficit rather than being the result of a dopamine induced shift in speed-accuracy trade-off (Mazzoni, Hristova and Krakauer, 2007; Baraduc *et al.*, 2013). Animal studies suggest a role of the dorsal striatum in the invigoration of movements (Niv, 2007; Turner and Desmurget, 2010; Wang, Miura and Uchida, 2013). In humans this is supported by the clinical observation of bradykinesia in dopamine-depleted PD patients, which improves with pharmacological replacement therapy (levodopa). A less investigated phenomenon is motor vigour in hyperdopaminergic states, although also schizophrenia, e.g., has been linked to a reduced likelihood to exert greater effort (Barch, Treadway and Schoen, 2014). While an "inverted-U-shaped" relationship between dopamine levels and working memory performance has been suggested (Cools and D'Esposito, 2011), this may also be the case for motor vigour. Healthy controls showed slower peak velocities and smaller amplitudes on both administered drugs when compared to placebo not only in this paradigm but also in the double-step paradigm discussed in the previous section. With reduced amplitude and speed, motor control laws such as Fitts's law predict smaller motor variability, due to motor noise which scales with the size of the motor command (Harris and Wolpert, 1998, 2006). This was the case for saccades after a single dose of Madopar.

However, precisely the opposite was observed with haloperidol (**Figure 3.3**). Slower and smaller movements were accompanied by paradoxically *larger* errors when compared to placebo, as observed in the last paradigm. As dopamine is thought to increase the precision signal that determines movement vigour, haloperidol might lead to slower and less accurate saccades potentially through a decreased signal-to-noise ratio. The control command required to improve precision might, however, be costly and could explain poorer performance in dopamine deplete states.

Motivation through both incentives improved performance across both velocity and reaction time in all three groups. There was no significant difference between the performance on win and loss trials apart from the stronger effect of positive incentives on peak velocity.

3.4.5.3. Madopar increased reward sensitivity of velocity

Most interestingly, Madopar increased reward sensitivity of peak velocity, which was not the case for haloperidol. It can, therefore, be concluded, that higher dopamine levels increased reward sensitivity of velocity in internally triggered saccades but not in the double-step paradigm. A possible explanation for these results could be that the double-step task involves interfering inhibitory processes in order to suppress the saccade to the distractor and/or subsequently redirect the "second" saccadic direction (Becker and Jürgens, 1979), which could alter reward processing. This could be supported by the observation that haloperidol, which disrupted inhibition leading to a greater proportion of erroneous trials in the double-step paradigm, indeed, also resulted in greater reward sensitivity via the same mechanisms. Overall, this supports findings from previous human and animal studies, which have suggested that dopamine increases the willingness to exert effort towards rewarded stimuli (Salamone, 2002) by relatively decreasing movement costs, without showing a detrimental effect on accuracy (Winkel *et al.*, 2012).

In summary, in this section I replicated the finding of reduced motor vigour on both drugs as well as increased accuracy on Madopar as shown in the double-step paradigm. Novel findings include impaired choice reaction times on haloperidol in this paradigm and most importantly increased reward sensitivity on Madopar measured by peak velocity.

3.5. Task III: Effect of incentives, memory load, and dopamine on memory-guided saccades

3.5.1. Background and hypothesis

The precision of visual working memory, defined as " the active maintenance of visual information to serve the needs of an ongoing task" (Luck and Vogel, 2013), has been found to be modulated by dopamine. The neurophysiology of working memory, often investigated using memory-guided saccades, is consistently linked to prefrontal cortex neuronal activity, and was found to be heavily dopamine-dependent (Fuster, 1973; Haven and Goldman-Rakic, 1995; Seamans and Yang, 2004). However, there have been surprisingly few human studies looking into the interaction between working memory and dopamine using saccadic eye movements. In this introduction I will first discuss published data exploring dopaminergic drug effects on memory guided saccades, then touch on proposed underlying mechanisms linking dopamine to working memory performance more generally and finally review data on reward sensitivity and dopamine.

Data from human studies often involve patients diagnosed with diseases known to be accompanied by dopamine imbalances. For example, dopamine-naïve PD patients showed impaired VWM performance, which improved on dopaminergic treatment. Deficits well documented in this cohort include premature saccades during delay periods and decreased accuracy of memory recall (Crawford, Henderson and Kennard, 1989; Hodgson *et al.*, 1999). Indeed, PD patients were found to show superior performance in

memory recall when “OFF” medication when compared to “ON” (Fallon *et al.*, 2019). Knowing that these patients often suffer from various comorbidities and that disease pathology may affect large parts of different dopaminergic pathways (Billino, Hennig and Gegenfurtner, 2017), results might be difficult to interpret and may not answer specific questions about the underlying processes. Pharmacological studies involving dopaminergic medication also yielded mixed results. In healthy controls, mnemonic ability in the absence of distractors improved after a single dose of cabergoline but showed overall greater distractibility (Fallon *et al.*, 2017), while in another cohort it either worsened or improved performance on the same drug depending on the participants’ baseline performance (Cools and D’Esposito, 2011). Work on haloperidol in contrast showed clearer results, impairing working memory recall and increasing the level of guessing (Frank and O’Reilly, 2006). An animal study mimicking chronic antipsychotic exposure leading to D1 receptor downregulation in the prefrontal cortex also found that a single add-on dose of a D1 receptor agonist reversed the observed severe working memory impairments (Castner, 2000).

Specific studies investigating the effect of drug manipulations on memory-guided saccades have found that dopamine antagonists had a detrimental effect on performance in monkeys (Sawaguchi and Goldman-Rakic, 1991, 1994; Sawaguchi, 2000, 2001). More recently a cohort of participants carrying the COMT polymorphism, thought to putatively have higher prefrontal dopamine levels, were found to perform worse in memory-guided saccades than in visually guided saccades indicating a detrimental effect of dopamine on spatial memory representation (Billino, Hennig and Gegenfurtner, 2017). Dopamine depletion can also attenuate activity in the supplementary motor area, which has been shown to lead to impairments specifically in sequences of memory-guided saccades while relatively sparing single remembered saccades (Gaymard, Pierrot-Deseilligny and Rivaud, 1990). More recent evidence suggests a much more complex relationship between dopamine levels and cognitive performance, however. Whether dopamine improves or impairs working memory may depend heavily on a number of factors,

including the individual's baseline performance as well as baseline dopamine level. This idea is further developed by the suggestion performance may follow an "inverted-U-shaped" relationship (Cools and D'Esposito, 2011). Both more (Sahakian *et al.*, 1985; Murphy *et al.*, 1996; Zahrt *et al.*, 1997; Fallon *et al.*, 2017) and less (Sawaguchi, Matsumura and Kubota, 1990; Seamans, Floresco and Phillips, 1998) dopamine was found to alter working memory performance in a number of human and animal studies.

But what are the underlying mechanisms linking dopamine to WM performance? Dopamine has been implicated in WM maintenance (Haven and Goldman-Rakic, 1995; Floresco and Magyar, 2006; Vijayraghavan *et al.*, 2007; Fischer *et al.*, 2010; Eckart *et al.*, 2014; Rypma *et al.*, 2015). While striatal dopamine modulates WM through activity in the prefrontal cortex (Chatham and Badre, 2015), additional evidence has shown that the BG modulate sensory cortex activity by increasing the activation of task-relevant areas and decreasing it in task irrelevant ones (Schouwenburg, Ouden and Cools, 2015). Indeed, dopamine also seems to have a crucial role in feedback signalling from previous movements when making sequential movements (Friston *et al.*, 2012).

An additional question remains whether different dopaminergic levels influence reward sensitivity of memory-guided saccades and if so, in which way. Findings from the same task in the previous chapter showed saccadic velocity and reaction time to improve with motivation. Reward sensitivity of peak velocity, however, showed a trend toward weaker effects with higher memory loads, possibly indicating an increase in maintenance costs in the presence of multiple targets. Of interest, no difference was found between the effect of reward anticipation and penalty avoidance on saccadic properties in this task. In monkeys it has been shown that the ventrolateral PFC may be modulating information in working memory on the basis of reward expectation in an incentivised paradigm (Kennerley and Wallis, 2009). In a large online study no effect of monetary reward was found in humans

(Berg, Zou and Ma, 2020). Although the task was arguably not ideal for studying motivation due to its between-subject design, the negative result has been confirmed by a few other studies, showing attention can be shifted within the limited capacity system by reward but its limitations not overcome (Morey *et al.*, 2011b; Wallis *et al.*, 2015; Allen, 2019). If capacity limits are, indeed, strictly obeyed, even when we are motivated as indicated in the data of the previous chapter, then a saccadic task should show a dissociation, with strong effects of motivation on vigour but not on memory precision. This would confirm that the negative results are not simply due to insufficient or ineffective motivation but constitute a true performance limit.

Memory-guided saccades have been extensively studied in the past (Ohtsuka, Sawa and Takeda, 1989; Pierrot-Deseilligny *et al.*, 1991; Ditterich, Eggert and Straube, 1998; Sawaguchi, 2000; Brown *et al.*, 2004; Le Heron, MacAskill and Anderson, 2005; Müri *et al.*, 2009), but *sequences* of remembered saccades have received less attention (Gaymard, Pierrot-Deseilligny and Rivaud, 1990; Vermersch *et al.*, 1994; Mcsorley, Gilchrist and Mccloy, 2019). In addition to studying saccadic generation, initiation, memory maintenance and recall, using sequences of remembered saccades, may add further knowledge towards the influence of different memory loads and the role of serial position in recall processes and oculomotor properties.

In light of the discussed above I here aim to answer the following open question: **(1)** What impact do artificially altered dopamine levels have on saccadic performance and memory recall, with a special interest in precision? **(2)** Will higher dopamine increase reward sensitivity as in internally triggered saccades and may this effect be influenced by memory load? **(3)** Might there be differences in the effects of reward valence in different dopaminergic states?

3.5.2. Statistical analysis

Data handling was identical to that described in **section 2.3.4**. The mixed model used for the previous paradigms was also applied to this task. Filter criteria for data analysis were the same as for the memory-guided saccade task reported in the previous chapter (**section 2.3.4**).

From the total of 90 recorded datasets (30 participants each completing 3 sessions), 1 dataset had to be excluded due to technical issues. This concerned one dataset within the haloperidol arm. Each participant completed 9 blocks of each 36 trials amounting to a total of 324 trials per participant. Ten practice trials completed at the beginning of the first block were excluded from the analysis.

A random intercept model was chosen with the within-subject factors of reward (3 levels: -50, 0 and 50p with 0p as a reference), drug (2 levels: Madopar vs. placebo and haloperidol vs. placebo) and memory load (2 levels: high vs. low) as well as serial position (4 levels: saccade 1-4 within the sequence, **Table 3.17**). Since saccades later in a sequence may be strongly influenced by previous errors within the sequence, a separate analysis was performed using only the *initial* saccades. This allowed assessment of the effect of memory load on the first saccade, which was either to the single remembered location or was the first saccade made within the sequence of four. A subsequent analysis then examined all 4 saccades made when a sequence had to be remembered, assessing the effect of "serial position" on the parameter of interest for just the high-load condition. Initially an omnibus analysis was performed with all three drug groups together. Subsequently the analysis was repeated, and two sub-analyses were run (placebo vs. haloperidol and placebo vs. Madopar) for both the "memory load" and "serial position" analyses (**Figure 3.18**).

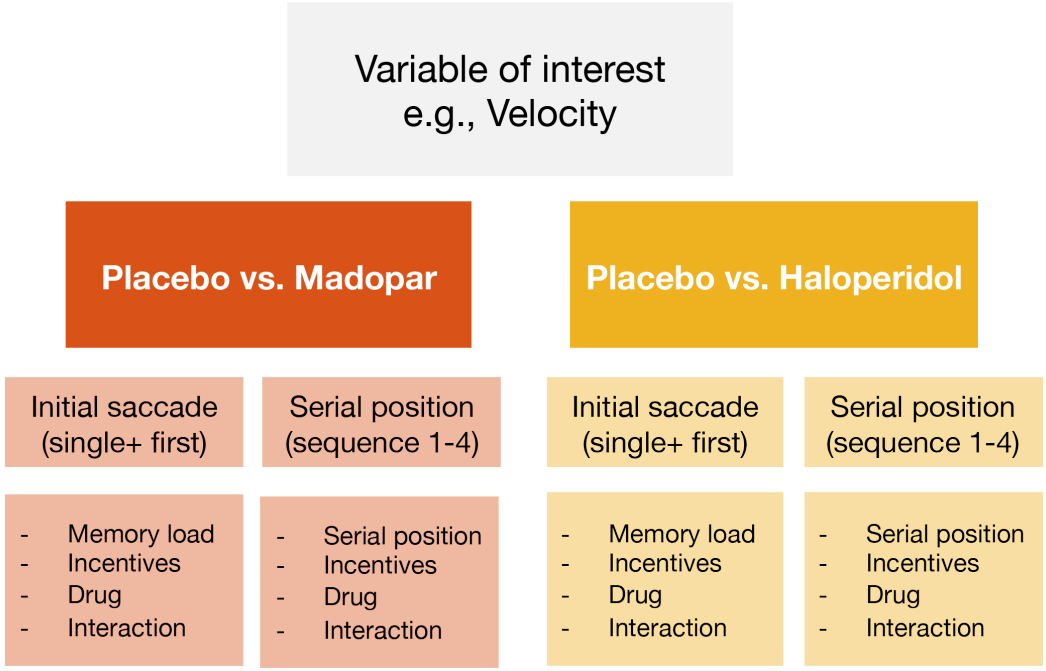

Figure 3.18 Memory-guided saccades- drug study, hierarchical structure of mixed model used for statistical analyses: A total of 4 analyses were performed per variable of interest including the following within-subject factors: (1) Memory load (2 levels), (2) incentives (3 levels. 0p as reference), (3) drug (2 levels: placebo vs. Madopar & placebo vs. haloperidol), (4) serial order and (5) interaction terms between them.

For simplicity reasons, F-statistics will only be reported from the former analysis of memory load in this chapter. F- statistics from the "serial position" analysis were reported within the text where additional information was retrieved from them. Tables with full F- statistics for the sequence of saccades are attached in the appendix (**Chapter 8**). Reaction times were only analysed for the former and was defined as the time between the go-signal (black screen) and when the criteria on velocity of $30°s^{-1}$, and acceleration > $8000°s^{-2}$ were fulfilled. Saccadic velocities were extracted for all saccades per subject separately. In order to assess endpoint accuracy in a task with variable saccadic sizes (variable distances between targets), Euclidian distance between saccadic endpoints and target locations was calculated. The saccade was considered correct and used for further analysis if its amplitude was larger than 2° and its landing point within an 8° radius around

the actual target location. This landing position threshold was chosen according to distribution of data on the histogram of all endpoints made by all participants during the trial (**Figure 3.19**). Distances greater than 8° were considered trials where the target was forgotten.

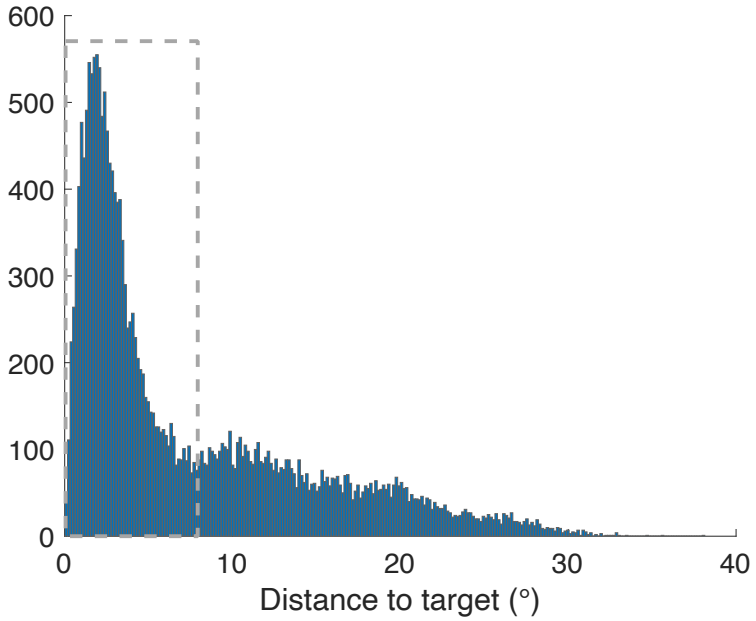

Figure 3.19 Memory-guided saccades- drug study: Histogram of all endpoint errors of all trials and participants (Euclidian distance between saccadic endpoint and target location). Saccades within the grey box were classified as "correct" and included in further analyses.

The analysis was performed in R and SPSS and the following codes were used. Post-hoc comparisons were conducted using Bonferroni correction.

R	lmer (var ~ incentives * saccade number * drug + (1 | ID), data)
SPSS	MIXED *var* BY drug incentives saccade number /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE)

	/FIXED=incentives drug saccade number incentives*drug incentives* saccade number drug* saccade number incentives*drug* saccade number | SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC)

Table 3.17 Memory-guided saccades- drug study: Model used for statistical analysis in R and SPSS. "var" = variable of interest, "drug" (2-level within-subject factor for each drug vs. placebo), "incentives" represent the different incentive conditions (3-level within-subject factor: "lose", "nil", "win"), "saccade number" = either assessing effect of "memory load" (2-level factor: single vs. first saccade of sequence) in the first analysis or serial position (4 levels: saccade number 1-4 in sequence) in the second.

3.5.3. Results

3.5.3.1. Madopar improved memory precision

Euclidean distance between saccadic endpoint and target location was calculated as a measure of the quality of memory recall. Omnibus analysis showed that high memory load caused participants to be less accurate (omnibus: $p<.001$). This effect was also present in both separate drug analyses (Madopar vs. placebo ß= 0.92° (0.03); haloperidol vs. placebo: ß= 0.86° (0.03), $p< .001$, **Table 3.18, Figure 3.20**). The overall drug effect found in omnibus analysis ($p< .001$) was driven by the haloperidol vs. placebo contrast only and showed haloperidol to be detrimental for accuracy. The interaction between reward and memory load in the haloperidol vs. placebo analysis describes what is reflected in **Figure 3.20,** which is a stronger reward sensitivity in low memory load conditions. There was no main effect of Madopar on endpoint accuracy of the initial saccades ($p= .751$) and no main effect of reward on accuracy in either drug arms (omnibus: $p= .40$). Neither of the drugs altered reward sensitivity of endpoint accuracy (omnibus: $p= .34$, see **Table 3.18** for all interaction terms and main effects).

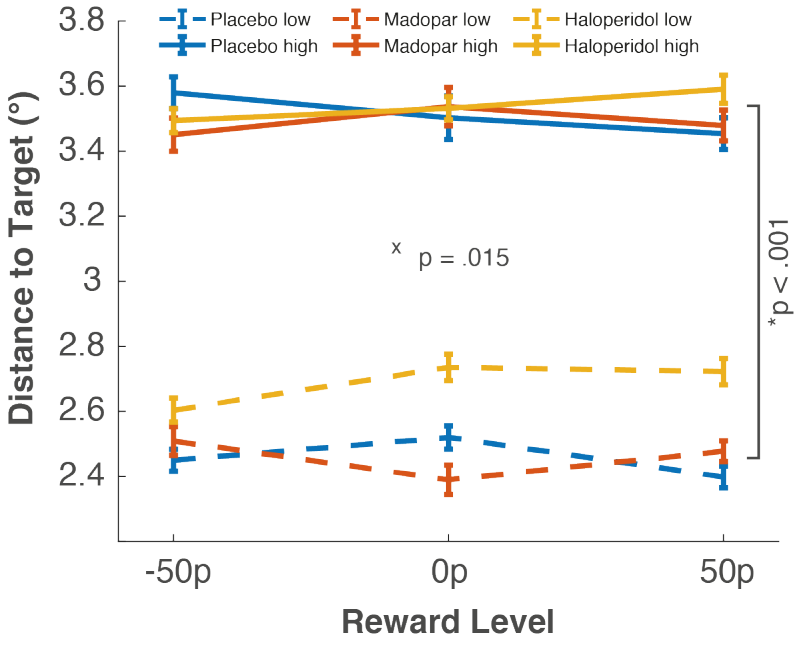

Figure 3.20 Memory-guided saccades- drug study: Participants were significantly more accurate when memory load was small. Haloperidol had a detrimental effect on accuracy in low memory load only.

Within the sequence there were two main effects found. The first saccade was interestingly significantly less accurate than the following three ($p < .001$, 1st saccade vs. 2nd saccade: ß= 0.29° (0.03), $p < .001$, **Figure 3.21**), which coincides with the first saccade being the fastest when looking at velocity (see next section). No difference was found between the following saccades within the sequence. A main drug effect found in omnibus analysis ($p = .001$) showed that Madopar caused participants to be significantly more accurate (ß= -0.08° (0.02), $p = .002$), while there was no significant difference between haloperidol and placebo ($p = 1.0$). Memory precision within the sequence was not altered by reward in either of the drug arms, nor were there any significant interaction terms present (full F-statistics, see **appendix 8.1**).

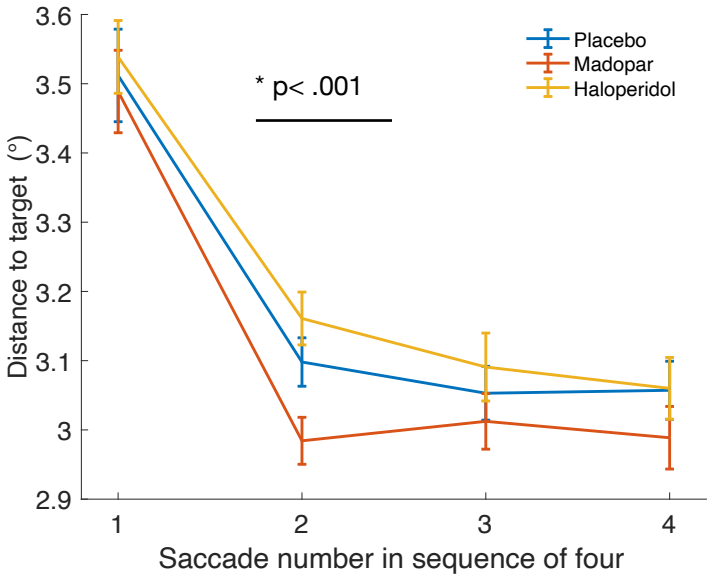

Figure 3.21 Memory-guided saccades- drug study: Saccades were more accurate on Madopar, especially those of higher serial position. The first saccade of the sequence was least accurate in all three study arms.

		F_A	p
MADOPAR			
	reward	(2, 14336.42) = 1.08	= .388
	drug	(1, 14354.77) = 0.10	= .751
	memory load (1/4)	(1, 14342.21) = 1061.66	< .001
	drug* memory load	(2, 14335.32) = 0.632	= .532
	drug*reward	(1, 14335.98) = 1.63	= .196
	reward*memory load	(1, 14334.35) = 0.94	= .333
	reward*drug*memory load	(2, 14335.04) = 2.03	= .132
HALOPERIDOL			
	reward	(2, 13755.72) = 1.32	= .266
	drug	(1, 13781.91) = 33.03	< .001
	memory load (1/4)	(1, 13760.42) = 860.47	< .001
	drug* memory load	(2, 13755.44) = 1.87	= .154
	drug*reward	(1, 13755.20) = 0.64	= .528
	reward*memory load	(1, 13757.09) = 5.92	= .015
	reward*drug*memory load	(2, 13755.28) = 0.12	= .888

Table 3.18 Memory-guided saccades- drug study, F-statistics for initial saccades including data from the single saccade and the first saccade within the sequence of four: Euclidean distance to target.

3.5.3.2. Madopar increased reward sensitivity of peak velocity in low memory load conditions

In a next step, I examined the vigour of the initial saccades. An omnibus analysis including all three groups (placebo, Madopar and haloperidol) showed two main effects: Memory load and Incentives (**Figure 3.22**). These were complemented by subsequent sub-analyses for each drug arm vs. placebo. These effects were present for both sub-analyses, results of which are reported below (F-statistics, see **Table 3.19**).

In the sub-analysis Madopar vs. placebo it was found that participants were faster when incentivised (win: ß= 396.89°/s (48.39), p< .001, lose: ß= 406.41°/s (48.20), p< .001) with no difference between the two incentive valences (p= 1.0). There was an additional interaction between reward and drug, where Madopar increased reward sensitivity when compared to placebo (F (2, 14264.0) = 4.23, p= .015) and an interaction between reward and memory load (F (2, 14364.00) = 3.66, p= .021), indicating that this was only the case when memory load was low. There was no main effect of drug (F1, 14364.9) = 0.00, p= .99) and apart from a main effect of memory load (F (1, 14364.0) = 90.20, p< .001) no other significant interactions. Running the model on data from the single saccade with just the unrewarded trials, there was a drug effect reflected by reduced motor vigour on Madopar (F (1, 2362.37) = 6.93; ß= -239.31°/s (90.89), p= .009).

In the analysis haloperidol vs. placebo there were just two main effects, as seen in omnibus analysis, namely, that of reward (2, 13784.0) = 46.36, p< .001) and of memory load (F1, 13784.0) = 83.12, p< .001). Participants were faster when incentivised (win: ß= 396.89°/s (48.39), p< .001, lose: ß= 406.41°/s (48.20, p< .001) with no difference between the two incentive valences (p= 1.0). Memory load again slowed them down. Haloperidol did, however, not affect velocity (main effect of drug p= .96) nor interact with reward sensitivity (interaction between reward and drug p= .11) or memory

load (interaction between memory load and drug p= .44), the former having been the case for Madopar vs. placebo.

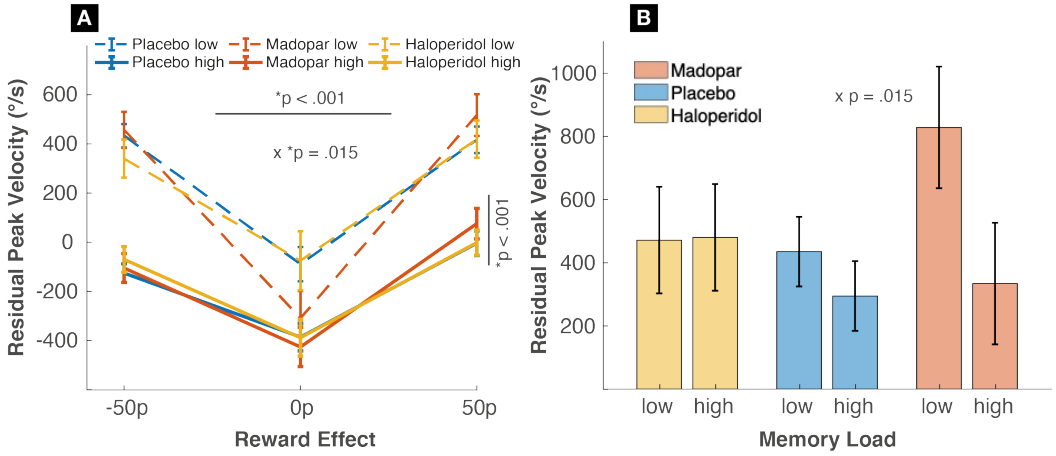

Figure 3.22 Memory-guided saccades- drug study, residual peak velocity: Comparing single saccade to the first saccade of a sequence of four. (A) Reward speeded up all three study arms, more so when memory load was low (x interaction between reward and memory load) (B) Difference between unrewarded and rewarded (both incentive conditions) for both single and first saccade of sequence. Madopar caused participants to be more reward sensitive (x interaction between reward drug).

Looking at the saccades completed within a remembered sequence, analyses of the drugs did not differ, so omnibus statistics are reported (full statistics, see appendix 0). The main effect of reward was present in both drug arms and not influenced by the saccade's serial position (reward*serial position: p= .101). Reward of both valences led to increased peak velocities (win: ß= 455.06°/s (30.82), lose: ß= 357.46°/s (30.75), p< .001). The first saccade was, however, faster than subsequent ones (1st vs. 2nd: ß= 165.30°/s (34.69), p< .001) with no difference between the latter ones (p= 1.0).

		F_A	p
MADOPAR			
	reward	(2, 14364.00) = 57.79	< .001
	drug	(1, 14364.00) = 0.00	= .999
	memory load (1/4)	(1, 14364.00) = 90.20	< .001
	reward*drug	(2, 14364.00) = 4.23	= .015
	reward* memory load	(2, 14364.00) = 3.88	= .021
	drug*memory load	(1, 14364.00) = 1.01	= .315
	reward*drug*memory load	(2, 14364.00) = 1.15	= .316
HALOPERIDOL			
	reward	(2, 13784.00) = 46.36	< .001
	drug	(1, 13784.00) = 0.00	= .966
	memory load (1/4)	(1, 13784.00) = 83.12	< .001
	reward*drug	(2, 13784.00) = 2.19	= .111
	reward* memory load	(2, 13784.00) = 0.36	= .697
	drug*memory load	(1, 13784.00) = 0.59	= .444
	reward*drug*memory load	(2, 13784.00) = 0.16	= .851

Table 3.19 Memory-guided saccades- drug study, F-statistics for initial saccades including data from the single saccade and the first saccade within the sequence of four: Residual peak velocity.

3.5.3.3. Reaction times were shortened by Madopar and prolonged by haloperidol

Three main effects on reaction times were found in omnibus analysis, namely, reward, drug, and memory load (**Figure 3.23**). Participants were faster when incentivised (omnibus-win: ß= -8.59 ms (3.35), p= .031, lose: ß= -12.49 ms (3.34), p= .001). Here neither of the drugs influenced reward sensitivity (Madopar p= .470, haloperidol: p= .602). High memory load resulted in slower reaction times in both drug comparisons with no difference in between them (omnibus: ß= 22.82 ms (2.77), p<.001). While Madopar showed a weak significant effect of shortening response times (ß= -6.53 ms (3.21), p= .042), haloperidol showed a stronger effect into the opposite direction (ß= 15.96 ms (3.46), p< .001). This is a novel observation as Madopar was not found to influence reaction times in either of the previous paradigms. There was also

no interaction between drug and memory load (omnibus: p= .63, full F-statistics for sub-analyses, see **Table 3.20**).

		F_A	p
MADOPAR			
	reward	(2, 16945.44) = 4.39	= .012
	drug	(1, 16947.52) = 4.24	= .042
	memory load (1/4)	(1, 16963.02) = 60.96	< .001
	reward*drug	(2, 16945.19) = 0.76	= .470
	reward* memory load	(2, 16945.41) = 0.31	= .733
	drug*memory load	(1, 16947.28) = 0.91	= .763
	reward*drug*memory load	(2, 16945.18) = 0.04	= .964
HALOPERIDOL			
	reward	(2, 16597.31) = 4.67	= .009
	drug	(1, 16613.64) = 21.28	< .001
	memory load (1/4)	(1, 16611.53) = 41.03	< .001
	reward*drug	(2, 16597.23) = 0.51	= .602
	reward* memory load	(2, 16597.31) = 0.12	= .891
	drug*memory load	(1, 16599.72) = 1.16	= .282
	reward*drug*memory load	(2, 16597.24) = 0.46	= .632

Table 3.20 Memory-guided saccades- drug study, F-statistics-for initial saccades including data from the single saccade and the first saccade within the sequence of four: Reaction time.

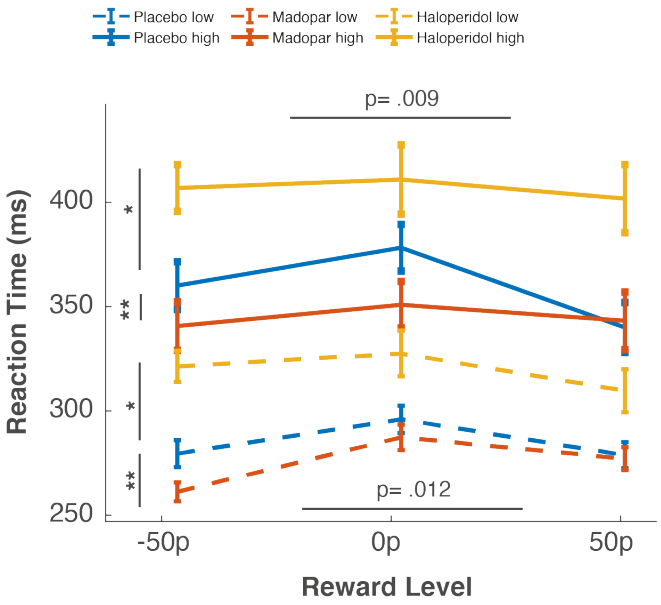

Figure 3.23 Memory-guided saccades- drug study: Reaction time of the initial saccades made in high and low memory load conditions. Low memory load led to faster reaction times, as did Madopar with a weak effect of drug (** p= .042). Haloperidol slowed participants down significantly (* p< .001).

3.5.4. Discussion

3.5.4.1. Madopar increased reward sensitivity of motor vigour, while memory load reduced it

Firstly, the results replicated the expected increase in velocity of the initial saccades with both types of incentive. This index of reward sensitivity was greater on Madopar, suggesting a shift in cost-benefit ratio through increased dopamine (Manohar *et al.*, 2015). The interaction with memory load could also support the conclusion that the costs of higher memory load would be subtracted from the overall benefit and, therefore, decrease movement vigour for the elicited saccade in light of a limited capacity system. Haloperidol did not affect velocity nor reward sensitivity.

