Frontostriatal contributions to reward processing

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I, Sanjay George Manohar, 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

Dopaminergic projections to striatum and prefrontal cortex are thought to signal rewards, thereby energising movement, facilitating learning, and motivating effort. Extensive evidence links reward to attention and to dopamine. However a direct characterisation of how dopamine influences reward sensitivity in humans is lacking.

This thesis examines the effects of dopamine and reward on eye movements. First, I introduced incentive manipulations into an “oculomotor capture” task, in which involuntary saccades are generated towards salient distractors. Whereas rewards increased both speed and accuracy, penalties slowed responses while increasing accuracy. A previously unreported effect is described, in which missed rewards capture attention.

Subsequently, I developed a new paradigm that manipulates incentives trial-to-trial, during a speeded saccadic distraction task. In healthy volunteers, reward reduced distractibility and increased vigour (in terms of reaction time and velocity), and pupillary dilatation reflected reward expectation. This new task was then employed in a pharmacological study, in which I found that the dopaminergic D2-selective agonist cabergoline increased reward sensitivity in healthy volunteers.

Parkinson's disease (PD) results in dopamine deficiency. PD patients performing my task had reduced reward sensitivity in saccade velocity and distractibility, as well as pupil dilatation. Patients were compared on versus off their dopaminergic medication, and although oculomotor vigour did not improve, medication normalised their blunted autonomic responses.

Finally, 20 patients with medial prefrontal damage following subarachnoid haemorrhage performed the oculomotor task. Using lesion mapping, I found specific medial orbitofrontal regions in which damage correlated with reduced reward sensitivity.

The results demonstrate that the extent to which reward invigorates behaviour is influenced by dopamine. Importantly, reward improves both speed and accuracy, contravening the theoretically predicted trade-off. To resolve this paradox, I develop an extension of optimal control theory that includes a costly precision signal. This model helps conceptualise reward's power to improve both speed and accuracy.

Contents in Brief

Table of Contents

Table of Contents

List of Figures

1. Introduction

2. Missed rewards capture attention

3. Trial-to-trial incentives influence oculomotor capture

4. Cabergoline increases reward sensitivity of distraction

5. Effect of Parkinson's disease and medication

6. Abnormal reward sensitivity after medial prefrontal lesions

7. Control cost explains the effect of reward

8. General discussion

List of Tables

List of Equations

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I would like to remember the late Prof. Jon Driver, who was my secondary supervisor, and whose untimely passing left us all bereft of a towering intellect. His inspiration over the years formed the seeds of this PhD, and I hope that this thesis strives to some extent in the direction of one of Jon's goals - the influence of reward on attention in the brain.

I would like to thank my parents and my brother, who have given me immense support throughout my childhood and adult life, and who are almost certainly more proud than I am of my PhD accomplishments so far. Particular thanks go to my wife Rina for her patience and resolute belief in me over the last four years.

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1. General Introduction

Rewards are defined by being the objects of all strivings. Without rewards, neither action nor decision can be motivated. Equivalently, one might say that rewards are *valuable* to the organism (McClure, Daw, and Montague 2003). Rewards may be apparent or covert, they may be objects or abstract goals, they may be real or imaginary, they may be for immediate consumption or even be transposed onto other people. Reward manifests in behaviour in a number of ways, depending on how it is represented:

- When it is part of a future *plan*, it is called a goal.
- When it is *predicted* in the future, it is called expected reward.
- When an actual reward is measured *relative to the expected reward*, it is a reward prediction error.
- When rewards are represented as *consequences of actions*, they are informative feedback (Dayan and Balleine, 2002).

Research has explored how rewards might be bound, under various circumstances, to *objects*, *actions*, *locations*, and *times* (in the form of memories) (Murphy and Miller 1955; Gaffan 1979; Takikawa, Kawagoe, and Hikosaka 2002a; Rushworth et al. 2004; Lisman, Grace, and Duzel 2011). Common to all these, reward appears to imbue things with *salience* (Berridge, 2012), that is, a significance that makes the reward's context more relevant for the future. When salience drives action, this has been referred to as motivation; when salience drives perception, it is called attention.

In this thesis, I consider the relationship between attention and reward, the role of dopamine in modulating attention as a function of incentives and the effects of brain

pathology in human medial prefrontal cortex and in Parkinson's disease (PD) on attentional responses modulated by reward.

1.1. Attention: defining salience and goals

Attention is our ability to selectively process stimuli in the environment (Broadbent, 1958; Driver, 2001; Treisman and Gelade, 1980). An archetypal example is the property of the visual system to focus only on a subregion of space (Duncan, 1980; Posner et al., 1980). Attention allows the exclusion of some elements of the environment, and inclusion of other elements, in further sensory processing, in decision-making, and in the generation of actions (Posner and Petersen, 1990).

Sometimes we direct attention to items because they have high sensory salience. At other times, we direct attention to items because we expect them to be useful, even when they are not perceptually salient (Bacon and Egeth, 1994). Sensory salience is usually considered to be a property of the stimulus that is not dependent on the state of the observer, for example loud noises in a quiet setting, or sudden lights in a dark environment (Itti and Koch, 2001; Koch and Ullman, 1985). However, sensory salience is not *inherently* a property of stimuli alone; rather it is a function of both the stimulus and the organism: what counts as salient for an organism is determined by its sense organs, and how information encoded by them is processed.

Thus sensory salience is fundamentally determined by evolution: salient items command our attention more than non-salient items probably because they indicate an important, time-critical change in the environment. For example, loud noises or sudden visual onsets are salient to many animals, perhaps because they permit rapid detection

of predators or prey, and therefore have survival implications. Under this framework, one might *define* salience simply as that which commands our attention.

Attention can on the other hand also be guided by an organism's own internal state. This might be governed by beliefs (e.g. Pavani et al., 2000), prior conditioning (e.g. Dayan et al., 2000), or task-dependent setting of priorities (e.g. Hodgson et al., 2000). One important subset of these state-dependent effects is the *goal-directed control of attention* (Corbetta and Shulman, 2002). An enormous variety of cognitive tasks have been used to study goal-directed attention, ranging from simple cueing, predictability, and search templates, to complex task-switching (Ridderinkhof et al. 2011).

A common feature of all these forms of control is their flexibility (Norman and Shallice, 1980; Picton et al., 2006; Stuss et al., 1995), and to distinguish such control from *stimulus-driven orienting of attention*, they are sometimes termed 'top-down' control mechanisms. Flexibility implies performance can vary; but not simply because of limitations due to attention or resources dwindling. It implies that performance can vary specifically in ways that benefit an organism, and critically, that performance can be influenced by *reward* (Pessoa, 2009; Ursu and Carter, 2005).

In the studies presented in this thesis, I aim to manipulate rewards and penalties to measure how expectation of reward can influence the control of attention. The main question I intend to answer is: to what extent and in what ways can rewards and penalties alter the processing of visually salient events? First, in **section 1.2.2**., I introduce the issue of attention and reward, then in **section 1.2.3**, I consider the use of gaze shifts as a marker of the deployment of attention, and finally in **section 1.2.4**, I review current understanding of the interaction of top-down and bottom-up signals in the orienting of attention, particularly with respect to the effects of salient abrupt visual

onsets which often capture attention and gaze. **Sections 1.2.5** to **1.2.8** examine four influential experimental paradigms which have hitherto been used to study reward in attention: contingent attentional capture, reward association, trial-to-trial priming, and location-specific reward.

1.2. Attention and reward

In the following section I will review some evidence that attention is under the *control of goals*, which are assigned *value* according to reward. Firstly, I will discuss how one might quantify rewards, and then comment on how attentional selection might be improved by incentives. I will then explore some key studies that demonstrate that under some circumstances, attentional capture is indeed influenced by goals. Finally I discuss paradigms in which learnt reward associations guide attention, and conclude that in those particular studies, rewards act not as goals, but rather to *amplify* low-level perceptual salience.

1.2.1. Reward and utility

Microeconomics, which concerns itself with how individuals make decisions based upon preferences, heuristics and assets, distinguishes clearly between value and utility (Rangel et al., 2008; Stuphorn, 2006). Whereas value exists in the world, between people, utility is the subjective quantity that is assigned to a valued reward. Utility is a construct designed to allow seemingly contradictory behaviours to be understood. For example, in the Allais paradox (Allais, 1953), people are offered a choice between the two options

A: (certain £1m)

B: (89% chance of £1m, 10% chance of £5m, or 1% chance of nothing)

and it turns out that people prefer A (certain £1m) to B. The expected value of B is of course 39% larger than the value of A, but we might like to say that its *utility* is smaller. This can be captured by a utility function showing risk aversion, in that compared to the default of £1m, the 1% outcome of getting zero is highly unpleasant (**Figure 1.1**) —in fact it is worth sacrificing £390,000.

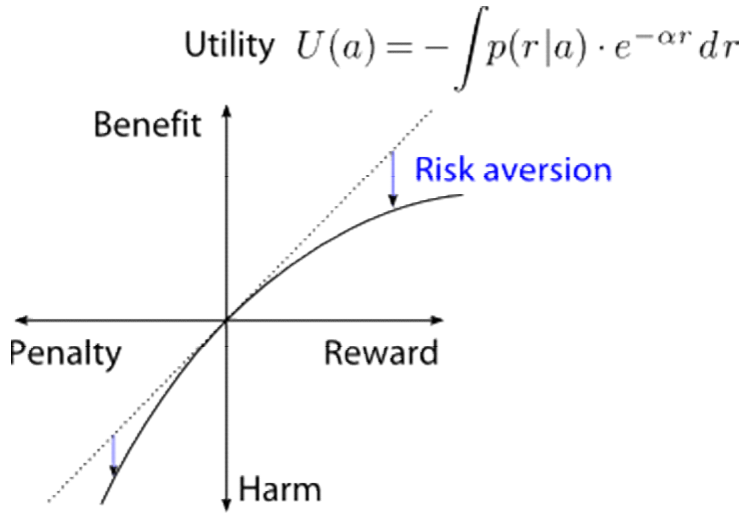


Figure 1.1: Utility links an organism's needs to rewards in its environment.
It makes ecological sense for losses to be overweighted compared to gains, if the *status quo* does not pose an imminent danger. Therefore the utility function is often concave. The simplest utility function for a particular state or action can be specified as the product of probability and an exponential function of reward, integrated over all possible outcomes.

However when people are given a choice between:

C: (10% chance of 5m, 90% chance of nothing)

D: (11% chance of 1m, 89% chance of nothing)

people generally prefer C to D. There is a 1% greater chance of getting zero in C than D, and C is again worth £390,000 more than D in terms of expected value. So in this

situation, simple expected value cannot account for why people will tolerate a 1% chance of losing in C>D, but not in A>B. The standard explanations are that:

a) probabilities also obey a subjective scaling law, such a subjectively weighted utility (Karmarkar, 1979)

b) utility functions have a reference point, such that the 'zero-point' of A/B is different to C/D (cumulative prospect theory, (Tversky and Kahneman, 1992))

c) a second criterion is in play, such as aspiration levels in the security-potential/aspiration model (Lopes and Oden, 1999)

d) a priority heuristic is used, meaning that some attributes are not used for decision-making unless other attributes have drawn a tie (Brandstätter et al., 2006).

These considerations of *loss aversion* and *probability discounting* have directed several studies of the representation of subjective reward value in the brain during decisions (Glimcher and Rustichini, 2004; Platt and Glimcher, 1999; Tobler et al., 2008). However, an economic approach is less often applied to motivation by rewards, especially in humans (Berridge and Robinson, 2003; Niv et al., 2006). Motivation, the mechanism by which reward can overcome behavioural costs, has proved more difficult to study.

1.2.2. Economics of distraction

In a teleological sense, one might expect anticipation of the reward value of a goal to exert an influence on *stimulus-driven* orienting of attention, e.g. as indexed by distraction mediated by abrupt visual onsets. In particular, if an organism expects a high value from continuing its current goal, it makes economic sense for it to ignore

distractions more effectively. The balance is tipped in favour of the goal precisely when the danger posed by ignoring the distraction is *smaller* than the expected value of the current goal.

In animal studies, reward and penalty are the only methods of manipulating *goal-driven* attention. Goals are set by making primary rewards contingent on the stimulus or action, and thus the neural attention and reward expectation are usually conflated (Bendiksby and Platt, 2006; Maunsell, 2004). Rewards in human studies have often consisted merely of "correct" or "incorrect" feedback. More recently monetary rewards have been explored, and in some cases, primary rewards, such as food or drink (Kringelbach et al., 2003; Levy and Glimcher, 2011). Using reward in the study of human cognitive control has the advantage of allowing quantitative assay of goal-directed effects, both in magnitude and valence, as well as paralleling the animal neurophysiological literature. The consensus is that real monetary rewards may have almost the same incentive salience as 'virtual' money rewards (Bickel et al., 2009; Irwin et al., 1992).

Over the last 10 years, the use of reward has gained currency in human studies of goal-directed control. Rewards *attenuate* distractor effects in the Eriksen flanker task (Hübner and Schlösser, 2010) and Stroop task (Krebs et al., 2011). These reports provide fresh evidence that reward manipulations cannot easily be accounted for purely in term of speed-accuracy trade-off or ‘criterion shifts’: a true motivational change appears to be involved. But motivation by rewards and penalties play rather different roles in controlling behaviour (O’Doherty et al. 2001; Frank, Seeberger, and O’Reilly 2004) , and may have different neural representations (Roesch and Olson, 2004, see Bissonette et al., 2014 for a recent review). One might expect, then, that they would

influence attention in an asymmetrical way. For example, penalty might conceivably increase caution whereas reward might promote impulsive responding; perhaps penalty might even repel attention.

More recently, interest has arisen in the effects of reward on the orienting of attention in the face of distractors (Kiss, Driver, and Eimer 2009; Kristjánsson, Sigurjónsdóttir, and Driver 2010; Hickey, Chelazzi, and Theeuwes 2010a; Anderson, Laurent, and Yantis 2011a). However, to my knowledge, no studies to date have parametrically varied reward and penalty in a distraction task.

But how best to measure the effects of reward and penalty on the deployment of attention? Typically, we can either measure orienting movements (overt attention, Posner 1980; Posner and Cohen 1984) or attentional changes in the absence of movement (covert attention) e.g. selectively listening to one conversation in a cocktail party (Cherry, 1953). In this study I focus on eye movements, but there are many reasons—discussed below—to believe that both overt and covert attention have neural mechanisms in common, with eye movements providing an objective index of where attention is prioritised.

1.2.3. Parallels between overt and covert attention

Helmholtz (von Helmholtz, 1962) noted that even when he kept his eyes fixed on the same spot, he was able to move his attention from one location to another, with the consequence that he was better at detecting brief flashes at the location he was attending to, independent of their retinal location. This suggested that overt and covert attention can be dissociated. Since then a wealth of behavioural data shows that visual processing can be enhanced in regions of space independently of fixation location (Eriksen and

Eriksen 1974; Posner, Snyder, and Davidson 1980). Many metaphors alluded to the spatiotemporal properties of attention, including filters, spotlights and zoom lenses (Eriksen and St James, 1986; LaBerge, 1983).

More rigorously, Remington (1980) attempted to separate shifts of attention from saccades using peripheral and central arrow cues, as well as modulating target location probability. He showed that, when required, subjects could sometimes detect probes better at locations short of the saccade target even 20ms before a saccade, arguing for separability of overt and covert attention.

However subsequent studies suggested that attention and eye movements are actually very closely related. In a visual search task, saccadic latencies vary in tandem with the movement of attention (McPeek et al., 1999). Furthermore, in many situations, attention obligatorily follows saccades. When saccades and endogenous (target-probability driven) attention are required in opposite directions, responses are faster to the saccade targets until about 200 ms after the saccade (Shepherd et al., 1986). Similarly, making a saccade just after identifying a letter improves letter identification at the saccade target, and worsened identification at the opposite location, even when saccade direction was kept constant within a block (Hoffman and Subramaniam, 1995). These authors also found reaction times (RTs) were longer when concomitant saccades were required. These findings strongly suggest that eye movements and the movement of attention might share some common mechanisms.

A stronger proposal is that orienting of visuospatial attention is effectively identical with preparation of eye movements (Rizzolatti et al., 1987; Sheliga et al., 1994). In support of this, the same spatially selective neurones in superficial layers of superior colliculus are active in a saccadic task and a visual detection task for a given

expected stimulus location (Wurtz and Goldberg, 1989). Both overt and covert attention also appear to share neural mechanisms as demonstrated by PET studies in humans (Corbetta et al. 1993) and fMRI (Corbetta 1998; Corbetta and Shulman 1998).

For these reasons, I argue that an experimental stimulus that provokes eye movements also draws attention to that location (although the converse does not always hold—see Belopolsky and Theeuwes 2012) . Measuring saccades also has some advantages. Firstly, in a situation in which, on a single given trial, attention may or may not move, measuring gaze shifts I would argue gives a direct indication that attention has moved, unlike in measures of covert attention. Secondly, saccadic reaction time (SRT) arguably provides a better index of the moment at which attention shifts, than manual reaction times, because of the close connection between attention shifts and eye movements, discussed above.

1.2.4. Top-down versus bottom-up guidance of attention

One way to test the effect of rewards on the processing of visual salience is to investigate the effects of abrupt visually salient stimului. Such stimuli are known to attract both eye movements and covert attention (Posner 1980). Salience is thought to direct attention via so-called ‘bottom-up mechanisms’ (Itti and Koch, 2001; van Zoest and Donk, 2004). One would expect that rewards and penalties, by virtue of being motivational, would generate effects in line with other goal-directed (or ‘top-down’) factors that influence attention (Maunsell, 2004). I will therefore discuss some important instances of the interaction between other goal-directed and stimulus-driven factors in guiding attention.

The earliest investigators of top-down factors manipulated the spatial expectation of a target, and measured accuracy of target detection or identification. Cues that predicted where a target would subsequently appear caused subjects to pay more attention to one location than another, and improved their performance. Posner (1980) found that such predictive cues had qualitatively different effects than a distracting irrelevant flash. Distracting flashes could also improve detection, but the effect was short-lived and if the target appeared late (e.g. 1 second after the flash), the effect was actually reversed. From this arose Posner's theoretical distinction between endogenously and exogenously directed attention: endogenous guidance was typically voluntary and required effortful processing, whereas exogenous guidance was deemed *involuntary* (does not require volition) and *automatic*.

A key question over the last two decades, which I hope to address in this study, has been the extent of automaticity, that is, whether exogenous processes can be overridden. Jonides (1981) provided evidence that they cannot: irrelevant transients at the target location 150 ms before a target did speed detection even when the flash statistically predicted the target to be at the opposite location. The benefit was not even mitigated by prior knowledge of the target being at a different given location, nor when subjects performed another concomitant task. A benefit at the transient location was always accompanied by a cost at other locations. It seemed that exogenous flashes exerted an *obligatory* pull on attention—a hypothesis which received confirmation from Theeuwes (1991), who noted that an irrelevant colour singleton slows search.

This began an unresolved debate between those who proposed that bottom-up processes that commanded attention could *never be fully suppressed* (Theeuwes 1991b; Belopolsky, Schreij, and Theeuwes 2010), and those who argued that top-down

processes could *always attenuate* attentional capture (Remington, Johnston, and Yantis 1992; Folk and Annett 1994).

In favour of the indefeasibility of salience, work on visual search has shown that colour singletons 'pop out'—they can be spotted much easier than targets individuated by conjunctions of features (Treisman and Gelade, 1980; Wolfe, 1994). Likewise, finding a sudden onset in an array of gradual onsets is also easy and independent of the set size (Yantis and Johnson, 1990).

However, salient items sometimes fail to capture attention even when they are the target. Subjects identify a target letter faster and without a set-size cost if it is an onset oddball, but not if it is a colour oddball, luminance increment oddball, or a luminance offset oddball (Jonides and Yantis 1988; Folk and Annett 1994), suggesting that attention might only be captured by onsets. If subjects simply have to report whether a colour or luminance singleton is present, RT is independent of set size in both cases (Folk and Annett, 1994), showing that colour singletons can be processed rapidly even though they do not guide attention.

One explanation for these findings could be that *onsets* of new objects play a special role in generating involuntary capture. In conditions when attention is initially unfocused, irrelevant visual offsets are equally as effective as irrelevant onsets in capturing attention, but when attention is endogenously directed beforehand, only onsets are effective (Theeuwes, 1991a). When 'partial' offsets and onsets which do not create or destroy visual objects are used, set-size effects have been found, indicating the capture is not fully automatic. Object creation may thus be a special case in its attention-capturing power (Watson and Humphreys, 1995).

1.2.5. Attentional capture on covert and overt attention tasks

Can prior goals alter whether attention is captured by salient stimuli? Studies to date have been surprisingly inconclusive. An important facet of the goals *vs*. salience debate is the "contingent capture" task (Folk, Remington, and Johnston 1992). In this influential paradigm, prior expectations of target *features* influence the effectiveness of a distractor in capturing attention.

The experiment involved comparing the speed of identifying a target when the target was a singleton *onset* among other simultaneous distractors, versus when it was a *colour* singleton. These two types of target were preceded by a non-informative cue which was either an onset or colour singleton, at a valid or invalid location (**Figure 1.2**).

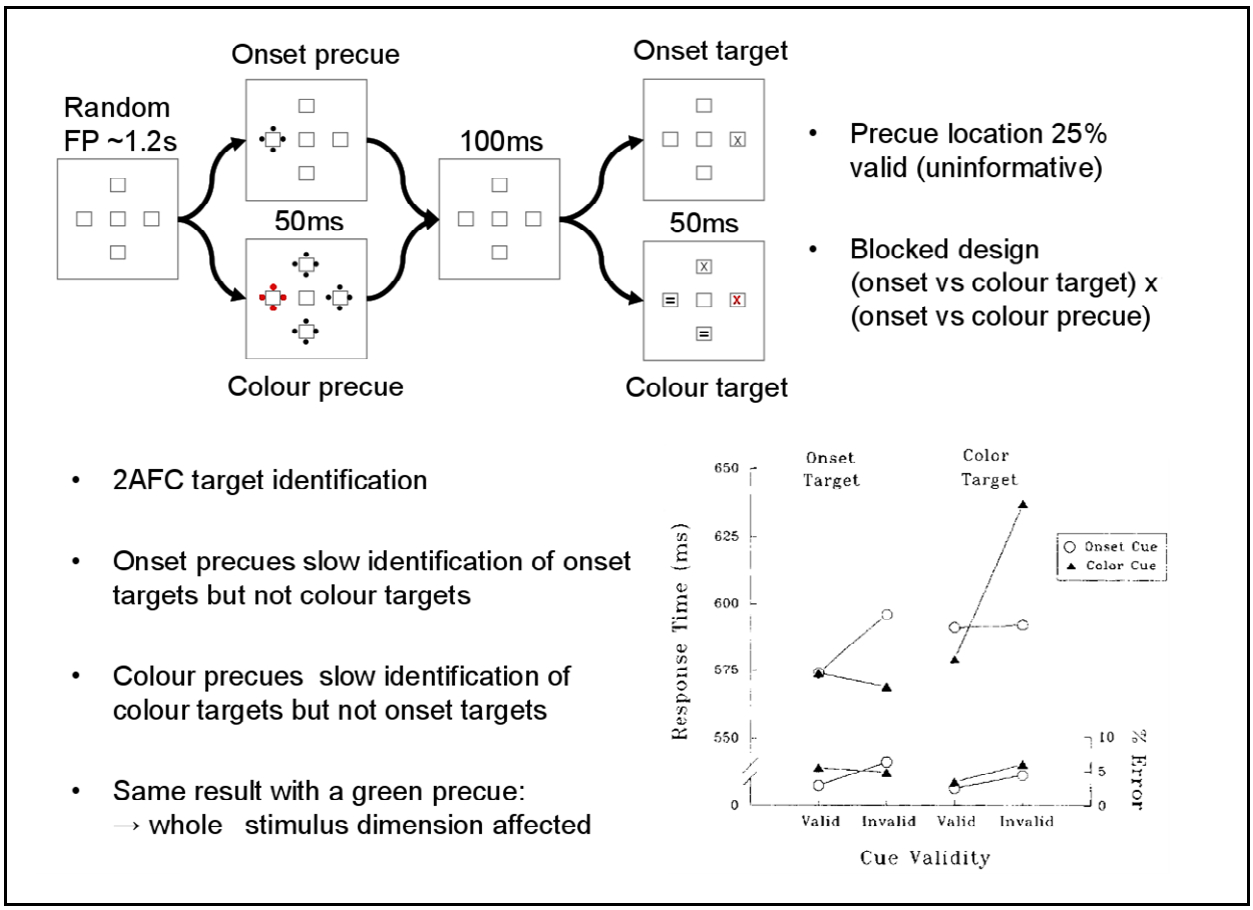


Figure 1.2: The contingent capture paradigm (Folk, Remington & Johnston, 1992).
An irrelevant precue influences the speed of detecting a subsequent target. The precue can either be in the same location (valid) as the target, or a different location (invalid). If the target is identified by its colour, then coloured precues are more distracting. If the target is identified by being an onset, then an onset precue is more distracting.

These irrelevant spatial precues produce interference only when the target was defined by the *same feature dimension* (i.e. both colour or both onsets), suggesting that involuntary shifts of attention depends on the current goal (see also Folk and Remington, 1999).

However, there are limits to the specificity of filtering in contingent capture. Although feature dimensions can be selected, individual colours cannot (Remington, Johnston, and Yantis 1992). Moreover, even having a clear attentional set for a colour *cannot* fully prevent distraction by an irrelevant onset (Schreij et al., 2008). It is not clear whether such effects reflect true attentional capture, or simply non-spatial alerting effects or filtering costs (Folk Remington and Wu, 2009). One way to distinguish these alternatives is that if contingent capture were truly related to attentional set, it ought to be under voluntary control. This is not always the case, since completely nonpredictive precues can capture attention even if subjects are adopting an attentional set for a different colour (Belopolsky, Schreij, and Theeuwes (2010)..

Thus the findings from contingent capture experiments using manual reaction time as an index of attentional deployment are inconclusive. They raise the question of the precise mechanism of top-down control in attentional capture. An alternative way to study attentional capture is to use gaze shifts as a more direct probe of the location of attentional deployment.

Theeuwes et al. (1998) devised a paradigm where an eye movement was required to a target that was defined as the item in the display that does not change in colour. On some trials, a distractor was present, which caused an erroneous eye movement to the distractor (**Figure 1.3**). This 'capture' of the eyes can be used to measure how attention is allocated in a bottom-up or involuntary manner.

In the oculomotor capture paradigm, the first eye movement is to the distractor on up to 40% of trials, and depends on the target-to-distractor angle relative to fixation; a maximum is found at about 90 degrees (Theeuwes et al. 1998). The effect is strongest when a new object appears at a novel location, rather than a location that was previously occupied. Fascinatingly, subjects are often unaware of many of their saccadic errors.

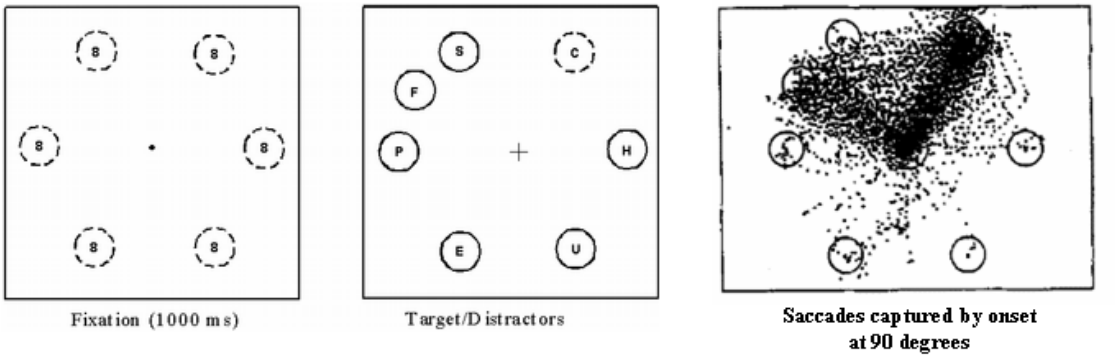


Figure 1.3: The oculomotor capture paradigm of Theeuwes et al., 1998.
Six discs are initially present, of which five change colour, and the saccade target is identified as the item that does not change. Simultaneously, a new object appears in the display. A proportion of saccades are erroneously directed towards the new object, an effect known as 'oculomotor capture'.

Even when examining only "correct" saccades, i.e. those that landed on the target, a curvature of the saccade's trajectory can be measured. Early saccades tend to curve *towards* the distractor, whereas late saccades tend to curve *away* from it (Theeuwes and Godijn 2012).

1.2.6. Reward associations and attention

Can a top-down set for a specific feature modulate capture—covert or overt—by that feature? A few recent studies have probed this using *reward* manipulations, and interestingly, the answer appears to be 'yes'. Most studies to date of reward in visual attention use an associative learning paradigm, in which reward value varies with a specific visual feature, e.g. target colour. Typically, there is a training phase, in which red and green targets (for example) are associated with high and low reward respectively (e.g. Anderson, Laurent, and Yantis 2011b). In a subsequent testing phase, without reward, attentional capture is measured for irrelevant (distractor) items of each of these colours.

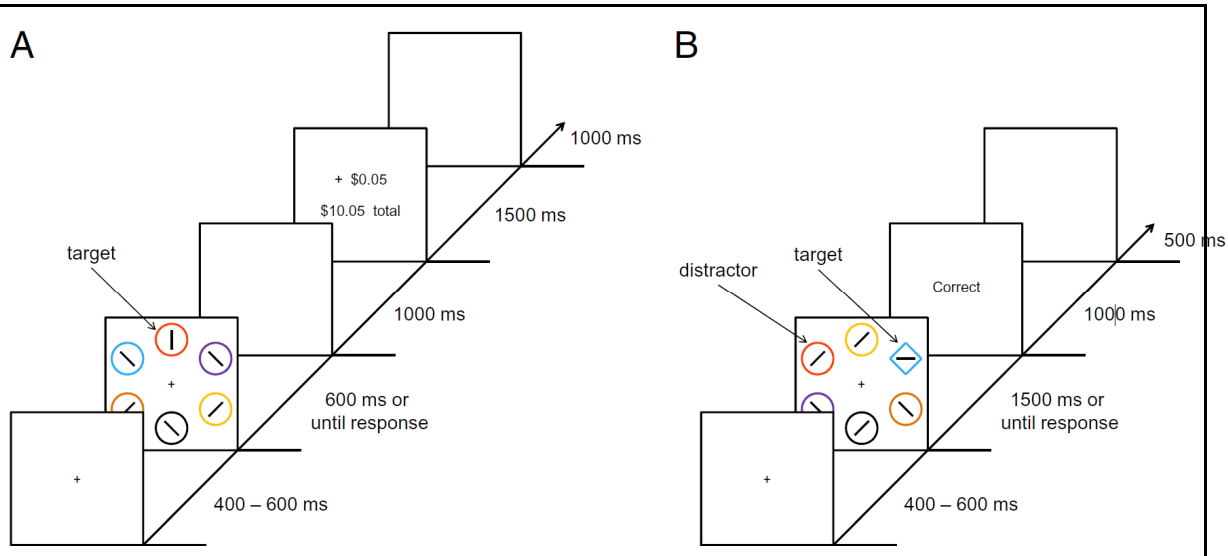


Figure 1.4: Reward associations capture attention: the experiment of Anderson, Laurent and Yantis, 2011b.

A) Participants identified a target line segment as horizontal or vertical, and reward magnitude was contingent on the colour of the surrounding shape. B) In a subsequent test phase, subjects were slower to detect a target when a distractor was present that had previously been associated with high reward, compared to low reward.

In one associative reward-learning study, Anderson Laurent and Yantis (2011b) trained 26 participants to determine the orientation of a line segment inside a coloured shape, over more than a thousand trials. The line segment could be either horizontal or vertical (**Figure 1.4A**). This target item was embedded in an array of distractors, comprising shapes of different colours, each containing a line segment that was at 45 degrees to vertical or horizontal—i.e. distractors could not generate response competition. In the learning phase, the target was always in a red or green shape, and distractors were always in other colours. Thus the colour of a shape indicated the target line with 100% fidelity, but was not strictly necessary for identifying the target, and was uncorrelated with the response required. The enclosing shapes were always constant. Crucially, after every correct response, subjects received reward contingent on the colour of the shape surrounding target, either 1 cent or 5 cents.

In the subsequent test phase, participants had to perform a similar orientation discrimination on a horizontal or vertical line segment, amongst distractors which were at 45 degrees (**Figure 1.4B**). In this phase, the target was designed to pop out, being enclosed in a shape that was unique compared to the distractors. Crucially the colours of these shapes were irrelevant, but on 50% of the trials one of the distractors was red or green (the target was never red or green). The key finding was that RT was faster when a distractor in a previously high-reward colour was present, compared to when a low-reward colour distractor was present. Both red and green distractors resulted in slower RTs than when all distractors were neutral colours. This suggests that features previously associated with rewards are more distracting.

The authors concluded that, since the distractors were neither physically salient, nor goal-relevant (i.e. had no features in common with the target), the reward effect

cannot be accounted for by simple bottom-up or top-down accounts, unless reward association itself contributes to perceptual salience. They also found that individuals with lower working memory capacity were more susceptible to this reward effect.

Subsequent studies have shown that eye movements are also more likely to be directed towards colours associated with high-reward (Anderson and Yantis 2012), and there is even generalisation of these effects from visual search to a flanker task (Anderson, Laurent, and Yantis 2012).

To my knowledge, only one reward-association study has been performed using the oculomotor capture task. In that study (Theeuwes and Belopolsky 2012), during training, subjects made saccades to the horizontal or vertical bar amongst other shapes, and were rewarded higher for horizontal than vertical bars (or vice versa). In a subsequent test phase, they had to look towards an equiluminant colour change, but on two-thirds of trials a horizontal or vertical bar was added to the display. The orientation previously associated with high reward produced more oculomotor capture than the orientation associated with low reward (Theeuwes and Belopolsky 2012).

These experiments argue that stimulus-reward associations can influence allocation of attention at an early stage of processing. Classical theories of attention have often given a special role to *spatial location* in attentional selection (Broadbent 1958; Tsal and Lavie 1988; Theeuwes, Van der Burg, and Belopolsky 2008). Therefore an interesting question is whether a spatial location associated with reward also influences the *subsequent* guidance of attention, a question that I focus on in some of my experiments.

1.2.7. Trial-to-trial effects in reward association studies

After making a response, subsequent effects on behaviour are often indexed experimentally by trial-to-trial effects. These have classically been shown to affect anticipation (Granjon and Reynard, 1977), conflict resolution (Gratton et al., 1992; Nieuwenhuis et al., 2006), and task switching (Rogers and Monsell, 1995). Trial-to-trial effects in visual search have also been reported, both for distractor and target identity (Hickey and Theeuwes, 2008; Pinto et al., 2005), as well as for location (Shore and Klein, 2001). An open question is whether short-term reward effects also occur.

Trial-to-trial effects of reward have been documented in associative learning paradigms (Anderson, Laurent, and Yantis 2011a), resulting in forms of priming for the previously highly-rewarded feature.

Such effects have prompted several researchers to ask the question: is it just current rewards that influence orienting, or could *previous* successes and failures to obtain reward also contribute? Recent studies have demonstrated that, on short timescales, *reward can influence distraction* (Camara, Manohar and Husain 2013; Della Libera and Chelazzi, 2009).

A consistent finding in visual search is that, on trials where a feature is selected for, and a subsequent response is rewarded, this feature attracts attention on the next trial (Hickey et al., 2009, 2010b, 2011; Kristjánsson et al., 2010). Studies that have examined the 'priming of pop-out' in visual search show that this is greater on rewarded trials, with *persistence of colour-based selection* on to the next trial, despite colour being an irrelevant feature (Hickey et al., 2006).

Indeed, it has been hypothesised that rewards affect initial target localisation, but not subsequent attentional filtering of distractors (Hickey et al., 2011). In this latter study, distractors and targets could either be the same colour or a different colour to the previous trial. By comparing constant—versus variable—coloured distractors and targets, Hickey et al. were able to separate the contribution of feature-priming to target selection and distractor inhibition. They found that previous rewards speeded search for the previous trial's *target* colour, but had no effect on the ability to filter out the previous trial's distractor colour. They hypothesised that rewards affect initial target localisation, but not subsequent attentional filtering of distractors. This design, which separates the repetition of features in the target or distractor, inspired my study of **section 2.3** which uses spatial location. In a follow-up study that employed pop-out of both colour and orientation, in a much larger display array, reward influenced the effect of the features selected on the previous trial upon both subsequent targets *and* subsequent distractors (Hickey and van Zoest, 2013).

These studies all examined the effect of reward on specific features of targets, rather than spatial locations per se. Location-specific slowing for search targets preceded by a distractor that had previously been associated with reward has also been observed (Anderson, Laurent, and Yantis 2011a). But, using this covert attention paradigm, the investigators were unable to determine on which trials attention actually went to a given location. Furthermore, as Theeuwes and Belopolsky (2012) point out, it is not possible to distinguish true bottom-up attentional capture from increased "attentional holding" due to difficulty distinguishing targets from distractors. However, measuring gaze shifts provides a way potentially to circumvent such problems, a strategy I employ in the studies reported here.

1.2.8. Spatially Contingent Rewards

One very direct way to examine how stimulus salience and reward might be integrated is to study simple visual saccades to a rewarded region with an immediately neighbouring penalised region, while varying the visual salience of these two regions (Stritzke et al., 2009). Here penalties have a small but significant effect on reducing the variability of saccadic endpoints. The generated biases can be accounted for by a linear model weighting luminance (stimulus salience) and reward to determine saccadic endpoints (Schütz and Gegenfurtner, 2010). Interestingly this model reveals that *earlier* saccades are governed more by stimulus salience than later saccades.

A tidy interpretation of this is that value information is gradually integrated during the course of a trial, a view supported by the finding that later saccades curve more towards the rewarded region than earlier saccades (Schütz et al., 2012a). Similar intra-trial reward-integration effects have been observed in monkeys (Markowitz et al., 2011). These findings are contrary to the suggestion of Hickey et al. (Hickey et al., 2011), that reward is effective in the initial target localisation phase but not the later distractor-filtering stage. One solution to these apparently contradictory proposals is that spatially contingent rewards follow a different time-course of integration to feature-contingent rewards.

Two previous investigations used oculomotor capture to measure the location-specific effect of reward on orienting. In one study, subjects learnt that rewards are greater on one side of space than another (asymmetrical reward), and these spatial differences in expectation of reward modulated oculomotor preparation (Milstein and Dorris, 2007a). Crucially, the proportion of oculomotor capture to irrelevant but salient onsets was greater on the higher-reward side.

In a related study in which the timing of the distractor was varied, a build-up of reward-related modulation was seen over time within each trial (Ding and Hikosaka, 2007a). Both these experiments show a location-specificity in the effect of reward on oculomotor preparation. However, the studies both examined reward-location associations that had been gradually learnt over time. To my knowledge, no study has systematically studied the immediate location-specific effect of reward, as opposed to learned reward contingencies.

How can a single system explain the multitude of effects of contingent capture, feature associations, trial-to-trial effects and spatial reward biases? To solve this, some authors have proposed a *priority map* or integrative map, in which goals, memories and biases, and physical stimulus salience are combined on a two-dimensional representation (Awh et al., 2012; Fecteau and Munoz, 2006; Wolfe, 1994). Although the brain localisation of priority maps is a subject of debate, there is consensus that it is likely to integrate input from both occipital and frontal brain areas, and exert influences on both the temporal and parietal pathways of sensory processing (Bisley and Goldberg, 2010; Ipata et al., 2009).

To summarise what is known of the interaction between attention and reward, long term training by associating colours and spatial locations with reward can appear to create salience much like perceptual salience. However there is also some evidence that flexible control over bottom-up factors can be driven by rewards.

1.3. Neuroscience of reward and attention

1.3.1. Neural encoding of reward

In this section I consider some key evidence regarding neuronal responses to rewards. In particular, I critically examine evidence that dopamine's primary role is to signal reward, using data from single-cell recordings in midbrain, striatum and cortex. Finally I discuss evidence that medial prefrontal cortex represents rewards, drawing on functional imaging and animal lesion studies.

Early neuronal studies of reward used intracranial self-stimulation (Bramham and Milner, 1954; Poschel et al., 1974; Smith and Coons, 1970). A network of connected loci that supported self-stimulation—including the medial forebrain bundle, septal nuclei, mediodorsal thalamus, lateral hypothalamus, amygdala, nucleus accumbens and orbitofrontal cortex (OFC)—were found to be activated by the sight or taste of food, specifically when the animals were hungry (Ono et al., 1980; Rolls, 1972; Rolls et al., 1980).

The medial forebrain bundle, which most strongly reinforced self-stimulation, carries five major catecholamine pathways: the dorsal and ventral noradrenergic bundles, and the nigrostriatal, mesolimbic and mesocortical dopaminergic pathways. Ablation studies showed that septal nuclei, amygdala and OFC are activated by but not necessary for self-stimulation, whereas nucleus accumbens and medial forebrain bundle must be intact for self-stimulation to occur in other areas (Rolls, 1974). Self-stimulation was dampened by monoamine blockers such as chlorpromazine, and potentiated by monoamine agonists such as amphetamine, leading to the catecholamine hypothesis of reward (Wise, 1980; Wise and Rompre, 1989) .

Noradrenaline was a strong candidate for the mediator of the reinforcing effects of reward (Ritter and Stein, 1974), but distinguishing the effects of noradrenaline and dopamine proved difficult. This was in part because self-stimulation effects were confounded by alertness and attention, but also due to the neuroanatomical and pharmacological overlap of the two transmitter systems (Mason, 1979; Mason and Iversen, 1977; Rolls, 1971). Locus coeruleus neurones were active during feeding behaviour and supported self-stimulation (Ritter and Stein, 1973); substantia nigra and ventral tegmental neurones were also active during feeding, but did not support self-stimulation (Mora et al., 1977).

With the advent of more selective receptor blockers (such as pimozide) and selective agonists (such as pirebidil and apomorphine), stronger evidence accumulated for dopamine as the mediator of reward (Mora et al., 1976; Yokel and Wise, 1975); for reviews see (Wise, 1980; Wise and Rompre, 1989). Noradrenergic pathways are necessary for aversive conditioning and context conditioning, suggestive of a role in attention or arousal (Cole and Robbins, 1987; Selden et al., 1990).

Dopamine's role in reward has been refined and debated by various authors who approach the problem with different questions. Three views on its role could be summarised as follows: dopamine

1) mediates the experience of pleasure (*hedonic value*)
2) provides motivational drive (*behavioural incentive*)
3) causes *association* of stimuli to unconditioned rewards during learning.

Evidence for a role in pleasure include dopamine's strong operant reinforcing value, correlations between receptor binding and pleasure ratings for drugs, and correlations between addiction and dopamine levels (Volkow et al., 1999, 2009; Wise et al., 1978). As a motivational drive, dopamine appears to 'excite' animals to act, making them more eager; organisms require it to make an effort for a reward, and to discount rewards over time when they have to wait (Berridge, 2007; Crow, 1973; Ishiwari et al., 2004; Robbins and Everitt, 2007; Salamone et al., 2005, 2007). Finally, in its role as the "glue" that binds a stimulus to unexpected rewards, dopamine is necessary for Pavlovian learning, it parallels the degree of stimulus-reward association, and dopamine release is well predicted by the error signal in formal learning models (Dickinson et al., 2000; Everitt and Robbins, 2005; Flagel et al., 2011; Montague et al., 1996; Schultz, 2002).

It is less often discussed that dopamine release also signals *aversive* events (Bromberg-Martin et al., 2010a), casting doubt upon much of the above theorising. In a foraging situation, receipt of a reward indicates the devaluation of the current option (Charnov, 1976; Hayden et al., 2011a), and under such circumstances dopamine still signals the reward (Nakahara et al., 2004).

1.3.2. Properties of dopaminergic neurones

The human substantia nigra pars compacta contains around 7×10^5 dopaminergic neurones, and projects primarily to the caudate and putamen with a divergence factor of about 400 to 1 (Schultz, 1998). Dopaminergic neurones from the ventral tegmentum project to limbic structures including hippocampus and ventral striatum, and to the prefrontal cortex (Gasbarri et al., 1997; Lisman et al., 2011; Rossato et al., 2009). Approximately 75% fire phasically to the *rewarding* properties of a wide variety of

stimuli, and about 20% of these also respond to *aversive* stimuli. The responses can have a latencies as low as 50 ms, and are often no more than 3 to 6 additional spikes on a spontaneous background of 1 to 9 spikes/s (Redgrave et al., 1999). During association of a stimulus with reward, they show single-trial transfer to the conditioned stimulus, and generalise to stimuli with a similar appearance, in certain contexts. The same neurones also respond to *novelty*: for stimuli with low perceptual salience, responses decay over 3 to 5 trials; for high-salience stimuli such as loud noises, there may be minimal adaptation (Mirenowicz and Schultz, 1994; Schultz, 1998).

Dopamine release has two unusual properties. First, out of one neurone's 500,000 varicosities, 60% are *extrasynaptic*, and can increase extracellular dopamine concentrations 60-fold for an extended period of 200 ms. Second, the release of dopamine at a terminal can be decoupled from the firing of the dopaminergic neurone by local neurones in target regions, leading to tonic dopamine release. Dopamine then binds to G-protein-coupled receptors, allowing a slow but flexible modulation of the postsynaptic membrane potential. D1-class receptors are adenylate cyclase-coupled (G_s, excitatory), comprising subtypes D1 and D5, and are exclusively postsynaptic. D2-class receptors, comprising D2 D3 and D4 subtypes, inhibit adenylate cyclase (G_i, inhibitory), and are found both postsynaptically and presynaptically (Beaulieu and Gainetdinov, 2011).

The main striatal target of nigral dopamine neurones are GABAergic medium spiny neurones (MSNs). D1 receptors are most abundant, and cells expressing D1 receptors project to the internal globus pallidus, whose cells are also GABAergic. The result of activating these D1-expressing cells is thus said to be excitatory at the thalamus, giving rise to the "direct pathway"; the D2-expressing cells project to the

external pallidum, and activating them is thus said to be inhibitory at the thalamus (Albin et al., 1989; Graybiel, 1990; Surmeier et al., 2007). To complicate matters, each spiny neurone expresses both D1- and D2-receptors (Aizman et al., 2000). Each MSN receives approximately 10,000 cortical terminals, 5000 ventral thalamic afferents, and 1000 dopaminergic varicosities (Smith et al., 2006; Wickens, 2009). Approximately 400,000 corticostriatal axons terminate in the volume of one MSN dendritic tree, but each axon only produces 40 synapses in this volume, which itself contains 3000 MSNs. Thus each corticostriatal axon only contacts <1% of the MSNs in its arborisation, so due to the 100-to-1 convergence, any two neighbouring MSNs are unlikely to share an input (Bar-Gad and Bergman, 2001).

The effect of dopamine in the striatum is mixed and context-dependent; when a striatal neurone is inactive, D1 receptors close sodium channels, but when the neurone is depolarised, they open calcium channels, causing "plateau potentials" (Hernández-López et al., 1997). In light of these differential state-dependent effects, it has been suggested that D1 stimulation may *increase the nonlinearity in the integration* of glutamatergic cortical inputs. Equivalently, it may stabilise the membrane potential, in one of two states. In contrast, D2-receptor activation appears to *always decrease* responsivity of striatal cells to glutamatergic inputs (Cepeda et al., 1993; Surmeier et al., 2007).

Compartment models generate different behaviour than one might expect: D1 stimulation delays and reduces spiking but increases early temporal integration; D2 stimulation increases spiking but decreases integration (Moyer et al., 2007). Functionally, this may lead to time-dependent effects, in which tonic dopamine attenuates NMDA-driven responses, whereas phasic release potentiates them (Cepeda

and Levine, 1998; Haber et al., 2000). Striatal interneurones, comprising 5% of striatal cells, may be cholinergic or GABAergic, and also bear dopamine receptors, but are poorly understood.

In prefrontal cortex, dopamine action at D1 receptors can facilitate LTP, while D2 receptor stimulation facilitates LTD (Gurden et al., 2000; Otani et al., 1998). In the dentate gyrus and CA1 cell fields, D1 receptors facilitate LTP and inhibit LTD. D1 blockade can abolish learning in rats (Lemon and Manahan-Vaughan, 2006) and spatial working memory in primates (Sawaguchi and Goldman-Rakic, 1991). Due to this complementary effect of D1- and D2-class receptors, general stimulation of both dopamine receptor classes (e.g. by the non-selective agonist pergolide) enhances intracortical inhibition (Ziemann et al., 1996) and yet increases cortical excitability. Prefrontal dopamine might also have distant effects: injection of D1agonists into FEF can produce effects very similar to attention in V4 neurones (Noudoost and Moore, 2011a, 2011b)—an effect which has been interpreted as a mechanism for top-down attention.

1.3.3. The functional role of striatal dopamine in humans

Dopamine has many proposed functions in humans, and influences a wide variety of behaviours, being central in motor control, learning, memory, and motivation (Hallett 1990; Sawaguchi and Goldman-Rakic 1991; Wise 2004; Flagel et al. 2011; Lisman, Grace, and Duzel 2011; Berridge and Kringelbach 2013). Dopaminergic dysfunction has been implicated in schizophrenia (Williams-Gray et al., 2006), chorea (Jahanshahi et al., 2013; Lee and Marsden, 1994; Martin, 1927), dystonia (Berardelli et al., 1998; Bhatia and Marsden, 1994; Perlmutter et al., 1997; Schicatano et al., 1997), impulse control disorders (Sinha et al., 2013), obsessive-compulsive disorder, Tourette's

syndrome (Denckla, Bemporad, and MacKay 1976; Gravino 2013), attention deficit hyperactivity disorder, and addiction (Trifilieff and Martinez; Volkow et al., 2009). A variety of lines of evidence are available, but perhaps the most direct method available in humans is PET.

Dopamine release can be measured relatively specifically using PET ligands such as 11C-raclopide. Binding potential changes have been observed during amphetamine and alcohol use (Boileau et al., 2003; Drevets et al., 2001), enjoying food (Small et al., 2003), psychological life stress (Pruessner et al., 2004), and by TMS to motor cortex (Strafella et al., 2003), but not during exercise (Wang et al., 2000).

Direct evidence of dynamic, reward-related dopamine release as a function of performance has been observed while playing video games (Koepp et al., 1998). One study reported that, when actions result in uncertain rewards, dopamine is released in medial caudate and lateral putamen, whereas when actions produce expected rewards, dopamine is released in caudate head—but curiously found no changes in ventral striatum (Zald et al., 2004).

Several PET studies have examined correlations between *tonic* dopamine levels in the striatum, and behavioural traits. Tonic striatal dopamine levels correlate with choking under pressure (underperformance when incentives are high) (Aarts et al., 2014; Silston and Mobbs 2014). Greater ventral striatal dopamine is associated with disinhibitory personality traits (Lawrence and Brooks, 2014) and hedonic pleasure on a self-report scale (Volkow et al., 2002), as well as decreased aggression (Schlüter et al., 2013), but do not appear to be directly associated with gambling tendencies or maladaptive decision making (Linnet, 2013).

Recreational drug users' ratings of "highs" correlated strongly with striatal DAT occupancy as well as D2 receptor availability in OFC and ACC (Volkow and Fowler, 2000; Volkow et al., 2001, 2002). When response inhibition is performed under rewarding conditions, compared to a non-rewarded feedback-only condition, dynamic PET with 11C-raclopride ligand reveals increased dopamine levels in the nucleus accumbens (Jonasson et al., 2014).

Complementing PET studies, recent fMRI studies have shown increased BOLD signal in the midbrain in correlation with rewards, which may reflect the mechanism by which the dopaminergic, serotonergic, and other ascending brainstem pathways might be activated (Düzel et al., 2009). Tractography complements tracer studies demonstrating that the primary target of dopamine from the dorsomedial substantia nigra is the ventral striatum (Chowdhury et al., 2013).

Mathematical models of learning suggest that dopamine and serotonin are both important in inhibition and reward processing (Daw et al., 2002), leading to interactions between reward/penalty and aversion/approach behaviour (Boureau and Dayan, 2011; Guitart-Masip et al., 2014). One hypothesis is that serotonin and dopamine control different aspects of learning in go/nogo tasks with positive and negative outcomes (Guitart-Masip et al., 2012), and in support of this, a large reversal learning study has found that dopamine transporter (DAT1) polymorphisms increase perseveration on incorrect responses during reversal, whereas serotonin transporter (SERT) polymorphisms alter lose-shift behaviour (den Ouden et al., 2013).

1.3.4. Cortical regions responding to reward

Reward alters brain activity in a wide range of brain areas. Functional imaging in humans and single-cell physiology in primates have given complementary evidence for the presence of reward signals. With present methods, it has not been possible to distinguish between *modulation of ongoing processing* by rewards (in the form of motivation, relevance or salience) and *representation* of reward values (e.g. for comparison or selection). But whatever its functional role, the effect of reward appears to be ubiquitous.

1.3.4.1. Functional imaging of reward signals in prefrontal cortex

In humans and primates, prefrontal cortex is often subdivided first according to the three brain surfaces: orbital, medial, and dorsolateral. The medial surface is divided into the cingulate gyrus and sulcus, dorsomedial cortex superiorly, and the ventromedial PFC inferiorly which wraps onto the gyrus rectus on the orbital surface. Anterior cingulate cortex (ACC) is further subdivided into dorsal, rostral, pregenual and subgenual areas (Gittins and Harrison, 2004; Johansen-Berg et al., 2008). The orbital surface of the brain is divided into medial and lateral portions, with the most posterior regions in close proximity to the anterior perforated substance and ventral striatum, and in continuity with anterior insula (Kahnt et al., 2012). In functional imaging, the term orbitofrontal is sometimes avoided as cytoarchitectonic boundaries cannot be delineated; the term “ventromedial PFC” generally does not include the central and lateral zones of OFC.

Orbitofrontal cortex (OFC) activation has been shown to correlate with a mixture of reward-related variables (for a review, see Levy and Glimcher, 2012). In choice situations, there are effects of reward size (O’Doherty et al. 2001; O’Doherty et

al. 2002; Spicer et al. 2007; Croxson et al. 2009), expected value (Breiter et al., 2001; Hare et al., 2008; Kahnt et al., 2010), relative value (Elliott et al., 2008), and subjective utility (Elliott et al., 2003; Stuphorn, 2006; Tom et al., 2007). When there are two options, there is encoding of both net value (O'Doherty et al. 2001) and attended item reward (Lim et al., 2011). The response is modulated by regret, for example the relative value of unchosen or counterfactual rewards (Boorman et al., 2011; Camille et al., 2004; Coricelli et al., 2005; Ursu and Carter, 2005), but not by cognitive emotional regulation (Staudinger et al., 2009).

Careful distinction of the roles of stimulus, response and outcome shows differences between *medial and lateral* OFC. Lateral OFC was more active when a reward association needed to be updated, whereas medial OFC correlated with the expected and actual reward levels (Noonan et al., 2011). Medial OFC may be involved in computing reward prediction errors (Bellebaum et al., 2012; Rolls et al., 2008), whereas mid- and lateral OFC may be more active in situations of greater uncertainty (Elliott et al., 1999; Tobler et al., 2007) and may encode risks (Elliott et al., 2003; Engelmann and Tamir, 2009). Another study has suggested that medial OFC encodes willingness to pay whereas lateral OFC encodes willingness to accept compensation (Martino et al., 2009). A final possibility is that reward signals in OFC are specific to actions (Li and Daw, 2011; McClure et al., 2003b), and that lateral OFC is specifically involved in behavioural shifts, independently of negative feedback (Cools et al., 2002).

Other studies have postulated a *postero-anterior* division of function, e.g. a gradient of increasing abstraction (Sescousse et al., 2010), or the encoding of a reward's identity independently of its value (Klein-Flügge et al., 2013).

While encoding value may be a canonical role of OFC, several studies have shown increased activation in OFC in seemingly unrelated domains, for example in tasks that require theory of mind (Gallagher and Frith, 2003), humour comprehension (Goel and Dolan, 2001; Wild et al., 2003), moral decisions (Moll et al., 2002) and contextual memory (Frey and Petrides, 2000, 2003). Such varied involvement may indicate that our understanding of representations in OFC remains incomplete.

Anterior cingulate cortex (ACC) activation has been suggested to be caused by an even wider range of situations, including task difficulty, response conflict detection or resolution, error detection or prediction, signalling negative reward prediction errors or surprise, estimating risk or uncertainty, and switching between exploitation and exploration (Carter et al., 1999; Kennerley et al., 2006; Kolling et al., 2012; Paus, 2001; Rushworth and Behrens, 2008; Rushworth et al., 2004; Shenhav et al., 2013),.

ACC was identified in many early PET studies as becoming more metabolically active when task *difficulty* increased (Paus et al. 1998). Further studies confirmed that is activated during Stroop conflict, particularly on incongruent trials that follow congruent trials (Kerns et al., 2004), and in task switching studies (e.g., classifying a letter as vowel/consonant versus upper/lower case). ACC is active when a new task must be activated, compared to reactivating a recent task (Dreher and Berman, 2002). ACC has thus been thought to be active in situations of high *response conflict* (Botvinick et al., 2001; Carter et al., 1999).

Although conflict does explain this activation, *errors* could also be responsible. For example, ACC is more active after no-go task commission errors (Garavan et al., 2003), and ACC is thought to be a source of the error-related negativity in the evoked potential (Carter et al. 1998; Yeung, Botvinick, and Cohen 2004). But because this

effect is also observed in oddball tasks, it might be attributable to the low frequency of such events (Braver et al., 2001). In a flanker interference paradigm, dorsal areas (pre-SMA) activated by conflict have been distinguished from more ventral areas (anterior cingulate sulcus / cingulate motor area), which were activated when errors were committed (Ullsperger and von Cramon, 2001). This has been corroborated in the go-nogo task (Garavan et al., 2003). A distinction has also been suggested between rostral pre-SMA, which was activated during a change-of-plan, and caudal pre-SMA which was activated during free choice (Nachev et al., 2005, 2008).

One difficulty with the conflict hypothesis is that conflict is persistently confounded with reaction time (Grinband et al., 2011; Nachev, 2006, 2011). Recently, reward-based interpretations of dorsomedial function have been proposed (Sallet et al., 2007).

When a stream of rewards is occasionally punctuated with reduced rewards, ACC is more active after the reduced rewards, suggestive of a negative *reward prediction error* signal (Knutson et al. 2000; Bush et al. 2002; Knutson et al. 2003). These prediction errors appear to be specific to action plans (Jocham et al., 2009; Kennerley et al., 2011), and specific for self-generated action, rather than externally guided actions (Walton et al., 2004).

A further candidate role for ACC activations is in signalling *surprise*—i.e. the absolute value of prediction error. This account predicts activation for both positive and negative feedback, as long as the feedback is unexpected (Holroyd et al., 2009).

In addition to the above distinctions of action selection, conflict, error detection and effort, dorsomedial cortex activation is also increased during a *risky* decision,

whereas ventromedial areas are more active during receipt of rewards (Cohen et al., 2005; Ernst et al., 2004; Xue et al., 2009). When surprise is frequent, it is possible for an organism to anticipate or expect that surprise—producing uncertainty. Cingulate cortex appears to be active in situations of increased uncertainty (Hayden et al., 2011a; Rushworth and Behrens, 2008; Walton et al., 2007), and may track the values of alternatives to the current option during foraging (Kolling et al., 2012; Mobbs et al., 2013)—findings which support neurophysiological recordings in primate ACC (Blanchard and Hayden, 2014; Hayden et al., 2011a).

Although neuroeconomic and reward-learning constructs have been a core element of investigation of dorsomedial areas, in human life these general mechanisms are likely harnessed in a number of other situations including embarrassment (Berthoz et al., 2002), working memory (Petit et al., 1998), social cognition (Apps and Ramnani, 2014; Behrens et al., 2008, 2009; Zheng et al., 2014), and effort discounting (Croxson et al. 2009; Kurniawan et al. 2013; Shenhav, Botvinick, and Cohen 2013; Bonelle et al., submitted).

Subcortical areas that show haemodynamic changes with rewards include the ventral striatum especially nucleus accumbens (Berns et al., 2001; Breiter et al., 2001; Elliott et al., 2000; Tanaka et al., 2004), caudate, and ventral tegmental area (Düzel et al., 2009; Knutson et al., 2000)—areas which are known to receive projections from OFC and ACC (Carr and Sesack, 2000; Vázquez-Borsetti et al., 2011).

1.3.4.2. Single-cell physiology of cortical reward signals

Vision provides a clear case of how reward signals may operate in the brain. Cells in early visual areas respond more strongly to stimuli and features associated with reward (Shuler and Bear, 2006, Stănişor et al., 2013). This effect is seen progressively more

strongly in higher visual areas. Cells in the lateral intraparietal area encode spatially specific rewards (Platt and Glimcher, 1999; Sugrue et al., 2004), but also independently encode motor reaction time (Bendiksby and Platt, 2006), and relative reward values (Rorie et al., 2010). Neurones in dorsomedial prefrontal cortex prominently increase or decrease their firing rates both during and after reward (Seo and Lee, 2009; So and Stuphorn, 2010). This suggests that there is a gradual progression from posterior to anterior, encoding stimulus reward value, action value, and the actual delivery of reward (Cisek and Kalaska, 2010). Even within prefrontal cortex, reward values can be bound to stimuli, states, or actions, and these bindings may be learnt through predictions and prediction-errors.

Neurones in **orbitofrontal cortex** exhibit firing rates proportional to stimulus-related reward and predicted reward (Hikosaka and Watanabe, 2000; Padoa-Schioppa and Assad, 2006; Wallis and Miller, 2003), and it is possible to find cells there that are active only for specific conjunctions between reward and stimulus (Thorpe et al., 1983). These neurones may be involved in relative and qualitative aspects of value (Rolls, 2000; Tremblay and Schultz, 1999). The ventromedial portion may be further sub-specialised for subjective appraisal or comparison of values (Bouret and Richmond, 2010; Noonan et al., 2010).

Neurones in **cingulate cortex** show reward-related activity, but also exhibit post-error activity (Amiez et al., 2005; Matsumoto et al., 2007) and increased firing when an action needs to be changed (Quilodran et al., 2008; Shima and Tanji, 1998). For example in a saccadic countermanding (stop signal) task, 5-10% of neurones fired more after uncancelled (error) saccades, but were uncorrelated with RT, and of these 25% also responded to omitted reward, and 25% to unexpected rewards (Ito et al.,

2003). In contrast supplementary eye field (SEF) neurones, on the same task, exhibited increased firing when saccadic RT was longer, suggesting conflict-driven activity, whilst others fired in advance of an expected reward (Stuphorn et al., 2000).

Characteristically, there are cells in cingulate areas that fire specifically for only particular action-reward combinations, for example in an asymmetrically rewarded go/nogo task (Matsumoto et al., 2003). When sequential movements are required, neuronal responses are specific not for the action itself, but for the serial position in the sequence (Procyk et al., 2000). ACC is also coupled to reward-sensitive areas of the basal ganglia: activity of VTA dopaminergic neurones can induce increased firing in ACC (Onn and Wang, 2005); and caudate nucleus areas signalling reward also receive extensive projections from ACC (Ding and Hikosaka, 2006; Yanike and Ferrera, 2014).

Both orbitofrontal and cingulate areas contain populations of neurones whose firing rates encode combinations of reward, risk and effort; but anterior cingulate contains the greatest population of cells that encode all three simultaneously (Kennerley et al., 2008). Some recent paradigms have interpreted ACC neurones firing in response to reward as signals that mediate the switch between exploration and exploitation (Quilodran et al., 2008).

1.3.4.3. Lesions of non-human primate prefrontal cortex

In animals, the terminology ventromedial PFC and medial OFC are sometimes distinguished – a practice that is uncommon in human functional imaging (Kringelbach, 2005). Histologically, medial OFC (area 13) can be distinguished from the medial wall areas that include subgenual ACC.

Lesions to OFC in animals leads to perseveration, disinhibition, emotional disturbances and altered reward preferences (Dias et al., 1996; Iversen and Mishkin, 1970). Healthy individuals are able to modify preferences according to desires—as manifest by devaluation of food rewards by satiation. Bilateral OFC lesions prevents these dynamic preference shifts, but only when the food selection is mediated by a food-object pairing. OFC may be required for using stimulus-reward associations (Izquierdo et al., 2004), but impaired devaluation of rewards themselves has also been found in OFC lesions, as well as amygdala lesions (Rhodes and Murray, 2013). Lateral OFC lesions impair devaluation of reward by satiation, whereas medial lesions (in the gyrus rectus) preserve devaluation but impair extinction (Rudebeck and Murray, 2011a, 2011b).

OFC-lesioned monkeys are also impaired at reversal learning, despite being able to correctly learn the initial reward mapping (Izquierdo et al., 2004). The specific deficit in reversal appears to be with suppressing stimulus-reward pairings (Jones and Mishkin, 1972), perhaps due to a failure to use context information to suppress habitual behaviour (Dias et al., 1996). However, it seems unlikely that OFC *alone* encodes reward preferences, according to a study of rat OFC inactivation: reversal learning did take place, but could not be *expressed* in behaviour after OFC was reactivated. If OFC was again inactivated later, the reversed preferences re-emerged (Keiflin et al., 2013).

Lesions to dorsomedial prefrontal cortex, in contrast, lead to surprisingly subtle deficits: reduced post-error performance monitoring and impairments in pairing actions with reward values (Rushworth et al. 2004). Lesions to ACC sulcus reduced the ability to sustain a correct response after positive feedback (Kennerley et al., 2006; Rudebeck et al., 2008), and reduced the ability to select actions that led to high-

probability rewards in probabilistic action-outcome matching. Cingulate sulcal lesions did not affect stimulus-response learning is some studies (Rudebeck et al., 2006), though a recent report has revealed that bilateral ACC lesions also led to problems using rewards in reversal learning of object-reward associations, as well as difficulty switching responses in reversal learning of action-reward associations (Chudasama et al., 2013). In contrast with OFC lesions, devaluation by satiation was unaffected.

