Investigating the Role of Striatal Dopamine in Attentional Inhibition

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Contents

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Abbreviations

ADHD . . . . . Attention-Deficit/Hyperactivity Disorder

ANOVA . . . . . Analysis of Variance

BIS . . . . . Barratt Impulsiveness Scale

D2 . . . . . Dopamine 2

DAT . . . . . Dopamine Active Transporter

EBR . . . . . Eye Blink Rate

EEG . . . . . Electroencephalography

ERP . . . . . Event-Related Potential

IOR . . . . . Inhibition of Return

PET . . . . . Positron Emission Tomography

RT . . . . . Reaction Time

Abstract

Inhibition of Return (IOR) is an attentional inhibitory mechanism, which is proposed to prevent the unnecessary re-inspection of attended stimuli. As such, IOR is thought to improve the efficiency of cognitive processes such as visual search. Previous studies have identified an important role for the neurotransmitter dopamine in IOR, especially in the striatum of the brain. However, there have been no IOR studies of the direct effects of dopamine depletion on healthy individuals—and previous studies have utilised less targeted dopamine manipulations.

Furthermore, trait impulsivity is associated with abnormalities in striatal dopamine signalling, which may relate to impaired inhibition in various forms. However, it is unclear how IOR is affected by trait impulsivity due to key methodological issues and inconsistencies in previous studies. Therefore, trait impulsivity offers an indirect means of investigating dopamine in IOR, whilst also contributing to the understanding of trait impulsivity in general.

In this thesis, the effects of direct striatal dopamine manipulations on IOR were measured using a selective D2 agonist and antagonist (Chapter 6); and the relationship between trait impulsivity and IOR was investigated (Chapters 3 & 4). Event-related potentials (ERPs) were employed to determine which stages of cognitive processing were affected by striatal dopamine in IOR (Chapters 4 & 6). Additionally, methodological issues surrounding the measurement of ERPs in IOR were addressed—including how ERPs are used to investigate the mechanisms underlying IOR (Chapter 5).

Results showed that both dopamine manipulations reduced the IOR response. This supports previous findings of an 'inverted-U' relationship, and extends them to include the direct effect of dopamine depletion. Furthermore, this is the first observation of excessive and insufficient dopamine for IOR in the same participant group (i.e. three points on the inverted-U). The studies of trait impulsivity and IOR demonstrated that the relationship was dependent on motivational states: Higher levels of motivation increased IOR in high-impulsives (who have low baseline striatal dopamine levels), but reduced IOR in low-impulsives (who have high baseline levels). Motivation is associated with increased striatal dopamine—hence these results also support an inverted-U relationship between striatal dopamine and IOR. Furthermore, they indicate that attentional inhibition may be recovered in trait impulsivity if individuals are motivated.

The investigation of striatal dopamine using ERPs was largely inconclusive. This may reflect the complex effects of striatal dopamine on multiple processing stages, or that processes outside those measured in these studies were affected. However, the investigation of ERP methodology was more fruitful—indicating that the traditional approach to measuring ERPs may lack sensitivity to small ERP modulations. Instead, it is suggested that a range of analysis techniques be used, especially exploring the relationships between ERPs and behaviour. In applying such analyses, it emerged that modulations of both sensory orienting and selective attention may underpin IOR.

Declaration

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Dedicated to Patricia Willetts, Sandra Willetts, and Roger Carrington.

Preface

You are looking for your friend in a crowded country pub. From your vantage point atop the stairs, you can see a throng of thirsty people jostling to be served at the bar. If you don't find your friend quickly, he might miss you out of this round.

Either you need more considerate friends, or you need to efficiently sample visual information from the environment to find him. Your attention system may help you in a very specific way—by preventing the re-inspection of parts of the scene. For instance, someone is wearing the same jacket as your friend, so your attention is initially drawn to him. But even as he moves through the crowd your attention system is subsequently biased away from evaluating him again and again. Thus your attentional 'spotlight' is free to scan new people and parts of the scene. This mechanism is called inhibition of return (IOR), and is the focus of this thesis.

Cognitive science researchers take a more sober approach to IOR, and discuss how it may have evolved to facilitate foraging (Wang & Klein, 2010). IOR is a remarkably robust phenomenon, enduring over thirty years of use and scrutiny in research (Lupiáñez, Klein & Bartolomeo, 2006; Klein, 2000). For example, it has been used to measure the dynamics of attention systems across the lifespan (Poliakoff, Coward, Lowe & O'Boyle, 2007; Langley, Fuentes, Vivas & Saville, 2007) and in neuropsychological disorders (Mushquash, Fawcett & Klein, 2012; Poliakoff et al., 2003). Consequently, researchers at least agree that IOR represents *something* fundamental that the attention system is doing. It has even been measured in predatory archer fish, which were trained to shoot jets of water at targets on a screen[1] (Gabay, Leibovich, Ben-Simon, Henik & Segev, 2013).

This thesis investigates the role of the neurotransmitter dopamine in IOR—more specifically—striatal dopamine. It is easy to justify studying the role of dopamine in a cognitive mechanism, as I am sure we can agree that it has its biochemical fingers in just about every cognitive pie. But there are more specific reasons for investigating striatal dopamine in IOR. Firstly, it is implicated in certain neurological disorders, such as ADHD, Parkinson's disease, and Schizophrenia (Nasrallah, 2008; Li, Sham, Owen & He, 2006). Dopaminergic treatments for these disorders can

[1] Suggested possible future research direction to back-translate the fish paradigm to study undergraduate students.

negatively impact attentional inhibition due to their diffuse effects on dopamine systems (Hasan et al., 2013; Advokat, 2010). Therefore it may be valuable to understand the specificity of dopamine in attentional systems to inform more selective treatments. Secondly, striatal dopamine can be relatively easily manipulated in the brain, both pharmacologically (Bäckman et al., 2011) and naturally (Salamone & Correa, 2012). Hence better understanding may inform methods for enhancing attentional inhibition—even in healthy individuals.

Put simply, striatal dopamine is something that *changes* in the brain, and can *be changed*. It is not the be-all and end-all of attentional mechanisms, and is not the only neurotransmitter implicated in IOR (e.g. Gabay, Pertzov & Henik, 2011). But striatal dopamine arguably has the most practical applications and real-world implications, which—in my view—makes its investigation worthwhile. Not to mention, drinking beer in a country pub increases dopamine. So it completes the backstory rather nicely.

However, even after focusing on a specific attentional mechanism, brain region, and neurotransmitter in this thesis—there remained more layers of complexity than could possibly be addressed within the time of my PhD. Luckily, I was able to work with capable supervisors who helped me find the signals in the noise. The PhD project was conceived by Wael El-Deredy and Joanna Neill: Wael—with his experience of studying dopamine and mastery of EEG. He is somehow able to simultaneously consider the big picture and the minutia of research projects, making discussions with him invaluable (and often mind-bending). And Jo—with her comprehensive experience of neuropharmacology in humans and animals, especially regarding attention and impulsivity. Wael and Jo thankfully plucked me out of my undergraduate obscurity with an excellent project proposal, which I have since frankensteined to make my own.