3.5.4.2. Madopar improved memory recall processes, while haloperidol prolonged them

As hypothesised, I confirmed a detrimental effect of memory load on saccadic reaction time. Recalling a sequence required longer periods of time for saccadic planning than remembering a single saccade. In terms of drug effects, Madopar, indeed, shortened reaction times, while haloperidol caused participants to be slower. This was the first time we found Madopar to influence reaction times. On the previously described tasks Madopar showed no effect on simple reaction time nor on choice reaction time. This may lead to the interpretation that Madopar specifically improved parts of the memory recall process rather than the movement initiation itself. It, however, is important to point out that there was no interaction between the drug effect and memory load, which indicates a dopamine dependent alteration in a process *independent* of the memory load. The previously described improvement of reaction times on incentives was again replicated.

3.5.4.3. Madopar, but not incentives, improved memory precision within a saccade sequence

It was shown that higher memory load worsened memory precision in this task. This was expected and has been observed in a high number of working memory tasks. Additionally, the first saccade within a sequence was significantly less accurate than the following saccades. This coincided with the first saccade also showing the greatest motor vigour (velocity), which may result in greater noise within the motor command of this particular saccade. The "decay effect" also provides an explanatory model, describing a positive relationship between memory decay and time passed since target display, which is longest for the first target at the time of the sequence planning (Brown, 1958). Haloperidol had a detrimental effect on accuracy on the single remembered saccade, relatively sparing precision of the sequence, which is the opposite effect that was reported by Gaymard et al. (Gaymard, Pierrot-Deseilligny and Rivaud, 1990). The reason for an absent drug effect of haloperidol in the higher memory load conditions could be the longer preparation time for those conditions caused by the duration of the sequence display. This and prolonged reaction times may balance out the slower preparational processes for the first saccade in this drug arm. Under this interpretation, haloperidol does not affect memory per se, but rather action control and initiation. In contrast, Madopar increased memory precision, but mainly in *later* serial positions, pointing to an advantage of higher dopamine levels in memory retrieval after longer time periods. It has more generally been discussed that supranormal dopamine activity in the PFC is unlikely to have any detrimental effects (Westbrook and Braver, 2016), which my data supports. As reported in the previous chapter, it was again confirmed that memory precision was not influenced by motivation, reflecting evidence of a limited capacity system.

An intriguing feature of these results is the contrast between motivational effects and dopaminergic effects. The prospect of reward and loss could not improve memory accuracy as shown in previous studies (Morey *et al.*, 2011a;

Atkinson *et al.*, 2018). Dopaminergic drugs, however, did improve memory in studies involving PD patients (Lange *et al.*, 1992; Fallon *et al.*, 2019). This dissociation suggests that incentivisation may not operate via increasing dopamine.

On the other hand, incentives did improve movement vigour, both velocity and RT. These same motor parameters were also speeded up by Madopar and slowed with haloperidol, in keeping with invigoration by reward being mediated by dopamine (Niv *et al.*, 2006; Niv, 2007). Surprisingly, incentivisation by reward and penalty yielded comparable benefits, which might be expected to differ if they were directly governed by dopamine. In this experiment, the expectation of penalty was interleaved with reward trials and would be expected to be accompanied by negative reward prediction errors, associated with phasic dips in dopamine (Schultz, 2016b, 2016d, 2016a). Instead, reward and penalty contingencies in a task might be appraised by a common, high-level cognitive system that activates motivational drive via alternative routes (Manohar *et al.*, 2017; Grogan *et al.*, 2020). But in line with motivational vigour (including penalty avoidance) having a dopaminergic basis, as proposed by (Panigrahi *et al.*, 2015; Devesse and Olivier, 2016; Manohar *et al.*, 2017), we observed increased reward sensitivity with Madopar for both types of incentives.

3.6. Additional measures of reward sensitivity

3.6.1. Background

"Attention is the process of optimising precision" (Friston, 2010). Eye tracking allows to measure not only saccadic properties but also record EBR and pupillometry data. These two measures have been used to assess brain functions like attention in the recent years (van Reekum, Stuss and Ostrander, 2005; Fried *et al.*, 2014; Eckstein *et al.*, 2017). Previous evidence also suggests that pupillometry may be a helpful tool to objectively measure reward processing and the influence of reward-related motivation on attention and cognitive control (Chiew and Braver, 2013). Reward as well as reward expectation have been shown to modulate pupil size (Delaville, De Deurwaerdère and Benazzouz, 2011; Manohar and Husain, 2015; Manohar *et al.*, 2017), showing that changes in pupil size are greater in response to incentives than in unrewarded conditions. Changes in pupil diameter following incentives might help to understand goal-directed behaviour and have recently been used to explore motivation and reward sensitivity in pathologies such as PD. Patients diagnosed with PD showed reduced pupil response to reward when "OFF" medication , while dopaminergic medication restored their pupillary reward sensitivity (Manohar and Husain, 2015). Pupil size also provides important insights into cognitive processes and arousal and how they may influence pupil diameter (Lehmann and Corneil, 2016). The exact mechanisms in which both dopamine and noradrenaline are involved in controlling pupillary and cognitive processes, however, remain elusive. One suggested anatomical correlate may be noradrenergic locus coeruleus projections originating in the pons (Aston-Jones and Cohen, 2005).

The identified relationship between pupil size, attention and reward sensitivity (Bijleveld, Custers and Aarts, 2009) opens a unique avenue to objectively measure non-motor symptoms like apathy in patients suffering from dopamine depletion and may allow to identify patients more vulnerable to developing impulse control disorders on dopamine agonists by potentially

using it as a proxy for “baseline” dopamine activity. Due to the lack of available biomarkers, clinicians currently need to rely on binary and subjective questionnaire scores that do not reflect the dynamic processes during reward anticipation and decision-making.

3.6.2. Is pupillometry a reliable measure of reward sensitivity?

Previously published data showed that pupil responses were not only modulated by reward, but that the extent of reward sensitivity was predicted by a self-reported motivation questionnaire (the LARS-e subscale assessing motivation) in healthy controls (Muhammed, 2018). The same group also investigated the effect of haloperidol on pupil size in reward and loss conditions. A correlation between the AMI-ES (emotional sensitivity) scores and pupil reward sensitivity was found. For many decades research has been looking into the neurochemistry of personality traits (Gray, 1973) with a more recent hypothesis being that questionnaires assessing personality traits may indirectly index a person’s baseline dopamine level and may, hence, be used to predict the effect of drug manipulation on (pupillary) reward sensitivity (Muhammed, 2018).

Pupillometry data recorded during the double-step paradigm (further details about the task and demographics **section 2.1**) will be discussed in the following section in order to shed light on the underlying physiological processes of goal-directed behaviour. Comparing results of both drug manipulations to participants’ normal baseline behaviour may help to understand how these measures could be used as a non-invasive way of estimating an individual’s baseline dopamine level in the future. AMI scores were furthermore matched as an analogue dopamine proxy to the pupillometry data to look for a relationship between baseline motivation and drug effects in each group.

3.6.2.1. Pupillometry data handling

Pupil size was recorded from all participants throughout the double-step paradigm by the SR Eyelink 1000 and was measured in arbitrary eye tracker units. They are units of visual angle calculated by the number of pixels that form the recorded image of the pupil. Pupillary change used in this section was calculated as the difference between the mean proportional pupil size in the time between 1200-1400ms after auditory cue onset and the pupil size before cue onset. This time window was chosen to allow for the sluggishness of the pupillary response after the reward cue and was determined as a window of interest in previous studies (Manohar and Husain, 2015) and unpublished data (Muhammed, 2018). Pupillary reward sensitivity was defined as the mean pupillary diameter change on rewarded trials vs. 0p conditions (10p-0p; 50-0p). Greater change in diameter indicates higher reward sensitivity. Baseline pupil size was calculated as the mean pupil size at the beginning of each trial before reward cue.

3.6.2.2. Statistical analysis

Statistical analysis was performed using a mixed linear model with reward and drug as within-subject factors. Reward was used as a linear factor (0p - 10p -50p) and drug analysis was performed, as previously, in two separate analyses, Madopar vs. placebo and haloperidol vs. placebo. Post-hoc comparisons were done using Bonferroni correction. For correlations with the AMI questionnaire a median split into “low” and “high” scores was performed and included as a within-subject factor in the linear mixed model. Statistics were completed using SPSS.

3.6.2.3. Results

There was a significant difference in baseline pupil size between drug states (main effect of drug: $F(2, 54.12) = 6.11$, $p = .004$, **Figure 3.24 (A)**). Pairwise comparison showed that Madopar did not significantly alter baseline pupil size ($p = .10$), while participants on haloperidol showed a significantly smaller

pupil baseline size (ß= -494.95 a.u. (177.11), p= .022). Including AMI score ("high" vs. "low") into the model there were no main effect or interaction present (**Table 3.21**).

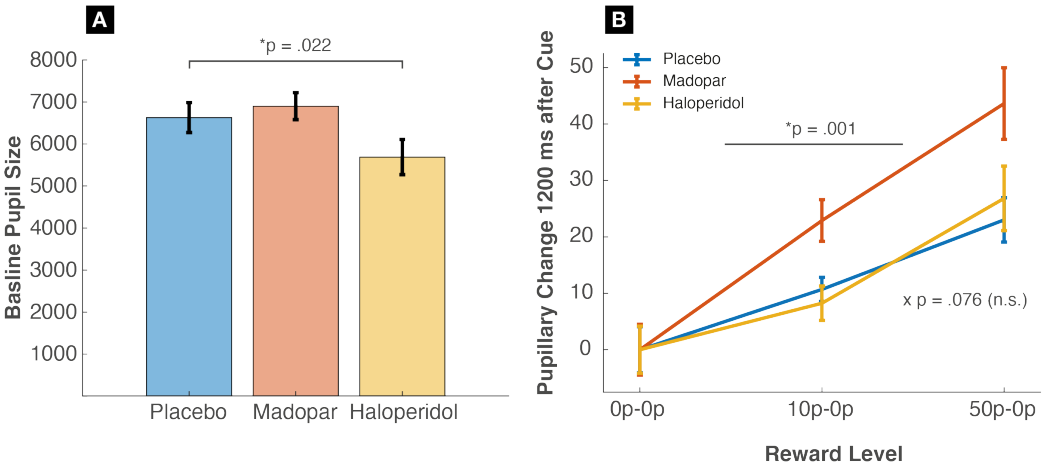

Figure 3.24 Pupillometry-reward sensitivity: (A) Baseline pupil size was reduced on haloperidol. (B) Pupil change at 1200ms after cue onset in different reward levels relative to 0p conditions; here a trend towards an interaction between pupillary reward sensitivity and Madopar was found (p= .076).

Being the primary pupillary measure, I looked at the proportional pupil change between cue onset and 1200-1400ms thereafter. A main effect of reward was present across both drug comparisons (p< .001, **Table 3.21, Figure 3.24 (B)**). Pupil change was, thus, greater when reward was on offer and confirmed what was reflected by other saccadic measures discussed in this thesis. Madopar also showed a trend towards an increase in reward sensitivity (interaction between drug and reward: F (1, 142.00) = 3.21, p= .076). This is in line with previous findings of Madopar increasing pupillary reward sensitivity in PD (Manohar and Husain, 2015) and was also reflected by the increased reward sensitivity of saccadic peak velocity in my data. This interaction between drug and reward was absent in the comparison between haloperidol and placebo (p= .685). Including the AMI score (high vs. low) as a within-subject factor into the mixed linear model did not notably change the results summarised below (**Table 3.21**) and did also not show a main effect

of AMI scores (Madopar vs. placebo p= .87, haloperidol vs. placebo p= .78) nor interaction between them and other factors listed below.

		F_A	p
MADOPAR			
	reward	(1, 139.00) = 36.15	< .001
	drug	(1, 139.00) = 5.77	= .018
	AMI	(1, 27.00) = 0.03	= .869
	drug* AMI	(1, 139.00) = 0.24	= .626
	drug*reward	(1, 139.00) = 3.16	= .078
	AMI*reward	(1,139.00) = 0.36	= .551
	drug*AMI*reward	(1, 139.00) = 0.01	= .912
HALOPERIDOL			
	reward	(1, 130.93) = 23.03	< .001
	drug	(1, 134.87) = 0.04	= .834
	AMI	(1, 24.76) = 0.07	= .788
	drug* AMI	(1, 134.88) = 1.57	= .213
	drug*reward	(1, 130.93) = 0.15	= .698
	AMI*reward	(1, 130.93) = 0.21	= .646
	drug*AMI*reward	(1, 130.93) = 1.44	= .233

Table 3.21 Pupillometry: F-statistics.

3.6.2.4. Discussion

The main findings in this section were an effect of haloperidol on pupil diameter at baseline and a trend towards an interaction between pupillary reward sensitivity and Madopar. Haloperidol reduced baseline pupil size significantly, which has been reported previously and was described as a mixed peripheral and alpha adrenergic side effect of the drug (Sharpe, Pickworth and Martin, 1977; Pretorius *et al.*, 2001). Pupil reward sensitivity was present in all three drug states. Of special interest, the trend towards greater reward sensitivity after a single dose of Madopar (p= .076) was in line with the finding that Madopar also increased reward sensitivity measured by saccadic peak velocity in two other paradigms. The time interval used for this analysis was chosen accounting for the pupil's sluggish response (Lehmann and Corneil, 2016), and due to pupillary changes observed in other studies using the same paradigm (Manohar and Husain, 2015), it may ,however, well

be the case that extending the analysis time frame may add further information on the dynamics of reward processing, which is a limitation of this analysis. The absence of an effect of haloperidol on pupil reward sensitivity is, however, also supported by unpublished data, using a longer (1700-2500ms) time frame after incentive cue onset (Muhammed, 2018). These results taken together complement findings from our saccadic paradigms in earlier sections, where haloperidol did not alter reward effects, while Madopar showed a task- and variable-dependent increase in reward sensitivity measured by saccadic peak velocity. Our findings also support additional available evidence that pupillometry provides a reliable tool of measuring reward sensitivity in disease and health.

3.6.3. Can spontaneous blink rate be used as a proxy of dopamine activity?

3.6.3.1. Background and hypothesis

Spontaneous blinking is one the most frequent movements in everyday life. Humans blink about 15-20 times per minute (Doughty, 2001), which amounts to a total of 20.000-30.000 blinks a day, although inter-subject variability is high (Al-Abdulmunem and Briggs, 1999). Because blinking is necessary to keep the eyes' corneal tear film intact (Evinger, 2010), spontaneous EBR is controlled by corneal afferent inputs. This, however, would only require about 3-4 blinks per minute. Blinks can also not be fully eliminated through anaesthesia of the cornea and conjunctiva (Naase *et al.*, 2005), which points to processes involved in addition to the corneal afferents. There is evidence suggesting that the spinal trigeminal complex acts as a blink generator (Kaminer, Powers and Evinger, 2011). This is of special interest because of the role of the basal ganglia as a gateway to the trigeminal complex via the superior colliculus and the nucleus raphe (Basso and Evinger, 1996; Gnadt *et al.*, 1997). This way, the BG are involved in controlling and modulating input to the trigeminal complex and could, hence, influence EBR. Higher levels of dopamine, e.g., have been shown to increase EBR, while dopamine depletion

led to a decrease (Karson, 1983; Elsworth and Nichols, 1991; Kleven and Koek, 1996). This has also been observed in diseases like PD, shown to reduce EBR (Shukla, 1985; Agostino *et al.*, 1987), whilst patients diagnosed with schizophrenia often show an increase in EBR (Helms and Godwin, 1985; Karson, Dykman and Paige, 1990; Mackert *et al.*, 1990; Sandyk, 1990), reduced under treatment with dopamine blocking agents (Karson *et al.*, 1981). Another animal study reported increased EBR after a single dose of apomorphine and decreased EBR after haloperidol administration (Kaminer, Powers and Evinger, 2011). A number of studies have looked into the relationship of dopamine and EBR suggesting higher EBR to correlate with higher dopamine function, but also with greater distractibility. It has also been shown that reward anticipation and reward feedback modulate EBR (Dang *et al.*, 2017). In stark contrast to this, more recent evidence, however, points to an absent or even negative relationship between dopamine levels and EBR (Kleven and Koek, 1996; van der Post *et al.*, 2004; Mohr *et al.*, 2005; Fried *et al.*, 2014; Dang *et al.*, 2017; Ligneul *et al.*, 2018). My study design offers a unique opportunity to compare the two drug manipulations to the participant's baseline EBR and match the findings with evidence from saccadic data, pupillometry and measures of intrinsic motivation (AMI questionnaire). Endogenous dopamine and exogenous drugs may affect EBR by distinct but overlapping mechanisms. To further dissect this, I matched EBR data from thirty healthy volunteers on Madopar, haloperidol and placebo with their AMI and UPPS-P questionnaire scores.

Based on previous reports we expect to find dopaminergic drugs to modulate spontaneous EBR and aim to clarify whether the degree thereof and the direction (increase/decrease) may depend on a participant's intrinsic baseline motivation (AMI score). If Madopar leads to an inhibition of the trigeminal complex, via effects on the nucleus raphe magnus, it may result in increased spontaneous blinking while we would expect haloperidol to decrease it depending on its pre/post-synaptic effects and furthermore depending on each participant's dopamine baseline level.

3.6.3.2. Demographics

Data included in this section were recorded from the same cohort as described in **section 2.1.2** as the recording was part of the same study.

3.6.3.3. Methods and statistical analysis

At the beginning of each testing day, before participants completed the first saccadic paradigm, a three-minute recording was obtained during which participants were seated in front of a computer screen, their heads positioned on the head and chin rest. They were then asked to look at a grey fixation cross on a black screen for three minutes while the number of blinks was recorded by the SR Eyelink 1000. They were not instructed in any way how often to blink and were not told that the recording was made to assess EBR, but that they were free to blink as often as they felt was comfortable for them, to make sure participants were not deliberately avoiding to blink. The number of blinks per minute was then calculated per subject for each drug and subsequently correlated with AMI scores. Data analysis was performed with SPSS and R and a mixed linear model was fitted using drug and AMI (median split: low vs. high) as within-subject factors.

3.6.3.4. Results

3.6.3.4.1. Madopar increased blink rate- but diminished the correlation with self-reported motivation traits

The mean EBR per minute recorded in our cohort was 16.84 blinks/min (±14.31) for placebo, 21.93 blinks/min (±14.95) for Madopar and 20.57 blinks/min (±14.98) for haloperidol. Adults on average blink about 14x/minute. This rate can be influenced by different pathologies, recording methods, gender, smoking habits, and the individual's dopamine levels. Participants on Madopar showed a significantly higher baseline EBR when compared to placebo ($F(1, 28.64) = 4.65$, $p = .040$, **Figure 3.25**). In contrast to a number of reports, there was no significant difference of EBR when comparing placebo to haloperidol ($F(1, 29) = 2.99$, $p = .094$), although there was a weak trend

towards an increase in numbers of blink per minute when compared to placebo.

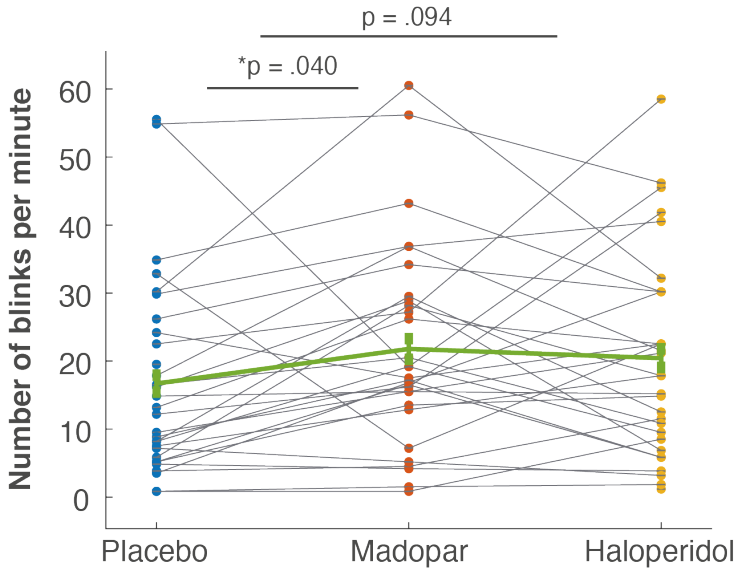

Figure 3.25 Spontaneous EBR per minute: There was a significant increase in blink rate on Madopar. A weak trend pointed towards an increase in EBR on haloperidol too, which did not reach significance (bold green line represents the mean EBR across all subjects).

In the next step, AMI scores (Apathy Motivation Index) were included into the model (median split “high” vs. “low”) indicating participants’ individual levels of intrinsic motivation. Participants with higher AMI score, indicating greater intrinsic motivation, showed a higher EBR on baseline recording on both placebo and haloperidol ($F(1, 28) = 4.23$, $p = .049$; ß= 9.58 blinks/min (4.66), **Figure 3.26)**. Madopar in contrast attenuated the effect of AMI scores due to the overall increase in EBR (**Figure 3.25**), which was independent of the AMI score ($p = .131$). Interestingly, after adding AMI in as a factor, the increase in EBR on haloperidol showed a slightly stronger trend when compared to placebo ($F(1, 28) = 3.46$, $p = .073$).

In summary, while highly motivated participants showed a higher EBR on both placebo and haloperidol when compared to their less motivated peers, this effect was masked by a single dose of Madopar leading to an overall increase

in spontaneous EBR independent of the motivational state. There was no difference between Madopar and haloperidol in EBR (drug: p= .915) and no other interactions were found. As dopamine polymorphisms have been shown to correlate with impulsive behaviour (Blaine *et al.*, 1996) and this in turn with spontaneous blink rate (Korponay *et al.*, 2018), I also included the participants' UPPS-P subscale scores (premeditation, urgency, sensation-seeking and perseverance) into the analysis. In linear regression, however, no correlation was found between either of the UPPS-P subscales and EBR (omnibus for total UPPS-P score: F (1, 28.00) = 1.25, p= .247)). Thus, the personality traits we measured did not explain the increase in EBR on Madopar.

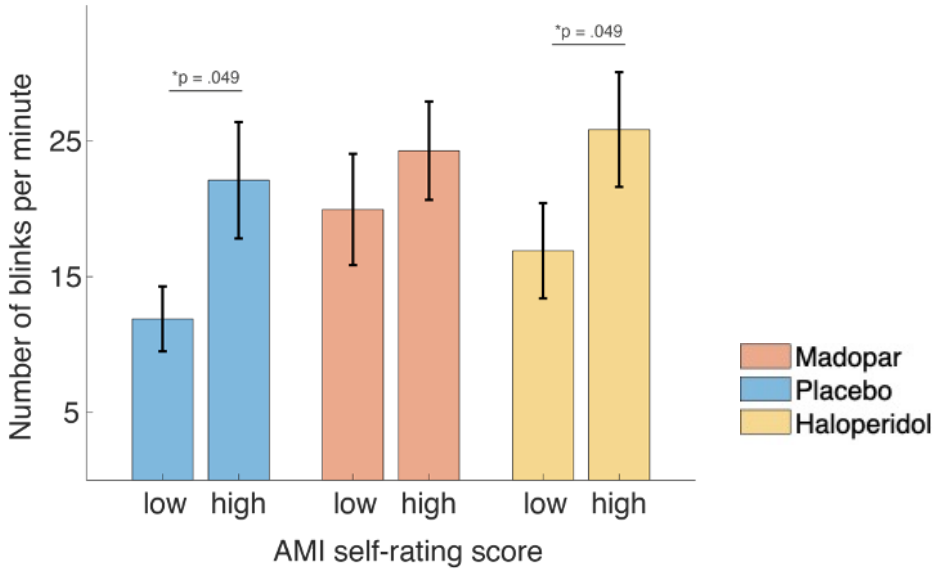

Figure 3.26 EBR and apathy motivation index score: Placebo and haloperidol showed higher EBR in participants that considered themselves "motivated" when compared to low AMI score ratings. Madopar showed an overall increase in EBR and no effect of self-rated motivation levels.

3.6.3.5. Discussion

Results from a number of pharmacological studies on animals and humans have previously been in favour of a positive relationship between central dopaminergic activity and EBR (Karson *et al.*, 1982; Elsworth and Nichols, 1991; Chen *et al.*, 1996; Kaminer, Powers and Evinger, 2011; Jongkees and Colzato, 2016; Mathar *et al.*, 2018). More recent evidence, however, points to an absent or negative relationship between the two (Kleven and Koek, 1996; van der Post *et al.*, 2004; Mohr *et al.*, 2005; Fried *et al.*, 2014; Dang *et al.*, 2017; Ligneul *et al.*, 2018). In these data I found a single dose of Madopar to increase the overall EBR significantly when compared to placebo EBR (p= .040), haloperidol, if anything, also showed a weak trend towards an increase in EBR (p= .094/= .073 n.s.). Indeed, a correlation between EBR and reward seeking behaviour has been found recently (Barkley-levenson and Galv, 2017) in adolescent but not adult volunteer and EBR has also shown to be modulated by reward anticipation and response (Peckham and Johnson, 2016). A link between EBR and self-reported reward sensitivity showed that high motivation in participants coincided with higher EBR both after exposure to haloperidol and on placebo. This was, however, not the case for the Madopar group, where Madopar increased EBR relatively more in the low AMI group, pointing towards a stronger effect of Madopar on participants with lower motivation/dopamine baseline activity. This is in line with findings from saccadic parameter where measures of accuracy (departure angle and error rate) were improved by Madopar only in the cohort where AMI scores were low. It has, however, also been reported that increased EBR correlates with disinhibition and higher error rate (Chan and Chen, 2004) which again would not accommodate my hypothesis. In summary, while a role of dopamine in EBR modulation might be supported by a huge number of papers, other neurotransmitters may also play an important role and may account for the great variety of findings (Naicker *et al.*, 2016).

3.7. Brief summary of findings in Chapter 3

The main findings in this chapter were:

- Both drugs decreased saccadic velocity and amplitudes, potentially following an “inverted-U-shaped” relationship, reflecting the effect of dopamine alterations on motor vigour.
- Madopar improved accuracy, specifically when AMI scores were low, indicating beneficial effects of additional dopamine only when baseline dopamine is low. This AMI-score dependent effect was absent in haloperidol potentially indicating that AMI questionnaires may track D1-receptor occupancy only.
- Madopar increased reward sensitivity of peak velocity of internally triggered and memory-guided saccades. The absence of this effect in the double-step paradigm may be related to inhibitory processes needed for the suppression of the initial saccades that may alter reward processing, potentially underpinned by the effect of haloperidol showing a trend towards higher reward sensitivity.
- Haloperidol increased reaction times of internally triggered as well as memory-guided saccades, potentially due to slowed preparational processes caused by lower dopamine levels. The reduction of latencies in the double-step paradigm may be explained by reduced inhibitory control.
- Reward anticipation and penalty avoidance again had comparable effects on most saccadic parameters, with the exception being peak velocity of internally triggered saccades, where incentives of positive valence exerted a stronger effect than penalty.

4. Influence on ventral tegmental area DBS on saccades and reward sensitivity

4.1. Methods

4.1.1. Background and hypothesis

Anatomically the ventral tegmental area (VTA) lies on the floor of the midbrain, adjacent to the substantia nigra and with the latter builds one of the two most important dopaminergic areas of the brain. While it contains a multitude of cell populations, the majority are dopaminergic projections from different parts of the brain. The VTA is part of the mesolimbic and mesocortical dopaminergic pathways, projecting to the prefrontal cortex and nucleus accumbens among other regions. Dopaminergic neurons in the VTA and the nucleus accumbens are involved in processes of reward signalling, motivation, exertion of effort, learning and cognition. Not surprisingly, dysfunctions in these areas have been linked to depression, addiction and other psychiatric disorders (Salamone and Correa, 2012). Moreover, the VTA is known to be closely involved in pain processing and DBS of the VTA has more recently been used to treat a relatively small number of patients suffering from severe refractory headaches (Akram *et al.*, 2016). Deep brain stimulation of other brain regions like the subthalamic nucleus and the globus pallidus, e.g., has also become an established treatment for movement disorders such as PD, dystonia, or essential tremor. DBS has been successfully used for a variety of patients in the last decades, although its exact mechanisms remain elusive. Patients treated with DBS, however, provide a unique opportunity for clinicians and basic scientists to study the physiological mechanisms in these brain areas and the effect of electrical stimulation of specific brain regions on motor and cognitive control in vivo. A cohort of 18 patients, who underwent VTA DBS surgery at the NHNN, was followed-up in a study assessing patients' cognitive performance pre- and post-surgery. No differences were found in the assessments of IQ, verbal and non-verbal memory, executive function and attention (Cappon *et al.*, 2019).

Patients included in this publication were tested pre-surgery and again 10-18 months post-operatively with their stimulation “ON”.

The aim of this study was to further investigate the effects of stimulation of the VTA and its potential consequences on goal-directed behaviour and decision-making comparing stimulation settings “ON” and “OFF”. I hypothesised that depending on the stimulation’s effect on central dopaminergic activity, differences in behaviour when patients are “ON” and “OFF” stimulation could be observed. Quite obviously, data from human studies on the effect of VTA stimulation are scarce and, to my knowledge, this is the first time data on saccadic properties have been recorded in this cohort. To shed light on possible effects of VTA DBS, patients completed a shortened version of the double-step paradigm to assess if/what effect DBS stimulation has on saccadic properties including distractibility and reward sensitivity. Additionally, pupillometry data were recorded during this task. A visual working memory task was furthermore included in the study schedule, results of which will be discussed in later sections.

4.1.2. Consent

This study was approved by the UCLH Research Ethics Committee (IRAS Number: 203446) and written informed consent was obtained in accordance with the Declaration of Helsinki. Participants were recruited at the National Hospital for Neurology and Neurosurgery and the study was conducted at the UCL Institute of Neurology. Travel costs and/or accommodation were reimbursed.

4.1.3. Demographics and recruitment

Eleven patients were recruited through the Outpatient Department at the National Hospital for Neurology and Neurosurgery. They all had a past medical history of either therapy refractory cluster headache, SUNCT (Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing) or SUNA (Short-lasting unilateral neuralgiform headache with

autonomic symptoms) and had received either unilateral (n= 6) or bilateral (n= 5) ventral tegmental area deep brain stimulation for pain management. Exclusion criteria included **(1)** significant cognitive impairment (MMST <22/30), **(2)** severe visual impairment that made completion of the task impossible, **(3)** nystagmus if it interfered with eye tracker recording, **(4)** treatment with centrally acting drugs **only if** changed in between the two sessions and **(5)** patients who were sensitive to or would not tolerate changes to their DBS settings at all. Eleven patients agreed to participate in this study (49.45 ± 14.22 years). Detailed demographics as well as information about each patient's clinical diagnosis and DBS location are summarised in **Table 4.1)**.

ID	GENDER	AGE	DIAGNOSIS	LOCATION OF DBS		
				RIGHT VTA	LEFT VTA	BILATERAL
1	**Female**	31	Chronic cluster headache	x		
2	**Female**	57	Chronic cluster headache	x		
3	**Male**	47	Chronic cluster headache			x
4	**Female**	39	Chronic cluster headache			x
5	**Male**	47	Chronic cluster headache		x	
6	**Male**	57	Chronic cluster headache			x
7	**Female**	79	SUNCT	x		
8	**Male**	67	Chronic cluster headache			x
9	**Female**	30	SUNCT	x		
10	**Male**	50	SUNA	x		
11	**Female**	40	SUNCT			x

Table 4.1 VTA-DBS: Demographics of patients with ventral tegmental area deep brain stimulation.

4.1.4. Study schedule

The study followed a cross-over design where all participants attended 2 sessions. After informed consent had been given participants started with their DBS switched "ON", followed by it being switched "OFF" or vice versa (AB-BA design) for each of the two sessions. The order of the latter was randomised across all participants. Since patients were well aware of their stimulation settings, blinding for DBS settings would not have been

appropriate. Switching DBS stimulation “OFF/ON” was followed by a waiting period of > 30 minutes before testing started to allow for the effects of the DBS change to settle and for potential visual symptoms to fade (**Figure 4.1**). This time frame was chosen following protocols of previous DBS studies.