In summary, reward affects large areas of the brain, depending upon the task in question, but its effects are most consistently seen in a connected subset of areas including the substantia nigra and ventral tegmentum, ventral striatum especially nucleus accumbens, and the medial prefrontal cortex, including OFC and ACC. Dopamine may be a key player, but its role is not well defined, since it appears whenever the organism is excited. Subcortical and cortical areas most likely function as a unit, since all levels of the system can encode information that is behaviourally highly sophisticated. OFC and ACC do appear to have different profiles of activity in response to rewards, whether it be described as associations with actions versus objects, representation of internal reward versus environmental reward, or counterfactual rewards versus prediction errors.

1.4. Human lesion studies in reward-related cortical areas

The classical “frontal syndrome” can include a vast array of cognitive features, including apathy, bradyphrenia, emotional lability, disinhibition, distractibility, difficulty with cognitive estimation, humour, proverb interpretation, theory of mind, word generation, and prominent working memory deficits. This gamut of symptoms has been operationalised in many ways, for example distinguishing dorsolateral executive, orbitofrontal inhibitory, and medial motivational components (Cummings, 1995).

Human prefrontal cortex is more amenable to such fractionation than in other animals, since it accounts for 30% of the human cerebral cortex, compared to 7% in macaque and 4% in rabbits, with expansions in DLPFC, SMA and lateral OFC, as well as the almost unprecedented appearance of frontopolar cortex (Ongür and Price, 2000; Walker, 1940). Notably, lesions to human PFC cause even more subtle deficits than in other primates.

It is a truism that all purposive behaviour is goal-directed, and as such is execution is governed by motivational incentives. Many of the neurological impairments following PFC lesions which have historically been described as deficits of cognitive control, inhibition, decision-making and attention are amenable to an alternative description: in terms of reward and neuroeconomic optimality. Both orbital and medial patients consistently show impairments that could be interpreted as reward-related deficits.

1.4.1. Human lesions to orbitofrontal cortex

Human OFC anatomy is highly variable (Kringelbach and Rolls, 2004), and is phylogenetically more primitive than frontopolar and dorsolateral cortex. Architectonically, it comprises a mixture of agranular cortex posteriorly, dysgranular cortex centrally, and granular isocortex anteriorly (Braak 1980; Ongür and Price 2000). Brodmann's original classification (Brodmann, 1909, 1914) labelled the major portion of the orbital surface as area 11. Walker (Walker, 1940) subdivided OFC into 20 architectonic subregions. On the basis of tracer studies demonstrating input and output connectivity, the area can be divided into orbital and medial areas. The orbital portion is a convergence area for all sensory modalities; medial regions send prolific efferents to the hypothalamus and brainstem (Kringelbach, 2005; Ongür et al., 2003).

OFC lesions lead to an assortment of cognitive changes that can be hard to pinpoint experimentally, yet disabling in daily life. For example, relatively subtle impairments in social, emotional, moral, appetitive and evaluative judgements have often been reported (Milner 1963; Drewe 1975; Rolls et al. 1994; Anderson et al. 1999; Godefroy, Cabaret, and Rousseaux 1994; Stuss and Knight 2002; Dolan 1999; Ciaramelli et al. 2007). Accordingly patients may have difficulties with detecting deception, and with theory of mind tasks (Stone et al., 1998; Stuss and Anderson, 2004; Stuss et al., 2001a). Although a single unified explanation of such pervasive behavioural changes seems unlikely, some of these impairments might be describable in terms of the handling and representation of rewards.

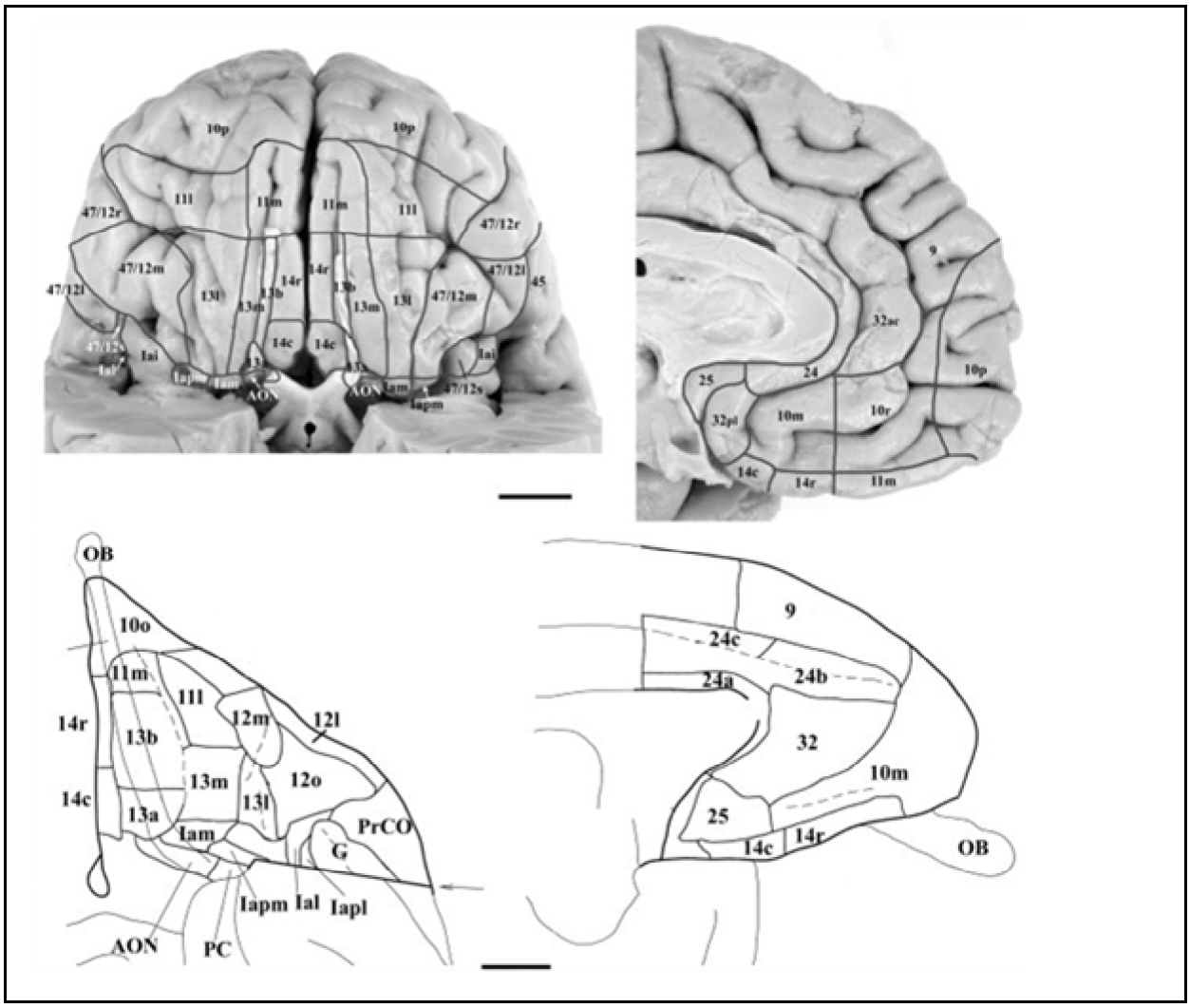


Figure 1.5: Architectonic subdivisions of ventral frontal regions
Histologically defined boundaries in human (above) and macaque (below). Taken from Ongur, Ferry and Price (2003)

The *Iowa Gambling Task* was one of the earliest behavioural measures revealing reward-related changes in these patients (Bechara et al. 1994), showing that these patients are more influenced by immediate punishment than by delayed reward, and therefore make economically unsound choices (Bechara, Tranel, and Damasio 2000; Fellows and Farah 2005b; Maia and McClelland 2004). Lesions to OFC cortex specifically lead to increased bet size in gambling tasks (Studer et al., 2013), greater risk-taking (Floden et al., 2008) and longer deliberation times (Manes et al., 2002) without changes in probabilistic reasoning, although similar risk effects can also be seen after non-ventromedial lesions (Clark et al., 2003). Interestingly, these patients also lacked normal anticipatory autonomic responses to risk, as measured by galvanic skin responses (Bechara et al. 1997; Bechara et al. 2005). It is therefore possible that subconscious autonomic activation, which is a well-recognised function of orbital cortex in lower animals, could be an important component of decision-making—as "somatic markers" (Bechara et al. 1994; Damasio 2008). In **chapters 3-6** I will consider pupil dilatation in response to incentives as a potential marker for altered reward processing.

A study of 5 OFC patients showed reduced risk aversion compared to healthy controls, and remarkably, found that patients were consequently closer to theoretically optimal behaviour (Hsu et al., 2005), a finding that has been paralleled in animal OFC lesions (Pais-Vieira et al., 2007) and also human amygdala lesions (Martino et al., 2010). A larger study of nine OFC patients on a 5-card variant of the Iowa gambling task revealed two subgroups of patients—5 of the nine showed strong risk-taking

behaviour, but 4 had normal risk aversion (Sanfey et al., 2003)—without clear lesion location differences. In a changing environment, OFC patients had difficulty in flexibly adjusting behaviour to select the highest reward option, as seen in *reversal learning* tasks (Fellows and Farah, 2003; Hornak et al., 2004)—a deficit that can be explained in terms of learning rate given a reward prediction error. This appears to be due to insensitivity both for rewards and penalties (Berlin et al., 2004). In parallel with some primate lesion studies, not only is stimulus-reward learning impaired, but also personal *preference judgements* have been shown to be inconsistent in OFC patients (Fellows and Farah, 2007).

To explain impulsivity in OFC patients, it has been hypothesised that they might *discount time* more steeply, that is, have preferences for sooner smaller rewards, than waiting for larger rewards (Sellitto et al., 2010) as seen after animal OFC lesions (Mobini et al., 2002). Impulsivity in these patients is unlikely to result from disinhibition (Solbakk et al., 2014). Rather, such individuals overestimate how much time has passed, perhaps indicating a faster subjective sense of time (Berlin et al., 2004). However no direct evidence for altered temporal discounting has been found in patients, to explain the link with impulsivity (Fellows and Farah, 2005b). Rather, these authors reported that when OFC patients were asked to "think of 5 events that may happen to you in the rest of your life", and to estimate how far into the future these may occur, the future extension of their events was much shorter (5.6 years) than controls (13 years) or dorsolateral prefrontal patients (9.4 years).

Tying together these many deficits into a single function, computational step or representation type remains contentious (reviewed in Zald and Andreotti 2010), but evaluation appears to be a common denominator. A general framework that treats OFC

as providing reinforcement context signals has been recently proposed (Wilson et al., 2014). In this promising account, OFC is responsible for representing the world in terms of goal contexts for reinforcement learning.

1.4.2. Human lesions to dorsomedial prefrontal cortex

Dorsomedial prefrontal regions include supplementary motor cortex (SMA), pre-supplementary motor cortex (pre-SMA) cingulate sulcus and cingulate gyrus, as well as pregenual cortex. Compared to orbitofrontal cortex, this area is characterised as more motor than sensory, and indeed SMA efferents contribute to 10% of the corticospinal tract (Dum and Strick, 1991).

Large lesions to bilateral ACC have reportedly caused akinetic mutism (Barris and Schuman, 1953; Jürgens and von Cramon, 1982) and emergence of primitive reflexes (Shahani et al., 1970).

One might predict, given the prominent error-related activities found in imaging and electrophysiological studies, that dorsomedial lesions in humans might lead to learning deficits. There is only scant evidence that patients are less likely to change their response after negative feedback (Floden et al., 2008) and they do not seem to have altered error-related responses (Løvstad et al., 2012), although patients with lateral prefrontal lesions do (Gehring and Knight, 2000; Woods and Knight, 1986).

Focal damage to supplementary motor area may cause contralateral alien limb syndrome, in which patients are unable to inhibit afforded actions (Goldberg et al., 1981). Consistent with a role of dorsomedial cortex in motor planning, isolated ACC lesions can lead to effector-specific impairments on response-mapping tasks (Turken and Swick, 1999) and impaired suppression of reflexive movements (Paus et al., 1991).

Similarly, isolated lesions of pre-SMA can lead to effector-specific impairments in response inhibition (Nachev et al., 2007; Sumner et al., 2007; Verfaellie and Heilman, 1987) and task switching (Parton et al., 2005). This response disinhibition may be nonspecific, as measured by impaired stop signal reaction times (a feature more commonly associated with right inferior frontal damage), and associated with slower, more variable response times (Picton et al., 2007). Bilateral lesions result in increased costs of response conflict in Stroop (Stuss et al., 2001b) and faster forgetting of task-set instructions in Wisconsin card sort (Stuss et al., 2000).

To what extent do these reward-related areas control attention? Most human lesion studies of distractibility tend to implicate the whole of prefrontal cortex. Several prefrontal lesion studies show difficulty adhering to a current goal (Howes and Boller 1975; Wilkins, Shallice, and McCarthy 1987; Rueckert and Grafman 1996; Robertson et al. 1997; Molenberghs et al. 2009), and to complement these, other studies demonstrate impaired ability to focus attention (Woods and Knight 1986; Barceló, Suwazono, and Knight 2000; Knight 1984, reviewed in Manohar et al., 2013).

1.4.3. Human subcortical lesions

Isolated focal lesions to the basal ganglia are rare. When they occur, a common cognitive symptom is abulia—a lack of will, motivation, or self-generated action—most commonly caused by damage to the caudate (Bhatia and Marsden, 1994; Schmidt et al., 2008a). Bilateral lesions to the globus pallidus can also lead to profound behavioural apathy, a syndrome which has been considered to be a disorder of motivation, perhaps as a result of insensitivity to reward (Adam et al., 2013; Schmidt et al., 2008b). Indeed, these authors showed that a direct dopamine receptor agonist can reverse reward insensitivity and behavioural apathy in a patient with bilateral globus pallidus lesions.

1.5. Reward and dopamine in Parkinson's disease

1.5.1. Parkinson's disease and dopamine

Dopamine depletion is closely connected to, if not the primary cause of, the symptoms of PD (Hornykiewicz, 2001): difficulty initiating movements, slowness of movements, and increased muscle rigidity (Jankovic, 2008). Symptoms appear when dopamine concentrations in the putamen fall to about 80% of normal levels (Kish et al., 1988; Otsuka et al., 1996), and striatal dopamine binding can be abnormal up to 25 years before symptom onset (Fuente-Fernández, 2013). The motor disorders in PD are significantly improved by the dopamine precursor levodopa, dopamine breakdown inhibitors such as selegiline and entacapone, D2 dopamine receptor agonists bromocriptine, ergots, apomorphine and ropinirole. Pharmacologically these drugs increase dopamine receptor stimulation in the dorsal striatum (Connolly and Lang, 2014).

For small movements, PD patients have normal movement velocities, but as the movement distance is increased, in PD the velocity remains constant and the movement takes longer, whereas in healthy controls the velocity scales up with distance and the movement time remains constant (Flowers 1975; Flowers 1976; Hallett and Marsden 1979). The inability to increase velocity could be attributable to inability to extend the duration of the normal triphasic pattern of agonist and antagonist activity that comprises a ballistic movement (Hallett and Khoshbin, 1980).

Although PD has classically been considered as a disorder of the motor system, over the last 10 years it has become increasingly clear that a range of cognitive disturbances accompany the disease (Yarnall, 2014). These include depression, anxiety,

apathy, hallucinations, delusions, sleep disturbance, pain, and a loss of the sense of smell (Kumar et al., 2002; Modugno et al., 2013); REM sleep behavioural disorder is the most common parasomnia, in which patients appear to "act out their dreams", and may precede the motor onset of PD by years or decades (Boeve et al., 2004; Schenck et al., 1996). The variety of motor and cognitive symptoms in PD can be organised with reference to the primary dopamine pathways in the brain: nigrostriatal, mesocortical and mesolimbic.

About 15% of patients, when treated with dopaminergic medication, develop impulse control disorders including pathological gambling, compulsive shopping, compulsive eating, hypersexuality, and "punding": repetitive obsessive purposeless but high-level behaviours such as collecting, sorting or disassembling (Maréchal et al., 2014; Voon et al., 2006, 2007; Weintraub et al., 2006). Dopamine medications themselves are commonly the object of compulsion, with a number of patients demanding rapid drug escalation and continuing to request more tablets despite the severe side effects of dyskinetic choreiform movements (Evans and Lees, 2004). This may be accompanied by euphoria, inappropriate joy, racing thoughts and grandiose ideation, resembling mania; withdrawal states and craving can occur, similar to amphetamine withdrawal (Lawrence et al., 2003).

About 60% of patients will develop apathy during the course of the disease (Aarsland et al., 2009; Pedersen et al., 2009; Starkstein, 2009) which can be decomposed into reductions in action initiation, emotional responsiveness, self-interest and curiosity. Apathy in PD may be partly attributable to a low-dopamine state (for review see Sinha, Manohar and Husain 2013), and be improved by methylphenidate (Chatterjee and Fahn, 2002; Mendonça et al., 2007).

The motivational changes seen in PD may be distinct from those in depression and frontal dementia, and give rise to several rather interesting phenomena. *Kinesia paradoxa* occurs when PD patients (or rats with dopaminergic lesions) who are severely akinetic in a standard environment, may be able to move very fast in situations of extreme motivation (e.g. running from a fire, or for rats, swimming when dropped in a water bath) (Keefe et al., 1989). Motor symptoms in PD also exhibit strong placebo effects, whose magnitude correlates with the amount of placebo-induced dopamine release in dorsal striatum, as measured by PET (de la Fuente-Fernández and Stoessl, 2002).

Care must be taken in studying cognition in PD patients, since they may be impaired in a wide range of tasks including the tower of London (Owen et al. 1995), Wisconsin card sort (Owen et al. 1993; Price, Filoteo, and Maddox 2009; Jahanshahi et al. 2002), working memory (Lewis et al., 2005), word fluency (Dalrymple-Alford et al., 1994), and spatial attention (Briand et al., 2001a; Filoteo and Maddox, 1999; Wright et al., 1990). Patients may have concurrent brain atrophy (Burton et al., 2004; Matsui et al., 2007), depression (Gotham et al., 1986), and dementia (Kehagia et al., 2010). These considerations must be accounted for both when selecting patients, and in interpreting behavioural data.

1.5.2. Reward and Parkinson's disease

Given that dopamine is central in both motivation and signalling reward, and that PD patients have deficits in both dopamine and motivation, it is unsurprising to find that reward processing is aberrant in PD.

Probabilistic reversal learning is generally impaired in PD patients (Swainson et al., 2000), and patients similarly have difficulty with switching set in the Wisconsin card sort (Canavan et al., 1989), though whether this is due to perseverative errors (as after lesions to OFC or ventral striatum) or to noisy responding, has been a matter of debate.

During a classification task with feedback, often thought to be more sensitive to dorsal striatal function, PD patients show specific impairments in shifting classification from one feature dimension to another (extradimensional set-shifting), and on task-switching e.g. between letter- and digit-naming (Downes et al., 1989; Lange et al., 1992). However, withdrawal of medication has different effects on the tasks: probabilistic reversal learning is improved, whereas task-set switching is worse (Cools et al., 2001a). One explanation of this phenomenon is that PD selectively depletes dopamine from the dorsal striatum, and replacing dopamine causes a relative "overdosing" of the ventral striatum (Cools et al., 2003, 2010a).

In a highly influential study, Frank and colleagues asked PD patients to select one of two abstract symbols, after which they were rewarded or penalised (**Figure 1.6**, (Frank et al., 2004). PD patients ON medication were better at selecting symbols associated with a high probability of reward, but worse at avoiding the low-probability symbols. Patients OFF medication were worse at selecting high-probability items, and better at avoiding the low-probability symbols. The investigators concluded that dopamine improves probabilistic learning by reward, whereas depletion by contrast improves learning from penalties. A similar effect occurs when patients are required to classify a single stimulus under rewarded *vs*. penalised probabilistic feedback: reward

learning is faster ON, whereas penalty learning is faster OFF medication (Bodi et al., 2009).

Frank et al. explained performance by considering the "direct pathway" (D1) to facilitate execution of a planned response, and the "indirect pathway" (D2) suppressing competing responses. The authors assume that phasic dopamine during rewards activates and increases plasticity in the direct pathway, and at the same time deactivates the indirect pathway, driving learning to facilitate reinforced responses. Conversely, low dopamine during penalties activates the indirect pathway, driving avoidance learning (Frank, 2005). Their addition of this extra D1 vs. D2 dimension to a simple reinforcement learning model increases its explanatory scope.

This is consistent with evidence that D2 agonists impair reinforcement learning of actions (Pizzagalli et al., 2008). A follow-up study in healthy volunteers taking the D2 agonist cabergoline and the D2 blocker haloperidol showed that cabergoline improved learning by penalty, similar to PD patients OFF medication; haloperidol in contrast improved reward learning. This is of course quite interesting, since Parkinsonism is a common side effect of haloperidol, and cabergoline treats PD. To account for all this, the model had to be extended to include pre- and post-synaptic dopamine (Pizzagalli et al., 2008)—once again increasing its scope, and arguably decreasing its power.

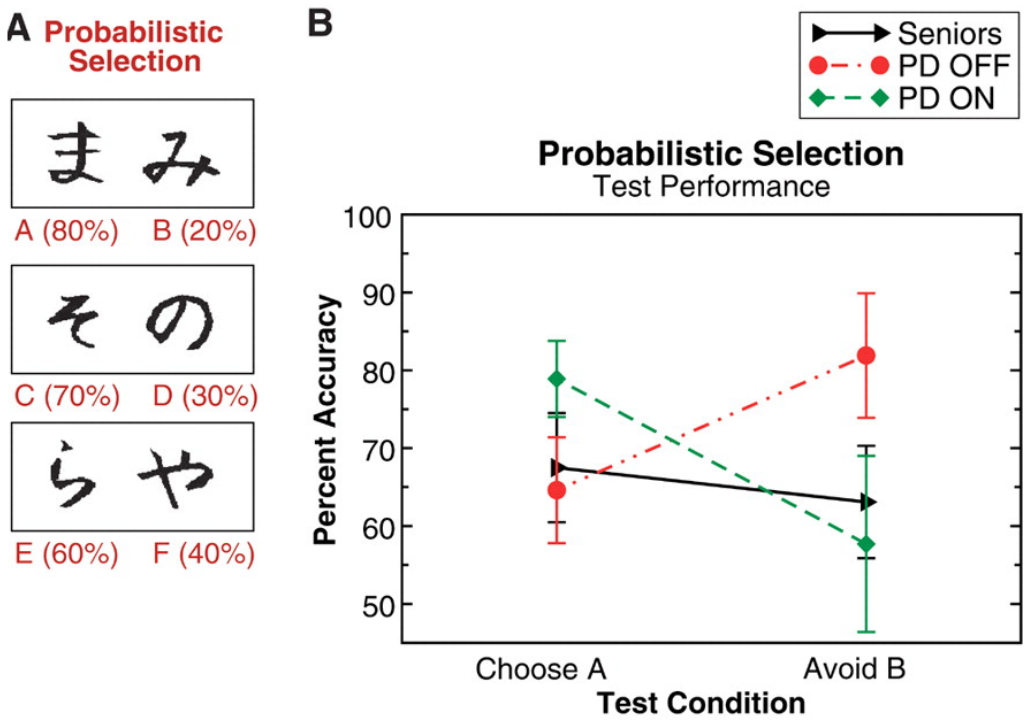


Figure 1.6: Dopamine's differential effect on positive and negative feedback.
Task and results of Frank, Seeberger and O'Reilly (2004). A) Patients on and off medication had to learn which of two symbols to choose, based on probabilistic reward and penalty. In the training phase, symbols were always paired as illustrated. In a test phase, in which the pairs were mixed up, patients were better at avoiding penalised symbols when OFF, but better at selecting rewarded symbols when ON.

1.5.3. Functional imaging of reward modulated responses in PD

A few studies have examined changes in brain activity in PD as a function of reward. PD patients may have blunted activation of the ventral striatum by reward predictions, with supranormal activation of those same regions by actual rewards (Schott et al., 2007), and they may activate more brain areas in response to rewards than controls (Künig et al., 2000; Rowe et al., 2008). The error responses in dorsal striatum may be attenuated (Schonberg et al., 2010), whereas ventral striatum may be hyperresponsive in patients with impulse control disorders (Steeves et al., 2009). In a study of reversal learning in eight PD patients on and off levodopa, dopamine increased the response of

the ventral striatum at the moment of reversal (Cools et al., 2007). Another study showed similar levodopa-induced increases of ventral striatal reward responses, but a *diminution* of OFC reward responses with dopamine agonists, which could be attributable to differences between phasic and tonic stimulation (van Eimeren et al., 2009).

1.5.4. Novel theories of motor deficits in PD: the central role of vigour

The planning of movement can be conceived as taking place by optimising a cost function according to an internal model of motor control (Wolpert and Ghahramani, 2000). In systems terms, the motor system receives proprioceptive inputs, and a command; from these it must generate appropriate muscle-level instructions. In mathematical terms, the motor system must solve an inverse problem to find the correct instructions, given that instructions cause certain effects (Wolpert, 1997). Since many trajectories and speed profiles are possible to achieve a given goal position, additional constraints must be in play—termed cost functions. The *cost* of a particular movement plan may be given in terms of time, energy, or accuracy. In mathematical terms, these costs can equally be described as priors on the inference from proprioceptive states to motor instructions (Friston 2011).

In animals, the control of movement timing and speed is strongly influenced by reward schedule (Niv et al., 2005; Weiner and Joel, 2002). Using the notion that an action is expensive because of how fast it must be performed, a simple *cost function* proportional to 1/RT can be constructed, and results in an optimal responding rate that is proportional to the square root of the average reward rate (Niv, 2007; Niv et al., 2006).

Theories of vigour have contrasted the paucity of movement in PD with the increased drive to responding elicited by dopamine agonists. The comparison suggests that in terms of motor control, symptoms of Parkinsonism are manifestations of *reduced willingness to exert effort*, equivalent to an *increase in the cost of movement* (Mazzoni et al., 2007). Evidence that might count towards this would be an interaction between reward and bradykinesia in PD. Mazzoni and colleagues (2007) reported that patients with PD have difficulty in controlling their movement velocity in response to reward feedback. The authors suggested that this was due to impaired action costing in the face of reward, but their result might also be interpreted as a pure learning deficit (Mazzoni et al., 2007). Indeed, a contrasting theory has been recently put forward that frames some PD symptoms in terms of aberrant learning in the no-go pathway (Xiao-Xi, 2012). A detailed investigation of reward's effect on motor and decision performance may shed light on this discrepancy.

1.6. Plan of thesis

My aim is to measure attentional capture using eye movements, and study how it is modulated by incentives. I aim to characterise the behavioural effects of reward, and how they interact with high and low dopaminergic states, and whether they are dependent on medial prefrontal cortex. The chapters of this thesis address the following empirical questions:

1. Do incentives have a direct impact on distraction as measured by oculomotor capture?
2. Can recent reward history influence distractibility, for example on a trial-to-trial basis?

3. Can autonomic measures, i.e. pupil dilatation, reflect incentivisation by reward?
4. What is the effect of a dopamine agonist (cabergoline) on the reward modulation of distraction in healthy people?
5. Do patients with dopamine depletion—Parkinson's disease—have altered reward modulation? And can dopaminergic medication restore any deficits?
6. Do lesions of medial prefrontal cortex in humans influence reward-based incentivisation of distraction?
7. Are there specific regions of the medial frontal lobe that are more or less critical for reward sensitivity in the guidance of attention?

2. Missed rewards capture attention

2.1. Introduction

Distraction is obviously disadvantageous in certain situations, but beneficial in others. In an evolutionary context, distraction would allow us to be alert to rare but highly significant events. For example, rapidly orienting towards the movement of a predator seen in peripheral vision might be life-saving (Shelley-Tremblay and Rosén, 1996). Rapid attentional capture by low-level sensory properties could increase fitness even if it were weak—i.e. not imperative. Although it has been suggested that distraction evolved in this way (Anderson, 2013; Johnston and Strayer, 2001), to my knowledge it has not previously been framed economically.

Intuitively, when distraction occurs, it is at the expense of attention to any ongoing task at hand. Orienting to a distractor is only of net benefit when the dangers of ignoring a distraction outweigh the gains from continuing with the current goal. Because of this, evolution ought to precisely titrate distractibility to the level of risk in our environment. Higher levels of environmental uncertainty (quantified as risk, or variance in outcome) should breed correspondingly higher levels of distractibility. Avoiding distraction is essentially taking a small risk, in order to reap a reward (**Figure 2.1**).

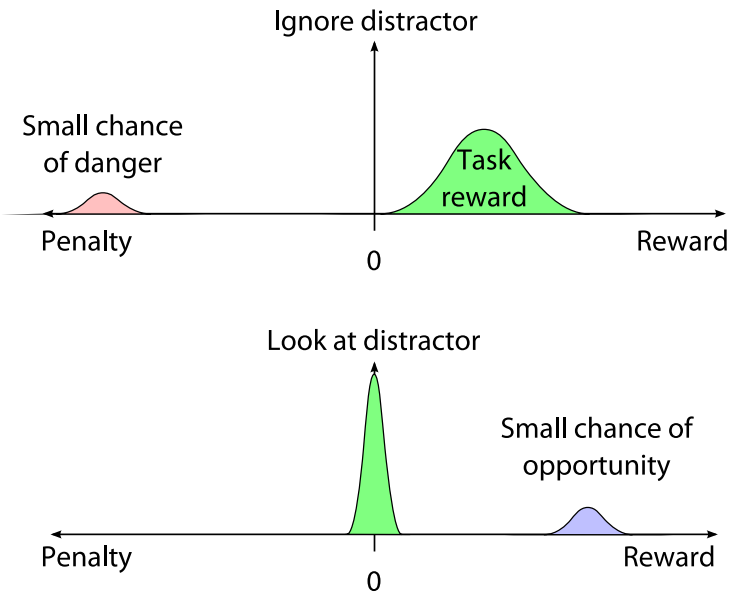


Figure 2.1: Economics of distraction

Distraction by perceptually salient stimuli may be beneficial or counterproductive, depending on the situation. The panels illustrate the economical trade-offs involved when avoiding distraction, or being distracted. a) If a distractor is ignored, the ongoing yield of the rewarding task is obtained, but there is a potential risk of danger. b) If attention is captured by a distractor, the danger can be avoided, and a benefit might be derived if the distractor poses a new opportunity; however the rewards of continuing the ongoing task are lost. Whether or not distraction makes economical sense will thus depend upon our estimates of risk, opportunity, and ongoing task reward. Optimising distraction rate by ongoing task rewards may be critical for survival.

Crucially, trading off risk for reward makes predictions about how changes in reward might influence distractibility. In particular, if the value of avoiding distraction is high, distractibility should decrease. Similarly, if distraction is penalised distractibility will also fall. It is interesting to note that this account classifies distractibility as a form of risk aversion.

Conversely, we can think of ongoing activities as requiring continuous motivational incentives to make them economically worthwhile—i.e. worth filtering out other possible actions. When higher rewards are available, a subject should engage more "effort" to obtain them. Here, effort acts as an effective cost, encapsulating risk

aversion. The overall cost can be framed economically as effort discounting (Hursh, 1980; Kahneman, 1973; Pessoa, 2009).

According to the first sense (economic motivation), the predictions about how reward should influence distraction could be summarised as follows:

$$P(\text{Distraction}) = \Psi\,[U\,(\text{possible opportunity}) - U(\text{possible danger}) - U(\text{task reward})] \quad (2.1)$$

where $\Psi(x)$ is a sigmoid function such as $1/(1+e^{-x})$, and $U(r)$ is the utility of an outcome r. The sensitivity to environmental uncertainty is governed by the concavity of U (i.e. $\frac{d^2U}{dr^2}$). If this is negative (**Figure 1.1)**, then distractibility should increase in environments with greater dangers, or with lower task-related gains.

Incentivising performance with rewards attenuates distractor effects in the Eriksen flanker task (Hübner and Schlösser, 2010) and the Stroop task (Krebs et al., 2011). In particular, performance improvements cannot easily be accounted for purely in term of speed-accuracy trade-off or 'criterion shifts': reward induces a true motivational change. But motivation by rewards and penalties play different roles in controlling behaviour (O'Doherty et al. 2001; Frank, Seeberger, and O'Reilly 2004), and may be represented differently at the neural level (Roesch and Olson, 2004). Might rewards and penalties then influence distractibility in different ways? Attention is biased towards previously rewarded features (Anderson et al., 2011a; Hickey et al., 2010a; Kiss et al., 2009a; Kristjánsson et al., 2010), which may faciltate decision making and foraging (Krajbich et al., 2012; Manohar and Husain, 2013), but no reverse effect has been seen for penalties (Wang et al., 2013).

To my knowledge, no studies to date have parametrically varied incentive levels in a distractor-avoidance task. If motivation influences distractibility, incentivising with either rewards or penalties should reduce distraction, but without trading off speed. Interestingly, vigour theory provides a strikingly different prediction (Dayan, 2012a; Niv, 2009; Niv et al., 2007). The ongoing reward rate determines the optimal rate of responding. If distraction were penalised, although this motivates behaviour, it would not speed responses.

Reward has been found to have short-term effects on subsequent trials; in particular, attentional priming and negative priming are both modulated by reward (Anderson et al., 2011a; Hickey et al., 2011). But how might information be retained from trial-to-trial? Rewards might be held in working memory (Camara, Manohar, and Husain 2013), and it has previously been shown that working memory contents can influence distraction (Theeuwes, Olivers, and Chizk 2005; Theeuwes, Belopolsky, and Olivers 2009). Signals other than reward might also be retained from trial to trial. According to theories of reinforcement learning, outcomes on previous trials generate a 'prediction error' which is critical in altering subsequent behaviour (Sutton and Barto, 1990). In a spatial task, the strongest negative prediction errors will occur at locations where *rewards were previously missed*. If this information were critical for learning, it might be retained in memory, and subsequently influence spatial orienting.

These considerations led me to study the spatial effect of reward and penalty on distractibility. I used oculomotor capture (Kramer et al., 1999) as an index of distractibility in humans. In my version of this task, six red discs were shown, one of which remained red (the saccade target) while another disc turned bright yellow, becoming suddenly salient (the distractor). Subjects made speeded saccades towards the

target, but the simultaneous bright distractor often subversively 'captured' the eyes. Although oculomotor capture depends upon several features of the task e.g. target-distractor similarity (Mulckhuyse et al., 2008), it cannot fully be voluntarily overridden.

To examine how incentive influences oculomotor capture, subjects were awarded money for their speed of looking at the target, but incurred a penalty if they looked at the distractor. First, I systematically and explicitly varied the reward for making saccades to the target, and the penalty for shifting gaze to the distractor. I predicted that blocks with *higher reward and higher penalty would lead to less distraction*. Next, I examined the effect of the previous trial's reward and penalty, upon performance, predicting that capture would be greater *if the distractor is in a location that was rewarded on the previous trial*.

2.2. Study 1: Block-to-block manipulation of incentives

2.2.1. Method

The aim of the study was to test how varying the amount of expected reward influences oculomotor capture generated by a visual transient. To this end, I modified the oculomotor capture paradigm (Theeuwes 1991a). Subjects were instructed that they would see six red circles, and when the fixation cross disappeared, four would turn grey, one would turn yellow, and the remaining circle is the target and would remain red (**Figure 2.2**). They must move their eyes to the disc that remained red (the target), and not to look the disc that turned yellow (the distractor).

Subjects received the following further instructions: the faster they directed gaze to the target, the more money they would make. If they were too slow, they would

obtain zero reward, and if they looked at the yellow distractor, they could lose money. Thus subjects were rewarded for every saccade to the correct target according to their speed, and/or penalised for every saccade that was captured. Monetary feedback was presented after each trial. In Study 1, the maximum reward available and the flat penalty for errors, were manipulated between blocks. Subjects were explicitly shown these values at the start of each block.

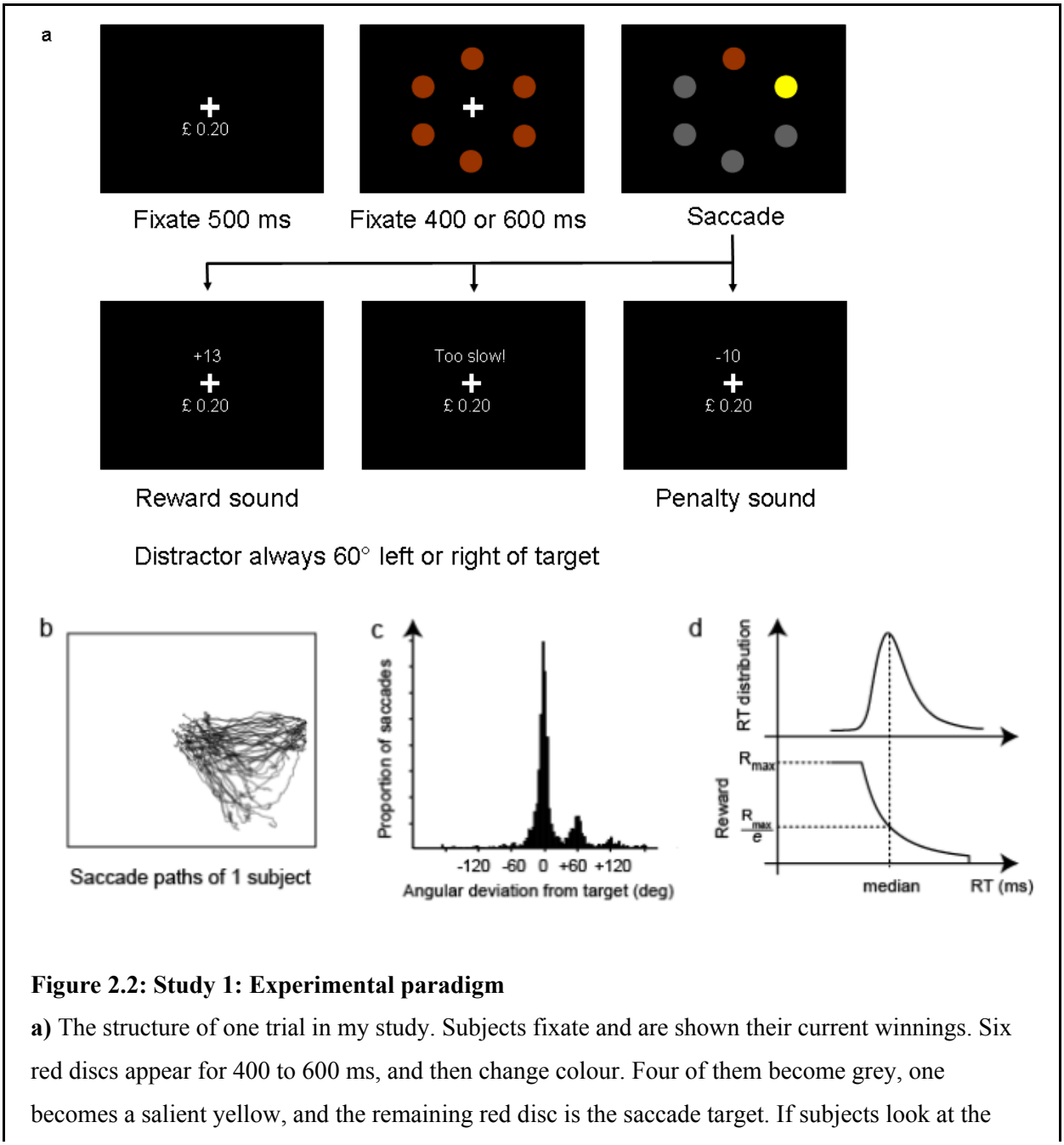


Figure 2.2: Study 1: Experimental paradigm

a) The structure of one trial in my study. Subjects fixate and are shown their current winnings. Six red discs appear for 400 to 600 ms, and then change colour. Four of them become grey, one becomes a salient yellow, and the remaining red disc is the saccade target. If subjects look at the

target first, they are rewarded according to their speed; if they look at the yellow distractor, they may be penalised. **b)** An example of the overlaid saccades from one block of trials, rotated to the canonical orientation, showing oculomotor capture on some trials. **c)** Histogram of the angular direction of the initial saccade, relative to the direction of the target; example data from one subject. **d)** For correct saccades to the target, subjects were rewarded according to their speed, with a falloff matched to their median reaction time.

2.2.1.1. Subjects

Fifteen subjects from the University subject pool (age range 19-24, 11 female, with normal or corrected-to-normal vision) all gave informed consent. The study was approved by UCL research ethics committee. Subjects were instructed that they would be paid according to their performance, and that they would earn between £10–15.

2.2.1.2. Apparatus

A PC running Matlab (The MathWorks) plus Psychophysics Toolbox under windows was used to present stimuli on a CRT with resolution 1024x768 pixels at 100 Hz. A frame-mounted Eyelink 1000 (SR Research) infrared tracker monitored left eye position relative to the screen, sampled at 1 kHz. Eye movements were parsed online by the Eyelink PC and sent to the presentation PC over a patch cable, to provide trial-by-trial feedback. Subjects sat 60cm from the 21” display against forehead- and chin-rest. Randomised 9-point calibration was performed at the start of the experiment and after 5 blocks.

2.2.1.3. Stimuli

A white fixation cross measuring 1.5 degrees was displayed at the centre of the screen on a black background, surrounded by 6 dark red discs (31% beam intensity) each subtending 3 degrees of arc, with centres equally spaced on an invisible circle of radius 11.0 degrees from the fixation point. The total reward accumulated by the subject so far

was displayed numerically, centred 2.4 degrees below the fixation cross in digits 1.5 degrees high. This display remained until fixation had been maintained for a flatly distributed random foreperiod between 750 and 1050 ms. The fixation cross was then erased, and simultaneously, four of the six discs became dark grey (12.5% intensity), one remained dark red, and one became bright yellow. The yellow distractor was always one of the two discs *immediately next* to the dark red target (see **Figure 2.2a**).Thus on every trial there was a red target disc and a neighbouring yellow distractor disc.

The endpoint and landing time of the first saccade that landed outside a circle radius 5 degrees was determined online and used to determine trial outcome (see reward function below). At that moment, feedback sound was played and the amount won or lost on that trial was displayed numerically in the centre of the screen, for 300 ms.

2.2.1.4. Design

Subjects performed 10 blocks of 56 trials each. Prior to each block, subjects were numerically shown their maximum reward attainable if they looked at the target quickly, and also the penalty they would receive if they looked at the distractor. The block began after a keypress. The maximum reward and fixed penalty for each block was one of 5 conditions:

- 10p maximum reward (to target) and 10p penalty (to distractor)
- 10p maximum reward and 2p penalty
- 10p maximum reward with no penalty
- 20p maximum reward with no penalty
- 30p maximum reward with no penalty.

Henceforth I will call these conditions [+10,-10], [+10,-2], [+10,0], [+20,0] and [+30,0] respectively. The range of penalty levels was chosen to be smaller than the reward

magnitudes, as pilot studies showed that a penalty of -10p was approximately as effective as a reward of 30p in motivating faster RTs.

The order of the 5 conditions was manipulated in a Latin square across subjects, with the last 5 blocks using the reverse order of the first 5. There were therefore 5 different block orders, and 3 subjects performed each order. On each trial, foreperiod and target location was randomised, and the distractor was randomised to be one position either clockwise or anticlockwise of the target. Before the experiment, subjects performed 32 practice trials.

2.2.1.5. Reward functions and penalties

The saccade endpoint was categorised into one of 6 bins according to the nearest disc. If the saccade landed on a grey disc, or if the endpoint was greater than 15 degrees distant from fixation, a reward of zero was given. If the endpoint was nearest to the yellow disc, the penalty value was displayed. This penalty was always constant within a block. By contrast, rewards (to targets) varied as a function of the maximum reward for a block and the saccadic reaction time in the following way:

$$\text{Reward} = R_{max} \cdot \min\left(e^{\frac{t_{min}-RT}{\tau}}, 1\right) \tag{2.2}$$

truncated to the nearest integer, where *RT* was the time of initiation of the saccade. Median saccadic reaction time in the practice trials was used as the 37% falloff point for reward magnitude (to determine τ), with a minimum RT cut-off (t_{min}) at the 10th percentile (faster than this, reward was maximal, see **Figure 2.2d**). If this reward value was zero, the words ‘Too slow’ were displayed instead of the number ‘0’.

Feedback sound was played based on the trial reward; a buzz if a penalty was incurred, a low pitched bleep if zero reward, a high-pitched ping if a reward of 15p of lower was obtained, and a 'ker-ching' cash-register sound was played if a reward of over 15p was obtained. Sounds lasted 250 ms and were matched for amplitude.

2.2.2. Results

On each trial of the task, subjects saw six locations spaced around a circle, and were required to make a rapid saccade to the location which did not change colour. A coloured bright distractor was present at a neighbouring location (**Figure 2.2a**). The first saccade was determined using a combined velocity and acceleration criterion. To quantify the pull of the distractor on each trial, I measured the first saccade's deviation towards the distractor, i.e. the angle from the fixation cross of the saccade endpoint relative to the direction of the target (see **Figure 2.2c** for an example in one subject). The saccade was also classified by the location nearest to its endpoint, as being towards the target (correct), the distractor (capture error), or to a different location. The proportion of trials where the eyes were captured by the distractor, and the angle of deviation, formed my primary measures of distraction by the salient onset.

2.2.2.1. Reward and penalty reduce oculomotor capture

The proportion of capture was determined for each reward condition (**Figure 2.3a**). The block's reward and penalty level ([+10,-10], [+10,-2], [+10,0], [+20,0], or [+30,0]) significantly modulated the proportion of oculomotor capture (1-way ANOVA over block type, $F(4,56)=4.34$, $p<0.004$): as predicted, distractors captured the eyes less when they were highly penalised [+10 -10] compared to the condition where there was no penalty, i.e. [+10,0] (2-tailed $t(14)=3.69$, $p<0.002$). Introducing penalties can therefore reduce salience-driven attentional capture.

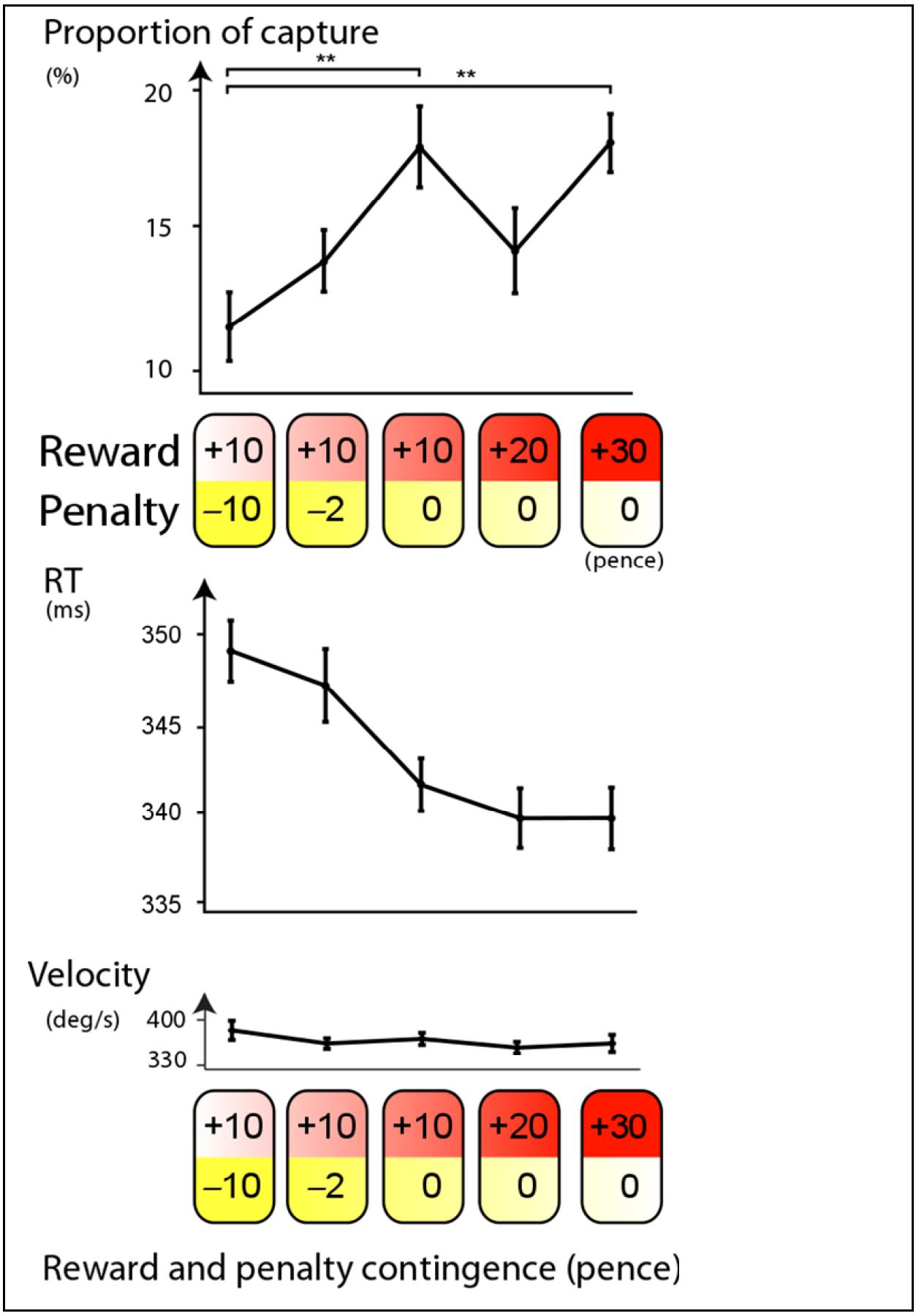

Proportion of capture
(%)
20
15
10
**
**
Reward
Penalty
+10
–10
+10
–2
+10
0
+20
0
+30
0
(pence)
RT
(ms)
350
345
340
335
Velocity
(deg/s)
400
330
+10
–10
+10
–2
+10
0
+20
0
+30
0
Reward and penalty contingence (pence)

Figure 2.3: Study 1: Improvement by reward and penalty, with choking under pressure.
a) The proportion of trials on which the eyes were erroneously captured by the salient distractor is shown, for the different blocks. As the possible penalty for distraction was increased (towards left), subjects were better at avoiding distraction. When potential rewards were increased moderately, subjects again improved. However when reward was maximal (far right), 'choking under pressure' was observed: capture was again high. **b)** Reaction times were fastest when rewards were high, and slowest when penalty was high. **c)** For each reward condition, trials were binned according to reaction time, and the conditional accuracy was plotted. Under moderate rewards [+20 -0], the accuracy curve is shifted upwards despite speeding of responses -- a finding which cannot be explained by trading speed for accuracy.

Moderately high rewards [+20,0] also reduced capture rates by 5.5% (SEM 1.6%), relative to low rewards ($p=0.028$ one-tailed). But counter-intuitively, very high rewards [+30,0] did not reduce capture rates compared with low rewards [+10,0] ($t(14)=0.3$, $p>0.5$). Rather, the highest rewards actually *increased* capture compared to the moderate-reward condition (two-tailed $t(14)$, $p=0.049$), and relative to the high-penalty condition [+10,-10] (two-tailed $t(14)=-3.69$, $p<0.002$) (**Figure 2.3a**). Very high incentives, therefore, were ineffective at preventing oculomotor distraction. A similar analysis of the raw deviation angles of saccades showed the same pattern of significant effects.

One might suspect the order in which subjects experienced the reward conditions would be important. However, although there was a main effect of subject ($p<0.01$) on capture, there was no effect of block order ($F(4,40)=0.43$, $p>0.5$), and no interaction of reward condition with block order ($F(16,40)=1.29$, $p>0.05$). This indicates that the counterbalanced order of reward-condition blocks was effective.

Were these reward- and penalty-related improvements due simply to subjects being more cautious? Analysis of median saccadic reaction times revealed that subjects

were significantly slower in high-penalty blocks than high-reward blocks (t(14)=3.38, two-tailed p=0.004) (**Figure 2.3b**). In other words, the possibility of penalties made subjects both slower and more accurate. However, increasing rewards showed a trend to *speeding up* reaction times (t(14)=1.09, p=0.29), compared to low rewards [10,0]. This was true in the moderate reward condition [20,0] *even though* distraction was reduced. Thus the reduction in distraction due to reward cannot be explained by caution. Note that reaction time appears to relate to the block's average reward rate, and as expected, the total winnings in each block vary with expected value, with subjects winning on average £5.20 on high reward blocks, and losing £1.53 on high penalty blocks.

2.2.2.2. Rewards speed RT, Penalties cause slowing

This asymmetrical relation between reaction time and distraction is portrayed using conditional speed-accuracy functions for each condition (**Figure 2.4**). The proportion of correct saccades in each of 5 RT bins was calculated for each reward condition, and the mean function across subjects was plotted. As expected, in all 5 reward conditions there was a strong positive correlation of accuracy with RT (all r^2 in range 0.88 to 0.95, all p<0.002, **Figure 2.4**).

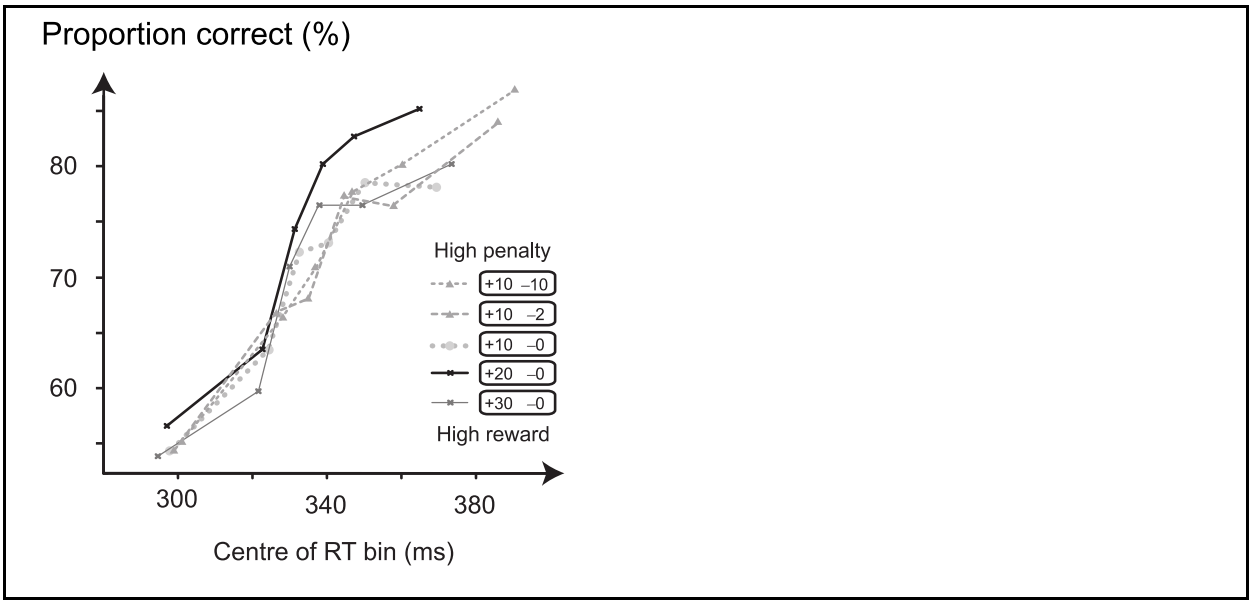


Figure 2.4: Conditional accuracy function for Study 1.
Accuracy rises from 50% at the earliest RT bin, to over 80% for the slowest RT bin. When reward is moderately increased, there is an increase in accuracy as well as shortening of reaction times.

It was observed that, for the slower trials, different reward conditions produced different effects on the speed-accuracy gradient. Therefore I estimated the slope of the speed-accuracy relation for each reward condition in each subject, using a median split of RTs. Medium-high rewards [+20,0] had a significantly steeper accuracy:speed function (mean gradient 517 %/s ± 82, compared with 316 ± 98, $t(14)=2.34$, $p=0.018$), indicating that the benefit of reward in this case *cannot* be explained simply by a speed-accuracy trade-off.

2.2.2.3. No effect of reward on saccade velocity

The peak speed was calculated for each correct saccade, using 5 ms averaging windows for velocity. The mean peak speed for the 5 reward conditions were compared using 1-way repeated-measures analysis of variance. There was no effect of reward or penalty on velocity ($p>0.05$).

2.2.2.4. Reward reduces blink rate, but penalty increases it

The proportion of trials that were aborted due to a blink was counted in each block. There was a significant main effect of reward condition (**Figure 2.5**, $F(4,74)=2.67$, $p=0.042$), and pairwise t-tests showed a significant difference between the [-10,+30] and [-2,+30] conditions ($p<0.05$ corrected with Tukey's LSD); the two penalty conditions had 5.7% and 5.0% less capture than the +30p condition.

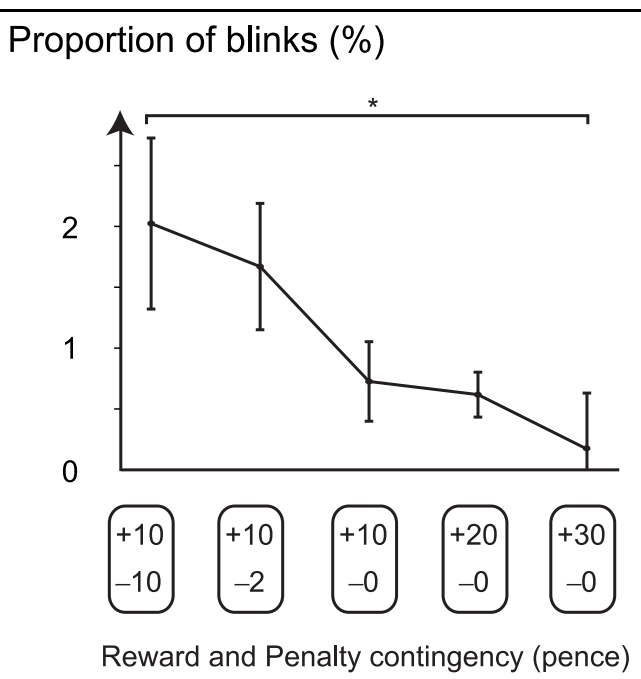


Figure 2.5: Blink rate during the task is reduced by high rewards, compared to high penalties. The proportion of trials that contained blinks during the foreperiod was calculated in each block. Error bars indicate standard error of the mean. The error rates differed by one-way ANOVA (p=0.042), and pairwise comparisons showed more blinks during between the high-penalty condition than high-reward.

2.2.2.5. Effect of trial history

To test whether capture was dependent on reward history, I divided trials into those where the current distractor location previously contained a target or a distractor on the preceding trial. There was significantly more capture when the distractor was previously a target ($F(1,14)=14.6$, $p=0.0019$). Similarly, I divided trials into those where the current *target* location was previously a target or distractor; but there was no effect of what was previously at the target location ($F=0.0$).

Subjects are captured more by a distractor when a target was previously at that location. This differs from previously described reward priming effects (Hickey, Chelazzi & Theeuwes, 2010; Anderson, Laurent & Yantis, 2011) in being spatially

specific. I propose this is because each location retains its reward status from the previous trial. But could this effect simply reflect a tendency for subjects to repeat their last action? Since there are more correct than incorrect trials, one could explain it simply as a "perseverative" tendency to be captured to a location that was recently looked at.

To refute this, trials were broken down as above, then subdivided according to where the subject looked on the previous trial. A 2-way ANOVA was used to separate the effects of the distractor being at the previously-looked-at location, versus being the target or distractor. There was no main effect of where the subject previously looked ($F(1,56)=0.52$), but there was a significant interaction with whether the distractor location previously contained a target or distractor ($F(1,56)=8.7$, $p=0.0046$). This indicates there is an effect of where the eyes previously went, which interacts with the location history. This effect was investigated in detail in the next experiment.

2.2.3. Discussion

This experiment measured the effect of rewards and penalties on distractibility, using the paradigm of oculomotor capture (Theeuwes et al. 1998), in which the eyes are drawn to a visually salient distractor, rather than a non-salient target that was identified by being the only item that did not change.

There were three main findings. Firstly, the results demonstrated that oculomotor capture can be decreased when there are penalties or rewards at stake. In the case of penalty, accuracy improved at the cost of speed; for rewards, subjects were both faster and more accurate. The effect of valence is therefore *asymmetrical* with regard to speed. Secondly, for very high rewards, subjects were paradoxically captured more by

the distractors. Finally, in a post-hoc analysis of trial history, oculomotor capture by a distractor was greater when that distractor location was previously occupied by a valued target.

This experiment differs from previous work on reward and distraction, in that I do not manipulate prior reward-feature associations by learning. Rather, the total incentives are manipulated, showing a pure motivational effect on distractibility.

2.2.3.1. How do rewards and penalties reduce distraction?

Rewards increase response frequency in free operant tasks (Dickinson and Balleine, 2002), a fact which has been explained in terms of response vigour (Niv et al., 2007, 2007). Starting with two premises, that a fast response is more costly to execute, and that making more responses yields more reward, an optimal response-time can be calculated. The optimum depends on the reward schedule, and in particular, as the average reward rate increases, the optimal response time shortens. Average reward rate may be represented in the brain by tonic dopamine levels in nucleus accumbens. Although Niv et al. did not explicitly discuss penalty, it might be expected to prolong response times. This could potentially explain the observed effect of reward and penalty on the *speed* of responses (**Figure 2.3b**). However, responding faster without trading off accuracy would require something further, such as effort (Hübner and Schlösser, 2010). To see this, notice that simply combining an accuracy bonus, error cost, and time pressure cannot lead to both speed and accuracy increases—unless the constraint "going faster means more errors" is somehow removed. I discuss this quandary and offer a solution in **Chapter 7**.

It is likely that subjects deployed more cognitive resources in the moderate-reward [+20] condition, allowing *both* faster responses *and* decreased distractibility.

Such a motivating effect has been noted in monkeys, where asymmetrical reward speeds both visually elicited saccades and memory-guided saccades without trading-off accuracy (Takikawa et al., 2002b; Watanabe et al., 2003), and two recent human studies have demonstrated an increased ability to resolve conflict under rewarded conditions in the Stroop task and Eriksen flanker task (Hübner and Schlösser, 2010; Krebs et al., 2011). Such results imply that motivation by reward is not a trade-off but a *true increase* in effort; in my study, this motivational effect was specific to *positive* valence incentive rewards, rather than penalties.

Effort is a determinant of attentional resources (Tomporowski and Tinsley, 1996), but how might it be mediated? (Sarter et al., 2006) suggest that motivational effects on attention are mediated by basal forebrain cholinergic projections to prefrontal cortex, under the control of nucleus accumbens and anterior cingulate cortex, which are in turn under the influence of dopaminergic reward circuits. Such a mechanism might also provide an explanation for the unusual phenomenon of *increased* capture at high reward levels, discussed next.

2.2.3.2. Choking under pressure

A second asymmetry between reward and penalty was the paradoxical worsening of performance in the highest reward condition (**Figure 2.3a**). This is the first study to my knowledge where a rapid orienting task has shown this biphasic relation under quantitative manipulations of reward.

Although intuitively one expects motivation to lead to *improvements* in performance, *impaired* performance has often been noted in connection with high stakes. Explanations of such 'choking under pressure' include high-arousal levels (Yerkes and Dodson, 1908), highly emotional states (Easterbrook, 1959), or raised self-

awareness (Baumeister, 1984). Choking can be alleviated by background sound (Mesagno et al., 2009), and worsened by spectators (note my study was conducted in a quiet room with the experimenter observing throughout). It is normally seen in overlearnt, skilled tasks, but recent experiments have extended this to higher cognitive tasks (Gimmig et al., 2006).

A recent fMRI study revealed choking in a game where expectation of high reward gave worse performance than low reward (Mobbs et al., 2009). They suggested that framing outcomes in terms of loss might cause anxiety-driven reduction in performance. My results do not support this claim; in particular I found choking with high rewards but not with penalties. But importantly, they found increased activity in ventral midbrain and striatum, suggestive of a dopaminergic basis: as dopamine levels increase, attentional performance follows an inverted-U-shape (Bodi et al., 2009; Cools et al., 2001a). The asymmetry of my results is also compatible with the known nonlinearity of dopaminergic activity under rewards versus penalties (Schultz et al., 1997). Although dopaminergic neurones do not encode absolute rewards, they do encode perceptual salience alongside relative reward (Schultz, 1998), which are precisely the signals that would be needed to compute the *trade-off* between distraction and motivation. The pallidal and subgenual cingulate encoding of very high rewards is strongly dependent upon reward history, which might account for this variable and often suboptimal effect (Elliott et al., 2000).

Do these results have a bearing on the mechanisms of preventing distraction? At first glance it appears that our motivational modulation invalidates the strong hypothesis that stimulus-driven capture is inevitable. Yet, my findings may be consistent with the hypothesis that reward cannot improve the *earliest* phase of distractor filtering. The

slowing caused by penalty could account for its reducing distraction, and rewards appear to have their effects on later saccades in the distribution only (**Figure 2.3c**), consistent with previous findings (Wijnen and Ridderinkhof, 2009). However the lack of effect of reward on capture of the fastest saccades is ***not*** consistent with Hickey et al.'s (Hickey et al., 2011) suggestion that reward has an early effect on target selection. Rather, it favours the models which posit increasing effects of reward over time in the trial (e.g. Ding and Hikosaka 2007; Schütz, Trommershäuser, and Gegenfurtner 2012).

Finally, I found a trial-to-trial effect on oculomotor capture: the eyes were distracted more to locations that were targets on the previous trial. Furthermore, distraction appeared to be greatest when that target on the previous trial was *not* looked at. However, since the first experiment was not designed to examine trial-to-trial effects, some of the trials used to look at the history of the distractor location, also had rewards and penalties previously at the target location, and the proportions of these trials was not balanced. This motivated the second experiment.

2.3. Study 2: Effects of reward history on distraction

2.3.1. Method

I was interested in the effect of reward and penalty history in the previous trial on oculomotor capture in the current trial. The stimuli and instructions were similar to study 1, except with all blocks having identical maximum reward and penalty values. Critically, I also manipulated the history of targets and distractors at each location.

2.3.1.1. Subjects

10 subjects (aged 20–33, 5 female, with normal or corrected-to-normal vision), were recruited from an advert. They were instructed that they would be paid according to their performance.