I was ecstatic when Ellen Poliakoff agreed to join the supervisory team shortly after the project began. The project really clicked into place with Ellen's guidance. She has conducted several IOR studies in the past, including in patients with Parkinson's disease (Poliakoff et al., 2003). Hence she was able to expertly advise on both IOR methodology and the putative involvement of striatal dopamine. Importantly, Ellen cultivated my existing 'attention nerd' tendencies, and even presented me with a badge which proclaims 'I ♥ IOR' as encouragement during deepest, darkest data collection.

Consequently, I was able to take this multidisciplinary approach to investigating the role of striatal dopamine in IOR, described herein. I hope that you enjoy reading it and that you are not inhibited from returning after this terrible pun.

Chapter 1

Introduction

The following introductory chapter will provide an overview of the areas of literature most relevant for this thesis: Firstly, the characteristics and neurobiological basis of IOR will be addressed. Secondly, previous studies of striatal dopamine in IOR will be described, following a more general introduction to dopamine. Thirdly, trait impulsivity will be addressed, including the IOR-impulsivity relationship, and its connection with striatal dopamine. Finally, the aims of the thesis will be described, followed by an overview of the subsequent chapters.

1.1 Inhibition of Return

If a target appears in a recently attended spatial location (within 300ms), individuals are much faster at responding to it than if it appears in a novel location. This phenomenon is referred to as facilitation. Conversely, if a target appears after 300ms, individuals respond more slowly to another target in the same location (see Figure 1.1A). The inhibitory effect was termed IOR by Posner, Rafal, Choate and Vaughan (1985), following its initial observation in 1984 by Posner and Cohen. Over thirty years later, and the same broad definition of IOR still holds; IOR is a decrement in performance[1] at previously-attended locations (Klein, 2000; Lupiáñez et al., 2006; Chica & Lupiáñez, 2009).

Tasks measuring visual IOR typically involve the presentation of a target stimulus, to which the participant manually responds (e.g. by pressing a button). This provides a measure of reaction time (RT) to the target. It is preceded by an uninformative cue stimulus, which appears either in the same location as the target (cued trial), or in a different location (uncued trial), after various stimulus-onset asynchronies (see Figure 1.1B) (Klein, 2000). IOR is measured as slower RTs to targets in cued versus

[1] Here, 'performance decrement' refers to the inhibition of attention, which manifests in delayed RTs. However, it can also mean impaired accuracy for discerning target features (e.g. Thompson & Taylor, 2015; Mayr, 2001). There is a complex line of research concerned with speed-accuracy trade-offs in IOR tasks, which contribute to debates surrounding IOR as input- or output-based mechanism. The interested reader is directed to Lupiáñez, Martín-Arévalo and Chica (2013) and Taylor (2000).

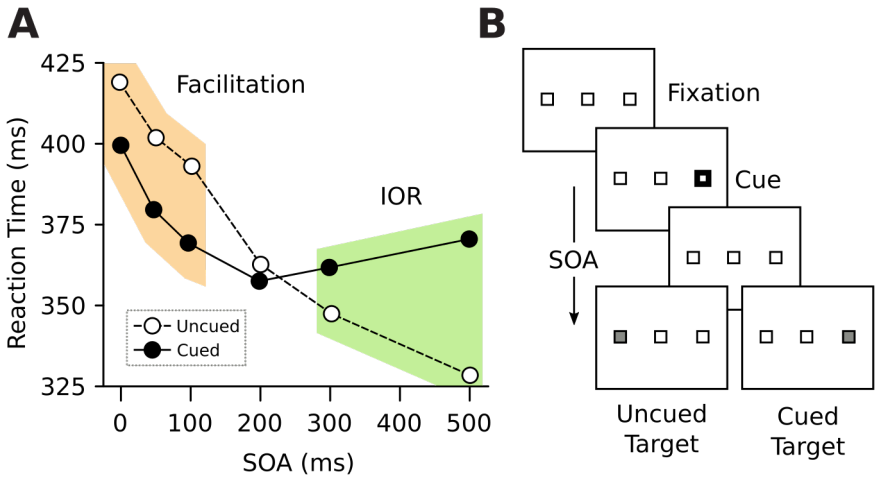

Figure 1.1: (A) Example graph depicting the crossover point between facilitation and inhibition of reaction times (RTs) to cued versus uncued targets, as a function of stimulus onset asynchrony (SOA). (B) Example stimulus displays of a classic Posner cuing paradigm. Figure adapted from Klein (2000).

uncued locations (Klein, 2000). This method is usually referred to as the classic Posner cuing or cue-target paradigm (Klein, 2000; Posner & Cohen, 1984; Posner et al., 1985).

The inhibitory effect has been shown to last for up to 4.8 seconds (Samuel & Kat, 2003; Poliakoff, Spence, O'Boyle, McGlone & Cody, 2002), and act over a spatial gradient strongest at the cued location itself (Macinnes & Klein, 2003b). IOR has also been observed for objects, even if moved in space (Tipper, Driver & Weaver, 1991; Tipper, Weaver, Jerreat & Burak, 1994; Leek, Reppa & Tipper, 2003; Tipper, Jordan & Weaver, 1999), and is weakened or abolished if the initial context is altered; for example, if the background is changed from a crowd of people to plain white (Klein & Macinnes, 1999; Macinnes & Klein, 2003b). Furthermore, IOR operates independently for objects and scenes (Leek et al., 2003), and affects around four previously-attended items or locations in a search display (Wang & Klein, 2010). Taken together, these features have led researchers to consider IOR as an adaptive attentional mechanism—facilitating visual search by biasing attention away from locations that have already been inspected (Klein, 2000; Wang & Klein, 2010).

1.1.1 Tasks and Forms

Since its conception, researchers have modified features of the traditional Posner cuing paradigm, usually to investigate the boundary characteristics of IOR itself. For example, if the task involves discrimination of target features (e.g. colour or

shape) IOR emerges later than in simple detection tasks (Lupiáñez, Milliken, Solano, Weaver & Tipper, 2001). Others have measured IOR in multi-item search arrays to explore its relation to visual search (Müller & von Mühlenen, 2000; Snyder & Kingstone, 2007). IOR has also been investigated non-spatially (Law, Pratt & Abrams, 1995; Mondor, Breau & Milliken, 1998) and in different sensory modalities (Schmidt, 1996; Spence & Driver, 1998; Poliakoff et al., 2002).

IOR tasks may utilise a 'cue-back' procedure, which is the presentation of a stimulus at fixation between the cue and target presentation (Pratt & Fischer, 2002; Prime, Visser & Ward, 2006). This serves to re-centralise participants' focus, preventing prolonged facilitation effects at lateralised locations (Pratt & Fischer, 2002; Prime et al., 2006). As such, cue-back paradigms produce earlier, more robust IOR effects in experiments[2] (e.g. MacPherson, Klein & Moore, 2003; Prime & Ward, 2004; McDonald, Hickey, Green & Whitman, 2008).

Another task feature which may influence attention disengagement in IOR is the ratio of cued to uncued trials. It is generally accepted that cues should be uninformative, in that their location is not predictive of the target location (Klein, 2000). It may be argued that predictive cues influence expectations, which is a more complex top-down influence on the orienting system than true IOR (Lupiáñez et al., 2004). Nevertheless, some studies may include a higher proportion of cued trials in their IOR studies (e.g. Poy, Eixarch & Avila, 2004; Avila, 1995). Hence researchers should take care when interpreting or comparing the finding of these studies (this is discussed further in relation to trait impulsivity in section 1.3.1).