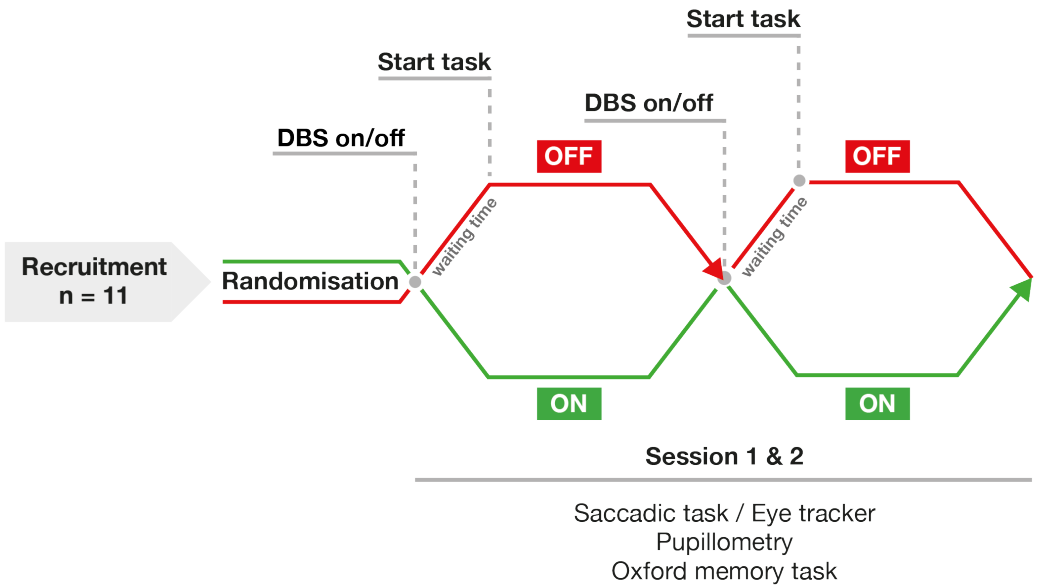

Figure 4.1 VTA-DBS- Study schedule: After participants were recruited at the Outpatient Department of the National Hospital for Neurology and Neurosurgery (NHNN) and written informed consent was obtained, patients were randomly assigned to either the “ON-OFF” or “OFF-ON” arm of the study. After each manipulation to the DBS settings (switching “ON” or “OFF") there was a waiting period of >30 minutes. Following the waiting periods identical testing sessions were completed. This meant that participants completed the same tasks four times in total (2x “ON” and 2x “OFF”). This included the eye tracking task described in section 2.1.4, pupillometry recordings and the working memory task described in section 5.2.3. The completion of the tasks itself took between 45-60 minutes (excl. waiting periods).

4.2. Revisiting Task I: Effect of reward and DBS stimulation on avoiding an early distractor

4.2.1. Eye tracking paradigm

A shortened version of the same saccadic paradigm as described in **section 2.1.4** was used to assess the effect of DBS on reward-related saccadic behaviour and distractibility. Every participant completed two blocks of each 54 trials per session per DBS setting and 10 practice trials at the beginning of the first block, the latter being excluded from data analysis. Thus, 216 datapoints (saccades) were recorded per participant and included in the analysis.

4.2.2. Statistical analysis and data handling

The task as well as the reward calculation was identical to the task described in detail in **section 2.1.6**. The same mixed linear model with random intercept was used to analyse the data (**section 2.1.7**). Data from both "ON" and both "OFF" sessions were combined before analysis. Due to the high variance observed on the level of subjects, I further included DBS location (= bilateral vs. unilateral) into the model and found a significant main effect of DBS location and/or an interaction between DBS stimulation effect and DBS location on a number of variables. I checked the models for best fit and continued with the random intercept model including DBS location as a factor.

Analysis was performed in SPSS and R. Results reported below are from the R analysis. Within-subject factors included the following: **(1)** Reward (linear factor 0-10-50p), **(2)** DBS status (2 levels: "ON" and "OFF"), **(3)** DBS location (2 levels: bilateral and unilateral) and **(4)** interaction terms between the three. Post-hoc comparisons were done using Bonferroni correction (**Table 4.2**).

R	lmer (var ~ reward * DBS status* DBS location + (1 | ID), data)
SPSS	MIXED *var* BY DBS status DBS location WITH reward /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE) /FIXED= reward DBS-status DBS location reward*DBS status DBS location*reward DBS location*DBS status| SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC).

Table 4.2 Double-step paradigm- VTA-DBS: Model used for statistical analysis in R and SPSS (DBS status: 2 levels "ON" and "OFF", DBS location: 2 levels "unilateral" and "bilateral", reward: linear factor 0p-10p-50p).

4.2.3. Results

4.2.3.1. VTA DBS reduced saccadic vigour

Saccadic velocity changed significantly with DBS stimulation status (**Figure 4.2(A)**) and was greater when electrodes were "OFF" ($p<.001$, F-statistics, see **Table 4.3**). There was no significant difference found comparing unilateral to bilateral stimulation ($p= .84$). Most interestingly, reward sensitivity of saccadic velocity, repeatedly reported in the previous chapters, was absent in both "ON" and "OFF" conditions ($p= .18$) and no interaction between reward and DBS stimulation was found.

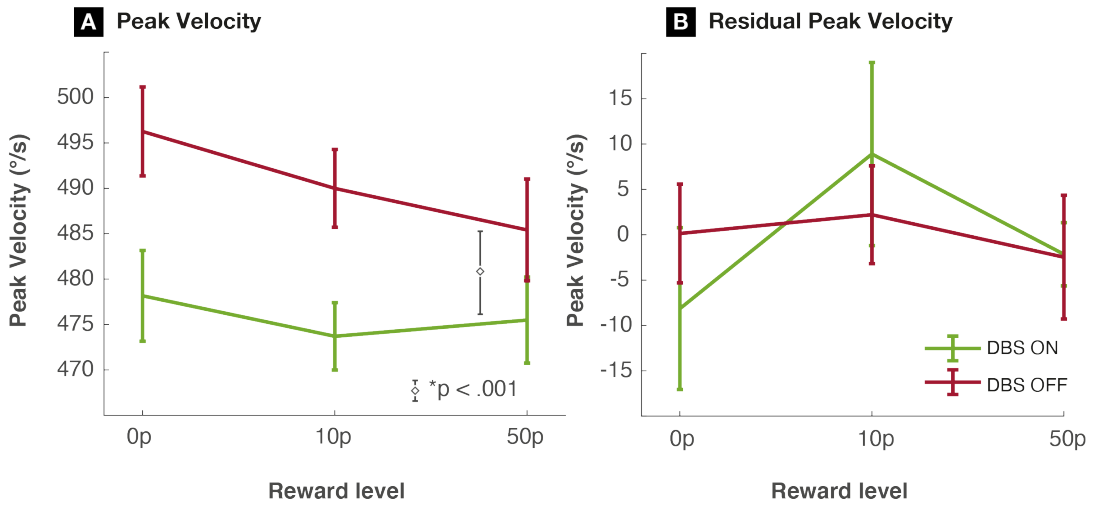

Figure 4.2 Double-step paradigm- VTA-DBS: (A) DBS stimulation slowed saccadic peak velocity. (B) Residual peak velocity, after performing linear regression with size of saccadic amplitude, showed no effect of DBS stimulation. There was no main effect of DBS location on either of the variables.

	F_A	p	ß (°/s) ± SE
reward	(1, 2046.2) = 1.79	= .18	
DBS	(1, 2046.2) = 22.013	<.001	10.12± 2.16
DBS location	(1, 9.0) = 0.05	= .84	
reward* DBS	(1, 2046.1) = 0.49	= .49	
reward* DBS location	(1, 2046.2) = 0.06	= .80	
DBS * DBS location	(1, 2046.2) = 0.17	= .68	
reward* DBS * DBS location	(1, 2046.1) = 0.08	= .78	

Table 4.3 Double-step paradigm VTA-DBS, F statistics: Saccadic peak velocity.

This effect of DBS stimulation on peak velocity, however, vanished after regressing out the effect of amplitude size on peak velocity (**Table 4.4**). Of note, residual peak velocity did also not show an effect of motivation and no other interactions were found (**Figure 4.2 (B)**).

	F_A	p	ß (°/s) ± SE
reward	(1, 2048.0) = 0.35	= .87	
DBS	(1, 2048.0) = 0.02	= .88	
DBS location	(1, 9.0) = 0.01	= .92	
reward* DBS	(1, 2048.0) = 0.48	= .49	
reward* DBS location	(1, 2048.0) = 0.10	= .75	
DBS * DBS location	(1, 2048.0) = 0.01	= .93	
reward* DBS * DBS location	(1, 2048.0) = 0.77	= .38	

Table 4.4 Double-step paradigm VTA-DBS, F statistics: Residual peak velocity.

4.2.3.2. DBS caused a decrease in motor vigour, even more so in the presence of bilateral stimulation

Saccadic amplitudes were overall hypometric considering a distance between fixation point and target location of 11.4°, although they were significantly larger when DBS was "OFF" (p<.001). Amplitude size was also not modulated by motivation through reward (p= .45) and no interaction between the two was found (p= .64, **Table 4.5**). There was a trend towards an effect of DBS location (p= .075) reflected on **Figure 4.3**, by overall smaller amplitudes in the bilateral DBS group when compared to unilateral stimulation. In both cases amplitudes were smaller when stimulation was "ON".

	F_A	P	ß (°) ± SE
reward	(1, 2074.2) = 0.40	= .53	
DBS	(1, 2074.2) = 33.07	<.001	0.49± 0.10
DBS location	(1, 10.4) = 3.92	= .075	
reward* DBS	(1, 2073.7) = 0.52	= .47	
reward* DBS location	(1, 2074.2) = 1.10	= .29	
DBS * DBS location	(1, 2074.2) = 1.57	= .21	
reward* DBS * DBS location	(1, 2073.7) = 2.05	= .15	

Table 4.5 Double-step paradigm VTA-DBS, F statistics: Amplitude.

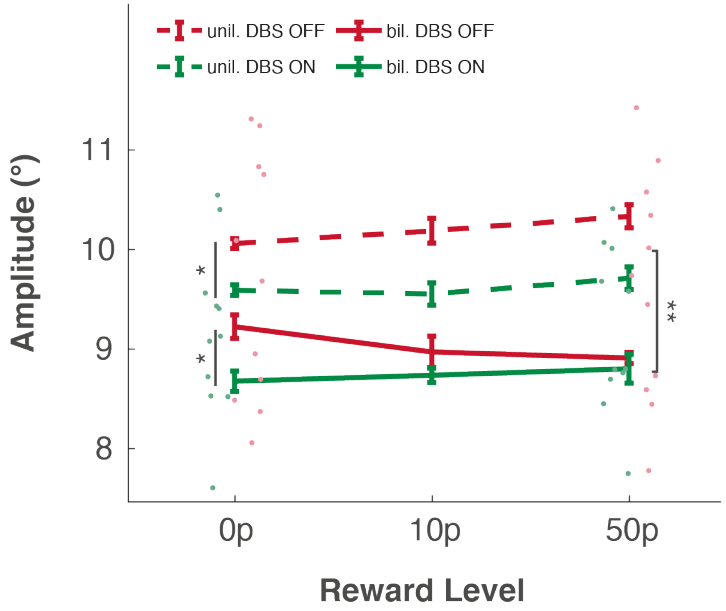

Figure 4.3 Double-step paradigm VTA-DBS: Amplitude size. Stimulation caused hypometric saccades (* p< .001). This was more so the case for bilateral stimulation when compared to unilateral data (** p= .075 n.s.).

4.2.3.3. Speedier reaction times when bilateral stimulation is "ON"

An interaction between DBS location and DBS status was present (p< .001). Participants were significantly faster in the bilateral stimulation "ON" status than in any of the other three conditions. This is reflected in **Figure 4.4** by a visibly diminished difference of reaction times "ON" vs. "OFF" in the unilateral DBS group, while there is a significant difference when looking at the bilateral DBS cohort (pairwise comparison bilateral "OFF" vs. "ON": ß= -34.59 ms (9.24), p< .001). There were no other main effects or interaction found (**Table 4.6**). Again, there was an absent effect of motivation (p= .58).

	F_A	P	ß (ms) ± SE
reward	(1, 1990.77) = 0.30	= .58	
DBS	(1, 1990.45) = 5.54	= .019	-13.81± 5.87
DBS location	(1, 9.01) = 0.10	= .76	
reward* DBS	(1, 1990.18) = 0.16	= .69	
reward* DBS location	(1, 1990.77) = 0.001	= .98	
DBS * DBS location	(1, 1990.45) = 12.50	< .001	
reward*DBS*DBS location	(1, 1990.18) = 0.08	= .78	

Table 4.6 Double-step paradigm VTA-DBS, F statistics: Reaction time.

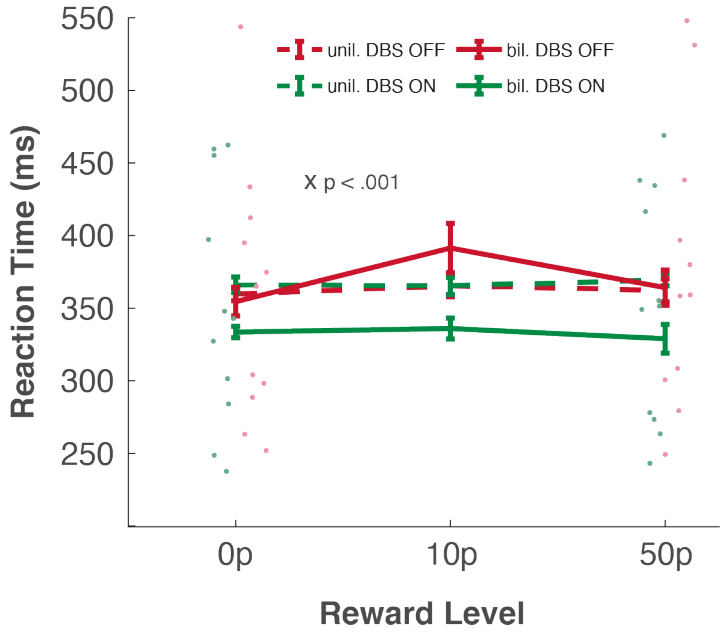

Figure 4.4 Double-step paradigm VTA-DBS: Reaction time. No difference between DBS settings "ON" and "OFF" when unilateral electrodes were in place, but speedier responses if bilateral stimulation is switched "ON".

4.2.3.4. Motivation through reward had no effect on measures of accuracy or distractibility

There was no main effect of reward on neither the proportion of oculomotor capture (p= .69) nor on distractor pull (p= .157). Nor were there any main effects of DBS or DBS location on the two. When looking at the distractor pull there was, however, a trend towards an interaction between reward and DBS location (p= .095, n.s.), which did not reach significance (**Figure 4.5**). This

interaction would indicate a higher level of reward sensitivity in the unilateral DBS cohort. No other interactions or main effects were found on departure angle (**Table 4.7**).

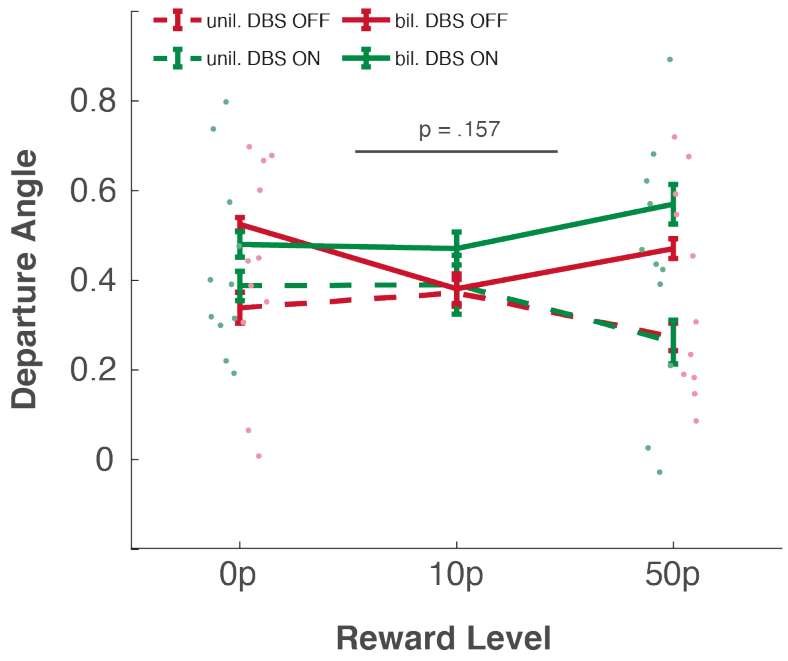

Figure 4.5 Double-step paradigm VTA-DBS: Departure Angle. No significant main effects or interactions were observed.

	F_A	p
reward	(1, 4371.45) = 1.28	= .26
DBS	(1, 4371.32) = 2.01	= .16
DBS location	(1, 10.36) = 1.05	= .33
reward* DBS	(1, 4371.45) = 0.56	= .45
reward* DBS location	(1, 4371.45) = 2.78	= .09
DBS * DBS location	(1, 4371.32) = 0.21	= .65
reward*DBS*DBS location	(1, 4371.45) = 2.19	= .14

Table 4.7 Double-step paradigm VTA-DBS - F statistics: Departure Angle

There were no other significant main effects/interactions found on proportion of erroneous trials (**Figure 4.6, Table 4.8**).

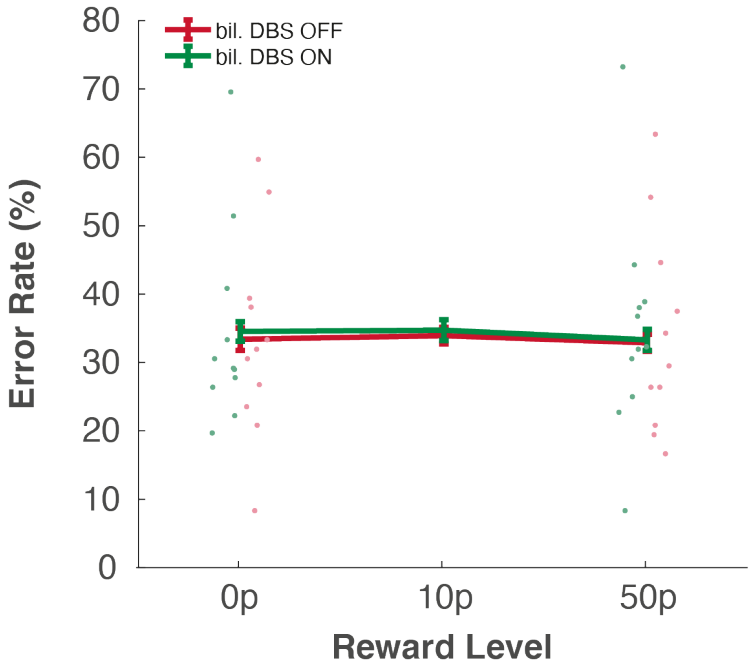

Figure 4.6 Double-step paradigm VTA-DBS: Proportion of erroneous trials.

	F_A	p
reward	(1, 49) = 0.15	= .69
DBS	(1, 49) = 0.37	= .55
DBS location	(1, 9) = 0.21	= .89
reward* DBS	(1, 49) = 0.00	= .99
reward* DBS location	(1, 49) = 0.18	= .68
DBS * DBS location	(1, 49) = 1.97	= .17

Table 4.8 Double-step paradigm VTA-DBS, F statistics: Proportion of erroneous trials.

4.2.4. Pupillary reward sensitivity in patients with VTA DBS

4.2.4.1. Demographics

Pupillometry data were recorded during the double-step paradigm as described in detail in **section 3.6.2.1** from the cohort of VTA DBS patients (demographical data, see **Table 4.1**).

4.2.4.2. Eye tracker data handling and statistical analysis

Average pupil change used in this section was measured by the proportional change of pupil size between cue onset and the mean pupil size 1200-1400 ms after auditory cue onset and was measured in arbitrary Eyelink units. Pupillary reward sensitivity was calculated as the mean pupillary diameter change on rewarded vs. unrewarded conditions (10p-0p; 50-0p). Statistical analysis was performed using a mixed model as described in **section 3.6.2.2.** Instead of the factor "drug", analysis here was run with factors DBS status (2 levels: "ON" vs. "OFF") and DBS location (2 levels: unilateral vs. bilateral). Reward was used as a two-level within-subject factor comparing unrewarded trials with high reward trials (0p vs. 50p). For the analysis of baseline pupil size, reward was dropped from the analysis and the model repeated including DBS stimulation and location. Statistics and post-hoc comparisons were carried out in SPSS using Bonferroni correction (**Table 4.9**):

SPSS	MIXED pupillary change BY reward DBS stimulation DBS location /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN (95) MXITER (100) MXSTEP (10) SCORING (1) SINGULAR (0.000000000001) HCONVERGE (0, ABSOLUTE) LCONVERGE (0, ABSOLUTE) PCONVERGE (0.000001, ABSOLUTE) /FIXED= reward DBS-stimulation DBS-stimulation*reward DBS location*reward DBS location*DBS stimulation DBS location*DBS stimulation*reward | SSTYPE (3) /METHOD=REML /RANDOM=INTERCEPT | SUBJECT (ID) COVTYPE (VC).

Table 4.9 Pupillometry VTA-DBS: Model used for statistical analysis in SPSS (DBS status: 2 levels "ON" and "OFF", DBS location: 2 levels "unilateral" and "bilateral", reward: 2-levels: 0p vs. 50p).

4.2.4.3. Results

There was one main effect found in this analysis. Reward significantly increased pupillary reward sensitivity (F (1, 36) = 5.63, p= .023) leading to a larger pupil size on rewarded trials when compared to unrewarded trials (ß= 12.79 a.u. (5.39), **Figure 4.7**). Neither DBS stimulation (F (1, 36) = 0.025, p= .875) nor DBS location (F (1, 36) = 1.93, p= .173) led to a significant effect on pupillary reward sensitivity and none of the interaction terms were significant. Pupil size at baseline did not differ either with DBS status ("ON" vs. "OFF", F (1, 9) = 0.02, p= .90) nor with DBS location (bilateral vs. unilateral, F (1, 9) = 0.83, p= .39). No interaction terms were present.

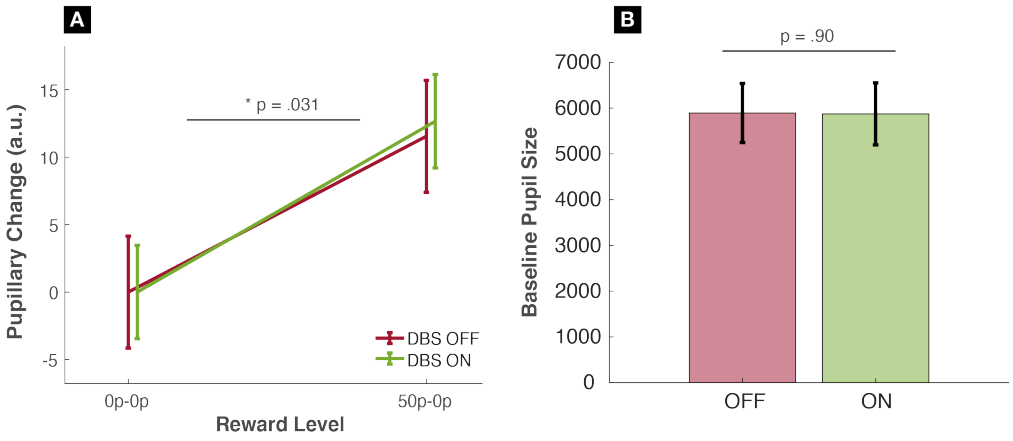

Figure 4.7 Pupillometry VTA-DBS: (A) Reward sensitivity in DBS "ON" and "OFF" rewarded trials vs. 0p condition. Pupil size was significantly larger after reward cues. (B) Pupil size at baseline showed no effect of DBS stimulation.

4.2.5. Discussion

The first intriguing finding in this cohort was the consistent lack of reward sensitivity on all of the saccadic parameters within the double-step paradigm. This is in stark contrast to the findings I reported in the study on healthy controls on the same task. The observation of a lack of reward sensitivity in this cohort points towards a disruption within the reward processing mechanisms. There are a number of publications pointing towards potential dopamine depletion and, hence, reduced reward sensitivity in patients suffering from chronic pain, e.g., providing a neat explanation for these findings: Firstly, there is evidence that chronic pain alters mesolimibic dopaminergic signalling (Zhang, Kiyatkin and Stein, 1994; Altier and Stewart, 1999). This is underpinned on the one hand by the fact that increases in mesolimbic dopamine were shown to mediate tonic pain (Altier and Stewart, 1999), on the other hand, that acute pain leads to an increase in dopamine release and chronic pain can ultimately lead to a hypodopaminergic state through reduced D2 receptor binding and presynaptic dopamine activity (Jääskeläinen *et al.*, 2001; Hagelberg, Forssell, Aalto, *et al.*, 2003; Hagelberg, Forssell, Rinne, *et al.*, 2003; Wood *et al.*, 2007; Martikainen *et al.*, 2015). This was also reported from animal studies, showing decreased c-Fos expression in the VTA in the presence of chronic pain (Narita *et al.*, 2003). As the patients participating in this study have had a history of years of severe cluster headaches or other forms of severe therapy refractory headaches before receiving VTA DBS surgery, these explanatory models would have fitted nicely making the second, very intriguing and surely novel finding, even more surprising. The DBS patients tested, showed preserved reward sensitivity measured by pupillary modulation. Now this, points towards preserved supratentorial reward processing mechanisms, but lost motor consequences in our VTA DBS cohort. Mechanisms of pupillary reward sensitivity have also not shown an effect of neither DBS stimulation nor location pointing to a problem linking motivation into action in this group. This fits neatly into the assumption that the VTA has a role of an interface between limbic and motor system.

A less expected finding, but also potentially in line with the VTA's role in relaying motor commands, was that stimulation caused a decrease in motor vigour. This effect was overall stronger for bilateral DBS. Unilateral stimulation also caused hypometric saccades but to a lesser extent and in either location effects were stronger when electrodes were switched "ON". Reaction times were faster when bilateral DBS was switched on in comparison to any of the other conditions (bilateral "OFF" and unilateral "ON" and "OFF"). This, indeed, partially mimics the pattern we found in healthy participants on haloperidol, where decreased motor vigour and shorter reaction times were observed, although the observed detrimental effect on accuracy is lacking in the DBS cohort.

Thirdly and worth discussing, are the different observations in unilateral and bilateral stimulation. The close link between dopaminergic activity of both cerebral hemispheres has been shown by a number of neurochemical studies. Both pharmacological and electrolytic studies leading to unilateral disruption of the nigrostriatal system have been shown to increase the contralateral dopaminergic activity (Chéramy *et al.*, 1981; Robinson and Whishaw, 1988), while others have not found a difference (Santiago, Cano and Westerink, 1993). Another group found evidence for a functional interdependence of both sides of the mesocorticolimbic system observing a facilitatory effect of a unilateral lesion of the VTA in rats when stimulating the contralateral VTA (Jurkowlaniec, Tokarski and Trojniar, 2003). This could mean that while unilateral stimulation may change dopaminergic signalling on one side, the contralateral side might be compensating for the change in overall dopamine activity, leading to weaker effects on the parameter measured. If, however, both sides are stimulated, these compensatory mechanisms are disabled, and stimulation may lead to a more significant change in behaviour.

5. Dopamine and VTA-DBS in spatial working memory

5.1. Background and hypothesis

In order to optimise our performance, we require a balance between "on-line stabilisation of task-relevant information and flexible updating of irrelevant information" when facing new/additional information (Cools and D'Esposito, 2011). This is thought to be ensured by two interacting dopaminergic pathways (DA-PFC loop and DA-striatal loop). According to this view, tonic release of dopamine into the prefrontal cortex (PFC) may assist the precision and persistence of current task goal representations (i.e., cognitive stability), while phasic dopamine in the striatum may enable cognitive flexibility through shifting and updating of task goal representations (Yee and Braver, 2018). This balance has been found to be essential for abilities like planning, learning, reasoning, and spatial processing. The prefrontal cortex receives a large number of dopaminergic projections from a variety of brain structures including the ventral tegmental area and the brainstem and has been identified as the brain area with the highest concentration of dopamine (anterior-posterior gradient) (Brown, Crane and Goldman, 1979; Haven and Goldman-Rakic, 1995). It has, therefore, been suggested that dopamine is heavily involved in working memory processes, which we previously explored in **section 3.5.1** using memory-guided saccades. In this paradigm we found Madopar to improve not only endpoint precision but also reaction times to some extent, whereas both those variables were worsened by haloperidol. While saccades offer a precise dynamic measurement, most day-to-day uses of spatial working memory involve non-ocular responses. We here, hence, also collected data from a tablet-based short-term memory task, assessing recall of both object identity and location. The task was completed by two separate cohorts: **(1)** Thirty healthy controls as part of the drug study (see **section 3.2.1**) who received placebo, Madopar and haloperidol and **(2)** eleven VTA-DBS patients (see **section 4.1.3**) tested "ON" and "OFF" their DBS stimulation.

Variations of this task have previously been used to study different pathologies including limbic encephalitis, temporal lobe lobectomy and Alzheimer disease (Pertzov *et al.*, 2012; Zokaei *et al.*, 2016, 2019, 2020; Board *et al.*, 2019), the novelty being a new analogue reporting method, including measurements of spatial precision that allow separation of component processes in memory, such as capacity (measured by the effect of increasing the number of memory items stored at once) and binding of items (indexed by the presence of "swap" errors where participants report the wrong item's location). These different component processes may be differently affected by drug manipulation and/or DBS stimulation, making this task a helpful tool to explore this further.

But what is already known from disease models and drug studies? There is body of evidence that PD patients have distinct deficits in working memory with reduced memory precision and an increased proportion of overall "swap errors", the latter being unmodulated by dopaminergic treatment, pointing towards the involvement of non-dopaminergic mechanisms (Zokaei *et al.*, 2014; Rolinski *et al.*, 2015; Zokaei and Husain, 2019). Working memory studies involving PD patients reported mixed effects of dopaminergic replacement therapy, some stating no effect (Torta *et al.*, 2009) others impaired cognitive processing speed and increased distractibility (Poewe *et al.*, 1991; Cools *et al.*, 2010; Uitvlugt *et al.*, 2016) and others improved misbinding performance, latency and accuracy (Lange *et al.*, 1992; Fallon *et al.*, 2019). Another study showed that PD patients improved their memory recall when "OFF" medication not only when compared to "ON" medication, but even showed superior performance "OFF" medication when compared to age-matched controls (Fallon *et al.*, 2017), pointing towards a beneficial aspect of dopamine depletion for working memory performance. In healthy volunteers the dopamine agonist bromocriptine was found to improve short-term spatial memory (Mehta *et al.*, 2001). Haloperidol was found to increase errors on a spatial working memory test (McCartan *et al.*, 2001). Sulpiride, a D2 receptor antagonist, was shown to mimic deficits usually observed in PD (Mehta *et al.*, 2004). The D2 agonist cabergoline was found to improve the

precision of working memory without inducing higher levels of distractibility (Fallon *et al.*, 2017).

Several hypotheses were raised to explain these findings, which were partially discussed earlier (see **section 1.3**). These include firstly, that optimal dopamine levels could be task dependent. Secondly, that dopaminergic treatment in disease could lead to dopamine excess in brain areas relatively spared from dopamine depletion (the dopamine overdose hypothesis). And thirdly, the "inverted-U-shaped" relationship of dopamine and cognitive processes, which states that the effect of drugs may also depend on the individual's baseline dopamine level. In terms of the VTA cohort hypotheses are much less clear and to my knowledge no comparable data have been published previously. The main findings of the memory-guided saccades data discussed in **section 3.5** showed that higher memory load significantly slowed participants down (reaction time). In terms of drug effect, we found Madopar to improve the accuracy of saccadic eye movements and haloperidol to prolong reaction times without causing a deterioration in precision.

I, here, aim to investigate whether similar effects of both Madopar and haloperidol on working memory precision and speed of recall could be observed using a tablet-based spatial memory task (Oxford memory test). Both drugs may have a detrimental effect on different subdomains of cognitive control and working memory. Based on previous findings on healthy controls I hypothesise that haloperidol may decrease memory precision and increase the number of swap errors, while Madopar may increase distractibility and processing speed (identification time). Since bilateral DBS stimulation improved reaction times in the double-step paradigm (**section 4.2.3**), it may cautiously be speculated that identification times may be improved with stimulation in the VTA DBS cohort. Based on the interdependence of both cerebral hemispheres, unilateral lesions can cause a contralateral upregulation of dopaminergic activity termed "contralateral facilitation effect" (as discussed in **section 4.2.5**). As this may affect the data

collected in this cohort, DBS location (bilateral vs. unilateral) will also be added into the model as it was done in the previous section.

5.2. Dopaminergic drug effects on visual working memory

5.2.1. Demographics

The same participants previously described in **section 3.2.1** completed this task (30 participants, 31.76 +/- 12.34 years, 16 females, 14 males). They received either placebo, Madopar dispersible 100/25mg or 2.5mg of haloperidol. Of the 30 participants recruited, the following number have completed this task per drug due to technical difficulties or participants' time constraints: Placebo: 28; Madopar: 29; haloperidol 29.

5.2.2. Experimental setup

The Oxford memory test (OMT) app, version v1.5.1, was downloaded onto a touch screen tablet (IPS LCD capacitive touchscreen, 9.7 inches, 291cm^2, 1536 x 2048 pixels, 4:3 ratio (~264 ppi density). Participants were seated at a desk in front of the tablet.

5.2.3. Short-term memory task (Oxford memory test)

In each trial, participants were presented with either 1 or 3 (simultaneous) randomly located fractal object(s) on the screen. Participants were instructed to remember the objects and their locations while a blank screen was displayed for 4 seconds. Subsequently two fractals were presented along the meridian of the screen, one of which was one of the previously presented ones (target fractal) and the other one was a distractor. The distractor was part of the general pool of fractal images presented across the experiment. Participants were then required to touch the item they recalled (**identification performance**) and drag it to its remembered location (**localisation performance**). For illustration, see **Figure 5.1** below.