2.3.1.2. Stimuli

The stimuli were identical to those in Experiment 1, except that during the fixation period, the 6 dark red discs were not visible. They appeared, instead, after fixation had been acquired for 400 ms, and remained visible for the foreperiod. In this experiment the foreperiod varied from 400 to 600 ms. The dark red discs were brighter than in Experiment 1, with an intensity of 25%.

2.3.1.3. Design

In order to examine the effect of location repetition, the target and distractor on the current trial could either be in different locations, or in the same locations, as the previous trial (**Figure 2.6a**). Additionally, when occupying the same locations, the target and distractor could be in switched positions: the target appearing at the previous distractor location, and the distractor appearing at the target location. I predicted that an identical configuration would lead to reduced oculomotor capture, whereas swapped locations would lead to increased capture, compared to the "neutral" non-repeated condition. Such an effect could be due to two separable causes: saccades to the target could be *facilitated* if the location was previously occupied by a target, or *inhibited* by a previous distractor. Similarly, saccades to the current *distractor* could be facilitated if its location was previously a target, or inhibited by a previous distractor.

In order to disentangle these two possibilities, four more conditions were employed (**Figure 2.6b**). In these conditions, only one of the locations was repeated.

The target alone, or the distractor alone, was at the same location as either the target or distractor on the previous trial. Note that two of these conditions (top two in figure) examine the history of the current distractor location, and the other two (lower two in figure) examine the history of the current target location.

Thus in total, there were 7 ways in which the positions of distractor and target could be related to the positions on the previous trial. They could both remain in the same position; the distractor could move while the target remained fixed, or vice versa; the new target location could be the old distractor location while the distractor moves; or the new distractor location could be the old target location while the target moves; or finally, the distractor and target could switch locations. Each of these 7 transition types was equally probable. Each subject performed 10 blocks. The experiment took between 45 minutes and 1 hour.

Figure 2.6: Study 2: Design to examine trial-to-trial effects
I manipulated the location of the target and distractor on the previous trial according to the seven possibilities shown. a) The target and distractor could appear in completely new locations, or at the same locations as on the previous trial. They could also occupy the same locations as before, but be swapped around so that the target and distractor are flipped, compared to the previous trial. b) Four more conditions were used to determine the cause of the speeding by repetition, and slowing by reversal of target and distractor locations. In these conditions, only one location was repeated.

2.3.1.4. Reward

Maximum reward was fixed at 20p, and penalty fixed at 2p. Subjects were informed of this at the start of the experiment, and therefore no further instruction was needed at the start of each block regarding reward and penalty. The same rules and equation governed reward as in Experiment 1. The reward falloff time was fixed with a time constant of 25ms, and minimum time t_{min} was adjusted to subjects' practice performance as before.

2.3.2. Results

2.3.2.1. Manipulation of trial history

On each trial the locations of target and distractor were chosen from the seven possible transitions (**Figure 2.6**). The penalty and the maximum reward were held constant. I calculated angular deviations and proportions of capture as previously, for each of the transitions.

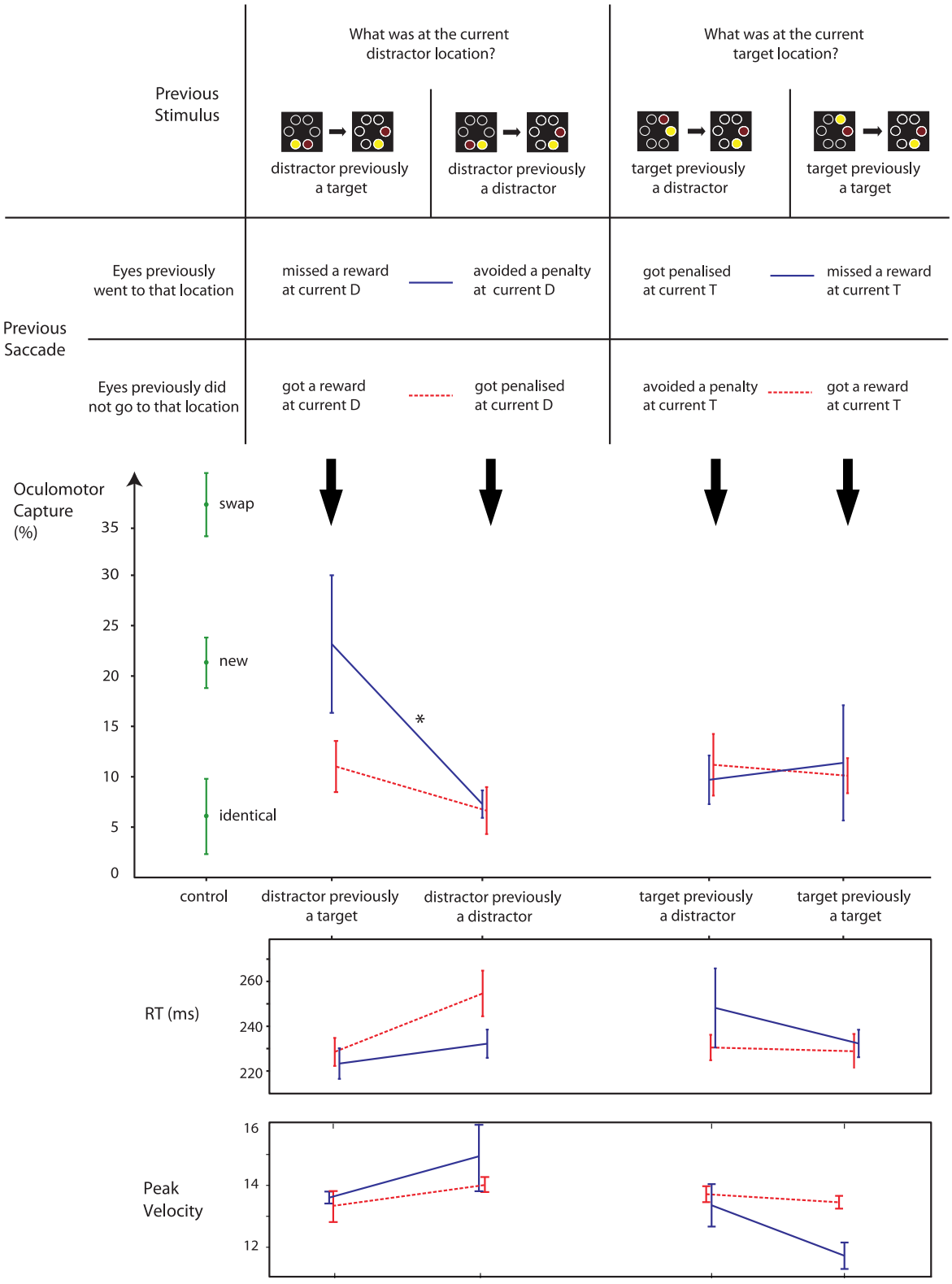


Figure 2.7: Results of the study 2: Effect of missed rewards

a) Trials were first broken down according to what was previously at the current target or distractor location. I then examined separately whether subjects had previously looked at this location or not. To do this, trials were broken down according to the outcome of the previous trial: rewards or

penalties could have previously been obtained or missed. **b)** The red and blue lines correspond to the eight conditions above in (a). Distraction was increased only in the condition where subjects *previously missed a reward at the current distractor location*. The proportion of capture on the three control trial-types (see Figure 2.6) are shown on the left. **c)** Reaction times are shown for the conditions corresponding to the conditions above.

As predicted, on trials which were identical to their antecedents, capture was minimal (6%), and on trials with swapped target and distractor locations, capture was maximal (38%). Neutral trials, where neither target nor distractor locations previously contained a colour, had intermediate capture (21%).

As in study 1, I compared trials in which the current distractor location was previously a target, with trials in which the current distractor was previously a distractor. For each subject, I first examined the proportion of saccades that went to the distractor, as compared to the proportion of saccades that went to any other non-target, non-distractor location (i.e. an irrelevant, grey disc). There was significantly more oculomotor capture when the current distractor location had been occupied by a target in the previous trial – and this was specific for saccades to the distractor location (**Figure 2.7**, interaction between previous distractor status and error type, $F(9,1)=11.3$, $p=0.008$). This confirms that a previous reward can increase oculomotor capture to a distractor at that location. Could this increased capture be due to faster responding? There was no evidence for a difference in median error reaction times between the location-history conditions (i.e. when the distractor was previously a target, *vs*. when it was previously a distractor, paired 2-tailed $t(18)=0.42$, $p=0.68$).

But could the effect of trial history be due *perceptual priming* of a target location? Or perhaps due to subjects looking to the same location just previously (i.e. a perceptual or *motor repetition* facilitation effect)?

2.3.2.2. Effect of previous trial outcome

To clarify this issue, I subdivided trials according to where subjects had previously looked (**Figure 2.7a**). For the trials whose history differed only at the *distractor*-location, I divided them according to whether subjects previously

(1) looked at the location of the current distractor
(i.e. action-repetition would result in penalty) or
(2) looked at a location which was neither a current reward or penalty
(action-repetition would not result in reward or penalty).

Similarly, trials where *target*-location history was manipulated were divided according to whether subjects previously looked at the location of the current target or not.

This factor, saccade-history, was analysed orthogonally to location-history (**Figure 2.7a**). As above, the distractor being at the previous target location significantly reduced capture ($F(1,36)=18.7$, $p=<0.01$). Additionally, there was more capture when the current distractor location was also the endpoint of the previous trial's saccade ($F(1,36)=6.3$, $p=0.017$). But crucially, location history interacts with previous gaze: the effect of what was previously at the distractor location was +19% when it was previously looked at, compared to +29% when it was not looked at (significant interaction, $F(1,36)=5.3$, $p=0.027$). Capture is therefore increased when the distractor was previously a target, but only when subjects did *not* get the reward there. In other words, distraction was greatest when subjects previously *missed* a reward at the current *distractor* location (**Figure 2.7b**).

This effect is unlikely to be explainable in terms of response times, as there was no corresponding interaction for reaction times (**Figure 2.7c**). Although there was a trend for subjects to be slower when the distractor was previously a distractor (main

effect of location-history $F(1,14)=3.5$, $p=0.08$), they are not significantly slower or faster after they previously received a reward at the current distractor than when they missed one there (i.e. there is post-error distractibility *without* speeding). This dissociation argues against a simple speed-accuracy trade-off.

2.3.3. Discussion

To investigate the trial-to-trial effect found in study 1, study 2 manipulated the location history of each trial. Again, I found distraction was greatest when the distractor location was previously occupied by a valued target. However, this was only the case when subjects did *not* actually get the reward at that valued target – i.e. when they were previously distracted to a different location, and had missed the reward at the location which subsequently became the distractor. I attribute this interaction to 'missed rewards'.

2.3.3.1. Explaining the "missed-rewards" effect

Motor priming or perseveration cannot explain my findings, as subjects are *less* likely to repeat the previous eye movement on the current trial. Inhibition of return (IOR) thus initially appears to be a candidate for explaining the increased capture after a saccade to the location that becomes the next target. Conditional IOR has been suggested previously to explain such effects (Hodgson et al., 2002a). However, my effect is specific to cases where that location was previously a distractor. No decrease in capture is seen when subjects saccade to a target that is subsequently a distractor. To explain my results, inhibition of return would have to occur *only* if the location was penalised. .

One might ask whether this location-specific increase in capture could be explained as 'error correction' responses. Rabbitt (1966) showed that there are more

errors after an error trial. He proposed (Rabbitt and Rodgers 1977) that some of these 'double-errors' could be accounted for as corrections of the previous error. My experiment has shown that after missing a rewarded target, subjects are more likely to be captured by a salient distractor at that location. I think this is unlikely to be a corrective response. Firstly, error corrections occur within a few hundred milliseconds of the error response (Rabbitt 1966b; Rabbitt 2002), and are thought to be initiated almost contemporaneously with the error. In my study, subjects were required to re-fixate at the origin after each trial, followed by a foreperiod of at least 500ms. Secondly, there was a trend for the effect in Experiment 1 to be modulated by reward and penalty size (3-way interaction of reward level with the history, p=0.298). This implicates reward in increasing distraction. Thirdly, there was no corresponding decrease in capture when subjects previously missed a reward at the current target location. This suggests the effect is specific to increasing the effective salience of singleton distractors, not simply the preparation of a corrective movement.

An alternative interpretation of the finding could be that subjects adopt a strategy, for example, win-stay, lose-switch. I argue that the pattern seen in **Figure 2.7b** could not be explained by strategy alone, for two reasons: firstly, such a strategy is not seen for the outcome previously at the target location; the effect is valence-specific, i.e. subjects are *not* captured more when they previously *attained* the reward at the current distractor location. Secondly, even if a more complex strategy is invoked, for example specifically including valence histories, the effect is location-specific. Distractibility is contingent upon *where* the target and distractor appear on the new trial: subjects are *not* captured less if the current *target* location was previously a missed reward.

For these reasons, I think these effects are most parsimoniously explained by distraction being specifically enhanced by missed rewards.

2.3.3.2. Relation to previous studies

The results are consistent with previous work on the capture of attention when a feature has previously been rewarded (Della Libera and Chelazzi, 2009; Hickey et al., 2010a). It may be helpful to compare my findings with a related experiment on feature-based selection. In a search paradigm, if a colour singleton distractor changes colour from trial to trial with the other items' colour remaining constant, reward has no effect on ability to filter out the previous distractor colour. But conversely, if a colour singleton remains the same colour, and the other items' colour changes from trial to trial, reward improves selection of the previous target colour (Hickey et al., 2011). The authors interpret this as suggesting that rewards facilitate target selection priming but have little effect on the priming of distractor filtering.

My findings parallel this study in the spatial domain. Reward at the target location gives that location a selection advantage on the next trial, whereas the penalised distractor does not carry spatial inhibition to the next trial. Hickey et al. find that the reward effect of boosting the previous target feature operates both by improving performance when the target repeats, and by worsening performance when the target changes. But in my study, we find that the reward effect at the previous target location only has an effect if a distractor appears at that location.

2.4. General discussion

Study 1 demonstrates that the available rewards or penalties can modulate the amount of oculomotor capture. Subjects are slower and more accurate with penalties, and are faster

and more accurate with moderate rewards (**Figure 2.3**). The highest reward level in my study appears to result in "choking under pressure". Distraction was greatest for short-latency saccades. I interpret the results as demonstrating that attentional capture by bottom-up salience can be reduced by motivation, particularly later during a trial.

Study 2 shows a specific spatial interaction between rewards on the previous trial and oculomotor distraction. This entails a spatially-specific representation of reward that is present before the onset of a stimulus. Only when a reward was previously missed is distraction enhanced at that location (**Figure 2.7a**); I interpret this as a lingering, but spatially specific, reward prediction error signal.

The persistence of a spatially specific representation of past outcomes, e.g. reward and penalty, appear to guide attention subsequently. Recently interest has grown in possible links between working memory and attention, motivated by findings on the maintenance of attentional templates (Olivers et al., 2011). The focus of attention can literally *be* an item in working memory (Cowan, 2011) and can exert facilitatory or inhibitory effects on externally directed attention (Olivers, 2009). Although the focus of these theories has been primarily on object features, applicability to spatial locations could explain why persistence of reward and penalty representations can influence future orienting.

Analogies can be drawn with the findings from set-switching tasks, in which subjects have to either ignore a previously relevant feature, or attend to a previously irrelevant feature. A recent study has shown that affective stimuli can modulate feature selection (Dreisbach and Goschke, 2004). Viewing faces with a positive affect facilitates ignoring a distractor that was previously relevant, but impairs attending to a

target that was previously irrelevant. If reward has similar effects to positive affect, there is a case that a common dopaminergic mechanism underlies both phenomena.

What psychological mechanism could be responsible for this modulation of capture by missed rewards? One candidate is a spatial reward-expectation map. Milstein and Dorris (2007) showed that reward expectation can be location-specific, and can modulate the preparation of eye movements. The effect of spatial reward expectation on oculomotor capture builds up over time during each trial (Ding and Hikosaka, 2007a). My study has the implication that these maps retain information from trial-to-trial, and critically that they interact with reward feedback mechanisms.

However, in the oculomotor capture paradigm, attention appears to be prioritised to locations where there is a negative reward prediction error. This seems to be different to studies of top-down attentional modulation by reward, in which items that are associated with reward (i.e. carry a positive reward prediction error) are prioritised. Why might this be? The relatively short inter-trial interval I used may prevent preparatory effects before each trial. One possibility is that early direction of attention to locations uses an *independent* reward map. Specifically, reward expectation at a location has a stronger effect on oculomotor preparation when it was *not obtained* on the previous trial.

2.4.1. Conclusion

I have shown that in an oculomotor task with reward for fast responding, increasing the available reward causes both faster responding and reduced oculomotor capture, but can result in choking under pressure when the reward is very high. Adding increasing penalties for capture also reduces capture, but with concomitant slowing. I then showed that capture depends in a specific way on what happened on the previous trial: subjects

are captured when the distractor is at a location that was previously a target, but that this occurs specifically when the eyes were captured by the distractor on the previous trial - i.e. if that previous target was missed. The findings are consistent with a late-effect of reward. I suggest that this spatially specific effect of previous errors corresponds to the retention of a reward prediction error in a spatial map.

3. Trial-to-trial incentives influence capture

3.1. Introduction

Chapter 2 demonstrated two effects: firstly that from block to block, subjects were able to use current reward levels to adjust their propensity to be distracted, as indexed by oculomotor or gaze capture. Secondly, distractibility showed rapid dynamic changes from trial-to-trial as a function of how much money was obtained, and from which location. Since study 2.1 kept reward expectation constant for a whole block of trials, effects may have been weakened by subjects adapting to the current reward level during a block.

Furthermore, because the studies in chapter 2 used colours to identify the target and distractor, the effects may also have been driven by reward-to-colour associations learned during the block, as reported in some previous investigations (Anderson et al., 2011a; Della Libera and Chelazzi, 2006; Hickey and van Zoest, 2012a; Hickey et al., 2010c).

Although such *long-term* reward associations have been extensively examined (Ding and Hikosaka, 2006; Tachibana and Hikosaka, 2012; Watanabe et al., 2001), relatively few studies have manipulated reward cues *trial-by-trial*. A natural next question, therefore, is whether humans can use explicit moment-to-moment incentives to adjust their distractibility, an issue that I investigated in the experiments reported here.

In monkeys, cues predicting high rewards can reduce breaks of fixation, speed saccadic latencies and velocities, and improve memory (Kennerley and Wallis, 2009;

Leon and Shadlen, 1999) but they can also promote distraction by themselves capturing attention (Peck et al., 2009). In humans, reward incentives can shorten prosaccade latencies, and improve both the accuracy and speed of antisaccades (Blaukopf and DiGirolamo, 2006; Jazbec et al., 2005; Mueller et al., 2010; Ross et al., 2011).

These studies, and others (Blaukopf and DiGirolamo, 2006; Ross et al., 2011), used a visual cue to signify incentive, such that the reward cue could itself capture attention. These stimulus-specific effects could be explained if reward facilitated preparation of *specific* motor plans—akin to goal-tracking in rats—and therefore differs from the *global* motivation increase we observed in Study 2.2. One potential way to minimise any motor plans towards the reward cue would be to use a non-visual reward cue, a strategy I elected to employ in the present study.

The missed reward effect demonstrated in chapter 2 was dependent on location history from the previous trial. Other studies specifically using rewarded saccades have shown that a spatial map of reward value can effectively bias subsequent fixations towards highly rewarded locations (Ding and Hikosaka, 2007b; Milstein and Dorris, 2007b). Such a 'map'-like representation might well have been responsible for the effect we observed in Chapter 2 where missed rewards captured attention. But between trials, subjects had to refixate the central cross. This makes it difficult to know whether the effect was truly location-based, or *action-based*. In other words, if a reward is missed at a particular location, we cannot tell whether saccades *in that direction* are facilitated (e.g. due to motor program facilitation), or saccades to that location *in space* are facilitated (e.g. due to a spatial 'map' of reward). After an error, planning of error-correction responses may also cause effects on the subsequent trial (Rabbitt 1966;

Rabbitt 2002), again consistent with the view that the observed missed reward effect could also be explained as motor planning.

To tease apart the motor plan history from spatial location history, in the current study I developed a task in which subjects did not refixate a central fixation point between trials. Specifically, in this task I used a design in which participants gazed between three locations (three circles in top panel of **Figure 3.1**). On each trial, the currently fixated item was the point of departure for the next saccade. The target would be one of the other two locations, while the distractor would appear at various intervals prior to the target at the third possible location. Moreover, none of the locations themselves would have a visual cue that signalled the potential reward if the target was acquired. Instead, in this new task, the stake was announced by an auditory recording heard at the beginning of each trial.

In addition to the likelihood of being distracted, there are reasons to suspect that reaction times or saccade velocities might be speeded by incentives (Chen et al., 2013; Haith et al., 2012; Xu-Wilson et al., 2009)—perhaps to simultaneously maximise reward and minimise effort (Niv et al., 2007). But if reaction times are speeded, and distraction is also reduced, one might expect to see signs of increased top-down control *during* the motor responses. Saccades have traditionally been thought of as ballistic movements that, once initiated, continue to the planned target rapidly without further input. The brainstem circuits for implementing this ballistic control have been studied and modelled extensively in cat, rabbit and primates (Ramat et al., 2007; Robinson, 1968, 1981). Intriguingly, recording from the brainstem and frontal eye fields have shown that early activation of neurones encoding distractors are associated with curved saccades (McPeek, 2006; McPeek et al., 2003; Port and Wurtz, 2003).

These observations suggest that distortion of the trajectories of saccades induced by a distractor might reveal mechanisms of how distraction is controlled (Bhutani et al., 2012; Van der Stigchel, 2010). In particular, given that *reward* can modulate saccade direction (Stritzke et al., 2009), reward modulation of curvature induced by a distractor would suggest that rewards can alter early distractor activity in neuronal oculomotor maps (Hickey and van Zoest, 2012a; Schütz et al., 2012a). If incentives could increase the control exerted at this low level, we might expect to observe greater curvature away from the distractor.

Finally, effortful control in cognition has also been linked to arousal and noradrenergic activity (Aston-Jones and Cohen, 2005). Pupillary dilatation is associated with effort, emotion and surprise signals (Preuschoff, 't Hart, and Einhauser 2011; Beatty 1982; Bradley et al. 2008; Satterthwaite et al. 2007), which may reflect noradrenergic activity in the locus coeruleus (Gilzenrat et al. 2010; Aston-Jones and Cohen 2005; Murphy et al. 2011). As such, pupillary responses to reward cues might provide an independent measure of subjective or even subconscious appraisal of reward (Bijleveld et al., 2009; Laeng et al., 2012). We therefore hypothesised that highly motivating cues ought to evoke pupillary dilatation.

One additional aspect of the effects of reward on distractibility I wanted to investigate is the effect of ageing. Some previous reports have generally observed increased distractibility with age using oculomotor (Kim et al., 2007; Machado et al., 2009) and verbal tasks (e.g. Kim et al. 2007). However, no previous investigation has reported on how rewards modulate distractibility with age. Hence, I also elected to examine this issue.

3.2. Study 1: Rewards modulate oculomotor capture

3.2.1. Methods

3.2.1.1. Participants

Twenty-seven healthy male volunteers were recruited from an advert, age range 18 to 36, all with normal or corrected-to-normal vision. Subjects were instructed that they would be paid according to their performance, with a minimum of £8 and maximum £12. Three subjects did not complete the task due to eye tracking difficulties and time constraints, so 24 subjects were analysed.

3.2.1.2. Materials

Participants sat 60 cm in front of a 21" CRT with resolution 1024x768 pixels at 100 Hz. Stimuli were presented on a PC running Matlab (The MathWorks) and Psychophysics Toolbox under Windows. A frame-mounted Eyelink 1000 (SR Research) infrared tracker monitored left eye position relative to the screen, sampled at 1 kHz. Eye movements were parsed online by the Eyelink PC and sent to the presentation PC over a patch cable, to provide immediate feedback. Randomised 9-point calibration was performed at the start of the experiment.

3.2.1.3. Task

Participants were instructed to move their eyes as fast as possible to the disc that was illuminated *second*. They were told that the first disc that lit up would be a distractor, and the second, the target. Three screen locations were indicated by dim grey discs, each 4° diameter, arranged in an equilateral triangle 11.4° apart (**Figure 3.1A**). One disc was illuminated brightly at the start of the trial, and participants were required to fixate

this for 500 ms to start the trial. Then participants heard a recording of a voice speaking the maximum reward available for that particular trial. Three reward levels were used: 0p, 10p or 50p. This indicated the maximum amount participants could win on a trial, if they looked very fast towards the target (second disc) that was illuminated. Simultaneous with the voice, the fixation disc changed colour to yellow, approximately equiluminant to the bright disc, to indicate the start of the trial.

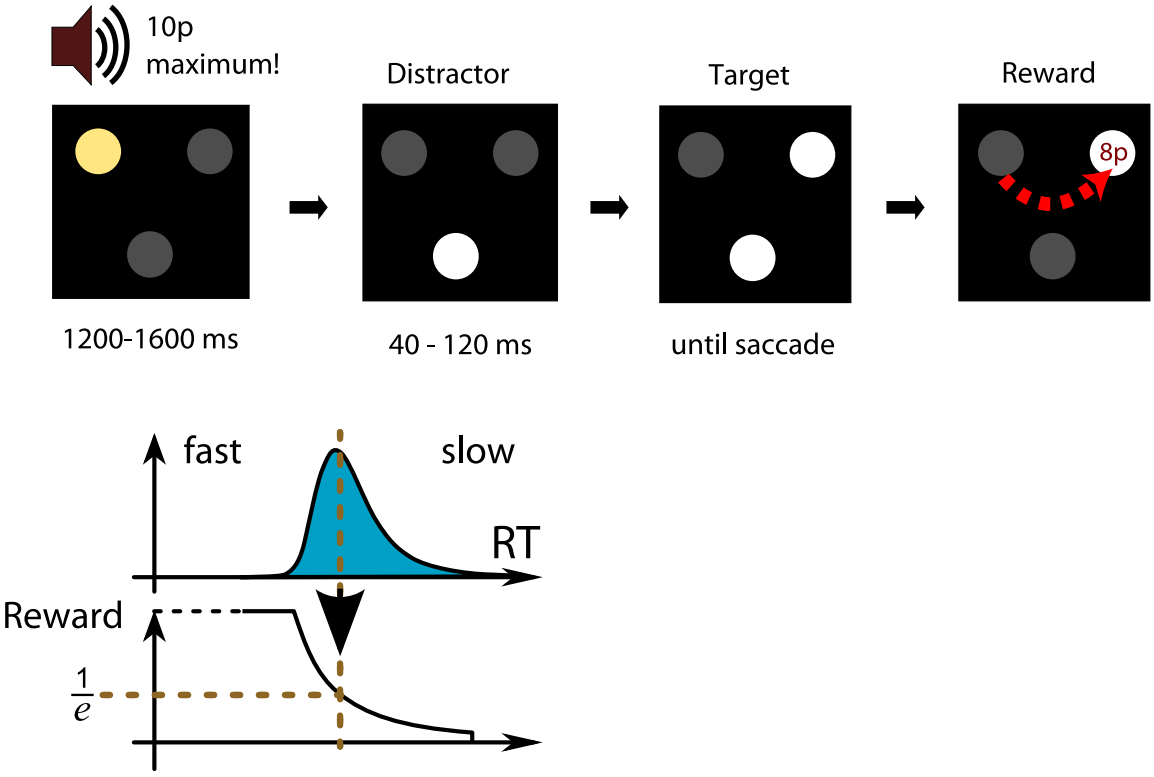


Figure 3.1: Oculomotor capture task with trial-wise incentives

A) Three equidistant discs were dimly illuminated. At the start of each trial, participants had to fixate one disc which was brightened. A recorded voice gave an auditory reward cue, one of "0p maximum", "10p maximum" or "50p maximum", which indicated the amount of money that could be won if subjects were accurate and fast on that trial. After a variable foreperiod, the other two discs were illuminated asynchronously, with a delay of 40 to 120 ms. Subjects were instructed to look as fast as possible to the second disc—thus the first onset acted as an early onset distractor, and the second disc indicated the target.

B) After gaze arrived at the target, subjects were rewarded according to reaction time. Reward was calculated as a fraction of the maximum available, using an exponential falloff. The falloff was

determined adaptively using quantiles of the last 20 trials, in order to maintain the difficulty level over the course of the experiment.

After a non-ageing foreperiod of 1200-1600 ms, the fixation disc (the current point of regard) was dimmed, while one of the other discs brightened (the distractor). After a variable interval, the third disc (the target) was illuminated. This display remained until gaze arrived at the target. The time taken to reach the target (from fixation offset until gaze arrived at the target) was used to calculate reward (**Figure 3.1B**) as follows:

$$\text{Reward}(t) = R_{max} \cdot \min\left(e^{\frac{\tau_2 - t}{\tau_1}}, 1\right) \quad (3.1)$$

to the nearest penny, where R is reward for the current trial, *t* is the time taken to reach the target, R_{max} is the maximum reward that could be won on a given trial, and τ_1 and τ_2 are adaptive reward criteria (see below).

Reward was displayed as a red integer in the target disc as soon as the target was reached. This was accompanied by a bell sound when the reward was 10p or greater, or a 'cash register' sound when 30p or greater was won. Importantly, the target location was then used as the starting point for the next trial—thus trials formed a *continuous sequence* of saccades moving around in a triangle. The next trial's target was chosen randomly from the two possible destinations so that, over the experiment, all three locations were equiprobable as target or distractor.

Unknown to participants, the RT criteria τ_1 and τ_2 were adaptively adjusted using the last 20 trials. The criteria tracked quantiles of the RT distribution, keeping 10% of trials faster than τ_1 and 30% of trials slower than τ_2. This ensured that

participants experienced the full range of outcomes irrespective of their baseline reaction speed.

Participants performed 5 blocks of 54 trials each, with a 2 minute break between blocks. There were three reward cues of 0p, 10p, 50p, three possible starting locations, two possible target locations relative to this starting location, and three possible delays between the distractor and target of 40 ms, 80 ms, or 120 ms—termed the stimulus-onset asynchrony (SOA). Thus each block consisted of 18 trials for each reward level.

3.2.1.4. Trajectory Classification

Saccades were parsed using criteria on velocity of 30° s^{-1}, acceleration > 8000° s^{-2} and amplitude > 0.15°. Saccadic reaction times were calculated as the time from cue onset until this threshold was exceeded. Responses were classified according to the trajectory of the eyes after initiation of the first saccade (**Figure 3.2**).

For the first saccade made during the response period, the *angle of departure* was calculated relative to the target and distractor. The trial was classed as an error if the first saccade's amplitude was greater than 5°, and its endpoint was closer to the distractor than to the target. The next saccade whose amplitude was greater than 5° and whose endpoint was closer to the target was counted as an *error-correction*.

Trials were classed as correct if the first saccade was larger than 5° and its endpoint was closer to the target than the distractor. Correct trials could be further subdivided according to the angle of departure. Saccades could be straight to the target (angle within ±15° from target direction), or be pulled towards the distractor, or pushed away from the distractor (see **Figure 3.2**). This provided a sensitive measure of the pull of the

distractor (Van der Stigchel et al., 2006). Trials with blinks before the first 5° saccade were discarded (3% of all trials).

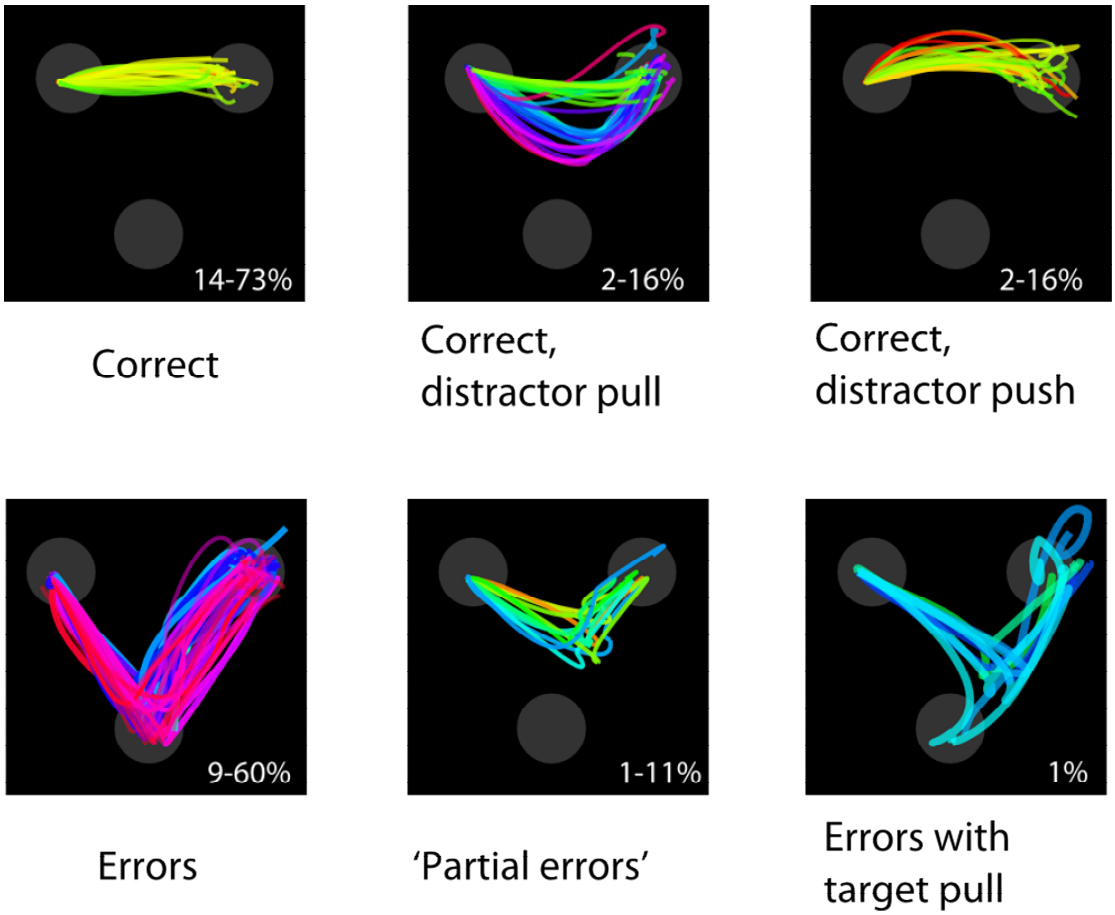


Figure 3.2: Trajectory classification
The path of gaze was classified according to whether the first saccade terminated on the target, distractor, or in-between. 'Correct' trials, where the first saccade was to the target, were further subdivided according to the curvature of the saccade. In this figure, each trial is coloured according to the initial direction of the eye velocity.

3.2.2. Results

3.2.2.1. Effects of reward

On average, errors were made on 35% of trials (s.d. 15%). On correct trials, *peak saccade velocity* was calculated for the first saccade with amplitude greater than 1

degree. Trials were grouped according to incentive, and one-way ANOVA was performed on the velocities. Saccades were faster on trials when high reward cues were presented, with a mean velocity of 483° s^{-1} compared with 464° s^{-1} in low reward trials (**Figure 3.3**, $F(1,47)=40.3$, $p<0.001$). Thus a key effect of incentive was to significantly invigorate gaze responses, as indexed by saccadic peak velocity. This effect of reward on saccadic velocity was highly robust, with a positive velocity gradient present in 22 out of 24 subjects, reaching significance at the single subject level in 12 subjects (within-subject regression or velocity against incentive, $p<0.05$).

We also examined the amplitude of this first saccade. Amplitudes were also found to be larger with increasing reward, with a mean hypometria of 0.04° with high reward compared to 0.26° for low reward ($F(1,47)=13.3$, $p<0.001$). It is well known that saccade amplitude is a strong determinant of velocity—a phenomenon known as the "main sequence" (Bahill, Clark & Stark 1975). Longer saccades have proportionally faster peak velocities. Could the modulation of velocity by reward (as in **Figure 3.3D**) be explained by these amplitude effects? A stepwise regression was used to remove the variance in velocity explained by amplitude. Reward was then used to predict the residuals from this regression, such that any effect here could not be attributed to the modulation of amplitude. Reward still influenced velocity ($F>2.75$, $p<0.05$), independently of amplitude, at the group level, and in 11 of the 12 subjects who showed significant velocity effects before.

Reaction times on correct trials were measured from distractor onset until the onset of the first saccade >1° in amplitude. The mean reaction time on correct trials was 245 ms (s.e.m. 47 ms). RT was 11 ms faster in the high-reward condition compared to no-reward (main effect of reward, $F(1,47)=9.62$, $p=0.0032$). Thus incentive increased

response speed both in terms of saccadic velocity and RT. Did this adversely affect distractibility?

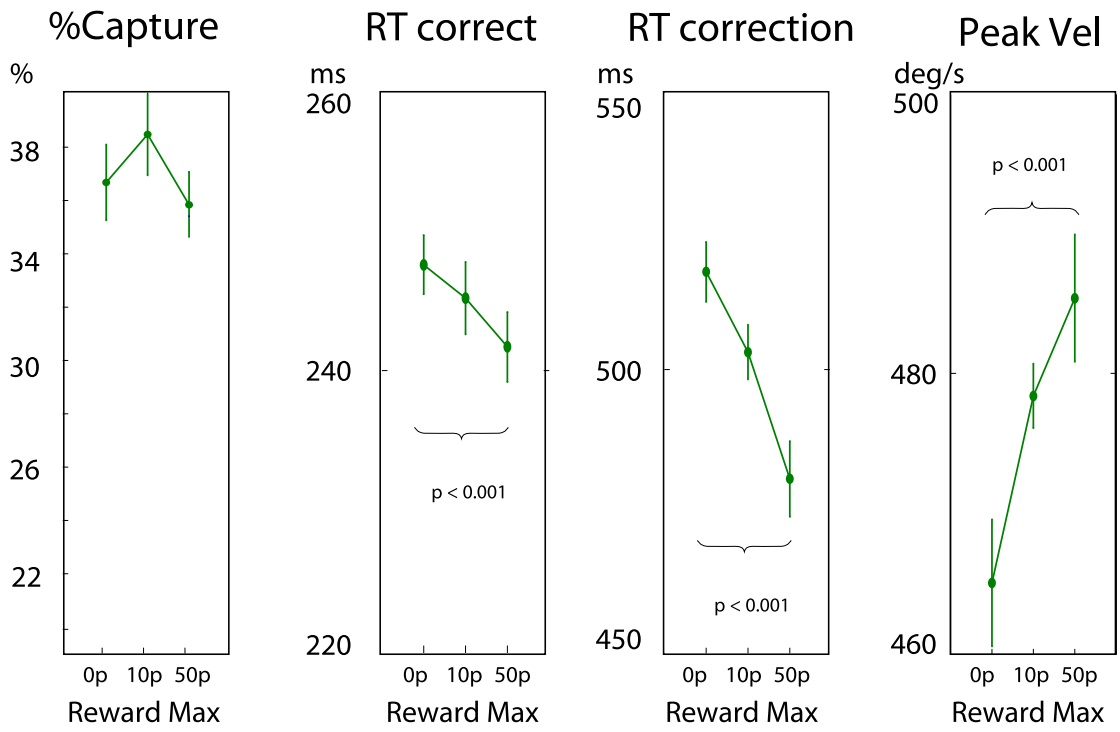


Figure 3.3: Effects of reward on saccades in young volunteers

A) For each of the three reward incentive conditions, I plotted the proportion of trials on which the first saccade after the onset went to the distractor. These errors to the distractor were termed "oculomotor capture". There was no effect of reward in these subjects. Error bars are within-subjects standard error of the mean.

B) For trials which were correct, i.e. the first saccade went to the target, we plotted the mean time from distractor onset until the start of the first saccade—i.e. the saccadic reaction time. RTs were faster for higher incentives.

C) For trials on which an oculomotor capture occurred, i.e. the first saccade went to the distractor, I plotted the mean time until the correction of the error—i.e. the total time until the target was reached. The correction time was speeded by rewards.

D) For each correct trial, the peak saccade velocity was calculated. The mean peak velocity was speeded by rewards.

Importantly, there was no effect of incentive on the proportion of oculomotor capture errors (**Figure 3.3**; arcsine-transformed, $p>0.05$). Thus control of gaze, indexed

by velocity and RT, was modulated by incentives but without an overall cost in terms of percentage of trials in which participants were distracted by the non-target. However, on capture trials (i.e. when gaze was distracted, defined as trials in which the first saccade >1° landed closer to the distractor than the target) saccadic reaction times were significantly faster ($F(1,47)=9.6$, $p=0.0032$) and there was a trend to speeding by reward ($F(1,47)=3.35$, $p=0.073$). On capture trials, the time taken to correct the error (i.e. time until the start of first saccade that ended in the target circle) was also computed. Correction RTs were also faster when higher rewards were available ($F(47,1)=21.9$, $p<0.001$), occurring 276 ms after the error in high reward trials, compared to 307 ms in low reward trials.

3.2.2.2. Saccades curve away from the distractor

To quantify curvature, we calculated the angle of departure of each correct saccade, relative to the saccade's endpoint direction. A positive value indicates that the saccade was initially directed more towards the distractor; so although the saccade *accelerated away* from the distractor, we describe this as curvature toward the distractor (**Figure 3.2B**). Similarly, negative value indicates a saccade that was initially directed more away from the distractor (**Figure 3.2C**). As in other studies (Hickey and van Zoest, 2012a; Schütz, Trommershäuser, and Gegenfurtner 2012), saccades overall tended to curve away from the distractor, with a mean of 3.6°. Curvature of saccades was not modulated by reward level in these participants, though there was a trend for reward to increase curvature away from the distractor ($F(1,47)=3.76$, $p=0.058$).

3.2.2.2. Higher incentives dilate the pupils

At the start of the trial, once fixation was stable, the auditory reward cue was played with a simultaneous brightening of the fixated disc, followed by a 1200 ms to 1600 ms

foreperiod. I analysed the pupillary response to the cue during this interval, relative to baseline. The mean change in pupil size at 1200 ms after the auditory cue was plotted for each reward condition (**Figure 3.5A**). The pupils were significantly more dilated after high-reward cues, compared to low reward cues ($F(1,47)=31.5$, $p<0.001$). To visualise this, the pupil diameter trace after the cue was smoothed over 10 ms time bins, interpolating over gaps under 500 ms. At each time bin, a linear model was used to extract the dependence of pupil size on the cued maximum reward, and on the winnings on the previous trial (**Figure 3.4**):

$$\Delta\text{Pupil} = \beta_0 + \beta_1 \cdot \text{Incentive}_t + \beta_2 \cdot \text{Winnings}_{t-1} + \beta_3 \cdot \text{Incentive}_{t-1} + \varepsilon \quad (3.2)$$

where ΔPupil represents change in pupil size at one moment in a trial, β_i are the fitted coefficients for each contribution, depending on the type of the current trial *t* and previous trial *t*-1, and ε is a Gaussian random variable. This expresses pupillary trace as a linear combination of four functions: the grand average of all trials, and the main effects of current incentive, previous winnings, and previous incentive.

The lines in figure 3.4 (β_1, β_3 and β_3) represent the effect strengths of each factor in the above equation, as they vary over the foreperiod, after the incentive cue. Positive deviations indicate that the factor dilated the pupil, whereas negative deviations indicate constriction.

The current trial's incentive caused significant pupillary dilatation. The effect is given by β_1 (**Figure 3.4**, yellow trace). When β_1 is positive, it indicates that the pupil size change from the pre-cue baseline correlated positively with the amount of money signalled by the incentive cue. Thus the yellow trace shows the extent to which pupil size was influenced by the reward cue. This incentive effect β_1 became significantly

different from zero 560ms after cue onset (criterion $t(24)<0.05$). This positive deflection indicates that higher rewards caused pupillary *dilatation*, relative to low rewards.

The previous trial's reward incentive influenced pupil diameter in the opposite direction to the current trial's reward cue, indicated by a significantly negative value for β_3 from 564 ms after the auditory cue (**Figure 3.4**, blue trace). The negative value of β_3 indicates that previous incentive size was negatively correlated with pupil change, i.e. when the incentive on the previous trial was high, the pupil was more constricted on the current trial, compared to baseline. Thus, high previous incentives caused relative pupillary constriction compared to previously low incentives. This suggests the pupil encodes the current trial incentive *relative* to the previous trial. It takes about 560 ms for the pupil to reflect this relative value.

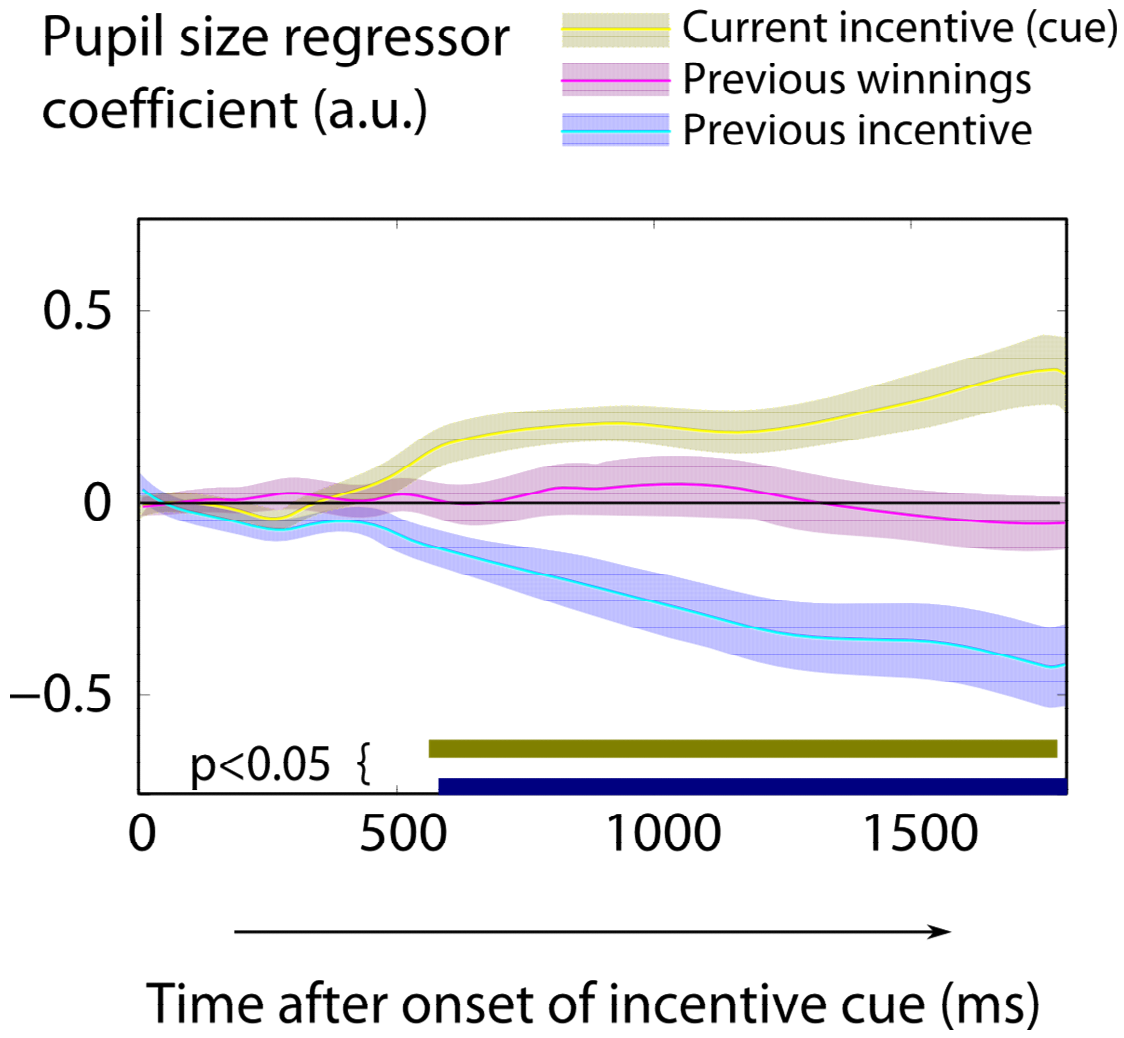


Figure 3.4: Incentives influence the pupil after the reward cue

For each moment after the auditory reward cue, the pupil size was regressed against the cued incentive (3 levels, treated as a continuous regressor) and the amount won on the previous trial. The mean value of the regressor (i.e. the slope or sensitivity to reward) across subjects was plotted. The shaded area represents the standard error of the mean across subjects.

To test whether the reward sensitivity of the pupil predicts how sensitive a subject's RT is to reward, I compared the gradient of pupil change *vs*. reward, with the gradient of RT *vs.* reward, for each subject. The correlation across subjects for these two measures is shown in **Figure 3.5B** (green circles; purple circles show the comparable analysis for study 3, below). The two measures of reward sensitivity did not correlate significantly across individuals (r^2=0.003, p=0.80), suggesting that subjects whose RT

was sensitive to reward did not necessarily have pupils responsive to reward. Rather, the amount of reward modulation of action timing is independent of autonomic reward responses, as indicated by pupil size.

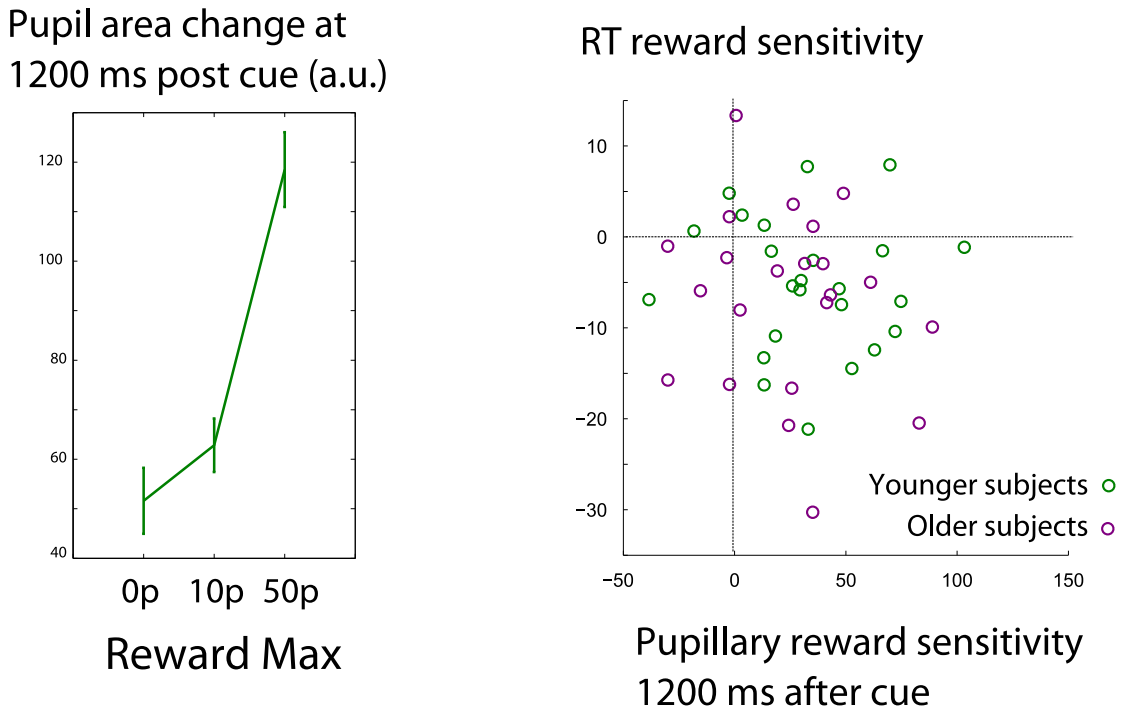


Figure 3.5: Pupillary sensitivity to reward cues

A) For each trial, we took the pupil size at 1200 ms post-cue minus the baseline on that trial. The mean change in pupil size was plotted for each reward incentive condition. High reward cues cause dilatation of the pupil, relative to low reward cues.

B) To examine whether the sensitivity of the pupil to reward is related to performance, we plotted the slope of the pupil-to-incentive function for each subject on the abscissa, and the slope of the RT-to-incentive function on the ordinate. There was no correlation between participants' pupil reward sensitivity and RT reward sensitivity. Data in green are from Study 1; data in purple are from Study 3, Section 3.4.2.3.

3.3. Study 2: Practice in oculomotor capture

To assess reliability and practice effects, I examined performance again in some of the participants after a fortnight.

3.3.1. Method

Of the 27 subjects who completed experiment 1, 21 were able to return for repeat testing after 2 weeks. Subjects were instructed again as in section 3.2.1.3, and performed the same behavioural task. Two subjects only completed 4 out of 5 blocks due to time constraints, and so 19 subjects were analysed.

3.3.2. Results

3.3.2.1. RT and reward sensitivity are reliable across sessions

Reaction times correlated across the two sessions, establishing the validity of the measure (**Figure 3.6**, r^2=0.37, p<0.005). Reward sensitivity was calculated for each subject in each session using linear regression over the reaction time on correct trials. Reward sensitivity—the regression slope—also correlated significantly across the two sessions (r^2=0.31, p<0.01).

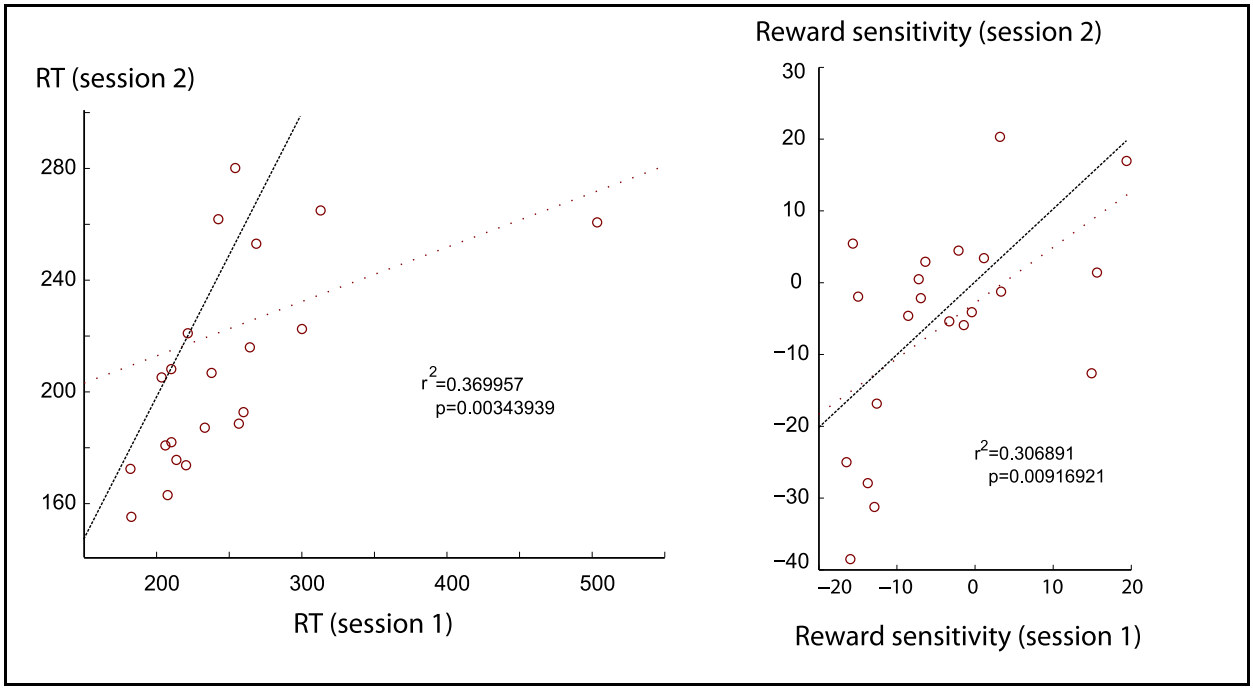


Figure 3.6: Session-to-session reliability

A) Session 2 took place 1 to 3 weeks after session 1. The mean RT for correct saccades in session 1 correlates with the mean RT in session 2. The dotted line indicates the linear fit, and the black line indicates 1:1 correspondence. Note that RTs were generally faster in session 2 (i.e. below the black line). B) The RT-to-incentive function yields a slope, indicating reward sensitivity of RT. This measure also correlated well across the two sessions. The coincidence of the black and dotted lines suggests the absence of an overall practice effect.

3.3.2.2. Practice does not affect reward sensitivity

A within-subjects ANOVA was performed to examine the effect of practice. Error rates were significantly lower in session two (**Figure 3.7A**, reduced from 37% to 33%, $F(1.102)=10.2$, $p=0.0018$), but there was no interaction with reward ($p>0.05$). Reaction times on correct trials and error-correction trials were both significantly faster in session 2 (both $F(1,102)>40$, $p<0.001$) with no interaction with reward ($p>0.05$). There was no difference in peak velocity between the two sessions and importantly the relationship between reward and peak velocity remained unchanged. (**Figure 3.7D**).

The net curvature away from the distractor was on average 4.1°, comparable to study 1. Notably this was not significantly different from the curvature in session 1, and there was no effect of reward ($p=0.61$).

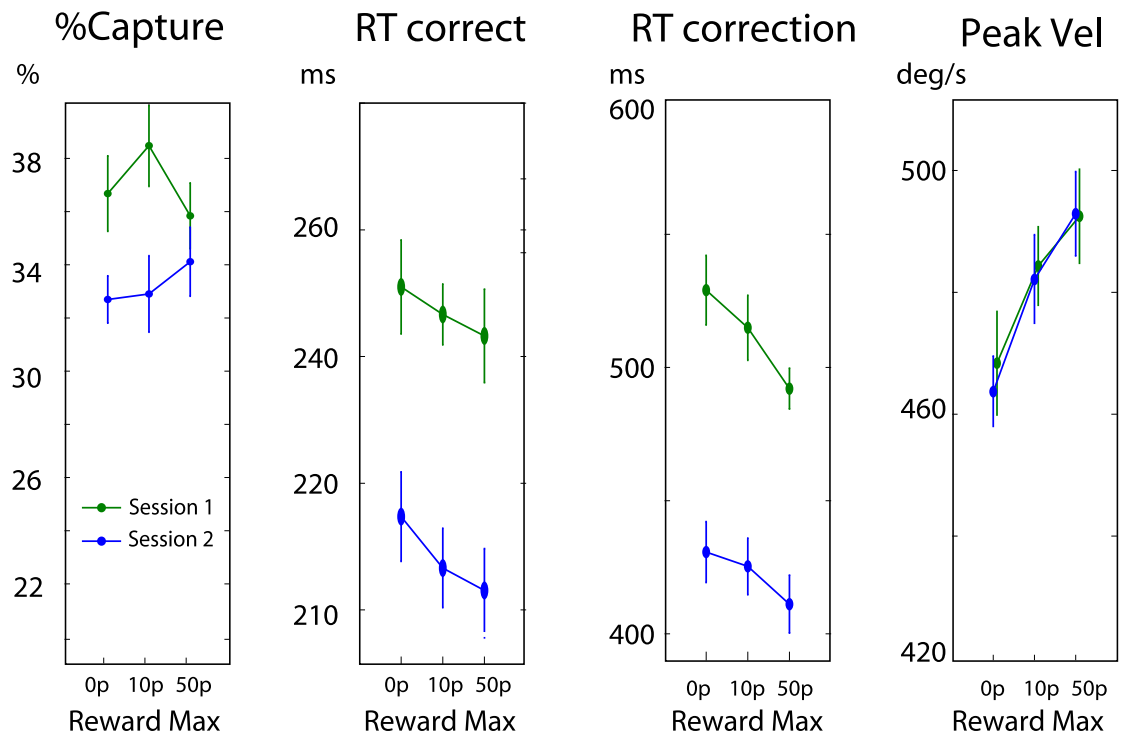


Figure 3.7: Effect of practice and reward on saccades

Lines in green are the same data as shown in **Figure 3.3**, but using only the subjects who returned in experiment 2. Data from session 2 is shown in blue.

A) The proportion of trials on which oculomotor capture errors occurred was lower in session 2. There were no significant effects of reward nor interaction.

B) RTs in session 2 were faster than in session 1. Speeding by reward was again evident, with no interaction with practice.

C) The time to correct an error was speeded both by reward and by practice, with no interaction.

D) Peak saccade velocity was speeded by reward, and did not differ between the two sessions.

3.4. Study 3: Age and oculomotor capture

Age is known to slow reaction times (Botwinick, Brinley, and Robbin 1958; Rabbitt 1964). We wished to compare whether reward effects would be similar in an older group of participants, compared to our subjects in study 1.

3.4.1. Methods

22 healthy older volunteers were recruited from an advert. The mean age was 62 years (range 41 to 76), and all had normal or corrected-to-normal vision. All participants performed a variant of the same oculomotor capture task as in Experiment 1.

3.4.1.3. Oculomotor capture task

The oculomotor capture task was similar to that in Study 1 and 2, except that the asynchrony between the distractor and saccade target was fixed at 80 ms, and an additional 500 ms delay was inserted after the saccade but before reward feedback. Subjects performed 4 blocks, totalling 216 trials, giving 72 trials in each reward condition.

3.4.1.4. Questionnaire measures

Impulsivity has previously been implicated in distractibility by rewards (Anderson et al., 2011a). To study whether saccadic measures of reward sensitivity correlated either with reward-seeking or impulsivity traits, participants completed two established questionnaires. The UPPS impulsive behaviour scale (Whiteside et al., 2005) measures lack of premeditation, urgency, sensation-seeking and lack of perseverance. The BIS/BAS behavioural inhibition and activation scales (Carver and White, 1994) yield three scores: a behavioural inhibition scale, reward sensitivity, drive, and fun-seeking.

Other studies have suggested that individuals with low working memory capacity are especially vulnerable to attentional capture (Anderson et al., 2011a; Fukuda and Vogel, 2009); therefore we also measured forward and backward digit spans.

3.4.2. Results

3.4.2.1. Older participants are more sensitive to reward

Since older controls performed one block fewer than younger controls, only the first 4 blocks from Experiment 1 were used in the comparison. A between-subjects mixed effects ANOVA (intercept nested within group) was used to compare the groups.

The net difference in *oculomotor capture* between younger and older participants was not significant ($F(1,96)=2.93$, $p=0.094$), but there was a significant interaction, with older subjects being significantly improved by reward ($F(1,96)=0.0053$). In other words, they were less liable to capture, as incentives increased, whereas this was not the case for younger participants (**Fig. 3.8**).

Older subjects had significantly slower reaction times, both for correct saccades and error corrections ($F(1,96)=14.8$, $p<0.001$ and 9.4, $p=0.0036$ respectively), in keeping with previous reports (Sharpe and Zackon, 1987). They had strong reduction of RT by reward ($F(1,43)=14.3$, $p<0.001$, effect size 14 ms) but with no interaction of age with reward ($F(1,96)=1.95$, $p>0.05$). There were no age-related differences for saccade velocity, and importantly the significant relationship between reward and peak velocity was present in older participants, just as in their younger counterparts ($F(1,43)=35.1$, $p<0.001$). The velocity slope was positive in 20 out of 22 subjects, and significant in 9 (within-subject regressions of velocity against incentive, $p<0.05$). In keeping with previous studies, their velocities were comparable to those of younger participants (Sharpe and Zackon, 1987).

3.4.2.2. Different patterns of incentivisation with age

As in the previous two studies, there was net curvature away from the distractor of 5.8°. There was no significant difference of curvature between younger and older participants ($p>0.05$) and no overall effect of reward ($F(1,65)=1.30$, $p>0.05$).

These findings show some interesting differences between younger and older participants. In young people, there was no effect of incentive on the proportion of oculomotor capture errors. Thus control of gaze, indexed by velocity and RT, was modulated by incentives, but without effects on distraction. However, in older people, although rewards affected both RT and saccade velocity in a similar fashion to young people, incentive additionally reduced distractibility.

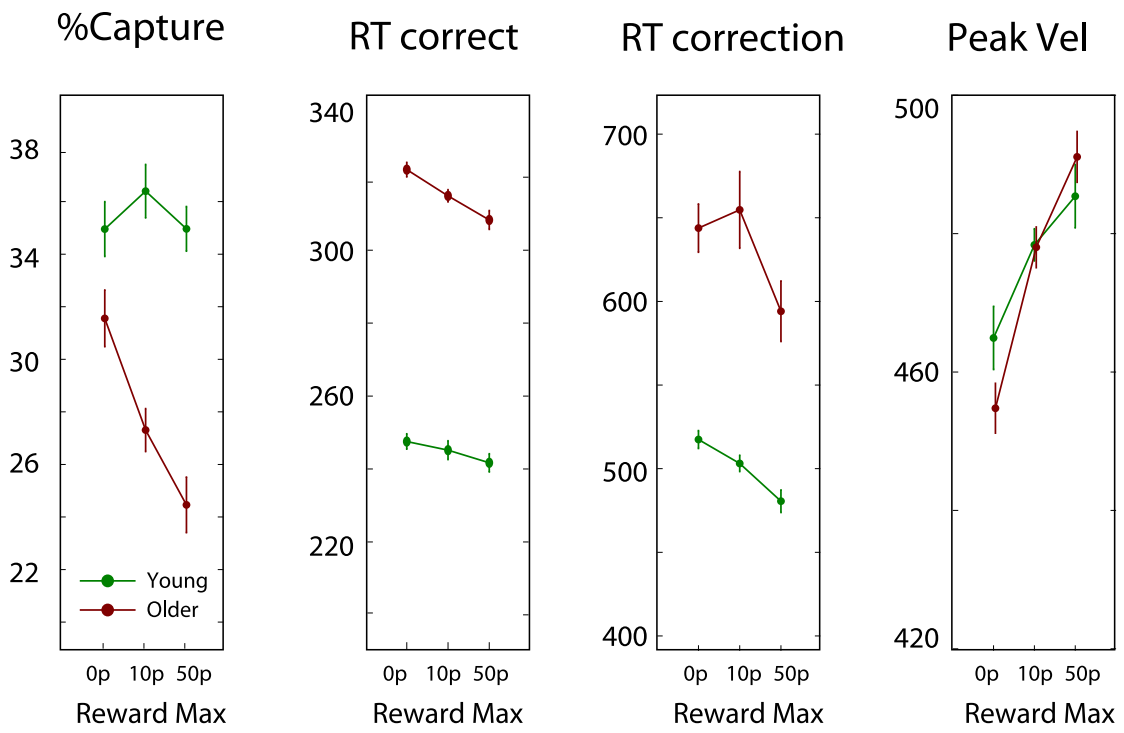


Figure 3.8: Effect of age and reward on saccades

Green lines represent the younger volunteers from experiment 1, same as **Figure 3.3**. Red lines are data from the older volunteers in experiment 3.