Some IOR tasks may utilise ballistic eye movements (saccades) to targets instead of manual responses (Taylor, 2000; Rafal, Posner, Friedman, Inhoff & Bernstein, 1988; Klein & Macinnes, 1999; Kingstone & Pratt, 1999). Hunt and Kingstone (2003) demonstrated a double-dissociation between ocular (saccadic) and non-ocular IOR—suggesting that these may be distinct forms that should not be directly compared (Briand, Larrison & Sereno, 2000; Hunt & Kingstone, 2003; MacInnes, Krüger & Hunt, 2015). As such, eye movements are often discouraged in IOR tasks to ensure that IOR is a reflection of the allocation of attention, rather than motoric/gaze effects (Klein, 2000; Hilchey et al., 2014; Hunt & Kingstone, 2003; MacInnes et al., 2015). However, this debate is ongoing in the literature (see Hilchey, Klein & Ivanoff, 2012), and it is likely that spatial attention is linked closely to the eye movement system (Theeuwes, Belopolsky & Olivers, 2009). This thesis is not

[2]The explanation here for how cue-back procedures influence IOR reflects the 'traditional re-orienting hypothesis' of IOR. Put simply, this means that IOR occurs following attentional disengagement (Macinnes & Klein, 2003a; Ivanoff & Taylor, 2006). However, see Martín-Arévalo, Kingstone and Lupiáñez (2013) for an alternative 'detection cost' account.

concerned with the distinction between ocular and non-ocular IOR, and considers IOR as an attentional inhibitory mechanism. Therefore, further discussions are largely focused on the non-ocular form of IOR.

Lastly, IOR has been measured without cues, but instead by presenting continuous streams of targets—termed a target-target paradigm (Prime & Ward, 2002; Spence & Driver, 1998). In cue-target paradigms, participants must inhibit their motoric responses to cues. Participants must then overcome this motoric inhibition if a target appears in the cued location, potentially slowing RTs (Poliakoff et al., 2007; Coward, Poliakoff, O'boyle & Lowe, 2004; Poliakoff et al., 2002). IOR magnitudes are generally smaller in target-target versus cue-target paradigms (Coward et al., 2004; Poliakoff et al., 2002; Poliakoff et al., 2007), suggesting that motoric inhibition enhances IOR beyond purely attentional effects. Therefore target-target designs are proposed to circumvent the motoric confound caused by cues in cue-target paradigms (Poliakoff et al., 2003).

As a consequence of these variations, there is growing concern that IOR tasks may access different forms or 'flavours' of IOR, which researchers commonly overlook and "lump together" (see Dukewich & Klein, 2015, for a review). As such, it is important to consider these methodological features when designing and interpreting IOR studies. It is not uncommon that discrepancies between findings can be explained by task variations that interfere with IOR characteristics (e.g. Hilchey et al., 2012; Mushquash et al., 2012). Nevertheless, these issues do not render comparisons in the literature fruitless, as long as researchers are mindful of inconsistencies and maintain internal consistency where possible.

1.1.2 Sensory vs. Attentional Causes

The name 'IOR' implies both cause and effect—insinuating that IOR is the result of the inhibition of cognitive processes (Berlucchi, 2006). However, whilst the effects of IOR are robustly observed in behaviour, the underlying causes are subject to considerable debate (Martín-Arévalo, Chica & Lupiáñez, 2016; Satel, Hilchey, Wang, Reiss & Klein, 2014; Prime & Ward, 2004). For the purposes of this thesis, this vast and complex area of research is confined to the following question: Is IOR caused by the inhibition of either *sensory/perceptual* or *attentional* processes? This question is not trivial, as it concerns if IOR is simply the inevitable result of changes in sensory 'energy'—or the more complex inhibition of attentional orienting (Berlucchi, 2006).

In order to contribute to this debate, components of electroencephalography (EEG) can be used to measure the timing and strength of certain attentional events—called event-related potentials (ERPs— Luck, 2011); EEG methodology

is addressed in more detail in the General Methods section (2.2). The majority of ERP studies of IOR indicate that sensory/perceptual ERPs are smaller or delayed in cued versus uncued conditions (e.g. McDonald, Ward & Kiehl, 1999; Prime & Ward, 2006; Prime & Ward, 2004; Wascher & Tipper, 2004; Chica & Lupiáñez, 2009). And more recent attempts have shown similar modulations of selective attention ERPs (McDonald et al., 2008; Martín-Arévalo, Chica & Lupiáñez, 2014; Yang, Yao, Ding, Qi & Lei, 2012). This supports the idea originally proposed by Posner himself (1985), that IOR is caused both by inhibited sensory/perceptual *and* attentional processes (Posner et al., 1985).

However, these ERP studies have since been criticised for their use of the more traditional Posner cuing paradigm, in which singleton cues are followed by singleton targets (McDonald, Ward & Kiehl, 1999; Prime & Ward, 2006). Stimuli induce a certain pattern of neuronal cell firing in the sensory system of the brain/retina (Kohn & Whitsel, 2002). This period of excitation is followed by a period of recovery or refraction—during which these cells are less responsive to incoming stimuli (Kohn & Whitsel, 2002). As such, the same cells require a higher level of stimulation to produce the same strength of response as before (Eimer, 2014; Kohn & Whitsel, 2002). Therefore, stimulation by a target following a cue at the same location would produce a smaller sensory response (Eimer, 1994). Consequently, cue-target paradigms using singletons may predispose the sensory/perceptual effects observed in EEG studies of IOR (McDonald, Ward & Kiehl, 1999; Prime & Ward, 2006).

McDonald and colleagues investigated this issue in 2008, and designed a target-target IOR task which balanced sensory stimulation across the display. They achieved this by presenting targets alongside visually-matched non-targets. This similarly stimulated cued and uncued locations, thus circumventing the sensory refraction imbalance for cued locations. Using this task, they observed a behavioural IOR effect, and reduced selective attention (i.e. N2pc) to cued versus uncued targets. Furthermore, they found no significant differences between cued and uncued sensory ERPs (i.e. P1/N1, McDonald et al., 2008). This contrasts with the vast majority of ERP studies of IOR, which employed more traditional task designs (see Martín-Arévalo et al., 2016, for a review). Therefore, the findings of McDonald et al. (2008) may be taken as evidence that IOR is caused by the inhibition of selective attention to cued locations.

However, null findings do not necessarily disprove the involvement of the sensory system; it could be that the task designed by McDonald et al. (2008) reduced, but did not eradicate sensory modulations. The authors admit that their findings cannot rule out the involvement of other cognitive processes in IOR. As such,

it remains somewhat ambiguous whether sensory versus attentional modulations alone are necessary to cause IOR.

This invites the question of how studies can more sensitively identify which ERPs reflect the causes of IOR. Some IOR studies have measured correlations between ERPs and RTs to more strongly establish the relationship between cognition and behaviour. For example, Satel, Hilchey, Wang, Story and Klein (2013) found that IOR magnitudes (cued minus uncued RTs) correlated with P1 modulations in a non-ocular visual IOR task; and Jones and Forster (2014) found a correlation between the 'negative difference' marker of selective attention and tactile IOR magnitudes. This technique compliments the more standard approach of looking for a difference between cued and uncued conditions (Martín-Arévalo et al., 2016).