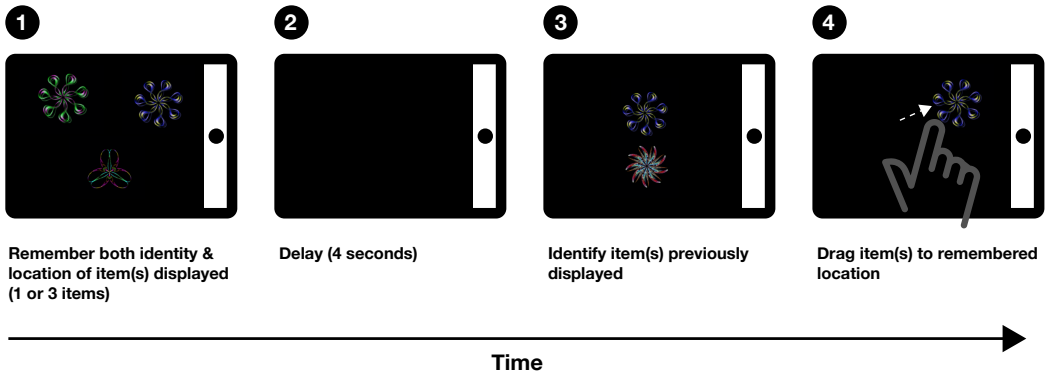

Figure 5.1 Oxford memory test: task instructions. Details see section 5.2.3.

The task consisted of 4 practice trials followed by two blocks with a total of 40 trials. The 40 trials were split equally between two conditions: encoding of 1 item and encoding of 3 items. The locations of the fractals were determined in a pseudorandom manner with the following restrictions: They were displayed with a minimum of 3.9° from the edges of the screen and 6.5° from the centre of screen and 9° of distance from each other in order to avoid spatial uncertainty as a result of overcrowding.

I looked at the following measures to further investigate the role of dopamine on working memory:

- Memory for **object identity** was measured as the proportion of trials where the correct object was chosen in the test array.
- **Identification time** was calculated as the time taken to correctly identify the target.
- **Localisation error** was computed as the Euclidean distance between the centre of the target object after it had been dragged to its remembered location and its true (original) location in the memory array. It was only measured on trials where an object was correctly identified.
- Number of **swap errors**, where the location of the target fractal was swapped with that of another fractal in the original memory array. The

number of swap errors was indexed by the percentage of correctly identified objects placed within 4.5° eccentricity of other fractals in the original array. As in previous studies, a threshold of 4.5° was used because objects were never presented less than 9° from each other in the memory array. Using a cut-off of 4.5° means that the reported location of an object could never be attributed to more than one object.

- **Random guessing,** or errors due to chance, quantifies the proportion of times an item's location is completely forgotten. This corresponds to the proportion of responding randomly to the target location, which is defined as a location which is not within the 4.5° eccentricity from neither the correct target location nor the location of other objects displayed during the trial.

5.2.4. Statistical analysis

The data output from the OMT app contained one value per subject and set size for each variable of interest. Accounting for the missing datasets a mixed linear analysis was performed using set size (number of fractals) and drug (placebo vs. Madopar and placebo vs. haloperidol) as within-subject factors in SPSS and R. Fitting my hypothesis a random intercept model with restricted maximum likelihood method was used. (R model: model <- lmer (*var* ~ items * drug + (1 | ID), data). "Var" was replaced by the variable of interest as described above. The model looked for both main effects of drug (within subject factor with 2 levels) and memory load (within subject factor with 2 levels: 1 or 3 items) as well as interactions between the two. For the analysis of the proportion of misbinding, which could only occur in high memory load conditions, the mixed linear analysis with the factor drug only (within subject factor with 2 levels) was performed.

5.2.5. Results

5.2.5.1. Object identity: Memory load decreased the proportion of correctly identified fractals

There was a significant main effect of memory load on the proportion of correctly identified objects in both drug comparisons (p< .001, F-statistics, see **Table 5.1**). Participants performed significantly better in the conditions with less memory load independent of the drug (**Figure 5.2**). No main effect of drug in either of the drug manipulation groups was found (Madopar vs. placebo p= .880, haloperidol vs. placebo p= .141). There was no interaction found between the number of items and the drug groups.

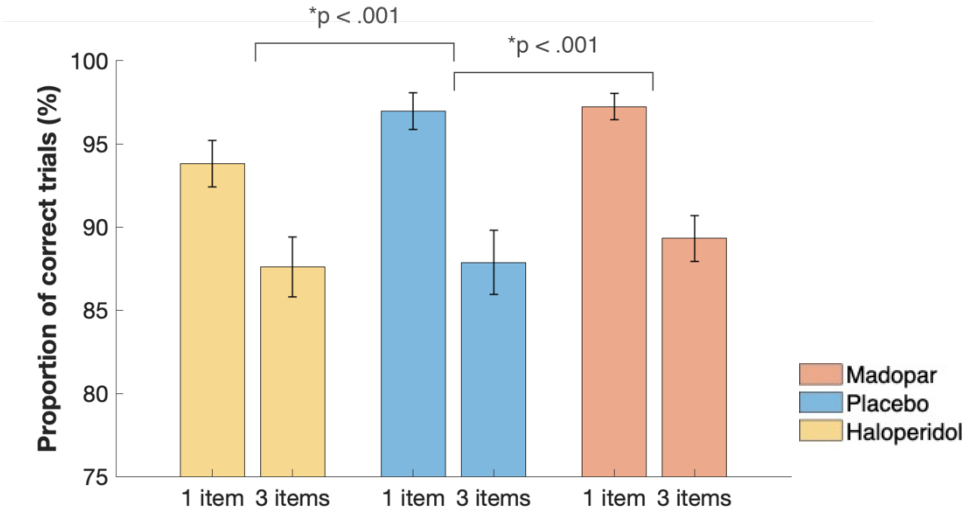

Figure 5.2 Oxford memory test, drug study: Proportion of correct identified fractals.

		F_A	p	ß (%) ± SE
MADOPAR				
	items	(1, 81.90) = 58.36	< .001	-8.5± 1.1
	drug	(1, 85.11) = 0.505	= .479	
	items*drug	(1, 81.89) = 0.278	= .599	
HALOPERIDOL				
	items	(1, 81.77) = 39.84	< .001	-7.7± 1.2
	drug	(1, 84.68) = 2.12	= .148	
	items*drug	(1, 81.77) = 1.43	= .235	

Table 5.1 Oxford memory test- drug study, F-statistics: Object identity.

5.2.5.2. Localisation error: Haloperidol and high memory load decreased endpoint accuracy

There was a strong main effect of memory load for both drug groups vs. placebo (p< .001, F-statistics see, **Table 5.2**). Participants' endpoints were significantly further away from the target when three items were presented at the beginning of the trial than compared to one item conditions (**Figure 5.3**). Participants on haloperidol were also significantly less accurate (p= .013) when compared to placebo. Madopar did not have an effect on endpoint accuracy (p= .882). Neither of the set size effects was found to be influenced by the respective drugs.

		F_A	p	ß (px) ± SE
MADOPAR				
	item	(1, 81.43) = 122.08	< .001	86.33± 7.8
	drug	(1, 84.13) = 0.022	= .882	
	item*drug	(1, 81.43) = 0.972	= .327	
HALOPERIDOL				
	items	(1, 80.87) = 153.68	< .001	94.27±.7.6
	drug	(1, 83.39) = 6.14	= .015	19.18±.7.7
	items*drug	(1, 80.87) = 0.001	= .975	

Table 5.2 Oxford memory test- drug study, F-statistics: Localisation error.

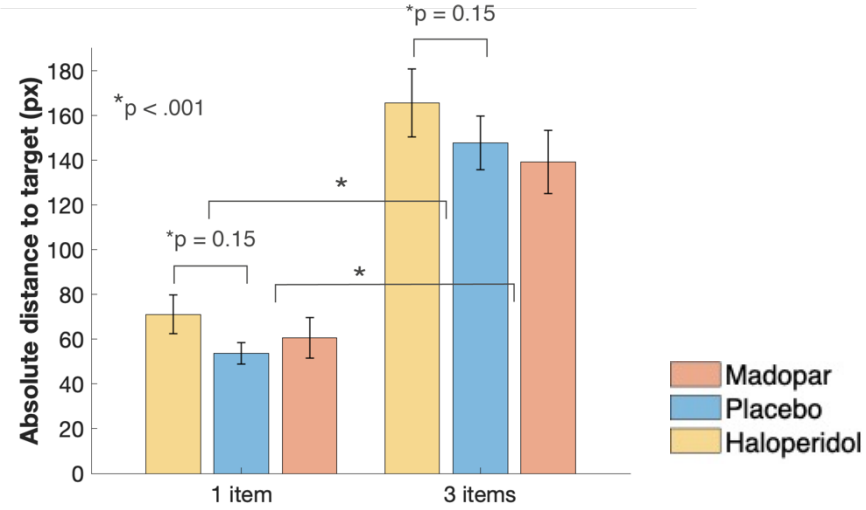

Figure 5.3 Oxford memory test, drug study: Localisation error. Distance between endpoint where fractal was positioned by participants and actual target location.

5.2.5.3. Neither of the drugs influenced the proportion of swap errors

There was no effect of drug found on the proportion of trials where participants placed the target in closer proximity to the location of a distractor fractal than the correct target location (Madopar (F (1, 26.84) = .281, p=.60) and haloperidol (F (1, 26.59) =1.07, p= .31).

5.2.5.4. Haloperidol and high memory load increased the proportion of guessing

Haloperidol increased the number of trials where the item location was completely forgotten (p= .023, F-statistics, see **Table 5.3**), which was not the case for Madopar (p= .17; **Figure 5.4)**. While higher memory load led to a greater proportion of guessing in the Madopar vs. placebo analysis (p= .04), the set size effect in the haloperidol comparison was attenuated by an overall worsened performance (main effect of set size haloperidol vs. placebo p= .078). This was supported by pairwise comparison: On haloperidol there was no effect of set size (F (1, 28) = 0.13, p= .72), which was also the case for Madopar (F (1, 28) = 0.56, p= .47), while the set size effect was strongest in the placebo cohort (F (1, 27) = 14.44, p= .001).

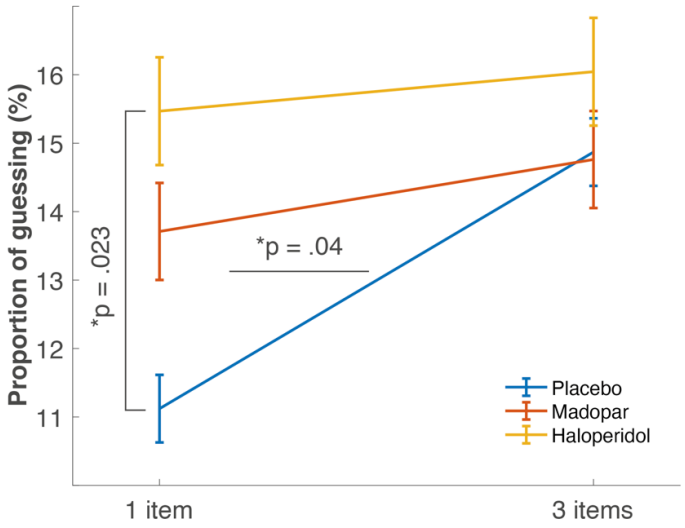

Figure 5.4 Oxford memory test, drug study: Proportion of trials where items were forgotten.

		F_A	p	ß (%) ± SE
MADOPAR				
	item	(1, 81.35) = 4.34	= .040	2.4± 1.2
	drug	(1, 82.88) = 1.89	= .173	
	item*drug	(1, 81.35) = 1.37	= .245	
HALOPERIDOL				
	item	(1, 80.99) = 3.19	= .078	
	drug	(1, 82.87) = 5.39	= .023	2.9± 1.2
	item*drug	(1, 80.99) = 1.71	= .193	

Table 5.3 Oxford memory test- drug study, F-statistics: Proportion of random guessing.

5.2.5.5. Haloperidol prolonged identification time

It took participants significantly longer to identify the target in the three items conditions than in the one item conditions (p< .001, F-statistics, see **Table 5.4**). Haloperidol led to slightly longer identification times when compared to placebo (main effect of drug p= .021), but no effect of drug was found in the Madopar vs. placebo data (p= .74). No interaction was found between item and drug in either drug analysis (**Figure 5.5**).

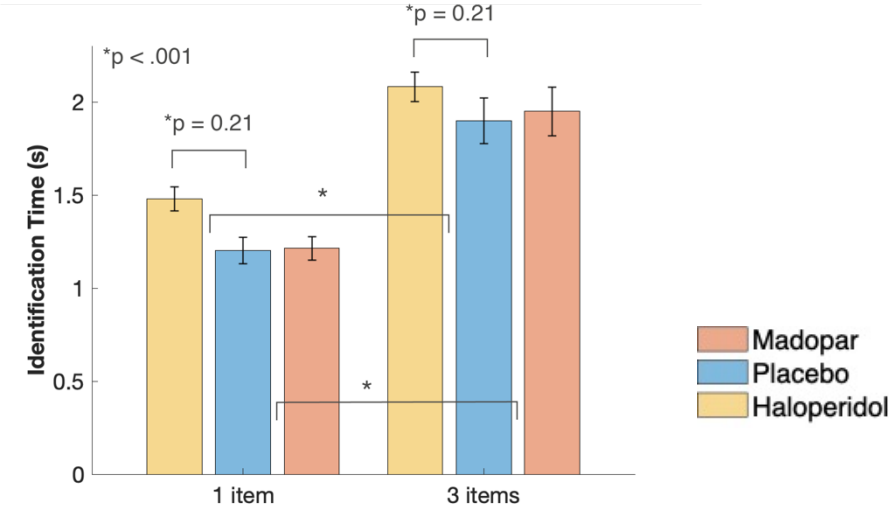

Figure 5.5 Oxford memory test, drug study: Identification time. It took participants significantly longer to identify a target when memory load was high (3 items). Haloperidol led to longer reaction times in both memory load conditions.

		F_A	p	ß (s) ± SE
MADOPAR				
	item	(1, 80.09) = 138.44	< .001	0.715± 0.06
	drug	(1, 83.09) = 0.114	= .737	
	item*drug	(1, 80.09) = 0.120	= .729	
HALOPERIDOL				
	item	(1, 82.44) = 44.56	< .001	0.648± 0.09
	drug	(1, 86.66) = 5.52	= .021	0.229± 0.09
	item*drug	(1, 82.44) = 0.235	= .637	

Table 5.4 Oxford memory test- drug study, F-statistics: Identification time.

5.2.6. Discussion

As expected, higher memory load caused participants to show a deterioration in both object identity and location performance and prolonged identification time compared to when only one item had to be stored in working memory. No effect of Madopar was found on any of the parameters, including swap errors and proportion of trials where items were forgotten. Despite not producing a significant interaction, it may be of interest that both drugs at least weakened the effect of memory load when compared to placebo. This was due to a higher proportion of forgotten trials especially in the low memory conditions (n.s.). Despite other expectations, there was no improvement of identification time on Madopar. An explanation for this observation, may be that identification time does not reflect classic motor reaction time, which would be much faster, but the time taken to identify the correct fractal. Taken together with the improvements seen in saccadic memory, this suggests that the cognitive process of matching stimuli in memory might be less sensitive to dopaminergic stimulation than motor speed.

Haloperidol, however, followed a similar pattern as observed in the saccadic task. It led to greater inaccuracy (absolute error), increased identification time and showed a higher proportion of trials where fractals were forgotten completely. These findings, however, are especially interesting in light of the absence of an effect of haloperidol on the overall proportion of correct trials. This makes the findings less likely to be solely attributed to drowsiness/drug

side effects. However, no interactions between memory load on either of the drugs were found, suggesting they did not affect memory capacity itself.

5.3. The role of VTA in spatial working memory

5.3.1. Demographics and task

The task used and the experimental setup was identical to the one described in the previous section (further details **sections 5.2.2 and 5.2.3)**. Eleven patients with ventral tegmental area DBS completed the task. Their demographics are to be found in **Table 4.1**. Participants completed the task twice per session (each 1x "ON" and 1x "OFF), in counterbalanced order. Each participant, therefore, completed 40 trials "ON" and 40 "OFF" in each of the two sessions.

5.3.2. Statistical analysis

Data variables of interest were calculated as above, for each subject and DBS state ("ON" and "OFF"). A random intercept model was used to analyse the data with R and SPSS, the data reported in the following chapter are from the R analysis:

model <- lmer (*var* ~ items * DBS status* DBS location + (1 | ID), data)

With *var* being replaced by data from the five variables of interest (proportion of correctly identified items, absolute error, proportion of guessing, proportion of swap errors and identification time), I looked for main effects of memory load (number of items/set size) and stimulation effects from the DBS ("ON" vs. "OFF") as well as the influence of DBS location (unilateral vs. bilateral) on the participants' performance and the interactions between them (further details about variables and how they were calculated, see **section 5.2.3**).

5.3.3. Results

5.3.3.1. Object identity: Bilateral DBS stimulation impaired performance for high memory load selectively

I found two interactions (between DBS location and DBS stimulation & DBS location and memory load) in the analysis of the proportion of correctly identified fractals (**Figure 5.6**). DBS stimulation only had a significant effect on the proportion of correctly identified trials when bilateral DBS was in place. Here stimulation "ON" improved performance in the bilateral DBS cohort when compared to "OFF" (interaction between DBS location and DBS stimulation ß= 5.6% (2.0), p= .006), while no difference of stimulation ("ON" vs. "OFF") was found in the unilateral DBS cohort (p= .61). The second interaction showed that patients with bilateral DBS had a larger set size effect (ß= -15.0% (2.0), p< .001) than patients with unilateral DBS (ß= 5% (1.8), p= .007). A trend towards an overall worsening of performance on bilateral vs. unilateral DBS was found (p= .051). There were no other interactions found (F-statistics for main effects, see **Table 5.5**).

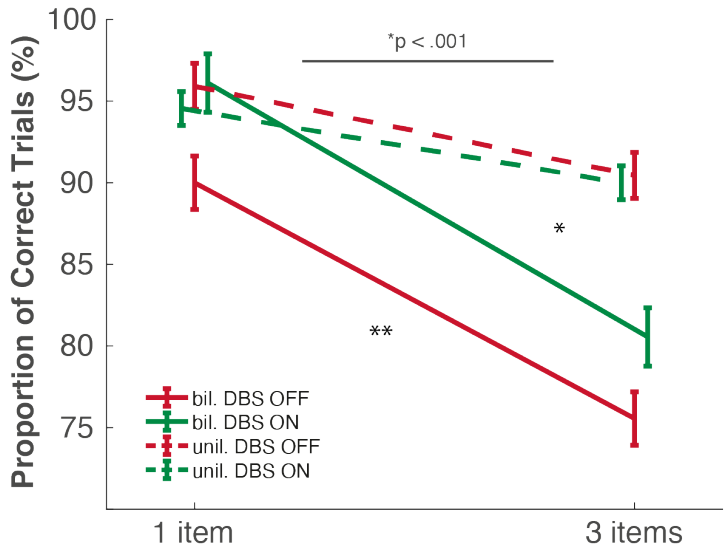

Figure 5.6 Oxford memory test- VTA-DBS: Proportion of correctly identified fractals (dashed lines= unilateral DBS, solid lines= bilateral DBS); * interaction between set size and DBS location p< .001, ** interaction between DBS location and stimulation-effect p= .018.

	F_A	p	ß (%) ± SE
items	(1, 63.38) = 56.83	< .001	-10.0 ± 1.3
DBS	(1, 63.38) = 3.06	= .085	
DBS location	(1, 9.35) = 4.98	= .051	-7.4± 3.3
items* DBS	(1, 63.38) = 0.001	= .970	
DBS * DBS location	(1, 63.38) = 5.94	= .018	
DBS location*items	(1, 63.38) = 14.21	< .001	
DBS * DBS location*items	(1, 63.38) = 0.15	= .705	

Table 5.5 Oxford memory test- VTA-DBS, F statistics: Proportion of correctly identified fractals.

5.3.3.2. Localisation error: Bilateral DBS showed worst memory precision when it was "OFF"

A significant interaction between DBS stimulation and DBS location was found in the analysis of data on memory precision measured by the Euclidean distance between the location where the fractal was positioned and the true target location (**Figure 5.7)**. Bilateral electrodes caused patients to become less accurate when stimulation was switched "OFF" compared to "ON" (ß= 35.64 px (10.18), p= .001, **Table 5.6**). There was no significant difference of DBS stimulation on unilateral DBS patients (p= .83) nor was there a difference of DBS stimulation ("ON" vs. "OFF") in the unilateral DBS cohort (p= .69). Higher memory worsened accuracy overall (ß= 131.97 px (6.87), p< .001).

	F_A	p	ß (px) ± SE
items	(1, 63.27) = 369.48	< .001	131.97 ± 6.86
DBS	(1, 63.27) = 5.42	= .023	-15.98 ± 6.87
DBS location	(1, 9.21) = 0.97	= .35	
items* DBS	(1, 63.27) = 2.72	= .104	
items* DBS location	(1, 63.27) = 2.81	= .099	
DBS * DBS location	(1, 63.27) = 8.19	= .006	
items* DBS * DBS location	(1, 63.27) = 1.68	= .199	

Table 5.6 Oxford memory test- VTA-DBS, F statistics: Localisation error

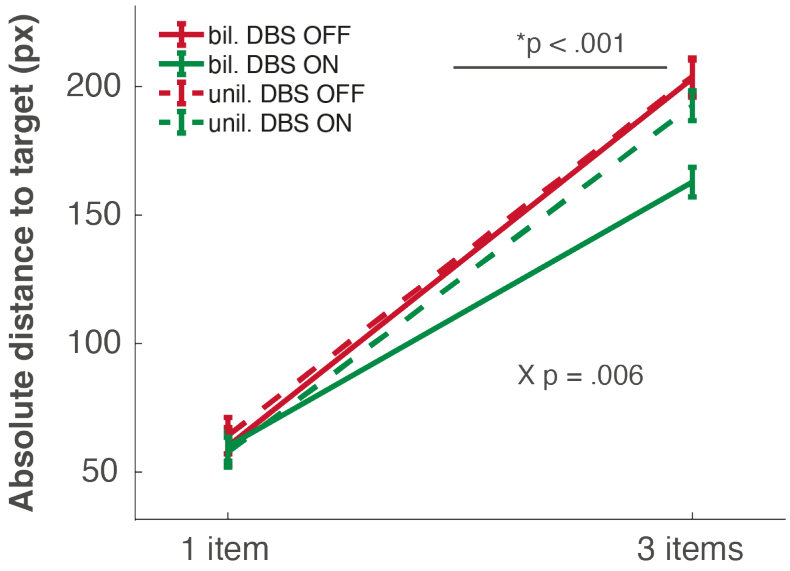

Figure 5.7 Oxford memory task- VTA-DBS: Localisation error (dashed lines= unilateral DBS, solid lines= bilateral DBS, x interaction between DBS stimulation and DBS location).

5.3.3.3. Swap errors increased by bilateral stimulation

There was no main effect of DBS stimulation (p= .25, **Figure 5.8**) on the proportion of swap errors (**Table 5.7**). A significant interaction between DBS stimulation and DBS location showed, though, that participants improved their performance when "ON" bilateral stimulation (ß= -6.6% (2.5), p= .014) as compared to "OFF" bilateral stimulation, while there was no difference of stimulation when looking at the unilateral cohort "ON" and "OFF" (p= .25). Bilateral DBS also had a detrimental effect on performance when compared to unilateral DBS only when stimulation was "OFF" (ß= 11.8% (3.8), p= .008). There was no effect of DBS location when electrodes were "ON" (p= .51). Patients with bilateral DBS performed slightly worse overall, showing a non-significant trend for a main effect of DBS location (ß= 7.2% (3.4), p= .062, n.s.).

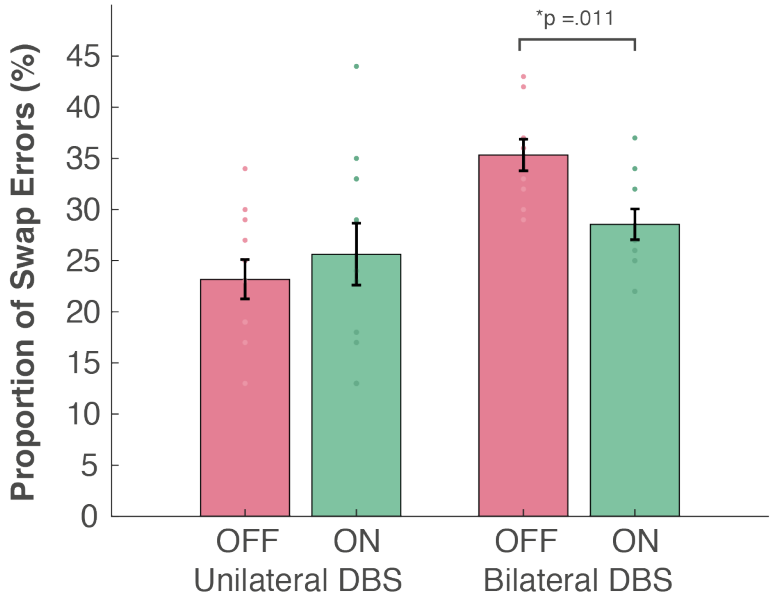

Figure 5.8 Oxford memory test- VTA-DBS: Swap errors. Patients showed significantly more swap errors when stimulation was "OFF" in the bilateral DBS cohort (interaction between DBS stimulation and DBS location x p= .011).

	F_A	p
DBS	(1, 27.25) = 1.37	= .25
DBS location	(1, 9.14) = 4.50	= .062
DBS*DBS location	(1, 27.25) = 7.48	= .011

Table 5.7 Oxford memory test- VTA-DBS, F-statistics Swap errors.

5.3.3.4. Random guessing increased by bilateral stimulation "OFF"

The proportion of trials where fractals were completely forgotten was significantly higher in high memory load conditions when compared to conditions where only one item had to be recalled (**Figure 5.9**; p= .008, F-statistics **Table 5.8**). There was no significant main effect of DBS stimulation (p= .33) or DBS location (p= .14), although, similarly to accuracy measured by endpoint error and the proportion of swap errors, the proportion of trials where fractals were completely forgotten was significantly worsened by bilateral DBS stimulation *only* when electrodes were "OFF" (ß= -5.2% (2.2),

p= .023), shown by an interaction between DBS and DBS location (p= .016). No stimulation effect was found in the unilateral DBS group (p= .27) and no difference between the unilateral and bilateral “ON” cohort was found (p= .812). No other main effects or interactions were found.

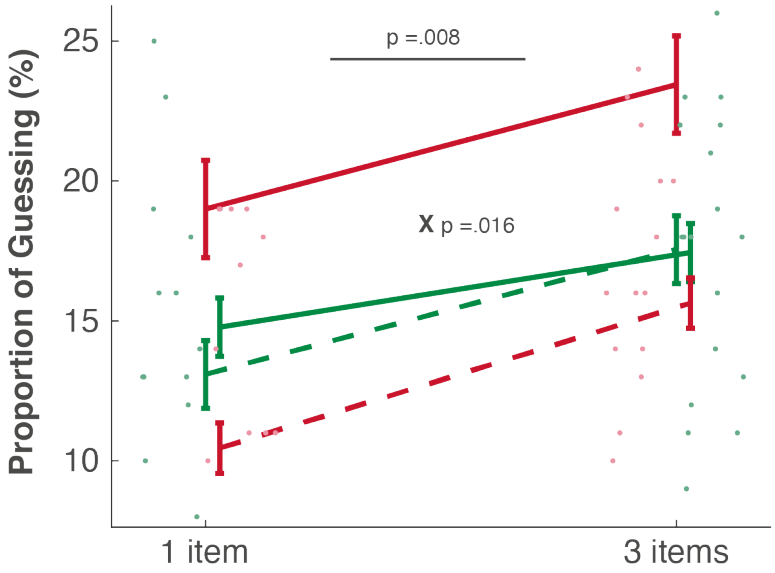

Figure 5.9 Oxford memory test- VTA-DBS: Proportion of trials where item(s) was/were completely forgotten (dashed lines= unilateral DBS, solid lines= bilateral DBS).

	F_A	p	ß (%) ± SE
items	(1, 63.53) = 7.63	= .008	4.2 ± 1.5
DBS	(1, 9.39) = 0.97	= .33	
DBS location	(1, 63.53) = 2.62	= .14	
items* DBS	(1, 63.53) = 0.17	= .68	
items* DBS location	(1, 63.53) = 0.17	= .68	
DBS * DBS location	(1, 63.53) = 6.17	= .016	
items* DBS * DBS location	(1, 63.53) = 0.001	= .922	

Table 5.8 Oxford memory test- VTA-DBS, F-statistics: Proportion of guessing.

5.3.3.5. Identification time was unaffected by stimulation

Identification time varied significantly with memory load (**Figure 5.10**). It took participants longer to identify the correct fractal if memory load was high (p< .001). There were no other main effects or interactions found for this variable (for F-statistics, see **Table 5.9**).

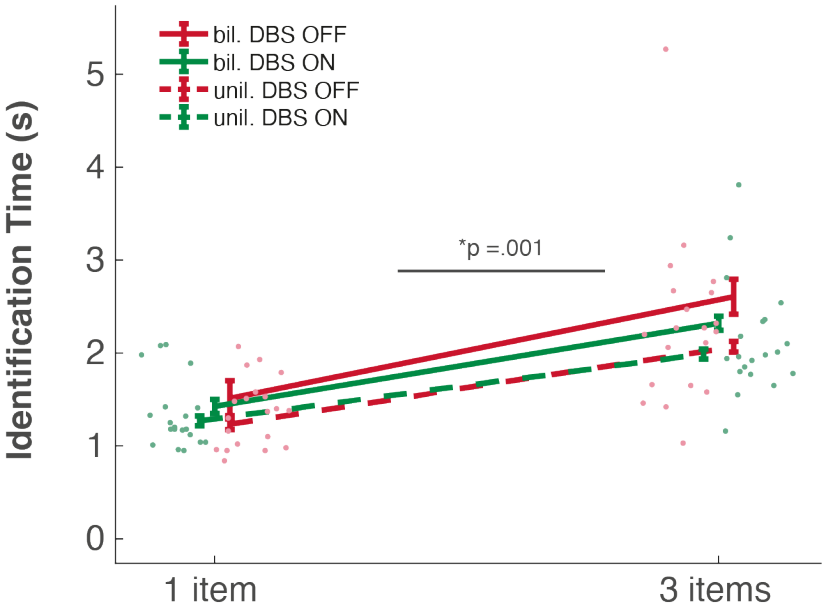

Figure 5.10 Oxford memory test- VTA-DBS: Identification time (dashed lines= unilateral DBS, solid lines= bilateral DBS).

	F_A	p	ß (s) ± SE
items	(1, 63.24) = 7.63	< .001	0.88 ± 0.097
DBS	(1, 9.22) = 0.97	= .29	
DBS location	(1, 63.24) = 2.62	= .20	
items*DBS	(1, 63.24) = 0.17	= .41	
items*DBS location	(1, 63.24) = 0.17	= .27	
DBS*DBS location	(1, 63.24= 6.17	= .39	
Items*DBS*DBS location	(1, 63.24) = 0.001	= .83	

Table 5.9 Oxford memory test- VTA-DBS, F-statistics: Identification time.

5.3.4. Discussion

While the detrimental effects of memory load I reported above are well documented in the literature, the more intriguing question that had to be answered here was whether there is an effect of DBS stimulation within the ventral tegmental area on spatial working memory performance, and whether set size effects could be altered by it, which both was the case. In fact, bilateral DBS when electrodes were switched "OFF" showed the worst performance overall and showed a pronounced set size effect in memory precision when compared to bilateral "ON" and the data from unilateral DBS. None of the variables showed an effect of DBS stimulation within the unilateral DBS group, as similarly reported and discussed in previous sections.

Interestingly the enhancing effect of bilateral DBS stimulation was not found in the analysis of deliberation time, where no difference among the four groups was identified. The only effect found on deliberation time was that of memory load.

Limitations for interpreting these results may, firstly, be the small number of participants, which is explained by the overall small number of patients who underwent this surgery. Secondly, the lack of a cohort of age-matched control subjects with long standing cluster headache, that would enable to establish whether bilateral DBS stimulation actually relatively improves or whether unilateral DBS and bilateral DBS switched "ON" *relatively worsens* performance. The data suggest that DBS causes a change within VTA neuronal signalling, which is stronger in bilateral stimulation, potentially due to the contralateral facilitation effect which may be compensating for stimulation effects in unilateral stimulation. It may be possible that lesions caused by the DBS electrodes lead to a decrease in dopamine activity within the VTA that is compensated for when electrodes are switched "ON" and in the case of unilateral DBS by the contralateral (intact) VTA. In other words, this may reflect a degree of left-right redundancy built into dopaminergic midbrain signals. Since data on human studies in this context are lacking, I

here can only use animal data to further look into this theory. Bilateral baclofen infusions to the VTA of rats have, for example, been found to disrupt short-term working memory in a spatial navigation task (Martig *et al.*, 2010). Intrahippocampal dopamine agonists have improved spatial memory (Packard and White, 1991), 6-OHDA lesions impair performance on spatial tasks (Gasbarri *et al.*, 1996), and D2 antagonism in the ventral hippocampus disrupts spatial working memory performance (Wilkerson and Levin, 1999). These findings point towards a critical role of dopamine in spatial memory tasks and would be in favour of the idea that DBS stimulation leads to improved performance through increases in dopamine activity in the ventral tegmental area if it is in situ bilateral. This theoretical view is corroborated by the worsened performance observed on haloperidol.