A) In older participants, reward reduced the proportion of oculomotor capture errors. There was an age interaction, in that younger volunteers lacked this incentive speeding effect.

B & C) Older participants had longer saccadic RTs and slower error-correction RTs than younger participants. However they still showed reward-related speeding, with no age interaction.
D) Saccade velocities showed the same pattern of speeding by reward incentives in both younger and older groups.

3.4.2.3. Pupil size in older controls

Examining pupillary reward sensitivity revealed, as in study 1, that pupil dilatation is greater after high rewards in older participants. As in study 1, the sensitivity of pupils to reward was uncorrelated with the sensitivity of RT to reward, across individuals (r^2=0.030, p=0.44, **Figure 3.5B**), suggesting independent autonomic and motor reward sensitivities.

3.4.2.4. Reward reduces curvature in older controls

Saccade curvature towards the distractor was reduced by reward in older participants (F(2,42)=3.35, p=0.045), in agreement with previous studies (Hickey and van Zoest 2012; Schütz, Trommershäuser, and Gegenfurtner 2012).

3.4.2.4. Missed rewards capture attention

To test whether missed rewards capture attention, we grouped trials according to whether subjects were returning to the same location that they came from two trials ago ("returning"), or were going to the other, alternate location ("new location") (**Figure 3.9**). Further, I subdivided trials according to their RT two trials ago (i.e. how quickly they previously arrived at the current location on "returning" trials, or how quickly they previously arrived at the alternate location on "new location" trials), and by the incentive two trials ago.

This analysis enables us to separate trials on which the current distractor or target was previously highly rewarded or not, depending on whether subjects *could have*

won at that location. For example, a trial with a high maximum reward but slow RT, would result in a 'missed reward', in comparison to trials with equal speed but zero maximum reward. In other words, by dividing trials according to reaction times, we separated out the amount won from the amount that could have been won. Reward is only missed if money could have been won, but participants were too slow to obtain it. We can then test whether oculomotor capture is increased specifically to locations at which reward was previously *missed*, as in **Chapter 2**. Trials were excluded if oculomotor capture occurred on the previous or 2-back trial.

A 3-way mixed effects ANOVA with factors of 2-back maximum reward, 2-back RT (high or low, median split across all trials), and location history (returning *vs*. new location) was performed on capture rates. This resulted in 12 conditions, with 18 trials per condition (**Figure 3.9**). There were significant main effects of location history, with more capture when cued to shift gaze to a new location compared to returning to the previous location ($F(235,1)=34.1$, $p<0.001$), and of 2-back RT, with more capture after faster RTs ($F(235,1)=4.58$, $p=0.033$).

There were also significant interactions of 2-back speed with location history. Faster RTs to a location resulted in *reduced capture* when the same location became the subsequent target, but *increased capture* when it became the distractor. However, importantly there was a 3-way interaction between 2-back speed, maximum reward and location history. If a high stake was won, participants were *less captured* (compared to zero stake) when that location became a target (dotted green line). But they were *more captured* when that location became a distractor (solid green). In contrast if participants did not obtain the high stake at a location, then subsequently capture was increased when that location became a target (dotted purple), and reduced when it became a target

(solid purple; interaction F(1,235)=7.19, p=0.0079; breakdown 2x2 ANOVA for 0p condition: effect of location but no interaction p=0.14; 10p and 50p condition: significant interaction, both F(1,63)>19, p<0.001). Capture was therefore specifically increased when a high reward was previously available at a location, suggesting that attention is captured by a potential high reward that was missed on the previous trial.

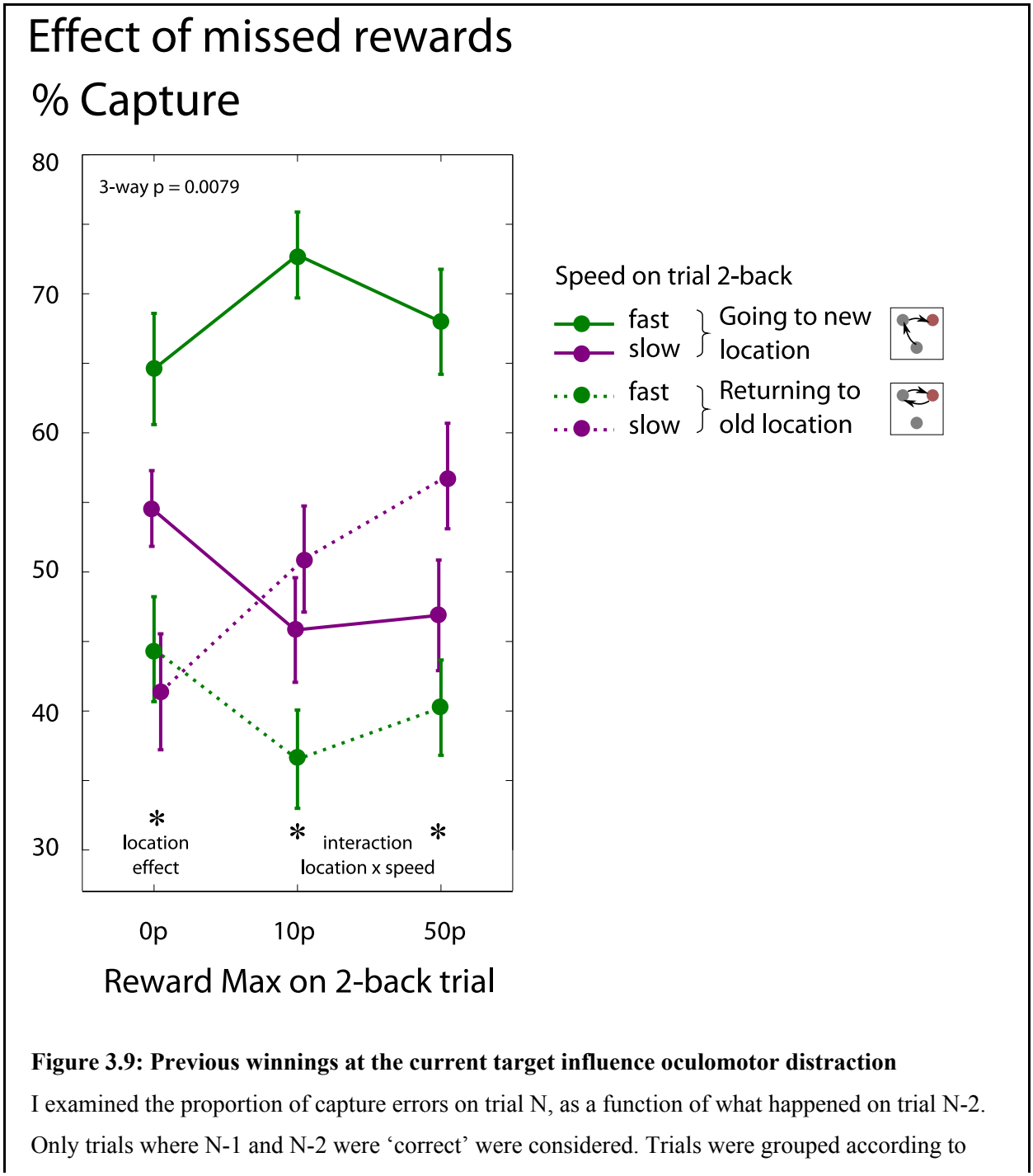


Figure 3.9: Previous winnings at the current target influence oculomotor distraction

I examined the proportion of capture errors on trial N, as a function of what happened on trial N-2. Only trials where N-1 and N-2 were 'correct' were considered. Trials were grouped according to

whether trial N-2 had a fast or slow RT (green *vs*. purple, median split), and according to the maximum available reward on trial N-2. For example, a "50p maximum" results in high or low wins depending on the RT, whereas a "0p maximum" results in 0p irrespective of RT. Depending on the location history, the amount won on trial N-2 would have been at either the current target location (dotted lines) or at the current distractor location (solid lines). I found a 3-way interaction of N-2 reward maximum x N-2 target location (current target *vs*. distractor) x N-2 speed (p=0.008). Specifically, when no reward was available, there was less distraction when returning to the previous location, irrespective of speed. However when rewards were available, fast saccades on N-2 caused more capture if they were to the current distractor, but less capture if they were to the current target. Importantly the effect is driven by the dotted purple line; this shows that specifically when responses were slow and possible reward was high, capture is greater at the distractor where the *reward was missed*.

3.4.2.5. Questionnaire measures

The four BIS/BAS and four UPPS subscale factors for each individual were correlated against the five primary saccadic measures: oculomotor capture, RT, pupillary response to the cue, saccade velocity and amplitude. The correlation matrix for the 22 older participants (**Figure 3.10**) shows 4 weak correlations between behavioural measures; although these are reported, none of these survived correction for multiple comparisons.

Subjects with larger pupillary responses had faster saccade velocities (r^2=0.51, p=0.016); subjects with high oculomotor capture reduce their capture in response to reward more (r^2=0.53, p=0.012); subjects with smaller saccade amplitudes show a greater increase in amplitude for rewards (r^2=0.47, p=0.027); and pupillary reward sensitivity correlates with velocity reward sensitivity (r^2=0.43, p=0.047). Very weak correlations were noted between the behavioural activation scale "fun-seeking" subscale, which correlated both positively with RT (r^2=0.46, p=0.031) and negatively with the reduction of oculomotor capture by reward (r^2=0.43, p=0.047).

There was no correlation of working memory capacity, as measured by digit span, with oculomotor capture (r^2=0.003, p>0.05) nor with RT (r^2=0.094, p>0.05).

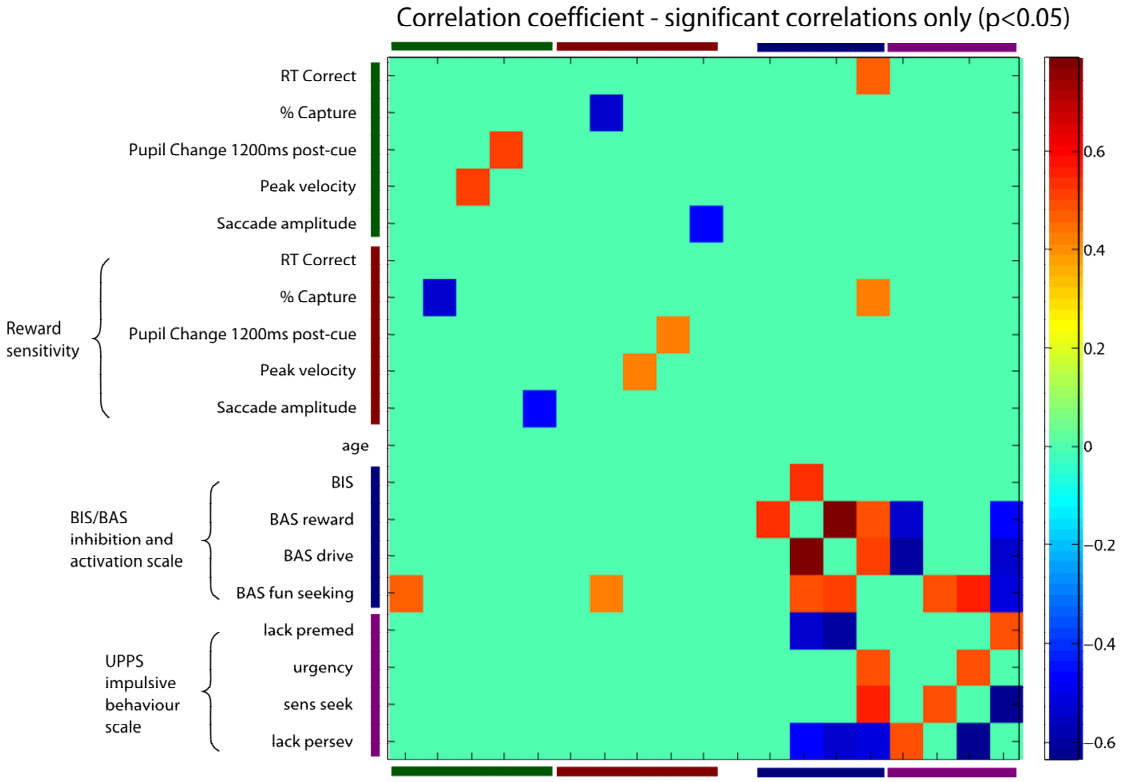


Figure 3.10: Correlation of saccadic measures and questionnaire factors

For the 22 subjects in experiment 3, five saccadic measures—RT, errors, pupillary response to cue, velocity and amplitude—and their corresponding reward sensitivity slope were correlated with questionnaire measures. The autocorrelation matrix shows the r^2 values, thresholded at p<0.05. Although several questionnaire measures correlated with each other, only the BAS fun-seeking scale correlated with saccades—positively with RT and negatively with reward-related reduction of capture. None of these survived correction for multiple comparisons.

3.5. Discussion

The results of the experiments reported here showed that rewards can significantly alter behaviour on an oculomotor capture paradigm with trial-by-trial alteration of incentive cues. Participants showed strong modulation of speed as a function of trial-to-trial incentive, as revealed by several measures including peak saccade velocity, correct reaction time, and error correction time (**Figure 3.3**). The trajectories of saccades on average curved away from distractors, and there was a trend for these to be pushed further from the distractor when incentives were high. Older subjects, although slower to respond, tended to respond to incentive by additionally reducing their distractibility, as measured by oculomotor capture (**Figure 3.8**). We also obtained an independent physiological measure of reward sensitivity: pupils dilated more in response to higher reward cues than low reward (**Figure 3.4**).

3.5.1. Reward increases saccade velocity

We found that saccade velocities consistently scaled with reward. This aligns with recent findings in monkeys for incentivised prosaccades (Chen et al., 2013) and asymmetrically rewarded saccades (Tachibana and Hikosaka, 2012). Both these studies have found that when rewards are high, animals increase their saccade velocity. In both these studies, due to the extensive practice required, effects could have been due to conditioned changes in saccade-generating circuitry. Similarly, humans produce faster saccade velocities to stimuli such as faces which possess reward associations (Xu-Wilson et al., 2009), but again these effects might be generated by primitive or reflexive reward mechanisms. Our study extends these findings to cognitive rewards, which are flexibly controlled by explicit verbal cues. Taken together with previous work, our

velocity effects strongly suggest that explicit incentives influence motor planning at a relatively low level in saccadic programming.

What parts of the saccadic system might be responsible for the effect of reward on peak velocity? According to models of saccade generation, velocity is programmed in the midbrain's medium-lead burst neurones (Van Gisbergen et al., 1981) or in the superior colliculus (van Opstal and Goossens, 2008). These areas receive extensive projections from the caudate nucleus, which likely supplies the cognitive signals that give context to the selection of saccade programs. Recordings from caudate nucleus show that reward-learning can alter the preferred direction of cells in the caudate nucleus, an alteration which parallels changes in saccade velocities with reward (Kawagoe et al., 1998). The spatially selective reward-induced changes of such caudate cells may in turn be derived from input from midbrain dopamine neurones (Kawagoe et al., 2004). Thus a midbrain-to-caudate-to-midbrain circuit might mediate the spatially specific effects of cognitive reward.

These dopaminergic signals may help to optimise yield of rewards in conditions where actions require effort. The speed and timing of movements must be selected to account for vigour costs (Niv et al., 2007) and temporal discounting (Haith et al., 2012; Shadmehr, 2010a). Optimal control frameworks regard such choices as minimising a cost function: in such frameworks, the cost of going faster depends on the rate of responding (Niv et al. 2007) or force exerted (Shadmehr 2010). The benefits of vigorous responding are incorporated either as the increase in reward rate (Niv et al. 2007), or in terms of temporal discounting over the time until reward (Shadmehr 2010). Both these accounts explain (a) why very fast responses become costly, and (b) why there is an incentive to respond quicker. Our task's relatively long and static inter-trial interval

(~2.7 to 3.2 seconds) meant that we could not distinguish between these two alternatives. However, both the vigour cost and temporal discounting views postulate that dopamine is critical in coupling movement speed to reward, an issue that I investigate in subsequent chapters.

3.5.2. Reduced distraction in older participants

The results appear to go against previous reports of increased distractibility with ageing (Kim et al., 2007; Machado et al., 2009). In the current study, older subjects were both slower and more accurate, suggesting that they trade off speed for accuracy. One possibility is that they were more sensitive to reward because they were slower: later in a trial, reward processing may be more influential. This seems unlikely because we found no across-individuals relation between RT and reward sensitivity, i.e. slower subjects were not more reward-sensitive. A previous study of ageing on motivation used simple RT, and found no difference in reward sensitivity between older and younger participants, but they acknowledge this could have been due to hearing problems or learning effects (Botwinick et al., 1958). Interestingly some studies have found that ageing slows velocity of manual movements and saccades (Irving et al., 2006; Pierson and Montoye, 1958), whereas others have not (Munoz et al., 1998, see Irving et al., 2006 for review); we found no effect of ageing: saccades were faster with higher rewards, regardless of age.

Examination of reward sensitivity over ages has given mixed results, with one study demonstrating worse attentional selection with reward in children and older adults, but improvements with reward in young adults (Störmer et al., 2014). Using a mixed prosaccade and antisaccade design, Jazbec et al. (2006) compared incentive motivation in adolescents and adults. They found adults (mean age 27) were less

modulated by reward than adolescents (mean age 15), whereas in our Study 2.3, we found that older volunteers (mean age 62) were more reward sensitive than younger adults (mean age 24). Although our task and the Jazbec task are not directly comparable—Jazbec et al. used reward, penalty or neutral cues, with a 500ms deadline and fixed reward sizes—the two results together suggest a biphasic change in reward sensitivity with age, with a minimum in young adults, paralleling the U-shaped age-dependence of simple reaction times (Hogin et al., 1960).

3.5.3. Motivation by rewards, not Distraction by rewards

We found that our incentives induced both faster saccades and reduced capture, i.e. fewer errors towards the early onset distractor. Yet some previous studies have shown increased distractibility with rewards (Blaukopf and DiGirolamo, 2005; Ross et al., 2011). Why this difference?

The task in this chapter might be considered to be a hybrid of an onset capture task (Jonides and Yantis, 1988) and a simple antisaccade task (Hallett, 1978). Two groups have used reward in antisaccade paradigms, but with subtly different results. The task of Ross et al. (2011) used lateralised reward cues 600 ms before each saccade indicating reward or penalty incentives for correct responses. The reward cues could thus be either congruent or incongruent to the stimulus location. Similar to the current study, they found that in both pro- and antisaccade blocks, incentives speeded RTs compared to neutral cues.

Independently, they demonstrated that visual reward cues themselves command attention. For prosaccades, reward cues opposite to the subsequent target speeded RTs compared to cues on the same side—consistent with IOR. For antisaccades, incentive

benefits were strongest if the cue was congruent with the saccade target. This latter effect might effectively be due to the reward cue enhancing the visual salience of a location, or amplifying a saccadic motor program to its location. The authors did not control for the visual salience of their cues, and so the incentive-specific effects on antisaccades are especially difficult to interpret. History effects were not examined in that study, and would likely be weak since every trial required refixation of the screen centre, and rewards were presented centrally. Our current study deals with these issues using auditory reward cues, and by using a continuous task, in which the previous target location becomes the starting point for the next trial.

Unlike Ross et al., Blaukopf and DeGirolamo (2005, 2006) counterbalanced the reward cue colours, such that visual salience could not explain their effects. They used 4 reward conditions—reward or penalty, large or small—however their reward cue also doubled as the go cue. As a result, any reward effect in their task involves only the most rapid processing of the reward cue; moreover subjects relied on learnt association of colour with incentive. They found that cues indicating high incentives can, maladaptively, attract the eyes and speed errors. They also find slowing of RTs when incentives are high, perhaps due to "capture of resources" by the value of the reward cue. In contrast, we found speeding with high incentives; this is most likely because although auditory reward cues may command attention, they are not tied to a screen location, and thus would not be expected to interfere with the oculomotor task.

In short, by using auditory reward cues, our study isolated the motivational effects of incentives, removing the spatially directed effects of a visual cue.

3.5.4. Limitations

3.5.4.1 Uncorrelated measures of reward sensitivity

The RT measure of reward sensitivity correlates across sessions, and is not altered by practice. A separate, physiological measure of reward sensitivity was obtained by pupillometry. This did not correlate with RT sensitivity to reward across subjects. There are at least two possible explanations for this. Firstly, reward sensitivity might be a composite of two independent traits: one determines pupil modulation, the other contributes to RT modulation by reward cues. Affective autonomic responses to reward might be tied to *arousal*, and unrelated to motor *vigour* (Sara, 2009). As an alternative explanation, the lack of correlation could be due to the wide variability in pupil baseline size across participants; pupil dynamics are nonlinear at the extremes of its range (Usui and Stark, 1982), and it is possible that differences in reward slope between individuals is masked by absolute difference in pupil size. In the younger subjects, our results were more in keeping with the latter explanation, as there was a strong negative correlation between baseline pupil diameter and pupil sensitivity to reward (r^2=0.23, p=0.01). However in older subjects, there was no such correlation (r^2=0.04, p>0.1) suggesting independent effects of reward on arousal and vigour.

3.5.4.2 Errors as distractor pull or lack of attention at target onset?

It is possible that differences in capture rate could be explained, not as attentional capture by the distractor, but simply as errors of judgement in discriminating onset times. For subjects who are less able to detect the delay between the distractor and target, their capture rate would be pushed towards 50%.

Against this, saccades with faster reaction times had much higher error rates than slower responses—i.e. errors were more likely to be short-latency. If subjects had

"missed" the onset, one might expect the errors to be slower than correct trials, as in situations where a decision is difficult. The proportion of capture for early RT bins often *exceeded* 50%. We conclude that our error rate reflects the degree of pull of the distractor, i.e. true oculomotor capture.

Also against this, the SOAs used here (40-120 ms) are much greater than previously reported thresholds for visual temporal order discrimination, which tend to be under 10 ms for stimuli similar to those used here (Artieda et al., 1992; Westheimer, 1983; Westheimer and McKee, 1977). Supporting this, longer SOAs resulted in a trend to longer RTs of correct saccades, suggesting that longer SOAs were in fact more difficult than shorter SOAs, consistent with the known effect of earlier onsets possessing greater visual salience.

3.5.5 Conclusion

The new task introduced here shows that saccade velocity and reaction times are consistently sensitive to reward incentives. Distractibility, as measured by oculomotor capture by an early distractor, can also be modulated at least in older participants, who in our study were more sensitive to reward than younger subjects. Velocity speeding by incentives supports theories of response vigour in which the motor system optimises the timing of action to maximise reward (Haith et al., 2012; Yu and Dayan, 2005). Two different measures of reward sensitivity can be obtained from behavioural vigour and autonomic responses to incentives.

4. Cabergoline increases reward sensitivity of oculomotor distraction

4.1. Introduction

Several lines of research, from both animal and human studies, have suggested that there is a very close relationship between neural systems subserving attention and those encoding rewards (Assad, 2003; Bendiksby and Platt, 2006; Ernst et al., 2004; Louie et al., 2011; Malhotra et al., 2013; Maunsell, 2004; Peck et al., 2009; Small et al., 2005; Sugrue et al., 2004). But how might these cognitive processes interact? Recent studies have revealed one potential mechanism by demonstrating that rewards can attract attention in a similar way to perceptually salient stimuli (Anderson et al., 2011a; Berridge and Robinson, 1998; Hickey et al., 2006, 2010d; Kiss et al., 2009b; Rothkirch et al., 2013). For example, visual search is slowed when a distractor is presented in a colour that was previously associated with high reward, than with low reward (Anderson et al., 2011b).

Recent studies have also investigated how saccade velocities may be controlled by current goals (for review see Shadmehr et al., 2010b). For a given amplitude of saccade, its peak velocity can be increased by the presence of reward (Chen et al., 2013), suggesting that motivation influences motor control as well as attention shifting.

What brain systems are responsible for coupling attention to reward? An attractive candidate is dopamine, which in animal studies signals reward and motivation, but is also released in response to perceptually salient events (Dayan, 2012b; de la Fuente-Fernández et al., 2002; Schultz et al., 1997). Many studies of dopamine in humans have focused on reinforcement learning (Cools et al., 2009; Frank

and O'Reilly, 2006; Pizzagalli et al., 2008; Ray and Strafella, 2010; Santesso et al., 2009; Voon et al., 2010). But according to models of basal ganglia function, reinforcement learning might be intimately linked with the filtering of irrelevant stimuli (O'Reilly and Frank, 2006). In support of this, dopamine has been implicated in the control of attention. Dopamine excess may increase oculomotor distractibility (Crawford et al., 1995; Duka and Lupp, 1997; Howes et al., 2012), while dopamine receptor blockade can protect against distraction in some situations (Mehta et al., 2004). Dopamine may be critical in mapping rewards to spatial locations (Takikawa et al., 2004) and in generating trial-to-trial effects in saccades (Barton et al., 2006).

Could dopamine mediate the effects of reward incentives on attention? One way to quantify the sensitivity of attention to rewards is to measure involuntarily evoked saccades to a distractor—so called "oculomotor capture" (Anderson et al., 2012; Ding and Hikosaka, 2007c; Milstein and Dorris, 2007a; Theeuwes and Belopolsky, 2012). Specifically, we focus on three indices that have previously been shown to be modulated by reward. Saccadic reaction times and velocities are speeded by expectation of high rewards in primates (Chen et al., 2013; Nakamura and Hikosaka, 2006; Roesch and Olson, 2003; Takikawa et al., 2002c). Furthermore when the target and a distractor are not collinear, saccades may be curved, and the curvature is also modulated by reward (Hickey and van Zoest, 2012b; Schütz et al., 2012a; Theeuwes et al., 1998). Saccade direction and in-flight curvature may represent the output of different neural control mechanisms (Chen-Harris et al., 2008).

One explanation for reward modulation of response timing is that the motor control system optimises a reward *vs.* effort trade-off. According to this logic, faster actions require more effort, but if actions are slow then less reward can be harvested

(Niv et al., 2006; Shadmehr et al., 2010b). The concept of response vigour formalises this intuition (Mazzoni et al., 2007; Niv et al., 2007; Salamone and Correa, 2002). In this framework, the timing of action is determined both by the cost of responding faster, and the baseline average reward rate. When baseline reward rate is high, the optimal rate of responding rises. It has been proposed that tonic dopamine regulates vigour and can act as an estimate of the current average reward rate (Niv et al., 2007; Robbins and Everitt, 2007). If this is the case, dopamine agonists might be expected to speed responses, mimicking the effect of a higher baseline reward rate. The optimality view subsumes the two older complementary interpretations of dopamine in mediating pleasure *vs.* the willingness to exert effort (Edwards et al., 1979; Hursh, 1980; Neill and Justice, 1981).

Consistent with a role in motivating action, studies of D2 agonists in rodents have shown increases in motor behaviour (Ross et al., 1989), but due to mixed pre- and post-synaptic effects, the dose-dependence is biphasic. Moreover, there is evidence of cross-species differences, necessitating translation into human studies (Broos et al., 2012; Ralph and Caine, 2005). In humans, D2 agonists are known to trigger impulse control disorders in patients with Parkinson's disease (Weintraub et al., 2006), and D2 activation is a strong candidate mechanism through which stimulant drugs cause addiction (Centonze et al., 2004; Dalley et al., 2007; Ma et al., 2014; Self et al., 1996).

Paradoxically, D2 agonists may also *reduce* impulsivity as measured by a 5-choice serial response task (Fernando et al., 2012). In keeping with this, reduced striatal D2 receptors are a consistent finding in individuals suffering from compulsive eating, drug addictions and ADHD (Volkow et al., 1990, 2003, 2007). To explain this, it has been suggested that motivation is “the opposite of impulsivity… the ability to resist

behaviour initiation, and exert greater effort in order to obtain a more valuable outcome" (Trifilieff and Martinez 2014). These two distinct roles of dopamine in initiating *vs*. desisting from action might be reflected in the direct and indirect pathways of the basal ganglia, in which D2 receptors control an inhibitory 'No-go' pathway (Gerfen and Surmeier, 2011; Graybiel, 1990; Zarrindast and Minaian, 1991).

Thus, a crucial difference in predicting the effect of D2 stimulation is whether the behaviour in question is automatic or volitional. However most pharmacological manipulations carried out in humans to date have studied explicit volitional choices (Mehta et al., 2000, 2004; Robbins, 2000). Low doses of D2 agonists may speed up simple and choice reaction times (Rihet et al., 2002; Schück et al., 2002) and increase error rates (Rammsayer and Stahl, 2006). In one study, the D2 agonist bromocriptine was found to reduce distractor interference in the Stroop task (Roesch-Ely et al., 2005). We ask specifically, does D2 stimulation increase the vigour of exogenously afforded movements? And when incentives are increased, is the effect of motivation altered by D2 stimulation?

Here we used the novel task described in chapter 3, that uses oculomotor capture to measure how dopamine influences the effects of reward. To modulate dopamine receptor activation, participants took Cabergoline, a long-acting D2 dopamine receptor agonist, in a double-blinded, placebo-controlled crossover design. Cabergoline is a full agonist at D2 subtype 2 receptors, with partial agonist effects at subtype 3 and 4 receptors, and has a half life of 60 hours in the bloodstream (Fariello, 1998; Kvernmo et al., 2006; Sharif et al., 2009). Cabergoline has been shown to modulate stop signal reaction times, alter cortical plasticity, and induce learning biases in humans (Frank and O'Reilly, 2006; Korchounov et al., 2007; Nandam et al., 2013; Shoptaw et al., 2005),

and its use is associated with pathological gambling in Parkinson's disease (Weintraub, 2010). We hypothesised that reward would speed saccades, but cabergoline would alter the sensitivity to reward.

4.2. Methods

4.2.1. Participants

Twenty healthy male volunteers were recruited from an advert, mean age 26.5 years (range 18 to 36), all with normal or corrected-to-normal vision. They were screened to exclude chronic medical or mental illnesses, and also completed the following questionnaires: Barratt impulsiveness scale (BIS, Patton et al., 1995), UPPS impulsive behaviour scale (Whiteside et al., 2005), and Lille apathy rating survey (LARS, Sockeel et al., 2006).

Each participant attended one drug session and one placebo session in randomised order. To minimise learning effects, all had practised 6 blocks of the task on two occasions, one week before the experiment and 2-4 weeks before the experiment. They were instructed that they would be paid a baseline fee plus a bonus proportional to the rewards they earned. One eye movement data set was corrupted so data from 19 people were analysed. On the drug and placebo sessions, participants attended at 8 am and took 20mg of domperidone, which blocks D2 receptors outside the brain, minimising side effects such as nausea (Parkes, 1986; Shindler et al., 1984). After 20 minutes they took either 1.5mg of cabergoline or placebo tablet crushed into orange squash. After 2 hours, blood pressure and pulse were measured. Testing began at least 2 hours post-dose, to allow blood concentration to peak (Del Dotto and Bonuccelli, 2003). After the task, participants completed a 17-item visual analogue rating scale of mood to rule out the

possibility that cabergoline caused other potentially confounding cognitive effects (Herbert et al., 1976), in addition to a 9-item rating scale of physical side effects specific to cabergoline.

4.2.2. Task

The materials and task were identical to that used in chapter 3. The time between the distractor and target onsets was varied between 40 ms and 120 ms, and the same adaptive reward schedule was used to maintain a constant difficulty level. Participants performed 7 blocks (rather than 5), each comprising 54 trials, with a 2 minute break between blocks. This came to a total of 378 trials, lasting approximately 60 minutes.

4.2.4. Curvature metric

Previous measures of curvature have taken the trajectory on each trial and calculated a single value that characterises its curvature, e.g. the maximal linear or angular deviation from a straight line trajectory (McPeek et al., 2003; Theeuwes et al., 2005), or equivalently the quadratic component of a polynomial fit (Ludwig and Gilchrist, 2003), or area between the trajectory and a straight line (McSorley et al., 2004). This method might lose useful information about the online control of the eye movement, which in light of the previous findings in velocity, may be one of the ways in which reward influences eye movements.

In order to capture all the information available, a linear model was used to extract the influence of various parameters for all points along the trajectory of the saccade. I aligned all saccades such that the direction of the target was constant, and normalised distances to keep saccade amplitude constant. At each time-point during the saccade, I calculated the perpendicular deviation of gaze from a straight line connecting

the start-point to the target. Positive values indicated that gaze deviated in the direction towards the distractor, whereas negative values indicated deviation away from the distractor. Trial-wise regressors such as reaction time, incentive, and previous trial effects could then be entered into a generalised linear model to extract their effects on the push or pull of the distractor, over the course of the saccades.

This method has the advantages of a) giving a measure of distractor push or pull over the course of the trajectory, and b) being able to estimate the effects of multiple factors simultaneously. Additionally it has the potential to be used with more sophisticated statistical tests such as permutation testing and mixed-effects analysis (see below).

4.2.5. Delta plots

Delta plots analyse the differences between two distributions, and are commonly used for reaction times when two conditions are present during a block (Ridderinkhof et al. 2004). The plot is constructed by grouping trials by RT bin— "Vincentisation" of the distribution (Ratcliff, 1979; Vincent, 1912)—and then taking the RT difference between the conditions at each RT bin. The resulting values index the amount of influence that the experimental manipulation has, as a function of time within the trial. In the case of this experiment, the contrast of interest is the difference between reward and no-reward conditions. (Comparison of drug *vs*. no-drug using distributional analysis is not appropriate as the data are from two different sessions, and thus corresponding quantiles of the two distributions are not necessarily comparable).

Traditional delta plots divide data using 4 or 5 quantile bins (quartiles or quintiles; McSorley, Haggard and Walker 2009), and although quintile binning provides

a much richer parameterisation of the data than a simple mean or median (Dawson, 1988), there are drawbacks. First, the assumption is made that 5 bins is the appropriate number, secondly, the bin edges that are chosen are essentially arbitrary, and thirdly, information is necessarily lost in the binning process (Rouder and Speckman, 2004). Furthermore, parametric statistical approaches rely heavily on selecting appropriate hypotheses about the different RT bins. To overcome these limitations, I devised a continuous version of the delta plot, in which a sliding bin was used. In this analysis, a 20% quantile bin is moved smoothly over the two RT distributions, and the means are subtracted, to give a point-wise estimate of the effect of reward.

Statistical comparison of continuous data requires some sophistication, since values in neighbouring windows are necessarily highly correlated. To correct for multiple comparisons, a permutation test can be performed by randomly re-arranging the three reward conditions within each subject's data, and computing across the whole time series the maximum value of the t-statistic (Nichols and Holmes, 2002). The resulting null distribution of *maximum t* over all the permutations can be thresholded at a given alpha-level to control the family-wise error rate (the probability that any one of the many *t*-tests across the timepoints will be positive, over all permutations). Comparing the t-statistic of the actual data to the bootstrapped null distribution yields the times at which there are significant effects of reward.

Delta plots may be used to examine the differences between distributions of any kind. Generic commented MATLAB code for producing continuous delta plots for arbitrary data, with a permutation test between conditions to control family-wise error rate, is available on my website and is reproduced in **Appendix 1**.

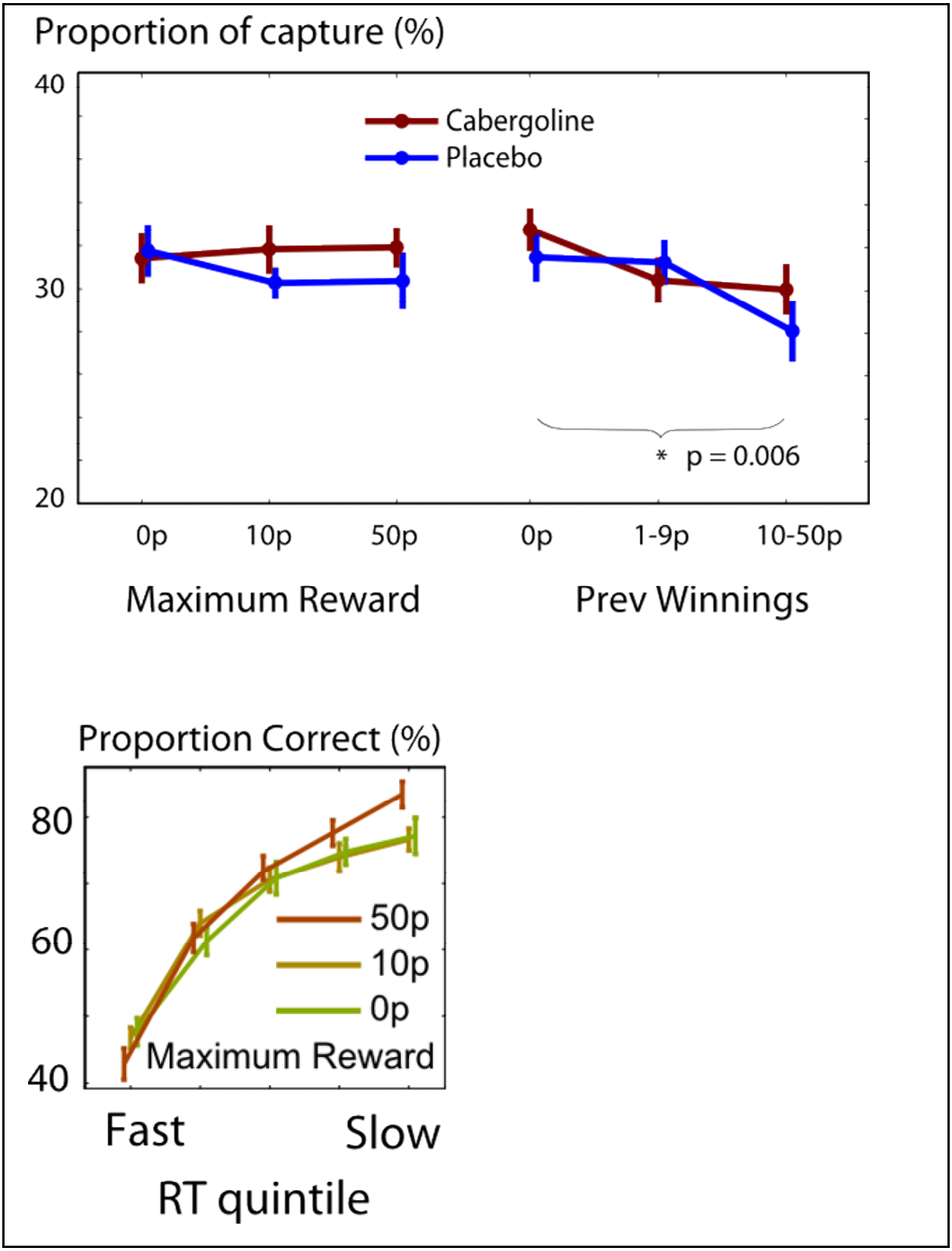
4.3. Results

In this task participants fixated one of three locations, then saw the two other locations illuminated, with asynchronous onsets (**Figure 3.1A**). They had to direct their gaze towards the disc that came on second (the target) while ignoring the first disc (distractor), and were rewarded according to the time taken to arrive at the target (**Figure 3.1B**). But on 32% of trials, participants made erroneous movements towards the first onset (distractor), a phenomenon termed oculomotor capture (Theeuwes et al., 1998). Even on correct trials, the eyes were often pulled towards the distractor (**Figure 3.2**).

To investigate the reward sensitivity of distraction, we manipulated the incentive (maximum potential winnings) on each trial using an auditory cue which indicated how much monetary reward was available for a fast correct saccade to the target. We now examine how reward and cabergoline influence the probability of distraction, reaction times and saccade velocities, and then we analyse the curvature of saccades toward or away from the distractor.

4.3.1 Probability of distraction influenced by previous reward

The proportion of distracted trials varied from 9% to 73% across individuals. Incentive did not significantly affect this (**Figure 4.1A**, $t(18)=1.69$, $p=0.19$). Furthermore, the incentive on the previous trial did not predict subsequent distraction. However the amount of money won on the previous trial did affect oculomotor capture on the subsequent trial: the more a participant won, the more accurate they were likely to be on the next trial (grouped as high, medium 1-9p, or low winnings, $F(1,18)=4.44$, $p=0.010$). Previous winnings was therefore included as a factor in the subsequent analysis.


Proportion of capture (%)
40
30
20
Cabergoline
Placebo
* p = 0.006
0p
10p
50p
0p
1-9p
10-50p
Maximum Reward
Prev Winnings
Proportion Correct (%)
80
60
40
50p
10p
0p
Maximum Reward
Fast
Slow
RT quintile

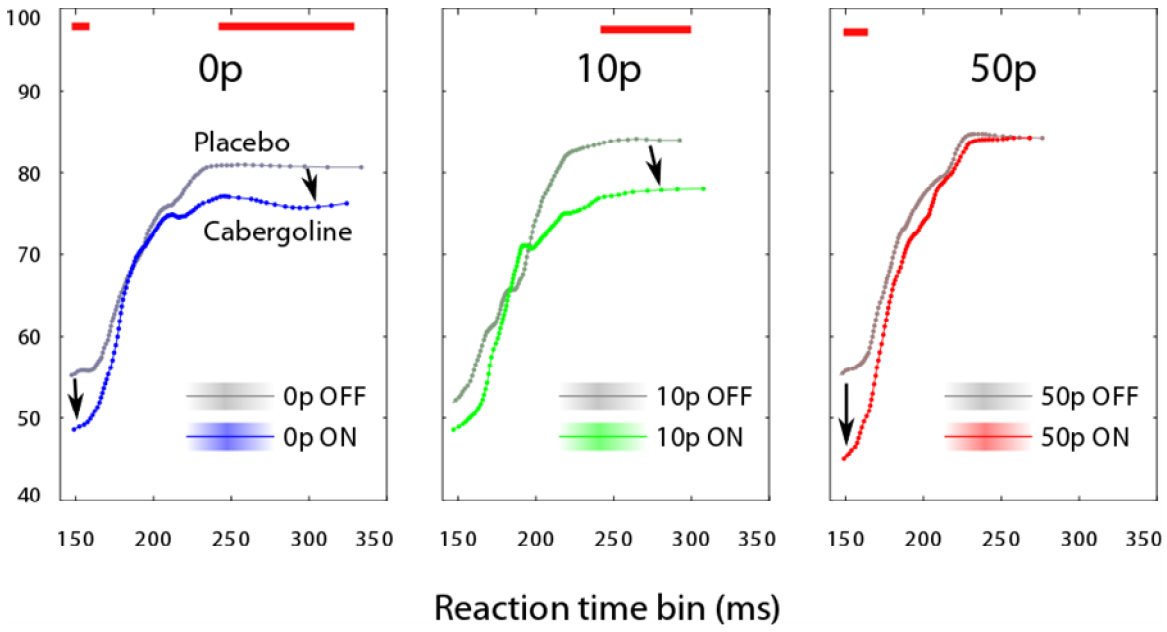


Figure 4.1: Proportion of capture was not influenced by cabergoline

A) (pervious page) The level of reward does not significantly alter the proportion of trials on which participants were distracted. The D_2 agonist cabergoline does not significantly increase proportion of distracted saccades. However, winning a high amount on the previous trial speeded RT. **B)** The conditional accuracy function, binned according to RT, shows that early saccades are likely to be errors. The effect of reward occurs, again, primarily at later timepoints in the trial. **C)** Continuous conditional accuracy functions, showing effect of drug (red bars show where $p<0.05$ by permutation test)

Cabergoline did not significantly affect the probability of distraction (4-way mixed-effects ANOVA for incentive × previous winnings × drug on/off × session order, $F(1,315)=2.41$, $p>0.05$). There were also no order effects between participants who took the drug or placebo first ($t(18)=0.83$, $p>0.05$). There was no difference in distraction between the three possible starting locations, nor between clockwise and anticlockwise saccades, so results were collapsed across locations. A conditional accuracy plot was constructed for each reward level using bins centred on RT quintiles (**Figure 4.1B**). This illustrates that the earliest saccades had <50% chance of going to the target, whereas the latest saccades were 80% accurate.

Continuous versions of the continuous accuracy function were constructed using a sliding window (**Figure 4.1C**), and the effect of drug was tested by permuting the ON and OFF data for each subject (5000 random permutations out of 524,000 possible), and correcting for the maximum *t* value over all time points. Cabergoline decreased accuracy significantly at later RTs (> 240 ms), most prominently in the 0p and 10p incentive conditions.

4.3.2. Cabergoline increased sensitivity of saccade velocity to reward

Velocities of correct saccades were significantly speeded by reward, in keeping with previous findings (Chen et al., 2013; Takikawa et al., 2002d) (**Figure 4.2A**, $F(1,315)=16.9$, $p<0.001$). Cabergoline slowed velocities significantly ($F(1,315)=5.38$, $p=0.021$). Crucially, cabergoline slowed saccade velocities specifically when reward was low (interaction of drug with reward, $F(1,315)=5.68$, $p=0.018$). Cabergoline thereby increased sensitivity of saccadic velocity to incentive magnitude, steepening the gradient of the velocity–reward plot, compared to placebo (**Figure 4.2A**).

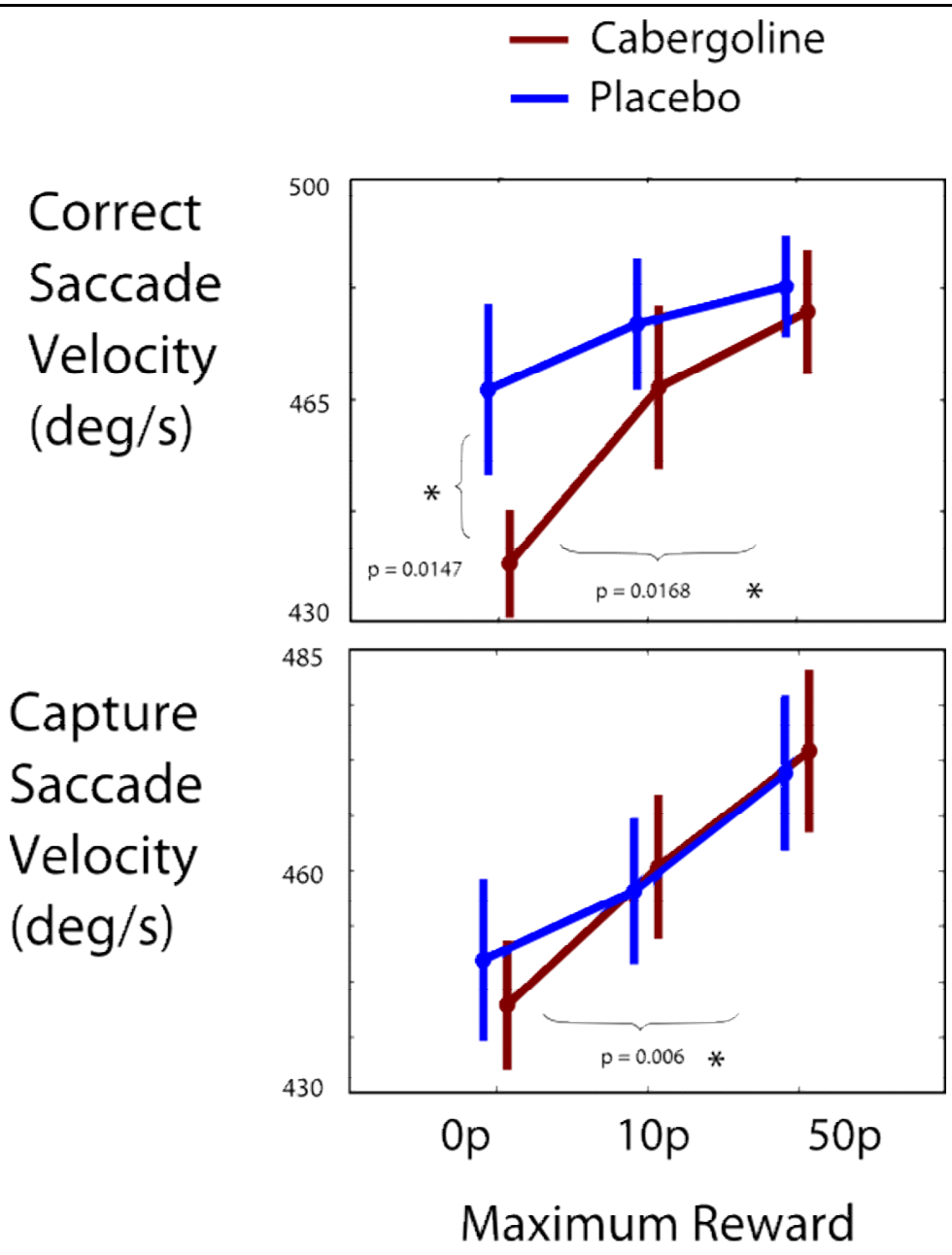


Figure 4.2: Peak saccade velocity is increased with reward, but more so on cabergoline
A) Correct saccade velocities were slowed by the D2 agonist, but specifically when reward incentives were low—such that cabergoline increased reward sensitivity (reward x drug interaction, p=0.018) **B**) There was no drug effect on error saccade velocities, although reward significantly speeded them.

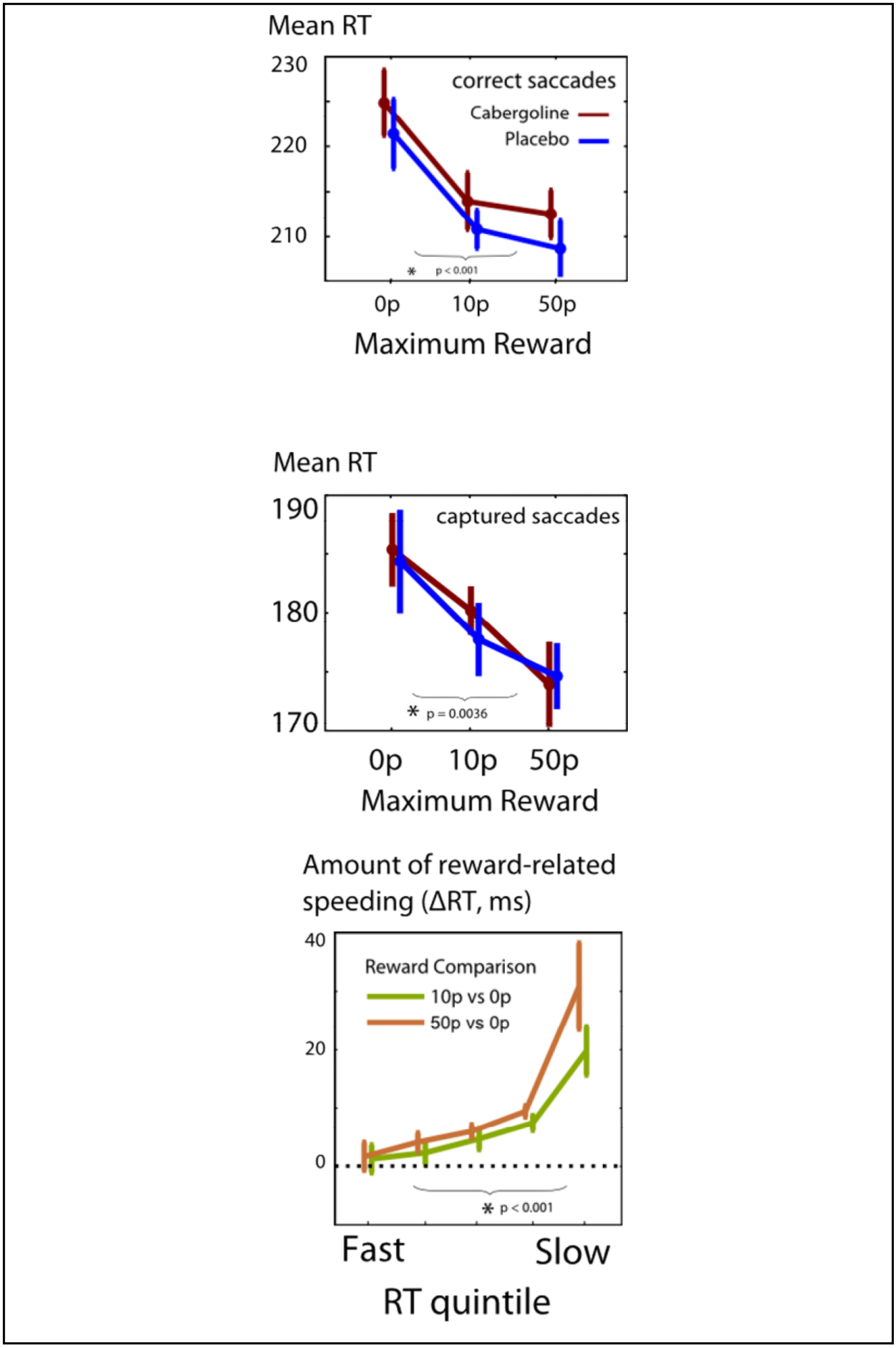
Practice speeded the velocity of correct saccades ($F(1,315)=5.30$, p=0.022), although previous winnings did not ($F=2.40$, p=0.12). Post-hoc tests revealed that reward had significant effects both on cabergoline ($F(2,36)=10.3$; $p<0.001$) and placebo

(F=3.3; p=0.047); and that there was significant drug effect at 0p reward (t(18)=1.85, p=0.040) but not at 10p or 50p (p>0.05).

For *error* saccades, both incentive and practice speeded velocity (**Figure 4.2B**, F(1,315)=17.5 and 8.7, p<0.001 and 0.003 respectively), but here there was no effect of cabergoline, nor any significant interaction. Saccade amplitudes were increased by incentives, for both correct and error saccades (F(1,315)=10.7, p=0.001 and F=5.04, p=0.03 respectively). Amplitudes were not significantly affected by cabergoline or practice; nor were there any significant interactions.

4.3.3. Saccadic reaction times speeded by incentives

Reaction times were calculated from fixation offset until the initiation time of the first saccade that was >1 degree. For *correct saccades*, incentives significantly speeded reaction time (**Figure 4.3A**, F(1,315)=28, p<0.001). In contrast to the effect of drug on saccade velocity, there was no RT modulation by cabergoline, previous winnings nor practice, and no interactions (all F(1,315)<0.8, p>0.05). Precisely the same pattern was observed for *error saccades*, in that reward significantly speeded their latency (**Figure 4.3B**, F=4.74, p=0.03).


Mean RT
230
220
210
correct saccades
Cabergoline
Placebo
* p < 0.001
0p
10p
50p
Maximum Reward
Mean RT
190
180
170
captured saccades
* p = 0.0036
0p
10p
50p
Maximum Reward
Amount of reward-related speeding (ΔRT, ms)
40
20
0
Reward Comparison
10p vs 0p
50p vs 0p
* p < 0.001
Fast
Slow
RT quintile

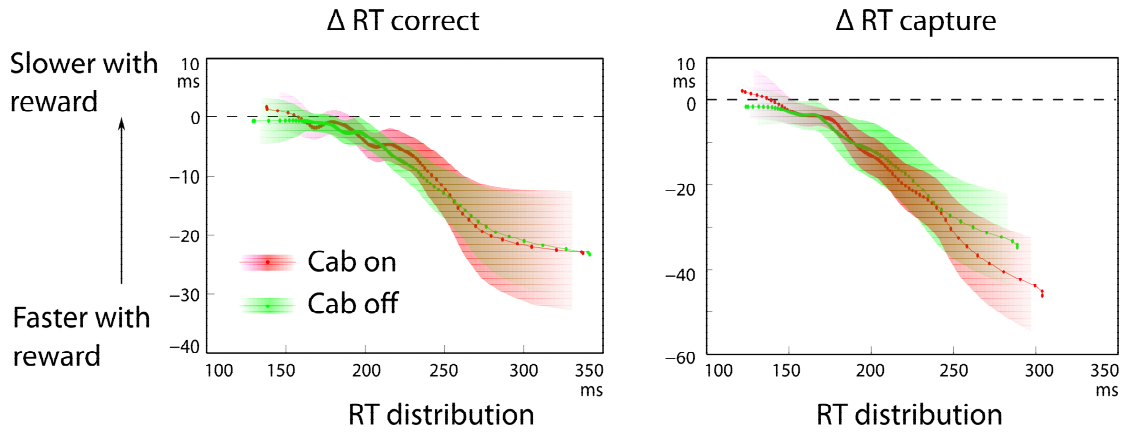


Figure 4.3: Reaction time was speeded by reward

A) Saccadic latencies for correct saccades are speeded by reward incentives. There was no significant effect of cabergoline. **B**) Latencies for error saccades are also speeded by incentives. There is no effect of cabergoline. **C)** Traditional delta plot: Correct responses for each reward condition are binned by reaction time, and the distance between RT distributions in a pair of conditions is calculated at each bin. A positive value indicates that the higher-reward condition was faster than the lower-reward condition, at that particular time bin. Speeding due to rewards was greatest at later timepoints within a trial. There was no drug effect. **D)** Continuous delta plots showed more clearly the lack of effect of cabergoline on RT reward sensitivity.

Correct trials were binned according to their RT, and RT difference between reward conditions plotted for each RT bin. The resulting "delta plot" (Ridderinkhof et al., 2004b) shows the effect of reward on RT, over time during the trial. Calculating RT with 50p incentive minus RT with 0p incentive gives positive values, indicating that reward decreases RT. The effect of reward on speeding responses was significantly greater for later saccades (**Figure 4.3C**, main effect of RT bin, $F(4,341)=23.8$, $p<0.001$), consistent with previous studies showing a build-up of reward's effect during a trial (Ding and Hikosaka, 2007c). Cabergoline did not influence the shape of the delta plot, and there was no interaction with time ($F(1,341)=0.042$, $p>0.05$, and $F(4,341)=0.097$, $p>0.05$ respectively). A delta plot was produced with the new

continuous sampling algorithm (section 4.2.5), and a permutation test on the deltas confirmed that no effect of cabergoline could be detected (**Figure 4.3D**).

Reaction time variability, taken as the standard deviation of saccadic latency across trials for each condition, was reduced by rewards ($F(1,91)=9.86$, $p=0.002$), but was unaffected by cabergoline or practice ($p>0.05$).

4.3.4. Curvature away from distractors increased by reward but reduced by cabergoline

In the placebo condition, saccades that landed correctly on the target curved on average 2.5 degrees (± 1.7 s.e.m.) in the direction away from the distractor. This mean "repulsion" from the distractor was significantly increased by rewards (**Figure 4.4A**, $F(1,315)=10.7$, $p=0.001$), and reward interacted with drug ($p=0.018$). But was this due to more saccades curving away, or fewer saccades curving towards the distractor?

Correct saccades were classified by their angle of departure into direct saccades, those pulled towards the distractor, or those repelled away from the distractor (threshold 15 degrees, **Figure 4.4B**). The proportion of saccades curving *towards* the distractor was unaffected by reward or by cabergoline. In contrast, the proportion of saccades that curved away from the distractor increased with higher rewards ($F(1,315)=5.71$, $p=0.017$). Cabergoline strongly reduced this distractor repulsion ($F(1,315=13.7$, $p<0.001$), but with no significant interaction or practice effect.

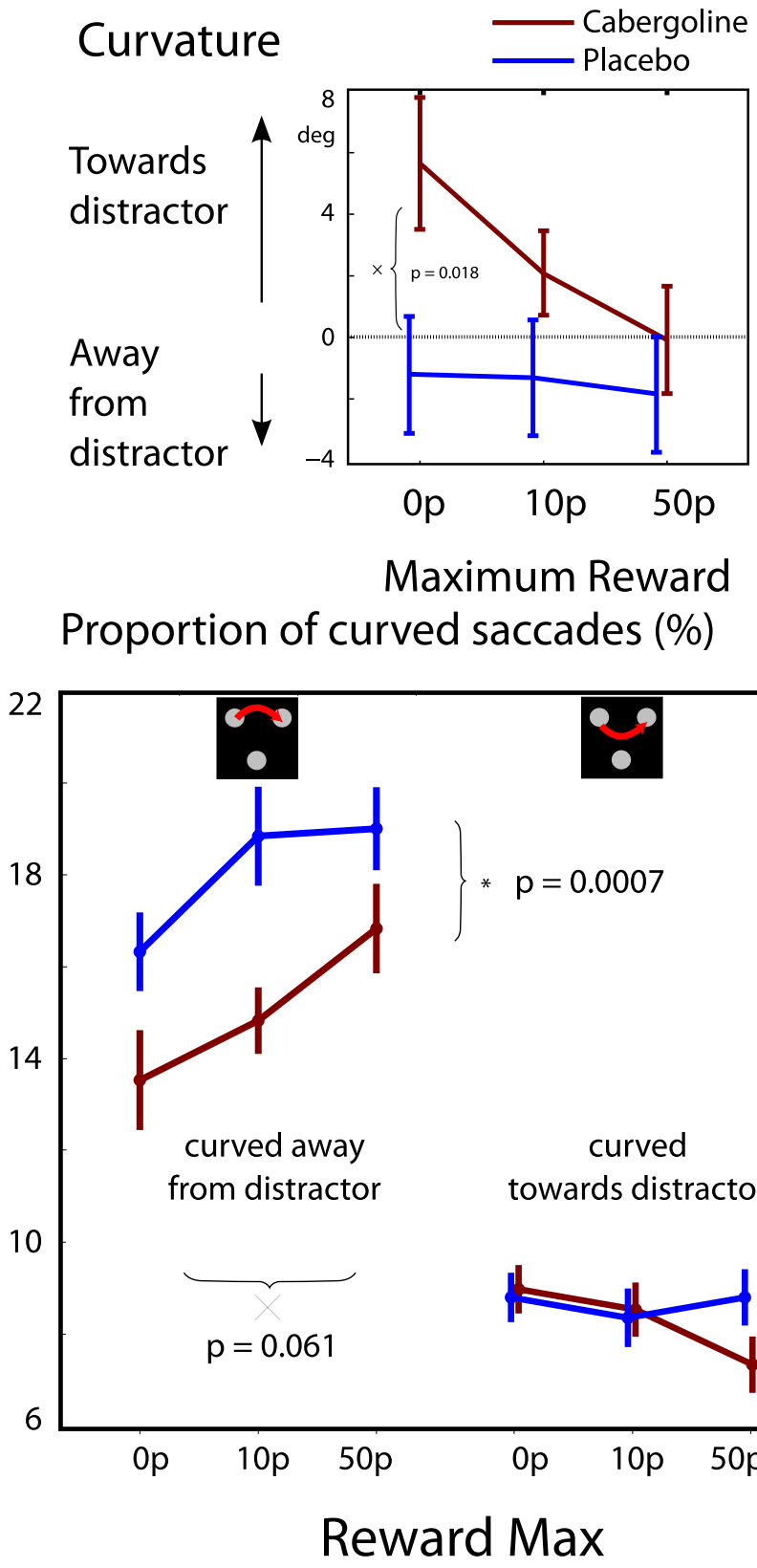


Figure 4.4: Effect of reward and drug on saccade curvature

A) Curvature of initial saccades that ended on the target (i.e., "correct" trials). Negative values indicate saccades curved away from the distractor. The eyes curved away from the distractor with

increasing reward. **B**) Rewards increased the proportion of saccades that curved away from the distractor ("repulsion"). Cabergoline had an additive effect of reducing this repulsion. For saccades curving *towards* the distractor, there was no effect of reward or drug.

Trials were binned according to RT quintiles (Mulckhuyse et al., 2009), and the angle of departure for each RT bin was plotted (**Figure 4.5A**). Thus, in figure 4.5B, positive values indicate that correct saccades curved towards the distractor, whereas negative values indicate they curved away from the distractor. Similarly in figure 4.5A, negative values indicate that error saccades to the distractor curved towards the target, whereas positive values indicate curvature in the opposite direction. In agreement with previous studies, early saccades curved more towards the distractor, whereas late saccades curved towards the target, often attributed to an increase in top-down control over the course of the trial (Mulckhuyse et al., 2009; Walker et al., 2006). This was the case for both error and correct saccades (main effect of time in trial, $F(4,161)=16.8$, $p<0.001$ and $F(4,161)=2.96$, $p=0.022$ respectively).

Cabergoline influenced the curvature on error trials. Cabergoline was associated with later errors veering a little more *towards the target* (interaction of drug with time, $F(4,161)=2.61$, $p=0.032$). Thus, cabergoline actually *reduced* late distraction in the trial. No effect of drug on correct saccade curvature was observed in this binned analysis.