Additionally, Berlucchi (2006) highlights that "There is more than inhibition to IOR" (p.1069)—meaning that IOR is not just inhibition of cued locations, but also facilitation of uncued locations. As mentioned, studies of IOR usually measure the compound difference between cued and uncued conditions. Yet cued and uncued themselves relate to different processes (Engelmann & Pessoa, 2007; Berlucchi, 2006), and may therefore be reflected in different ERP modulations. Therefore, future research regarding IOR causes may benefit from measuring ERP relationships as well as the separate contributions of cued and uncued conditions.

1.1.3 Neurobiological Basis

The superior colliculus is thought to mediate both the allocation of visual spatial attention and eye movements, making it a strong candidate for IOR involvement (see Cavanaugh & Wurtz, 2004). Indeed, several converging lines of evidence support a central role for the superior colliculus in IOR: The earliest evidence came from abolished IOR in patients with supranuclear palsy (Posner et al., 1985; Rafal et al., 1988), who suffer progressive degeneration of parts of the midbrain (Kato, Arai & Hattori, 2003). This has since been bolstered by electrophysiological studies of the primate superior colliculus (Dorris, Klein, Everling & Munoz, 2002; Fecteau & Munoz, 2005; Bell, Fecteau & Munoz, 2004); as well as lesion studies in humans (Sereno, Briand, Amador & Szapiel, 2006; Sapir, Soroker, Berger & Henik, 1999). More recently, Anderson and Rees (2011) measured brain activity in the human superior colliculus using functional magnetic resonance imaging (fMRI) during an IOR task; they found that it was less active in cued trials, and more active in uncued trials (compared to neutral).

It has been suggested that the superior colliculus is central to a wider network of brain regions involved in IOR (Bell et al., 2004; Anderson & Rees, 2011). This is

reasonable considering that it receives inputs from the prefrontal, parietal, temporal, and primary visual cortices, as well as retinal and extra-striate regions (Fecteau & Munoz, 2005). Furthermore, there is growing evidence that cortical structures play a substantial role in IOR (Christie, Hilchey & Klein, 2013; Mayer, Seidenberg, Dorflinger & Rao, 2004). For instance, transcranial magnetic stimulation of the frontal eye fields abolishes IOR (Ro, Farnè & Chang, 2003); lesions of the parietal cortex disrupt remapping of 'inhibitory tags' in IOR (van Koningsbruggen, Gabay, Sapir, Henik & Rafal, 2010; Sapir, Hayes, Henik, Danziger & Rafal, 2004); and object-based IOR fails to pass between hemifields in split brain patients (Tipper et al., 1997). Therefore, it appears that whilst the superior colliculus may generate inhibitory tags, cortical structures may be important for their maintenance (Gabay, Pertzov, Cohen, Avidan & Henik, 2013; Krüger & Hunt, 2013; Rafal, Davies & Lauder, 2006).

Studies of neurological disorders implicate other brain regions in the IOR response. For example, patients with Parkinson's disease and Huntington's disease have reduced basal ganglia function, and show reduced/abnormal IOR responses (Poliakoff et al., 2003; Possin, Filoteo, Song & Salmon, 2009; Fielding, Georgiou-Karistianis & White, 2006; Couette, Bachoud-Levi, Brugieres, Sieroff & Bartolomeo, 2008). Basal ganglia disruptions may influence IOR in several ways, as they are functionally connected to cortical and subcortical brain regions—including the superior colliculus (Hikosaka, Takikawa & Kawagoe, 2000; Poliakoff et al., 2003). Patients with Schizophrenia show diffuse abnormalities in cortical and subcortical brain regions, and show smaller IOR magnitudes than healthy controls (Mushquash et al., 2012; Sereno & Holzman, 1995; Gouzoulis-Mayfrank et al., 2007). Patients with obsessive-compulsive disorder show IOR deficits in the left visual field (Rankins, Bradshaw, Moss & Georgiou-Karistianis, 2004)—which correspond to reduced white matter volume in the right hemisphere (including the parietal cortex and basal ganglia) (Rao, Arasappa, Reddy, Venkatasubramanian & Reddy, 2015). These diverse findings indicate that IOR evolves across the attention network in the brain (Fecteau & Munoz, 2005).

Furthermore, neurological disorders implicate a role for neurotransmitters in IOR, such as excess and insufficient levels of striatal dopamine in patients with Schizophrenia and Parkinson's disease, respectively (Poliakoff et al., 2003; Gouzoulis-Mayfrank et al., 2007). Dopamine is arguably the most compelling neurochemical candidate for a role in IOR. As such, the role of dopamine will be considered in more detail in a separate section (1.2.2). What follows is an overview of findings regarding the role of other neurotransmitters in IOR.

Evidence of a neurotransmitters involvement is often gleaned from pharma-

cological manipulations. For example, Davidson, Cutrell and Marrocco (1999) administered the acetylcholine antagonist scopolamine to primates, which reduced the magnitude of IOR. Conversely, cannabis users may have higher acetylcholine levels in the prefrontal cortex due to the effect of cannabinoids (Verrico, Jentsch, Dazzi & Roth, 2003), and show increased IOR magnitudes (Vivas, Estevez, Chamberlain, Panagis & Flores, 2012). This suggests a positive relationship between IOR and acetylcholine levels in the brain. However, these effects may also be attributed to striatal dopamine, as both scopolamine and cannabinoids significantly alter striatal dopamine signalling (Di Giovanni & Shi, 2009; Ameri, 1999).

The effect of dimethyltryptamine on IOR was measured in healthy volunteers (Gouzoulis-Mayfrank et al., 2002; Daumann et al., 2008); a drug which acts on serotonin receptors to produce psychedelic effects (Pierce & Peroutka, 1989; Smith, Canton, Barrett & Sanders-Bush, 1998). They found that the drug reduced the IOR response, indicating that high levels of serotonin (especially in the cortex) negatively affect IOR (Gouzoulis-Mayfrank et al., 2002; Daumann et al., 2008). However, dimethyltryptamine has diffuse effects on other neurotransmitters, especially dopamine—making it difficult to delineate its specific effects (Ray, 2010).

Abroms and Fillmore (2004) showed that alcohol reduces the duration of the IOR effect, potentially caused by an increase in γ-Aminobutyric acid (GABA) in the brain (Lovinger, 2008). This fits with the multitude of other findings regarding the detrimental effects of alcohol on cognitive inhibition (Fillmore & Vogel-Sprott, 2000; Bartholow, Dickter & Sestir, 2006; Hirsh, Galinsky & Zhong, 2011; Feola, de Wit & Richards, 2000; Marczinski & Fillmore, 2003). However, again, alcohol has non-selective effects on several other neurotransmitters (Lovinger, 2008).

Lastly, pupil diameter is thought to reflect the level of noradrenaline in the locus coeruleus of the brain (Matsui et al., 2004; Aston-Jones, Rajkowski, Kubiak & Alexinsky, 1994); and a positive relationship was found between pupil diameter and IOR magnitude (Gabay et al., 2011). Noradrenaline signalling has also been implicated in other forms of attentional inhibition (Chamberlain et al., 2006); and the noradrenaline-increasing drug atomoxetine has been shown to improve inhibitory abilities in individuals with ADHD (Chamberlain et al., 2007). However, atomoxetine effects dopamine transmission in the prefrontal cortex—making the mechanism of its therapeutic effects unclear (del Campo, Chamberlain, Sahakian & Robbins, 2011; Chamberlain et al., 2007).