6. General Discussion

6.1. Overview, limitations, and future work

The basal ganglia have been found to play an important role in reward expectation and reward processing - the foundation of goal-directed behaviour (Rock *et al.*, 2013). Recently it has been suggested that impulse control disorders and apathy, both commonly observed symptoms in PD, could be "opposite extremes of a dopamine-dependent spectrum of motivated decision-making" (Suri and Schultz, 1999). Indeed, fatigue in multiple sclerosis or post-stroke patients, described as an "aversion to effort", has also been reported to improve with dopaminergic treatment, suggesting a common pathophysiological substrate (Sinha, Manohar and Husain, 2013). This work aimed to further explore the dopaminergic mechanisms underlying these observations with the following questions in mind: Is there a non-invasive dopamine proxy which could help identify prodromal PD? Could we optimise treatment strategies for these patients predicting their reaction to dopaminergic treatment? And how could we identify those at risk of developing ICDs on dopamine agonist treatment? I will summarize my findings below, add possible interpretations and discuss limitations as well as remaining questions that require further exploration.

6.1.1. Motivation and baseline dopamine

In **Chapter 2**, three incentivised saccadic paradigms were run on healthy young volunteers. Previous findings of motivation through reward improving both saccadic velocity *and* accuracy simultaneously, violating the long-established speed-accuracy trade-off, were confirmed (**Figure 2.7**). This was in line with our predictions and with frameworks suggesting improved performance through noise reduction in motor and cognitive control (Manohar *et al.*, 2015). The cost of these control mechanisms may be accounted for by the reward on offer, although the subjective "value" of a reward/cost may vary depending on the individual's dopaminergic state reflected by the choice for low effort/low reward options in dopamine depleted states (Muhammed,

Manohar and Husain, 2015). Additionally, a variety of other factors have been identified including personality traits, gene polymorphism, gender and age (Cools and D'Esposito, 2011) explaining the great variety of findings in the field. This underlines the need for biomarkers such as non-invasive dopamine proxies to enable recruitment of more homogeneous study populations for future research.

6.1.2. Reward valence

The effects of incentives of difference valence on human behaviour are a matter of ongoing controversy. Relatively few studies assessed the effect of monetary reward anticipation and penalty avoidance concurrently in the same task, especially using saccades. Evidence collected in the latter two saccadic tasks in **Chapter 2** show that effects of both incentive conditions were not dissociable, as both incentives improved performance such as decreasing reaction time and increasing velocity to a similar degree (**Figure 3.14, Figure 3.22**). A statistical difference between them was absent. This finding was surprising as there is evidence going back as far as the Aversion Theory (Kahneman and Tversky, 1979) predicting otherwise. These results support the idea that both loss avoidance and reward anticipation may be assigned the same "net-value" potentially by different neuron subgroups, leading to improved performance and the allocation of resources. Indeed, this is in line with findings from an fMRI study, showing similar activation pattern in the nucleus accumbens for both appetitive and aversive stimuli if incentives were contingent, which was the case for all paradigms in this chapter (Kawasaki and Yamaguchi, 2013). This said, a clear differentiation of neural substrates involved in these processes cannot be made on the basis of my data. Recent literature, however, suggested a central role of the dorsal anterior cingulate cortex (dACC) in allocating effort, based on the subjective motivational value of a goal and the subjective experience of effort (Shenhav *et al.*, 2017). My findings could, therefore, be integrated into the "expected value of control framework" (Shenhav *et al.*, 2017) which suggests that the allocation of resources (cognitive control) may depend on the expected gains (reward and

penalty avoidance) discounting the perceived costs of the control command. The perception of the latter two may, however, be highly dopamine dependent.

6.1.3. Entropy and motivation

As decision value and confidence influence goal-directed behaviour and were found to reflect the perceived "desirability" of a goal, it is of special interest that the effect of motivation through both types of incentives was not altered by neither greater decision uncertainty nor higher memory load in my data. Greater memory load as well as a higher number of choice alternatives led to slower and less accurate saccades (**Figure 2.18**, **Figure 3.14**), although there was no evidence to indicate that incentives to compensate for the increased costs of higher entropy levels in the tasks. This suggests a fixed optimal balance between speed and accuracy for a certain level of entropy. An intriguing finding in this context was, that reward sensitivity of velocity in memory-guided saccades was higher for low memory load conditions when compared to high memory load, which does suggest a shift in cost-benefit ratio in the presence of higher dopamine levels. This was not the case for reward sensitivity of velocity in different uncertainty conditions (Task II). Madopar increased reward sensitivity independent of uncertainty, which may suggest higher costs for memory recall than for decision uncertainty.

6.1.4. Pharmacological manipulation- future directions?

Following on from these findings, **Chapter 3** revisited the above paradigms adding a pharmacological manipulation of dopamine levels to further assess the neurochemical mechanisms and more specifically the role of dopamine in goal-directed behaviour, motivation and effort. While the role of dopamine in the signalling of positive incentives has been investigated intensively, the modulation of saccadic properties to loss is yet to be fully understood. While previous evidence suggested that dopamine has a stronger role in positive reinforcement learning than in negative (Frank, Seeberger and O'Reilly, 2004;

Bódi *et al.*, 2009; Nagy *et al.*, 2012), this was not the case for motivation in my data. Higher dopamine levels (Madopar) increased reward sensitivity, which was most interestingly the case for both incentive valences, similarly suggesting different underlying mechanisms for learning and motivation. A possible explanation for this may be the different roles of phasic dopamine vs. tonic dopamine which may imply a more prominent role of the former in learning and the latter in motivational processes. A logic next step would certainly be to test this hypothesis in a cohort of PD patients especially with the question of the effect of penalty vs. reward on above parameters. It may, however, also be suggested that motivational processes involve other than/additional neurotransmitter systems to dopamine such as serotonin, which has more recently been suggested to also be implicated in negative reinforcement learning (Daw, Kakade and Dayan, 2002; Bayer and Glimcher, 2005; Bang et al., 2020). As my experiments do not allow to judge upon non-dopaminergic mechanisms, future work is needed to further investigate these complex mechanisms.

Decreased motor vigour, in both dopaminergic drug manipulations, was another rather surprising finding in my data (**Figure 3.5**), as dopamine has previously been found to invigorate saccadic responses (Grogan *et al.*, 2020). While tonic dopamine in the striatum is associated with controlling movement vigour, my findings suggest a more complex interaction, potentially following an "inverted-U-shaped" relationship between dopamine levels and motor vigour in healthy participants. Another explanation may be the different dopamine receptor subgroups involved in the two drug manipulations. While it is less surprising that haloperidol (D2 receptor antagonist) decreased motor vigour, the effect observed after a single dose of Madopar may represent a more mixed picture, most likely by action on both the direct and the indirect pathway simultaneously. Reduced motor vigour was accompanied by improved accuracy in the Madopar data (**Figure 3.3**) and worsened accuracy as well as increased reaction times in the haloperidol data (**Figure 3.14)**. These observations suggest a linear relationship between dopamine levels and precision signals potentially explained by dopamine improving the signal-

to-noise ratio (**Figure 3.12**) or worsening it in dopamine deplete states. It is, however, assumed that a number of additional neurotransmitters such as noradrenalin, acetylcholine and serotonin are involved in these mechanisms and a specific role for noradrenalin energising behaviour when facing challenges has been suggested (Varazzani *et al.*, 2015).

6.1.5. Ventral tegmental area and action invigoration

While these drug manipulations shed more light on the role of dopamine in motor and cognitive control measured by saccades, no statement could be made about the distinct roles of different dopaminergic pathways. In **Chapter 4**, I specifically modulated the mesolimbic pathway. A fascinating result emerged, suggesting that the patients with VTA DBS recruited for this study did not show reward sensitivity on saccadic parameters. Crucially, electrical stimulation did not restore reward sensitivity when compared to DBS "OFF" and the overall effect was more pronounced in the bilateral VTA DBS cohort when compared to unilateral DBS. An important caveat for interpreting results here is, however, the very low sample size, due to the relatively low number of surgically treated cluster headaches. Saccadic data on reward sensitivity and VTA DBS have to my knowledge so far only been reported in animal studies (Trojniar and Staszewska, 1994; Trojniar and Klejbor, 1999). The absence of a reward effect on either of the saccadic parameters is particularly interesting given that pupillary reward sensitivity was preserved in this cohort (**Figure 4.7**), pointing towards a specific role of VTA in mediating the motoric aspects of motivation, but not the reward sensitivity per se. This is neatly in line with the VTA's described role in translating motivation into action (Mogenson, Jones and Yim, 1980), which I argue could be disrupted by VTA DBS or the underlying chronic pain syndrome. This is, however, contrasted by recent evidence from monkeys which points towards a role of the SNc in the computation of effort-reward trade-off in choice decision (Varazzani *et al.*, 2015). In any case these findings support the idea of different neural systems being involved in autonomic reward responses vs. action invigoration. In this context another group also suggested different anatomical correlates for action vs. emotion signalling (Grabenhorst, Rolls and Parris, 2008). As it

remains unclear whether these results stem from the DBS electrodes, stimulation effects, underlying disease pathology or potentially are consequences of the chronic pain syndrome accompanying this diagnosis, it may be an exciting opportunity to match these data with data from patients with therapy refractory headaches/chronic pain syndromes without or before their DBS surgery and age-matched healthy controls to further dissect the origin of our findings. A bigger sample size, of course, would also be desired, which, may be difficult considering the unique cohort. This would, however, be necessary to compare results with age-matched controls, to further comment on the probable effects of disease pathology, chronic pain syndrome and DBS electrodes as well as stimulation on performance.

6.1.6. Dopamine and working memory

Cognitive impairments are common in PD and can in some cases even precede the onset of motor symptoms. These may include problems in executive functions and attention, one of the most prominent deficits, however, being visual working memory impairments. These deficits have been linked to dopamine depletion as some aspects were shown to improve with dopamine therapy although some did not (Cools, 2006). The pharmacological manipulation with both Madopar and haloperidol as well as the electrical modulation of the mesocorticolimbic system by VTA DBS, therefore, provided a great opportunity to investigate the role of different dopamine pathways in cognitive control, more specifically in working memory (**Chapter 5**). As expected, higher memory load caused participants to show a deterioration in both identification and localisation performance. This was reflected by a smaller proportion of trials where fractals were correctly identified and accurately positioned.

An unexpected finding was the lack of an effect of Madopar and motivation on working memory performance, potentially reflecting the already “optimal” performance in a cohort of young healthy controls. The effect of dopamine stimulation in the PFC has, however, been shown to depend on a variety of factors, e.g., one being a bidirectional modulation via D1 and D2 receptor

activation by Madopar, which may also explain our findings (Seamans and Yang, 2004). It ultimately remains an interesting question, worth further investigating why Madopar improved memory precision in the saccadic task but did not on the tablet-based task. Haloperidol on the other hand, showed the expected worsening of memory precision most likely through mechanisms of dopamine depletion. VTA deep brain stimulation improved memory precision in the bilateral cohort, especially when memory load was high, which in light of animal studies may be suggestive of VTA stimulation leading to increased dopaminergic stimulation of the PFC (Lewis and Donnell, 2000). Patients with bilateral DBS did worse in the identification performance when compared to unilateral DBS, especially when electrodes were "OFF" and improved to the level of unilateral DBS when stimulation was "ON". This may suggest a disruption of mesocorticolimbic signals by the DBS electrodes per se that is ameliorated by stimulation. While it is yet unclear what implications this may have on the application of DBS in this and other areas of the brain, the data collected surely underpin the need for further studies into the role of VTA DBS in humans.

6.2. Conclusion

In conclusion, this thesis examined dopaminergic mechanisms underlying optimal goal-directed behaviours. Novel oculomotor tasks were devised using different types of saccades to investigate the interaction between reward anticipation, punishment avoidance and dopamine and their roles in shifting the cost-benefit ratio of actions/decisions. Data was collected in healthy controls using not only eye movements but also pupillary responses in a pharmacological study and in a cohort of patients who had undergone VTA DBS surgery. These cohorts were chosen to assess the effects of dopaminergic modulation in both the nigrostriatal as well as the mesolimbic pathways. Incentives of both valences influenced motivated behaviour improving saccadic vigour and distractibility in the cohort of healthy participants, while Madopar additionally increased reward sensitivity of velocity seemingly shifting the cost-benefit ratio. The opposite was however

not observed after haloperidol administration, which did not affect reward sensitivity, potentially explained by a mixed effect of haloperidol on pre- and post-synaptic receptors. Both drugs decreased motor vigour, which may be due to the effect Madopar has on both the direct and the indirect pathway.
A role of the VTA in goal-directed behaviour, likely translating motivation into motor action, is suggested. This hypothesis is based on the observation that saccadic reward sensitivity in this cohort was absent, while pupillary response to reward remained intact.

There are however a number of limitations to this body of work discussed in more detail in earlier chapters, of which I here want to recapture a few. While one could surely argue that the sample size of 30 participants for the drug study is rather small, given the risk of potential drug side effects, the intent was to keep the number as small as possible without compromising on statistical power. Secondly, the effect of a small dose of Haloperidol on each participant was observed to be highly variable, potentially because its plasma concentration also depends on body fat and habitus. A milligram per kg bodyweight approach may, hence, offer an alternative for future studies. Arguing for an “inverted-U-shaped” relationship between dopamine levels and performance, we used questionnaires as dopamine baseline proxies. Although this was a helpful tool for this body of work, including a more accurate measure would surely be desirable and help interpret results in future experiments. In this context pharmacological functional imaging, e.g., may help to further dissect dopaminergic from non-dopaminergic mechanisms influencing saccadic performance and to interpret results reliably, also accounting for individual baseline differences. Finally, it will also need to be clarified, whether a single dose of an (anti-) dopaminergic drug is actually useful for mimicking diseases such as Parkinson’s disease as it induces a phasic dopamine decrease rather than a tonic hypodopaminergic state.

Saccades and pupillometry may, however, represent an inexpensive and easy tool to help identifying more uniform study cohorts for future research and

may in future be used for treatment monitoring in patients. Eventually, I want to emphasise the importance of such research as it may have implications on patients' lives by aiding early diagnosis and facilitating tailored treatment strategies for neurodegenerative diseases such as PD.

7. Bibliography

Adam, R. *et al.* (2013) 'Dopamine reverses reward insensitivity in apathy following globus pallidus lesions', *Cortex , 49 (5) pp. 1292-1303. (2013)*. Elsevier Masson.

Agostino, R. *et al.* (1987) 'Corneal and blink reflexes in Parkinson's disease with "on-off" fluctuations', *Movement disorders*. Hoboken: Wiley Subscription Services, Inc., A Wiley Company, 2(4), pp. 227–235.

Akram, H. *et al.* (2016) 'Ventral tegmental area deep brain stimulation for refractory chronic cluster headache', pp. 1676–1682.

Al-Abdulmunem, M. and Briggs, S. T. (1999) 'Spontaneous blink rate of a normal population sample', *International Contact Lens Clinic*, 26(2), pp. 29–32. doi: https://doi.org/10.1016/S0892-8967(99)00016-4.

Albin, R. L., Young, A. B. and Penney, J. B. (1989) 'The functional anatomy of basal ganglia disorders', *Trends in neurosciences (Regular ed.)*. England: Elsevier BV, 12(10), pp. 366–375.

Allen, R. J. (2019) 'Prioritizing Targets and Minimizing Distraction Within Limited Capacity Working Memory', *Journal of cognition*. Ubiquity Press, 2(1).

Altier, N. and Stewart, J. (1999) 'The role of dopamine in the nucleus accumbens in analgesia', *Life sciences (1973)*. Netherlands: Elsevier BV, 65(22), pp. 2269–2287.

Anderson, B. A., Laurent, P. A. and Yantis, S. (2012) 'Generalization of value-based attentional priority', *Visual cognition*. England: Informa UK Limited, 20(6), pp. 647–658.

Anderson, T. J. and MacAskill, M. R. (2013) 'Eye movements in patients with neurodegenerative disorders', *Nature Reviews Neurology*. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved., 9, p. 74. Available at: https://doi.org/10.1038/nrneurol.2012.273.

Ang, Y. *et al.* (2017) 'Distinct Subtypes of Apathy Revealed by the Apathy Motivation Index Distinct Subtypes of Apathy Revealed by the Apathy Motivation Index', (January). doi: 10.1371/journal.pone.0169938.

Antonini, A. *et al.* (1997) 'Long-term changes of striatal dopamine D2 Receptors in patients with Parkinson's disease: A study with positron emission tomography and [11C]Raclopride', *Movement disorders*. Hoboken: Wiley Subscription Services, Inc., A Wiley Company, 12(1), pp. 33–38.

Armstrong, I. T. *et al.* (2002) 'Control of saccades in Parkinson's disease', *Brain and cognition*, 49(2), p. 198—201. Available at: http://europepmc.org/abstract/MED/15259388.

Assad, J. A. (2003) 'Neural coding of behavioral relevance in parietal cortex', *Current opinion in neurobiology*. England: Elsevier Ltd, 13(2), pp. 194–197.

Aston-Jones, G. and Cohen, J. D. (2005) 'An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance.', *Annual review of neuroscience*. United States, 28, pp. 403–450. doi: 10.1146/annurev.neuro.28.061604.135709.

Atkinson, A. L. *et al.* (2018) 'Are there multiple ways to direct attention in working memory?', 1424, pp. 115–126. doi: 10.1111/nyas.13634.

Bahill, A. T., Clark, M. R. and Stark, L. (1975) 'The Main Sequence, A Tool for Studying Human Eye Movements.', *Mathematical Biosciences*, 24, pp. 191–204. doi: 10.1016/0025-5564(75)90075-9.

Baloyannis, S., Vassiliki, C. and Baloyannis, I. (2005) *Morphological alterations of the synapses in the locus coeruleus in Parkinson's disease*.

Bang, D. *et al.* (2020) 'Article Sub-second Dopamine and Serotonin Signaling in Human Striatum during Perceptual Decision-Making ll ll Sub-second Dopamine and Serotonin Signaling in Human Striatum during Perceptual Decision-Making', *Neuron*. Elsevier Inc., 108(5), pp. 999-1010.e6. doi: 10.1016/j.neuron.2020.09.015.

Baraduc, P. *et al.* (2013) 'A common optimization principle for motor execution in healthy subjects and parkinsonian patients', *The Journal of neuroscience*. United States: Society for Neuroscience, 33(2), pp. 665–677.

Barch, D. M., Treadway, M. T. and Schoen, N. (2014) 'Effort , Anhedonia ,

and Function in Schizophrenia : Reduced Effort Allocation Predicts Amotivation and Functional Impairment', 123(2), pp. 387–397. doi: 10.1037/a0036299.

Barkley-levenson, E. and Galv, A. (2017) 'Short report: Eye blink rate predicts reward decisions in adolescents', *Develomental Science*, 20(April 2016), pp. 1–11. doi: 10.1111/desc.12412.

Basso, M. A. and Evinger, C. (1996) 'An Explanation for Reflex Blink Hyperexcitability in Parkinson's Disease. II. Nucleus Raphe Magnus', *The Journal of neuroscience*. United States: Society for Neuroscience, 16(22), pp. 7318–7330.

Basso, M. A. and Liu, P. (2007) 'Context-Dependent Effects of Substantia Nigra Stimulation on Eye Movements', *Journal of Neurophysiology*. United States: American Physiological Society, 97(6), pp. 4129–4142.

Bayer, H. M. and Glimcher, P. W. (2005) 'Midbrain Dopamine Neurons Encode a Quantitative Reward Prediction Error Signal', *Neuron (Cambridge, Mass.)*. United States: Elsevier Inc, 47(1), pp. 129–141.

Bays, P. M. (2014) 'Noise in Neural Populations Accounts for Errors in Working Memory', 34(10), pp. 3632–3645. doi: 10.1523/JNEUROSCI.3204-13.2014.

Bays, P. M. and Husain, M. (2008) 'Dynamic Shifts of Limited Working Memory Resources in Human Vision', *Science*, 321(5890), pp. 851–854.

Becker, W. and Jürgens, R. (1979) 'An Analysis of the saccadic system by menas of double step stimuli', *Vision Res.*, 19(1974), pp. 967–983.

Beierholm, U. *et al.* (2013) 'Dopamine modulates reward-related vigor.', *Neuropsychopharmacology*, 38(8), pp. 1495–503. doi: 10.1038/npp.2013.48.

Beigi, M. *et al.* (2016) 'Levodopa medication improves incidental sequence learning in Parkinson's disease', *Neuropsychologia*. England: Elsevier Ltd, 93(Pt A), pp. 53–60.

Bendiksby, M. S. and Platt, M. L. (2006) 'Neural correlates of reward and attention in macaque area LIP', *Neuropsychologia*. England: Elsevier Ltd, 44(12), pp. 2411–2420.

Beradelli, A. *et al.* (2001) 'Pathophysiology of bradykinesia in Parkinson's disease', *Brain (London, England : 1878)*. Oxford: Oxford University Press, 124(Pt 11), pp. 2131–2146.

Berg, R. Van Den and Ma, W. J. (2018) 'A resource-rational theory of set size effects in human visual working memory', pp. 1–31.

Berg, R. Van Den, Zou, Q. and Ma, W. J. (2020) 'No effect of monetary reward in a visual working memory task', pp. 1–13.

Bhatia, K. P. and Marsden, C. D. D. (1994) 'The behavioural and motor consequences of focal lesions of the basal ganglia in man', *Brain (London, England : 1878)*. England: Oxford University Press (OUP), 117(4), pp. 859–876. doi: 10.1093/brain/117.4.859.

Bibi, R. and Edelman, J. A. (2009) 'The influence of motor training on human express saccade production.', *Journal of neurophysiology*, 102(6), pp. 3101–3110. doi: 10.1152/jn.90710.2008.

Bijleveld, E., Custers, R. and Aarts, H. (2009) 'The Unconscious Eye Opener: Pupil Dilation Reveals Strategic Recruitment of Resources Upon Presentation of Subliminal Reward Cues', *Psychological Science*. SAGE Publications Inc, 20(11), pp. 1313–1315. doi: 10.1111/j.1467-9280.2009.02443.x.

Billino, J., Hennig, J. and Gegenfurtner, K. R. (2017) 'Association between COMT genotype and the control of memory guided saccades : Individual differences in healthy adults reveal a detrimental role of dopamine', *Vision Research*. Elsevier Ltd, 141, pp. 170–180. doi: 10.1016/j.visres.2016.10.001.

Bissonette, G. B. *et al.* (2014) 'Impact of appetitive and aversive outcomes on brain responses: linking the animal and human literatures.', *Frontiers in systems neuroscience*. Switzerland, 8, p. 24. doi: 10.3389/fnsys.2014.00024.

Blaine, D. *et al.* (1996) 'Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking', *Nature genetics*. London: Nature Publishing Group, 12(1), pp. 78–80.

Board, A. G. *et al.* (2019) 'Neurobiology of Aging Dissociable effects of the apolipoprotein-E (APOE) gene on short- and long-term memories',

Neurobiology of aging, 73, pp. 115–122. doi: 10.1016/j.neurobiolaging.2018.09.017.

Bódi, N. *et al.* (2009) 'Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients', *Brain (London, England : 1878)*. England: Oxford University Press, 132(9), pp. 2385–2395.

Bohnen, N. I. *et al.* (2006) 'Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia', *Journal of neurology*. Darmstadt: Steinkopff-Verlag, 253(2), pp. 242–247.

Le Bouc, R. *et al.* (2016) 'Computational Dissection of Dopamine Motor and Motivational Functions in Humans', *The Journal of neuroscience*. United States: Society for Neuroscience, 36(25), pp. 6623–6633.

Braem, S., Duthoo, W. and Notebaert, W. (2013) 'Punishment sensitivity predicts the impact of punishment on cognitive control.', *PloS one*. United States, 8(9), p. e74106. doi: 10.1371/journal.pone.0074106.

Bromberg-Martin, E. S., Matsumoto, M. and Hikosaka, O. (2010) 'Dopamine in motivational control: rewarding, aversive, and alerting.', *Neuron*. United States, 68(5), pp. 815–834. doi: 10.1016/j.neuron.2010.11.022.

Brooks, B. A., Fuchs, A. F. and Finocchio, D. (1986) 'Saccadic eye movement deficits in the MPTP monkey model of Parkinson's disease', *Brain research*. Netherlands: Elsevier B.V, 383(1), pp. 402–407.

Broos, N. *et al.* (2012) 'The Relationship between Impulsive Choice and Impulsive Action: A Cross-Species Translational Study', *PloS one*. United States: Public Library of Science, 7(5), pp. e36781--e36781.

Brown, J. (1958) 'Some tests of the decay theory of immediate memory', *Quarterly journal of experimental psychology*. London: Taylor & Francis Group, 10(1), pp. 12–21.

Brown, L. L., Smith, D. M. and Goldbloom, L. M. (1998) 'Organizing principles of cortical integration in the rat neostriatum: Corticostriate map of the body surface is an ordered lattice of curved laminae and radial points', *Journal of comparative neurology (1911)*. New York:

John Wiley & Sons, Inc, 392(4), pp. 468–488.

Brown, M. R. G. *et al.* (2004) 'Comparison of Memory- and Visually Guided Saccades Using Event-Related fMRI', *Journal of Neurophysiology*. United States: American Physiological Society, 91(2), pp. 873–889.

Brown, R. M., Crane, A. M. and Goldman, P. S. (1979) 'Regional distribution of monoamines in teh cerebral cortex and subcortical strucutres of teh rhesus monkey: Concentrations and in vivo synthesis rates', *Brain Research*, 168, pp. 133–150.

Brown, V. J. and Robbins, T. W. (1991) 'Simple and choice reaction time performance following unilateral striatal dopamine depletion in the rat. Impaired motor readiness but preserved response preparation', *Brain (London, England : 1878)*. England, 114 (Pt 1B)(1), pp. 513–525.

Brozoski, T. *et al.* (1979) 'Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey', *Science (American Association for the Advancement of Science)*. United States: American Association for the Advancement of Science (AAAS), 205(4409), pp. 929–932.

Buhusi, C. V and Meck, W. H. (2005) 'What makes us tick? Functional and neural mechanisms of interval timing', *Nature reviews. Neuroscience*. London: Nature Publishing Group, 6(10), pp. 755–765.

Burak, Y. and Fiete, I. R. (2012) 'Fundamental limits on persistent activity in networks of noisy neurons.', *Proceedings of the National Academy of Sciences of the United States of America*. United States, 109(43), pp. 17645–17650. doi: 10.1073/pnas.1117386109.

Camerer, C. F. and Hogarth, R. M. (1999) 'The Effects of Financial Incentives in Experiments: A Review and Capital-Labor-Production Framework', *Journal of risk and uncertainty*. Boston: Kluwer Academic Publishers, 19(1/3), pp. 7–42.

Cappon, D. *et al.* (2019) 'Ventral tegmental area deep brain stimulation for chronic cluster headache: Effects on cognition, mood, pain report behaviour and quality of life', *Cephalalgia (2019) (In press).*

Carli, M., Evenden, J. L. and Robbins, T. W. (1985) 'Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not

sensory attention', *Nature*, 313(6004), pp. 679–682. doi: 10.1038/313679a0.

Carman, L. S. and Schneider, G. E. (1992) 'Orienting behavior in hamsters with lesions of superior colliculus, pretectum, and visual cortex', *Experimental brain research*. Germany, 90(1), p. 79.

Carolina, Z. and Kowler, E. (1987) 'Planning sequences of saccades', *Vision Res.*, 27(8), pp. 1327–1341.

Carsten, T. *et al.* (2019) 'Are Losses More Effective Than Rewards in Improving Performance in a Cognitive Task?', *Motivation science*. Washington: Educational Publishing Foundation, 5(3), pp. 257–268.

Carter, R. M. *et al.* (2009) 'Activation in the VTA and nucleus accumbens increases in anticipation of both gains and losses', *Frontiers in behavioral neuroscience*. Switzerland: Frontiers Media S.A, 3, p. 21.

Carver, C. S. and White, T. L. (1994) 'Behavioral Inhibition, Behavioral Activation, and Affective Responses to Impending Reward and Punishment: The BIS/BAS Scales', *Journal of personality and social psychology*. American Psychological Association, 67(2), pp. 319–333.

Casey, B. J., Durston, S. and Fossella, J. A. (2001) 'Evidence for a mechanistic model of cognitive control', *Clinical Neuroscience Research*. Elsevier, 1(4), pp. 267–282.

Castner, S. A. (2000) 'Reversal of Antipsychotic-Induced Working Memory Deficits by Short-Term Dopamine D1 Receptor Stimulation', *Science (American Association for the Advancement of Science)*. United States: American Association for the Advancement of Science (AAAS), 287(5460), pp. 2020–2022.

Chan, R. C. K. and Chen, E. Y. H. (2004) 'Blink Rate Does Matter: A Study of Blink Rate, Sustained Attention, and Neurological Signs in Schizophrenia', *The Journal of Nervous and Mental Disease*, 192(11). Available at: https://journals.lww.com/jonmd/Fulltext/2004/11000/Blink_Rate_Does_Matter__A_Study_of_Blink_Rate,.8.aspx.

Chatham, C. H. and Badre, D. (2015) 'Multiple gates on working memory', *Current opinion in behavioral sciences*. Netherlands: Elsevier BV, 1,

pp. 23–31.

Chaudhuri, K. R. and Schapira, A. H. V (2009) 'Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment', *The Lancet Neurology*, 8(5), pp. 464–474. doi: https://doi.org/10.1016/S1474-4422(09)70068-7.

Chen, E. Y. H. *et al.* (1996) 'Blink Rate , Neurocognitive Impairments , and Symptoms in Schizophrenia'.

Chen, L. *et al.* (2013) 'Cognitive regulation of saccadic velocity by reward prospect', *The European journal of neuroscience*. France: Wiley, 38(3), pp. 2434–2444. doi: 10.1111/ejn.12247.

Chen, L. L. *et al.* (2014) 'Monetary reward speeds up voluntary saccades', *Frontiers in Integrative Neuroscience*, 8(June), pp. 1–12. doi: 10.3389/fnint.2014.00048.

Chen, X., Holland, P. and Galea, J. M. (2018) 'The effects of reward and punishment on motor skill learning', *Current Opinion in Behavioral Sciences*. Elsevier Ltd, 20, pp. 83–88. doi: 10.1016/j.cobeha.2017.11.011.

Chéramy, A. *et al.* (1981) 'Involvement of the thalamus in the reciprocal regulation of the two nigrostriatal dopaminergic pathways', *Neuroscience*. United States: Elsevier Ltd, 6(12), pp. 2657,2659-2661,2668.

Chevalier, G. *et al.* (1985) 'Disinhibition as a basic process in the expression of striatal functions. I. The striato-nigral influence on tecto-spinal/tecto-diencephalic neurons', *Brain research*. Netherlands: Elsevier B.V, 334(2), pp. 215–226.

Chiew, K. and Braver, T. (2011) 'Positive Affect Versus Reward: Emotional and Motivational Influences on Cognitive Control', *Frontiers in Psychology*, 2, p. 279. doi: 10.3389/fpsyg.2011.00279.

Chiew, K. S. and Braver, T. S. (2013) 'Temporal dynamics of motivation-cognitive control interactions revealed by high-resolution pupillometry', *Frontiers in Psychology*, 4(JAN). doi: 10.3389/fpsyg.2013.00015.

Chong, T. T.-J. *et al.* (2015) 'Dopamine enhances willingness to exert effort

for reward in Parkinson's disease.', *Cortex; a journal devoted to the study of the nervous system and behavior*. Italy, 69, pp. 40–46. doi: 10.1016/j.cortex.2015.04.003.

Chowdhury, R. *et al.* (2013) 'Dopamine restores reward prediction errors in old age', *Nature neuroscience*. United States: Springer Science and Business Media LLC, 16(5), pp. 648–653.

Cilia, R. and van Eimeren, T. (2011) 'Impulse control disorders in Parkinson's disease: seeking a roadmap toward a better understanding.', *Brain structure & function*, 216(4), pp. 289–299. doi: 10.1007/s00429-011-0314-0.

Codol, O. *et al.* (2020) 'Reward-based improvements in motor control are driven by multiple error-reducing mechanisms Reward-based improvements in motor control are driven by multiple error-reducing mechanisms', *JNeursci*, 10(March).

Compte, A. *et al.* (2000) 'Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model.', *Cerebral cortex (New York, N.Y. : 1991)*. United States, 10(9), pp. 910–923.

Connolly, B. S. and Lang, A. E. (2014) 'Pharmacological Treatment of Parkinson Disease: A Review', *JAMA : the journal of the American Medical Association*. Chicago, IL: American Medical Association, 311(16), pp. 1670–1683.

Cools, R. *et al.* (2001) 'Enhanced or Impaired Cognitive Function in Parkinson's Disease as a Function of Dopaminergic Medication and Task Demands', *Cerebral Cortex*, 11(12), pp. 1136–1143. doi: 10.1093/cercor/11.12.1136.