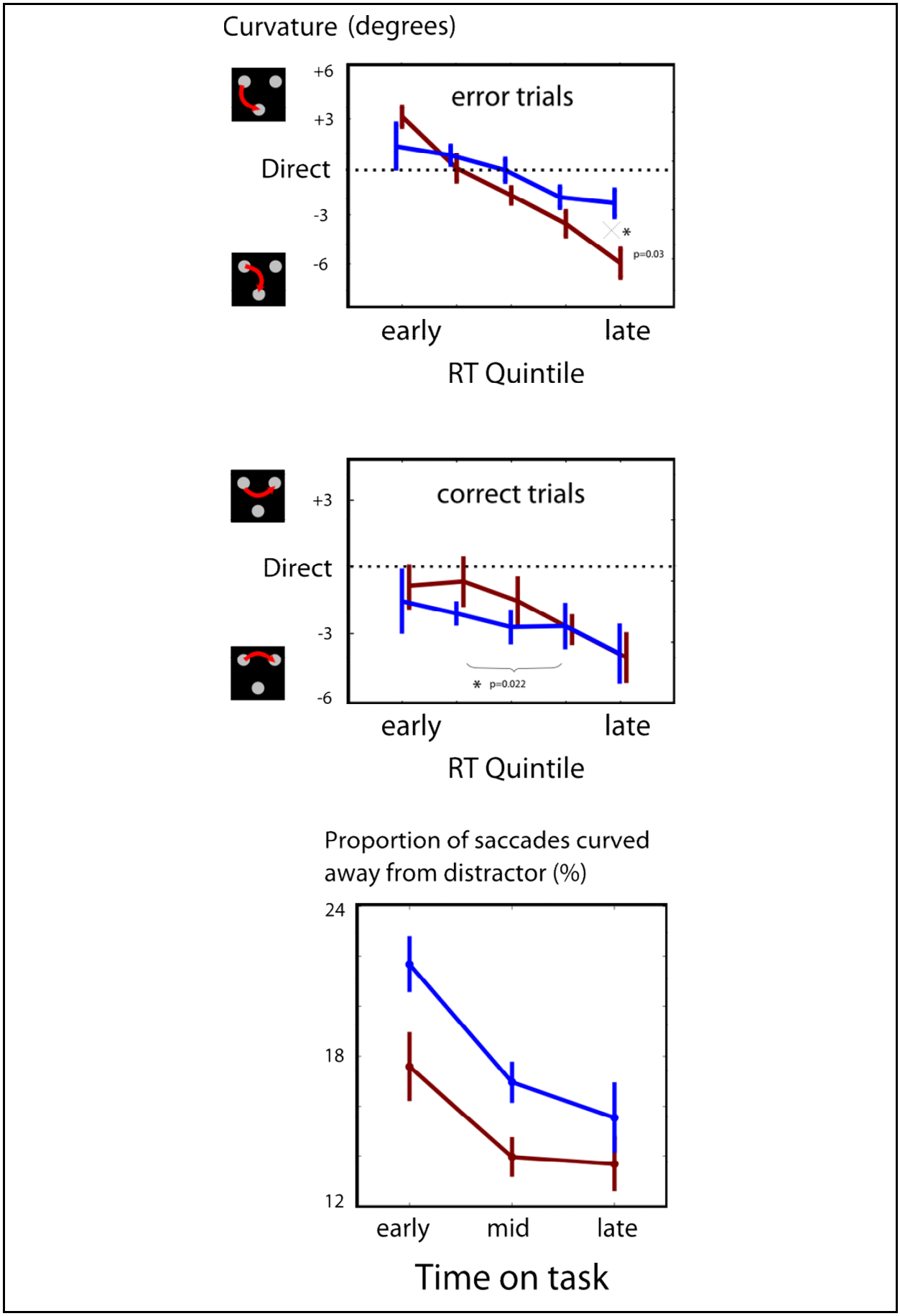

Curvature (degrees)
+6
+3
Direct
-3
-6
error trials
*
p=0.03
early
late
RT Quintile
+3
Direct
-3
-6
correct trials
* p=0.022
early
late
RT Quintile
Proportion of saccades curved away from distractor (%)
24
18
12
early
mid
late
Time on task

Figure 4.5: Curvature away from the distractor is stronger for late responses
A) and **B**) Binning trials by reaction time revealed a general tendency of later correct saccades to curve away from the distractor, and later errors curved towards the target. On cabergoline, later errors (initial saccades that ended on the distractor) had an increased pull towards the target. **C**) Curvature reduced over time during the task.

One interpretation of this curvature result is that cabergoline increases distractibility. It is therefore important to rule out the possibility that cabergoline simply increases fatigue. Curvature towards the distractor increased with time on task (3-way ANOVA over early, middle and late thirds of trials × drug × session, $F(1,113)=16.3$, $p<0.001$). In other words, later in a session, participants become increasingly distractible (**Figure 4.5C**). But crucially, this attentional decline did not interact with drug ($p>0.05$), suggesting that cabergoline did not increase the rate of fatigue.

To visualise the effects of cabergoline on curvature, the actual trajectory of each correct saccade was compared to an 'ideal' straight line to the target. The deflection from this straight path was calculated as a function of time during the saccade. These deflections were aligned and superimposed (**Figure 4.6A**). The resulting curve shows the average curvature of the path of the eyes, over the course of the saccade. Then the factors that might influence the deflection were used as regressors in a general linear model, at each timepoint during the saccade. This gives a set of curves in which positive and negative deflections indicate an influence of a given factor on a saccade curving toward or away from the distractor (**Figure 4.6B**). In these figures, the regression was performed independently for each subject, and the shaded area is the standard error between subjects.

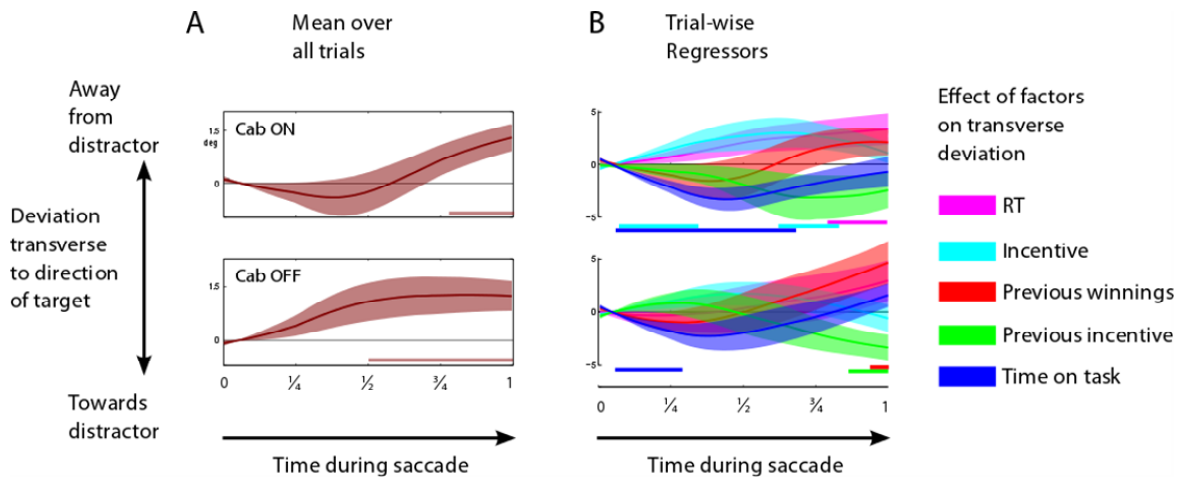


Figure 4.6: Curvature towards or away from the distractor, during the course of each saccade Positive values indicate repulsion from the distractor, whereas negative values indicate a pull towards the distractor. **A**) Cabergoline reduces early repulsion from the distractor. Bars below the figure indicate the times when the deflection is significantly different from zero. **B**) The trajectories on individual trials were correlated against reaction time, incentive, previous trial winnings and incentive, and time on task using a general linear model. Incentive had a greater effect (i.e. reducing distraction) when on cabergoline (cyan). However, cabergoline increased the influence of time on task (i.e. fatigue, blue) and RT (i.e. the slower the saccade, the less distraction, magenta).

Cabergoline had effects of increasing the effect of incentive on causing repulsion from the distractor. On cabergoline, there was a significant effect both early and late in the trajectory, of incentive to cause curvature away from the distractor (**Figure 4.6B**, positive cyan curve). Additionally, cabergoline increased distractor pull as a function of time on task (blue), but caused long-latency saccades to be more repelled from the distractor (magenta). Cabergoline may therefore increase distractibility with fatigue as participants tire, yet increase the effect of cognitive control as it evolves over the course of an individual trial.

4.3.5. Error correction

After an error, the task required participants to look towards the correct target to continue. The time between the capture saccade and the correction saccade was measured as the correction delay. Mean correction delay was 253 ms (+/-64 ms). Reward significantly speeded corrections, with a mean of 270 ms for the 0p condition, and 236 ms for the 50p condition (**Figure 4.7A**, $F(1,314)=18.4$, $p<0.001$). High previous winnings speeded corrections on subsequent trials ($F(1,314)=11.9$, $p<0.001$), and there was also a significant practice effect across sessions ($F(1,314)=7.55$, $p=0.006$), but cabergoline did not significantly affect correction time ($F(1,314)=2.2$, $p=0.14$).

Trials were binned according to the RT of the error saccade, and the mean correction delay for each bin was plotted (**Figure 4.7B**). Corrections were fastest for mid-speed errors; it took longer to correct early errors and late errors (effect of error time, $F(4,161)=10.7$, $p<0.001$). Cabergoline speeded the time to correct errors but there was no interaction with error RT bins, indicating a global speeding effect (main effect of drug, $F(1,161)=4.22$, $p=0.041$).

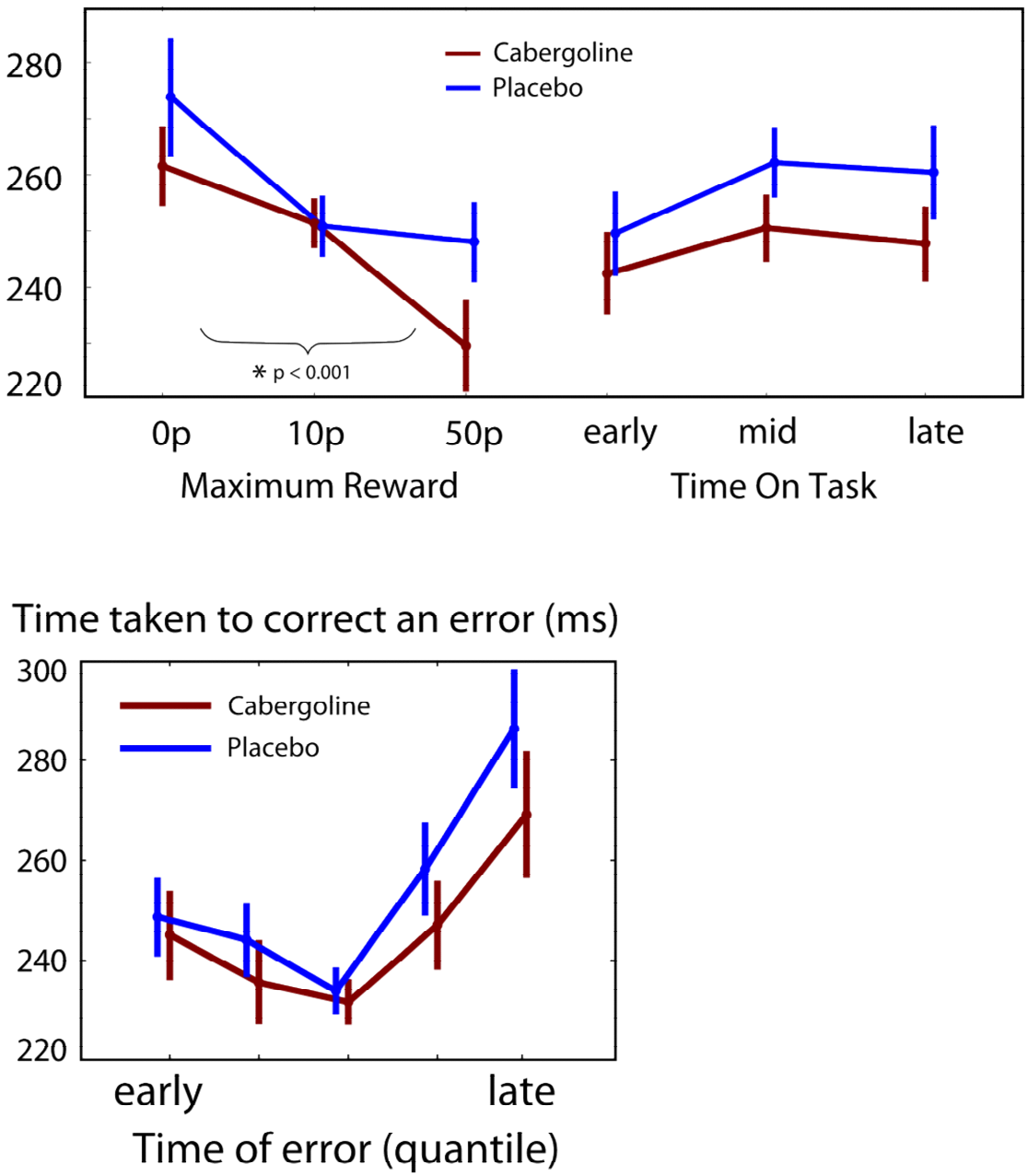


Figure 4.7: Error corrections were speeded by reward

A) Error correction latency is the time from an error saccade to the distractor, until it was corrected by a saccade to the target. Error corrections were speeded by reward. There was a trend for cabergoline to speed error corrections, but there was no effect of time on task.

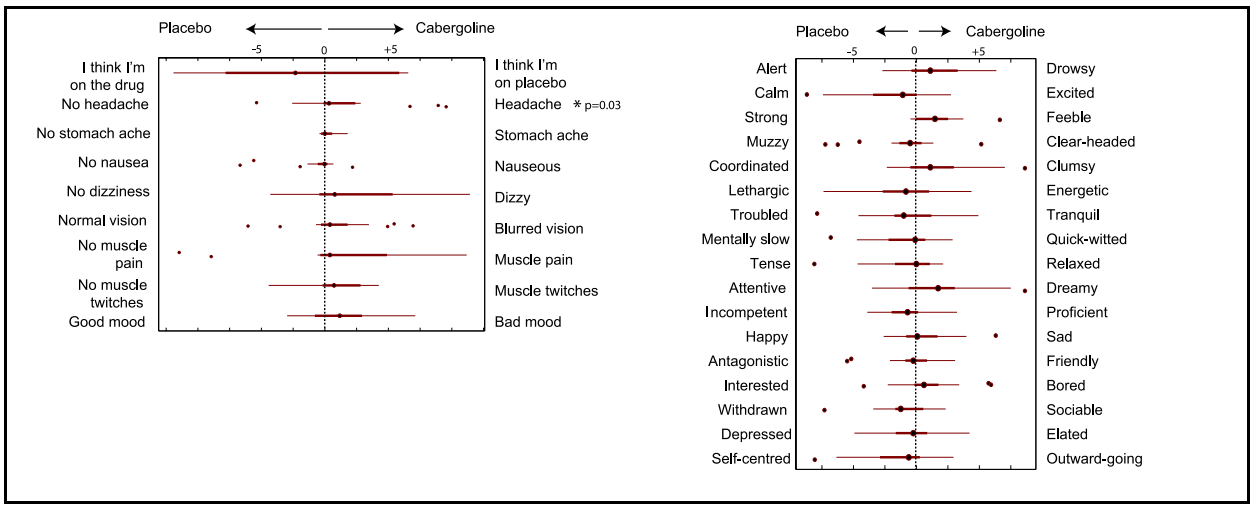
B) Error correction latency was plotted as a function of the error onset time. Errors that occurred earlier were slower to correct, as were errors that occurred later. Cabergoline speeded error corrections overall, but there was no interaction with error time bins.

4.3.6. Questionnaire measures

4.3.6.1. State measures

To assess whether the drug effects could be explained indirectly by mental state or physical changes, we compared visual analogue rating scales after the drug and placebo sessions (**Figure 4.8A** and **B**). Only the headache rating differed significantly between the two groups (t(18), p=0.03 without correcting for 17 multiple comparisons). Of note, there were no differences in ratings for arousal, alertness, sociability, anxiety, nor mood. We also asked subjects to rate, on each session, whether they thought they were on the drug; there was no difference in ratings between the drug and placebo sessions. To assess whether headache might explain the effects of cabergoline, we correlated individual subjects' cabergoline effect with their headache scores. There was no correlation for the effect on reward sensitivity of velocity (r^2=0.009, p=0.69) nor for the effect on proportion of saccades that curved away from the distractor (r^2=0.0002, p=0.95)—suggesting that headache was not a factor in our findings.

We found no effect of drug on blood pressure or pulse (**Figure 4.8C**).



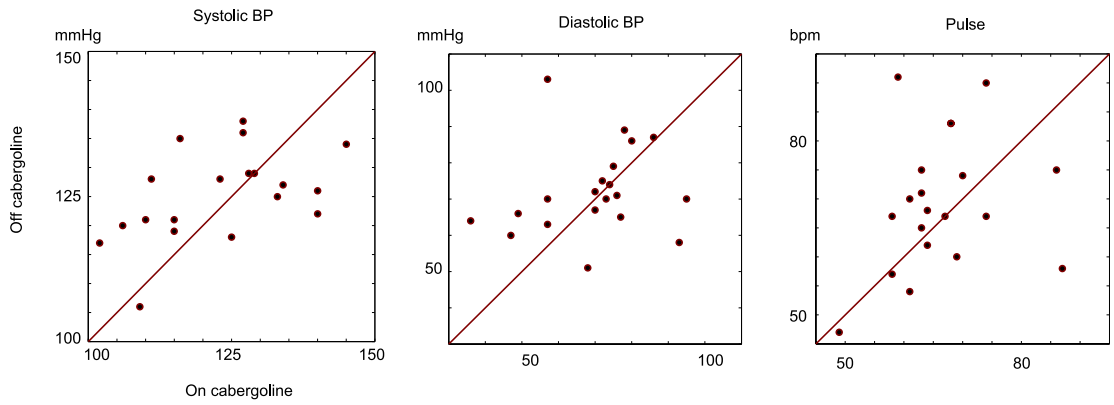


Figure 4.8: Visual analogue ratings and cardiovascular effects

A) Rating scales for side effects ON minus OFF the drug; zero indicates no change in rating. Headache ratings were higher on cabergoline (uncorrected p=0.03). Headache ratings did not correlate with the measures of interest which were modulated by cabergoline, suggesting that side-effects could not explain the findings. **B**) Rating scales for mental state showed no differences on or off the drug. **C**) We found no systematic differences in blood pressure or pulse on drug and placebo sessions.

4.3.6.2. Trait measures

Previous studies have shown that certain dopamine receptor polymorphisms correlate with behavioural traits (Ebstein et al., 1996; Munafò et al., 2008), and may underlie propensities to impulsive behaviour. We therefore asked whether questionnaire-based impulsiveness trait measures could predict the effects of D2 receptor stimulation in our participants.

We first computed the three BIS questionnaire factors (attentional, motor and planning impulsiveness) and four UPPS subscales (premeditation, urgency, sensation-seeking and perseverance). For each of these seven measures, we performed linear regression against reaction time, velocity, error rate, and reward sensitivity measures. There were no significant correlations with BIS or UPPS traits, and no interaction with cabergoline. Thus the personality traits we measured did not explain variability between subjects in reward sensitivity or effect of cabergoline.

4.4. Discussion

We manipulated reward expectation in a saccadic distraction task and examined the effects of cabergoline, a dopamine receptor agonist with high selectivity for D2 receptors, using a double-blinded placebo crossover design. Participants had to shift gaze to a target while avoiding a distractor, but on a substantial proportion of trials they erroneously looked at the distractor. When high rewards were available, there was speeding both of reaction times and velocities of eye movements. Cabergoline slowed saccade velocities, specifically only on the trials where incentives were low (**Figure 4.3A**). Tonic dopamine D2 receptor stimulation thereby *increased sensitivity* of saccade velocity to rewards.

Correct saccades sometimes curved towards or away from the distractor, a measure which can provide a sensitive index of the influence of the distractor (Hickey and van Zoest, 2012b; Mulckhuyse et al., 2009). Curvature away from the distractor was increased by high incentives. Although cabergoline did not affect accuracy or reaction times, it decreased curvature away from the distractor. This was most evident for early correct trials; for late error trials, cabergoline caused curvature towards the target.

4.4.1. Dopaminergic effects on saccadic velocity and RT

Our finding that reward speeds saccade velocity is in keeping with recent studies of rewarded prosaccades in monkeys (Chen et al., 2013) and saccades towards rewarding images in humans (Xu-Wilson et al., 2009). A dopaminergic basis for such effects has been suggested (Niv et al., 2007; Shadmehr et al., 2010b), in which tonic dopamine levels signal the ongoing reward rate of a task, thus indicating the "missed opportunity

cost" of responding slowly. A naïve application of such vigour models might predict that a tonic D2 agonist would increase the optimal speed of movements. But dopamine is also thought to be maintained in a tightly balanced range, where both excesses and deficits of dopamine can lead to detrimental effects, on either side of an optimal 'sweet spot' (Clatworthy et al., 2009; Seamans and Robbins, 2010), perhaps under the control of presynaptic activation of D2 receptors.

Our finding that D2 activation selectively slows saccades when incentives are low is therefore doubly interesting, showing both an increase in reward sensitivity, but a reduction in the "motivational value" of low rewards. This might be predicted if the indirect pathway signalled recent rewards, as in recent computational models (Morita et al., 2013). Physiologically, D2 agonists may block the indirect pathway's response to weak cortical inputs, but have no effect on strong inputs (Azdad et al., 2008). I conjecture that D2 stimulation of the indirect pathway might gate the reward-cue signal from the cortex, specifically when the reward is small, thus reducing the motivation conferred by the cue. Against this explanation, there is evidence in monkeys that D2 *blockade* can also increase reward sensitivity of saccadic RT, as measured in a simple saccadic paradigm (Nakamura and Hikosaka, 2006), suggesting that the story is more complex.

4.4.2. Dopamine alters curvature

We found net curvature away from distractors, as in other studies (Doyle and Walker, 2001; Godijn and Theeuwes, 2002a), but on many trials saccades also curved towards the distractor (**Figure 3.2**). "Repulsion" from the distractor was reduced on cabergoline (**Figure 4.4B**), supporting a role for dopamine in selection between afforded actions. D2 stimulation might decrease the efficiency with which the distractor is inhibited, by

reducing the competition between the two locations. This could also explain the seemingly paradoxical finding that on cabergoline, although correct saccades curve less away from the distractor, error saccades are increasingly pulled toward the target (**Figure 4.5b**). Reduced competition, or reduced mutual inhibition, between the target and distractor could explain these findings.

Saccadic curvature has previously been explained in terms of simultaneous activation of two movement plans (Aizawa and Wurtz, 1998; Mannan et al., 2010; McPeek and Keller, 2001). How might dopamine affect this? Predictive coding accounts have postulated that dopaminergic stimulation could increase the precision of representations of actions guided by bottom-up signals, promoting distractibility (Friston et al., 2009, 2012; Galea et al., 2012). In our task, this might increase the pull of both the target and the distractor, causing both movements to be simultaneously activated. This would account for both the curvature, and faster error correction.

4.4.3. Lack of effect on RT

If cabergoline reduced the mutual inhibition between target and distractor, it ought to result in prolonged RTs (Godijn and Theeuwes, 2002b), as predicted by integration models of decision making (Kopecz, 1995; Usher and McClelland, 2001). We did not find significant slowing, and error corrections were in fact faster, on cabergoline. D2 blockade *slows* saccadic RTs in primates (Nakamura and Hikosaka, 2006) and computational models of the indirect pathway predict speeding with D2 stimulation (Morita et al., 2013). This could explain why, despite greater concurrent activation (as evidenced by curvature), we see no slowing in RT.

Our task is closely related to an antisaccade task, since at the moment of appearance of the first onset (the distractor), participants can plan a saccade to the other location, which will become the target. The advantage of our task is that the information about which location is the target does not remain on the screen—information is given only by the order of onset. Once the target appears, the two locations become indistinguishable. Therefore, any in-flight corrections must be made on the basis of information already present before the saccade began. Curvature, in our task, cannot be generated by new, incoming information about which location is the target. This affords a pure measure of the time course of activation of control mechanisms.

4.4.4. Cabergoline shortens error correction latency

We found that on cabergoline, the interval between the start of an error saccade, and the start of the subsequent error-correction saccade, was shortened. This suggests that D2 stimulation improved either error detection or correction. This stands in contrast to one previous study that found increased error rates with the D2 agonist pergolide (Rammsayer and Stahl, 2006); in that study, the drug shortened the latency of the stimulus-locked evoked potential indicating enhanced stimulus processing. Their task was not designed to examine error-related potentials, but a plausible mechanism of error detection may involve dopaminergic prediction-error signals (Holroyd and Coles, 2002; Frank et al., 2007). Our result suggests that stimulation of D2 receptors may potentiate such an error signal, facilitating the generation of an error correction response.

4.4.5. Limitations

Could the velocity-slowing effect of dopamine be due to a general reduction in attention? This seems unlikely for two reasons. Firstly, our state questionnaires showed

no evidence for any effect of drug on alertness, arousal or mood. Secondly, cabergoline did not significantly increase RTs or RT variability, which are commonly taken to indicate reduced attentional arousal, vigilance and alertness (Paus et al., 1997; Stuss et al., 1989). This suggests that tonic D2 stimulation does not globally worsen performance. Thus slowing of velocities by cabergoline appears specifically coupled to the low incentive.

A more serious worry is whether our study was underpowered to detect an interaction between reward and cabergoline in RT and capture rate. For our group of 19 subjects, the standard error of the RT change between sessions was 5.5 ms, but the estimated effect size in this kind of drug study is uncertain. Moreover we deliberately used a relatively low dose of drug, to avoid side effects that might make any findings uninterpretable. We would argue that the presence of positive findings of *reward* on RT, and of cabergoline on curvature, suggest that any interactive RT effects of cabergoline with reward ought to be visible.

Questionnaire measures raise the possibility that subjects experienced more headache on cabergoline, which might confound the drug effect. I argue this is unlikely because there was 1) no corresponding effect of the drug on mood, 2) no correlation between headache score and size of drug effect, and 3) no *a priori* reason why headache might increase reward sensitivity.

Although pupil data was obtained in this experiment, cabergoline constricts the pupil. It was therefore difficult to interpret reward effects, due to large baseline shifts on the drug.

4.4.6. Conclusion

The D2-selective dopamine agonist cabergoline caused significant changes in the programming of eye movements, as measured by a saccadic distractor task. It had a reward-specific effect on saccade velocity, such that under low-reward conditions, dopaminergic stimulation selectively slowed saccade velocities. Cabergoline attenuated the repulsion effect of a salient distractor, irrespective of motivational state, without a measurable effect on the distractor's pull. These findings support a role for dopamine in signalling motivational vigour in motor programming, but also suggest that D2 stimulation increases conflict in selecting saccades to targets over distractors.

5. Effect of Parkinson's disease on saccades

5.1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is now known to be characterised by depletion of dopamine in several brain regions, including the substantia nigra (Jankovic, 2008). Cognitive changes are a clinically important dimension of PD, and include disorders of perception, learning, memory, executive control, mood and attention (Lange et al., 1992; Levin and Katzen, 1995; Litvan et al., 2011; Manohar et al., 2013; Owen et al., 1992; Shiner et al., 2012a). In particular motivational changes are increasingly recognised: pathological impulsivity is seen in about 14% of patients (Weintraub et al., 2010), and apathy in up to 60% in later stages of the condition (Starkstein, 2012). The motivational aspect is of considerable interest, as studying it may help tie together the motor and cognitive aspects of frontostriatal physiology (Ravizza et al., 2012).

A key feature of motivation is that it is not constant; even for the same task, it can vary from moment to moment, depending upon incentives. Current theories of response vigour suggest that *tonic* dopamine signals average reward rate, and causes rates of responding to increase when reward yield is higher (Mazzoni et al., 2007; Niv et al., 2007). Vigorous responding in animals is associated with increased tonic levels of dopamine (Niv et al., 2007; Salamone and Correa, 2002), and slowing in PD has previously been characterised as a failure to energise responses (Mazzoni et al., 2007; Shadmehr et al., 2010b). In this framework, reward expectation and tonic dopamine should *both* act to increase motivation, shortening response times.

One prediction of vigour theory is that when dopamine is depleted, motivation will be globally reduced, resulting in an apathetic state (Sinha et al., 2013), and insensitivity to reward. Vigour has previously been measured in PD using reaction times and movement speed (Mazzoni et al., 2007). These investigators found that PD patients are more sensitive to the cost of movement energy, when selecting arm movements. In summary, vigour theory predicts dopamine deficiency will lead to slow movements because effort is more costly.

However, an alternative explanation of slowing could be *increased noise* in a decision process (Cohen et al., 2002). Dopamine is thought to improve the signal-to-noise ratio by steepening the gain function at corticostriatal synapses (Da Cunha et al., 2012; Lewis and O'Donnell, 2000). Increasing the nonlinearity of cells in an integrator network (Gruber et al., 2006; Humphries et al., 2009) would lead to a system that is "biased to action", i.e. neurons will rapidly converge to an upper or lower threshold. Conversely, reducing the nonlinearity would slow down convergence, favouring intermediate states (Frank, 2005; Grossberg, 1988).

From a decision-making perspective, this suggests that dopamine might *increase decisiveness*. In contrast, a deficit of dopamine would bias a system to deliberate for longer. In decision terms, PD would increase the decision criterion, or threshold, for choice (Bogacz et al., 2006). Similar thoughts about dopamine have been raised in terms of the "precision" of population codes: a lower precision in predictive coding of action would lead to slowness of action (Friston et al., 2009). According to these views, then, dopamine deficient states might lead to slower and suboptimal action selection, because of increased noise in the decision-making process.

In order to distinguish between the vigour and noise hypotheses, I examined distractibility. Computational models predict that if dopamine increases the nonlinearity, or decisiveness, of the neuronal transfer function, it would make attractor neural networks *resistant to distraction* (Brunel and Wang, 2001). In keeping with this, deficits of selective attention are increasingly recognised in PD, most likely due to the hypo-dopaminergic state. A combination of deficits has been described, including increased distractor interference and attentional capture by salient stimuli (Botha and Carr, 2012; Briand et al., 2001b; Chan et al., 2005; Deijen et al., 2006; Zhou et al., 2012) as well as reduced cueing effects and impaired pop-out search (Filoteo et al., 1997; Mannan et al., 2008; Nys et al., 2010; Rodríguez-Ferreiro et al., 2010; Sampaio et al., 2011a; Troscianko and Calvert, 1993). Related effects are seen in reversal learning tasks: when a new feature must be selected, switching attention to a new feature-dimension is impaired by PD (Cools et al. 2010).

One explanation for effects observed on learning tasks invokes the role of dopamine in signalling reward (Frank 2005; Schultz 2007; Cools et al. 2009). Reversal learning has been shown to be sensitive to dopamine both in healthy volunteers and in PD (Bodi et al., 2009; Cools et al., 2006; Frank and O'Reilly, 2006; Shiner et al., 2012a), consistent with the role of dopamine in signalling phasic *reward prediction errors* in learning (Schultz et al., 1997; Steinberg et al., 2013). For example, probabilistic learning is reduced in unmedicated PD, e.g., for implicit sequences, categorisation and classification (Knowlton et al., 1996).

Dopaminergic treatment restores motor function but may "overdose" other regions of the basal ganglia which are relatively spared in PD, for example the ventral striatum. So in contrast, PD patients ON medication show impaired reversal learning—

as predicted by a connectionist model of dopamine in frontostriatal loops (Frank, 2005; Knowlton et al., 1996; Poldrack et al., 1999). Interestingly, such models of learning from rewards also suggest a role for dopamine in filtering, particularly for *preventing distractor interference* (Frank et al., 2001; Gruber et al., 2006; Machado et al., 2009; McNab and Klingberg, 2008).

If dopamine serves a dual purpose, both signalling reward and preventing distraction, one might expect rewards to modulate distraction. In healthy people, incentives do indeed influence distractibility: increasing attentional capture by salient stimuli associated with reward (Anderson et al., 2011a; Hickey and van Zoest, 2012b; Hickey et al., 2006; Kiss et al., 2009a) *and* reducing distractibility when incentives are high (Rothkirch et al., 2013; Schütz et al., 2012b). Do these effects of reward on distraction depend upon dopamine?

If so, then firstly, we might make the following predictions:

1) Distractibility in PD patients is modulated both by reward and by their dopaminergic state.
2) PD patients should have reduced sensitivity to distraction by rewards.
3) If dopaminergic drugs generally raised motivation levels, medication might improve reward sensitivity (Beierholm et al., 2013), due to *tonic* dopaminergic stimulation. However, if motivation were dependent on *phasic* dopamine signals, we might not expect drug effects on motivation.

In this study, I used a task that varies incentives while measuring oculomotor capture (as in chapters 3 and 4), to quantitatively measure the capture of attention by visually salient distractors. I measured distractibility of eye movements (oculomotor capture) in patients with PD while 'ON' and 'OFF' their normal dopaminergic medication, in two

separate sessions. To study dynamic changes in motivation level, participants were offered different reward incentives on each trial. This design allows examination of all three predictions described above.

In addition, I also used pupillometry to measure pupil responses to current and previous incentives, as well as past winnings. This measure potentially provides a probe of reward sensitivity and its modulation by dopamine without relying solely on measuring the vigour of action execution as our index of sensitivity. In addition, two control saccadic tasks (prosaccades and antisaccades) were also run to examine whether any effects on the oculomotor capture task might be explained simply by changes observed in these saccadic paradigms.

5.2. Oculomotor capture task

5.2.1. Methods

5.2.1.1. Participants

We studied how oculomotor capture was modulated by incentives in 16 patients with mild or moderate PD. Patients who fulfilled the criteria for the Queen Square Brain Bank for PD (Gibb and Lees, 1988; Hughes et al., 1992) were recruited from the neurology clinic at the National Hospital for Neurology and Neurosurgery. The mean UPDRS was 21.7 (s.d. 10.3). All patients were on medication; 11 were taking levodopa, and 9 were taking a dopamine agonist. The mean levodopa equivalent dose, calculated from standard conversions (Tomlinson et al., 2010) was 532 mg.

The mean age of the patients was 65 yrs (s.d. 9.8); the 22 control participants had a mean age of 62.4 (s.d. 8.9). Cognitive impairment was screened for using either

Montreal cognitive assessment (MoCA, Nasreddine et al., 2005) ≥ 26 or mini-mental state examination (MMSE) score ≥ 26; two patients had mild cognitive impairment with MoCA scores of 25. Two patients did not have cognitive tests but were still in full-time work. Digit span forwards and backwards was measured in the first session. Depression was excluded using the Hospital Anxiety and Depression scale (Zigmond and Snaith, 1983). All patients had normal or corrected-to-normal colour vision. Symptomatically, 2 patients had significant functional impairment as determined by Schwab and England ADL score (one patient 50%, one patient 60%, all other patients 80% or above).

5.2.1.2. Sessions

Each patient attended on two sessions, once ON medications, and once OFF medications, with the order randomised across patients. The mean time between the two sessions was 2.3 weeks, with a minimum of 1 week. Testing was at 9 am for most patients, and was always at the same time of day for both sessions, to match for diurnal variation. For the ON session, patients took their normal medications; all patients were on at least one morning tablet, either levodopa or a dopamine agonist. For the OFF session, patients omitted the morning tablets, and had taken their last dose of dopaminergic medication at least 12 hours before the session.

5.2.1.3 Oculomotor capture task

The oculomotor capture task was similar to that of Chapter 3 (Study 3.4). The distractor onset was fixed at 80 ms before the target. All patients performed 4 blocks of the task, giving 216 trials, with 72 trials per reward level.

5.2.2. Results

Participants had to look as quickly as possible towards the target, while avoiding an early onset distractor. Saccades were parsed as previously and classified based on endpoint. This enabled detection of oculomotor capture, measurement of peak saccade velocity, reaction time from target onset to start of saccade, and curvature of saccade trajectory.

5.2.2.1. Error rates showed reduced reward sensitivity in PD

Distractibility was quantified as the proportion of trials on which the eyes were captured by the distractor (oculomotor capture). Healthy control participants were distracted on average on 27.5% of trials (± s.e.m. 3.5%), whereas PD patients ON medication were captured on 22.3% (±3.4%), and OFF medication, 19.5% (±2.4%).

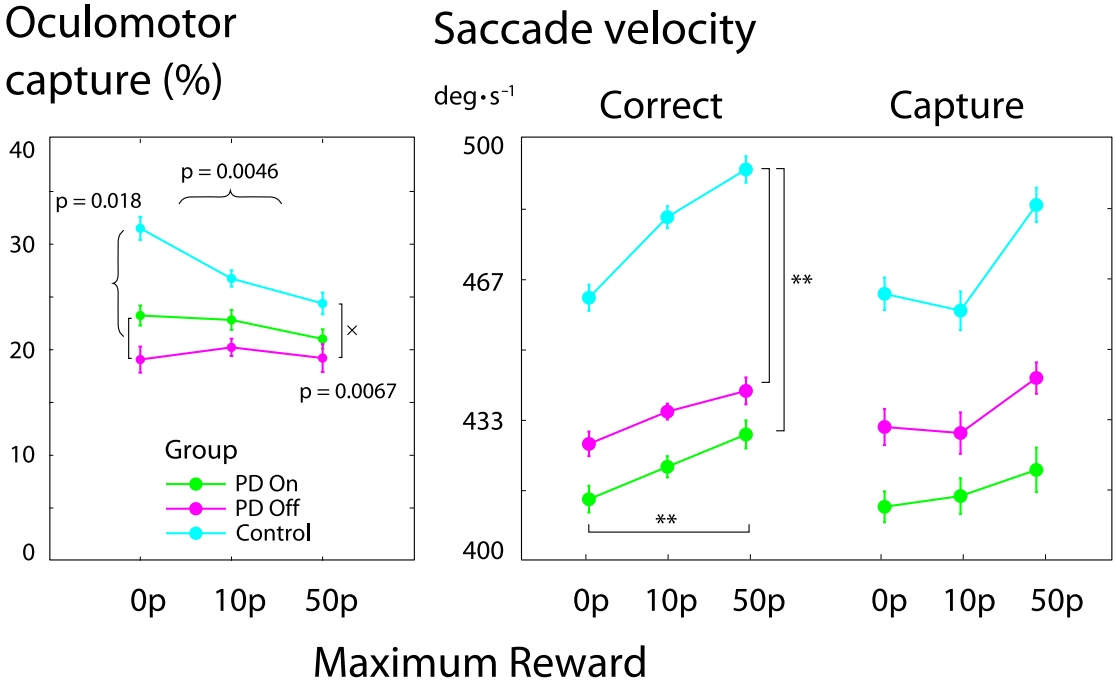


Figure 5.1: Performance across groups on capture (error) rate and peak saccade velocity **A**) PD patients made fewer errors than controls, but their error rates did not show the normal reduction with reward (interaction p=0.033). **B**) Saccade velocity for correct and capture trials.

Reward speeded velocities in all groups, but PD patients were significantly slower than controls ($p<0.001$). There was no significant effect of drug.

To compare the proportion of capture between groups, and to measure the effect of reward, a nested three-factor mixed-model ANOVA was used with reward level, group (PD *vs*. control) and drug (ON or OFF) with session order as a covariate. This analysis showed that, over all groups, reward significantly reduced capture errors (arcsine transformed, $F(1,115)=8.35$, $p=0.0046$), and that PD patients on average significantly made fewer errors than controls ($F(1,115)=5.94$, $p=0.018$). Additionally there was an interaction between reward effect and group, in that PD patients had *reduced sensitivity* to rewards compared to controls, observed as shallower slopes in **Figure 5.1A** ($F(1,115)=4.64$, $p=0.033$).

Follow-up pairwise ANOVAs separately compared PD ON medication or OFF medication with controls. PD patients OFF medication were significantly less sensitive to rewards than controls ($F(1.72)=7.80$, $p=0.0067$), but no reward interaction was seen for PD ON *vs.* controls. A within-subject ANOVA for PD ON *vs*. OFF did not reveal any effect of drug or interaction with reward. Thus, although higher incentives reduced distractibility, PD patients were generally less motivated by incentives than controls, as indexed by capture (error) rate.

Capture i.e. Error rate (s.d.) / %	Low reward	Medium reward	High reward
Controls	31.5 (3.7)	26.8 (3.6)	24.4 (3.6)
PD ON	23.2 (3.7)	22.8 (3.5)	21.0 (3.3)
PD OFF	19.1 (2.8)	20.2 (2.7)	19.2 (2.5)

Table 5.1: **Proportion of oculomotor capture (error) rate in each condition.** Values are averages over subjects for each group. Controls showed modulation by reward, but patients did not. There was no significant difference between patients ON and OFF medication, and no interaction, using a paired F-test.

5.2.2.2. Saccade velocity slowed in PD

A key finding, across all groups and within each group, was that peak velocity of correct saccades was speeded by reward ($F(1,115)=13.7$, $p<0.001$; **Figure 5.1**), in keeping with the results from Chapters 3 and 4. Control participants had higher velocities than patients, and pairwise comparisons showed that this was true whether patients were ON or OFF medication ($F(1,72)=6.62$ and 5.09, $p=0.014$ and 0.030 for ON and OFF respectively). Moreover, there was an interaction between group and reward, in that patients had significantly greater reward sensitivity than controls ($p=0.006$, $F(1,105)=8.05$). There was no effect of drug state, and there were no interactions with reward, indicating that reward sensitivity was not significantly altered, at least as in terms of saccade velocity, on dopaminergic medication. A similar pattern was observed for error saccades, i.e. those in which there was oculomotor capture.

5.2.2.3. PD patients have reduced sensitivity of RT to reward

Mean RTs of correct trials for control subjects were 315 ms (±s.d. 66 ms between subjects), compared to 372 ms (±110 ms) for PD patients ON medication, and 378 ms (±126 ms) OFF medication (**Figure 5.2**). RTs on correct trials was analysed as in

chapter 3. They demonstrated a trend for patients to be slower than controls ($F(1,115)=3.45$, $p=0.071$), but there was no significant effect of reward on RT, and no group interaction ($F<1.8$, $p>0.18$). RTs were speeded by practice ($F(1,115)=112$, $p<0.001$).

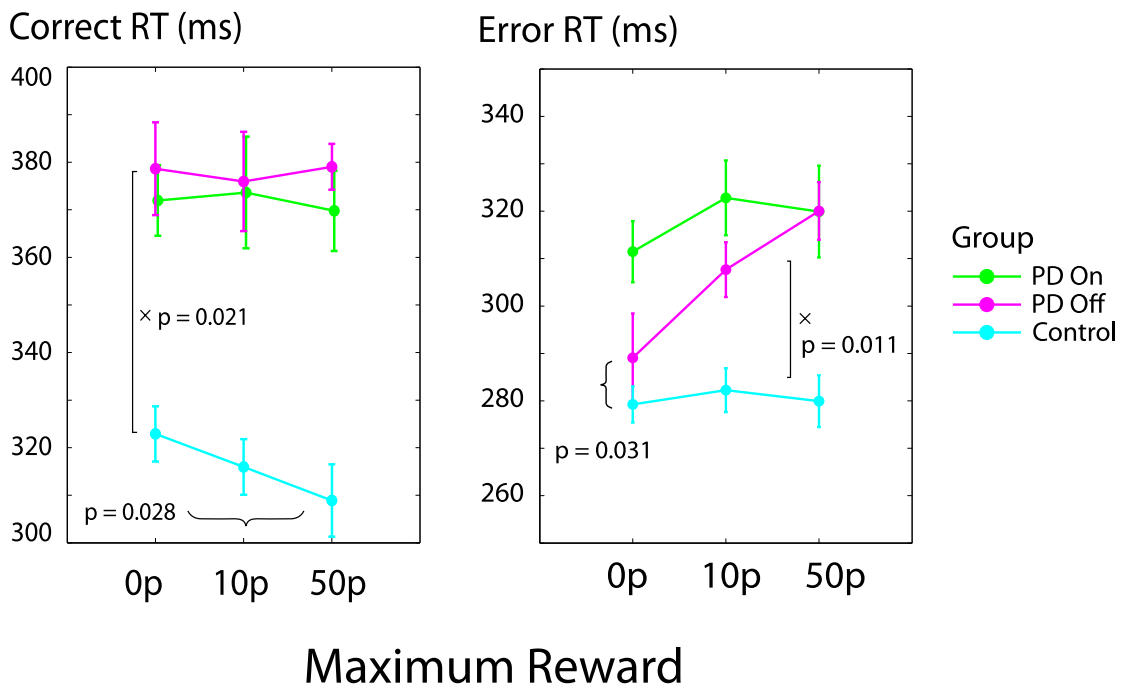


Figure 5.2: Reaction times show decreased reward sensitivity in PD

A) PD patients RTs were slower than controls, but they did not show the normal speeding with reward (interaction p=0.021). **B**) PD patients error RTs were also slowed compared to controls, but they were even slower when on medication (effect of drug p=0.031). When off medication, PD patients were more sensitive to rewards than controls (interaction of reward and drug, p=0.011).

Pairwise ANOVAs for PD OFF *vs*. controls showed a main effect of reward on reducing RTs ($F(1,72)=5.0$, $p=0.028$), so participants had shorter RTs when there was a greater reward on offer on a trial. There was also a significant interaction between reward and group ($F(1,72)=5.71$, $p=0.021$), with no effect of group, indicating that PD patients OFF medication were *less reward sensitive* than controls. Comparing PD ON with controls did not give rise to a significant interaction ($F(1,72)=3.54$, $p=0.06$), and

the within-subject comparison of patients ON and OFF showed no significant effects (all $p>0.5$). Thus, in terms of reaction time, PD patients OFF medication were significantly less reward sensitive than controls, but this was not the case when ON medication.

RT on capture trials was faster than on correct trials, consistent with previous findings (see chapter 3). However, capture RT was slowed down by medication in PD patients (effect of drug, $F(1,115)=4.74$, $p=0.031$). There was no overall effect of group, and no interaction with reward. There was no significant effect of PD ON *vs.* control, but the comparison of PD OFF to controls showed a significant interaction of group × reward, indicating PD OFF had *increased* reward sensitivity compared to controls ($F(1,72)=6.90$, $p=0.011$). In particular, in the no-reward condition, PD patients OFF medication had faster error RTs than controls. Thus lower incentives led to earlier distraction, specifically in patients OFF medication.

In order to examine the time-dependence of the reward effect, I used a delta plot to examine changes in the shape of the RT distribution (Ridderinkhof et al., 2004b, **Figure 5.3**). My method improves on previous approaches by removing the arbitrary assignment of bin edges. For each RT quantile, the difference between the reward conditions was calculated. This gives the effect of reward for each RT bin, as the 'delta' between two RT distributions. The delta function, i.e. the effect of reward over time, was calculated for each subject, aligned by quantile, and bin centres were averaged across subjects to obtain the mean delta and standard error across subjects.

On the graph, positive values signify that reward shortens the RT of saccades at a given quantile in the distribution. Delta plots thus give a sensitive analysis of how effects evolve in time during the response period (Wylie et al., 2009). Whereas controls

(blue) have positive values throughout the reward period, indicating shorter RT with rewards, patients OFF do not differ from zero, indicating no effect of reward on RT for any part of the RT distribution. The null hypothesis, that there was no effect of reward at any RT, was tested by permutation, and times at which $p<0.05$ are shown in **Figure 5.3**. The plots therefore demonstrate that reward insensitivity in PD is a feature throughout the response period.

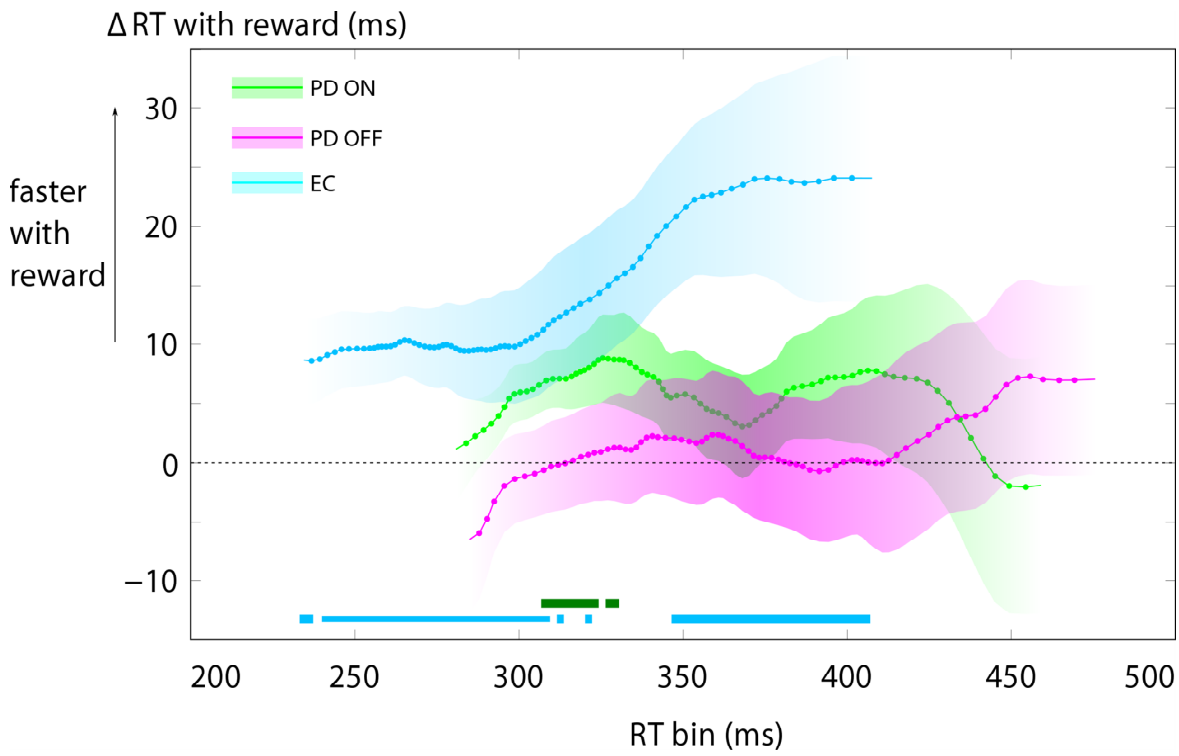


Figure 5.3: Delta plot of reaction time in PD and controls

The plot shows reward sensitivity as a function of time during the trial. For each RT bin, the RT difference between high and low reward trials is shown. A positive value means that saccade latency is shorter with higher reward. Healthy volunteers show earlier responding when rewards are high compared to when they are low (blue curve, negative values) throughout the response period, indicating incentivisation by reward. PD patients showed no significant speeding by reward when OFF (magenta). Bars below represent times at which $p<0.05$ by permutation test.

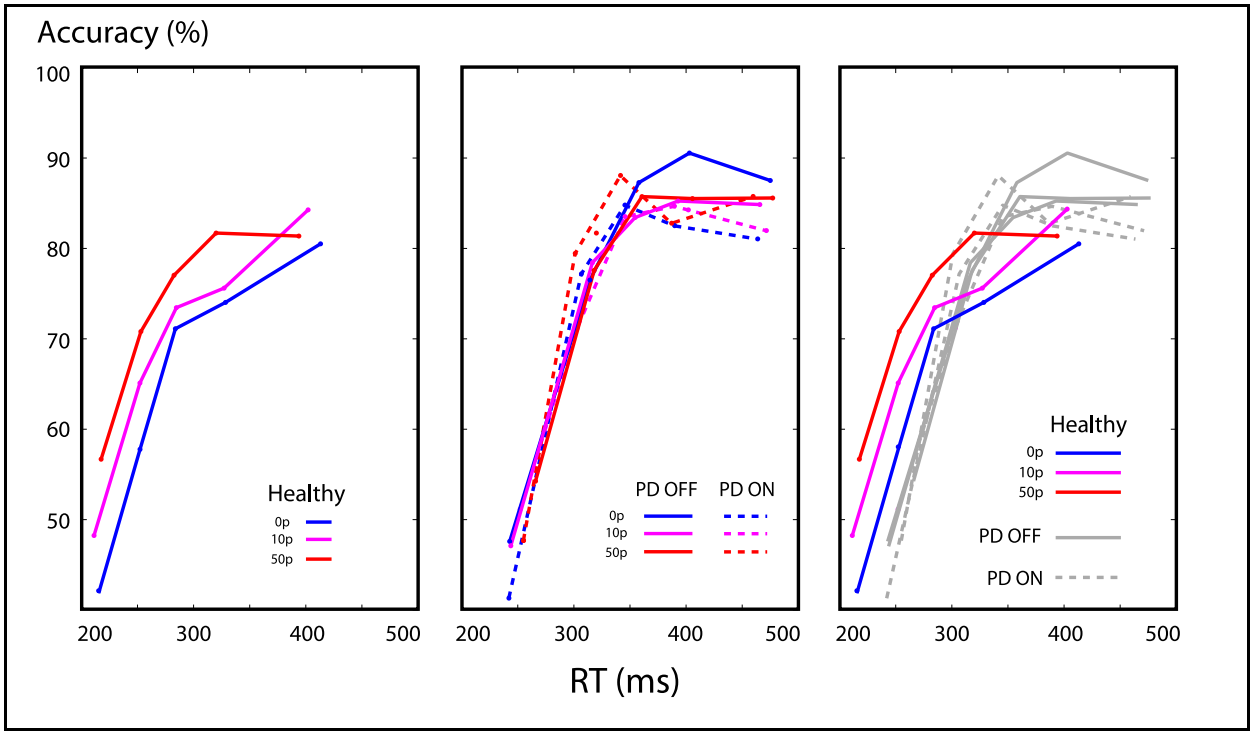
5.2.2.4. PD patients more accurate than controls, but only for slower responses

Why are PD patients *less distractible* than controls? It is well known that short-latency saccades are more likely to go towards distractors (Wijnen and Ridderinkhof, 2009), so we might expect that simple slowing associated with PD might result in reduced distraction. By calculating the likelihood of capture for saccades initiated at different times, we can examine the *timecourse of distractibility*. In order to determine if PD patients' improved accuracy was due simply to their being slower, all saccades were collated in each reward condition, and distributions were Vincentised (Ratcliff 1979) using overlapping bins one-fifth of a quantile wide. For these RT quintile bins, the proportion of saccades without oculomotor capture ('accuracy') for each bin was plotted (conditional accuracy function, **Figure 5.4**). The abscissa shows the mean RT of each bin; slowing due to PD is evident as a rightward shift of the curve here.

The resulting conditional accuracy function was similar both ON and OFF dopaminergic medication, but showed three striking differences compared to age-matched controls. Firstly, the shortest latency responses were no more accurate than controls, *despite being slower by around 40 ms*. Thus PD-related slowing in and of itself cannot explain the accuracy benefit.

Secondly, for slower saccades (at the 3rd and 4th quintile bins), PD patients were more accurate than controls—even at similar latencies, of around 350 to 400 ms. If the increased accuracy observed in PD were due simply to slowing, we would expect that early saccades would show the greatest improvement in PD. However, the greatest increase in accuracy is seen in later time bins. Thus, the improved accuracy at later durations is not attributable solely to the fact that patients are slower than controls.

Finally, trials were also broken down according to reward level. The curves demonstrate that patients, unlike controls, lack reward sensitivity at all response latencies. Continuous versions of the conditional accuracy function were created using the sliding window technique, and statistical comparison of the ON and OFF states was performed using permutation tests (**Figure 5.4**D and E). Medication reduced accuracy in a short time window from 360 to 450 ms ($p<0.05$).



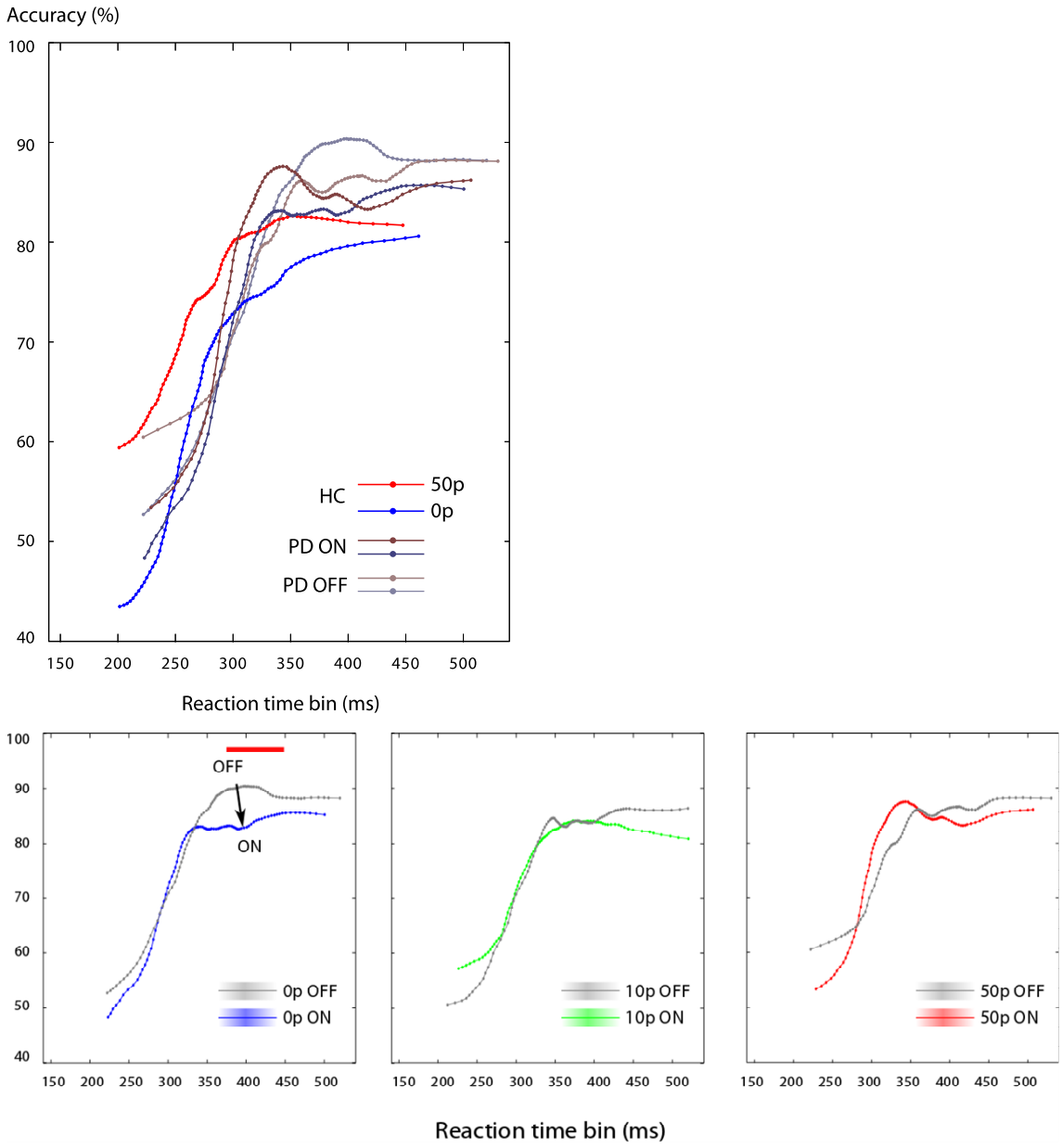


Figure 5.4: Conditional accuracy function for 3 levels of reward

For each subject and condition, trials were binned according to RT quintile, and accuracy (1 – capture rate) was calculated for each bin. **A**) Reward-modulation in healthy controls. **B**) Lack of modulation by reward in PD, and no difference between patients ON and OFF their dopaminergic medication. **C**) Comparison of PD patients and controls. At their slowest reaction times, patients were less accurate than controls at comparable speeds. At faster reaction times, they were more accurate than controls at comparable speeds. Therefore a speed-accuracy trade-off alone cannot explain patients' improved accuracy. If speed-accuracy trade-off explained the results, it would be demonstrated by the patients' curves largely overlying control curves.

D) Continuous-valued delta plot of the same data, showing clearly the early effect of reward on accuracy in controls, and the differential effects of PD upon fast and slow RT bins. **E**) Same data shown to compare PD patients ON and OFF medication, for each reward level. Red bar shows p<0.05 by permutation test.

5.2.2.5. Reward-related curvature away from distractors reduced in PD

Curvature was calculated as in chapter 4. The curvature of correct saccades did not show an effect of reward, nor of group, nor of drug. However, there was a significant interaction between reward and group, in that reward had different effects on curvature in PD and controls (**Figure 5.5A**, F(1,114)=5.49, p=0.021). Individually comparing PD OFF with controls showed this same interaction with reward. In controls reward induced a net curvature *away* from the distractor, but the effect of reward was opposite in PD OFF (F(1,72)=5.01, p=0.028) with a similar trend in PD ON (F(1,72)=3.94, p=0.051).

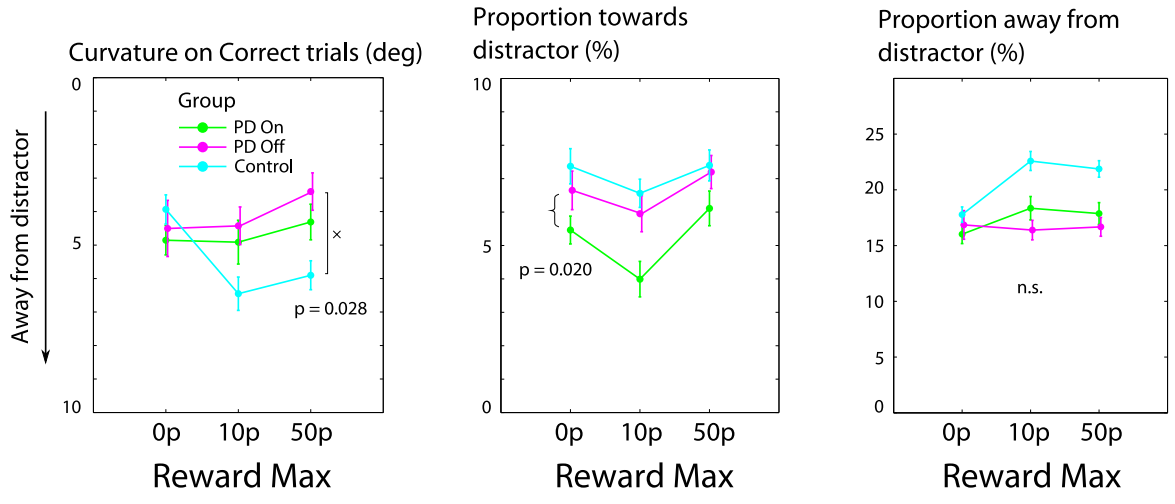


Figure 5.5: Dopaminergic medications reduce curvature towards distractors
A) Controls show less saccadic curvature when incentives are high. PD patients lack this modulation by reward (interaction p=0.021). **B**) The proportion of saccades that curved towards the distractor was reduced in PD patients on dopamine (p=0.020). **C**) The proportion of saccades that curved away from the distractor was unaffected by drug or reward.

To examine whether this curvature effect was due to increased distractor pull or decreased repulsion, the curved saccades were subdivided into those that curved towards and away from the distractor. Saccades that curved *towards* the distractor were fewer in patients ON medication, compared to OFF (**Figure 5.5B**, $F(1,71)=6.93$, $p=0.010$). There was no significant difference between patients and controls, no effect of reward, and no interaction. For saccades that curved *away* from the distractor, there was no effect (**Figure 5.5C**, all $p>0.05$). In other words, patients had less reward-related curvature away from the distractor overall, but dopaminergic medication helped to reduce the proportion of saccades that curved towards the distractor.

As in the previous chapter, we examined individual trajectories as a function of time during the saccade (**Figure 5.6A**). On average saccades curved away from the distractor. Linear regression was used to extract the effects of reaction time, incentive, and previous trial winnings and incentive, and time on task upon curvature. A positive value means that as the variable of interest increases, the saccade curves more away from the distractor. A negative value means that the saccade curves towards the distractor as the variable increases. Thus, the green curve demonstrates that even within the first quarter of the trajectory, the saccade is more likely to be repelled by the distractor when the previous incentive was high, compared to when it was low. The magenta curve's positive deflection demonstrates that on trials where the saccade was initiated later, i.e. longer saccadic latency, the saccade is repelled by the distractor, during the final part of the movement.

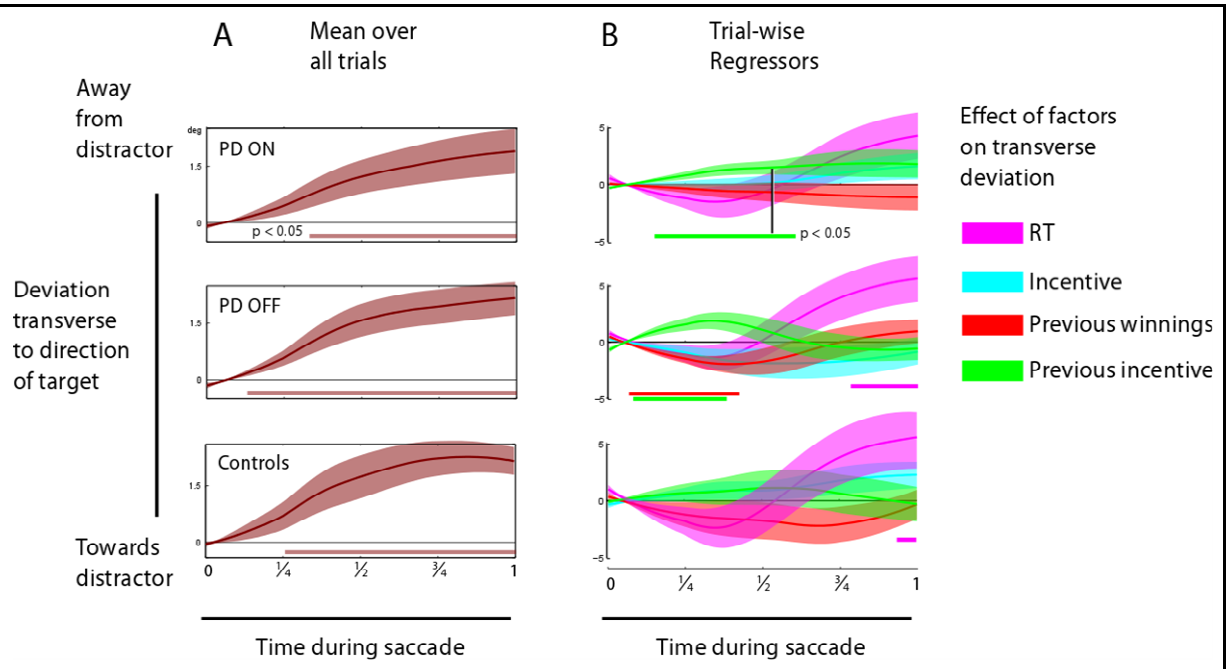


Figure 5.6: Averaged saccade trajectories for correct trials

Trajectories are shown as a function of time during the saccade, comparing PD ON and OFF with matched controls. A) Overall saccades curved away from the distractor. Positive deflections indicate curvature away from the distractor. B) Effect of reaction time, incentive, previous winnings and incentive, and time on task on the trajectory. Positive values indicate that the factor causes increased curvature away from the distractor, and negative values indicate increased distractor pull. Patients have significant effects of the previous incentive (green): previous high incentives cause repulsion from the distractor. When OFF, distractors have more pull after winning a high reward (red). Saccades with longer latencies tend to curve away from the distractor (magenta).