In summary, IOR is mediated by a diffuse network of structures originating from cortical and subcortical brain regions, especially the superior colliculus and frontal cortices. A range of neurotransmitters modulate the activity of these regions, affecting the behavioural manifestation of IOR. However, the studies discussed

above do not rule out the involvement of dopamine signalling in particular. Other, more direct lines of evidence indicate that dopamine may prove the most pertinent neurotransmitter for IOR (e.g. Fillmore, Rush & Abroms, 2005). As such, the role of dopamine in IOR will be addressed below, preceded by a more detailed introduction to dopamine.

1.2 Dopamine

Dopamine is a neurotransmitter synthesised within neurons of the substantia nigra pars compacta and ventral tegmental area in the midbrain (Björklund & Dunnett, 2007). From this complex, neurons project to the striatum, limbic and cortical brain areas (mesostriatal, mesolimbic and mesocortical pathways, respectively) (Björklund & Dunnett, 2007). In a broad sense, the mesostriatal pathway influences movement control, the mesolimbic is involved in motivated behaviour, and the mesocortical is implicated in learning and memory (Vallone, Picetti & Borrelli, 2000).

Dopamine is released from the midbrain in two distinct firing patterns; tonically, at low frequencies—providing baseline levels of dopamine to maintain stable motor control and postsynaptic mechanisms (Grace, 1991); and phasically, in more transient high-frequency bursts responding to acute reward-related reinforcement learning and motivational events (Schultz, 2007; Grace, 1991).

To achieve these effects on cognition and behaviour, extracellular dopamine is bound by five different G-protein coupled receptors, expressed on neuronal membranes throughout the brain (Vallone et al., 2000). Dopamine receptors are categorised as either D1-like (D1 & D5) or D2-like (D2, D3 & D4) based on their biochemical properties when stimulated by dopamine binding (Vallone et al., 2000). D1 and D2 are the most ubiquitous dopamine receptors, and can be found in several brain regions. However, D1 are most abundant the cerebral cortex (Jackson & Westlind-Danielsson, 1994), whereas D2 are most abundant in the striatum (Jackson & Westlind-Danielsson, 1994).

In cognition, phasic dopamine signalling is best known for its critical role in motivation and reward (Bromberg-Martin, Matsumoto & Hikosaka, 2010). It is proposed to act as a 'teaching signal', enabling us to learn which stimuli to approach or behaviours to execute in our environments (Wise, 2004). However, dopamine is increasingly recognised to play a role in more general attentional orienting processes (Bromberg-Martin et al., 2010). Dopamine in one particular brain region—the striatum—is particularly implicated in both rewarding and non-rewarding processes (Hikosaka et al., 2000; Horvitz, 2000). As such, striatal dopamine is the focus of this thesis, and is addressed in the following sections.

1.2.1 Striatal Dopamine in Attention

Striatal dopamine has been the focus of a multitude of studies of attention for several reasons—the most obvious being its distinct role in certain neurological disorders. For instance, patients with Parkinson's disease suffer loss of dopamine-generating neurons in the subtantia nigra, which supply the striatum with dopamine (Ayano, 2016b). The primary symptoms of Parkinson's disease include muscle tremors and loss of motor control (Ayano, 2016b). However, patients also suffer debilitating problems with attention, including dysfunctional mental flexibility, forward planning, and visuospatial skills (Caballol, Martí & Tolosa, 2007).

Patients with attention-deficit/hyperactivity disorder (ADHD) often struggle to focus, delay gratification, and inhibit thoughts and behaviours (Barkley, Edwards, Laneri, Fletcher & Metevia, 2001; Barkley, Murphy & Fischer, 2010). As such, ADHD patients are at risk of social maladjustment, unemployment and have a high propensity for substance abuse (Biederman et al., 1995; Biederman, 2005). Striatal dopamine is strongly implicated in the pathophysiology of ADHD—as individuals are thought to have lower baseline levels (Krause, Dresel, Krause, Kung & Tatsch, 2000; Kirley et al., 2002; Dougherty et al., 1999); and drugs which increase striatal dopamine can alleviate symptoms (Krause et al., 2000).

At the opposite end of the spectrum are patients with Schizophrenia—who are thought to have excessive amounts of dopamine in the striatum (Brunelin, Fecteau & Suaud-Chagny, 2013; Abi-Dargham et al., 2000). Schizophrenia is associated with psychotic symptoms, including delusions and hallucinations (Owen, Sawa & Mortensen, 2016). Patients also experience debilitating problems with attention, executive control, and memory (Owen et al., 2016). Medications used to treat the symptoms of Schizophrenia usually antagonise D2 receptors, reducing dopamine signalling in the striatum (Herrera-Estrella, Apiquian, Fresan & Sanchez-Torres, 2005; Brunelin et al., 2013).

These disorders illustrate just part of the vast literature surrounding striatal dopamine in attention, but they demonstrate a fundamental idea; that both excessive and insufficient levels of striatal dopamine can negatively impact various cognitive functions (Cools & D'Esposito, 2011). This is further supported by the baseline-dependent effects of dopaminergic drugs on cognition (e.g. Cools et al., 2009; Gibbs & D'Esposito, 2005). The level of dopamine which is optimal appears to differ depending on the cognitive function in question (Cools & D'Esposito, 2011)—which explains how dopaminergic drugs can often treat one cognitive impairment, but exacerbate another (see Figure 1.2) (Advokat, 2010).

Additionally, it is important to consider that the striatum shares extensive re-

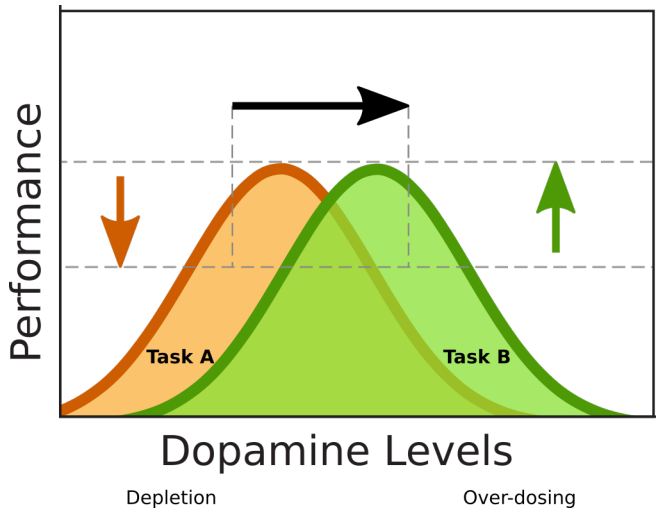

Figure 1.2: Dopamine levels which are optimal for performance in one cognitive task may be insufficient for optimal performance in another. Figure adapted from Cools and D'Esposito (2011).

ciprocal connections with the prefrontal cortex (van Schouwenburg, O'Shea, Mars, Rushworth & Cools, 2012); and dopamine signalling in one region strongly influences the other (van Schouwenburg et al., 2012). As such, many of the dopaminergic treatments which target the striatum also influence the prefrontal cortex, which may account for some of their therapeutic effects (Spencer, Devilbiss & Berridge, 2015; Koda et al., 2010). Indeed, the aforementioned disorders also show abnormal dopamine signalling in the prefrontal cortex—which may contribute to their aetiology (Kirley et al., 2002; Fusar-Poli et al., 2010; Zgaljardic, Borod, Foldi & Mattis, 2003; Spencer et al., 2007).