Cools, R. (2006) 'Dopaminergic modulation of cognitive function-implications for L -DOPA treatment in Parkinson ' s disease', 30, pp. 1–23. doi: 10.1016/j.neubiorev.2005.03.024.

Cools, R. *et al.* (2010) 'Enhanced frontal function in Parkinson's disease', *Brain (London, England : 1878)*. England: Oxford University Press, 133(1), pp. 225–233.

Cools, R. and D'Esposito, M. (2011) 'Inverted-U – Shaped Dopamine

Actions on Human Working Memory and Cognitive Control', *BPS*. Elsevier Inc., 69(12), pp. e113–e125. doi: 10.1016/j.biopsych.2011.03.028.

Cotzias, G. C., Papavasiliou, P. S. and Gellene, R. (1969) 'Modification of Parkinsonism — Chronic Treatment with L-Dopa', *New England Journal of Medicine*, 280(7), pp. 337–345. doi: 10.1056/NEJM196902132800701.

Cotzias, G. C., Van Woert, M. H. and Schiffer, L. M. (1967) 'Aromatic Amino Acids and Modification of Parkinsonism', *New England Journal of Medicine*, 276(7), pp. 374–379. doi: 10.1056/NEJM196702162760703.

Craig, A. D. (2002) 'How do you feel? Interoception: the sense of the physiological condition of the body', *Nature reviews. Neuroscience*. England: Nature Publishing Group, 3(8), pp. 655–666.

Craig, A. D. (2009) 'How do you feel - now? The anterior insula and human awareness', *Nature reviews. Neuroscience*. London: Nature Publishing Group, 10(1), pp. 59–70.

Crawford, T. J. *et al.* (1995) 'Saccadic abnormalities in psychotic patients . II . The role of neuroleptic treatment', pp. 473–483.

Crawford, T. J., Henderson, L. and Kennard, C. (1989) 'Abnormalities of nonvisuall-guided eye movements in Parkinson's disease', *Brain*, 112(6), pp. 1573–1586. doi: 10.1093/brain/112.6.1573.

Crevits, L. *et al.* (2000) 'Antisaccadic Effects of a Dopamine Agonist as Add-On Therapy in Advanced Parkinson's Patients', *Neuropsychobiology*. Basel, Switzerland: S. Karger AG, 42(4), pp. 202–206.

Crocker, A. D. (1997) 'The regulation of motor control: an evaluation of the role of dopamine receptors in the substantia nigra.', *Reviews in the neurosciences*. Germany, 8(1), pp. 55–76.

Cunnington, R. *et al.* (2002) 'The Preparation and Execution of Self-Initiated and Externally-Triggered Movement: A Study of Event-Related fMRI', *NeuroImage (Orlando, Fla.)*. United States: Elsevier Inc, 15(2), pp. 373–385.

Dahlstroem, A. and Fuxe, K. (1964) 'Evidence for the existence of

monoamine-containing neurons in the central nervous system', *Acta physiologica Scandinavica. Supplementum*. England, 62, pp. 1–55.

Dambacher, M., Hübner, R. and Schlösser, J. (2011) 'Monetary incentives in speeded perceptual decision: effects of penalizing errors versus slow responses', *Frontiers in psychology*. Switzerland: Frontiers Media S.A, 2, p. 248.

Dang, L. C. *et al.* (2017) 'Spontaneous Eye Blink Rate (EBR) Is Uncorrelated with Dopamine D2 Receptor Availability and Unmodulated by Dopamine Agonism in Healthy Adults', 4(October).

Davis, M. *et al.* (2010) 'Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety', *Neuropsychopharmacology (New York, N.Y.)*. England: Nature Publishing Group, 35(1), pp. 105–135.

Daw, N. D., Kakade, S. and Dayan, P. (2002) 'Opponent interactions between serotonin and dopamine', *Neural networks*. United States: Elsevier BV, 15(4–6), pp. 603–616.

Dayan, P. and Balleine, B. W. (2002) 'Reward, Motivation and Reinforcement Learning', *Neuron*, 36(10), pp. 285–298.

Delaville, C., De Deurwaerdère, P. and Benazzouz, A. (2011) 'Noradrenaline and Parkinson's Disease', *Frontiers in Systems Neuroscience*, 5, p. 31. doi: 10.3389/fnsys.2011.00031.

Delgado, M. R. (2007) 'Reward-Related Responses in the Human Striatum', *Annals of the New York Academy of Sciences*. Malden, USA: Blackwell Publishing, 1104(1), pp. 70–88.

Delgado, M. R. *et al.* (2008) 'The role of the striatum in aversive learning and aversive prediction errors', *Philosophical transactions. Biological sciences*. England: The Royal Society, 363(1511), pp. 3787–3800.

Deniau, J. M. and Chevalier, G. (1985) 'Disinhibition as a basic process in the expression of striatal functions. II. The striato-nigral influence on thalamocortical cells of the ventromedial thalamic nucleus', *Brain research*. Netherlands: Elsevier BV, 334(2), pp. 227–233.

Denk, F. *et al.* (2004) 'Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort',

Psychopharmacology (Berlin, Germany). Berlin/Heidelberg: Springer Science and Business Media LLC, 179(3), pp. 587–596.

Denny-Brown, D. (1968) 'Clinical symptomatology of diseases of the basal ganglia', *Handbook of clinical neurology*. North-Holland Amsterdam, 6, pp. 133–172.

Desmurget, M. and Turner, R. S. (2010) 'Motor sequences and the basal ganglia: kinematics, not habits', *The Journal of neuroscience*. United States: Society for Neuroscience, 30(22), pp. 7685–7690.

Devesse, S. and Olivier, E. (2016) 'Dopamine Manipulation Affects Response Vigor', 36(37), pp. 9516–9525. doi: 10.1523/JNEUROSCI.4467-15.2016.

Ding, L. and Hikosaka, O. (2007) 'Temporal Development of Asymmetric Reward-Induced Bias in Macaques', *Journal of Neurophysiology*. United States: Am Phys Soc, 97(1), pp. 57–61.

Ditterich, J., Eggert, T. and Straube, A. (1998) 'Fixation errors and timing in sequences of memory-guided saccades', 95, pp. 205–217.

Dodge, R. (1903) 'Five types of eye movment in the horizontal meridian plane of the field of regard', *American Journal of Physiology*, (8), pp. 307–329.

Dolan, R., Singer, T. and Seymour, B. (2007) 'The neurobiology of punishment', *Nature reviews. Neuroscience*. England: Nature Publishing Group, 8(4), pp. 300–311.

Doughty, M. J. (2001) 'Consideration of three types of spontaneous eyeblink activity in normal humans: during reading and video display terminal use, in primary gaze, and while in conversation.', *Optometry and vision science : official publication of the American Academy of Optometry*. United States, 78(10), pp. 712–725. doi: 10.1097/00006324-200110000-00011.

Doya, K. (2008) 'Modulators of decision making', *Nature neuroscience*. United States: Springer Science and Business Media LLC, 11(4), pp. 410–416.

Duka, T. and Lupp, A. (1997) 'The effects of incentive on antisaccades: is a dopaminergic mechanism involved?', *Behavioural pharmacology*.

England, 8(5), pp. 373–382.

Durstewitz, D. and Seamans, J. K. (2002) 'The computational role of dopamine D1 receptors in working memory', *Neural networks*. United States: Elsevier Ltd, 15(4), pp. 561–572.

Eckart, C. *et al.* (2014) 'Dopaminergic stimulation facilitates working memory and differentially affects prefrontal low theta oscillations', *NeuroImage (Orlando, Fla.)*. United States: Elsevier BV, 94, pp. 185–192.

Eckstein, M. K. *et al.* (2017) 'Beyond eye gaze: What else can eyetracking reveal about cognition and cognitive development?', *Developmental cognitive neuroscience*. Netherlands, 25, pp. 69–91. doi: 10.1016/j.dcn.2016.11.001.

Elsworth, D. and Nichols, E. (1991) 'D1 and D2 Dopamine Receptors Independently Regulate Spontaneous Blink Rate in the Vervet Monkey1', pp. 595–600.

Engelmann, J. B. and Pessoa, L. (2007) 'Motivation Sharpens Exogenous Spatial Attention', *Emotion (Washington, D.C.)*. United States: American Psychological Association, 7(3), pp. 668–674.

Ernst, M. *et al.* (2004) 'Choice selection and reward anticipation: an fMRI study', *Neuropsychologia*. England: Elsevier BV, 42(12), pp. 1585–1597.

Erro, R., Bhatia, K. P. and Tinazzi, M. (2015) 'Parkinsonism following neuroleptic exposure: A double-hit hypothesis?', *Movement Disorders*, 00(00), p. n/a-n/a. doi: 10.1002/mds.26209.

Everitt, B. J. *et al.* (2003) 'Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning', *Annals of the New York Academy of Sciences*. United States, 985(1), pp. 233–250.

Evinger, C. (2010) 'Eyelid Anatomy and the Pathophysiology of Blinking', in.

Fallon, J. H. (1988) 'Topographic organization of ascending dopaminergic projections', *Annals of the New York Academy of Sciences*. United States, 537(1 The Mesocorti), pp. 1–9.

Fallon, J. H. and Loughlin, S. E. (1995) 'Substantia nigra, In The Rat Nervous System (2nd edn)', *Academic Press*, pp. 215–237.

Fallon, S. J. *et al.* (2017) 'Dopamine Alters the Fidelity of Working Memory

Representations according to Attentional Demands', pp. 728–738. doi: 10.1162/jocn.

Fallon, S. J. *et al.* (2019) 'Dopamine affects short-term memory corruption over time in Parkinson ' s disease', *npj Parkinson's Disease*. Springer US, (June). doi: 10.1038/s41531-019-0088-2.

Fan, J. *et al.* (2008) 'Searching for the majority: algorithms of voluntary control', *PloS one*. United States: Public Library of Science, 3(10), pp. e3522--e3522.

Fan, J. (2014) 'An information theory account of cognitive control', *Frontiers in human neuroscience*. Switzerland: Frontiers Media SA, 8, p. 680.

Fellows, L. K. (2018) 'The Neuroscience of Human Decision-Making Through the Lens of Learning and Memory.', *Current topics in behavioral neurosciences*. Germany, 37, pp. 231–251. doi: 10.1007/7854_2016_468.

Fernando, A. B. P. *et al.* (2012) 'Modulation of high impulsivity and attentional performance in rats by selective direct and indirect dopaminergic and noradrenergic receptor agonists', *Psychopharmacology*, 219(2), pp. 341–352. doi: 10.1007/s00213-011-2408-z.

Fischer, H. *et al.* (2010) 'Simulating Neurocognitive Aging: Effects of a Dopaminergic Antagonist on Brain Activity During Working Memory', *Biological psychiatry (1969)*. United States: Elsevier Inc, 67(6), pp. 575–580.

Floresco, S. B. and Costa, V. D. (2013) 'Prefrontal dopamine and behavioral flexibility : shifting from an " inverted-U " toward a family of functions', 7(April), pp. 1–13. doi: 10.3389/fnins.2013.00062.

Floresco, S. B. and Magyar, O. (2006) 'Mesocortical dopamine modulation of executive functions : beyond working memory', pp. 567–585. doi: 10.1007/s00213-006-0404-5.

Frank, M. J. and O'Reilly, R. C. (2006) 'A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol.', *Behavioral neuroscience*. United States, 120(3), pp. 497–517. doi: 10.1037/0735-

7044.120.3.497.

Frank, M. J., Seeberger, L. C. and O'Reilly, R. C. (2004) 'By carrot or by stick: cognitive reinforcement learning in parkinsonism.', *Science (New York, N.Y.)*. United States, 306(5703), pp. 1940–1943. doi: 10.1126/science.1102941.

French, E. D. (1986) 'Effects of N-allylnormetazocine (SKF 10,047), phencyclidine, and other psychomotor stimulants in the rat following 6-hydroxydopamine lesion of the ventral tegmental area.', *Neuropharmacology*. England, 25(4), pp. 447–450. doi: 10.1016/0028-3908(86)90241-8.

Fried, M. *et al.* (2014) 'ADHD subjects fail to suppress eye blinks and microsaccades while anticipating visual stimuli but recover with medication', *Vision research*. Elsevier Ltd, 101, pp. 62–72. doi: 10.1016/j.visres.2014.05.004.

Friend, D. M. and Kravitz, A. V (2014) 'Working together: basal ganglia pathways in action selection.', *Trends in neurosciences*, 37(6), pp. 301–303. doi: 10.1016/j.tins.2014.04.004.

Friston, K. (2009) 'The free-energy principle : a rough guide to the brain ?', pp. 293–301. doi: 10.1016/j.tics.2009.04.005.

Friston, K. (2010) 'The free-energy principle: a unified brain theory?', *Nat Rev Neurosci*. Nature Publishing Group, 11(2), pp. 127–138. Available at: http://dx.doi.org/10.1038/nrn2787.

Friston, K. J. *et al.* (2012) 'Dopamine , Affordance and Active Inference', 8(1). doi: 10.1371/journal.pcbi.1002327.

Fröber, K. and Dreisbach, G. (2014) 'The differential influences of positive affect, random reward, and performance-contingent reward on cognitive control', *Cognitive, affective, & behavioral neuroscience*. New York: Springer US, 14(2), pp. 530–547.

Fuchs, A. F., Kaneko, C. R. and Scudder, C. A. (1985) 'Brainstem control of saccadic eye movements', *Annual review of neuroscience*. United States, 8(1), pp. 307–337.

Fuller, J. H. (1996) 'Eye position and target amplitude effects on human visual saccadic latencies', (October 1995), pp. 457–466.

Furlanetti, L. L., Coenen, V. A. and Döbrössy, M. D. (2016) 'Ventral tegmental area dopaminergic lesion-induced depressive phenotype in the rat is reversed by deep brain stimulation of the medial forebrain bundle'. Elsevier B.V., 299, pp. 132–140.

Fuster, J. M. (1973) 'Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory.', *Journal of neurophysiology*. United States, 36(1), pp. 61–78. doi: 10.1152/jn.1973.36.1.61.

Galea, J. M. *et al.* (2012) 'Action Reprogramming in Parkinson ' s Disease : Response to Prediction Error Is Modulated by Levels of Dopamine', 32(2), pp. 542–550. doi: 10.1523/JNEUROSCI.3621-11.2012.

Galea, J. M. *et al.* (2015) 'The dissociable effects of punishment and reward on motor learning.', *Nature neuroscience*. United States, 18(4), pp. 597–602. doi: 10.1038/nn.3956.

Gardner, E. L. (2011) 'Addiction and Brain Reward and Antireward Pathways', *Chronic Pain and Addiction*. Basel, Switzerland: S. Karger AG (Advances in Psychosomatic Medicine), 30, pp. 22–60.

Gasbarri, A. *et al.* (1996) 'Spatial memory impairment induced by lesion of the mesohippocampal dopaminergic system in the rat', *Neuroscience*, 74(4), pp. 1037–1044.

Gaymard, B., Pierrot-Deseilligny, C. and Rivaud, S. (1990) 'Impairment of sequences of memory-guided saccades after supplementary motor area lesions', *Annals of neurology*. Hoboken: Wiley Subscription Services, Inc., A Wiley Company, 28(5), pp. 622–626.

Gerfen, C. R., Herkenham, M. and Thibault, J. (1987) 'The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems', *The Journal of neuroscience*. United States: Soc Neuroscience, 7(12), pp. 3915–3934.

Ghilardi, M. F. *et al.* (2006) 'L-Dopa infusion does not improve explicit sequence learning in Parkinson's disease', *Parkinsonism & related disorders*. England: Elsevier Ltd, 13(3), pp. 146–151.

Gibson, J. M., Pimlott, R. and Kennard, C. (1987) 'Ocular motor and manual tracking in Parkinson's disease and the effect of treatment', *Journal*

of neurology, neurosurgery and psychiatry. England: BMJ Publishing Group LTD, 50(7), pp. 853–860. doi: 10.1136/jnnp.50.7.853.

Van Gisbergen, J. A., Robinson, D. A. and Gielen, S. (1981) 'A quantitative analysis of generation of saccadic eye movements by burst neurons', *Journal of neurophysiology*. United States: American Physiological Society, 45(3), pp. 417–442.

Glimcher, P. W. (2011) 'Understanding dopamine and reinforcement learning: The dopamine reward prediction error hypothesis', *PNAS*, 108(42), pp. 15647–15654. doi: 10.1073/pnas.1115170108.

Gnadt, J. W. *et al.* (1997) 'Influence of the superior colliculus on the primate blink reflex', *Experimental Brain Research*, 116(3), pp. 389–398. doi: 10.1007/PL00005767.

Gold, J. I. and Shadlen, M. N. (2007) 'The Neural Basis of Decision Making', *Annual Review of Neuroscience*, 30(1), pp. 535–574. doi: 10.1146/annurev.neuro.29.051605.113038.

Gong, M. and Li, S. (2014) 'Learned Reward Association Improves Visual Working Memory', *Journal of experimental psychology. Human perception and performance*. United States: American Psychological Association, 40(2), pp. 841–856.

Gotham, A. M., Brown, R. G. and Marsden, C. D. (1988) '"Frontal" cognitive function in patients with Parkinson's disease "on" and "off" levodopa', *Brain (London, England : 1878)*. England, 111 (Pt 2), pp. 299–321.

Gottlieb, J. (2012) 'Attention, Learning, and the Value of Information', *Neuron (Cambridge, Mass.)*. United States: Elsevier Inc, 76(2), pp. 281–295.

Grabenhorst, F., Rolls, E. T. and Parris, B. A. (2008) 'From affective value to decision-making in the prefrontal cortex', *The European journal of neuroscience*. Oxford, UK: Blackwell Publishing Ltd, 28(9), pp. 1930–1939.

Graef, S. *et al.* (2010) 'Differential influence of levodopa on reward-based learning in Parkinson's disease', *Frontiers in human neuroscience*. Switzerland: Frontiers Research Foundation, 4, p. 169.

Gray, J. A. (1973) ‘Causal theories of personality and how to test them’, *London: Academic Press*.

Graybiel, A. M. (1997) ‘The basal ganglia and cognitive pattern generators’, *Schizophrenia bulletin*. Oxford University Press, 23(3), pp. 459–469.

Green, L. and Myerson, J. (2004) ‘A Discounting Framework for Choice With Delayed and Probabilistic Rewards’, *Psychological bulletin*. United States: American Psychological Association, 130(5), pp. 769–792.

Griffiths, T. L., Lieder, F. and Goodman, N. D. (2015) ‘Rational use of cognitive resources: levels of analysis between the computational and the algorithmic.’, *Topics in cognitive science*. United States, 7(2), pp. 217–229. doi: 10.1111/tops.12142.

Grogan, J. P. *et al.* (2017) ‘Effects of dopamine on reinforcement learning and consolidation in Parkinson’s disease’, *eLife*. Edited by J. I. Gold. eLife Sciences Publications, Ltd, 6, p. e26801. doi: 10.7554/eLife.26801.

Grogan, J. P. *et al.* (2020) ‘Dopamine promotes instrumental motivation , but reduces reward-related vigour’, *eLife*, pp. 1–20.

Gruber, A. J. *et al.* (2006) ‘Dopamine modulation in the basal ganglia locks the gate to working memory’, *Journal of computational neuroscience*. Boston: Kluwer Academic Publishers, 20(2), pp. 153–166.

Guitart-masip, A. M. *et al.* (2012) ‘Action controls dopaminergic enhancement of reward representations’, 109(19), pp. 7511–7516. doi: 10.1073/pnas.

Guitart-masip, M. *et al.* (2011) ‘Vigor in the Face of Fluctuating Rates of Reward : An Experimental Examination’, pp. 3933–3938.

Guitart-Masip, M. *et al.* (2014) ‘Action versus valence in decision making’, *Trends in cognitive sciences*. England: Elsevier BV, 18(4), pp. 194–202.

Gurney, K., Prescott, T. J. and Redgrave, P. (2001) ‘A computational model of action selection in the basal ganglia. I. A new functional anatomy’, *Biological Cybernetics*, 84(6), pp. 401–410. doi: 10.1007/PL00007984.

Guttman, M. *et al.* (2007) ‘Brain serotonin transporter binding in non-

depressed patients with Parkinson's disease.', *European journal of neurology*. England, 14(5), pp. 523–528. doi: 10.1111/j.1468-1331.2007.01727.x.

Haber, S. N., Fudge, J. L. and McFarland, N. R. (2000) 'Striatonigrostriatal Pathways in Primates Form an Ascending Spiral from the Shell to the Dorsolateral Striatum', *The Journal of neuroscience*. United States: Society for Neuroscience, 20(6), pp. 2369–2382.

Haber, S. N. and Knutson, B. (2010) 'The Reward Circuit: Linking Primate Anatomy and Human Imaging', *Neuropsychopharmacology (New York, N.Y.)*. England: Nature Publishing Group, 35(1), pp. 4–26.

Hagelberg, N., Forssell, H., Aalto, S., *et al.* (2003) 'Altered dopamine D2 receptor binding in atypical facial pain', *Pain (Amsterdam)*. United States: Elsevier B.V, 106(1), pp. 43–48.

Hagelberg, N., Forssell, H., Rinne, J. O., *et al.* (2003) 'Striatal dopamine D1 and D2 receptors in burning mouth syndrome', *Pain (Amsterdam)*. United States: Elsevier B.V, 101(1), pp. 149–154.

Hagger, M. S. *et al.* (2010) 'Ego depletion and the strength model of self-control: a meta-analysis.', *Psychological bulletin*. United States, 136(4), pp. 495–525. doi: 10.1037/a0019486.

Hand, T. H. and Franklin, K. B. (1985) '6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation.', *Brain research*. Netherlands, 328(2), pp. 233–241. doi: 10.1016/0006-8993(85)91034-0.

Harris, C. M. and Wolpert, D. M. (1998) 'Signal-dependent noise determines motor planning.', *Nature*, 394(6695), pp. 780–4. doi: 10.1038/29528.

Harris, C. M. and Wolpert, D. M. (2006) 'The main sequence of saccades optimizes speed-accuracy trade-off.', *Biological cybernetics*. Germany, 95(1), pp. 21–29. doi: 10.1007/s00422-006-0064-x.

Haven, N. and Goldman-Rakic, P. S. (1995) 'Cellular basis of working memory', *Neuron (Cambridge, Mass.)*. United States: Elsevier BV, 14(3), pp. 477–485.

Hawkins, G. *et al.* (2012) 'Context Effects in Multi-Alternative Decision Making: Empirical Data and a Bayesian Model', *Cognitive science*.

Oxford, UK: Wiley, 36(3), pp. 498–516.

Hayhoe, M. and Ballard, D. (2005) ‘Eye movements in natural behavior’, *Trends in cognitive sciences*. England: Elsevier BV, 9(4), pp. 188–194.

Helms, P. M. and Godwin, C. D. (1985) ‘Abnormalities of Blink Rate in Psychoses " A Preliminary Report’, (1919), pp. 103–106.

Hermens, F. and Walker, R. (2010) ‘Gaze and arrow distractors influence saccade trajectories similarly’, 63(11), pp. 2120–2140. doi: 10.1080/17470211003718721.

Le Heron, C. J., MacAskill, M. R. and Anderson, T. J. (2005) ‘Memory-guided saccades in Parkinson’s disease: Long delays can improve performance’, *Experimental Brain Research*, 161(3), pp. 293–298. doi: 10.1007/s00221-004-2071-2.

Heywood, S. and Churcher, J. (1980) ‘Structure of the visual array and saccadic latency: implications for oculomotor control’, *Quarterly journal of experimental psychology*. England: Taylor & Francis Group, 32(2), pp. 335–341.

Hick, W. (1952) ‘On the rate of gain of information in children’, *Quarterly Journal of Experimental Psychology*, 4(1), pp. 11–26. doi: 10.1016/0022-0965(78)90002-4.

Hickey, C. and van Zoest, W. (2012) ‘Reward creates oculomotor salience’, *Current biology*. England: Elsevier Inc, 22(7), pp. R219--R220.

Hikida, T. *et al.* (2010) ‘Distinct Roles of Synaptic Transmission in Direct and Indirect Striatal Pathways to Reward and Aversive Behavior’, *Neuron (Cambridge, Mass.)*. United States: Elsevier Inc, 66(6), pp. 896–907.

Hikosaka, O. (1989) ‘Role of basal ganglia in saccades.’, *Revue neurologique*. France, 145(8–9), pp. 580–586.

Hikosaka, O. *et al.* (2013) ‘Why skill matters’, *Trends in cognitive sciences*. England: Elsevier BV, 17(9), pp. 434–441.

Hikosaka, O., Nakamura, K. and Nakahara, H. (2019) ‘Basal Ganglia Orient Eyes to Reward’, pp. 567–584. doi: 10.1152/jn.00458.2005.

Hill, P. D. T. J. A. and Keller, K. L. E. L. (2008) ‘Behavioral properties of saccades generated as a choice response’, pp. 355–364. doi: 10.1007/s00221-007-1239-y.

Hodgson, T. L. *et al.* (1999) 'Eye movements and spatial working memory inParkinsons disease', *Neuropsychologia*, 37(8), pp. 927–938. doi: https://doi.org/10.1016/S0028-3932(98)00151-1.

du Hoffmann, J. and Nicola, S. M. (2014) 'Dopamine invigorates reward seeking by promoting cue-evoked excitation in the nucleus accumbens.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*. United States, 34(43), pp. 14349–14364. doi: 10.1523/JNEUROSCI.3492-14.2014.

Hollerman, J. R., Tremblay, L. and Schultz, W. (2000) 'Involvement of basal ganglia and orbitofrontal cortex in goal-directed behavior', *Progress in Brain Research*. Netherlands: Elsevier Science & Technology, 126, pp. 193–215.

Holroyd, C. B. and McClure, S. M. (2015) 'Hierarchical control over effortful behavior by rodent medial frontal cortex: A computational model.', *Psychological review*. United States, 122(1), pp. 54–83. doi: 10.1037/a0038339.

Hood, A. J. *et al.* (2007) 'Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease', *Journal of neurology, neurosurgery and psychiatry*. England: BMJ, 78(6), pp. 565–570. doi: 10.1136/jnnp.2006.099754.

Horak, F. B. and Anderson, M. E. (1984) 'Influence of globus pallidus on arm movements in monkeys. II. Effects of stimulation', *Journal of neurophysiology*. Bethesda, MD: Am Phys Soc, 52(2), pp. 305–322.

Hotson, J. R., Langston, E. B. and Langston, J. W. (1986) 'Saccade Responses to Dopamine in Human MFP-Induced Parkinsonism', pp. 456–463.

Houk, J. C. *et al.* (2007) 'Action selection and refinement in subcortical loops through basal ganglia and cerebellum', *Philosophical transactions. Biological sciences*. England: The Royal Society, 362(1485), pp. 1573–1583.

Hu, H. (2016) 'Reward and Aversion', *Annual review of neuroscience*. United States: Annual Reviews, 39(1), pp. 297–324.

Hübner, R. and Schlösser, J. (2010) 'Monetary reward increases attentional

effort in the flanker task', *Psychonomic Bulletin & Review*, 17(6), pp. 821–826. doi: 10.3758/PBR.17.6.821.

Humphries, M. D., Stewart, R. D. and Gurney, K. N. (2006) 'A Physiologically Plausible Model of Action Selection and Oscillatory Activity in the Basal Ganglia', *The Journal of neuroscience*. United States: Soc Neuroscience, 26(50), pp. 12921–12942.

Husain, M. and Roiser, J. P. (2018) 'Neuroscience of apathy and anhedonia : a transdiagnostic approach', *Nature Reviews Neuroscience*. Springer US, 19(August). doi: 10.1038/s41583-018-0029-9.

Hutton, S. B. *et al.* (2002) 'Saccadic distractibility in first-episode schizophrenia', *Neuropsychologia*, 40(10), pp. 1729–1736. doi: https://doi.org/10.1016/S0028-3932(01)00145-2.

Ingle, D. (1973) 'Evolutionary Perspectives on the Function of the Optic Tectum (Part 1 of 2)', *Brain, behavior and evolution*. Basel, Switzerland, 8(3), pp. 211–223.

Inzlicht, M., Shenhav, A. and Olivola, C. Y. (2018) 'The Effort Paradox: Effort Is Both Costly and Valued.', *Trends in cognitive sciences*. England, 22(4), pp. 337–349. doi: 10.1016/j.tics.2018.01.007.

Jääskeläinen, S. K. *et al.* (2001) 'Role of the dopaminergic system in chronic pain – a fluorodopa-PET study', *Pain (Amsterdam)*. United States: Elsevier B.V, 90(3), pp. 257–260.

Jazbec, S. *et al.* (2005) 'Cognitive control under contingencies in anxious and depressed adolescents: an antisaccade task.', *Biological psychiatry*. United States, 58(8), pp. 632–639. doi: 10.1016/j.biopsych.2005.04.010.

Jazbec, S. *et al.* (2006) 'Age-related influence of contingencies on a saccade task.', *Experimental brain research*. Germany, 174(4), pp. 754–762. doi: 10.1007/s00221-006-0520-9.

Jenkins, I. H. *et al.* (2000) 'Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow', *Brain (London, England : 1878)*. England, 123 (Pt 6), pp. 1216–1228.

Jensen, J. *et al.* (2003) 'Direct Activation of the Ventral Striatum in

Anticipation of Aversive Stimuli', *Neuron (Cambridge, Mass.)*. United States: Elsevier BV, 40(6), pp. 1251–1257.

Jiang, Y., Kim, S.-I. and Bong, M. (2014) 'Effects of reward contingencies on brain activation during feedback processing', *Frontiers in human neuroscience*. Switzerland: Frontiers Research Foundation, 8, p. 656.

Jongkees, B. J. and Colzato, L. S. (2016) 'Spontaneous eye blink rate as predictor of dopamine-related cognitive function — A review', *Neuroscience and Biobehavioral Reviews*. Elsevier Ltd, 71, pp. 58–82. doi: 10.1016/j.neubiorev.2016.08.020.

Joti, P. *et al.* (2007) 'Impaired inhibitory oculomotor control in patients with Parkinson's disease', *Experimental brain research*. Berlin/Heidelberg: Springer-Verlag, 177(4), pp. 447–457.

Juras, G., Slomka, K. and Latash, M. (2009) 'Violations of Fitts' Law in a Ballistic Task', *Journal of Motor Behavior*. Routledge, 41(6), pp. 525–528. doi: 10.3200/35-08-015.

Jurkowlaniec, E., Tokarski, J. and Trojniar, W. (2003) 'Effect of unilateral ibotenate lesions of the ventral tegmental area on cortical and hippocampal EEG in freely behaving rats', pp. 369–375.

Kable, J. W. and Glimcher, P. W. (2007) 'The neural correlates of subjective value during intertemporal choice', *Nature neuroscience*. United States: Springer Science and Business Media LLC, 10(12), pp. 1625–1633.

Kahneman, D. (2003) 'A Perspective on Judgment and Choice: Mapping Bounded Rationality', *The American psychologist*. United States: American Psychological Association, 58(9), pp. 697–720.

Kahneman, D. and Tversky, A. (1979) 'Prospect Theory: An Analysis of Decision under Risk', *Econometrica*, 47(2), pp. 263–291.

Kaminer, J., Powers, A. and Evinger, C. (2011) 'Characterizing The Spontaneous Blink Generator: An Animal Model', *J Neurosci.*, 31(August), pp. 11256–11267. doi: 10.1523/JNEUROSCI.6218-10.2011.

Karson, C. *et al.* (1981) 'Neuroleptics decrease blinking in schizophrenic subjects.', *Biological psychiatry*. Elsevier Science.

Karson, C. N. *et al.* (1982) 'Haloperidol-Induced Changes in Blink Rates Correlate with Changes in BPRS Score', *British Journal of Psychiatry*. Cambridge University Press, 140(5), pp. 503–507. doi: 10.1192/bjp.140.5.503.

Karson, C. N. (1983) 'Spontaneous eye-blink rates and dopaminergic systems.', *Brain : a journal of neurology*. England, 106 (Pt 3), pp. 643–653. doi: 10.1093/brain/106.3.643.

Karson, C. N., Dykman, R. A. and Paige, S. R. (1990) 'Blink Rates in Schizophrenia', *Schizophrenia Bulletin*, 16(2), pp. 345–354. doi: 10.1093/schbul/16.2.345.

Kato, M. *et al.* (1995) 'Eye movements in monkeys with local dopamine depletion in the caudate nucleus. I. Deficits in spontaneous saccades', *The Journal of neuroscience*. United States: Society for Neuroscience, 15(1), pp. 912–927.

Kawagoe, R., Takikawa, Y. and Hikosaka, O. (1998) 'Expectation of reward modulates cognitive signals in the basal ganglia', *Nature neuroscience*. United States: Springer Science and Business Media LLC, 1(5), pp. 411–416.

Kawasaki, M. and Yamaguchi, Y. (2013) 'Frontal theta and beta synchronizations for monetary reward increase visual working memory capacity.', *Social cognitive and affective neuroscience*, 8(5), pp. 523–530. doi: 10.1093/scan/nss027.

Keller, K. L. E. L. and Heinen, S. J. (2005) 'Properties of saccades generated as a choice response', *Exp Brain Res*, 162, pp. 278–286. doi: 10.1007/s00221-004-2186-5.