5.2.2.6. Reduced pupillary reward sensitivity in PD patients OFF medication

To examine reward sensitivity of the pupil to the auditory reward cue, the pupil size was fitted to a general linear model as previously described in section 3. Regressors for the current reward cue's value, the previous trial's reward cue, and the amount of reward actually received on the previous trial were included. A constant regressor and a time-on-task regressor (trial number) were used to remove the components that were independent of reward. Parameter estimates at each timepoint were calculated using

least squares. For the three reward regressors, a positive value of the parameter estimate indicates that higher rewards correlated with increased pupil size. For example with regard to current incentive, a positive value indicates that higher incentives led to relative dilatation of the pupil compared to lower incentives.

Healthy controls (**Figure 5.7D**) showed positive effects of the current incentive, and negative effects of the previous trial's incentive. This means that the pupillary dilatation increased with the current trial's incentive, but was reduced after a previously high-incentive trial. PD patients ON mediation showed similar modulation of the pupil in response to the current trial reward cue, but the effect was delayed (**Figure 5.7A**, first significant at 1105 ms in PD, whereas in controls and PD OFF it became significant at 562 and 708 ms respectively). In addition, when patients were OFF medication, this incentive response was blunted, and only remained significant for a 280 ms window. Despite the blunting, the latency was normal (525 ms).

ON medication, patients additionally showed pupillary sensitivity to the winnings on the previous trial, in the opposite direction of the previous trial incentive. That is, pupil size encoded the difference between what patients won, and what they *could have* won. Previous trial winnings did not influence pupil response in controls, nor in patients OFF medication (**Figure 5.7C**, difference between ON and OFF conditions, significant between 890–1250 ms). The encoding of the previous trial's incentive was relatively preserved in PD.

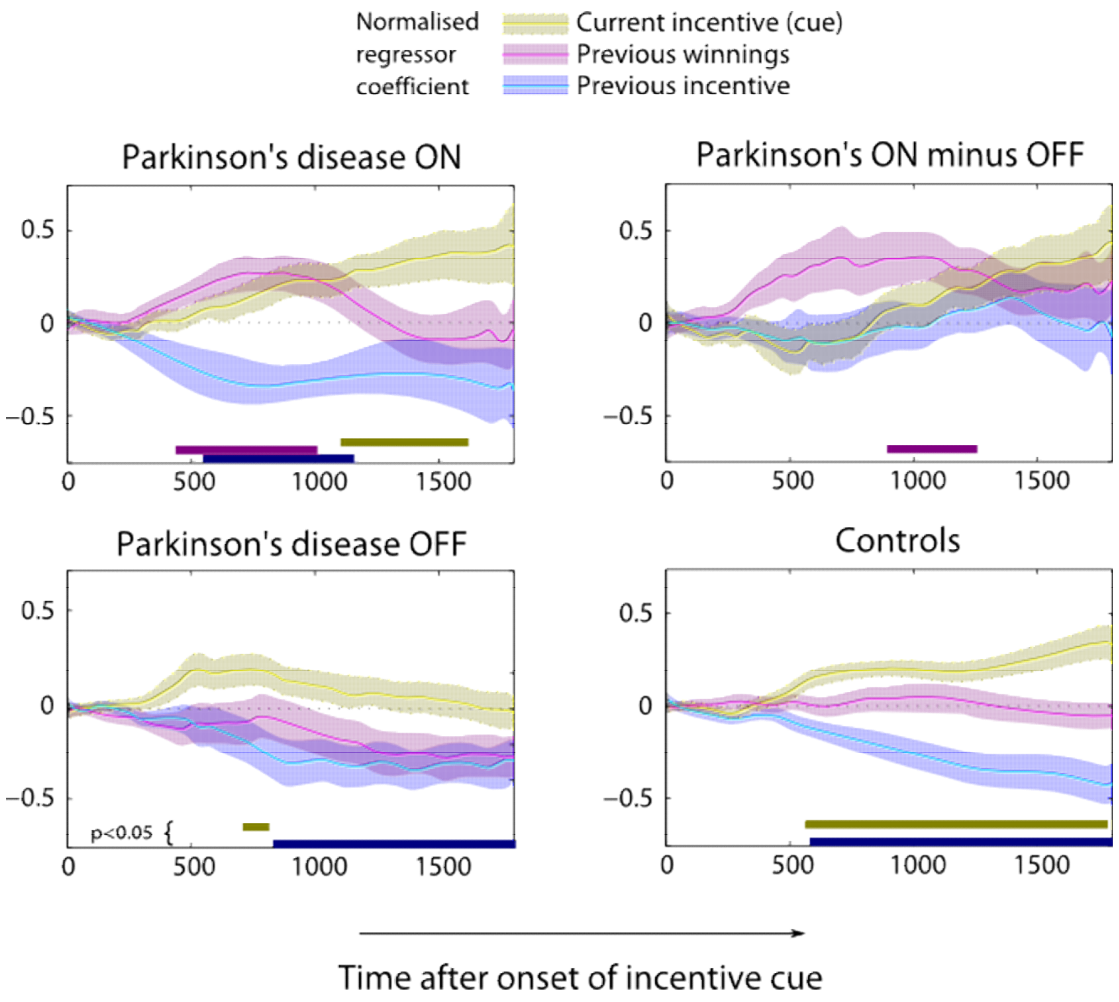


Figure 5.7: Pupil size after the reward cue is modulated by reward

Pupil size was analysed in the period following the reward cue. The vertical axis shows values of the regression coefficients, where positive values indicate that higher reward correlated with an increase in pupil size, and negative values indicate correlation with decreased pupil size. The yellow traces thus indicate the sensitivity of the pupil to current incentive, as a function of time, whereas pink and blue indicate the effect of previous trial winnings and incentive respectively. **A**) shows that PD patients ON medication show similar pupil sensitivity to incentive cues as controls (**D**) as evidenced by the up-going yellow trace. The positive deflection indicates that the pupil dilated more when the current incentive was high. **B**) shows that when PD patients were OFF medication, the pupil was less sensitive to incentive, with the yellow line not deviating far above from zero. **C**) shows the drug effect, A minus B. Medication increased pupillary responses to previous winnings. **D**) shows the normal pattern of pupillary response with larger pupil for higher current incentive, and smaller pupils for higher previous incentive. Shaded areas represent the standard error of the mean across subjects; for A-C, N=15; for D), N=22. Bars below the graphs indicate timepoints at which each regressor differed from zero (t-test, $p<0.05$).

5.2.2.7. No correlation with age or severity of PD

The slope of each individual's reward sensitivity function of peak saccade velocity when ON was uncorrelated with age (r^2=0.0003, p>0.05) and UPDRS score (0.025). The effect of drug on velocity was also uncorrelated with age (r^2=0.009) and UPDRS (r^2=0.002). The interaction term, which indicates the difference in reward slope when ON minus OFF medication, also did not correlate with age (r^2=0.051) or UPDRS (r^2=0.010).

5.3. Prosaccades and antisaccades in Parkinson's disease

The presence of distractors in PD has had varied effects on response times in previous studies (Deijen et al., 2006; Lueck et al., 1990; Terao et al., 2013). The slowing of saccades in PD that we observed in section 5.2 could have been due to the presence of the distractor, or could have been due to globally increased RTs, e.g. related to bradykinesia.

The prosaccade and antisaccade tasks were designed to be as similar as possible to the oculomotor capture task, with the exceptions of layout and the absence of reward. Thus they act as a control condition to provide baseline reaction times and velocities for reactive saccades and movements requiring endogenous control, which are aspects that may also be affected in PD (White et al., 1983).

5.3.1. Methods

Three dim discs were displayed on the screen: one central, and one 11 degrees to the left and to the right; each 4 degrees in diameter (**Figure 5.8**). Initially the central disc was brighter, and changed colour to yellow once fixation had been acquired for 500ms.

After a non-ageing foreperiod of between 500 and 1700ms (decay constant 400ms), the central disc dimmed and simultaneously either the left or the right disc brightened. In the prosaccade task, subjects were required to saccade to the disc that brightened; in the antisaccade task, they were required to saccade to the disc that remained dim. Once gaze arrived within 6.7 degrees of the target, the central disc was once again illuminated, and the next trial began.

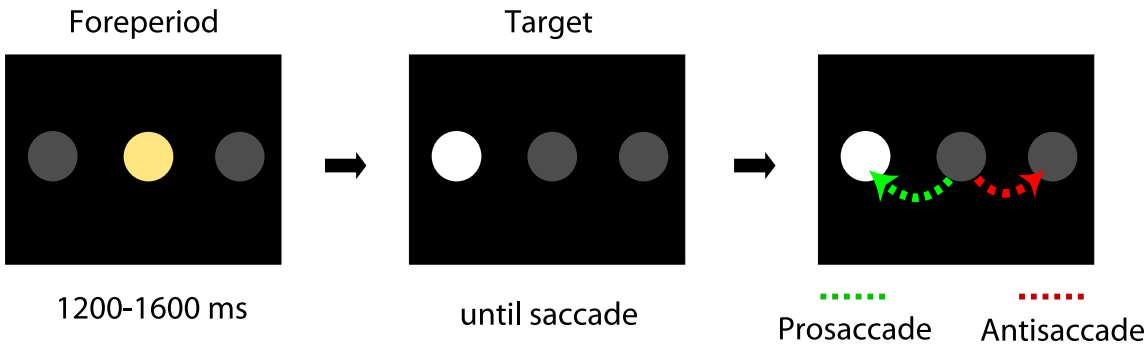


Figure 5.8: Prosaccade and antisaccade tasks
The stimuli were similar to those used for the oculomotor capture task. After 500ms of fixation, the central disc changed colour to indicate the start of the foreperiod. After a variable delay, one of the side discs was illuminated, and simultaneously the central disc was dimmed. In prosaccade blocks subjects had to shift their gaze to the illuminated disc, and after this the central disc was re-illuminated. In antisaccade blocks, subjects had to shift gaze from the centre to the opposite side of the screen to the luminance increment.

Participants performed 2 blocks of 48 trials each on the prosaccade task, followed by 2 blocks of 48 trials of the antisaccade task. In total, the four blocks took on average 10 minutes.

5.3.2. Results

Saccades were identified offline using the same velocity and acceleration criteria as in the oculomotor capture task. The first saccade after target onset that was greater than 1

degree in amplitude was taken as the response, and was classified as leftward or rightward.

5.3.2.1. Prosaccades

Prosaccade errors occurred on <1% of trials for all three groups. Saccadic RT was 224 ms for controls, 252 ms for PD ON, and 253 ms for PD OFF medication, with a significant slowing in PD ($F(1,15)=2.36$, $p=0.024$) but no drug effect. Saccade amplitudes were hypometric in PD ($F(1,15)=5.45$, $p<0.001$) with no effect of medication (means 10.8° ± 0.3 ON, 10.5° ± 0.3 OFF, compared with 12.0° ± 0.2 for controls). Importantly, there were no significant group differences in saccade velocity.

Previous reports have suggested abnormalities of inhibition of return (IOR) in Parkinson's disease (Briand et al., 2001b; Poliakoff et al., 2003). Although classical IOR is examined using a pre-cue up to 1 second before the target, we examined whether an analogous effect could be seen between trials. To this end, we grouped trials according to whether the target direction was the same as, or different to, the previous trial (**Figure 5.9**). Inhibition of return would be manifest as shorter RTs when the previous trial's target was in the opposite direction to the current target. We found equal IOR in all groups, with magnitude 22 ms (s.e.m. 6 ms) in controls, 27 ms (s.e.m. 9 ms) in PD ON, and 21 ms (s.e.m. 5 ms) in PD OFF ($p<0.05$ in each group, but no group differences $p>0.05$).

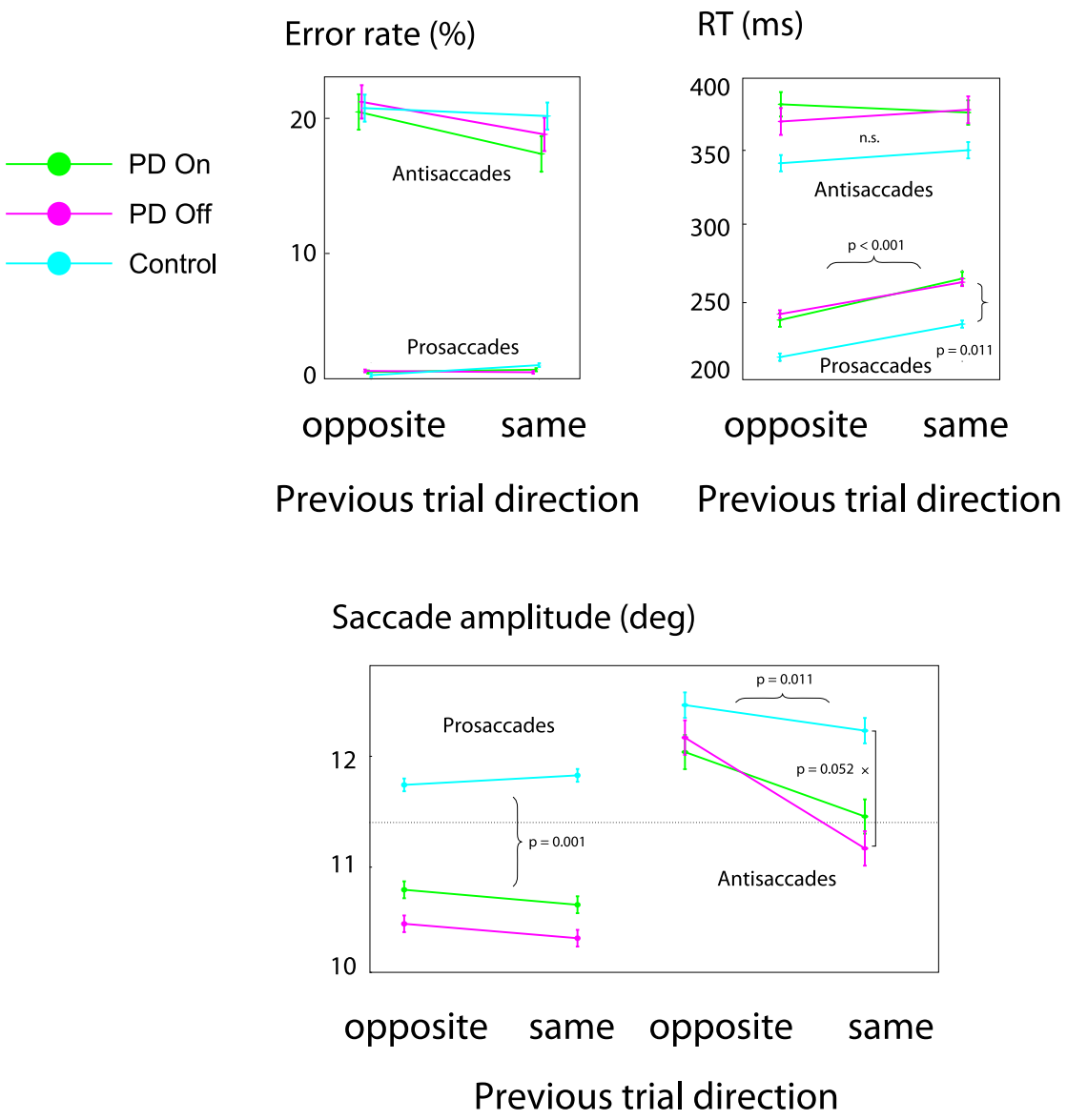


Figure 5.9: Results of the prosaccade and antisaccade tasks

A) For antisaccades, both controls and patients made approximately 20% errors. **B**) Parkinson's patients were slower than controls for both prosaccades and antisaccades. There was a significant trial-to-trial effect for prosaccades, in that saccade latency was shorter for saccades to the opposite direction than the previous trial. This "inhibition-of-return" effect was seen in both patients and controls. **C**) Patients showed hypometria for prosaccades, that is, the first saccade fell short of the target. For antisaccades, controls were hypermetric, overshooting the target. PD patients were less hypermetric, particularly when looking to the same direction as on the previous trial.

5.3.2.2. Antisaccades

A key finding here was that the error rate—perhaps analogous to capture rate in the previous study—did *not* differ between any of the groups (controls 20%, PD ON 19%, PD off 19%). Antisaccade RT was 343 ms for controls, 359 ms for PD ON, and 358 ms for PD OFF medication. No effect of previous trial direction was found ($p>0.05$). As with prosaccades, PD patients had smaller saccade amplitudes than controls (11.8° vs. 12.6°). Again, there were no group differences in saccade velocity.

5.3.2.3. Relationship between tasks

As our rewarded oculomotor task might be considered to be an adaptation of pro- and anti-saccade tasks, we examined how velocity and RT were related between the tasks. Participants' velocities in the prosaccade task were correlated with their saccade velocities in the oculomotor capture task (PD ON: $r^2=0.42$, $p=0.006$, OFF: $r^2=0.47$, $p<0.003$; Controls $r^2=0.31$, $p=0.009$). Similarly, reaction times in the two tasks were correlated. However the proportion of oculomotor capture and the number of antisaccade task errors was not significantly correlated ($r^2=0.11$, $p=0.21$).

5.3.2.4. Disease severity covaries with distractibility

Disease severity, as quantified by the UPDRS total score, correlated with the amount of oculomotor capture ($r^2=0.32$, $p=0.023$), but not with RT or velocity. Average digit span for patients was 6.3 forward and 3.8 backward, compared to 6.7 and 4.4 for controls. There was no correlation of working memory span with oculomotor capture rates or antisaccade errors.

5.4. Discussion

An oculomotor distraction task with variable incentives was used in patients with PD ON and OFF their dopaminergic medication. We found that whereas healthy controls showed faster RTs and increased accuracy with higher incentives, PD patients were *less sensitive to rewards* on both these measures (**Figure 5.1** and **5.2**). Saccade velocities were slowed in PD and, as with RT and accuracy, showed significantly reduced reward sensitivity.

We also measured saccade curvature, which indexes the pull of the distractor. In controls, incentives increased curvature away from the distractor, but not in PD. Patients ON medication had *decreased* curvature *towards* the distractor (**Figure 5.4**). Finally, in PD ON medication, we found abnormal pupil dilatation in response to reward history, which was absent when OFF drug and in control subjects (**Figure 5.5**).

5.4.1. Slowing and reduced reward sensitivity in PD implicates dopamine in vigour

We hypothesised that the dopamine deficiency of PD might lead to increased costing of action, as proposed by Mazzoni et al. (Mazzoni et al., 2007). Our finding of slowing of RT and saccade velocity is consistent with this. Intriguingly, the decrease in reward sensitivity, observed both in RT and distraction, runs in a direction that cannot be explained by speed-accuracy trade-off (**Figure 5.1A** and **5.2A**): compared to controls, patients were slowed the most in the high reward condition, but had the greatest error reduction at low reward levels. This suggests that what we are observing is a depletion of motivation, i.e. a reduction in the potency of rewards to induce motivation, as opposed to a speed-accuracy trade-off.

Data from the conditional accuracy functions (**Figure 5.3**) also argue against a speed-accuracy trade-off. For comparable speeds, patients are less accurate than controls at shorter RTs, and more accurate at longer RTs, i.e. the accuracy increases *more steeply* over time.

The pupil response to reward appears to partially support the motivational interpretation. Diminished pupillary reward sensitivity when off dopamine may reveal dopaminergic contributions to reward sensitivity. A curious effect of the previous trial's winnings upon the pupil emerged in PD patients when ON medication (**Figure 5.5**). The pupil dilated more in response to the reward cue, on the trials *after* a large reward had been won. The increase in tonic dopaminergic stimulation appears to cause 'carry over' of the reward signal from the previous trial, to the motivational period of the following trial – effectively, a post-reward facilitation. This might be an effect of altered of reward response kinetics induced by the medication.

5.4.2. Distractibility

Our patients had less oculomotor capture by distractors than controls, but in previous studies PD patients have been shown to have difficulty filtering distractors (Deijen et al., 2006; Machado et al., 2009). Why might this be? Machado et al. used peripheral irrelevant flankers which could be compatible or incompatible with the target that indicated which response was required. PD patients showed increased compatibility effects. Their task could not distinguish 1) whether the incompatibility or compatibility of the flanker drove the effect, 2) whether cue integration is simply better in PD, or 3) whether PD impairs spatial focusing of attention.

Our curvature results suggest that impaired distractor inhibition might be responsible. Deijen et al. (2006) used a task similar to ours without incentives, with unmedicated patients, but again found greater oculomotor capture in PD, unlike this study. It is possible that the lack of distractibility in our cohort is because they had all been on chronic dopaminergic treatment before testing, which radically alters the balance of receptors expressed in the striatum (Gerfen and Surmeier, 2011). Thus even our OFF session may not be comparable to the Deijen et al. study. A further possible reason for the difference is that, simply because the present study manipulates reward, our patients may start from a higher motivational level, compared to other studies.

One recent study has found *reduced distractibility* in PD OFF medication (Cools et al. 2010), consistent with reports of diminished exogenous orienting (Nys et al., 2010). One possible interpretation is that without dopamine, the striatum is less responsive and less able to update prefrontal processes with incoming information; alternatively low dopamine may simply reduce attention to appetitive stimuli (Shiner et al., 2012b).

5.4.3. Relation of oculomotor capture to antisaccade errors

Studies on antisaccades in PD have had mixed results (for a recent review see Yerram et al., 2013). Most likely, antisaccade latencies and errors in PD correlate positively with disease progression, and with other measures of executive function (Kitagawa et al., 1994). Patients in the early stage of the disease often have normal performance, whereas advanced patients have difficulty suppressing reflexive saccades in this task, which has been compared to disinhibition phenomena seen in the "frontal release" syndrome (Crevits and De Ridder, 1997; Fukushima et al., 1994; Lueck et al., 1990). In addition to the frontal contributions to distraction, dysfunction of attentional and oculomotor

regions has also been implicated in PD. PD patients lack normal increases in EEG posterior gamma power during saccades (Javaid et al., 2010) and show reduced recruitment of FEF and SEF during antisaccades and self-paced prosaccades on fMRI (Rieger et al., 2008; Yerram et al., 2013).

In PD, spatial attention is less effective in enhancing visual features (Sampaio et al., 2011a), accompanied by spatially specific deficits in orienting (Nys et al., 2010). In contrast, PD increases *exogenous* orienting—manifest by a greater exogenous pre-cue benefit (Briand et al. 2001; but see Kingstone et al. 2002), increased erroneous prosaccades during an antisaccade task (Chan et al., 2005), and generally greater distractor interference (Botha and Carr, 2012; Deijen et al., 2006; Zhou et al., 2012). However, prosaccades are slowed in PD, but are speeded by levodopa (Hotson et al., 1986) and STN DBS (Fawcett et al., 2010; Temel et al., 2008). Pop-out effects also seem to be reduced in patients (Filoteo et al., 1997; Mannan et al., 2008; Rodríguez-Ferreiro et al., 2010; Troscianko and Calvert, 1993). The reduced distractibility in our task (**Figure 5.1A**) thus supports a central role of dopamine in "bottom-up" sensory guidance of spatial attention.

5.4.4. Limitations

Previous studies have shown increased distractibility in PD. It could be argued that the reason I found patients *less distractible* than controls (i.e. less oculomotor capture), is that patients were tested on two sessions, whereas controls on a single session. But I argue firstly, the fact that error rates were comparable between groups permits comparison of the interaction effect of reward, which would otherwise be hard to interpret (we found no group difference between PD OFF and controls). Secondly, practice could not explain that PD patients are *slower* overall compared to controls, for

both correct and error responses (**Figure 5.2**). Thirdly, I included a practice term in the ANOVA, so any effects of practice should be factored out.

The longer RTs overall in PD could hamper interpretation of the interaction RT effects—i.e. decreased reward sensitivity (**Figure 5.2A**). However several studies demonstrate that RT differences scale with RT (Wang et al., 1998; Wilson et al., 1980). Thus with longer RTs, one should see larger RT effects of reward. In fact, our effect runs in the opposite direction; patients have smaller changes than controls. When considered in proportion to RT (i.e. as the ratio of the RT difference to the absolute RT; Luce, 1986), the observed reward-sensitivity effect is in fact *stronger*.

It is possible that the reason that correct RTs show reduced reward sensitivity in PD is due to saturation, or nonlinearity in the measure. In other words, could it be that patients are always performing at their fastest, with no room for improvement with reward? In my view, this suggestion misses the logic behind motivational manipulations. All motivation must by definition act against some "resistance", i.e. performance limits. If performance could be improved by extreme motivational states (e.g. in *kinesia paradoxa*), but is insensitive to laboratory manipulation of incentives, we may well find "ceiling performance". But this should not be considered as a ceiling effect, but rather as a disorder of the scaling of motivation, in terms of *effort cost*. In support of this, PD patients did have significant nonzero reward sensitivity, so they have some motivational effect, but of lower magnitude.

Could the results be explained by PD patients OFF medication being slower to perceive or process the reward cue? This is unlikely to be the case, as their error RT was abnormally sensitive to reward, indicating that they had processed the reward cue. In PD OFF medication, error reaction times were paradoxically faster when reward was

low (**Figure 5.1C**). A parallel effect has previously been described in response conflict: when conflict is high, correct RT is slowed but error RTs are actually faster. This is predicted by diffusion and accumulator models, in which errors occur due to faster build-up of evidence for the incorrect response (Teodorescu and Usher, 2013). In my oculomotor task, this pattern would arise if reward reduced distractor competition.

Comparing this study to the drug study of Section 4, D2-receptor stimulation increases reward sensitivity of saccade velocity and curvature, but contrary to expectation, treatment with dopaminergic drugs did not restore reward sensitivity in PD. Why this discrepancy between medication for PD *vs*. cabergoline?

A similar lack of effect of PD medication on the facilitatory effects of visual cues has been recently demonstrated (Anzak et al., 2012). One explanation of the negative finding is that bottom-up salience effects can be mediated by non-dopaminergic mechanisms, for example cholinergic arousal systems driven by the reticular activating system, which are also affected in PD (Anzak et al., 2011), but are not treated by standard dopaminergic medications.

Could my PD patients be too early in their disease stage for dopamine's effect to become apparent? This seems unlikely because significant differences from controls were evident. It is possible, though, that the patients were undermedicated. Heterogeneity in clinical populations, including genetic factors, may contribute, and increasing the study size may unmask effects (Williams-Gray et al., 2008). But perhaps a critical factor might be that reward cues induce *phasic* dopamine release, which is reduced in PD. These phasic responses to reward cues are likely to still be present in healthy controls. But in PD patients, without these reward-predicting signals, the saccadic system may be unable to energise responses when appropriate, even when

tonic dopaminergic stimulation is present. Moreover, chronic stimulation of dopamine receptors has complex effects on D1 and D2 receptor upregulation and downregulation (Subramaniam et al., 1992). This is likely to further hamper interpretation of the effect of dopamine in our patients, who had all been on long-term treatment.

5.4.5. Conclusion

We found evidence in support of reduced vigour in Parkinson's disease, linking the known reduction in reward learning to slowing of movements. By showing that distraction is reduced in PD, we favour a motivational account of dopamine, over a speed-accuracy trade-off. We found little effect of dopaminergic treatment on distraction or reaction time, but low dopamine states enhanced pupillary encoding of previous rewards.

6. Abnormal reward sensitivity after medial prefrontal lesions

6.1. Introduction

Much of our understanding of human medial frontal cortex is based on evidence from functional MRI studies, and from animal data. Both functional imaging, single cell recording, and animal lesion studies point to a role for orbitofrontal cortex (OFC) in representing reward signals, for the purpose of motivating goal-oriented behaviour (Rangel and Hare, 2010; Rudebeck and Murray, 2011a). If this is the case, a key prediction would be that lesions to orbitofrontal cortex should directly reduce the effect of rewards on incentivising action. However, to the best of my knowledge, no studies to date have *directly* measured sensitivity to incentives in humans following damage to prefrontal cortex.

Most studies of prefrontal lesions have examined patients with large, symptomatic lesions, sometimes bilateral. One reason for this is that smaller strokes may often go unnoticed (Feng et al., 2013), especially in the frontal lobes. This is partly because most strokes present with a neurological deficit. As a consequence, most lesions reported in the literature are large enough to declare themselves by causing clear symptoms such as weakness, incoordination, numbness or speech problems, warranting clinical brain imaging.

6.1.2. Subarachnoid haemorrhage

Subarachnoid haemorrhages (SAH) present a unique opportunity to study otherwise asymptomatic infarcts, because the patients present with severe headache often in the

absence of a focal neurological deficit. SAH occurs when an aneurysmal swelling of an artery ruptures (Gijn and Rinkel, 2001). The main consequence is arterial bleeding into the space around the brain. Focal brain damage can occur in areas of the brain that whose arterial supply comes from the affected blood vessel, but in most cases, the symptom that causes patients to attend is headache due to irritation of the meninges, rather than the brain damage itself.

The anterior cerebral artery (ACA) supplies much of the medial wall of the frontal lobe: medial OFC, gyrus rectus and ventromedial PFC (VMPFC), genu of the corpus callosum, infragenual and pregenual anterior cingulate cortex (ACC), and superiorly the dorsal ACC and part of the supplementary motor area (SMA) and pre-SMA. Infarcts in this vascular territory can be recognised on brain scans after SAH, despite causing no specific neurological symptoms (Umredkar et al., 2010). One study identified 12 silent infarcts in 32 patients who suffered SAH, and "the vast majority of these infarcts were not detected by clinical examination" (Helbok et al., 2011), even though many functional imaging studies have argued that medial PFC is a key region subserving several supremely human cognitive processes, such as perspective-taking, emotional control, counterfactual reasoning, evaluation of feedback and evidence, and hierarchical goal-driven planning (Stuss and Benson 1984; Clark et al. 2003; Fisher et al. 2011).

SAH occurs in younger patients than other strokes, and incidence is less biased by lifestyle factors (Suarez et al., 2006). These patients provide a valuable opportunity to study the effects of lesions in brain areas that produce minimal visible or symptomatic effects. Thus SAH patients come as close as we are likely to get to an incidental yet precisely timed, isolated region of infarction in an otherwise healthy

brain. Compared to most stroke patients, SAH patients are less likely to have subclinical microvascular disease affecting white matter and basal ganglia. Compared with epilepsy surgery patients, they are free from the effects of seizures and anticonvulsant medication on brain function.

6.1.3. Lesion studies to date

Patients with medial frontal damage have problems with memory, control and monitoring, as well as loss of motivation (Godefroy, 2013). In particular, they show increased distractibility when they have to ignore distractors (Chao and Knight, 1995; Woods and Knight, 1986), and increased capture by distractors (Guitton et al., 1985; Paus et al., 1991).

OFC lesions in primates lead to perseveration and impaired reversal learning (Dias et al., 1996; Iversen and Mishkin, 1970), but also altered subjective preferences (Baylis and Gaffan, 1991; Izquierdo et al., 2004). In humans, recognised features include impulsivity, anger, a faster subjective sense of time (Berlin et al., 2004) and a milder experience of regret (Camille et al., 2004). Patients may confabulate, and may have difficulty selecting memories based on context and time (Duarte et al., 2010; Gilboa et al., 2006; Schnider and Ptak, 1999). Unlike in primates, OFC patients are only mildly impaired on probabilistic learning (Chase et al., 2008). In experiments, they have difficulty choosing the best gamble when faced with a choice (Bechara et al., 1998; Fellows and Farah, 2005a), and a subgroup may be strong risk-takers (Sanfey et al., 2003) with, in some cases, increased temporal discounting (Fellows and Farah, 2005b; Sellitto et al., 2010). In attentional paradigms, lesions to OFC have been shown to reduce inhibition of return in a simple saccade paradigm (Hodgson et al., 2002a). There

have been very few inactivation studies of medial PFC in humans (Harmer et al., 2001; Rushworth et al., 2002) as this area is difficult to target.

Broadly, lesion studies can be interpreted as supporting an evaluative role for OFC, representing both reward values of stimuli, and goal states of the subject (Rangel and Hare, 2010).

ACC lesions in primates give rise to subtle changes in the learning of action values over time (Kennerley et al., 2006; Rushworth et al., 2004), in keeping with single-cell recordings demonstrating encoding of reward values, effort, and surprise (Hayden et al., 2011b; Kennerley et al., 2011), and with learning, error and conflict signals frequently seen on fMRI (Amiez et al., 2012; Botvinick et al., 1999; Braver et al., 2001; Carter et al., 1998; Ridderinkhof et al., 2007). In contrast, studies of patients with ACC damage have not provided a clear picture.

Bilateral ACC damage can lead to profound apathy, passivity, akinesia and mutism (Cohen et al., 1999), perhaps in keeping with cingulate inactivity seen in depression and schizophrenia (Bench et al., 1992; Dolan et al., 1995). The error-related negativity (ERN), which may localise to ACC (Hochman et al., 2012), can be diminished or absent (Modirrousta and Fellows, 2008; Stemmer et al., 2004), even though patients can appropriately correct errors. Loss of trial-to-trial conflict effects have been reported (di Pellegrino et al., 2007) with blunted autonomic responses (Cohen et al., 1994; Critchley et al., 2003), perhaps matching the functional activation seen with conflict and uncertainty (Behrens et al., 2007; Botvinick et al., 1999; Ghahremani et al., 2010). However, value learning itself is not generally impaired (Hornak et al., 2004).

Distractibility, as measured by attentional lapses, has long been associated with ACC damage (Degos et al., 1993; Janer and Pardo, 1991; Laplane et al., 1981), and a recent study has shown increased anticipatory responses following cingulotomy (Srinivasan et al., 2013), supporting fMRI evidence that ACC is activated by flexible attention (Silton et al., 2010). On the other hand, some studies have shown *reduced* effects of salient distractors (R.A. Cohen et al., 1994; Koski et al., 1998).

In this chapter, I examine how rewards are able to modulate distractibility in patients with ACC and OFC lesions. I use a the monetary-incentivised early distractor task from previous chapters to probe reward sensitivity, and standard pro-saccade and antisaccade tasks as a baseline.

6.2. Methods

6.2.1. Participants

22 patients were recruited from the National Hospital for Neurology and Neurosurgery. All had suffered subarachnoid haemorrhages from aneurysms of the anterior communicating artery, and as a consequence also sustained focal infarcts in the ACA territory. All patients were tested between 2 and 5 years after the event.

All had highly selective lesions involving medial frontal cortex, but with no neurological signs. On neurological examination, all patients had normal visual acuity and fields, full strength with normal sensation in all four limbs, and no speech or comprehension disturbances. One patient was on olanzepine (CB), and one was on citalopram 10mg (GB). None of the other 17 patients were on psychotropic medication,

and none were taking anticonvulsants. A summary of the history of individual patients is given in the appendix.

Of the 22 patients tested, one had severe fatigue and dropped out, and in one patient eye movements were technically difficult to record. One patient had downbeat nystagmus, which was mild enough to permit recording. Thus eye movement data was available for 20 patients in total.

Of these patients, 16 had returned to work, 2 were retired, and 2 had not gone back to work due to reduced memory and motivation. Three patients had noticed contralateral weakness of the arm/leg following the haemorrhage (2 in the dorsomedial group and 1 ventromedial). In two cases the weakness resolved within 2 weeks, and in the other case the weakness resolved gradually over a year. None of the patients had a past medical history of mental health problems or previous neurological illness. The age range was 28 to 70 years, mean 49.9 years.

Two patients had CT imaging as they were unable to have MRI (one patient had surgical clips that were not MRI-compatible, and the other had an implantable cardioverter-defibrillator). Of the remaining patients, 11 underwent dedicated 1 mm volumetric T1 imaging plus isometric FLAIR sequences. Seven patients were unable to attend for this, therefore previously acquired clinical sequences were analysed, which were similar but non-isometric. One patient was found to have a temporal lobe infarct in addition to OFC damage, and was therefore excluded before analysis, leaving 19 complete datasets.

Patients were tested with the Hospital Anxiety and Depression Scale to rule out post-stroke mood disorders. They also completed the Lille Apathy Rating Score (LARS,

Sockeel et al., 2006), which was modified such that each question was rated first with respect to patients' current lifestyle, then according to how the patient retrospectively felt they were like before the event, so that we had two assessments per individual.

Data was collected from 32 healthy control participants, with mean age was 50.6 years. Some of these controls were re-used from Study 5. They had no neurological or psychiatric illness and normal or corrected-to-normal vision.

6.2.2. Oculomotor capture task

The same task as in Chapter 5 was used.

6.2.3. Prosaccades and Antisaccades

The same task as in Chapter 5 was used.

6.2.4. Distribution of patients' lesions

Lesions of the 19 patients were manually traced using FSL and MRIcro, on top of the original scans. The scans and lesion masks were then registered to the MNI152 template. Clinical MRI scans were registered using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002); linear registration reduces the chance of misalignment due to the lesions (Brett et al., 2001; Crinion et al., 2007). The volumetric T1 scans were registered using FLIRT or SPM8 and the cost-function masking toolbox (Rorden et al., 2007), with a 5mm smoothing kernel.

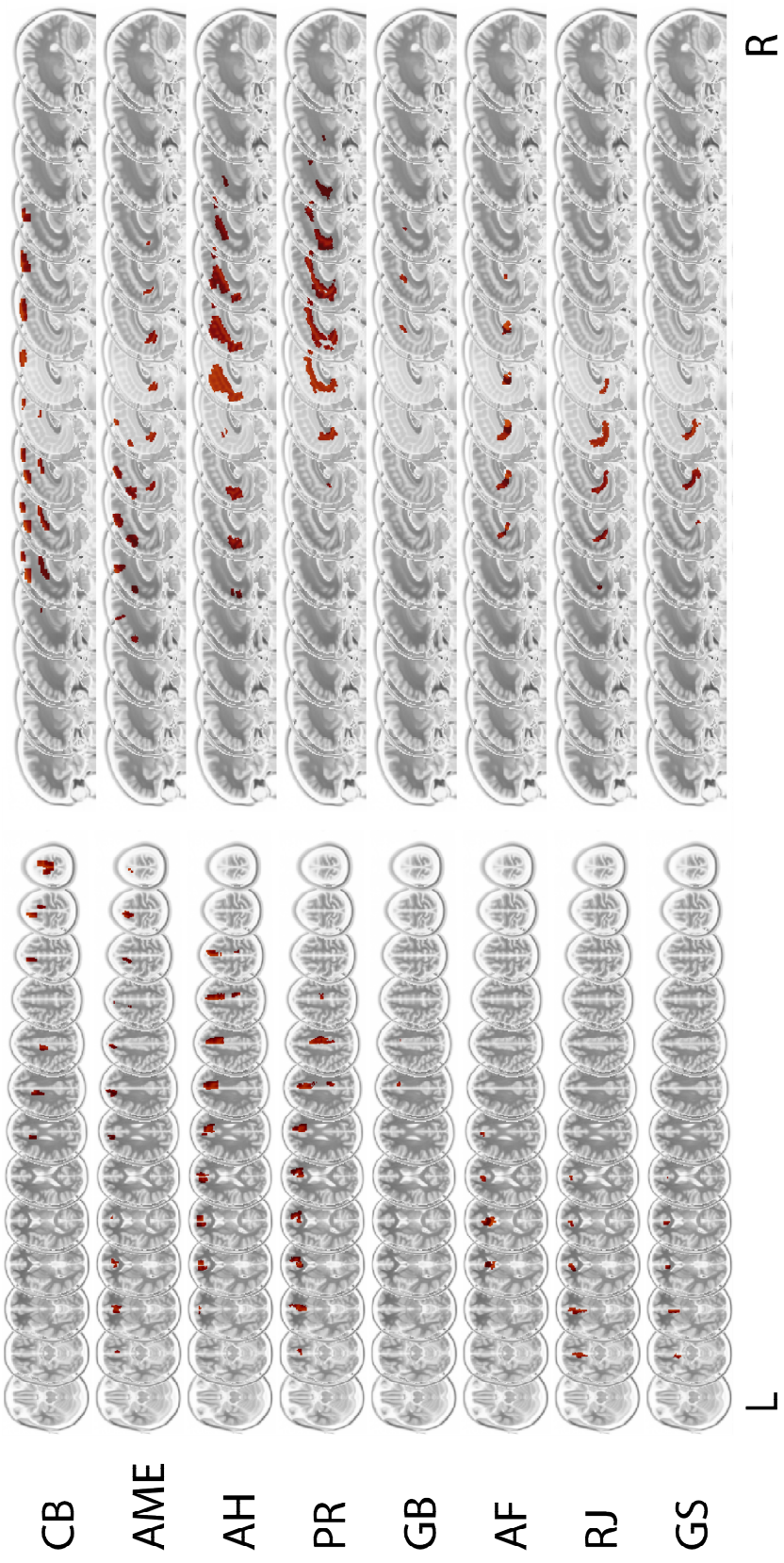
The demographics for the patient group are shown in **Table 6.1**. The 19 patients comprised 5 lesions to dorsal ACC (subjects 1 to 5), 3 lesions to rostral ACC (pregenual and subgenual, subjects 6-8), 4 lesions to anteromedial orbital/frontopolar cortex

(subjects 13 to 16), and 7 lesions to medial OFC (subjects 9 to 12, and 18 to 20). The mean lesion volume was 5.7 cm^3 (s.d. 5.6), but ranged from 0.1 to 19.1 cm^3.

An overlap map was constructed by counting the number of patients who had a lesion in each voxel (**Figure 6.2**).

Table 6.1: Demographics and lesion description for the 19 lesion patients. DS = digit span, LV= total lesion volume.

		Age	DS	LV	Lesion
1	CB	46	8	6.2	Bilateral dorsal ACC / SMA
2	AE	44	14	3.3	Left dorsal ACC + Right pregenual ACC
3	AH	45	13	16.6	Right dorsal ACC + bilateral pregenual ACC
4	PR	61		8.5	Right dorsal + pregenual ACC extending to PCC
5	GB	63	10	0.1	Small Right dorsal ACC
6	AF	56	7	1.7	Left pregenual + subgenual ACC
7	RJ	61	10	1.2	Left pregenual + subgenual ACC
8	GS	57	12	0.9	Left pregenual + subgenual ACC
9	AM	28	10	6.5	Left medial OFC and pregenual ACC
10	CJ	48		2.1	Left medial OFC
11	NR	46	13	9.1	Right medial OFC
12	MO	45	16	19.1	Right medial OFC
13	MN	55	10	2.6	Left anterior mOFC + medial frontopolar
14	EF	33	8	3.9	Bilateral mOFC + medial frontopolar
15	SP	43	8	11.5	Left medial OFC + medial frontopolar
16	FR	70	9	11.6	Left gyrus rectus + medial frontopolar
17	SW	32	15	1.9	Right gyrus rectus
18	EC	58	7	1.3	Right gyrus rectus
19	NF	49	11	0.5	Bilateral posterior medial OFC


R
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CB
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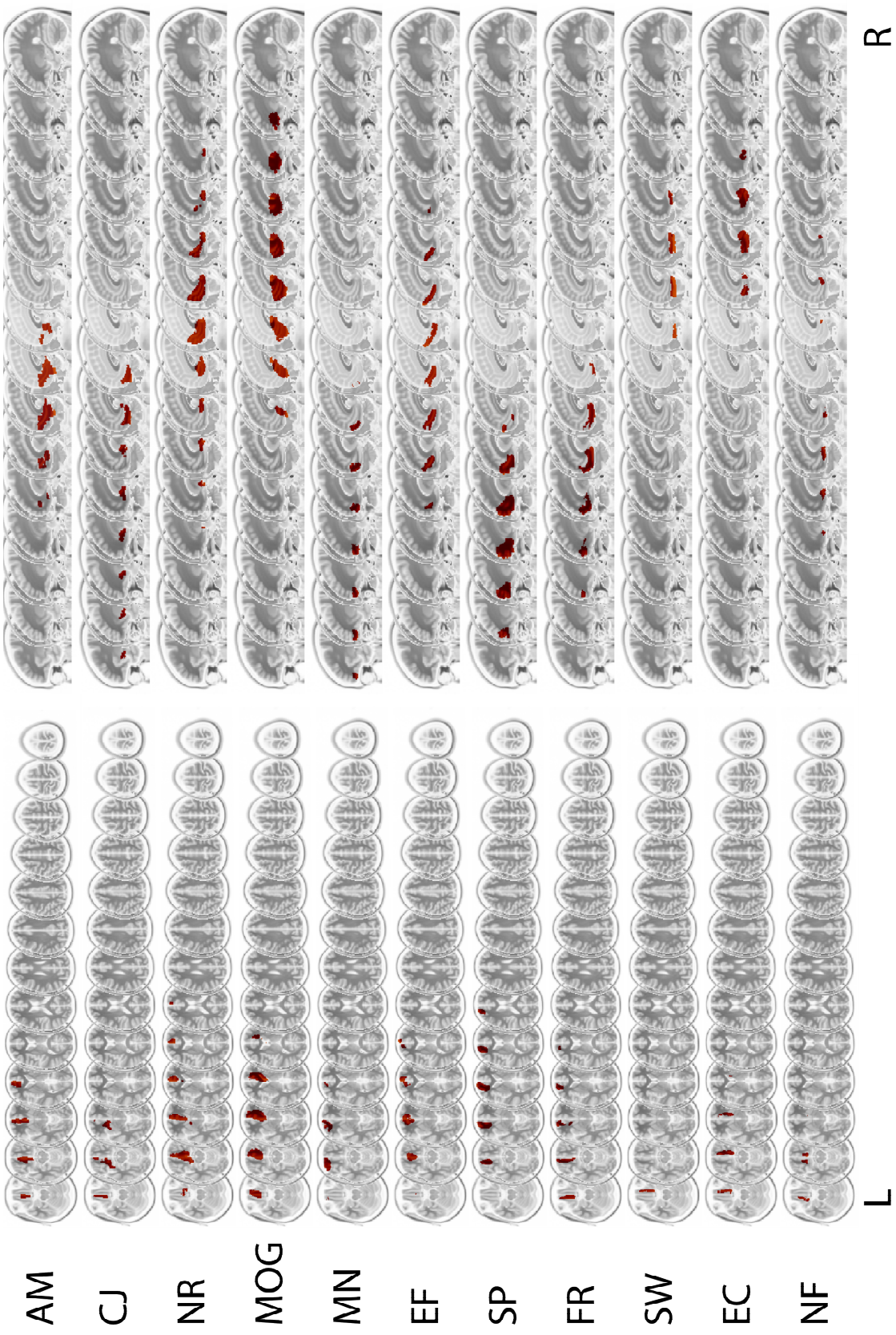
Figure 6.1: Lesion maps of individual patients.
In all images, left is left. Lesions were drawn onto the original scan then normalised to MNI152 coordinates. Masks are shown here superimposed on the template. Patients 1–8 had lesions predominantly in ACC, and 9–19 were predominantly in OFC.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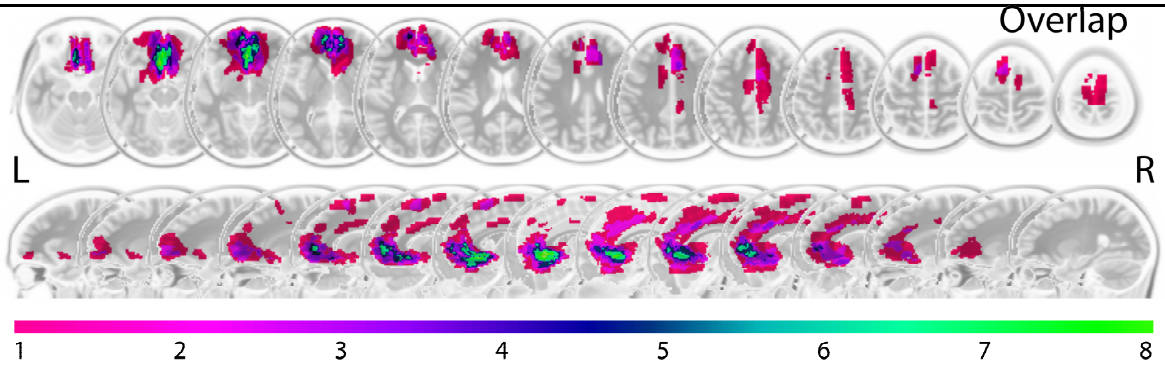


Figure 6.2: Lesion overlap map, axial and saggital

Darker red areas represent areas in which more patients were lesioned. The maximum lesion density was 8 out of 19 patients, centred on medial OFC. Note that parts of dorsal ACC have no lesion coverage.

6.3. Results

The proportion of trials on which gaze was captured by the early onset was measured, and the RT from the distractor onset until the start of the first saccade that had an amplitude of more than 3 degrees in the target direction was calculated. Saccade analysis followed the same details as in previous chapters, yielding peak saccade velocities and curvature.

6.3.1. Effect of individual lesions on reward sensitivity

The sensitivity of peak saccade *velocity* to rewards was calculated for each of the 19 patients. The value was compared to those of 32 age-matched healthy controls. The reward sensitivity values of both patients and controls were normally distributed by the Kolmogorov-Smirnov test ($p>0.5$, $\max|S\text{-}normcdf|=0.16$). Therefore the z-score of each patient relative to the controls' distribution was calculated. This was thresholded using the normal distribution, corrected for 19 independent multiple comparisons to give a family-wise type I error rate of 5%, when comparing each patient individually against

the reference population. This resulted in a corrected p-value of 0.0027, corresponding to Z=2.78 (Bonferroni method). Only one patient (CJ) had extremely low reward sensitivity with Z=3.13, while another (AM) exhibited very high reward sensitivity, Z=4.01 (**Figures 6.3A** and **B**).

Reward insensitivity in *RT* was also assessed, since this measure was shown to be independent of velocity sensitivity in chapter 3. One patient (AE) had greatly increased reward sensitivity, Z=3.86; another (case RJ) was extremely insensitive to rewards (Z=4.11) in the sense that his RT paradoxically increased with greater incentives (**Figure 6.3.3C** and **D**). This might reflect a more cautious approach to responding when greater rewards are on offer.

Since comparisons for both RT and velocity reward sensitivity were made, correction for multiple (38) comparisons was made. This gave a threshold of Z=3.01, so all four of these patients remain significantly different from the healthy controls. The lesion map of the 16 other patients, who did not individually show significant differences, is shown for comparison in **Figure 6.3.3C**. Subtraction maps of these four individual patients' lesions from the lesion map of the remainder of the patients revealed no areas that were uniquely lesioned in for reward insensitivity or hypersensitivity. Thus it was not possible to tell from this analysis whether damage to any specific brain area was responsible for the observed effects.

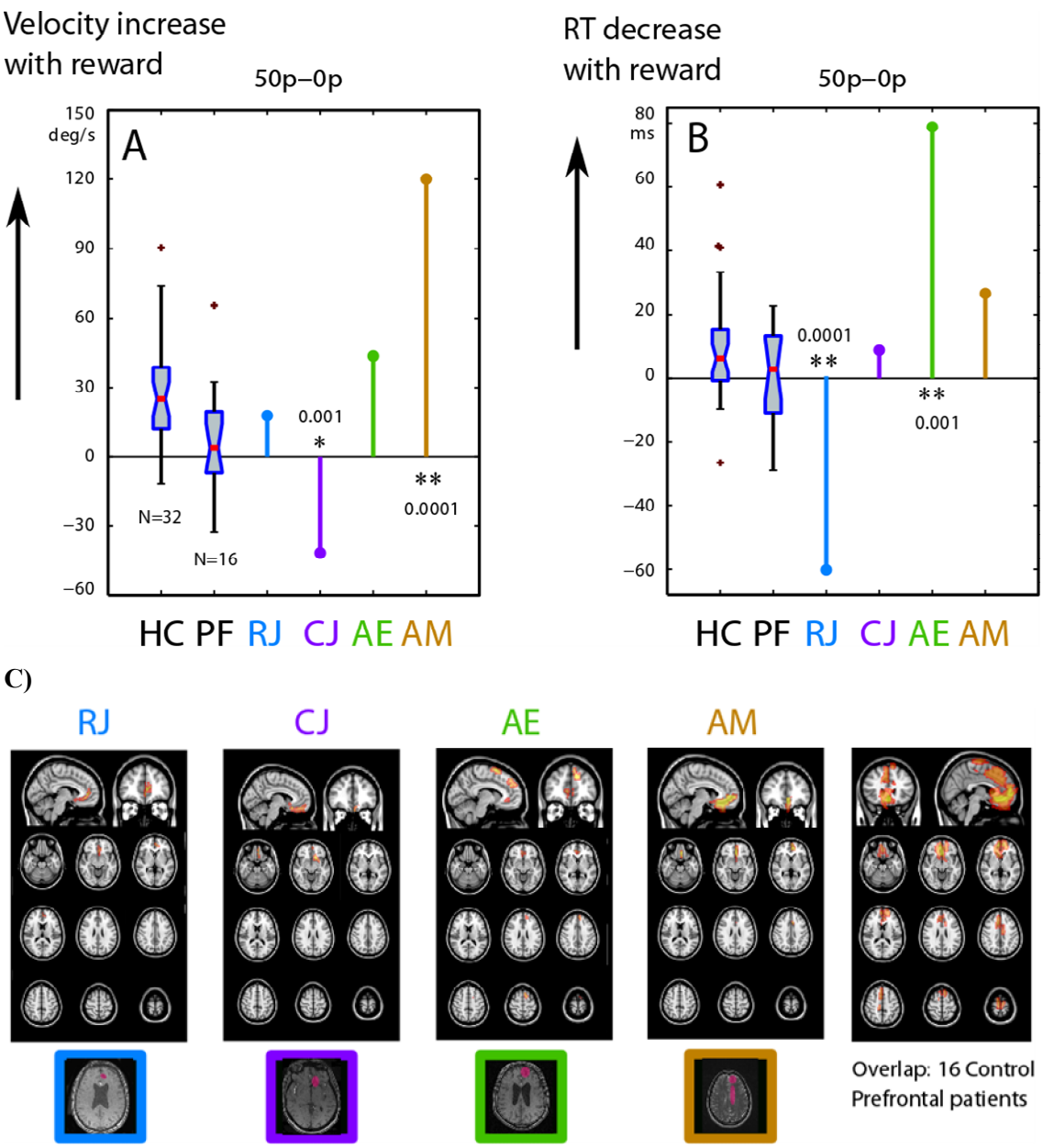


Figure 6.3: Specific patients with altered reward sensitivity

Individual patients showed striking differences from the control population, in their reward sensitivity. Graphs indicate how saccade velocity (A) and reaction time (B) vary with reward. Positive values indicate greater reward sensitivity. Each patient was compared with the 32 healthy controls (HC), and when fully corrected for multiple comparisons, four patients were significantly different. The remaining 16 patients' data are also shown (PF); red bar = median, box = interquartile range, notch = 5% median comparison interval, whiskers = farthest point within 1.5 quartiles of median, all points outsider the whiskers are drawn as crosses. **A**) Patient AM showed increased reward modulation of velocity, whereas patient CJ was less sensitive. **B**) Patient AE showed increased reward modulation of RT, whereas patient RJ showed paradoxical slowing by rewards.

C) The lesion maps of the four patients who showed abnormal reward sensitivity. Colour code matches the graph above. RJ and CJ have reduced reward sensitivity of RT and velocity respectively, and have lesions to subgenual ACC and OFC respectively. AM, who also has lesions in these locations, has abnormally *high* reward sensitivity of velocity.

6.3.2 Grouped comparison between ACC and OFC lesions

To facilitate pooling the results from all the lesions, I divided patients anatomically into two groups: those with lesions of ACC, and those with lesions of OFC. The OFC group had 11 patients, with lesions centred on the ventral surface; the ACC group of 8 patients included 5 dorsal and 3 subgenual ACC patients (AF, RJ, GS). The average demographics of the two resulting groups are shown in **Table 6.2**, and did not differ between groups.

	N	LV mean (sd) [range]	Age	Tot LARS	Digit Span
ACC	8	4.8 (5.6) [0.08-16.5]	54.1 (7.9) [19-44]	15.0 (6.0)	10.6 (2.6)
OFC	11	6.4 (5.8) [0.46-19.1]	46.1 (12.3) [28-70]	13.2 (6.9)	10.7 (3.1)

Table 6.2: Demographics of the two groups of prefrontal patients: anterior cingulate vs. orbitofrontal lesions. There was no significant difference between groups in age, apathy or working memory digit span. LV=lesion volume, LARS=Lille Apathy Rating Scale.

To examine the difference between groups, and the effect of reward, three 2-way mixed-effects ANOVAs were used, with factors of reward and group (ACC *vs*. Control, OFC *vs*. Control, and ACC *vs*. OFC).

6.3.2.1. Reduced sensitivity of velocity to reward in OFC lesions

As in previous chapters, peak saccade velocity of correct and capture saccades, the proportion of oculomotor capture errors, and saccadic reaction times of correct responses were calculated for each reward condition.

Peak saccade velocity was compared between patients and controls using mixed effects ANOVA (**Figure 6.4A**). Although there was no main effect of group, there was a significant interaction, indicating that patients overall had a different *sensitivity* of velocity to reward (interaction of group with reward, $F(1,102)=4.70$, $p=0.032$). When divided into ACC and OFC groups, there was again no main effect of group, but a trend to interaction of reward and group ($F(1,101)=2.49$, $p=0.088$).

Comparing OFC patients to controls gave a significant interaction between group and reward (**Figure 6.4B**, $F(1,86)=4.87$, $p=0.030$). In contrast, comparing ACC patients with controls showed no effect. Thus patients in the OFC group did not increase their velocity as much as controls in response to reward. The reward sensitivity, i.e. the increase in velocity in degrees per second per reward level, was, 5.7±6.2 for OFC, compared to 15.7±2.3 in controls and 9.3±5.9 in ACC. Although OFC patients appear to be slower, this was not significant ($F(1,86)=1.8$, $p=0.19$), with OFC patients attaining mean velocities of 440±21 deg/s, compared to controls 479±16 and ACC 490±34.

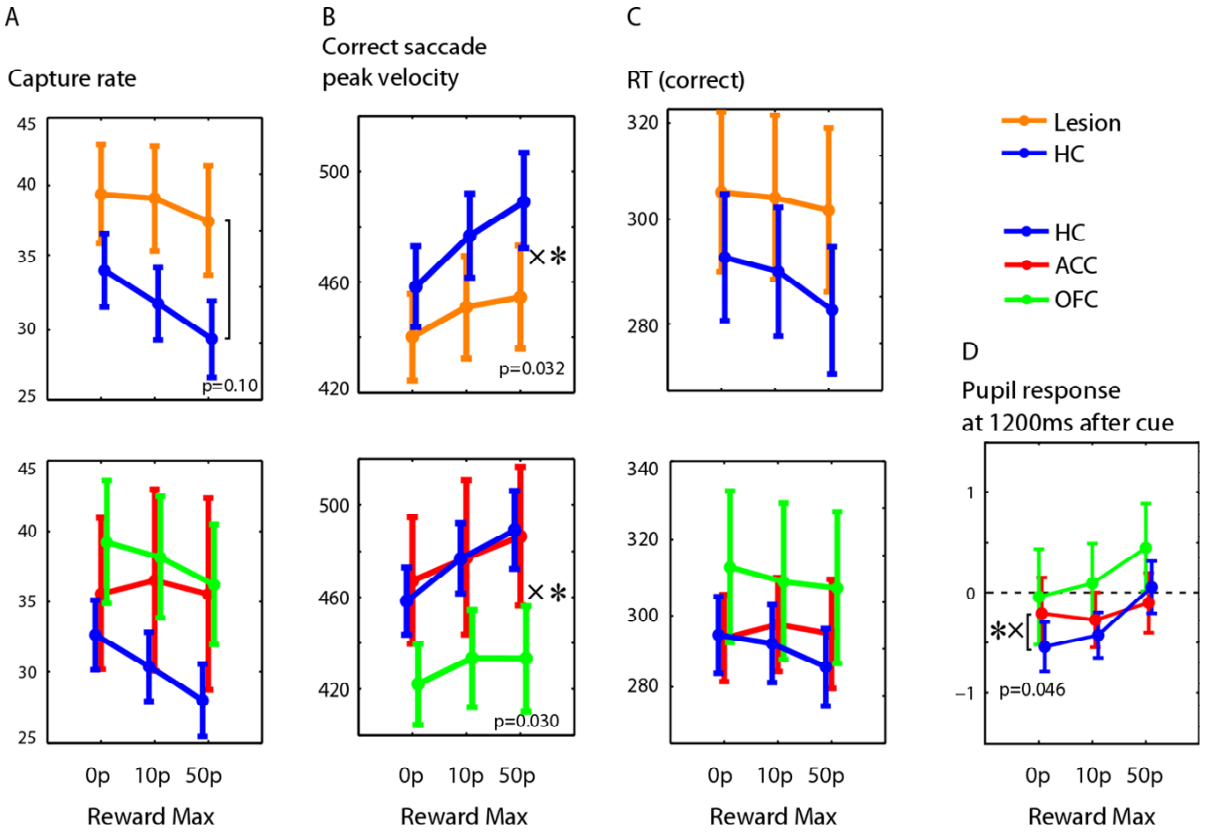


Figure 6.4: Saccadic parameters for the patients

Upper row: all patients grouped together; Lower row: patients divided according to lesion location. **A**) Oculomotor capture rate is the proportion of trials on which the first saccade went towards the distractors. Capture decreased with incentive, reflecting reduced distractibility. There was a trend for patients to have more oculomotor capture than controls, and a trend for an interaction between ACC and controls in their reward sensitivity. **B**) OFC patients had shallower gradient when modulating their velocity in response to reward. They were not significantly slower. **C**) RTs were shortened by incentives, but there were no differences between patients and controls. **D**) Pupil dilatation after the cue was increased by reward, but less so in ACC patients compared to controls.

6.3.2.2. No increase in oculomotor capture

Patients' mean capture rate was 39% ± s.e.m. 4%, compared to 31%±3% for controls. There was a main effect of reward, but only a weak trend of difference between patients and controls (arcsine transformed ANOVA, $F(1,102)=2.77$, $p=0.10$). The patients were then divided into two groups, ACC and OFC, as above, with three groups in the ANOVA. Again there was no difference between groups, but a trend for an interaction

of reward between ACC patients and control groups (F(1,78)=2.87, p=0.094). Reward sensitivity, was calculated as the slope of the capture rate per step in reward level. On average, ACC patients reduced their capture by 0.02%±1.4 per level of reward compared to 2.8%±0.9 for controls, and 1.8%±1.2 for OFC.

6.3.2.3. No effect of lesions on RT

Reaction times showed a main effect of reward (F(1,102)=5.3, p=0.023) but no difference between groups, and no interactions (**Figure 6.4C**). Reward sensitivity was calculated in milliseconds per reward level, so that a negative value means shortening of RT with reward. The sensitivity was +3.65 ± s.e.m. 4.0 for ACC patients, compared to -5.6±1.5 for controls, and -7.1±4.0 for OFC patients, indicating that ACC patients' reward sensitivity was not different from zero, unlike the other groups. However there was no significant interaction between groups on this measure.

6.3.2.4. Patients show a trend of greater curvature toward the distractor

Curvature towards or away from the distractor was calculated for correct responses to the target, as the maximal deviation angle of the saccade trajectory from a straight line (as in previous chapters). Patients exhibited a trend of increased curvature to the distractor (main effect of group, F(1,102)=3.93, p=0.053). Examining subgroups, OFC patients were significantly more curved to the distractor than controls (F(1,86)=4.23, p=0.046), but ACC patients were not (F(1,78)=1.13, p>0.05).

Was this due to increased pull of the distractor, or by decreased "repulsion"? By classing correct saccades as curved towards or away from the distractor, this could be attributable to a *lower proportion of "repelled" saccades* (F(1,86)=4.21, p=0.047), rather than an increase in the proportion curved toward the distractor.

Delta plots were compared to investigate whether the lack of mean RT effects conceals a change in the shape of the RT distribution. There were no effects of reward on the distribution of correct responses. Error responses were slowed by high rewards in the ACC group, but there were no statistical differences.

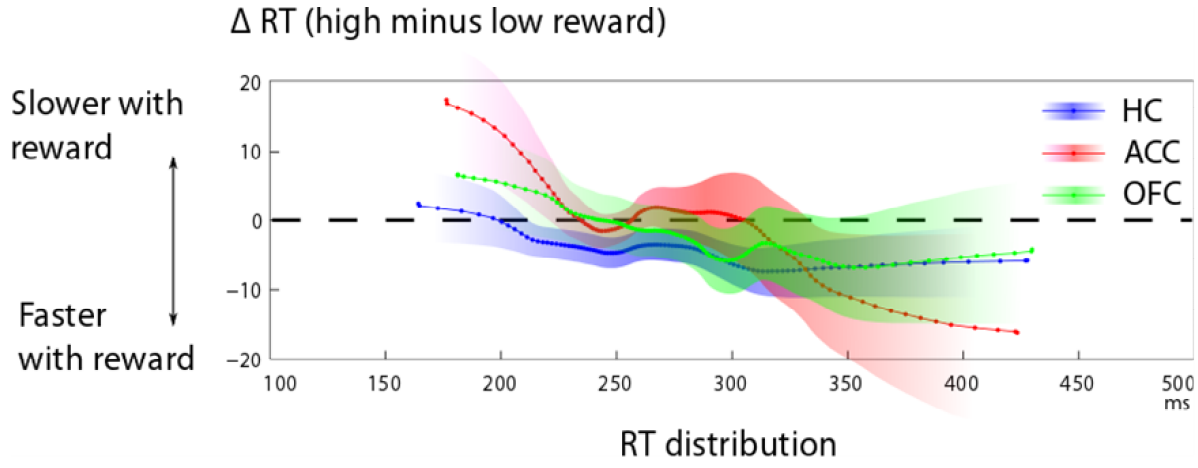


Figure 6.5: Delta plot showing how RT is influenced by reward, at different RT bins
Positive values indicate slowing by rewards. Healthy volunteers have negative values indicating shorter RTs in the high-incentive condition. There was no difference between the three groups.

6.3.2.5. Pupil signals reward less in ACC patients

Pupil dilatation in response to the reward cue was analysed as before, extracting the effects of incentive, previous winning, and previous incentive. The pupils dilated when the incentive was higher compared to lower, and constricted when the previous trial's incentive level was higher compared to lower—i.e. the same pattern as seen in previous chapters (**Figure 6.6**). However, comparison of the dilatation at 1200ms (the end of the foreperiod) demonstrated that modulation by reward was somewhat reduced in patients compared to controls (interaction of reward and group, $F(1,102)=4.62$, $p=0.034$).