In a healthy brain, these so-called frontostriatal connections function to ensure that individuals can both focus on complex tasks, and adapt to changes within the task (Cools & D'Esposito, 2011). More specifically, dopamine in the prefrontal cortex is thought to promote attentional stability—to maintain stable task goals, rules, and focus; whereas dopamine in the striatum is thought to promote flexibility—to enable attention switching and strategy updating (Cools & D'Esposito, 2011; Klanker, Feenstra & Denys, 2013; van Schouwenburg et al., 2012). Therefore, the relative balance of dopamine in the striatum versus the prefrontal cortex determines performance in tasks which require more flexibility versus stability (see Cools & D'Esposito, 2011, for an extensive review).

Why investigate the role of striatal dopamine in cognition if cortical dopamine is also important? Firstly, there are simply more tools available to measure striatal dopamine than cortical dopamine. For example, the main method of directly measuring neurotransmitter levels in the brain is positron emission tomography (PET)—which images the binding of radioactive ligands to receptors in the brain

(Bailey, Townsend, Valk & Maisey, 2005). However, presently available PET ligands are optimised for D2 receptors (Schreckenberger et al., 2004)—which are more abundant in the striatum than the prefrontal cortex (Jackson & Westlind-Danielsson, 1994).

Baseline striatal dopamine levels can also be inferred by measuring working memory capacity (Cools, Gibbs, Miyakawa, Jagust & D'Esposito, 2008); spontaneous eye blink rate (EBR) (Colzato, Slagter, Spapé & Hommel, 2008); and even personality traits such as impulsivity (Buckholtz et al., 2010). Trait impulsivity as a measure of baseline dopamine is of particular interest for this thesis, and is therefore addressed in more detail later in this chapter (1.3.2).

Furthermore, striatal dopamine is more amenable to manipulations than cortical dopamine. For instance, there are more drugs available which target D2 receptors in the striatum (see General Methods, 2.4), than D1 receptors in the prefrontal cortex (Cools & D'Esposito, 2011). Additionally, the striatum is at the core of the neural circuitry for reward (Haber & Knutson, 2010). Hence phasic striatal dopamine can also be increased with rewarding stimuli, such as food or money (Brown, McCutcheon, Cone, Ragozzino & Roitman, 2011; Bromberg-Martin et al., 2010).

Lastly—and of most relevance for this thesis—striatal dopamine has been strongly implicated in IOR (e.g. Poliakoff et al., 2003). The literature surrounding this will be addressed in the following section.

1.2.2 Striatal Dopamine in IOR

Overview

The aforementioned neurological disorders have also been studied in relation to IOR: Patients with Parkinson's disease show reduced IOR responses, both in visual and tactile domains (Fielding et al., 2006; Possin et al., 2009; Poliakoff et al., 2003). The latter demonstrates that patients with Parkinson's disease have abnormal attentional inhibition, rather than issues specific to the visual system (such as retinal dysfunctions associated with Parkinson's disease) (Poliakoff et al., 2003).

Regarding IOR in patients with Schizophrenia—some studies show blunted or abolished effects (Fuggetta, Bennett & Duke, 2015; Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2007); whilst others show that IOR may be intact (Kalogeropoulou, Woodruff & Vivas, 2015; Tang et al., 2015). These discrepancies are likely due to differences in task features, as studies showing intact IOR use the cue-back procedure (described in 1.1.1) (Mushquash et al., 2012). This indicates

that their abnormal IOR response may be caused by facilitation of cued targets masking IOR (Kalogeropoulou et al., 2015).

Children with ADHD show similar cuing effects in IOR as controls, but generally smaller IOR responses (Li, Chang & Lin, 2003). Furthermore, Adams, Derefinko, Milich and Fillmore (2008) examined subtypes of ADHD, and found that individuals with the combined-type—and those with comorbid oppositional defiant disorder—showed more profound IOR deficits than those with the inattentive subtype. This indicates that higher impulsivity may be more detrimental for IOR than inattention. This idea is explored in more detail in a subsequent section (1.3.1).

Lastly, although not a disorder *per se*, individuals with a history of cocaine abuse have reduced baseline levels of striatal dopamine (Volkow, Fowler & Wang, 1999)—and have reduced IOR responses (Colzato & Hommel, 2009).

These findings are in accordance with other studies of striatal dopamine in attention, indicating that excessive or insufficient levels of striatal dopamine can negatively affect IOR (1.2.1). However, the impairments in all of the aforementioned disorders are not constrained to striatal dopamine (Ayano, 2016b; Gouzoulis-Mayfrank et al., 2007). Furthermore, studies of neurological disorders are often confounded by inconsistencies in disorder severity, medication status, and the presence of comorbidities (see Mushquash et al., 2012).

IOR has also been investigated in healthy individuals with different baseline striatal dopamine levels via DAT1 genotypes. DAT1 is a gene which codes for the dopamine transporter protein, which removes excess extracellular dopamine from the striatum (Fuke et al., 2001). Polymorphisms of DAT1 are related to either higher or lower baseline striatal dopamine levels (9-repeat or 10-repeat alleles, respectively) (Bertolino et al., 2006). Colzato, Pratt and Hommel (2010) found that individuals with the 9-repeat allele have significantly higher IOR magnitudes than those with the 10-repeat allele—indicating that higher (but healthy) levels of striatal dopamine produce larger IOR magnitudes.

In order to investigate the more direct, causal effects of striatal dopamine on IOR, researchers have measured the influences of pharmacological manipulations. Firstly, Fillmore et al. (2005) administered the dopamine agonist *d*-amphetamine to healthy volunteers, and found that the drug enhanced IOR in a dose-dependent manner. However, *d*-amphetamine has non-selective effects on various dopamine receptors, as well as on serotonin and noradrenaline transporters (Heal, Smith, Gosden & Nutt, 2013)—which may have influenced IOR mechanisms.

To target the striatum more selectively, Rokem et al. (2012) administered the D2 agonist bromocriptine to healthy participants with different DAT1 genotypes.

They found that the drug reduced IOR in individuals with high baseline striatal dopamine levels, but increased IOR in those with a low baseline. This could be interpreted as direct evidence of 'too much' striatal dopamine for optimal IOR. However, it has been shown that D2 autoreceptors are preferentially activated in the presence of high levels of striatal dopamine (Maruya et al., 2003); and autoreceptors function to down-regulate dopamine release in the striatum (Gonon & Buda, 1985). Therefore, the authors postulate that the drug may have decreased dopamine levels in the striatum to negatively impact IOR (Rokem et al., 2012). In this circumstance, an outcome measure would have been useful to examine if dopamine levels were enhanced or depleted as a result of the drug.

The only studies which have measured the direct effects of dopamine depletion were in patients with Schizophrenia—with Gouzoulis-Mayfrank et al. (2007) showing that D2 antagonists may recover reduced IOR responses (although see Sapir, Dobrusin, Ben-Bashat & Henik, 2007). However, there have been no such investigations in healthy individuals, making it difficult to assess the contribution of the aforementioned disease-related confounds.