Kennerley, S. W. and Wallis, J. D. (2009) 'Reward-Dependent Modulation of Working Memory in Lateral Prefrontal Cortex', 29(10), pp. 3259–3270. doi: 10.1523/JNEUROSCI.5353-08.2009.

Kim, H. F. and Hikosaka, O. (2015) 'Parallel basal ganglia circuits for voluntary and automatic behaviour to reach rewards', *Brain*, 138(7), pp. 1776–1800. doi: 10.1093/brain/awv134.

Kim, Y.-J. *et al.* (2016) 'STEP signaling pathway mediates psychomotor stimulation and morphine withdrawal symptoms, but not for reward,

analgesia and tolerance', *Experimental & molecular medicine*. United States: Springer Nature B.V, 48(2), pp. e212--e212.

King, D. J. and Bell, P. (1990) 'Differential-Effects of temazepam and haloperidol on saccadic eye-movements and psychomotor performance', *British Journal of Clinical Pharmacology*, 29(5), pp. 590–590.

Klemmer, E. T. (1956) 'Time uncertainty in simple reaction time', *Journal of experimental psychology*, 51(3), pp. 3–8.

Kleven, M. S. and Koek, W. (1996) 'Differential effects of direct and indirect dopamine agonists on eye blink rate in cynomolgus monkeys.', *Journal of Pharmacology and Experimental Therapeutics*, 279(3), pp. 1211 LP – 1219. Available at: http://jpet.aspetjournals.org/content/279/3/1211.abstract.

Knecht, S. *et al.* (2004) 'Levodopa: Faster and better word learning in normal humans', *Annals of neurology*. Hoboken: Wiley, 56(1), pp. 20–26. doi: 10.1002/ana.20125.

Knolle, F. *et al.* (2018) 'Brain responses to different types of salience in antipsychotic naïve fi rst episode psychosis : An fMRI study', *Translational Psychiatry*. Springer US, pp. 1–13. doi: 10.1038/s41398-018-0250-3.

Koechlin, E. and Burnod, Y. (1996) 'Dual Population Coding in the Neocortex: A Model of Interaction between Representation and Attention in the Visual Cortex', *Journal of cognitive neuroscience*. United States: MIT Press, 8(4), pp. 353–370.

Koepp, M. J. *et al.* (1998) 'Evidence for striatal dopamine release during a video game', *Nature (London)*. England: Springer Science and Business Media LLC, 393(6682), pp. 266–268.

Koob, G. F., Stinus, L. and Le Moal, M. (1981) 'Hyperactivity and hypoactivity produced by lesions to the mesolimbic dopamine system.', *Behavioural brain research*. Netherlands, 3(3), pp. 341–359. doi: 10.1016/0166-4328(81)90004-8.

Korponay, C. *et al.* (2018) 'Neurobiological correlates of impulsivity in healthy adults: lower prefrontal gray matter volume and spontaneous

eye-blink rate but greater resting-state functional connectivity in basal ganglia- thalamo-cortical circuitry', *NeuroImage*, 157, pp. 288–296. doi: 10.1016/j.neuroimage.2017.06.015.Neurobiological.

Koziol, L. (2014) 'Cognitive Control, Reward, and the Basal Ganglia', in, pp. 61–64. doi: 10.1007/978-3-319-04477-4_18.

Kravitz, A. V and Kreitzer, A. C. (2012) 'Striatal mechanisms underlying movement, reinforcement, and punishment.', *Physiology (Bethesda, Md.)*, 27(3), pp. 167–177. doi: 10.1152/physiol.00004.2012.

Krawczyk, D. C. and D'Esposito, M. (2013) 'Modulation of working memory function by motivation through loss-aversion', *Human brain mapping*. Hoboken: Wiley Subscription Services, Inc., A Wiley Company, 34(4), pp. 762–774.

Krebs, R. M. *et al.* (2011) 'The Neural Underpinnings of How Reward Associations Can Both Guide and Misguide Attention', *The Journal of Neuroscience*, 31(26), pp. 9752 LP – 9759. doi: 10.1523/JNEUROSCI.0732-11.2011.

Kuhn, G. and Kingstone, A. (2009) 'Look away! Eyes and arrows engage oculomotor responses automatically', *Attention, Perception & Psychopathies*, 71(2), pp. 314–327. doi: 10.3758/APP.

Kulisevsky, J. *et al.* (2000) 'Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: A two-year follow-up study of previously untreated patients', *Movement disorders*. New York: John Wiley & Sons, Inc, 15(4), pp. 613–626.

Kveraga, K., Boucher, L. and Hughes, H. C. (2002) 'Saccades operate in violation of Hick's law', *Experimental Brain Research*, 146(3), pp. 307–314. doi: 10.1007/s00221-002-1168-8.

Kwak, Y. *et al.* (2010) 'Effect of Dopaminergic Medications on the Time Course of Explicit Motor Sequence Learning in Parkinson's Disease', *Journal of Neurophysiology*. United States: American Physiological Society, 103(2), pp. 942–949.

Kyllonen, P. C. and Christal, R. E. (1990) 'Reasoning ability is (little more than) working-memory capacity?!', *Intelligence*, 14(4), pp. 389–433. doi: https://doi.org/10.1016/S0160-2896(05)80012-1.

Lange, K. W. *et al.* (1992) 'l-Dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction', *Psychopharmacology (Berlin, Germany)*. Springer Science and Business Media LLC, 107(2–3), pp. 394–404.

Lauwereyns, J. *et al.* (2002) 'A neural correlate of response bias in monkey caudate nucleus', *Nature (London)*. England: Springer Science and Business Media LLC, 418(6896), pp. 413–417.

Lawrence, B. M. *et al.* (2008) 'An anti-Hick's effect in monkey and human saccade reaction times', *Journal of vision (Charlottesville, Va.)*. United States, 8(3), pp. 26.1--26.7.

Lawrence, B. M. (2010) 'An anti-Hick ' s effect for exogenous , but not endogenous , saccadic eye movements', pp. 115–118. doi: 10.1007/s00221-010-2301-8.

Lawrence, B. M. and Gardella, A. L. (2009) 'Saccades and reaches, behaving differently', *Experimental brain research*. Berlin/Heidelberg: Springer-Verlag, 195(3), pp. 413–418.

LeDoux, J. E. (2000) 'Emotion circuits in the brain', *Annual review of neuroscience*. Palo Alto, CA: Annual Reviews, 23(1), pp. 155–184.

Leentjens, A. F. G. (2011) 'The Role of Dopamine Agonists in the Treatment of Depression in Patients with Parkinson's Disease A Systematic Review', *Drugs (New York, N.Y.)*. Cham: Springer International Publishing, 71(3), pp. 273–286.

Lehmann, S. J. and Corneil, X. B. D. (2016) 'Transient Pupil Dilation after Subsaccadic Microstimulation of Primate Frontal Eye Fields', 36(13), pp. 3765–3776. doi: 10.1523/JNEUROSCI.4264-15.2016.

Leigh, R. J. and Zee, D. S. (1999) *The Neurology of Eye Movements : Text and CD-ROM: Text and CD-ROM*. Oxford University Press, USA. Available at: https://books.google.com/books?id=MGkDNwmRSKEC&pgis=1 (Accessed: 5 May 2016).

Leon, M. I. and Shadlen, M. N. (1999) 'Effect of expected reward magnitude on the response of neurons in the dorsolateral prefrontal cortex of the macaque.', *Neuron*. United States, 24(2), pp. 415–425.

Lewis, B. L. and Donnell, P. O. (2000) ‘Ventral Tegmental Area Afferents to the Prefrontal Cortex Maintain Membrane Potential “ Up ” States in Pyramidal Neurons via D 1 Dopamine Receptors’, pp. 1168–1175.

Li, Y. *et al.* (2016) ‘Serotonin neurons in the dorsal raphe nucleus encode reward signals’, *Nature communications*. England: Springer Science and Business Media LLC, 7(1), p. 10503.

Libera, C. Della and Chelazzi, L. (2016) ‘Visual Selective Attention and the Effects of Monetary Rewards’, *Psychological science*. Los Angeles, CA: SAGE Publications, 17(3), pp. 222–227.

Ligneul, R. *et al.* (2018) ‘Spontaneous eye blink rate and dopamine synthesis capacity : preliminary evidence for an absence of positive correlation’, 47(February), pp. 1081–1086. doi: 10.1111/ejn.13895.

Liu, X. U. N. *et al.* (2011) ‘Common and distinct networks underlying reward valence and processing stages: A meta-analysis of functional neuroimaging studies’, *Neuroscience and biobehavioral reviews*. Kidlington: Elsevier, 35(5), pp. 1219–1236.

Loughlin, S. E. and Fallon, J. H. (1984) ‘Substantia nigra and ventral tegmental area projections to cortex: Topography and collateralization’, *Neuroscience*, 11(2), pp. 425–435. doi: https://doi.org/10.1016/0306-4522(84)90034-4.

Louie, K., Grattan, L. E. and Glimcher, P. W. (2011) ‘Reward Value-Based Gain Control: Divisive Normalization in Parietal Cortex’, *The Journal of neuroscience*. United States: Society for Neuroscience, 31(29), pp. 10627–10639.

Lu, Z.-L. (2008) ‘Mechanisms of attention: Psychophysics, cognitive psychology, and cognitive neuroscience.’, *Kiso shinrigaku kenkyu*. Japan, 27(1), pp. 38–45.

Lu, Z. *et al.* (2019) ‘The effect of levodopa on saccades – Oxford Quantification in Parkinsonism study’, *Parkinsonism and Related Disorders*. England: Elsevier, 68(March), pp. 49–56. doi: 10.1016/j.parkreldis.2019.09.029.

Lucetti, C. *et al.* (2010) ‘Levodopa response in dementia with lewy bodies: a 1-year follow-up study.’, *Parkinsonism & related disorders*, 16(8), pp.

522–6. doi: 10.1016/j.parkreldis.2010.06.004.

Luck, S. J. and Vogel, E. K. (1997) 'The capacity of visual working memory for features and conjunctions', *Nature (London)*. England: Springer Science and Business Media LLC, 390(6657), pp. 279–281.

Luck, S. J. and Vogel, E. K. (2013) 'Visual working memory capacity : from psychophysics and neurobiology to individual differences', *Trends in Cognitive Sciences*. Elsevier Ltd, 17(8), pp. 391–400. doi: 10.1016/j.tics.2013.06.006.

Luigi, L. *et al.* (2011) 'Main sequence : An index for detecting mental workload variation in complex tasks', *Applied Ergonomics*. Elsevier Ltd, 42(6), pp. 807–813. doi: 10.1016/j.apergo.2011.01.003.

Lynch, G. *et al.* (1997) 'The effects of haloperidol on visual search, eye movements and psychomotor performance', *Psychopharmacology*. Berlin/Heidelberg: Springer-Verlag, 133(3), pp. 233–239. doi: 10.1007/s002130050396.

MacDonald, H. J. *et al.* (2016) 'Dopamine Gene Profiling to Predict Impulse Control and Effects of Dopamine Agonist Ropinirole', *Journal of cognitive neuroscience*. United States: MIT Press, 28(7), pp. 909–919.

Mackert, A. *et al.* (1990) 'Increased blink rate in drug-naive acute schizophrenic patients', *Biological psychiatry (1969)*. United States: Elsevier Inc, 27(11), pp. 1197–1202.

Maillet, A. *et al.* (2016) 'The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease', *Brain (London, England : 1878)*. England: Oxford University Press (OUP), 139(9), pp. 2486–2502.

Makwana, A. B., Cubillo, A. and Hare, T. A. (2019) 'Differential modulation of cognitive control networks by monetary reward and punishment'. doi: 10.1093/scan/nsz006.

Malhotra, P. A. *et al.* (2013) 'Reward modulates spatial neglect', *Journal of neurology, neurosurgery and psychiatry*. England: British Medical Association (Short report), 84(4), pp. 366–369.

Manohar, S. G. (2014) *Frontostriatal contributions to reward processing*, *Doctoral Thesis, UCL Institute of Cognitive Neuroscience and Institute*

of Neurology.

Manohar, S. G. *et al.* (2015) 'Reward Pays the Cost of Noise Reduction in Motor and Cognitive Control', *Current Biology*. Elsevier Ltd, 25(13), pp. 1707–1716. doi: 10.1016/j.cub.2015.05.038.

Manohar, S. G. *et al.* (2017) 'Distinct Motivational Effects of Contingent and Noncontingent Rewards'. doi: 10.1177/0956797617693326.

Manohar, S. G. *et al.* (2018) 'Motivation dynamically increases noise resistance by internal feedback during movement', *Neuropsychologia*. Elsevier Ltd, 123(October 2017), pp. 19–29. doi: 10.1016/j.neuropsychologia.2018.07.011.

Manohar, S. G. (2020) 'Tremor in Parkinson's disease inverts the effect of dopamine on reinforcement', *Brain*, 143(11), pp. 3178–3180. doi: 10.1093/brain/awaa363.

Manohar, S. G. and Husain, M. (2015) 'Reduced pupillary reward sensitivity in Parkinson ' s disease', (July), pp. 20–23. doi: 10.1038/npjparkd.2015.26.

Martig, A. K. *et al.* (2010) 'Context Dependent Effects of Ventral Tegmental Area Inactivation on Spatial Working Memory', 203(2), pp. 316–320. doi: 10.1016/j.bbr.2009.05.008.Context.

Martikainen, I. K. *et al.* (2015) 'Chronic Back Pain Is Associated with Alterations in Dopamine Neurotransmission in the Ventral Striatum', *The Journal of neuroscience*. United States: Society for Neuroscience, 35(27), pp. 9957–9965.

Mathar, D. *et al.* (2018) 'A potential link between gambling addiction severity and central dopamine levels : Evidence from spontaneous eye blink rates', (August), pp. 1–8. doi: 10.1038/s41598-018-31531-1.

Matsumoto, M. and Hikosaka, O. (2007) 'Lateral habenula as a source of negative reward signals in dopamine neurons.', *Nature*, 447(7148), pp. 1111–1115. doi: 10.1038/nature05860.

Maunsell, J. H. R. (2004) 'Neuronal representations of cognitive state: reward or attention?', *Trends in cognitive sciences*. England: Elsevier BV, 8(6), pp. 261–265.

Mavridis, M. *et al.* (1991) 'Effects of locus coeruleus lesions on parkinsonian

signs, striatal dopamine and substantia nigra cell loss after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in monkeys: A possible role for the locus coeruleus in the progression of Parkinson's disease', *Neuroscience*, 41(2), pp. 507–523. doi: https://doi.org/10.1016/0306-4522(91)90345-O.

Mazzoni, P., Hristova, A. and Krakauer, J. W. (2007) 'Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 27(27), pp. 7105–7116. doi: 10.1523/JNEUROSCI.0264-07.2007.

McCartan, D. *et al.* (2001) 'The differential effects of chlorpromazine and haloperidol on latent inhibition in healthy volunteers', *Journal of psychopharmacology (Oxford)*. London, Thousand Oaks, CA and New Delhi: SAGE Publications, 15(2), pp. 96–104.

Mcsorley, E., Gilchrist, I. D. and Mccloy, R. (2019) 'The programming of sequences of saccades', *Experimental Brain Research*. Springer Berlin Heidelberg, 237(4), pp. 1009–1018. doi: 10.1007/s00221-019-05481-7.

Meder, D. *et al.* (2019) 'NeuroImage The role of dopamine in the brain - lessons learned from Parkinson ' s disease', 190(May 2018), pp. 79–93. doi: 10.1016/j.neuroimage.2018.11.021.

Mehta, M. A. *et al.* (2001) 'Improved short-term spatial memory but impaired reversal learning following the dopamine D 2 agonist bromocriptine in human volunteers', pp. 10–20. doi: 10.1007/s002130100851.

Mehta, M. A. *et al.* (2004) 'Impaired set-shifting and dissociable effects on tests of spatial working memory following the dopamine D2 receptor antagonist sulpiride in human volunteers', *Psychopharmacology*, 176(3), pp. 331–342. doi: 10.1007/s00213-004-1899-2.

Michell, A. W. *et al.* (2006a) 'Saccadic latency distributions in Parkinson's disease and the effects of l-dopa', *Experimental brain research*. Berlin/Heidelberg: Springer-Verlag, 174(1), pp. 7–18.

Michell, A. W. *et al.* (2006b) 'Saccadic latency distributions in Parkinson's disease and the effects of L-dopa', *Experimental Brain Research*,

174(1), pp. 7–18. doi: 10.1007/s00221-006-0412-z.

Miller, E. K. and Cohen, J. D. (2001) 'An Integrative Theory of Prefrontal Cortex Function', *Annual review of neuroscience*. United States: Annual Reviews, 24(1), pp. 167–202.

Miller, G. A. (1956) 'The magical number seven, plus or minus two: some limits on our capacity for processing information', *Psychological review*. United States: American Psychological Association, 63(2), pp. 81–97.

Milstein, D. M. and Dorris, M. C. (2007) 'The Influence of Expected Value on Saccadic Preparation', *The Journal of neuroscience*. United States: Society for Neuroscience, 27(18), pp. 4810–4818. doi: 10.1523/JNEUROSCI.0577-07.2007.

Mink, J. W. (1996) 'The Basal Ganglia: Focused selection and inhibition of competing programs', *Progress in neurobiology*. England: Elsevier Ltd, 50(4), pp. 381–425.

Misiura, M. B. *et al.* (2017) 'Cognitive control, learning and clinical motor ratings are most highly associated with basal ganglia brain volumes in the premanifest Huntington's disease phenotype', *Journal of the International Neuropsychological Society: JINS*. NIH Public Access, 23(2), p. 159.

Mitchell, J. M. *et al.* (2018) 'Dopamine , time perception , and future time perspective', *Psychopharmacology*. Psychopharmacology, (235), pp. 2783–2793.

Miyazaki, K. W. *et al.* (2014) 'Optogenetic Activation of Dorsal Raphe Serotonin Neurons Enhances Patience for Future Rewards', *Current biology*. England: Elsevier BV, 24(17), pp. 2033–2040.

Mogenson, G. J., Jones, D. L. and Yim, C. Y. (1980) 'From motivation to action: functional interface between the limbic system and the motor system.', *Progress in neurobiology*. England, 14(2–3), pp. 69–97.

Mohr, C. *et al.* (2005) 'Blinking and schizotypal thinking', *Journal of Psychopharmacology*, 19(5), pp. 513–520. doi: 10.1177/0269881105056538.

Montague, P. R., Dayan, P. and Sejnowski, T. J. (1996) 'A framework for

mesencephalic dopamine systems based on predictive Hebbian learning', *The Journal of neuroscience*. United States: Society for Neuroscience, 16(5), pp. 1936–1947.

Montastruc, J. L. *et al.* (1989) 'Abnormal ocular movements in Parkinson's disease: Evidence for involvement of dopaminergic systems', *Brain*, 112(5), pp. 1193–1214. doi: 10.1093/brain/112.5.1193.

Morey, C. C. *et al.* (2011a) 'Flexible attention allocation to visual and auditory working memory tasks : manipulating reward induces a trade-off', pp. 458–472. doi: 10.3758/s13414-010-0031-4.

Morey, C. C. *et al.* (2011b) 'Flexible attention allocation to visual and auditory working memory tasks: manipulating reward induces a trade-off', *Attention, perception & psychophysics*. New York: Springer-Verlag, 73(2), pp. 458–472.

Muhammed, K. (2018) 'Mechanisms underlying apathy in health and Parkinson ' s disease', *PhD Thesis*.

Muhammed, K. *et al.* (2018) 'Voluntary modulation of saccadic peak velocity associated with individual differences in motivation', *Cortex*. Elsevier Ltd, 122(xxxx), pp. 1–15. doi: 10.1016/j.cortex.2018.12.001.

Muhammed, K., Manohar, S. and Husain, M. (2015) 'Mechanisms underlying apathy in Parkinson ' s disease', *The Lancet*. Elsevier Ltd, 385, p. S71. doi: 10.1016/S0140-6736(15)60386-5.

Muraven, M. and Baumeister, R. F. (2000) 'Self-regulation and depletion of limited resources: does self-control resemble a muscle?', *Psychological bulletin*. United States, 126(2), pp. 247–259.

Müri, R. M. *et al.* (2009) 'Performance of memory-guided sequences of saccades by normal subjects', 8107. doi: 10.3109/01658109709044126.

Murphy, B. L. *et al.* (1996) 'Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys', *Proceedings of the National Academy of Sciences - PNAS*. United States: Proceedings of the National Academy of Sciences, 93(3), pp. 1325–1329.

Naase, T. *et al.* (2005) 'An assessment of the pattern of spontaneous

eyeblink activity under the influence of topical ocular anaesthesia', *Graefe's archive for clinical and experimental ophthalmology*. Berlin/Heidelberg: Springer-Verlag, 243(4), pp. 306–312.

Nagy, H. *et al.* (2012) 'The effect of dopamine agonists on adaptive and aberrant salience in Parkinson's disease', *Neuropsychopharmacology (New York, N.Y.)*. Basingstoke: Nature Publishing Group, 37(4), pp. 950–958.

Naicker, P. *et al.* (2016) 'Central cholinergic pathway involvement in the regulation of pupil diameter, blink rate and cognitive function', *Neuroscience*, 334, pp. 180–190. doi: https://doi.org/10.1016/j.neuroscience.2016.08.009.

Nakamura, K. and Hikosaka, O. (2006) 'Role of Dopamine in the Primate Caudate Nucleus in Reward Modulation of Saccades', *The Journal of neuroscience*. United States: Soc Neuroscience, 26(20), pp. 5360–5369.

Nakamura, T. *et al.* (1991) 'Quantitative Analysis of Ocular Movements in Parkinson's Disease', *Acta Oto-Laryngologica*. Taylor & Francis, 111(sup481), pp. 559–562. doi: 10.3109/00016489109131470.

Narita, Minoru *et al.* (2003) 'Change in the expression of c-fos in the rat brain following sciatic nerve ligation', *Neuroscience letters*. Ireland: Elsevier Ireland Ltd, 352(3), pp. 231–233.

Nemanich, S. T. and Earhart, G. M. (2016) 'Freezing of gait is associated with increased saccade latency and variability in Parkinson's disease', *Clinical Neurophysiology*. International Federation of Clinical Neurophysiology, 127(6), pp. 2394–2401. doi: 10.1016/j.clinph.2016.03.017.

Niv, Y. *et al.* (2006) 'Tonic dopamine: opportunity costs and the control of response vigor', *Psychopharmacology (Berlin, Germany)*. Berlin/Heidelberg: Springer Science and Business Media LLC, 191(3), pp. 507–520. doi: 10.1007/s00213-006-0502-4.

Niv, Y. (2007) 'Cost, Benefit, Tonic, Phasic: What Do Response Rates Tell Us about Dopamine and Motivation', *Annals of the New York Academy of Sciences*. United States: Blackwell Publishing, 1104(1),

pp. 357–376.

Norbury, A. *et al.* (2015) 'Dopamine Regulates Approach-Avoidance in Human Sensation-Seeking', *The international journal of neuropsychopharmacology*. US: Oxford University Press, 18(10), pp. pyv041--pyv041.

O'Doherty, J. (2004) 'Dissociable Roles of Ventral and Dorsal Striatum in Instrumental Conditioning', *Science (American Association for the Advancement of Science)*. United States: American Association for the Advancement of Science (AAAS), 304(5669), pp. 452–454.

Obhi, S. S. and Haggard, P. (2004) 'Internally generated and externally triggered actions are physically distinct and independently controlled', pp. 518–523. doi: 10.1007/s00221-004-1911-4.

Ohtsuka, K., Sawa, M. and Takeda, M. (1989) 'Accuracy of Memory-Guided Saccades', pp. 53–56.

Oldham, S. *et al.* (2018) 'The anticipation and outcome phases of reward and loss processing: A neuroimaging meta-analysis of the monetary incentive delay task.', *Human brain mapping*, 39(8), pp. 3398–3418. doi: 10.1002/hbm.24184.

Olds, J. and Milner, P. (1954) 'Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain.', *Journal of comparative and physiological psychology*. United States, 47(6), pp. 419–427.

Opstal, A. J. van and Goossens, H. H. L. . (2008) 'Linear ensemble-coding in midbrain superior colliculus specifies the saccade kinematics', *Biological cybernetics*. Berlin/Heidelberg: Springer-Verlag, 98(6), pp. 561–577.

Ott, T. and Nieder, A. (2016) 'Dopamine D2 Receptors Enhance Population Dynamics in Primate Prefrontal Working Memory Circuits', *Cerebral cortex (New York, N.Y. 1991)*. United States: Oxford University Press (OUP), 27(9), pp. 4423–4435.

Ott, T. and Nieder, A. (2019) 'Dopamine and Cognitive Control in Prefrontal Cortex', *Trends in Cognitive Sciences*. Elsevier Ltd, 23(3), pp. 213–234. doi: 10.1016/j.tics.2018.12.006.

Packard, M. G. and White, N. M. (1991) ‘Dissociation of Hippocampus and Caudate Nucleus Memory Systems by Posttraining Intracerebral Injection of Dopamine Agonists’, *Behavioral neuroscience*. United States: American Psychological Association, 105(2), pp. 295–306.

Palminteri, S. *et al.* (2012) ‘Critical Roles for Anterior Insula and Dorsal Striatum in Punishment-Based Avoidance Learning’, *Neuron (Cambridge, Mass.)*. United States: Elsevier BV, 76(5), pp. 998–1009.

Palminteri, S. *et al.* (2015) ‘Contextual modulation of value signals in reward and punishment learning’, *Nature communications*. England: Springer Science and Business Media LLC, 6(1), p. 8096.

Panigrahi, B. *et al.* (2015) ‘Dopamine Is Required for the Neural Representation and Control of Movement Vigor Article Dopamine Is Required for the Neural Representation and Control of Movement Vigor’, *Cell*, 162, pp. 1418–1430. doi: 10.1016/j.cell.2015.08.014.

Parent, A. (1990) ‘Extrinsic connections of the basal ganglia’, *Trends in Neurosciences*. England: Elsevier Ltd, 13(7), pp. 254–258.

Paschke, L. M. *et al.* (2015) ‘Motivation by potential gains and losses affects control processes via different mechanisms in the attentional network’, *NeuroImage (Orlando, Fla.)*. United States: Elsevier Inc, 111, pp. 549–561.

Peck, C. J. *et al.* (2009) ‘Reward Modulates Attention Independently of Action Value in Posterior Parietal Cortex’, *The Journal of neuroscience*. United States: Soc Neuroscience, 29(36), pp. 11182–11191.

Peckham, A. D. and Johnson, S. L. (2016) ‘Spontaneous Eye-Blink Rate as an Index of Reward Responsivity: Validation and Links to Bipolar Disorder’, *Clinical psychological science*. Los Angeles, CA: SAGE Publications, 4(3), pp. 451–463.

Pertzov, Y. *et al.* (2012) ‘Forgetting What Was Where : The Fragility of Object- Location Binding’, 7(10). doi: 10.1371/journal.pone.0048214.

Pessiglione, M. *et al.* (2006) ‘Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans’, *Nature*. Nature Publishing Group, 442(7106), pp. 1042–1045.

Phani, S., Gonye, G. and Iacovitti, L. (2010) 'VTA neurons show a potentially protective transcriptional response to MPTP', *Brain research*. Netherlands: Elsevier B.V, 1343, pp. 1–13.

Pierrot-Deseilligny, C. *et al.* (1991) 'Cortical control of memory-guided saccades in man', *Experimental brain research*. Germany: Springer Science and Business Media LLC, 83(3), pp. 607–617.

Pine, A. *et al.* (2010) 'Dopamine, Time, and Impulsivity in Humans', *The Journal of neuroscience*. United States: Society for Neuroscience, 30(26), pp. 8888–8896.

Pleger, B. *et al.* (2009) 'Influence of Dopaminergically Mediated Reward on Somatosensory Decision-Making', *PLoS biology*. United States: Public Library of Science (PLoS), 7(7), pp. e1000164--e1000164.

Poewe, W. *et al.* (1991) 'High-speed memory scanning in Parkmson's disease: Adverse effects of levodopa', *Annals of neurology*. Hoboken: Wiley Subscription Services, Inc., A Wiley Company, 29(6), pp. 670–673.

Poletti, M. and Bonuccelli, U. (2013) 'Acute and chronic cognitive effects of levodopa and dopamine agonists on patients with Parkinson ' s disease : a review', pp. 101–113. doi: 10.1177/2045125312470130.

van der Post, J. *et al.* (2004) 'No evidence of the usefulness of eye blinking as a marker for central dopaminergic activity', *Journal of Psychopharmacology*, 18(1), pp. 109–114. doi: 10.1177/0269881104042832.

Potts, G. F. (2011) 'Impact of reward and punishment motivation on behavior monitoring as indexed by the error-related negativity', *International Journal of Psychophysiology*, 81(3), pp. 324–331. doi: https://doi.org/10.1016/j.ijpsycho.2011.07.020.

Pouget, P. (2015) 'The cortex is in overall control of " voluntary " eye movement', (October 2014), pp. 241–245. doi: 10.1038/eye.2014.284.

Prensa, L. *et al.* (2009) 'The nigrostriatal pathway: axonal collateralization and compartmental specificity', in *Birth, Life and Death of Dopaminergic Neurons in the Substantia Nigra*. Springer, pp. 49–58.

Pretorius, J. L. *et al.* (2001) 'Comparison of clozapine and haloperidol on

some autonomic and psychomotor functions, and on serum prolactin concentration, in healthy subjects', *British journal of clinical pharmacology*. Oxford, UK: Blackwell Publishing, 52(3), pp. 322–326.

Proctor, R. W. and Schneider, D. W. (2018) 'Hick's law for choice reaction time: A review', *Quarterly journal of experimental psychology (2006)*, 71(6), pp. 1281–1299. doi: 10.1080/17470218.2017.1322622.

Pullman, S. L. *et al.* (1988) 'Dopaminergic effects on simple and choice reaction time performance in Parkinson's disease', *Neurology*, 38(2), pp. 249 LP – 249. Available at: http://n.neurology.org/content/38/2/249.abstract.

Rafal, R. D. *et al.* (1984) 'Cognition and the basal ganglia. Separating mental and motor components of performance in Parkinson's disease', *Brain (London, England : 1878)*. England, 107 (Pt 4)(4), pp. 1083–1094.

Railo, H., Olkoniemi, H. and Eeronheimo, E. (2018) 'Dopamine and eye movement control in Parkinson ' s disease : deficits in corollary discharge signals ?', pp. 1–25. doi: 10.7717/peerj.6038.

Ralph, R. J. and Caine, S. B. (2005) 'Dopamine D1 and D2 Agonist Effects on Prepulse Inhibition and Locomotion: Comparison of Sprague-Dawley Rats to Swiss-Webster, 129X1/SvJ, C57BL/6J, and DBA/2J Mice', *The Journal of pharmacology and experimental therapeutics*. United States: American Society for Pharmacology & Experimental Therapeutics (ASPET), 312(2), pp. 733–741.

Rand, M. K. *et al.* (2000) 'Effects of accuracy constraints on reach-to-grasp movements in cerebellar patients', *Experimental brain research*. Berlin/Heidelberg: Springer-Verlag, 135(2), pp. 179–188.

van Reekum, R., Stuss, D. T. and Ostrander, L. (2005) 'Apathy: Why Care?', *The Journal of Neuropsychiatry and Clinical Neurosciences*, 17(1), pp. 7–19. doi: 10.1007/s00347-007-1672-0.

Reilly, J. L. *et al.* (2008) 'Pharmacological treatment effects on eye movement control', *Brain and Cognition*. Elsevier Inc., 68(3), pp. 415–435. doi: 10.1016/j.bandc.2008.08.026.

Remy, P. *et al.* (2005) 'Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system', *Brain*, 128(6), pp.

1314–1322. doi: 10.1093/brain/awh445.

Reppert, T. R. *et al.* (2015) 'Modulation of Saccade Vigor during Value-Based Decision Making', *Journal of Neuroscience*, 35(46), pp. 15369–15378. doi: 10.1523/JNEUROSCI.2621-15.2015.

Reynolds, J. N. J., Hyland, B. I. and Wickens, J. R. (2001) 'A cellular mechanism of reward-related learning'.

Richfield, E. K., Penney, J. B. and Young, A. B. (1989) 'Anatomical and affinity state comparisons between Dopamine D1 and D2 receptors in the rat central nervous system', *Neuroscience*, 30(3), pp. 767–777.

Richter, A. *et al.* (2013) 'Motivational salience and genetic variability of dopamine D2 receptor expression interact in the modulation of interference processing', *Frontiers in human neuroscience*, 7(June), pp. 1–22. doi: 10.3389/fnhum.2013.00250.

Rivaud-Pechoux, S. *et al.* (2000) 'Improvement of memory guided saccades in parkinsonian patients by high frequency subthalamic nucleus stimulation', *Journal of Neurology Neurosurgery and Psychiatry*, 68(3), pp. 381–384. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L30248719%5Cnhttp://dx.doi.org/10.1136/jnnp.68.3.381%5Cnhttp://sfx.bibl.ulaval.ca:9003/sfx_local?sid=EMBASE&issn=00223050&id=doi:10.1136%2Fjnnp.68.3.381&atitle=Improvement+of+memory+.