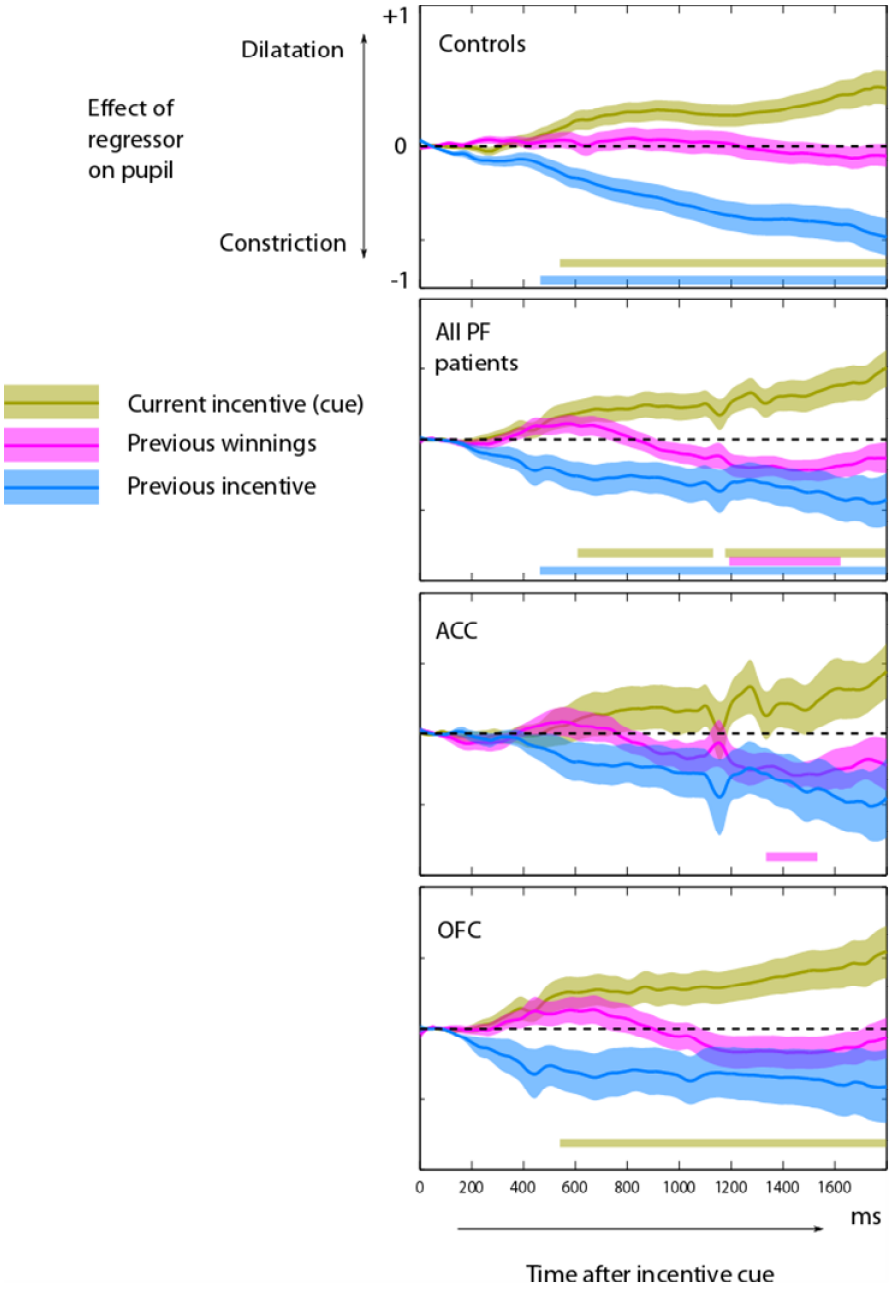


Figure 6.6: Effect of reward on pupil size, comparing patients and controls

The vertical axis is the change in pupil size after the time of the cue onset. The lines represent the relative contribution to pupil size from various sources. The yellow curve indicates the effect of the current reward cue: a positive value means that, when the cue was large, the pupil was more dilated, compared to when the cue was small. Top: In controls, the pupil dilates to a high reward cue (yellow), and as previously found, the pupil dilates more when the previous incentive was small (blue). PF patients have qualitatively similar pupillary effects. ACC patients had lower reward sensitivity, as evidenced by smaller deflection of the yellow curve (p=0.046).

Breaking patients down into ACC and OFC groups, the ACC patients had reduced pupillary reward sensitivity compared to controls (interaction between reward and group, $F(1,78)=4.13$, $p=0.046$) but OFC patients were not different to controls ($F(1,86)=1.76$, $p=0.19$). The difference between ACC and OFC was not significant.

We now have two measures on which patients are less reward sensitive than controls: saccade velocity and pupil dilatation. Are these two measures of insensitivity to reward related? They are likely to be independent, since the OFC group had low sensitivity of velocity, whereas the ACC group had low sensitivity of the pupil. Confirming this, there was no correlation across subjects for the slope of pupil dilatation with the slope of saccade velocity ($r^2=0.06$, $p>0.05$). This suggests that although lesions can attenuate both the modulation of velocity and pupil size, these two components are damaged independently.

6.3.2.6. Pre-response distractibility greater in patients

Numerous studies have indicated that prefrontal lesions increase distractibility in terms of attentional lapses. Although no significant increase in oculomotor distraction was seen, distractibility might be manifest in other ways, for example in the period in between trials. To assess this, eye data before the target onset was parsed, to count the number of anticipatory saccades. Anticipatory saccades during the cue-period constituted all saccades that occurred after the cue onset, but before the target onset (i.e. during the variable foreperiod of 1400 to 1600 ms). Overall, the number of anticipatory saccades was reduced when the cue was a high incentive compared to a low incentive ($F(1,102)=11.8$, $p<0.001$). Patients had a just-significant increase in anticipatory saccades compared to controls ($F(1,102)=4.36$, $p=0.042$; no interaction). When patients were subdivided into groups, there was no effect of group ($p>0.05$).

The number of blinks was also counted, between the end of the previous trial and the onset of the cue. This might provide a measure of sustained attention during the period before steady fixation had successfully been obtained. The number of blinks was no different in patients compared to controls ($p>0.05$).

6.3.3. Voxel-wise lesion-behaviour mapping

Although group-based analysis has been the standard for comparing linking lesions with behaviour (Fellows and Farah, 2005b; Milner, 1963; Shallice and Evans, 1978), recent increases in computational power have permitted statistical inference at the voxel level. In order to find which areas of the brain might be responsible for the reduced reward sensitivity in our patient group, voxel-wise lesion-behaviour mapping was used (Rorden et al., 2007). In this technique, for each voxel, its lesion status across all patients is used to predict the behavioural measure.

Lesion masks were smoothed to give values between 0 and 1 at each location for each subject. This value was used as a continuous predictor of reward sensitivity of velocity. The t-statistic for this regression was computed for each voxel to generate a statistical parametric map (**Figure 6.7A**). With uncorrected thresholding at $p<0.05$, $t(19)=1.74$, there were 873 significant voxels. To estimate the worst-case number of multiple comparisons, I took the total number of voxels which had lesions across all patients, and corrected for the 5mm radius kernel smoothing. There were 26256 lesioned voxels, which corresponds to 210 independent comparisons with 5mm resels (note that this is a conservative estimate, since it ignores spatial correlations in the lesion-state of neighbouring brain areas). With this number of multiple comparisons, Bonferroni correction gives $p<0.00024$, or $t(19)>4.20$. At this threshold, 63 voxels were

significant, all localised in the sulcus immediately anterior to the subcallosal ACC ("infralimbic" cortex in primates).

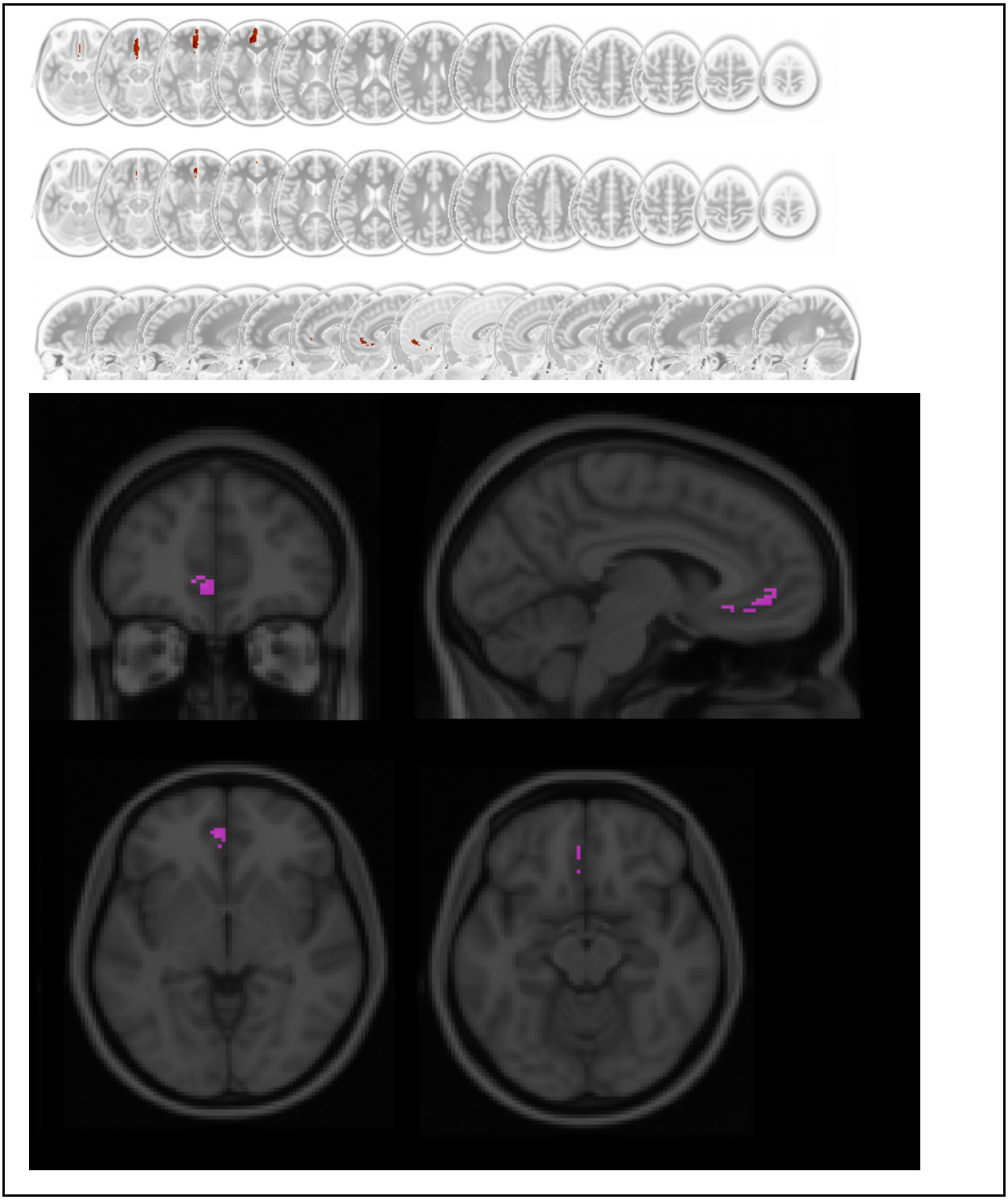


Figure 6.7: Regions in which lesions correlate with reduced reward sensitivity of velocity
The upper row shows the statistical parametric map from a linear regression. Coloured areas have uncorrected $p<0.05$. Lower two rows and main image show the same map thresholded conservatively at $t > 4.2$.

One possible confounding factor could be that patients are less reward sensitive simply as a function of their lesion size. This possibility is unlikely since reward sensitivity measures did not correlate with lesion volume (velocity: $r^2=0.099$; RT: $r^2=0.02$; Pupil: $r^2=0.19$; all $p>0.05$).

Another possibility is that reduced reward sensitivity occurs just because the lesion influences saccade velocity itself. In other words, if there were changes in baseline velocity due to lesions, (as noted above in the trend for OFC patients to have lower velocities), this might explain the reward-sensitivity findings. To rule this out, I calculated a voxel-based map to predict patients' overall mean velocity. This map had zero significant voxels, even at an uncorrected $p<0.05$, showing no brain areas where damage correlated with saccade velocity. This suggests that damage to the regions noted above do not lead to overall velocity changes.

6.3.4. Prosaccades show reduced IOR after OFC lesions

The latency of prosaccades was not different between the three groups. To examine inhibition of return (IOR) effects, trials were divided according to whether the previous trial's target was in the same direction or different direction. As expected for IOR, repeated-direction trials had slower RTs in controls ($t(20)=20.8$, $p<0.001$) and in ACC patients ($t(8)=14.4$, $p=0.005$), but there was no effect in OFC patients ($p>0.05$). Consistent with previous reports (Hodgson et al., 2002) I found evidence that OFC patients had attenuated IOR. There was an interaction between same/different location

and ACC *vs*. OFC groups (t(17)=4.66, p=0.045) but no interaction with OFC *vs*. controls or ACC *vs*. controls. Three of the OFC patients exhibited 'reversed IOR', with a 20 to 30 ms speeding when directions were repeated.

mean (s.d.)	Control		ACC		OFC	
Prosaccade RT (ms)	224	(39)	226	(25)	221	(46)
Prosaccade errors (%)	4.5	(1.4)	4.1	(6)	6.3	(2)
Prosaccade IOR effect (ms)	22	(21)	37	(29)	9	(26)
Antisaccade RT (ms)	343	(73)	304	(54)	317	(74)
Antisaccade errors (%)	28.5	(0.5)	20.2	(8.2)	28.2	(3.4)
Antisaccade IOR effect (ms)	5	(27)	28	(32)	-10	(25)

Table 6.3: Effect of ACC and OFC lesions on prosaccades and antisaccades. There were no significant effects except for reduced IOR in OFC patients.

For antisaccades, again the latency was not different between the three groups. Error rates were comparable between the three groups, compatible with normal distractibility in the rewarded task.

6.3.6. Apathy ratings

For each question in the LARS, two separate scores were recorded: first to quantify patients' current attitudes, and second, to ascertain how the patient felt they were before haemorrhage. The mean current LARS score was -13.4 (s.d. 7.1), with scores >= -16 indicating significant apathy. By this criterion, 13 of 19 patients were apathetic. The current LARS score (i.e. how patients were at the time of testing) was not different between groups, although there was a trend in the "Concern" subscale, for OFC patients to be slightly more apathetic (less concerned) than ACC (t=2.09, p=0.052).

The change in LARS scores (comparison with scores now with estimated scores prior to SAH) showed that overall, patients felt they were neither more nor less apathetic compared to pre-haemorrhage ($t(19)=0.73$, $p>0.05$). However examining individual subscales, there was significant decrease in motivation ($t(19)=2.91$, $p=0.008$), and a trend for reduced interests ($t(19)=1.83$, $p=0.083$). Grouped by lesion location, ACC patients had a significant decrease in motivation ($t(7)=3.0$, $p=0.015$), whereas OFC patients had become significantly more concerned than before—although they were still less concerned than ACC patients ($t(10)=3.3$, $p=0.010$) but without significant reduction in motivation.

In order to examine the brain areas which, when lesioned, increase apathy, voxel-based lesion correlation was performed with the three major subscales of the LARS. There were areas in anterior OFC which correlated with action initiation, but these did not survive correction for multiple comparisons (see **Appendix 9.5**).

6.3.7. No effect of laterality

Ten subjects had predominantly left-sided lesions, and nine had predominantly right-sided lesions. There was no significant difference between reward sensitivity in patients with left-sided versus right-sided lesions, both as measured by velocity ($t(18)=0.76$; $p>0.05$) and by reaction time ($t(18)=-0.06$, $p>0.05$). There was no difference in oculomotor capture rate between left and right-lesioned patients, and no difference in capture, RT or velocity of rightward *vs.* leftward saccades as a function of hemisphere.

6.4. Discussion

6.4.1. Summary

Using a rewarded oculomotor paradigm, I directly measured reward sensitivity in patients with focal ACC and OFC damage. Four patients had extreme values of reward sensitivity, but their lesions did not reveal a unique pattern. Dividing patients into two groups, those with OFC lesions showed decreased sensitivity to reward, as exhibited by a shallower reward slope of their velocity as a function of incentive. Reward generally improved accuracy and shortened reaction times, but less so in patients. Pupillary dilatation to reward was reduced in ACC patients. OFC lesions reduced inhibition of return, in keeping with previous studies (Hodgson et al., 2002a).

Since there were a variety of small lesions affecting medial cortex, it was possible to correlate lesion location with reward sensitivity. This yielded an area of ventromedial PFC that lay in the cingulate sulcus, just below the subgenual cingulate. This area may correspond to prelimbic or infralimbic cortex in lower mammals, an area extensively connected with the ventral striatum and medial temporal lobe (Beckmann et al., 2009). Posteromedial OFC lesions in animals have been shown to alter reward preferences, devaluation and extinction (Dias et al., 1996; Izquierdo et al., 2004; Rudebeck and Murray, 2011a). The data from this study thus provides causal evidence in humans for the hypothesis that reward representations for motivating action require posteromedial OFC.

This area, being densely interconnected with the ventral striatum, has been implicated in stimulus-reward pairing (Fellows and Farah, 2003; Roberts, 2006). One interpretation is that lesions to this area prevent reward cues from generating the

appropriate representation of stimulus value. This would not be in keeping with the autonomic findings, in that *pupillary* reward sensitivity may be spared: across subjects there was no correlation between velocity modulation and pupillary dilatation in response to reward. Some subjects have impaired reward sensitivity with normal pupil responses. This suggests that the deficit when this subregion is damaged lies in the motivation of action, guided by the incentive.

Rather than a monolithic function of encoding or processing reward, this posterior area may be responsible for the translation of incentives into actions (O'Doherty and Dolan, 2006). Such an account parallels the conclusions of the previous chapter, in which PD patients on medication had appropriate pupil dilatation to reward cues, but this was ineffectual at invigorating their saccades.

Thirteen of 19 of our patients would be considered to be pathologically apathetic as assessed on the LARS. Lesion location determined the *change* in apathy (i.e. difference between current state and patients' recollection of pre-SAH state). ACC patients had a significant decrease in motivation, whereas OFC patients had become significantly more concerned than before, without significant reduction in motivation.

One of the strengths of this study is that the patient group was relatively young, mostly still holding a job, and with no detectable neurological signs on examination. The lesions were confined to the vascular territory of the ACA. In commensurable studies of stroke patients, ischemic infarcts often co-occur with vascular risk factors, i.e. age, hypertension and diabetes. These factors make small lacunar infarcts, white matter disease and microinfarcts very likely in many patients (Kövari et al., 2004), and dementia develops in 25% of stroke patients within 3 months, compared to 3% in age-

matched controls (Kalaria and Ballard, 2001). This group is free of such effects and unlike similar surgical cohorts, none were on anticonvulsants.

6.4.2. Limitations

Three out of 20 patients had acute hydrocephalus at the time of the initial aneurysm, a condition which may cause diffuse damage to periventricular white matter (Haug et al., 2007). Two of these patients were in the ACC group. Given the small sample size and effect size, it is possible that the observed effects may not be directly attributable to the lesion locations. However it has previously been shown that, although acute hydrocephalus is a poor prognostic factor in the first 2 weeks after SAH (Hutter et al., 1998), the long term cognitive outcomes after 3 months are unaffected, as measured by standard clinical neuropsychometric testing (Kreiter et al., 2002). It still remains possible that more subtle effects, such as on motivation and attention, may persist.

Another issue is whether this study was sufficiently powered to detect effects. This power depends upon the variance of lesion (i.e. the balance of patients with or without lesions) in the area of interest (Kimberg et al., 2007). Thus, voxel-based lesion studies have varying power to detect effects at different areas in the brain. I used a simulation with 100,000 runs for each effect size to estimate the power to detect voxels with varying proportions of lesioning. Under the assumption that the effect size (of lesion upon action-initiation score) is 1 standard deviation from the unlesioned mean, then in voxels with an equal number of lesioned and unlesioned patients, the power is 60%. In contrast, in voxels with only 2 of 19 patients lesioned, the power is 31% (**Figure 6.8B**). If the effect size were 2 standard deviations, the best voxels have power 95%, and those with only 2 patients have power of 74%.

The most-frequently lesioned voxels in our data were in medial OFC. 75 voxels were lesioned in 7 patients, and 7 voxels were lesioned in 8 patients. The maps below are computed assuming a region-of-interest analysis, i.e. uncorrected p<0.05 (**Figure 6.8A**). One limitation of the study is that we do not know the actual effect size, i.e. how great a change in sensitivity would be expected after a lesion. It is therefore not possible to draw negative conclusions about the absence of an effect in voxels that do not show a correlation.

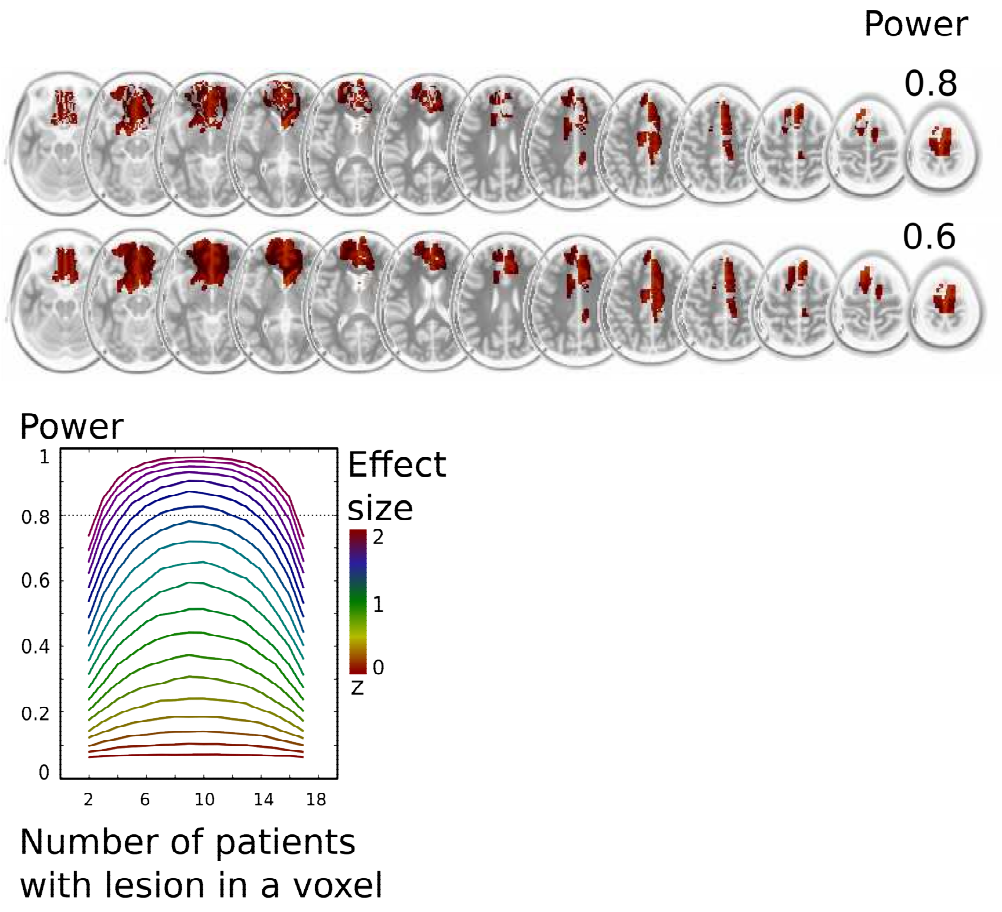


Figure 6.8: Power calculation for the cohort of medial PFC patients

A) A map of regions that have 80% (top) and 60% (bottom) power to detect a significant behavioural effect with size 2 s.d. from the control population. **B**) Simulation of how power varies depending on the number of patients, out of 19, who have a lesion at a particular location. The best power is of course found in voxels which are lesioned in half of the patients. In such voxels, there is 80% power to detect an effect size of 1.5 s.d.

In conclusion, although the study was able to provide evidence for a definite causal effect of OFC lesions in reducing reward sensitivity, it is not possible to conclude that other areas are not involved, particularly for effect sizes smaller than Z=2.

6.4.3. Conclusion

Damage to a small area of subgenual ACC is correlated with disrupted reward incentivisation of saccade velocity. In conjunction with the previous findings with dopamine and PD, it seems likely that the ventral striatum and posterior OFC function as a single unit in value processing.

7. Control cost explains the effect of reward

7.1. Introduction

7.1.1. Optimality and trade-off

A fundamental and long-established finding in motor control is the phenomenon of speed-accuracy trade-off: when movements get faster, they are less accurate (Fitts, 1966; Heitz, 2014; Salinas et al., 2014; Wickelgren, 1977). The speed-accuracy trade-off is central to almost all behavioural tasks, across species. According to optimal control theory, how accurately we make a movement is limited by noise (Bays and Wolpert, 2007; Davis and Vinter, 1985; Schmidt et al., 1979; Todorov, 2005). Because noise scales with the size of a motor command, it has been argued that to minimize the variance of movement end-points, there is an optimal duration and peak velocity for a given movement amplitude (Harris and Wolpert, 1998, 2006). In recent years, however, investigations on the effects of reward on movement have presented findings that are seemingly difficult to explain solely on the basis of motor or force costs.

In the previous chapters, I demonstrated that reward makes participants simultaneously both faster and more accurate in their responses. Motivation simultaneously increases *both* speed and accuracy, posing a serious challenge to theories of optimal control of movement, a finding confirmed in a range of studies in animals (Bendiksby and Platt, 2006; Chen et al., 2013; Opris et al., 2011; Takikawa et al., 2002d). In other words, the orthodoxy of the speed-accuracy trade-off is broken: movements are paradoxically both faster and more accurate when more reward is on offer. Similar effects have also been reported in humans (Blaukopf and DiGirolamo,

2006; Duka and Lupp, 1997; Jazbec et al., 2006; Mazzoni et al., 2007; Reppert et al., 2012; Shadmehr et al., 2010b).

Why should reward speed actions? Some investigators have proposed that temporal discounting of rewards, which gives a preference for earlier reward, explains the mounting time pressure as rewards increase (Haith et al., 2012; Shadmehr, 2010b; Shadmehr et al., 2010a; Xu-Wilson et al., 2009). Using a similar strategy, others have argued that movement duration and reaction time count as wasted time for an organism, thus driving fast responses when expected rewards are high (Niv et al., 2005, 2006, 2007).

Here I show that both of these theories yield comparable mathematical predictions about how reward increases vigour. However, crucially, neither gives a direct explanation of how reward can *simultaneously* increase accuracy. How is it possible to improve, if internal noise limits our performance? A consensus among optimal control approaches has been that error scales with the size of a motor command, and reward does not alter this relation (Hamilton et al., 2004; Qian et al., 2012; Reppert et al., 2012; Rigoux and Guigon, 2012). Is it possible that we are therefore suboptimal when we are not fully motivated? Or is there an *additional cost* to being precise, and if so, what is the nature of this cost?

One potentially important factor that has hitherto not been considered within this conceptual framework is the *cost of control*. Exerting control to improve precision might itself come at a cost, similar to the cost of motor commands in optimal control theory. Such a factor has been invoked recently to explain how incentive might increase

'cognitive control' by overcoming a cost (Holmes and Cohen, 2014; Shenhav et al., 2013). Here, for the first time to my knowledge, I provide a quantitative account of the cost of control, which extends traditional optimal motor control theories to explain how rewards might break speed-accuracy trade-offs. On this account, as reward is increased, the optimal speed and accuracy may both increase.

The dependence of error rate on reaction time is a classic instance of the speed-accuracy trade-off. The relationship is well described by a variety of rise-to-threshold accumulator models (for recent reviews see Standage et al., 2014; Summerfield and Tsetsos, 2012). Such models have been modified to incorporate invigoration by reward, postulating that the threshold can be preset to optimize reward (Bogacz et al., 2006). As they stand, accumulator models do not account for true motivational performance improvements. I applied the cost-of-control concept to these models, and demonstrate that, simply by allowing signal-to-noise ratio to be increased *at a cost*, accumulator models can explain the effects of reward.

In this thesis, I studied saccades – movements so fast that they are considered to be under ballistic control, in which feedback cannot influence the movement trajectory (Chen-Harris et al., 2008; Optican, 2005). The velocity of a saccade has often been regarded as rigidly determined by its amplitude (Bahill et al., 1975; Beers, 2007; Beers et al., 2004; Harris and Wolpert, 2006), until recent studies demonstrated modulation by reward (Chen et al., 2013, 2014). My model, which incorporates the cost of control, accounts well for the observed behaviour in which the classical speed-accuracy trade-off was broken.

In this chapter, I will discuss the shortcomings of existing trade-off models when motivation by reward is concerned. I then show that incorporating a control cost into

optimal motor control accounts for reward's effects on velocity and endpoint variability, and that a similar modification of the drift-diffusion model accounts for reward's effects of reaction time and error rates. Parameters fitted to the data from controls and PD patients capture differences between groups. Finally I discuss possible reasons why control should be costly—that is, if we can *sometimes* be extremely precise and fast, what could be the cost in real terms of doing this all the time.

7.1.2. Existing optimal control theory does not explain reward's effect

The findings in Chapter 2 demonstrated that reward can shorten reaction times, at the same time as improving accuracy in healthy people. The experiments reported in Chapter 3 revealed that saccade velocity can also be increased, whilst improving accuracy. This immediately poses a challenge for standard optimal control theories. In such accounts, the speed of a movement is determined by obtaining the highest speed and accuracy for the lowest energetic cost; therefore speed increases always come at a cost of accuracy (Harris and Wolpert, 2006; Todorov, 2004). The effects of reward do not fit with such a trade-off, since it is possible for us to be *both* fast and accurate when motivated. It would seem, *prima facie,* that we perform suboptimally when incentives are low.

I will now discuss current views on the biological mechanism of speed accuracy trade-off, and then consider in turn three possible accounts of reward's effects: temporal discounting, average reward rate, and risk. I explain why each of these also falls short. I finally put forward a model that can account for the effects, by incorporating *noise reduction at a cost*.

7.1.2.1. Previously proposed mechanisms of speed-accuracy trade-offs

If moving faster reduces accuracy, then emphasising accuracy should cause speed to suffer in order to boost accuracy. My results demonstrate this speed-accuracy trade-off in older participants and in PD, compared to younger controls. How might such a trade-off be generated at a neural level?

It has been tentatively hypothesised that such a trade-off may occur in the cortico-basal ganglia "circuit", in which ramping activity in cortical neurones may signal accumulation of information (Gold and Shadlen, 2007), whereas increasing activity in the caudate nucleus, under the control of DLPFC or SMA, might facilitate responding earlier but with less accuracy (Forstmann et al., 2008; van Veen et al., 2008). This would imply that the build-up and thresholding posited in race models might have separate anatomical correlates (Carpenter and Williams, 1995).

Alternatively, action may be withheld by activation of the subthalamic nucleus, under control of pre-SMA, ACC or the inferior frontal gyrus, leading to slower RT and more accurate responses (Aron and Poldrack, 2006; Bogacz et al., 2010; Niv, 2007). Control of threshold might also be achieved by plasticity in corticostriatal synapses dependent on dopamine (Lo and Wang, 2006). According to this model, the motor system non-linearly thresholds the cortical accumulated evidence, but its threshold is determined by inputs from internal pallidum or substantia nigra pars reticulata—which are ultimately under the control of prefrontal-striatal connections. All these anatomical speculations do not really further our understanding of what actually constrains speed and accuracy to be inversely related.

The limiting condition on how fast and accurately people can move may be the noise introduced in generating a motor command (Harris and Wolpert, 1998; Stevenson

et al., 2009; Todorov, 2005; Wolpert and Ghahramani, 2000): larger forces lead to larger variability in movement, and consequently reduced accuracy. If noise really is the limiting factor, and if the movement parameters are chosen *optimally*, then how can it be that motivation can improve performance further? Surely we would be behaving *sub*optimally, when we are not motivated?

7.1.2.2. Temporal discounting does not account for reward's effects

Recent modifications of optimal control theory have attempted to account for invigoration by reward. A solution might be that we *are* still optimal when incentives are low, but the cost of acting fast is effectively greater when reward is low (Shadmehr et al., 2010b). This mathematical trick inserts nonlinearity into the reward function, combining temporal discounting of reward, with cost of effort and error. Intuitively, if delayed rewards were *devalued* compared to sooner rewards, then as the reward increases, there is a pressure to respond sooner, i.e. an added cost of delayed responding. Due to this devaluation by time, optimal speeds would increase with reward level, and also with steepness of temporal discounting (Choi et al., 2014). Accordingly, individuals with steeper temporal discount functions respond more impulsively, in terms of speed and accuracy (Shadmehr et al., 2010b).

Temporal discounting may be modelled as an exponential or hyperbolic decay, such that the subjective value of a reward is higher if it is obtained earlier. Faster responding means earlier reward, yielding more utility (Shadmehr et al. 2010). This predicts that expected reward *R*, discount rate β, and effort scaling ε, determine the optimal response time *T*:

$$T \propto \frac{\sqrt{R} + \epsilon\beta}{R + \epsilon\beta} \tag{7.1}$$

movement time = (√ (expected reward of movement) + effort_scale ×

temporal_discount) …

See **Appendix 3** for mathematical derivation. Perhaps improbably, this trick assumes that *efforts* are *not* temporally discounted—that is, it requires that temporal discounting occurs at the level of reward, rather than at the level of net utility. Moreover to explain saccades, this approach requires temporal discounting to occur at timescales around 20 ms—which I believe is unprecedented. However for this discussion, the key problem with this account is that it rigidly predicts that reward increases error or variability.

7.1.2.3. Average reward rate does not account for reward's effects

An equivalent but slightly different formulation of this optimisation, that does not rely upon temporal discounting, can be given in terms of ongoing reward rate (Niv et al., 2007). In a scenario in which rewards are available over the course of an experiment, the *average* rate of reward can be estimated. If rewards are conditional on responses, then any time spent not responding corresponds to a cost proportional to this 'wasted' time. Reward therefore increases urgency, and time pressure in responding can be expressed in terms of an ongoing expected *rate of reward* (Niv, Daw and Dayan 2005). Time pressure manifests as a cost inversely proportional to response time. For optimal responding, the ongoing reward rate R* determines response time T:

$$T \propto \frac{1}{\sqrt{\bar{R}^*}} \tag{7.2}$$

movement time = 1 / √(expected optimal ongoing reward rate)

These two above approaches tackle the problem of impulsivity, and have independently arrived at a concept of vigour. In the former case, vigour is given as the ratio of effort

cost to temporal discount rate. In the latter case, vigour is a function of the ongoing reward rate (**Appendix 3**) and may be signalled by tonic dopamine (Mazzoni et al., 2007) as well as activity in nucleus accumbens (McGinty et al., 2013). The situation for vigour is illustrated in **Figure 7.2A**.

Both of these treatments of reaction vigour predict that movements are faster, and RT is shorter, when reward is present. As I have derived in Appendix 3, both make similar quantitative predictions. However, they are both unsatisfactory. Both theories require that reward increases movement error. That is, as the utility of responding early increases, we are willing to accept greater motor error.

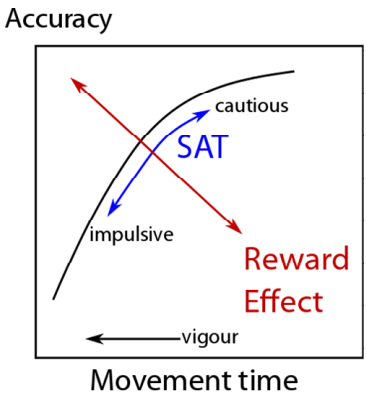


Figure 7.1: Speed-accuracy trade-off (SAT) does not explain the effects of reward
Optimal control theories explain reward's invigoration of action by positing that fast actions are more valuable (blue arrows). However on their own they do not explain how accuracy and speed can be modulated together (red arrows).

Thus *neither* theory explains how reward can maintain constant error rate (or even reduce error) in tandem with increasing movement speed. In particular, rewards can increase amplitude, speed and accuracy (Reppert et al., 2012; Takikawa et al., 2002b).

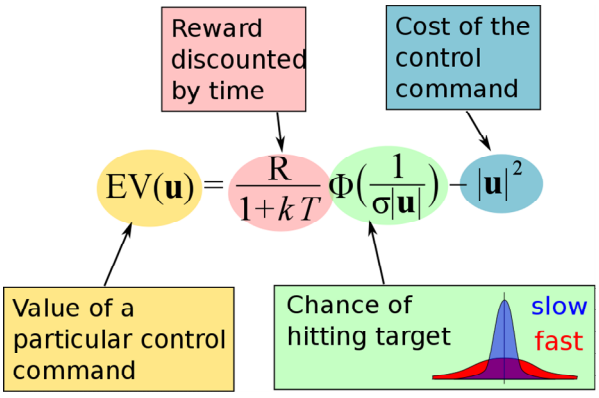
7.1.2.4. Risk does not account for reward's effects

One alternative explanation is that when rewards are higher, the effective risk of not obtaining the target is greater. Economically, for reward R,

$$\text{Risk} = R^2 \cdot P\,(\text{success}) \cdot P\,(\text{fail}). \tag{7.3}$$

Put simply, increasing rewards under risk make accuracy even more important, relative to speed. Risk aversion, therefore, would impose a greater weighting for accuracy when reward is high (Stritzke et al., 2009; Trommershäuser et al., 2008). This must then be simultaneously *combined* with a vigour effect on movement speed, as above. The combined account predicts that risk aversion, in conjunction with temporal discounting, might explain incentive effects. Risk-averse individuals are predicted to be slower and more accurate with reward, whereas temporal discounters speed up, sacrificing accuracy.

Putting together the components of risk and temporal discounting, the general form of models thus far, can be summarised in the following equation:



(7.4)

However even this account does not allow that the speed-accuracy constraint can be broken. That is because the cost of speed, or any other *'effort' cost*, for example

energy, is set against proportional noise (Diedrichsen et al., 2010), and other putative costs such as "attention" do not feature in this framework (Reppert et al., 2012).

Moreover, when extending the models to *hierarchical* motor control, it is not obvious how such costs might feature in higher-level control signals or policies. These higher-order, internal signals, which control the gain at lower levels of motor control, are not costly in standard motor control, but are important for establishing well-controlled action by applying appropriate contextual feedback. Taken with evidence from Chapter 2 and 3, I suggest that an explanation of vigour is called for that accounts for *improved accuracy*, and that the cost of non-motor command signals might be a missing ingredient.

7.2. Quantifying cost of control

7.2.1. Application to optimal motor control theory

A standard assumption of optimal control theory is that motor noise is proportional to the size of the motor command. Generating faster movements requires larger motor signals, so movement speed is limited when accuracy is required, because the motor command **u** is subject to greater neural noise. This proportional noise is usually assumed, because the plant output is a linear stochastic function of the control signal:

$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{B}\left(\mathbf{1} + \mathbf{C}_i\phi_i\right)\mathbf{u} \tag{7.5}$$

change in state = **A** * current state + **B** * motor command + **BC** * motor noise proportional to command

where **x** is the state of the system, **A** and **B** are operators representing state evolution and muscle effect. **C** is a set of motor noise matrices corresponding to a set of Gaussian random variables ϕ. This equation illustrates that the random variables ϕ multiply **u**, i.e. the perturbation by motor noise is multiplied by the size of the motor command—embodying the assumption that noise is proportional to the control signal.

In a feedback control system, noise can be counteracted by feedback signals. In a ballistic system that only estimates external states, it would *not* be possible for both accuracy and movement speed to increase simultaneously, for a given movement amplitude (Diedrichsen, Shadmehr and Ivry 2010). However, if some of the states **x** are internal, noise in estimation of these states can be counteracted by internal control signals. In the general case, the state estimate $\hat{\mathbf{x}}$ denotes not only representations of the world's state but also internal state, and the command **u** can produce both internal and external effects (Todorov 2005). Internal states can therefore be corrupted by internal noise, yet be steered towards optimality using internal components of control signals.

To make this transparent, we can reformulate the plant model to include an additional control signal that is able to reduce noise. This extra "response precision" signal might be thought of as increasing the signal-to-noise ratio in the generation of a force. If **u** splits into a force-determining component $\mathbf{u_F}$ and precision-determining component $\mathbf{u_P}$, we have

$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{B}\left(\mathbf{1} + \frac{\mathbf{C}_i\phi_i}{u_{P,i}}\right)\mathbf{u_F} \tag{7.6}$$

change in state = A * current state + B * motor command + BC * motor noise proportional to motor command / precision-command

In this equation, there may be as many precision commands as there are motor commands. In our saccadic task, all quantities are scalar, and there are only two control signals: the size of the force signal u_F and the amount of control exerted u_P. As u_P increases, the noise amplitude is scaled down. Optimal choice of action involves selecting a pair **u**, which minimises $|\mathbf{u}|^2$ and maximises reward. Effectively, permits noise to be reduced at a cost. A simple treatment is given below, for the case when a fixed reward *R* is given for saccades in a fixed radius, and assuming a constant profile of **u**(*t*) scaled over time and amplitude.

To derive the value from the motor command, we note first that for constant amplitude, the movement time is inversely proportional to the square root of force amplitude u_F. This is because the distance travelled $\propto \iint u_F dtdt$. Second, we note that the standard deviation of amplitude error is directly proportional to u_F as usual, but should now also be inversely proportional to precision u_P, which offers control over endpoint accuracy. The chance of landing in a region of diameter 1, when the endpoint variability is σ, is given by $2\Phi\left(\frac{1}{\sigma}\right)$, where $\Phi(x) = \frac{1}{\sqrt{2\pi}}\int_0^x e^{-s^2} ds$ denotes the normal error function. This gives an action value function EV(**u**) that is proportional to

$$EV(\mathbf{u}) \propto \frac{R}{1 + k/\sqrt{u_F}} 2\Phi\left(\frac{\sqrt{u_P}}{\sigma_0\sqrt{u_P} + \sigma u_F}\right) - |\mathbf{u}|^2 \tag{7.7}$$

Expected value of action = Reward / (1+ discount rate × movement time) × probability of landing on target – cost of control signal

where σ_0 is the baseline variability of endpoints, σ is variability that can be controlled by the precision signal u_P, and the temporal discount factor is denoted by *k*. The first term is the discounted reward multiplied by the probability of the Gaussian distribution of endpoints lying within a unit radius from the target, and the second term is the *cost of*

the command. σ is a single parameter in the model that encapsulates three different aspects of behaviour: a subject's baseline variability, the relative cost of a precision signal relative to energetic (force) cost, and also the target size. The units of **u** have been matched to reward, and scaling constants are absorbed into *k* and σ.

If *k* and σ are held fixed, then the costs of vigour and precision (**Figure 7.2A and B**) both constrain performance. Maximising the value over **u** gives an optimal speed and optimal accuracy as a function of reward (**Figure 7.2C**).

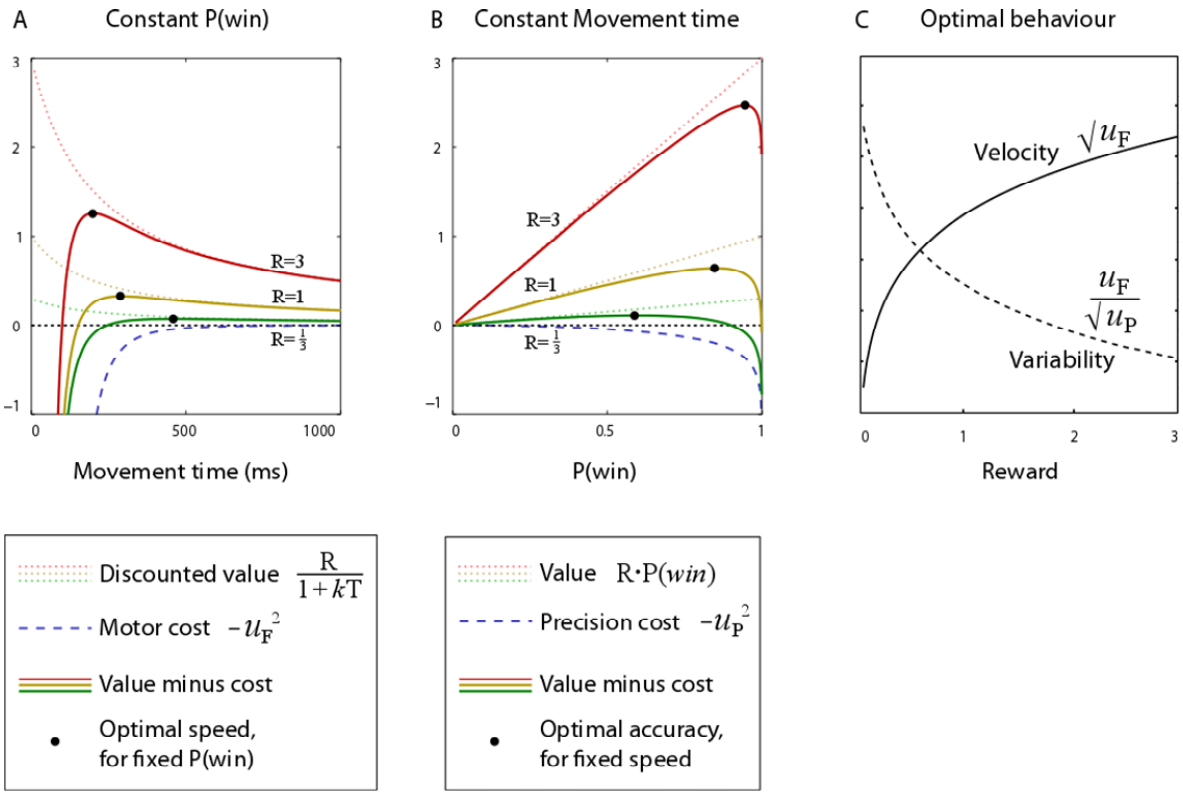


Figure 7.2: The costs of inaccuracy, sloth and control

If inaccuracy is expensive due to missing targets, sloth is expensive because of temporal discounting, and control is expensive due to implementation details, then a three-way balance obtains.

A) For a given reward *R*, temporal discounting causes the reward's subjective value to fall for longer movement times (dotted lines). However, moving faster entails greater energy expenditure (blue dashed line). The net value (solid lines) show that the optimal movement is faster with higher reward (Rigoux and Guigon 2012).

B) The cost of control allows the endpoint variability to be reduced at a cost. The probability of landing on a fixed-size target can be increased if a "precision cost" is paid (blue dashed line). The increases the average gain (dotted line), as shown for three different reward levels. The net value (solid lines) illustrates that the optimal movement is more precise with increasing reward.
C) If both speed and accuracy are both free to vary, the optimum pair can be determined as a function of reward. Reward increases the optimal movement speed, and when temporal discounting is not too large, reduces the optimal endpoint variability.

7.2.2. Numerical solutions for optimal motor control with precision cost

The solutions yield predictions for the control signals u_F and u_P as a function of reward R, and consequently, for saccade velocity and endpoint error. Analytic solutions do not exist, but predict that velocity varies with reward R, in the approximate form $a+\sqrt{(bR+1)}$, similar to the previous reward-rate (Niv et al. 2007) and temporal discounting (Choi, Vaswani and Shadmehr, 2014) formulations of vigour. Additionally, velocity depends on the internal noise σ, approximately in the form $\sqrt{(\sigma^2 + a\sigma + b)}$.

To obtain numerical solutions for the effect of reward R, temporal discount rate k, and motor noise σ on the optimal velocity and variability, the optimal values of u_P and u_F were calculated. Each pair $[u_P, u_F]$ is associated with a cost $J = -EV$ (**Figure 7.3A**). For each parameter triplet $[R, k, \sigma]$, the cost function was minimised using gradient descent from 10 random starting points. This was performed first for 50 levels of reward ranging from 0.05 to 3, and 50 levels of k ranging from 0.05 to 2 (**Figure 7.3B**, left), and then for the same 50 levels of reward, with 50 levels of noise ranging from 0.1 to 8 units (**Figure 7.3B, right**). The corresponding behavioural solutions for are portrayed in **Figure 7.3C** for k=1, for various rewards R and noise levels σ.

The two critical features are that the optimal velocity increases with reward, and when discounting is not too large, endpoint error *falls* with reward. Interestingly, under strong temporal discounting, i.e. when there is a strong preference for sooner rewards, endpoint error *increases* with reward, while trading off accuracy. Remarkably, this is precisely the effect that was found in section 2.2 (**Figure 2.3a**). In that experiment, error rate paradoxically increased with reward, while speed increased, and was explained as "choking" on reward. Choking is predicted for low-noise, high-urgency situations, when the discount rate is significantly faster than 1/(movement time).

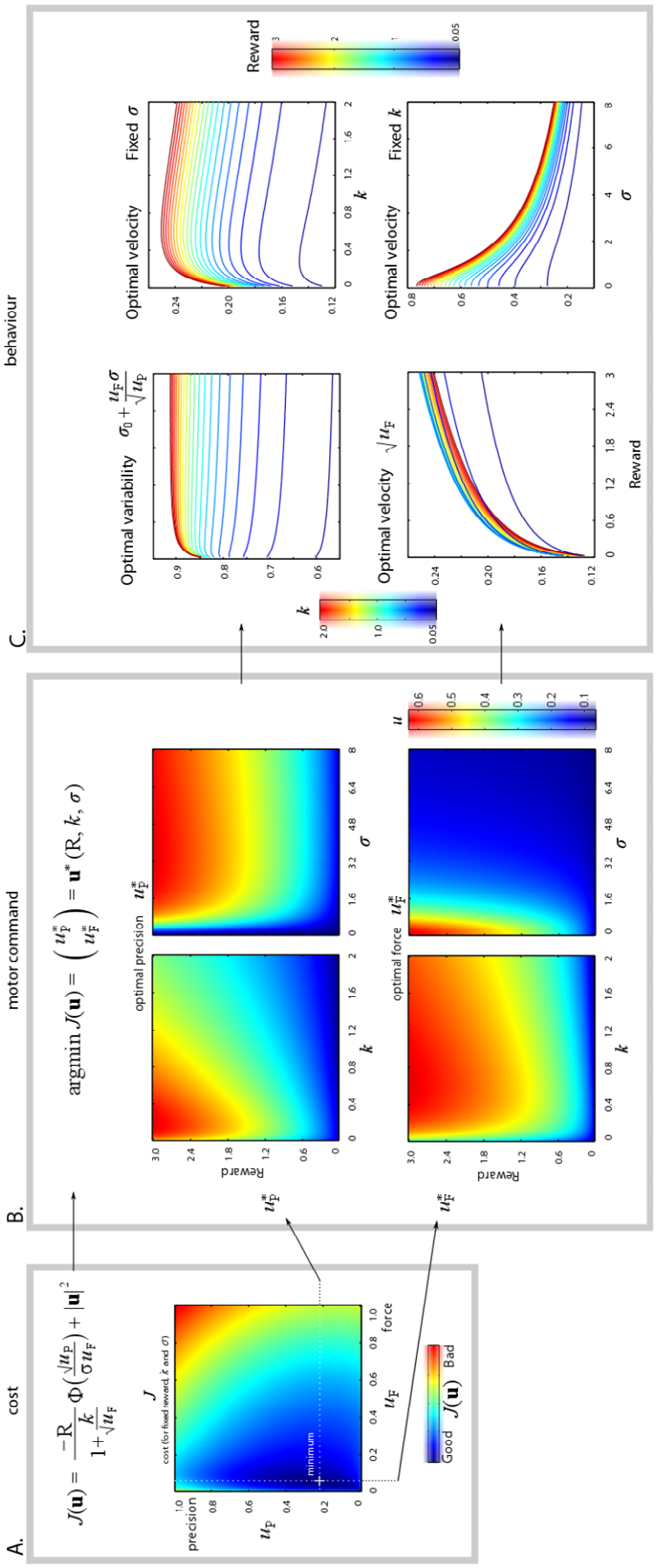

A.
cost
B.
motor command
C.
behaviour
optimal precision
optimal force
Reward
Optimal velocity
Fixed σ
Fixed k
Optimal variability
Good
Bad
minimum
precision
force

Figure 7.3: Optimal control model of the effect of reward incentive

In order to account for the ability of reward to improve both speed and accuracy, I hypothesised that in addition to a 'vigour' or force signal (u_F) that determines a movement's speed, individuals are also able to generate a 'precision' signal (u_P) that determines the amount of variability in a movement. Crucially, this precision signal is also costly.

A) Each given motor command, i.e. a pair of force and precision (u_P, u_F), gives rise to a cost J, composed of three elements. First, the reward available is temporally discounted by the time taken by the movement, e.g. by hyperbolic discounting $1/(1+k/u_F)$. Second, this reward is only obtained if the saccade is on target; I assume a Gaussian variation Φ of the endpoint proportional to the size of the motor command. Third, although we can go faster to reduce discounting (increasing u_F), and be more precise to reduce error (increasing u_P), both of these incur a cost proportional to the squared control signal, $\mathbf{u}^2$. This leads to an optimal combination of force and precision for each movement, where J is minimised.

B) The optimal motor command for a situation depends on the reward level, and on two subject-specific parameters: discount rate k and the internal controllable noise σ. Precision (upper panels) and force (lower panels) are differentially influenced by reward (y-axis). Moreover the effect of reward depends on k and σ (left and right panels respectively).

C) The generated commands determine the velocity and duration of each movement, and the amount of variability given a desired amplitude. Reward always increases velocity (left panels). A subject with low discounting (e.g. $k<0.5$) becomes less variable with higher reward, whereas a subject with high discount rates (e.g. $k>1$) tends to become more variable with higher reward (upper panels) as they are under greater time pressure.

7.2.3. Application to drift diffusion model

Can a similar approach also be used account for RT and oculomotor capture results? Standard speed-accuracy trade-offs are often specified in terms of a rise-to-threshold model, in which the threshold can be adjusted depending on the environment (Bogacz et al., 2006; Luce, 1986; Ratcliff, 1979). The accumulator is often described as

$$\frac{dA}{dt} = \mu + \sigma\mathcal{N} \tag{7.8}$$

In the drift-diffusion model (Smith and Ratcliff, 2004), the accumulator accumulates noise over time, and stops when a positive or negative threshold $\pm\theta$ is reached. As with motor control, these models have been modified to incorporate the invigorating effects of reward (Bogacz et al., 2006; Simen et al., 2006). These models show that adjustment of decision thresholds can generate certain observed speed-accuracy trade-offs. However, the effect of motivation by reward, as presented so far, clearly cannot be accounted for as a change in threshold in accumulator models, but would rather require a change in the rate of accumulation.

In order to improve both speed and accuracy, reward must effectively increase μ or decrease σ by increasing the signal-to-noise ratio of information accumulation. On traditional accounts, motivation is often stipulated to increase attention, perceptual gain, or alertness (Hickey et al., 2010d; Maunsell, 2004; Sarter et al., 2006; Watanabe, 2007), with consequent increases in this signal-to-noise ratio. But why would motivation do this? Here I treat control signals themselves as constituting a cost, similar to the cost of motor commands in optimal control theory. Reducing irrelevant signals (noise) is costly. In other words, the brain has capacity to effectively increase μ/σ, but that it sometimes chooses not to, and that this choice is an economic one. As with motor control costs, I insert a "precision control cost", u_P, which reduces noise:

$$\begin{aligned} \frac{dA}{dt} &= \mu + \frac{\sigma\mathcal{N}}{u_P} \\ EV\left(u_P, \theta\right) &\propto \frac{R}{1+kT} \cdot P\left(\text{correct}\right) - u_P^2 \end{aligned} \tag{7.9}$$

for a given reward R, reaction time T, and delay discount rate k. According to this, subjects accumulate a fixed μ with fixed baseline noise σ, but can adjust both their precision control u_P and response threshold θ in order to concurrently a) minimise error

rate, b) minimise reaction times *T*, and c) minimise the cost of control. Our modification here means that noise might be reduced at an expense, which would allow a lower threshold to be set for achieving a given accuracy level.

Note that the ability to attenuate noise is mathematically equivalent to an ability to amplify signal. An ability to multiplicatively increase μ would lead to identical results; indeed attention is often supposed to act in this manner (Carandini and Heeger, 1994; Reynolds and Heeger, 2009), but such models of attentional amplification generally assume subsequent divisive normalisation, so effectively attenuating noise (Boynton, 2005; Cohen and Maunsell, 2011).

My formulations of control cost are agnostic about the mechanism by which the precision signal operates. Noise could be reduced by increasing neuronal pools, by tighter negative feedback, or by somehow impeding propagation of irrelevant signals (discussed below in **section 7.2.4**). Whatever the nature of u_P, ultimately, the amount of control exerted is optimised to maximise reward. When temporal discounting of reward is considered, there is an optimal expenditure on precision that will speed up performance. Increasing incentives may therefore increase the optimal level of control, and thus break the speed-accuracy trade-off. Introducing the control cost explains quantitatively how motivation can cause a "true improvement" in performance.

7.2.4. Numerical simulations of drift diffusion with control cost

A drift-diffusion simulation of decisions was run, in which subjects can vary both their precision and response threshold, in order to optimise reward rate. In one run, 2000 trials were simulated, and results were averaged over 10 runs. Parameters that were varied included twelve levels of reward ranging from 0.25 to 3, eight levels of the signal

μ ranging from 1 to 8, and three levels of accumulator noise σ = 1, 2 and 3. Diffusion proceeded according to

$$\delta A = \left(\mu + \frac{\sigma \mathcal{N}}{u_P}\right) \delta t; A(0) = 0 \tag{7.10}$$

such that the accumulator A increases or decreases with mean rate μ, perturbed by a Gaussian random variable N which is scaled by the internal noise σ, divided by the precision signal u_P which a subject can increase to control the overall noise.

The reaction time for each trial was calculated as the first time step at which either A > θ or A < –θ . For each condition, the cost function (precision^2 minus reward) was calculated, assuming that reward that falls off over time as or $1/(1 + k \cdot RT)$. (similar results obtain for a $e^{-k \cdot RT}$ falloff, as in my experiments). The cost of one unit of precision was scaled to 70, to produce reaction times of the order 200 ms. In order to calculate the optimal precision u_P and threshold θ for each condition, the cost was minimised over u_P and θ. Minimisation was performed using a pattern search with 10 random starting points for each condition. Finally, the mean optimum RT and accuracy, corresponding to the optimum control parameters, was calculated for each condition.

$$\frac{dA}{dt} = \mu + \frac{\sigma}{u_P}N$$

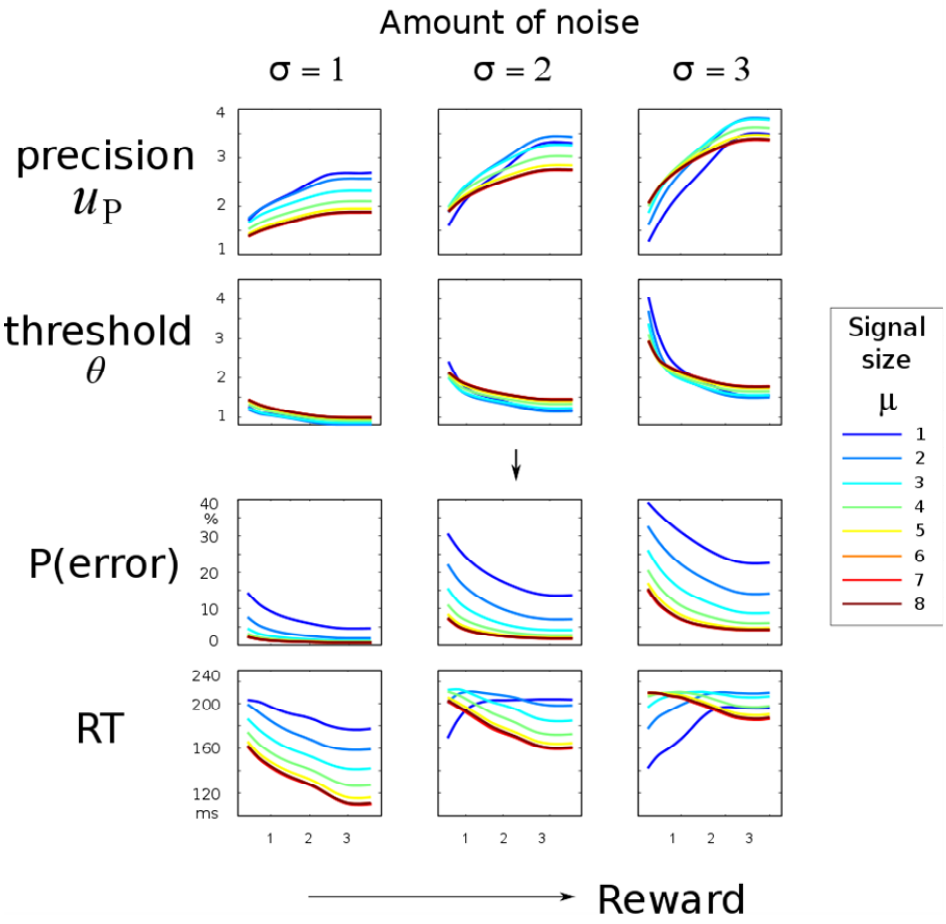


Figure 7.4: Simulated optima for drift-diffusion with control cost

Drift-diffusion was simulated with a variety of signal size (μ) which governs rate of rise, noise (σ), and reward levels. For each condition, the optimal pairing of threshold and precision is selected; precision allows the noise to be reduced, but at a cost. Reward is temporally discounted by the reaction time, and is proportional to accuracy—whether the decision terminates at the positive boundary. **A**) As reward increases, it is optimal increase the precision, and lower the decision threshold. **B**) This leads to improved accuracy. When the signal-to-noise ratio is high, reward encourages faster responding. However when the decision is noisy, reaction times actually increase with reward, despite falling thresholds, because the increased precision attenuates "fast-guessing".

The simulations showed that reward increased accuracy. The effect of reward on reaction time was variable: if signal-to-noise was high, then reward shortened the

optimal RT. In contrast, if signal-to-noise was low, i.e. at the highest levels of σ and lowest levels of μ, then increasing rewards led to longer RTs. This captures the intuition that when option selection is difficult and stakes are high, caution is the best policy. Note that in this case, despite a lower the threshold, caution is achieved by increasing the precision signal, preventing "fast guesses".

The simulation was also run using different scaling for precision units, and using a simple exponential reward-falloff function. The results were qualitatively similar, with reward improving both speed and accuracy. Some drift diffusion models have also included stochastic starting points of the accumulator, such that $A(0)$ is chosen from a uniform distribution in a range $\pm\alpha$ (Ratcliff, 1981; Ratcliff and McKoon, 2007; Ratcliff and Rouder, 1998). This extension enables diffusion models to account for the conditional accuracy function, in which early responses are more likely to be errors, seen in our data. I repeated the simulations with $\alpha=0.6$, rather than zero, and obtained qualitatively similar results.

7.3. Fitting of PD data to the model

The mean velocity and amplitude variability for the three reward conditions were fitted to the model, for each participant, by minimising the squared error using a simplex search. The three free parameters were: the temporal discount rate k, the controllable motor noise σ, and a baseline (fixed) variability σ_0. Fitting the model to each subject's data yielded best-fitting k, σ and σ_0, to explain their velocity and variability as a function of R. A high discount rate indicates high time pressure, in that rewards are quickly devalued by waiting. The noise σ represents endpoint variability, in units relative to the target size in this task. The baseline noise σ_0 is an additive contribution to

variability that increases the minimum endpoint dispersion for each subject. The control signal **u** thus predicted the velocity, as $\sqrt{u_F}$, and the variability as $\sigma_0+\sqrt{u_P}/(\sigma\ u_F)$.

The model parameters for each subject were compared using nonparametric tests (Wilcoxon signed rank test for comparing PD ON and OFF; Wilcoxon rank sum test for older vs. younger participants and PD vs controls). Older healthy participants had larger baseline noise σ_0 than their younger counterparts, reflecting their greater baseline variability, with little difference in reward sensitivity. PD patients, compared to older controls, had significantly increased controllable noise σ. This presumably reflects their tendency to go slower, in order to lower motor variability in the face of noise.