Potential Explanations

The studies described above have observed the effects of striatal dopamine on behavioural IOR. However, it is unclear how changes in dopamine may interact with neural mechanisms to influence IOR. Surprisingly, the majority of behavioural studies neglect to discuss this (e.g. Fillmore et al., 2005; Colzato & Hommel, 2009; Gouzoulis-Mayfrank et al., 2007). However, Colzato, Pratt and Hommel (2010) explain their findings in terms of the fontostriatal balance between flexibility and stability (see 1.2.1) (Cools & D'Esposito, 2011). More specifically, they postulate that IOR favours higher levels of striatal dopamine, as IOR is considered a mechanism of attention flexibility (Colzato, Pratt & Hommel, 2010; Klein, 2000). Therefore, individuals with insufficient striatal dopamine may experience an inflexible state—negatively impacting their ability to orient towards novel stimuli. Conversely, excessive striatal dopamine may induce an overly flexible state, impacting the ability to inhibit orienting back to 'old' stimuli (Cools & D'Esposito, 2011; Colzato, Pratt & Hommel, 2010)

How might these frontostriatal connections relate to the neurobiology of IOR? As described previously (1.1.3), the superior colliculus is thought to generate inhibitory tags—which are maintained by cortical regions (Fecteau & Munoz, 2005; Klein, 2000). Therefore, the balance between attention flexibility and stability may influence these structures. Without the necessary dopaminergic inputs from the striatum (Ikemoto, Yang & Tan, 2015), the superior colliculus may be less able to

produce inhibitory tags. Alternatively, the resulting inflexibility may impair attention disengagement—with the prefrontal cortex maintaining the inhibitory tag 'too strongly' (Fecteau & Munoz, 2005). Conversely, striatal dopamine hypersignalling may interfere with tag maintenance by the prefrontal cortex—as the frontostriatal balance is tipped away from the prefrontal cortex to the striatum (Cools & D'Esposito, 2011).

However—as highlighted by Colzato, Pratt and Hommel (2010)—it is difficult to draw such conclusions from behavioural studies alone. ERPs can help to explore how specific IOR processing stages may be affected by striatal dopamine signalling. For instance, patients with Schizophrenia showed reduced early sensory orienting (P1) to novel auditory stimuli in an oddball task (Ward, Catts, Fox, Michie & McConaghy, 1991). This indicates that excessive striatal dopamine may reduce the prioritisation of novel stimuli by the sensory system. If the same pattern were observed in an IOR task, it might suggest that inhibitory tag formation is not affected—instead indicating reduced prioritisation of uncued stimuli is to blame. Alternatively, if an inhibitory tag is produced but not maintained, then attention to cued stimuli may occur earlier (i.e. shorter latency of ERPs).

At the other end of the spectrum, Ahveninen and Ka (2000) showed that pharmacological depletion of striatal dopamine reduced the strength of selective attention ERPs to auditory tones in healthy volunteers. A similar effect has also been observed in patients with Parkinson's disease (Vieregge, Verleger, Wascher, Stüven & Kömpf, 1994). This suggests that striatal dopamine hyposignalling may negatively influence selective attention—but it remains unclear if this would differently affect the processing of cued versus uncued stimuli in an IOR task.

The only ERP studies of IOR which also include considerations of striatal dopamine have been conducted in patients with Schizophrenia. For instance, Fuggetta et al. (2015) found that patients exhibit later, but stronger selective attention (N2pc) across all stimuli. This indicates that excessive striatal dopamine levels affect selective attention in general, but does not explain their behavioural findings of impaired IOR in patients (Fuggetta et al., 2015).

Conversely, Tang et al. (2015) found no behavioural IOR differences between patients with Schizophrenia and controls—yet sensory orienting (N1) was weaker for cued targets in patients. The authors suggest that this N1 modulation is a marker of the preserved IOR responses of patients (Tang et al., 2015). However, the IOR task utilised singleton cues and singleton targets—which is thought to predispose such sensory effects in IOR (as addressed in 1.1.2) (McDonald et al., 2008).

In order to observe potential deficits in attentional flexibility caused by dopamine

depletion, it would be useful to measure attentional disengagement from stimuli. For instance, if depleted striatal dopamine produced weaker or delayed attentional disengagement, this could be taken as evidence for reduced attention flexibility. A candidate ERP termed *Pd* marks the termination of attention to a given visual stimulus (Sawaki, Geng & Luck, 2012; Sawaki & Luck, 2011). It signifies the moment when attention to a given stimulus is 'complete', and the attention system is free to orient towards different stimuli (Sawaki et al., 2012; Sawaki & Luck, 2011). However, there have been no previous investigations of how striatal dopamine may modulate Pd—either in IOR or other cognitive tasks.

To summarise, ERPs may be useful to investigate the role of striatal dopamine in IOR, as they can be used to measure the processing stages behind behaviour. More specifically, markers of sensory orienting, selective attention, and attention termination may contribute to the currently quiet conversation surrounding how dopamine interacts with neural mechanisms to produce IOR. For these reasons, ERPs were selected as a tool to investigate the role of striatal dopamine (see General Methods, 2.2)

1.3 Trait Impulsivity

In the early 1970s, psychologists at Stanford University conducted experiments to measure children's ability to delay gratification. Children were given the option to either receive an immediate treat (e.g. a marshmallow), or wait fifteen minutes to receive a larger treat (e.g. several marshmallows) (Mischel, Ebbesen & Raskoff Zeiss, 1972; Mischel & Ebbesen, 1970). A follow-up study ten years later indicated that the amount of time children waited was positively correlated with their later "academic and social competency"—including scores on university entrance exams (Mischel, Shoda & Rodriguez, 1989). The children's performance even predicted their achievements as adults up to forty years after the initial studies (Casey et al., 2011).

The reduced ability to delay gratification is just one of several characteristics or tendencies associated with trait impulsivity. Others include acting with little or no forethought, seeking novelty and sensations, and generally struggling to inhibit thoughts and actions (Eysenck & Eysenck, 1977; Zuckerman, Kuhlman, Joireman & Teta, 1993; Evenden, 1999). Features of impulsivity can be advantageous in certain circumstances, such as to grasp fleeting opportunities (Evenden, 1999). However, high trait impulsivity is associated with increased propensity to engage in risky behaviours, including violence, criminality, and substance abuse (Clark, Robbins, Ersche & Sahakian, 2006; Wilens & Morrison, 2011; Tremblay, Pihl,

Vitaro & Dobkin, 1994). Impulsivity is also a symptom of certain neurological disorders, including ADHD (Nigg, 2001) and Schizophrenia (Gut-Fayand et al., 2001).

As such, the causes, effects, and mechanisms of trait impulsivity have been widely investigated over the past several decades (Patton & Stanford, 1995; Dalley & Robbins, 2017; Bari & Robbins, 2013). The resulting literature is vast and complex, but one conclusion is clear; impulsivity is a heterogeneous trait which comprises several forms or subtypes (Bari & Robbins, 2013; Perales, Verdejo-García, Moya, Lozano & Pérez-García, 2009).