Robinson, O. J. *et al.* (2010) 'Dopamine precursor depletion improves punishment prediction during reversal learning in healthy females but not males.', *Psychopharmacology*. Germany, 211(2), pp. 187–195. doi: 10.1007/s00213-010-1880-1.

Robinson, T. E. and Whishaw, I. Q. (1988) 'Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: a microdialysis study in freely moving rats', *Brain research*. Netherlands: Elsevier B.V, 450(1), pp. 209–224.

Rock, P. L. *et al.* (2013) 'Short-Term Quetiapine Treatment Alters the Use of Reinforcement Signals during Risky Decision-Making and Promotes

the Choice of Negative Expected Values in Healthy Adult Males', 33(39), pp. 15588–15595. doi: 10.1523/JNEUROSCI.5721-11.2013.

Rolinski, M. *et al.* (2015) 'Visual short-term memory deficits in REM sleep behaviour disorder mirror those in Parkinson's disease', *Brain*, 139(1), pp. 47–53. doi: 10.1093/brain/awv334.

Ross, S. B., Jackson, D. M. and Edwards, S. R. (1989) 'The Involvement of Dopamine D1and D2Receptors in the Locomotor Stimulation Produced by (+)-Amphetamine in Naive and Dopamine-Depleted Mice', *Pharmacology & toxicology*, 64(1), pp. 72–77.

Rubin, A. J. *et al.* (1993) 'Quantitative longitudinal assessment of saccades in Huntington's disease', *Journal of clinical neuro-ophthalmology*, 13(1), p. 59—66. Available at: http://europepmc.org/abstract/MED/8501265.

Rutledge, R. B. *et al.* (2015) 'Dopaminergic Modulation of Decision Making and Subjective Well-Being', *Journal of Neuroscience , 35 (27) pp. 9811-9822. (2015)*.

Rypma, B. *et al.* (2015) 'Dopamine D1 Binding Potential Predicts Fusiform BOLD Activity during Face-Recognition Performance', *The Journal of neuroscience*. United States: Society for Neuroscience, 35(44), pp. 14702–14707.

Sahakian, B. J. *et al.* (1985) 'Association between learning and cortical catecholamines in non-drug-treated rats', *Psychopharmacology*. Germany, 86(3), pp. 339–343.

Sakuragi, S. and Sugiyama, Y. (2009) 'Effects of reward and punishment on task performance, mood and autonomic nervous function, and the interaction with personality.', *Journal of physiological anthropology*. England, 28(4), pp. 181–190.

Salamone, J. D. (2002) 'Motivational views of reinforcement : implications for understanding the behavioral functions of nucleus accumbens dopamine', 137.

Salamone, J. D. and Correa, M. (2012) 'The Mysterious Motivational Functions of Mesolimbic Dopamine', *Neuron*. doi: 10.1016/j.neuron.2012.10.021.

Sandyk, R. (1990) ‘The significance of eye blink rate in parkinsonism: a hypothesis.’, *The International journal of neuroscience*. England, 51(1–2), pp. 99–103. doi: 10.3109/00207459009000515.

Santiago, M., Cano, J. and Westerink, B. H. C. (1993) ‘Are bilateral nigrostriatal dopaminergic pathways functionally linked in the rat brain? A microdialysis study in conscious rats’, *Brain research*. Netherlands: Elsevier B.V, 628(1), pp. 187–192.

Sato, M. and Hikosaka, O. (2002) ‘Role of Primate Substantia Nigra Pars Reticulata in Reward-Oriented Saccadic Eye Movement’, *The Journal of neuroscience*. United States: Soc Neuroscience, 22(6), pp. 2363–2373.

Sawaguchi, T. (2000) ‘The role of D1-dopamine receptors in working memory-guided movements mediated by frontal cortical areas’, *Parkinsonism & Related Disorders*. Elsevier, 7(1), pp. 9–19. doi: 10.1016/S1353-8020(00)00044-4.

Sawaguchi, T. (2001) ‘The effects of dopamine and its antagonists on directional delay-period activity of prefrontal neurons in monkeys during an oculomotor delayed-response task’, *Neuroscience Research*, 41(2), pp. 115–128. doi: https://doi.org/10.1016/S0168-0102(01)00270-X.

Sawaguchi, T. and Goldman-Rakic, P. S. (1991) ‘D1 Dopamine Receptors in Prefrontal Cortex : Involvement in Working Memory Author (s): Toshiyuki Sawaguchi and Patricia S . Goldman-Rakic Published by : American Association for the Advancement of Science Stable URL : https://www.jstor.org/stable/287491’, *Science (American Association for the Advancement of Science)*, 251(4996), pp. 947–950.

Sawaguchi, T. and Goldman-Rakic, P. S. (1994) ‘The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task’, *Journal of Neurophysiology*, 71(2), pp. 515–528. doi: 10.1152/jn.1994.71.2.515.

Sawaguchi, T., Matsumura, M. and Kubota, K. (1990) ‘Effects of dopamine antagonists on neuronal activity related to a delayed response task in

monkey prefrontal cortex', *Journal of Neurophysiology*. United States: Am Phys Soc, 63(6), pp. 1401–1412.

Schaeffer, E. and Berg, D. (2017) 'Dopaminergic Therapies for Non-motor Symptoms in Parkinson ' s Disease', *CNS Drugs*. Springer International Publishing, 31(7), pp. 551–570. doi: 10.1007/s40263-017-0450-z.

Schall, J. D. (1995) 'Neural Basis of Saccade Target Selection', *Reviews in the neurosciences*, 6(1).

Schneider, J. S. *et al.* (2013) 'Levodopa improves motor deficits but can further disrupt cognition in a macaque Parkinson model.', *Movement disorders : official journal of the Movement Disorder Society*. United States, 28(5), pp. 663–667. doi: 10.1002/mds.25258.

Schouwenburg, M. R. van, Ouden, H. E. M. den and Cools, R. (2015) 'Selective attentional enhancement and inhibition of fronto-posterior connectivity by the Basal Ganglia during attention switching', *Cerebral cortex (New York, N.Y. 1991)*. United States, 25(6), pp. 1527–1534.

van Schouwenburg, M., Aarts, E. and Cools, R. (2010) 'Dopaminergic modulation of cognitive control: distinct roles for the prefrontal cortex and the basal ganglia', *Current pharmaceutical design*. Bentham Science Publishers, 16(18), pp. 2026–2032.

Schultz, W. *et al.* (1989) 'Saccadic reaction times, eye-arm coordination and spontaneous eye movements in normal and MPTP-treated monkeys', *Experimental brain research*. Germany, 78(2), p. 253.

Schultz, W. (2002) 'Getting Formal with Dopamine and Reward', 36, pp. 241–263.

Schultz, W. (2016a) 'Basic research', pp. 23–32.

Schultz, W. (2016b) 'Dopamine reward prediction- error signalling: a two-component response', *Nature Publishing Group*. Nature Publishing Group, 17(3), pp. 183–195. doi: 10.1038/nrn.2015.26.

Schultz, W. (2016c) 'Dopamine reward prediction-error signalling: a two-component response.', *Nature reviews. Neuroscience*. England, 17(3), pp. 183–195. doi: 10.1038/nrn.2015.26.

Schultz, W. (2016d) ‘Dopamine reward prediction error coding’, *Dialogues in clinical neuroscience*. France: Les Laboratoires Servier, 18(1), pp. 23–32.

Schütz, A. C., Trommershäuser, J. and Gegenfurtner, K. R. (2012) ‘Dynamic integration of information about salience and value for saccadic eye movements’, *Proceedings of the National Academy of Sciences - PNAS*. United States: National Academy of Sciences, 109(19), pp. 7547–7552.

Schwabe, K. *et al.* (2004) ‘Effects of neonatal lesions of the medial prefrontal cortex on adult rat behaviour.’, *Behavioural brain research*. Netherlands, 153(1), pp. 21–34. doi: 10.1016/j.bbr.2003.10.030.

Scudder, C. A., Kaneko, C. S. and Fuchs, A. F. (2002) ‘The brainstem burst generator for saccadic eye movements: a modern synthesis’, *Experimental brain research*. Germany, 142(4), pp. 439–462.

Seamans, J. K., Floresco, S. B. and Phillips, A. G. (1998) ‘D1 Receptor Modulation of Hippocampal-Prefrontal Cortical Circuits Integrating Spatial Memory with Executive Functions in the Rat’, *The Journal of neuroscience*. United States: Soc Neuroscience, 18(4), pp. 1613–1621.

Seamans, J. K. and Yang, C. R. (2004) ‘The principal features and mechanisms of dopamine modulation in the prefrontal cortex’, *Progress in Neurobiology*, 74(1), pp. 1–58. doi: https://doi.org/10.1016/j.pneurobio.2004.05.006.

Seo, M., Lee, E. and Averbeck, B. B. (2012) ‘Action selection and action value in frontal-striatal circuits Moonsang’, *Neuron*, 74(5), pp. 947–960. doi: 10.1016/j.neuron.2012.03.037.Action.

Shannon, C. E. (1949) *The mathematical theory of communication / by Claude E. Shannon and Warren Weaver*. Urbana: University of Illinois Press.

Sharot, T. *et al.* (2009) ‘Dopamine Enhances Expectation of Pleasure in Humans’, *Current biology*. England: Elsevier Inc, 19(24), pp. 2077–2080.

Sharpe, L. G., Pickworth, W. B. and Martin, W. R. (1977) ‘Actions of

amphetamine and antagonists on pupil diameter in the chronic sympathectomized dog', *Psychopharmacology*. Germany, 53(2), pp. 115–120.

Shaunak, S. *et al.* (1999) 'Remembered saccades with variable delay in Parkinson's disease', *Movement Disorders*. John Wiley & Sons, Ltd, 14(1), pp. 80–86. doi: 10.1002/1531-8257(199901)14:1<80::AID-MDS1014>3.0.CO;2-M.

Shelley-Tremblay, J. and Rosén, L. (1996) 'Attention Deficit Hyperactivity Disorder: An Evolutionary Perspective', *The Journal of Genetic Psychology*, (157), pp. 443–453.

Shenhav, A. *et al.* (2017) 'Toward a Rational and Mechanistic Account of Mental Effort', *Annual Review of Neuroscience*, 40(1), pp. 99–124. doi: 10.1146/annurev-neuro-072116-031526.

Shimura, T., Kamada, Y. and Yamamoto, T. (2002) 'Ventral tegmental lesions reduce overconsumption of normally preferred taste fluid in rats', *Behavioural brain research*. Shannon: Elsevier B.V, 134(1), pp. 123–130.

Shine, J. M. *et al.* (2013) 'Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia', *Brain*. Oxford University Press, 136(12), pp. 3671–3681.

Shiner, T. *et al.* (2012) 'Dopamine and performance in a reinforcement learning task: evidence from Parkinson's disease', *Brain (London, England : 1878)*. England: Oxford University Press (OUP), 135(6), pp. 1871–1883.

Shukla, D. (1985) 'Blink rate as clinical indicator', *Neurology*. United States, 35(2), p. 286.

Sinha, N., Manohar, S. and Husain, M. (2013) 'Impulsivity and apathy in Parkinson's disease.', *Journal of neuropsychology*. England, 7(2), pp. 255–283. doi: 10.1111/jnp.12013.

Small, D. M. *et al.* (2005) 'Monetary Incentives Enhance Processing in Brain Regions Mediating Top-down Control of Attention', *Cerebral cortex (New York, N.Y. 1991)*. United States: Oxford University Press (OUP),

15(12), pp. 1855–1865.

Small, D. M., Jones-Gotman, M. and Dagher, A. (2003) 'Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers', *NeuroImage (Orlando, Fla.)*. United States: Elsevier BV, 19(4), pp. 1709–1715.

Soares, S., Atallah, B. V and Paton, J. J. (2016) 'Midbrain dopamine neurons control judgment of time', *Science*. American Association for the Advancement of Science, 354(6317), pp. 1273–1277. doi: 10.1126/science.aah5234.

Spieser, L. *et al.* (2017) 'Beyond decision! Motor contribution to speed--accuracy trade-off in decision-making', *Psychonomic Bulletin & Review*, 24(3), pp. 950–956. doi: 10.3758/s13423-016-1172-9.

Di Stasi, L. L. *et al.* (2010) 'Saccadic Peak Velocity Sensitivity to Variations in Mental Workload', *Aviation, space, and environmental medicine*. United States: Aerospace Medical Association, 81(4), pp. 413–417.

Sugrue, L. P. (2004) 'Matching Behavior and the Representation of Value in the Parietal Cortex', *Science (American Association for the Advancement of Science)*. United States: American Association for the Advancement of Science (AAAS), 304(5678), pp. 1782–1787.

Suri, R. E. and Schultz, W. (1999) 'A neural network model with dopamine-like reinforcement signal that learns a spatial delayed response task.', *Neuroscience*. United States, 91(3), pp. 871–890.

Swainson, R. *et al.* (2000) 'Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication', *Neuropsychologia*. England: Elsevier Ltd, 38(5), pp. 596–612.

Taber, K. H. *et al.* (2012) 'Neuroanatomy of Dopamine: Reward and Addiction', *The Journal of Neuropsychiatry and Clinical Neurosciences*. United States: American Psychiatric Publishing, Inc, 24(1), pp. 1–4.

Tachibana, Y. and Hikosaka, O. (2012) 'The Primate Ventral Pallidum Encodes Expected Reward Value and Regulates Motor Action', *Neuron (Cambridge, Mass.)*. United States: Elsevier BV, 76(4), pp.

826–837.

Takikawa, Y. *et al.* (2002) ‘Modulation of saccadic eye movements by predicted reward outcome’, *Experimental Brain Research*. Germany: Springer Science and Business Media LLC, 142(2), pp. 284–291. doi: 10.1007/s00221-001-0928-1.

Termsarasab, P. *et al.* (2015) ‘The diagnostic value of saccades in movement disorder patients: a practical guide and review’, *Journal of Clinical Movement Disorders*. Journal of Clinical Movement Disorders, 2(1), p. 14. doi: 10.1186/s40734-015-0025-4.

Theeuwes, J. *et al.* (2016) ‘Our Eyes do Not Always Go Where we Want Them to Go: Capture of the Eyes by New Objects’, *Psychological science*. Los Angeles, CA: SAGE Publications, 9(5), pp. 379–385.

Theeuwes, J. and Belopolsky, A. V (2012) ‘Reward grabs the eye: Oculomotor capture by rewarding stimuli’, *Vision research (Oxford)*. England: Elsevier BV, 74, pp. 80–85.

Tom, S. M. *et al.* (2007) ‘The Neural Basis of Loss Aversion in Decision-Making Under Risk’, *Science (American Association for the Advancement of Science)*. United States: American Association for the Advancement of Science (AAAS), 315(5811), pp. 515–518.

Torta, D. M. E. *et al.* (2009) ‘On the role of dopamine replacement therapy in decision-making, working memory, and reward in Parkinson’s disease: Does the therapy-dose matter?’, *Brain and cognition*. United States: Elsevier Inc, 71(2), pp. 84–91.

Tremblay, L. *et al.* (2015) ‘Selective dysfunction of basal ganglia subterritories: From movement to behavioral disorders.’, *Movement disorders : official journal of the Movement Disorder Society*. United States, 30(9), pp. 1155–1170. doi: 10.1002/mds.26199.

Trojniar, W. and Klejbor, I. (1999) ‘Facilitatory effect of unilateral lesion of the ventral tegmental area on locomotor response to stimulation of the contralateral ventral tegmental area : involvement of GABAergic transmission’.

Trojniar, W. and Staszewska, M. (1994) ‘Unilateral damage to the ventral tegmental area facilitates feeding induced by stimulation of the

contralateral ventral tegmental area', 641, pp. 333–340.

Turner, R. S. and Desmurget, M. (2010) 'Basal ganglia contributions to motor control: a vigorous tutor', *Current opinion in neurobiology*. England: Elsevier Ltd, 20(6), pp. 704–716.

Uitvlugt, M. G. *et al.* (2016) 'The nature of working memory gating in Parkinson's disease: A multi-domain signal detection examination', *Cognitive, affective, & behavioral neuroscience*. New York: Springer US, 16(2), pp. 289–301.

Umemoto, A. *et al.* (2015) 'Task-specific effects of reward on task switching', *Psychological research*. Berlin/Heidelberg: Springer Berlin Heidelberg, 79(4), pp. 698–707.

Usher, M., Olami, Z. and McClelland, J. L. (2002) 'Hick's Law in a Stochastic Race Model with Speed–Accuracy Tradeoff', *Journal of mathematical psychology*. Elsevier Inc, 46(6), pp. 704–715.

Vaillancourt, D. E. *et al.* (2013) 'Dopamine overdose hypothesis: Evidence and clinical implications', *Mov Disord.*, 28(14), pp. 1920–1929. doi: 10.1002/mds.25687.Dopamine.

Varazzani, X. C. *et al.* (2015) 'Noradrenaline and Dopamine Neurons in the Reward / Effort Trade-Off : A Direct Electrophysiological Comparison in Behaving Monkeys', *Journal of Neuroscience*, 35(20), pp. 7866–7877. doi: 10.1523/JNEUROSCI.0454-15.2015.

Verguts, T. (2017) 'Binding by Random Bursts: A Computational Model of Cognitive Control.', *Journal of cognitive neuroscience*. United States, 29(6), pp. 1103–1118. doi: 10.1162/jocn_a_01117.

Vermersch, A. I. *et al.* (1994) 'Sequences of memory-guided saccades in Parkinson's disease.', *Annals of neurology*. United States, 35(4), pp. 487–490. doi: 10.1002/ana.410350419.

Vijayraghavan, S. *et al.* (2007) 'Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory', *Nature neuroscience*. United States: Springer Science and Business Media LLC, 10(3), pp. 376–384.

Visser, S. J. De *et al.* (2001) 'Biomarkers for the effects of antipsychotic drugs in healthy volunteers', pp. 119–132.

Vogel, E. K., Woodman, G. F. and Luck, S. J. (2001) ‘Storage of features, conjunctions, and objects in visual working memory’, *Journal of experimental psychology. Human perception and performance*, 27(1), pp. 92–114.

Volkow, N. D. *et al.* (2004) ‘Dopamine in drug abuse and addiction : results from imaging studies and treatment implications’, pp. 557–569. doi: 10.1038/sj.mp.4001507.

Voon, V. *et al.* (2010) ‘Impulsive choice and response in dopamine agonist-related impulse control behaviors’, *Psychopharmacology (Berlin, Germany)*. Germany: Springer, 207(4), pp. 645–659.

Wächter, T. *et al.* (2009) ‘Differential Effect of Reward and Punishment on Procedural Learning’, 29(2), pp. 436–443. doi: 10.1523/JNEUROSCI.4132-08.2009.

Wagner, A. D. *et al.* (1998) ‘Building memories: remembering and forgetting of verbal experiences as predicted by brain activity.’, *Science (New York, N.Y.)*. United States, 281(5380), pp. 1188–1191.

Wallis, G. *et al.* (2015) ‘Reward boosts working memory encoding over a brief temporal window’, *Visual cognition*. Routledge, 23(1–2), pp. 291–312.

Walton, M. E., Bannerman, D. M. and Rushworth, M. F. S. (2002) ‘The role of rat medial frontal cortex in effort-based decision making.’, *The Journal of neuroscience : the official journal of the Society for Neuroscience*. United States, 22(24), pp. 10996–11003.

Walton, M. M. G. and Freedman, E. G. (2014) ‘Activity of long-lead burst neurons in pontine reticular formation during head-unrestrained gaze shifts’, *Journal of neurophysiology*. United States: American Physiological Society, 111(2), pp. 300–312. doi: 10.1152/jn.00841.2012.

Wang, A. Y., Miura, K. and Uchida, N. (2013) ‘The dorsomedial striatum encodes net expected return, critical for energizing performance vigor’, *Nature neuroscience*. United States: Nature Publishing Group, 16(5), pp. 639–647.

Webb, T. J. *et al.* (2011) ‘Noise in attractor networks in the brain produced

by graded firing rate representations', *PLoS ONE*, 6(9). doi: 10.1371/journal.pone.0023630.

Weintraub, D. *et al.* (2006) 'Association of Dopamine Agonist Use With Impulse Control Disorders in Parkinson Disease', *Archives of Neurology*, 63(7), pp. 969–973. doi: 10.1001/archneur.63.7.969.

Weintraub, D. *et al.* (2010) 'Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients.', *Archives of neurology*. United States, 67(5), pp. 589–595. doi: 10.1001/archneurol.2010.65.

Westbrook, A. and Braver, T. S. (2016) 'Review Dopamine Does Double Duty in Motivating Cognitive Effort'. Elsevier. doi: 10.1016/j.neuron.2015.12.029.

Westbrook, A. and Frank, M. (2018) 'Dopamine and Proximity in Motivation and Cognitive Control.', *Current opinion in behavioral sciences*. Netherlands, 22, pp. 28–34. doi: 10.1016/j.cobeha.2017.12.011.

Wilkerson, A. and Levin, E. D. (1999) 'Ventral hippocampal dopamine D1 and D2 systems and spatial working memory in rats', *Neuroscience*. United States, 89(3), pp. 743–749.

Williams-Gray, C. H. *et al.* (2009) 'The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort', *Brain (London, England : 1878)*. England: Oxford University Press (OUP), 132(11), pp. 2958–2969.

Winkel, J. *et al.* (2012) 'Bromocriptine does not alter speed-accuracy tradeoff', *Frontiers in neuroscience*. Switzerland: Frontiers Research Foundation, 6, p. 126.

Winograd-Gurvich, C. T. *et al.* (2003) 'Hypometric primary saccades and increased variability in visually-guided saccades in Huntington's disease', *Neuropsychologia*. England: Elsevier Ltd, 41(12), pp. 1683–1692.

Wise, R. A. (2009) 'Roles for nigrostriatal — not just mesocorticolimbic — dopamine in reward and addiction', *Trends in neurosciences*, 32(10), pp. 517–524. doi: 10.1016/j.tins.2009.06.004.

Wood, P. B. *et al.* (2007) 'Fibromyalgia patients show an abnormal dopamine response to pain', *The European journal of neuroscience*.

Oxford, UK: Wiley, 25(12), pp. 3576–3582.

Woodward, N. D. *et al.* (2009) 'Corrigendum to "Cerebral morphology and dopamine D2/D3 receptor distribution in humans: A combined [18F]fallypride and voxel-based morphometry study" [NeuroImage 46 (2009) 31–38]', *NeuroImage (Orlando, Fla.)*. Elsevier Inc, 47(4), p. 2090.

Wu, T. *et al.* (2017) 'Hick – Hyman Law is Mediated by the Cognitive Control Network in the Brain', (January 2018), pp. 1–16. doi: 10.1093/cercor/bhx127.

Wylie, S. A. *et al.* (2010) 'The effect of Parkinson's disease on the dynamics of on-line and proactive cognitive control during action selection', *Journal of cognitive neuroscience*. MIT Press, 22(9), pp. 2058–2073.

Yee, D. M. *et al.* (2015) 'Humans Integrate Monetary and Liquid Incentives to Motivate Cognitive Task Performance', *Frontiers in psychology*. Switzerland: Frontiers Research Foundation, 6, p. 2037.

Yee, D. M. and Braver, T. S. (2018) 'Interactions of motivation and cognitive control', *Current Opinion in Behavioral Sciences*. Elsevier Ltd, 19, pp. 83–90. doi: 10.1016/j.cobeha.2017.11.009.

Yokochi, M. (2007) 'Mesolimbic and mesocortical pathways in Parkinson disease', *Brain and nerve= Shinkei kenkyu no shinpo*, 59(9), pp. 943–951.

Zahrt, J. *et al.* (1997) 'Supranormal Stimulation of D1 Dopamine Receptors in the Rodent Prefrontal Cortex Impairs Spatial Working Memory Performance', *The Journal of neuroscience*. United States: Soc Neuroscience, 17(21), pp. 8528–8535.

Zald, D. H. *et al.* (2010) 'The interrelationship of dopamine D2-like receptor availability in striatal and extrastriatal brain regions in healthy humans: A principal component analysis of [18F]fallypride binding', *NeuroImage (Orlando, Fla.)*. United States: Elsevier Inc, 51(1), pp. 53–62.

Zhang, H., Kiyatkin, E. A. and Stein, E. A. (1994) 'Behavioral and pharmacological modulation of ventral tegmental dendritic dopamine release', *Brain research*. Netherlands: Elsevier B.V, 656(1), pp. 59–70.

Zokaei, N. *et al.* (2014) 'Visual short-term memory deficits associated with GBA mutation and Parkinson's disease', *Brain*, 137(8), pp. 2303–2311. doi: 10.1093/brain/awu143.

Zokaei, N. *et al.* (2016) 'ScienceDirect Sex and APOE : A memory advantage in male APOE ε 4 carriers in midlife', *CORTEX*. Elsevier Ltd, 88, pp. 98–105. doi: 10.1016/j.cortex.2016.12.016.

Zokaei, N. *et al.* (2019) 'Binding deficits in visual short-term memory in patients with temporal lobe lobectomy', (November 2017), pp. 63–67. doi: 10.1002/hipo.22998.

Zokaei, N. *et al.* (2020) 'Short-term memory advantage for brief durations in human APOE ε 4 carriers', *Scientific Reports*. Springer US, pp. 1–10. doi: 10.1038/s41598-020-66114-6.

Zokaei, N. and Husain, M. (2019) 'Working Memory in Alzheimer's Disease and Parkinson's Disease.', *Hodgson T. (eds) Processes of Visuospatial Attention and Working Memory*, 41, pp. 325–344.

8. Appendix

8.1. Memory-guided saccades: Omnibus analyses

8.1.1. Precision measured by Euclidean distance to target

		F_A	p
Initial saccades			
	reward	(2, 21014.43) = 0.917	= .400
	drug	(2, 21028.64) = 16.72	< .001
	memory load (1/4)	(1, 21018.39) = 1386.87	< .001
	drug* memory load	(2, 21014.91) = 3.56	= .028
	drug*reward	(4, 21013.38) = 1.22	= .344
	reward*memory load	(2, 21013.23) = 0.65	= .528
	reward*drug*memory load	(4, 21013.27) = 1.72	= .142
Sequence			
	reward	(2, 36982.42) = 0.13	= .324
	drug	(2, 37004.53) = 7.18	= .001
	serial position	(3, 36981.58) = 80.19	< .001
	drug*reward	(4, 36980.29) = 1.02	= .398
	serial position*reward	(6, 36979.05) = 1.30	= .252
	drug*serial position	(6, 36979.62) = 0.91	= .482
	reward*drug*memory load	(12, 36979.04) = 0.81	= .645

8.1.2. Saccadic peak velocity

		F_A	p
Initial saccades			
	reward	(2, 21042.00) = 87.43	< .001
	drug	(2, 21042.00) = 0.002	= .999
	memory load (1/4)	(1, 21042.00) = 117.94	< .001
	reward*drug	(4, 21042.00) = 2.27	= .059
	reward* memory load	(2, 21042.00) = 2.77	= .063
	drug*memory load	(2, 21042.00) = 0.53	= .590
	reward*drug*memory load	(4, 21042.00) = 1.00	= .406
Sequence			
	reward	(2, 36932.41) = 121.67	< .001
	drug	(2, 15246.33) = 0.101	= .904
	serial position	(3, 36950.60) = 12.11	< .001

	serial position *reward	(6, 36984.16) = 0.04	= .101
	drug*reward	(4, 36988.47) = 1.06	= .377
	drug*memory load	(6, 36991.91) = 0.04	= 1.00
	reward*drug*memory load	(12, 36984.55) = 1.25	= .243

8.1.3. Saccadic reaction time

		F_A	p
Initial saccade			
	incentive	(2, 25118.35) = 7.31	= .001
	drug	(2, 25124.27) = 21.32	< .001
	memory load (1/4)	(1, 25132.67) = 67.99	< .001
	memory load*incentive	(2, 25118.34) = 0.01	= .990
	drug*incentive	(4, 25118.18) = 0.42	= .795
	drug*memory load	(2, 25118.34) = 1.59	= .202
	reward*drug*memory load	(4, 25118.17) = 0.41	= .802

AMI questionnaire

Below are a number of statements. Each statement asks you to think about your life over the last 2 weeks.
For each statement, select how appropriately it describes your life right now. Select "Completely true" if the statement describes you perfectly, "Completely untrue" if the statement does not describe you at all over the last 2 weeks, and use the answers in between accordingly.

		Completely UNTRUE	Mostly untrue	Neither true nor untrue	Quite true	Completely TRUE
1	I feel sad or upset when I hear bad news.	☐	☐	☐	☐	☐
2	I start conversations with random people.	☐	☐	☐	☐	☐
3	I enjoy doing things with people I have just met.	☐	☐	☐	☐	☐
4	I suggest activities for me and my friends to do.	☐	☐	☐	☐	☐
5	I make decisions firmly and without hesitation.	☐	☐	☐	☐	☐
6	After making a decision, I will wonder if I have made the wrong choice.	☐	☐	☐	☐	☐
7	Based on the last two weeks, I will say I care deeply about how my loved ones think of me.	☐	☐	☐	☐	☐
8	I go out with friends on a weekly basis.	☐	☐	☐	☐	☐
9	When I decide to do something, I am able to make an effort easily.	☐	☐	☐	☐	☐
10	I don't like to laze around.	☐	☐	☐	☐	☐
11	I get things done when they need to be done, without requiring reminders from others.	☐	☐	☐	☐	☐
12	When I decide to do something, I am motivated to see it through to the end.	☐	☐	☐	☐	☐

UPPSP-P

SHORT UPPS-P (Cyders et al., *Addictive Behaviors*, 2014)

Table 1. *Final Items Included in the SUPPS-P (Lynam, 2013)*

Negative Urgency (*M* = 1.35, *SD* = 0.70; Range: 0.00 – 3.00; α = 0.78)	
6. (17.)	When I feel bad, I will often do things I later regret in order to make myself feel better now. **(R)**
8. (22.)	Sometimes when I feel bad, I can't seem to stop what I am doing even though it is making me feel worse. **(R)**
13. (29.)	When I am upset I often act without thinking.* **(R)**
15. (34.)	When I feel rejected, I will often say things that I later regret.* **(R)**
Lack of Perseverance (*M* = 0.64, *SD* = 0.54; Range: 0.00 – 2.67; α = 0.79)	
1. (4.)	I generally like to see things through to the end.*
4. (14.)	Unfinished tasks really bother me.
7. (19.)	Once I get going on something I hate to stop.
11. (27.)	I finish what I start.
Lack of Premeditation (*M* = 0.80, *SD* = 0.56; Range: 0.00 – 2.50; α = 0.85)	
2. (6.)	My thinking is usually careful and purposeful.*
5. (16.)	I like to stop and think things over before I do them.
12. (28.)	I tend to value and follow a rational, "sensible" approach to things.
19. (48.)	I usually think carefully before doing anything.*
Sensation Seeking (*M* = 1.78, *SD* = 0.73; Range: 0.00 – 3.00; α = 0.74)	
9. (23.)	I quite enjoy taking risks.* **(R)**
14. (31.)	I welcome new and exciting experiences and sensations, even if they are a little frightening and unconventional.* **(R)**
16. (36.)	I would like to learn to fly an airplane. **(R)**
18. (46.)	I would enjoy the sensation of skiing very fast down a high mountain slope. **(R)**
Positive Urgency (*M* = 0.90, *SD* = 0.74; Range: 0.00 – 3.00; α = 0.85)	
3. (10.)	When I am in great mood, I tend to get into situations that could cause me problems. **(R)**
10. (20.)	I tend to lose control when I am in a great mood. **(R)**
17. (35.)	Others are shocked or worried about the things I do when I am feeling very excited. **(R)**
20. (52.)	I tend to act without thinking when I am really excited.* **(R)**

Note. Item numbers indicate the item order on the Short UPPS-P, whereas numbers in parentheses indicate the original item numbers on the UPPS-P. All items are rated on a four point scale from 1 (strongly agree) to 4 (strongly disagree). Items with an (R) are reverse coded, so that higher values indicate more impulsive behavior. Total subscale or Mean subscale scores can be calculated. * indicates that the item is also present in the French Short UPPS-P Scale. † indicates that the item is also present in the Spanish Short UPPS-P Scale.

(R) indicates the item needs to be reverse scored such 1=4, 2=3, 3=2, and 4=1

BIS/BAS

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses.

Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life.
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.
3. I go out of my way to get things I want.
4. When I'm doing well at something, I love to keep at it.
5. I'm always willing to try something new if I think it will be fun.
6. How I dress is important to me.
7. When I get something I want, I feel excited and energized.
8. Criticism or scolding hurts me quite a bit.
9. When I want something, I usually go all-out to get it.
10. I will often do things for no other reason than that they might be fun.
11. It's hard for me to find the time to do things such as get a haircut.
12. If I see a chance to get something, I want I move on it right away.
13. I feel pretty worried or upset when I think or know somebody is angry at me.
14. When I see an opportunity for something, I like I get excited right away.
15. I often act on the spur of the moment.
16. If I think something unpleasant is going to happen, I usually get pretty "worked up."
17. I often wonder why people act the way they do.
18. When good things happen to me, it affects me strongly.
19. I feel worried when I think I have done poorly at something important.
20. I crave excitement and new sensations.
21. When I go after something, I use a "no holds barred" approach.
22. I have very few fears compared to my friends.
23. It would excite me to win a contest.
24. I worry about making mistakes.