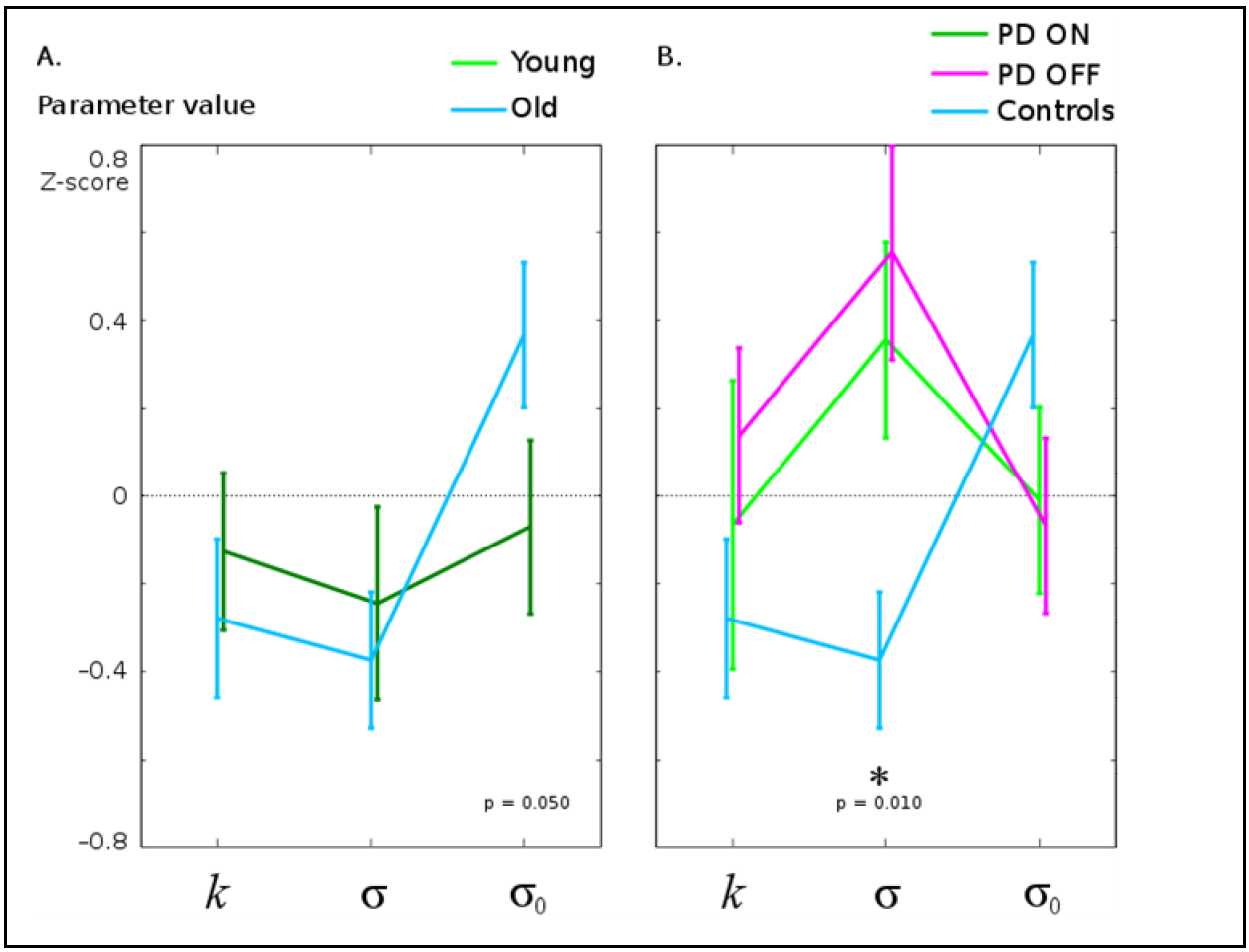


Figure 7.5: Motor control model parameters

Optimal motor control models were extended to incorporate the cost of precision. Each participant's velocities and amplitude variability was fitted, as a function of reward, to the model, and yielded three parameters per subject, describing their temporal discount rate *k*, the amount of motor noise σ that could be attenuated by precision, and their baseline (fixed) variability σ_0.
A) Old subjects had increased fixed noise (p=0.050). This reflects increased saccade endpoint variability with no consequences for control. **B**) Patients with PD had significantly increased controllable noise (p=0.010). This reflects their tendency to slow down, in order to further control noise while maintaining precision.

7.4. Discussion

7.4.1. Summary

Standard models of behaviour, including optimal motor control and the rise-to-threshold models, stipulate that human performance is limited by trade-offs. This is due to fundamental bounds due to intrinsic system noise. Consequently, these models do not account for motivation by reward. By introducing a cost for noise reduction, these models predict that when reward is high, we should in fact invest in reducing noise, to maximise gain. This cost mathematically encapsulates the notion of effort within existing frameworks. Crucially, PD patients have *increased* (controllable) *noise*, suggesting that dopamine could be critical in noise control.

7.4.2. Dopamine and cost of control

In both animals and humans, dopaminergic stimulation increases willingness to exert an effortful force for reward (Salamone et al., 2007; Treadway et al., 2012; Wardle et al., 2011). Indeed, it has been proposed that a key mechanism by which reward might potentially exert its effects on *vigour of response* is via dopamine (Beierholm et al.,

2013; Kojovic et al., 2014; Niv et al., 2005, 2007). But how is it possible to do this without trading off accuracy for speed? One possible explanation is via attention, e.g. amplifying relevant sensory signals or suppressing irrelevant signals. Such a mechanism is stipulated to require an effort cost and may involve dopamine (Ahveninen et al., 2000; Christian et al., 2006; Chudasama and Robbins, 2004; Clark et al., 1989; Coull et al., 1995; Kähkönen et al., 2001; Nieoullon, 2002; Salo et al., 1996; Servan-Schreiber et al., 1998; Shelley et al., 1997; Troscianko and Calvert, 1993).

Dopamine might be a critical modulator of speed and accuracy, due to its neuromodulatory effects on *noise* or *gain*. As noted above, the ability to reduce noise is formally identical to the ability to amplify signal then normalise. We can therefore consider PD as a brain state in which there is increased effective noise, or reduced effective gain on relevant signals. Since σ multiplies the variability term, it could equally be described as PD patients requiring larger target sizes for equivalent performance, or that healthy volunteers are effectively rendered Parkinsonian when targets are very small. Equivalently, a unit of precision is more expensive for PD patients: they require greater u_P to attain comparable speed and accuracy. All these aspects are interchangeable from the mathematical viewpoint. Arguably, the most neurally plausible interpretation is that dopamine controls noise levels.

Dopamine has been implicated in the speed accuracy trade-off by boosting action initiation (Pessiglione et al., 2005; Ratcliff and Frank, 2012), and by virtue of its effects on learning in the striatum, which might alter the threshold for reaching a decision (Bogacz et al., 2006; Wang, 2008). Alternatively, dopamine might exert its effects by directly modulating either neuronal transmission noise or gain (DeFrance et al., 1985; Kroener et al., 2009; Puumala and Sirviö, 1998; Seamans and Yang, 2004;

Seamans et al., 2001; Servan-Schreiber et al., 1990; Surmeier et al., 2007), or network coupling (Hammond et al., 2007; Onn et al., 2000). Via these neural-level mechanisms, dopamine could potentially improve performance (Ashby and Casale, 2003; Servan-Schreiber et al., 1990). However, these modulatory mechanisms have generally been treated as separate from the effect of reward on vigour, which is increasingly recognised to be under dopaminergic control (Beierholm et al., 2013; Niv et al., 2005, 2007). If reward motivates true improvements in speed and accuracy, as I suggest, then a likely candidate mechanism might be dopamine increasing the precision of neural control signals (Friston et al., 2009; Yu and Dayan, 2005).

This leaves open two crucial but linked questions: 1) How can noise be reduced, if it is an intrinsic property of a system? 2) Why should it be expensive to reduce noise, and what is the cost in real terms?

7.4.2. Neural mechanism of true performance improvements

If *noise* is the limiting factor in selection of action, for example, neural noise in the generation of the motor command, then how can this noise be reduced by reward? Noise is normally considered to be an intrinsic property of neurones, so special measures are needed to reduce it. This is really the only way to create a true *overall* improvement in performance, without any sacrifices.

I will now consider in turn three possible accounts of how neuronal noise might be reduced *at a cost*, and I explain why each of these falls short. Finally I discuss two possibilities which appear more promising: the entropy increase generated by control signals themselves, and the potential cost of ignoring irrelevant information.

First, noise might be minimised by *recruitment* of larger populations of neurones to represent the motor command. In this case, redundancy of representation (many cells communicating the same motor signal) facilitates an accurate motor command, thus allowing more speed. This follows from an assumption that population codes are "read out" by combining information across multiple noisy units (Pouget et al., 2003; Seung and Sompolinsky, 1993). Under this assumption, if more neurones are used to encode a signal, then that signal is less susceptible to degradation by noise (Faisal et al., 2008), such that when N independent channels are used, noise is reduced by a factor of $\sqrt{N}$.

This recruitment explanation is attractive for explaining why there is a limited resource. It makes the intuitive prediction that cellular firing and brain metabolic activity should generally increase with reward and performance, which appear to fit current data (Knutson and Cooper, 2005; Knutson et al., 2005; Platt and Glimcher, 1999; Serences, 2008; Tobler et al., 2007). I am not aware though of any evidence that neurones could be dynamically reassigned or remapped in this way, to one function or another. Moreover we are very far from having even a theoretical neuronal mechanism for how this recruitment or reallocation might arise.

A second approach is that the impact of noise can be mitigated by reducing *noise correlation*. Poisson spiking noise, which appears to accompany all decoded neuronal signals, is correlated between cells that encode the same variables (Zohary et al., 1994), and this noise correlation is a key contributor to the inefficacy of neuronal representations (Averbeck et al., 2006; Sompolinsky et al., 2001). It has been hypothesised that striatal dopamine plays a role in reducing correlation in cortical neurones (Courtemanche et al., 2003; Bar-Gad et al., 2003; Hammond et al., 2007). But theoretical considerations have shown that correlated noise only reduces Fisher

information when neuronal receptive fields are very similar, and correlations are very long-rage. Moreover in many situations, information content actually increases with noise correlation (Abbott and Dayan, 1999; Romo et al., 2003). Even more disappointingly, this does not explain how the resource limitation arises: why don't we always have decorrelated noise?

A third approach to noise reduction also invokes dopamine. It is possible that the ability of cortical neurones to switch between two modes of firing may underlie the ability to suppress noise. The pyramidal cell membrane may have a variable response to excitatory and inhibitory postsynaptic potentials: there may be a linear summation, or a highly nonlinear, potentially bistable response. The *degree of nonlinearity* has been proposed to be under dopaminergic control, e.g. by D1 receptor stimulation promoting NMDA (especially calcium) currents that alter membrane metastability (Ashby and Casale, 2003; Durstewitz and Seamans, 2002; Durstewitz et al., 2000; Nicola et al., 2000). However, computational neurophysiological simulations have recently shown the membrane bistability hypothesis to be less plausible. But even if a mechanism for it were elucidated, what would be the dynamic effect of increasing the nonlinearity? If pools of competing response neurones are responsible for generating the motor command, then as expected, it would promote faster decision times (Lo and Wang, 2006; Wang, 2002; Wong et al., 2007). But it is not clear that accuracy can be increased using this method.

7.4.3. No free lunch: entropy

The question as to what constraints limit *joint* improvements in speed and accuracy (**Figure 7.1**) is quite distinct from the question of what constrains speed and accuracy to trade-off with one another (Kurzban et al. 2014).

Trading off both speed and accuracy to save energetic costs may be a *pervasive feature of homeostasis*, stemming directly from the fact that energy is dissipated by any adaptive feedback process that corrects a perturbation (Lan et al., 2012). When a system's state deviates from a set-point, feedback signals cause a potential gradient (or equivalently a force) that restores the system to the same macroscopic state as previously. Although this force returns the system to the desired state, it does not do so via exactly the same route that the system was displaced along. The nonzero path integral of this force over the excursion of the system from the set point generates entropy (Tomé, 2006). The same principle applies to maintaining the *status quo* in the face of noise: when small random fluctuations are present—e.g. a random walk or Wiener process—a potential well or restoring force is also required to maintain the system in a constant state.

It turns out that maintaining the *status quo* is itself energy expensive. A control signal or, equivalently, restoring force $\mathbf{F} = \nabla V$ (which can be expressed as the gradient of some potential V on the manifold of states), counteracts the effects of microscopic fluctuations, even when the macroscopic state remains stationary. Due to this, entropy is continually generated and transferred to the environment. The entropy gain ΔS depends upon how tight the control is, and on how large the fluctuations are. The rate is given by the expectation of the following function of the control signal:

$$\frac{d}{dt}S = \left\langle \frac{1}{D}\mathbf{F} \cdot \mathbf{F} + \nabla \cdot \mathbf{F} \right\rangle \tag{7.11}$$

where D is the rate of diffusion away from the desired point, and $\nabla \cdot \mathbf{F}$ is the divergence of the restoring force, i.e. its local gain.

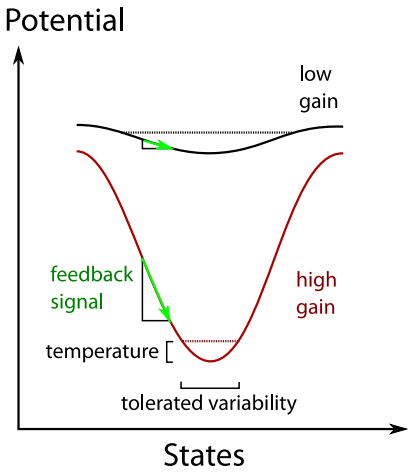


Figure 7.6: Feedback controllers expend energy in maintaining their desired state in the face of noise, depending on the gain.
If a system's state is subject to stochastic fluctuation (due to temperature), then to maintain a desired state, a restoring force is required. This force generates an "energy well", into which the system tends to fall. Thermal noise causes the system's state to vary around the set-point. To attain a small variability, steeper feedback functions are required.

To summarise, in non-stochastic systems, there is no such energy dissipation, and restoring the macrostate of the system also restores the microstate: no information is lost. In contrast, in a stochastic system, by virtue of the fact the system has temperature, the restoring forces do not restore microstates, and entropy must be dissipated to the environment in the form of heat. This general principle applies to any system that maintains macroscopic states, in the face of stochastic noise. Similar ideas have also been endorsed by Friston (2011). Thus, there is a fluctuation-dissipation relationship between dissipation of power and production of entropy (Tomé, 2006). How does this apply to vigour of movement?

The principle immediately suggests that simply by representing and implementing a control signal, for example prediction errors in perception or motor control (Huys and Dayan, 2009; Mumford, 1992), a system must expend energy. This

energy is a cost to the organism, and in the brain it is likely that the cost is in the form increasing entropy. This gives an *a priori* reason why the square of control signal and its gain ought to be minimised, from equation (2). Steepening the gradient of control increases energy expenditure, but allows the state to remain more faithfully at the desired set-point. *Dopamine*, perhaps in consort with acetylcholine and noradrenaline, may set the gain of such feedback (Friston, 2009; Yu and Dayan, 2005), which is evidenced by abnormal feedback control in PD (Beuter et al., 1990; Rickards and Cody, 1997; Schettino et al., 2006; Vaillancourt et al., 2001). Mechanistically, D1 receptor stimulation could increase control gain by steepening pyramidal cells' transfer functions (Gruber et al., 2006; Thurley et al., 2008), or by rapid potentiation in the synaptic membrane itself (Abbott et al., 1997).

At the level of the plant, increasing the gradient of the control signal translates almost directly to increasing the velocity of movement. In the oculomotor system, this control signal corresponds to the input to motoneurones from the medial longitudinal fasciculus (Robinson, 1973). At higher levels of the motor control hierarchy, steeper gradients imply faster correction of error, and may permit action initiation that is both faster *and* more precise.

7.4.4. No free lunch: relevance

A major question is how the brain can distinguish signals from noise at all. Distinguishing signal from noise is straightforward from an experimenter's viewpoint, but not from a cell's viewpoint. One view is that, the "noise" that needs to be attenuated in the brain is, in fact, constituted by potentially relevant but actually irrelevant stimuli. In particular, sense organs are tailored to transduce signals that are *potentially* important for survival.

In short, distractors that are filtered out are stimuli that might have been relevant, for example in the wild. For this reason, perhaps, it is costly for us to filter them out – costly because it might be dangerous. The mechanism that makes attention effortful is, then, an evolutionarily potent one. On this view, producing a precise motor output entails isolating the motor system from other competing signals. Those competing signals are currently irrelevant, and are termed noise. Attenuating them is expensive because it precludes reflexive responses that would have been useful in the wild—for example, saccades to visually salient objects. Attenuating these 'noise' signals precludes danger processing (recall **Figure 2.1**; Equation 2.1). This is a candidate for the "real" cost of control: excluding noise is actually, in the most natural setting, excluding potentially relevant signal.

7.4.5. Conclusion

Studies to date have suggested that costing of action, for example speed accuracy or economic cost, might be estimated and represented in the brain as a decision variable (Rangel and Hare, 2010). Metabolic activity in certain regions in the brain correlates strongly with the cost of an upcoming action (Croxson et al. 2009; for reiview see Kurniawan, Guitart-Masip, and Dolan 2011), both in limbic/ventromedial areas, and in areas involved in motor preparation (Bonnelle et al., submitted). Corroborating this, pre-SMA stimulation by TMS can improve invigoration by reward (Herz et al., 2014). It is likely that these brain areas perform the cost calculations that underlie motivation by reward—and they are also the cortical regions most strongly innervated by dopaminergic neurones arising in the midbrain (Van den Heuvel and Pasterkamp, 2008).

The results of chapter 5 demonstrated deficits in both reward-sensitivity and vigour in PD. I modelled these findings in terms of how action costs are evaluated in the brain—the cost of control—and how these may be translated into the precision and gain of control signals in generating movement. Dopamine depletion in Parkinson's disease has been hypothesised to lead to a deficit in vigour and thus slow movements—bradykinesia (Mazzoni et al., 2007; Schultz, 2007), but is also associated with decreased precision on motor tasks (Beuter et al., 1990; Galea et al., 2012; Schettino et al., 2006) and attentional difficulties (Brown and Marsden, 1990; Cools et al., 2001b; Obeso et al., 2013; Owen et al., 1991; Robbins, 2005; Sampaio et al., 2011b; Wright et al., 1993; Yamaguchi and Kobayashi, 1998). A parsimonious explanation for these findings, together with mine, might be that patients with PD are impaired in reducing motor noise in response to reward, which would manifest as inability to increase movement speed in response to incentive (Mazzoni et al., 2012).

8. General Discussion

8.1. Summary of findings

The mechanisms by which an organism's brain responds to rewards, and uses rewards to guide attention, have been studied by a variety of methods (reviewed in **Chapter 1**). However, few studies to date have used a direct measure of *sensitivity* to rewards. By providing reward incentives for fast eye movements to a target, while avoiding a distractor, I studied the factors that influence motivational influences on attention.

In **Chapter 2** I explored how oculomotor capture is influenced by reward. Oculomotor distractibility was measured by involuntary saccades made to a visually salient onset distractor, which appeared at the same time as a non-salient target that had to be fixated. In two studies, I first parametrically manipulated incentives and penalties across blocks, and then examined the trial-to-trial effects of reward history. The first experiment revealed that increasing reward incentives led to shorter saccadic RTs, whereas introducing penalties increased RT (**Figure 2.3**). Both reward and penalty improved accuracy, reducing oculomotor capture rates, but when rewards were maximal, there was a paradoxical increase in oculomotor capture. This suggests that incentives may increase both speed and accuracy, constituting a true performance improvement rather than trade-off, but at high reward levels 'choking under pressure' may arise.

The second study revealed that if the distractor location was previously a target, it was more likely to attract gaze, and elicit oculomotor capture. However this occurred only when there was oculomotor capture on the previous trial: that is, when the potential

reward was missed (**Figure 2.7**). Distraction is therefore greatest to locations that are seemingly 'primed' by missed rewards.

In light of these findings, in **Chapter 3** I designed a task that allows the incentive to be manipulated on each trial. A spoken reward cue was played during the foreperiod, and as previously, a speeded saccade to a target was made while avoiding a distractor (**Figure 3.1**). In this task the distractor was salient due to its early onset, only three locations were used, and the task was designed to be "continuous": the fixation point for the next trial was the end-location of the previous trial, in order to strengthen previous-trial location effects.

In the first study, conducted on 24 healthy young volunteers, rewards shortened reaction times while speeding peak saccade velocities (**Figure 3.3**). The degree of modulation of these measures, as a function of incentive, allowed quantification of *reward sensitivity*. In addition, pupillary dilatation in response to the auditory reward cue was modulated by reward size, providing an independent autonomic measure of reward sensitivity (**Figure 3.4**). The second experiment demonstrated that the measure of reward sensitivity for a given subject correlated well between sessions, when 19 subjects were tested a second time one week later, and was not altered by practice.

A third study explored the effect of age upon oculomotor capture and reward. Older participants (mean age 62) were significantly slower and more accurate, consistent with more conservative behaviour (**Figure 3.8**). Although reward had a stronger influence on improving accuracy in older than younger participants, there was no difference in reward sensitivity of RT or velocity, indicating that a) the improved accuracy was not due to speed-accuracy trade-off, and b) that reward sensitivity of velocity is a consistent finding across ages. I also explored the trial-to-trial effects in

this task, and found a corresponding effect to that found in Chapter 2: missed rewards capture attention (**Figure 3.9**).

In **Chapter 4** healthy male volunteers took the D2-selective agonist cabergoline, or placebo, in two separate sessions, in a randomised double-blinded protocol. As previously found, reward did not significantly affect oculomotor capture rates, but did speed saccade velocities and shorten reaction times (**Figure 4.3**). Cabergoline increased the slope of reward sensitivity as measured by saccade velocity. Interestingly, the effect was primarily on slowing down saccades when incentives were low – i.e., increasing the de-motivating effect of a lack of reward (**Figure 4.2**). This finding was also reflected in the curvature of saccades, such that when reward was low, cabergoline induced curvature towards the distractor (**Figure 4.4A**).

Chapter 5 examined whether 16 patients with Parkinson's disease (PD) had intact reward processing, as determined by the oculomotor capture task. PD primarily depletes dopamine and results in slow, stiff limb movements, but may also feature behavioural motivational disturbances (Czernecki et al., 2002; Pluck and Brown, 2002; Sinha et al., 2013). Patients performed the task both ON and OFF their usual dopaminergic medication, on two separate days, in counterbalanced order. They also performed a simple (unrewarded) pro-saccade and anti-saccade task as a control to rule out dopaminergic effects on saccades per se as a cause for any effects found. As expected, PD patients had slowed reaction times and velocities, but reduced oculomotor capture, compared to age-matched controls (**Figure 5.1**). Crucially, their sensitivity to reward was reduced, with a flatter slope of velocity as a function of incentive. This was accompanied by reduced pupillary sensitivity to reward.

When ON medication, PD patients showed no improvement in velocity, RT, nor in reward sensitivity (**Figure 5.1**). In contrast, pupil dilatation in response to reward was increased when ON compared to OFF, demonstrating that medication restored their autonomic measures of reward sensitivity, although behavioural measures on the task such as saccade velocity remained reward-insensitive (**Figure 5.5**).

In **Chapter 6**, I measured reward sensitivity in patients with focal ACC and OFC damage. Datasets from 19 patients were obtained, performing the rewarded oculomotor capture task as well as simple pro-saccades and anti-saccades. On the rewarded task, four patients had extreme values of reward sensitivity compared to a matched control group of 32 subjects, but their lesions did not reveal a unique pattern. In order to look for lesion-location effects, patients were divided into two groups, according to the predominant lesion location, OFC or ACC (ACC included subgenual cingulate). Those with OFC lesions showed decreased sensitivity to reward, as exhibited by a shallower reward slope of their *velocity* as a function of incentive (**Figure 6.3.4**). A complementary pattern was found with pupil dilatation: ACC lesions made the pupil less sensitive to reward. On a simple prosaccade task, OFC patients exhibited reduced inhibition of return, in keeping with previous studies (Hodgson et al., 2002b).

Voxelwise lesion-behaviour mapping was used find regions that, when lesioned, resulted in reduced reward sensitivity of peak saccade velocity. Damage to a small area of ventromedial PFC, just below the subgenual cingulate, correlated with loss of reward sensitivity.

Finally, in **Chapter 7**, I advanced a quantitative approach to studying motivation by reward. I first noted that existing models do not allow for genuine performance improvement by reward. I then demonstrated that introducing a costly control signal

that reduces noise allows existing models to account for the data. I discussed the possible interpretations of such a "control cost", in three ways: in terms of dopamine, entropy, and relevance.

8.2. Interpretation

8.2.1. Interaction between reward and dopamine

A key finding of these studies is that dopamine altered the effect of reward incentives on behaviour. This suggests that dopamine signals lie somewhere in the path between encoding an expected reward, and energising behaviour according to that reward.

In particular, the D2 agonist cabergoline slowed velocities and increased the pull of the distractor when reward was low, without altering accuracy or slowing RTs generally. PD flattened the sensitivity to rewards in addition to slowing velocity and RT, and dopamine replacement had the sole effect of improving pupillary reward responses. Tonic dopaminergic stimulation, therefore, appears to increase the gain of reward in different ways in PD and in health.

8.2.2 Saccadic vigour

Saccades have been the model system for motor control, and are perhaps the most well understood neurally (Robinson 1972). Although they are 'primitive', usually unconscious, and often reflexive (Schreij et al., 2008; Trappenberg et al., 2001), they may also be directed towards goals, or be voluntarily controlled. As discussed in the introduction, they are manifestations of the allocation of attention. The influences of motivation and goals on saccade control is much more poorly understood (Okada and Kobayashi, 2014).

The D2-agonist cabergoline caused an increase in the slope of reward sensitivity, but by slowing the velocities in the unrewarded condition (**Figure 4.3**). This finding is unexpected and might be explained in one of three ways.

Firstly, D2 receptors are associated with the *indirect pathway*, sometimes termed the "no-go" pathway in view of its postulated ultimately inhibitory GABA-ergic projections to thalamus (Alexander and Crutcher, 1990; Frank and Claus, 2006). Thus stimulation of D2 receptors might inhibit action in general, reducing vigour, but this might be overcome by reward signals. Another D2 agonist pramipexole has been shown to *reduce* the normal fMRI activation by rewarding and aversive stimuli in ventromedial PFC, OFC, striatum and dorsal ACC – just as though the rewards and penalties themselves had been devalued (McCabe et al., 2013). It is not clear at this stage how this links with the findings reported here on cabergoline.

Secondly, there might be *dose-dependent* effects: in order to ensure participants were blind to cabergoline or placebo, a low dose was used. Studies of D2 agonists reveal differential dose-dependent effects upon performance in different domains (Vaillancourt et al., 2013), and inverted-U-shaped effects on both cognition and at the cellular level (Cools, 2011; Stelzel et al., 2013; Zheng et al., 1999). The inter-subject variability present in drug effect (Appendix 2) would support this. Alternatively, tonic low doses of cabergoline might *presynaptically* inhibit dopamine release, such that vigour is reduced; this inhibition might be overcome by high motivation—leading to the observed effect on velocity.

A third possibility is that there are actually two effects at play: the D2 agonist might slow saccade velocities across the board, yet simultaneously increase sensitivity

to reward, increasing the slope. The net effect would be the observed drug-induced vigour decrement when reward is low (**Figure 4.3**).

Could any of these mechanisms also explain the results in PD? PD patients had slower and less reward-sensitive saccade velocities, and replacing dopamine did not increase either speed or reward sensitivity (**Figure 5.1**). This cannot be explained simply by a change in dopaminergic stimulation. Rather, the healthy reward response must be contrasted with the blunted response in patients even when medicated. It seems likely that phasic dopamine release is released to signal reward expectation (Bromberg-Martin et al., 2010b; Niv, 2007), and it is unlikely that D2 agonists can restore this.

It is fascinating, then, that pupillary responses to reward in PD patients were restored by medication. Do they also not require phasic dopamine? It is possible that autonomic reward responses are governed by a different, parallel, neural system than the invigoration of action. For example, the dorsal-action vs. ventral-emotion distinction proposed by some investigators might be one explanation (Grabenhorst et al., 2008). Alternatively the mesolimbic-nigrostriatal or even cortical-subcortical distinction may be relevant.

8.2.3. Anatomical considerations

The lesion-mapping suggests that damage to a small area of subgenual ACC is correlated with disrupted reward incentivisation of saccade velocity. In conjunction with the previous findings with dopamine and PD, it seems likely that the ventral striatum and posterior OFC function as a single unit in value processing (Haber et al., 2006). It is not straightforward to infer how precisely the lesion mapping localises the effect on

reward sensitivity, due to potential undersampling, correlated lesioning, and spatially heterogeneous statistical power (**Figure 6.4.1**).

Doubts nonwithstanding, I present the regions in which the degree of lesion correlates with pupil and velocity reward sensitivity, together in **Figure 7.3** in magenta and yellow respectively. Also shown are areas which lesion correlated with the LARS total apathy score, in cyan. There is considerable overlap of velocity and pupil areas in the depth of the medial orbital sulcus. Apathy scores also involve gyrus rectus as well as more anterodorsal regions of the medial left wall.

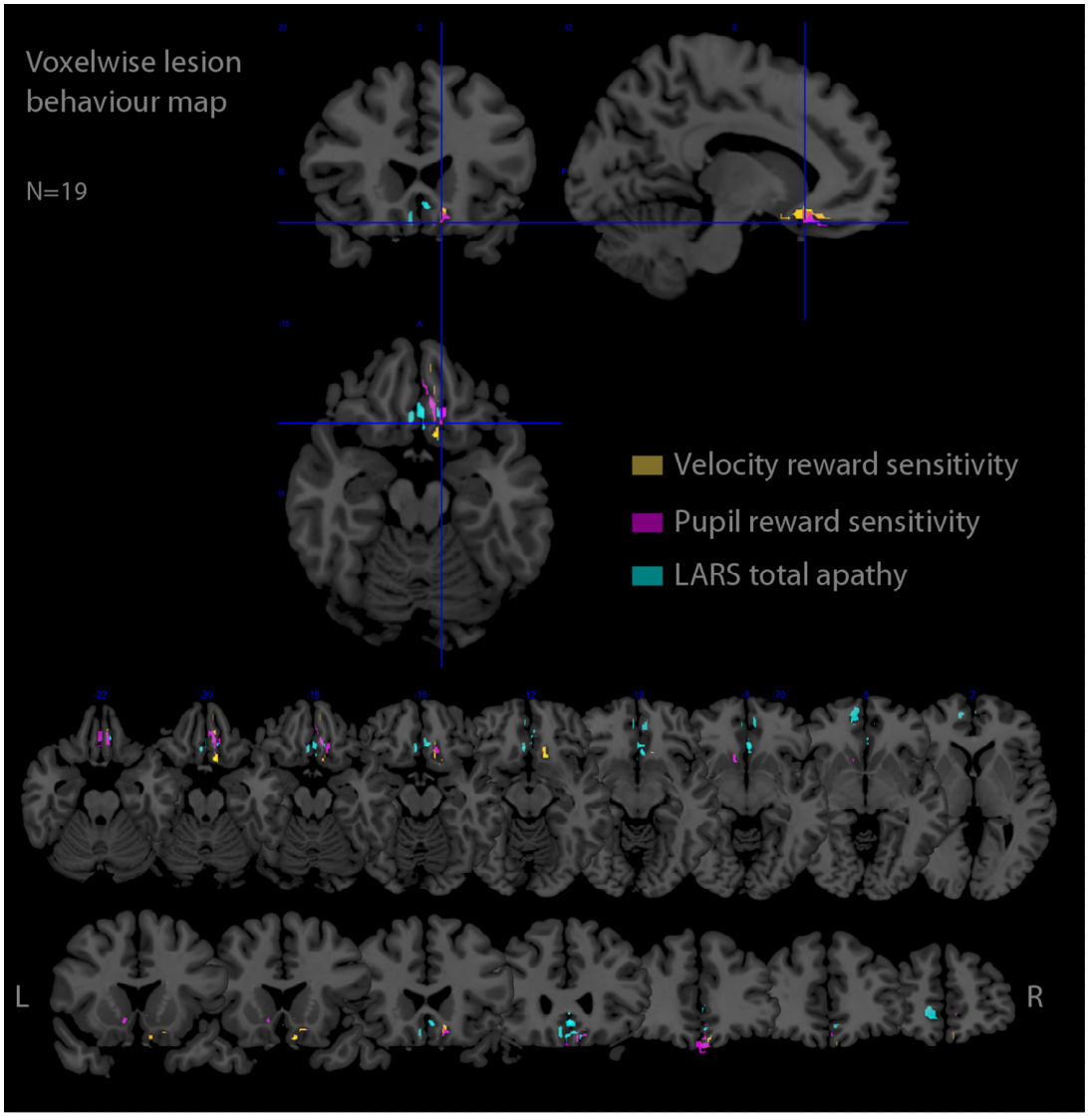


Figure 8.1: Combined voxelwise lesion-behaviour map
Overall lesion correlations with saccade velocity sensitivity to reward (yellow), size of pupil response to reward (magenta), and the LARS apathy score (cyan) for each lesion patient in Chapter 6. Medial orbitofrontal cortex appears to have the strongest correlations with these measurements.

Similar to my findings in PD, pupil sensitivity after lesions varied independently from velocity sensitivity. This suggests a possible role for OFC in translating reward into motivation, to invigorate motor control—whereas ACC may feed into autonomic arousal. This conclusion appears to be against some other lesion studies that find impaired autonomic responses after OFC lesions (Bechara et al., 1997). PD may irreversibly blocks the invigoration of reward, but its effect on the pupil is reversible—demonstrating that reward signals can still be generated and manifest in those individuals.

8.3. Future directions

Reward systems in the brain span many levels of explanation including neuroanatomical, electrochemical and computational. Consequentially, the parallel study of neuromodulatory pharmacology, focal frontal lesions, and neurodegenerative conditions appears to be a fruitful approach to understanding reward. Many outstanding questions appear amenable to this approach.

Simple extensions of this work could be to increase the sample size of PD and PFC patient groups. PD is known to be a heterogeneous condition (Foltynie et al., 2002; Lewis et al., 2003). In averaging the effects over 16 patients, the results presented here may well mask important relationships of reward sensitivity with individual patient characteristics. Increasing the sample size could provide power to differentiate between tremor-dominant and akinetic-rigid phenotypes, and between apathetic and non-

apathetic PD (Czernecki et al., 2002). In prefrontal patients, increasing the number of patients could provide greater lesion coverage over dorsolateral areas in particular dACC, SMA and pre-SMA, which in this study had lower power to detect lesion effects than in OFC.

A topical question to ask would be, whether reward sensitivity is determined by dopamine-related genetic polymorphisms. Variation in DRD2 receptor, COMT and DAT alleles may all govern sensitivity to reward (Camara et al., 2010; Frank and Hutchison, 2009; Krugel et al., 2009). In the study of Chapter 4 on cabergoline, the sample size would be insufficient to study the effect of genetic variation; a larger cohort would be required. Future studies ascertaining genetic determinants may have real-world applications, including tailoring medication for individual patients, as well as mechanisms of disease and addiction, and in understanding natural population variability in personality traits such as apathy and impulsivity.

8.3.1. Cost of control

Superficially, motivation by reward appears to do more than adjust behavioural parameters: it energises and improves. These aspects go beyond the gamut predicted by current optimal motor control theory, or rise-to-threshold decision models. By considering the cost of control in Chapter 7, these effects can be re-framed as optimising behavioural parameters—with the assumptions that noise in sensorimotor systems can be reduced at a cost, and that the brain is able to select the optimum level. It is possible that the control cost could be extended to other domains where resource limitations appear to be breached by motivation, for example working memory, cognitive effort, and even sport or performance arts. A strong prediction from this thesis

is that dopamine facilitates the ability to break the resource limitation. As yet, it is not clear how this position could relate to dopamine's role in reinforcement learning.

8.3.2. Motivation as reward contingence

One concern with the studies I have performed is that I have assumed that *expectation of reward* generates motivation. However, this may not be strictly correct: in a situation where reward is certain, there would be no motivation to do anything. In my task, reward was always contingent on fast accurate response; when the incentive is zero, there is no reason to act, as outcome is not contingent on behaviour. Under zero reward, it could be the lack of dependence, rather than the lack of reward, that demotivates. Conversely, penalties carry negative reward, yet lead to positive motivation.

In particular, neither the absolute reward *R*, nor the relative reward $R - \mathbb{E}(R)$, motivates action. Absolute relative reward $|R - \mathbb{E}(R)|$ is also ruled out, since it predicts zero motivation to act when reward equals the mean value. Rather, it is the *dependence* of reward upon behaviour $P(R|a)$ which motivates, i.e. the heterogeneity of conditional reward over possible actions (Solway and Botvinick, 2012). Imagine, for example, unconditional rewards, which in theory should not motivate any action whatsoever.

Future studies might consider isolating the motivating component as the contingence of reward upon behaviour. This could be mathematically expressed as the *mutual information* of the reward distribution and the behaviour distribution:

$$M = \sum_{action} P(\text{action}, reward)\, log\left(\frac{P(action, reward)}{P(action)P(reward)}\right) \tag{8.1}$$

or alternatively, for rewards *R* contingent on actions *A*, as the *variance* in reward that is accounted for by the choice of action:

$$\begin{aligned} &\mathbb{E}_A \left(R - \mathbb{E}_A(R)\right)^2 \\ &= \int_A \left[\int_R rP(r,a)dr - \iint_{A,R} rP(r,a)P(a)drda\right]^2 da \end{aligned} \tag{8.2}$$

On this account, we are only motivated to the extent that actions alter outcomes. An experiment could then be devised using probabilistic rewards, in which the key variable is not reward *per se*, but rather the degree to which reward depends on action. In particular, motivation can be increased or decreased experimentally, without increasing reward expectation. A fascinating question would be whether dopamine is also involved in this "reward-independent" motivation.

8.4. Conclusion

In this thesis, I have attempted to quantify reward's effect on attention, and how frontostriatal dopamine modulates this. Motivation by reward is central to improving human performance, yet we remain far from understanding its chemical and anatomical basis. Demonstrating specific effects on motivation in pharmacological manipulation, disease, and lesions illuminate this to some extent. In the process, I hope also to have produced useful quantitative models of how reward might enhance performance without trade-offs, and introduced new tools for reaction time analysis. Finally, my research delineates how we might begin to answer a central theoretical question: why do precision, physical effort, and avoiding distraction all share the common feature of requiring motivation? Future study should focus on the neuroscientific and computational commonalities between these phenomena.

Appendix

Appendix 9.1: MATLAB code for arbitrary delta plots with permutation test

The code here will generate delta plots for arbitrary data, automatically averaging across subjects and computing the difference between conditions for each quantile. A t-test is optionally performed to determine if the conditions are significantly different at any point in time, which is controlled for family-wise error rate rate using a permutation test.

```
function [mdelta, mbin, hplot, t_test_result, t_statistics, t_threshold] = ...
                    deltaPlot(DATA, varargin)
% function [mean_delta, mean_bincentre, hplot,
%           ttest_result, t_statistics, t_thresholds ]
%             = deltaPlots(DATA, [params...] )
%
% Create a delta plot (usually of reaction times) of the differences
% between conditions, at each quantile of the distribution.
%
% DATA ( SUBJECT, CONDITION, TRIAL )
%  OR
% DATA { SUBJECT, CONDITION } ( TRIAL )
%
% Creates delta plots averaged across subjects.
%
% for a simple delta plot there should be 2 conditions, i.e.
%   size(DATA) = subjects x 2 x trials
% if there are more than 2 conditions, each neighbouring pair is compared
% i.e. condition1-condition2, condition2-condition3, etc.
```

```
%
% If the different subjects / conditions have different numbers of trials,
% you can either use nan-padding (e.g. using nancat) or use the cell-array
% version of DATA.
%
% RESULT:
%
% mean_delta = the mean value of the difference between conditions, for
%              each bin
% mean_bincentre = the value at the centre of each of the bins
%
% if you request 'hplot' as output, it will plot the delta plot with dotted
% lines for error bars.
%
% if you request 't_test_result', then a permutation-based test will
% calculate the threshold for t, corrected for FDR of multiple comparisons
% across the bins, and will return 0 or 1 for each quantile.
%
% Delta plots - what do they mean?
% (Ridderinkhof 2002, Ratcliffe 1979)
%
% SGM 2014


% Default 100 bins, gaussian smoothing=0.1 of range, p<0.05


NB     = 100;            % number of quantile bins
SMOOTH = floor(NB/5);    % smoothing window (as a number of bins). < 2 means no smoothing
SMOOTH_FILTER = 'gauss'; % which smoothing function to use
ALPHA  = 0.05;           % if t-test is requested, then
TWO_TAILED = false;      % should I test if condition1 not equal to condition2?
WIDTH  = 0.2 ;           % width (in quantiles) of bins. Can be zero for a pure quantiled plot
PLOT_P = 0 ;             % show a horizontal bar where where p < alpha


if exist('parsepvpairs','file') % attempt to read in parameters
  [  NB,  WIDTH,  ALPHA,  SMOOTH,  TWO_TAILED] = parsepvpairs( ...
```

```
   {'NB','WIDTH','ALPHA','SMOOTH','TWO_TAILED'}, ...
   {100 , 0.2 ,    0.05,  1,       0          }, varargin{:});
elseif nargin>1, warning('parsepvpairs.m not found; parameters ignored!'); end



WIDTH=floor(WIDTH*NB); % convert width from a quantile fraction into a number of bins
if isnumeric(DATA)     % numeric array? convert to cells
  if ndims(DATA)<3, error('deltaplot:dimension','DATA should be an 3-dimensional array'); end
  for i=1:size(DATA,1) % each subject
    for j=1:size(DATA,2) % each condition
      DATA2{i,j}=squeeze(DATA(i,j,:));
    end % next condition
  end % next subject
  DATA=DATA2; % now it's DATA { SUBJECT, CONDITION } ( TRIAL )
end
NSubj = size(DATA,1); % number of subjects
NCond = size(DATA,2); % number of conditions

flattening = false;   % have we had to flatten any cells into columns (warn if so)
quantiles = linspace(0,1,NB);  % the actual quantiles to use
delta = nan(NSubj,NB, NCond-1); % create empty matrix for results: Delta between conditions
bin   = nan(NSubj,NB, NCond-1); % and this is for the abscissa.
for subject = 1:NSubj % for each subject
  for condition = 1:(NCond-1) % for each pair of neighbouring conditions
    c1 = DATA{subject,condition};       % get data for 1 subject for 2 conditions
    c2 = DATA{subject,condition+1};
    if ~isvector(c1) || ~isvector(c2),  % flatten to column vector if needed
      flattening=1; c1=flat(c1); c2=flat(c2);
    end
    q1 = quantile(c1, quantiles);   % create a vector of quantiles for each condition
    q2 = quantile(c2, quantiles);   % quantile ignores nans.
    if WIDTH == 0
      delta(subject,:,condition) = q1-q2;     % DELTA ( SUBJECT, QUANTILE, CONDITION_PAIR )
    else
      for i=1:(NB-WIDTH) % for each quantile bin
```

```
        meanc1 = nanmean( c1( c1>q1(i) & c1<q1(i+WIDTH) ) );  % c1 values within quantile range
        meanc2 = nanmean( c2( c2>q2(i) & c2<q2(i+WIDTH) ) );  % c2
        delta(subject,i,condition) = meanc1-meanc2;
      end
    end
    bin(subject,:,condition)   = (q1+q2)/2; % BIN   ( SUBJECT, QUANTILE, CONDITION_PAIR )
  end % next condition pair
end % next subject
if flattening, warning('deltaplot:flatten','Flattening matrix data into columns'); end

mbin=squeeze(nanmean(bin));    % average across subjects so can be plotted on single graph
                               % and remove first dimension, to give
                               % X ( QUANTILE, CONDITION_PAIR )
% take mean delta across subjects in each quantile bin
mdelta = permute(nanmean(delta),[2 3 1]);
% and calculate sd across subjects at each quantile bin
edelta = permute(( nanstd(delta)) / sqrt(NSubj),[2 3 1]);



if SMOOTH>1 % SMOOTH
  for j=1:NCond-1 % for each pair of conditions (smooth requires single column)
    mdelta(:,j) = smooth(mdelta(:,j) ,SMOOTH,SMOOTH_FILTER);
    edelta(:,j) = smooth(edelta(:,j) ,SMOOTH,SMOOTH_FILTER);
  end
end

if nargout>2  % requested plot handle? then PLOT GRAPH
  if NB<7     % this version with error bars is good for few bins
    hplot=errorBarPlot(delta, 'xaxisvalues',mbin);
  else        % this version shows a curve - is good for many bins!
    washeld=ishold();
    plot(mbin, mdelta, varargin{:}, 'Marker','.'); % plot mean delta for each bin
    hold on
    plot(mbin, mdelta+edelta, varargin{:}, 'LineStyle',':'); % error lines above
    plot(mbin, mdelta-edelta, varargin{:}, 'LineStyle',':'); % and below
```

```
    plot(xlim,[0 0],':'); % dotted zero-line = no difference between conditions
    if ~washeld, hold off; end
    ylabel(['\Delta']);
    xlabel('value');
    % create legend = "condition1-condition2" etc.
    labels = arrayfun(@(x) sprintf('condition%g-condition%g',x,x+1), [1:(NCond-1)]','uniform',0);
    % insert blanks for error-lines
    legend(flat([labels, repmat({''},NCond-1,1)]));
    hplot=gca; % return axes handle
  end
end

if nargout>3 % request t statistic
  % perform a permutation test to calculate the FDR across all bins
  for i=1:5000 % iterate 5000 times
    % what if the order of cond1 and cond2 were randomly chosen?
    randbool = (rand(NSubj,1)>0.5)*2-1; % +1 or -1 for each subject
    permuted_delta  = bsxfun(@times,randbool,delta); % delta with random swapping of cond1/cond2
    % t statistic for this permutation = mean / stderr_of_mean
    % PERMUTED_TSTATS ( QUANTILE, CONDITION_PAIR )
    permuted_tstats = permute(mean(permuted_delta) ./ std(permuted_delta), [2 3 1]) / sqrt(NSubj);
    % MAXT ( ITERATION, CONDITION_PAIR )
    maxt(i,:) = max(permuted_tstats, [], 1); % maximum t across all quantiles
                                             % (for each condition-pair separately)

    % this following line is for if you wanted
    % a two-tailed test, but at the moment I am assuming the hypothesis is
    % that condition1 is always bigger than condition2, so it's a 1-tailed
    % test.
    if TWO_TAILED
      mint(i,:) = min(permuted_tstats, [], 2);
    end
  end
  t_statistics  = squeeze(mean(delta) ./ std(delta)) / sqrt(NSubj); % actual t statistic!
  if TWO_TAILED
```

```
    t_threshold_lower = quantile(mint, ALPHA/2);   % find upper 2.5% of max-t values
    t_threshold_upper = quantile(maxt, 1-ALPHA/2); % find lower 2.5% of min-t values
    % null hypothesis rejected at 5% if either threshold is passed.
    t_test_result = bsxfun(@gt, t_statistics, t_threshold_upper)  ...
                |  bsxfun(@gt, t_statistics, t_threshold_lower);
  else
    t_threshold   = quantile(maxt,1-ALPHA);     % upper 5% of max-t values
    % null hypothesisi rejected at 5% if t_statistics > t_threshold.
    t_test_result = bsxfun(@gt, t_statistics, t_threshold);
  end
  if PLOT_P % PLOT the t test results?
    % This shows the significant points where delta is nonzero, below the graph as a bar.
    mainaxes = gca;
    rect=get(mainaxes,'position'); % select region in bottom 5% of axis
    axes('position',[rect(1) rect(2) rect(3),rect(4)*0.05]);
    imagesc(t_test_result'); axis off;
    % axes(mainaxes); % revert to main axes
  end
end
```

Appendix 9.2: Cabergoline effects in individual subjects

A large body of literature exists on the heterogeneity of dopaminergic drug effects in different individuals (van Holstein et al., 2011; Mueller et al., 2014; Schellekens et al., 2012; Wacker et al., 2013). The heterogeneity is a combination of receptor sensitivity differences (pharmacodynamic, e.g. Cohen et al. 2007), or differences in drug absorption and elimination (pharmacokinetic). It is important to explore inter-individual differences in drug effects, since it has implications for addiction, alcoholism and in selection of medication e.g. in PD (Arbouw et al., 2009; Finckh et al., 1997).

To examine whether individual subjects showed different effects of cabergoline on saccade velocity, I used a permutation test amongst trials, for each subject. Each trial was modelled with a linear effect of reward and cabergoline. The average practice effects (session 2 minus session 1 velocity effect and reward-sensitivity effect) were calculated over all subjects, and the mean effect of practice was subtracted from each subject's velocity. The second session was only 11 deg/s faster than session 1 overall, and had slightly reduced reward sensitivity, of magnitude 6 deg/s per unit reward. Note that this effect was not significant in the overall ANOVA ($p<0.05$). It is still necessary to subtract these values, however, otherwise it is not possible to say for certain whether an individual's effects were due to drug or to practice. Statistics were also calculated using ANOVA which yielded identical results, despite potentially violating the normality assumptions.

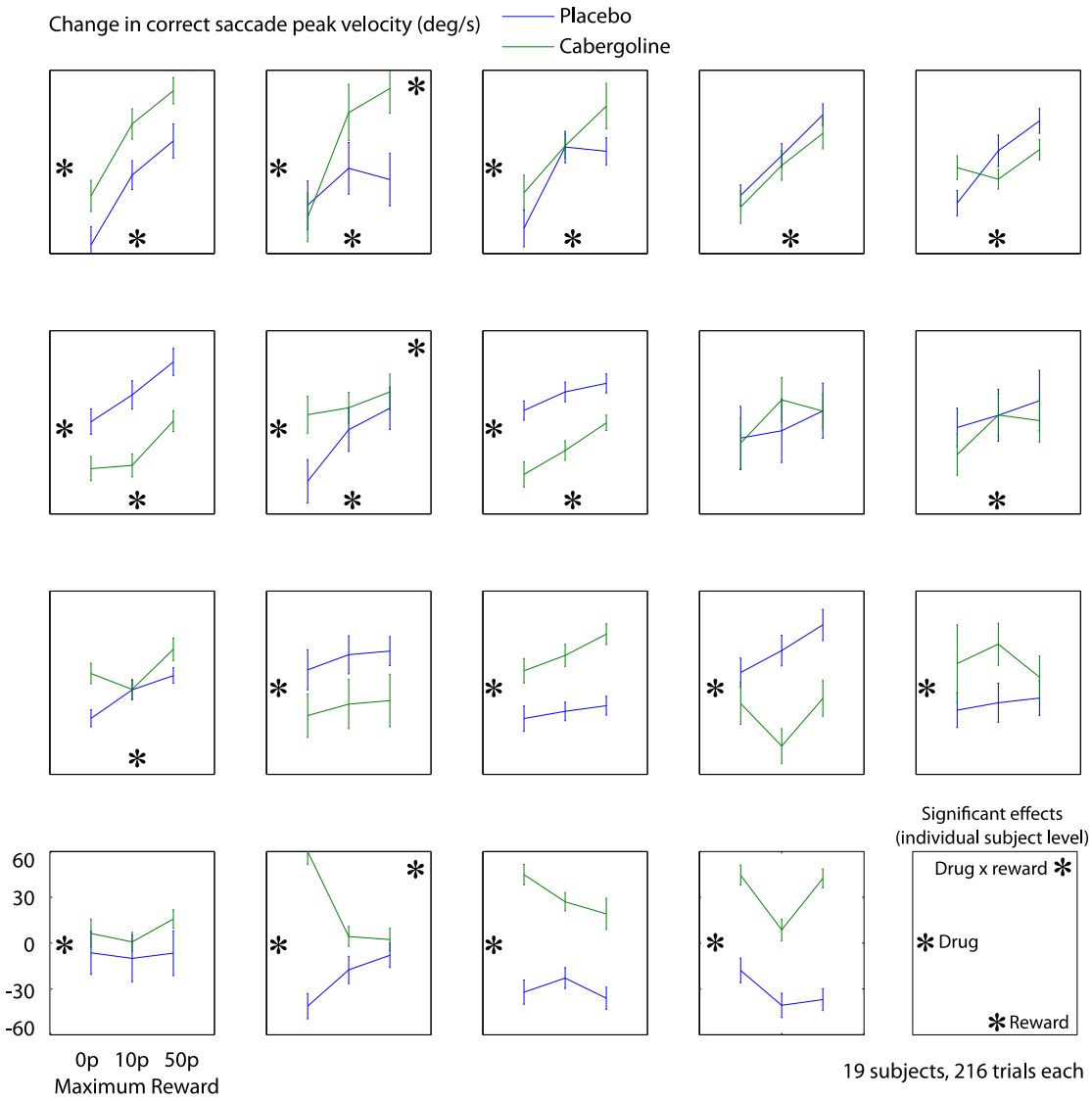


Figure 9.1: Mean saccade velocity as a function of reward for each subject, on and off cabergoline

Practice effects have been subtracted out. Error bars are the standard error of the mean, taken across the 72 trials in each condition. Asterisks indicate where a subject had significant but idiosyncratic effects of reward, drug or an interaction term. Reward effect was homogeneous, in that it only increased the velocity. In contrast, the effects of drug and the interaction could occur in *either* direction in different subjects.

Out of 19, 9 participants were significantly reward sensitive in both sessions, and 16 showed significant main effects of drug and placebo on overall saccade peak velocity.

This comprised 10 subjects with faster velocity on cabergoline, and 5 with decreased velocity (all $p<0.05$), and 3 with no effect. However only 3 had an interaction between reward and drug, two became more reward sensitive and one less sensitive on cabergoline.

What could explain the differing drug response ? One recent hypothesis is that genetic polymorphisms and baseline dopamine levels may determine the differential influence of dopaminergic manipulations (Cools et al. 2007; Cools et al. 2005), and these genes are also known to correlate with trait impulsivity (Ebstein et al. 1996; Dalley et al. 2007; Paloyelis et al. 2010). I therefore examined the change in sensitivity to reward with cabergoline, i.e. the difference in the slopes for each subject, were significantly correlated with the "motor impulsivity" subscale of the BIS questionnaire ($p=0.0099$, $r^2=0.33$). Subjects who were more impulsive had reduced reward sensitivity with cabergoline, whereas those who were less impulsive were more reward sensitive with the drug.

Accuracy was significantly improved with cabergoline in 4 participants and worsened in one. Cabergoline increased reward sensitivity of accuracy in one individual (who had no effect of reward overall).

Reward significantly shortened RT in 6 subjects, and slowed RT in one. Cabergoline shortened RT in 5 subjects (two of whom were speeded by reward), but also lengthened RT in 4 (all of whom had no main effect of reward). Drug interacted with rewards in 3 subjects, two of whom became less reward sensitive (both were also speeded by reward and drug), and one became more reward sensitive.

Appendix 9.3. Vigour in optimal control

<<< LATEX >>>

Appendix 9.4. Prefrontal lesion case histories

RJ is a 61-year-old shop-fitter, who had a SAH 2½ years ago. He took 2 months to recover mentally, and was working again at 3 months. He feels back to 100%, and is planning to retire in a years' time. He has no symptoms, but admits that he now enjoys his work less. His motivation has been gradually dwindling over the years but he does not attribute this to the SAH. He notices that he has become more laid back, and has a little less interest in things generally. On examination he had a fine mild symmetrical postural tremor of both hands. On observation he was well motivated and took the reward incentives very seriously.

CB is a 46-year old Brazilian lady who worked in a call centre, who had a SAH 2 years previously. She has little recall of the following month. The spent 3 months in neuro-rehabilitation due to poor balance. She currently complains of pronounced memory difficulties, and often cannot remember where she has put things. She feels incoordinated on the right side, has intermittent tinnitus, and blurred vision due to subhyaloid blood. On examination there was mild slowness of fine finger movements on the right side. There was nystagmus in the primary position with the fast phase to the right. She has been on olanzepine since discharge due to some early agitation during the amnestic phase. Although trailmaking, drawing, naming, response inhibition and verbal fluency were normal, she was only able to perform one of the serial 7's, and delayed recall was 0/5. She found the saccadic tasks difficult, and had to be reminded of the instructions on one occasion. She was easily distractible and in conversation she had very concrete mindset. She was sometimes tangential and forgot the initial question.

SP is a 43-year-old IT support worker who suffered a SAH 18 months ago. Since then he has noticed decreased concentration, fatigue, low mood and irritability. It took him 1 year to get back to work. On discussing any changes in his personality, he found it very hard to reflect upon these things. He felt he was less motivated, had a flatter affect, and was less regretful. In conversation, he sometimes cannot predict the effects of what he says on other people. Neurological examination was normal, and he performed well on all tasks.

AH is a 45-year-old construction director who had a SAH 3 years ago. He had a mild left hemiparesis, confusion and diplopia for 2 weeks, which completely resolved and now he only notices stiffness in fine movements of the left hand. He gets tired very easily, and lacks energy. He spontaneously reported that he has become more impulsive: he admits to spending frivolously on online shopping, and has learned to run things by his wife before committing. He is less tolerant, and has difficulty waiting: "everything has to be done yesterday!" His prospective memory is problematic and he uses his mobile phone extensively for reminders. He often says inappropriate things that he regrets, for example jokingly asking the chair of the board "when's it due?" in reference to her putting on weight. He laughs and cries more easily. He has become obsessive about hand cleaning, watches more TV, but gives up easily. His appetite has increased and he has put on weight. During the tasks he was uninterested and tired quickly.

CJ is a 48-year-old receptionist, who is now working part-time. She had a SAH 3 years ago, and went back to work after 18 months. She initially said that she has made a 100% recovery, though on questioning she admits to a poorer memory and frequent tiredness.

Her mother does the cooking now, and although she used to read avidly she has stopped now. She says that she does not dream any more. She feels she has become less talkative and more regretful, sad and worried. Examination was normal. She had difficulty with trail-making, and scored 3/5 on delayed recall. During tasks, she was distractible and fluctuated—two blocks of the saccadic task had to be restarted as she lost concentration. She anticipated the target with her eyes frequently. She had strong emotional responses to winning and losing.

PR is a 61-year-old lady who suffered a SAH 4 years ago, and was in intensive care for 5 weeks. She suffered with hallucinations for 1 year, but was then able to return to work. She did not fare well in the workplace and was referred for anger management. She describes that she has "lost her filter", and is much more blunt with her opinions, often upsetting family and friends. She tells me that she no longer feels guilt or regret after her mistakes. She finds it harder to make an effort, and is less emotionally driven—for example, she had to be pushed to go and see her new grandchild. She did not feel motivated to go, although she knew that she ought to be excited. She feels worry, sadness and happiness much less. She still suffers with decreased memory, tiredness, and insomnia. She was taking levodopa for some months as she had a mild tremor. On examination the tremor was not noticeable and there were no other neurological signs.

AM is a 28-year-old shop administrator who was planning to go to law school. She suffered a SAH 2 years ago, and had no deficits after the bleed. The aneurysm was treated a year later by coiling, but she developed a right-sided hemiparesis for 1 week afterwards. She initially had difficulty walking holding a knife, but made a full rapid recovery. She returned to full time work but gets tired very easily, and as a consequence

has stopped dancing and going to the gym. In terms of motivation, she describes herself as “9/10” for trying new things, but “2/10” for repetitive things. She spontaneously told me that she plays the lottery much more than she used to, now playing the euro-lottery, health lottery, work lottery as well as the normal local lotto. She has started spending more on clothes—and feels this is because her attitude has changed: “I’ll just use my next paycheck for it”. Her partner complains that she no longer saves any money, and she admits to being unable to forward-plan, in particular thinking “more short-term”.

MN is a 55-year-old previous legal secretary, who had a SAH 4 years ago. She was in a rehab unit for 3 months with right-sided weakness and cognitive changes. Her main problem has been tiring, concentration and low mood; she says she has made an 80% recovery. She angers more easily and worries more easily. She has become more aware of other people, and is less likely to give her own opinion spontaneously. On saccadic tasks she performed well but anticipated frequently.

GS is a 57-year-old lady working as a network-manager for a school, who had a SAH 3 years ago. She had double vision for some weeks, but then made a full recovery. She has noticed memory difficulties and fatigue since then, and she finds it harder to get to sleep. She feels she makes decisions quicker than before, and often before she has got enough information. She finds her job more tiring, but thinks she has become more novelty-seeking than before. She performed the saccadic tasks well.

MO is a 45-year-old lighting engineer who had a SAH 5 years ago. He had transient incoordination of his right hand, which has recovered although his handwriting is now worse than before. Other than this he is 100% back to normal. Examination was normal. On questioning he admits to being much more emotional than previously, for example

he becomes tearful during crescendos in music. He sometimes has difficulty working out why he is angry. He performed the tasks well.

FR is a 70-year-old retired gentleman who had a SAH 5 years ago. His only symptom is that he has lost his sense of smell, and his handwriting is less steady. Examination was normal. He remains active, going to the mosque 3 times a day. During saccades he made multiple breaks of fixation, and often regressed to the previous target during the fixation period between trials.

EF is a 33-year-old lady who works in business. She had a SAH 1 year ago. For 3 months she had double vision, tiredness and concentration problems, but now she is 95% back to normal. There is mild residual tiredness, but she is well motivated and has taken up golf recently. She was on prophylactic phenytoin for 6 months but is off medication now. Examination was normal. She was strongly motivated during the saccadic tasks.

SW is a 32-year-old teaching assistant who had a SAH 2 years ago. She noticed she has been more emotional, and has reduced energy levels, and impaired short term memory. She has not noticed any changes in her personality or motivation. On the saccadic tasks she was well motivated, but had some impersistence of gaze with several breaks of fixation in the antisaccade task.

NR is a 46-year-old solicitor who had a SAH 1 year ago. He was in neuro-rehabilitation for 5 months with memory difficulties. He has now recovered well and is back in part time work as a solicitor. He notices his thoughts are laboured and slow – he “can’t get out of first gear”. He feels he has become less experimental for example in cooking and

life choices, and finds he is easily discouraged and gives up quickly. He has attended a fatigue management course, but has only been able to return to half of his previous caseload, which was 300 per year. Examination was normal, and he performed the saccadic tasks well.

EC is a 58-year-old lady who had a SAH followed by coiling 3 years ago. After the coiling she had a left-sided hemiparesis requiring a walking stick. This recovered gradually over 1 month, and she went back to work part-time in her job at a charity shop. She has become much less emotional since the event. Examination was normal apart from mild bradykinesia in the left foot, with normal power. She performed the saccadic tasks well.

AE is a 44-year-old musician who suffered a SAH 3 years ago. He was initially off-balance but recovered fully. He has gone back to work and is recording new albums this year. He has a subtle left-sided postural tremor but no other neurological signs. He tells me that he finds it harder to tell lies now; he is more frank e.g. he once told his colleague "your record is rubbish". He feels he is slightly colder and less empathetic, but happier than before. He is less concerned or upset by things in general, e.g. on receiving a parking ticket. He is heavily reliant on his wife for pushing him to doing things, and his wife is writing a book about their journey.

RB is a 57-year-old building contractor who had a SAH. He has a normal examination. He continues to work and enjoys activities such as martial arts in his spare time. Since the event he has noticed occasional difficulty in finding names – he can often picture the face but not find the name, and has no difficulties with recognition. He denies short-term memory deficits, and was even able to remember my phone number from dialling

it earlier in the day. His verbal fluency was very poor, and on questioning he admits to tiredness, and cognitive slowing. His wife says he has lost the ability to admit when he is wrong. He now plays the lottery frequently, and though he has won a few tens of pounds, he often feels that he "should have won millions".

AF is a 56-year-old boiler-repairer who had a SAH 3 years ago. He was in rehabilitation for 6 weeks and is completely back to normal apart from tiredness. He has given up badminton due to his coordination being worse, but also feels sometimes that he can't be bothered to play. In his work, he finds it harder to persevere at difficult jobs, but has not noticed any other cognitive changes. He really did not find the tasks motivating, commenting about the rewards, "well, it's just numbers".

NF is a 49-year-old lady who worked as a computer programmer, but latterly a housewife. She sustained a SAH 8 months ago, and made a quick recovery. She has noticed grumpiness, reduced short-term memory, fatigue, and some anxiety; she feels 70% back to normal. She notices reduced sensation on the inside of her right foot. Cognitively, she finds it harder to be creative when put on the spot, and she "craves less novelty". She gives up easily, makes less effort, and feels "much more in acceptance of things" as they are. After the event, she went through a phase of being much more emotional, and is still somewhat more anxious. She finds multitasking particularly hard, and can't handle being interrupted. She found the saccadic tasks enjoyable but was tired by the end of 4 blocks.

GB is a 64-year-old retired nurse who had a SAH 1 year ago. She takes citalopram since the event although she does not have a formal diagnosis of depression. She has significant difficulty with fatigue and diminished concentration. She finds meeting

friends a chore. Nonetheless she feels she has become a little more curious and creative since the event. She finds herself more easily moved by news and films than previously, and is more susceptible to guilt and regret. Perception, recall, inhibition, fluency and drawing were in tact, but she scored only 1/3 on serial subtractions. Examination revealed a fine mild symmetrical postural tremor. She performed the saccadic tasks well.

Appendix 9.5. Exploratory VLSM with apathy subscales

The action initiation subscale of the LARS quantifies apathy towards self-generated, self-motivated behaviours. Scores on LARS have been found to be markedly worse in PD (Dujardin et al., 2007). I therefore asked whether damage to any frontal areas also influenced this measure, and performed voxelwise lesion-behaviour mapping using the total LARS apathy score, and the three major subscales: emotion, intellectual curiosity and action initiation.

The behavioural trait of action initiation apathy correlated with damage to left anterior / frontopolar OFC. Before correction for the four multiple comparisons, the maximum *t* was 5.8 and $p<0.05$. However after correction, the result was not significant. Anterior OFC is part of area 10, and consists of highly developed granular cortex. This area and has been shown to be activated in fMRI studies during deterministic reversal learning (Finger et al., 2008; Nashiro et al., 2012), and when an alternative action than the one being planned has a higher value (Boorman et al., 2009, 2011). It may have a role in filtering irrelevant memories (Schnider et al., 2000).

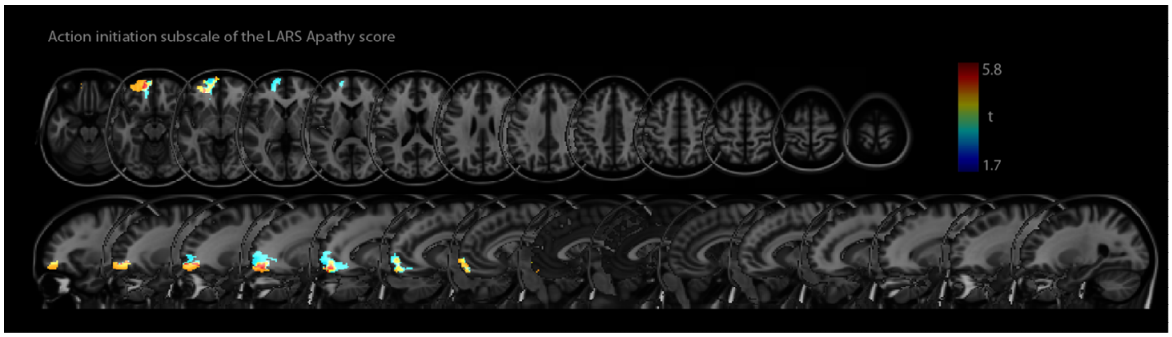


Figure 9.5: Voxelwise lesion-behaviour map of apathy traits
Voxels that correlated with total LARS score are shown in the top image. Blue areas correspond to increased apathy ratings. Right: voxels correlating with the action initiation subscale of the LARS. Red voxels correspond to reduced action initiation. Uncorrected threshold at $p<0.05$ corresponds to $t>1.7$; the maximum t value of 5.8 (seen for some left frontopolar voxels that correlate with

productivity) corresponds to $p<0.05$ corrected for ~5900 independent comparisons. Based on 5 mm smoothing, a t-value of 4.2 (yellow-green) is significant.

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