The Barratt Impulsiveness Scale (BIS) is one of the oldest, most widely used measures of trait impulsivity. and divides impulsivity into three main subtraits[3] to account for such heterogeneity (see Stanford et al., 2009, for a review). In short, these are attentional impulsivity, the inability to focus; motor impulsivity, acting without thinking; and non-planning impulsivity—impaired forethought (Stanford et al., 2009). These factors have been consistently demonstrated across studies, and have been supported by the analysis of large datasets (Patton & Stanford, 1995; Stanford et al., 2009).

Behavioural tasks are often utilised to investigate the mechanisms and characteristics of trait impulsivity (Dalley, Everitt & Robbins, 2011; Perales et al., 2009). For example, to measure the ability to interrupt a planned response—as in the stop-signal reaction time task (Eagle, Bari & Robbins, 2008); or the ability to withhold from responding for a period of time—as in serial reaction time tasks (Robbins, 2002). Others may evaluate more cognitive forms, such the inhibition of conflicting information in a Stroop task (Enticott, Ogloff & Bradshaw, 2006).

However, these tasks are generally concerned with disrupted top-down inhibitory control, in which individuals are consciously attempting to exert inhibition. Less widely investigated is the relationship between impulsivity and reflexive, unconscious attentional inhibition—as in IOR. As such, the IOR-impulsivity relationship is addressed in the following section.

1.3.1 Impulsivity and IOR

IOR is considered an attentional inhibitory mechanism which biases attention towards novel stimuli (Klein & Hilchey, 2011). These features of IOR are difficult

[3]There are a number of other ways to divide impulsivity, which depend on the methods of measurement. For example, using decision-based measures (Clark et al., 2006) or manual response tasks (e.g. Bari & Robbins, 2013). However, we focus on the BIS-11 due to its ubiquitous use, but also its link with striatal dopamine signalling (addressed in the General Methods chapter, 2.3).

to reconcile with trait impulsivity. On the one hand, trait impulsivity is associated with impaired inhibitory abilities (Evenden, 1999); which suggests that impulsive individuals would show impaired IOR. On the other hand, trait impulsivity is associated with the prioritisation of novelty (Eysenck & Eysenck, 1977); which suggests that impulsive individuals might show enhanced IOR.

To our knowledge, only three studies have directly investigated the relationship between trait impulsivity and IOR. Firstly, Avila (1995) employed a traditional cue-target IOR paradigm (Klein, 2000), and measured impulsivity using the 'sensitivity to reward' questionnaire (Torrubia, Ávila, Moltó & Caseras, 2001; Avila, 1995). The study demonstrated that individuals higher in trait impulsivity exhibited higher IOR magnitudes (Ball & Zuckerman, 1992; Avila, 1995).

A second study from the same lab produced similar results, but using central arrows as cues to direct attention (endogenous orienting) (Poy et al., 2004). They found no relationship between impulsivity and IOR using peripheral cues (exogenous orienting). Crucially, the central cue predicted the target location with 80% certainty (Poy et al., 2004), meaning that uncued targets violated expectations and were more novel than cued targets. Indeed, the number of cued trials was substantially higher than uncued trials in both of these studies (Avila, 1995; Poy et al., 2004). Impulsive individuals prioritise novelty more so than less impulsive individuals (Bidwell et al., 2015; Vanderschuren, Everitt, Dalley, Robbins & Everitt, 2004; Zhang, Hu et al., 2015), which may explain the results of these studies. Furthermore, both studies utilised the sensitivity to reward questionnaire as the sole measure of impulsivity, thus limiting their results to a narrow subset of trait impulsivity related to reward-seeking (Torrubia et al., 2001).

Poy et al. (2004) and Avila (1995) suggest that their findings emerge due to impulsive individuals having greater ability to shift attention to targets 'in an unexpected location' (i.e. uncued targets). However, it is unclear if this effect would still emerge if cued and uncued trials were represented equally.

The third study was conducted by Bucker and Theeuwes (2014), who also employed a traditional cue-target paradigm—but with balanced numbers of cued and uncued trials. However, the main focus of their study was to measure the effect of reward-induced motivation on IOR. As such, the task contained no neutral trials, only relatively low- or high-rewarding trials. Furthermore, they found no significant IOR effect in the low-reward condition whatsoever—and no significant relationship between impulsivity and IOR magnitude in either condition when using RTs. However, when using percentage accuracy scores instead of RTs to measure IOR, there was a significant positive IOR-impulsivity relationship—but only in the high-reward condition. This was taken to mean that high-impulsives gain

more of an attentional advantage from motivation than low-impulsives (Bucker & Theeuwes, 2014). However, they measured trait impulsivity using the behavioural inhibition/behavioural activation scales (Carver & White, 1994), which only relates to the reward-seeking form of impulsivity (Carver & White, 1994).

A number of other studies have measured IOR in individuals with ADHD, generally showing impaired IOR (Li et al., 2003; Swanson et al., 1991)—especially in the right hemisphere (Epstein, Conners, Erhardt, March & Swanson, 1997; Carter, Krener, Chaderjian, Northcutt & Wolfe, 1995; McDonald, Bennett, Chambers & Castiello, 1999). However, only one study examined subtypes of ADHD, and found that individuals with the inattentive subtype had relatively preserved IOR compared to the hyperactive-impulsive subtype (Adams et al., 2008). This indicates that impulsivity may be an important contributor to reduced IOR in ADHD.

The studies of ADHD provide various explanations for their findings, the most prominent being that patients 'anchor' attention too strongly to cued locations (McDonald, Bennett et al., 1999)—also referred to as a 'disengage deficit' (Epstein et al., 1997; Swanson et al., 1991). This may be observed in delayed or reduced strength of attentional disengagement, as reflected by the Pd ERP marker of attention termination (Sawaki & Luck, 2011). A recent ERP study demonstrated that individuals with ADHD show reduced Pd amplitudes for distracting stimuli, indicating impaired suppression of distractions (Wang et al., 2016). However, none have explored Pd in relation to attention termination and switching in ADHD.

Importantly, all of the studies discussed here employed the more traditional cue-target IOR paradigm. Cue-target paradigms produce motoric inhibition to the cue (as discussed in 1.1.1) (Poliakoff et al., 2007; Poliakoff et al., 2003). This may enhance IOR, as individuals must overcome this motoric inhibition to respond to cued targets (Poliakoff et al., 2007). High impulsive individuals may struggle to inhibit motoric responses more than less impulsives (Dalley et al., 2011). As such, impulsive individuals may need to produce stronger inhibition to the cue, thus increasing the additive effect of cues on attentional IOR.

Furthermore, all of these studies presented lateralised, singleton cues and targets. This may produce a sensory refractory period at cued locations (McDonald et al., 2008) (also addressed in the previous section; 1.1.1). Trait impulsivity is associated with abnormalities in sensory orienting to stimuli in several ways. For example, higher impulsivity is related to stronger sensory responses to intense stimuli (Lijffijt, Lane, Moeller, Steinberg & Swann, 2015); and stronger sensory orienting towards rewarding stimuli (Mason, O'Sullivan, Blackburn, Bentall & El-Deredy, 2012). As such, it is unclear how unbalanced sensory stimulation in an IOR task may affect performance.

In summary, the behavioural studies of trait impulsivity and IOR produce inconsistent findings. This is likely due to several methodological issues, such as the choice of IOR paradigm and/or measure of trait impulsivity. Furthermore, ERPs may help to investigate the cognitive processes underpinning behavioural IOR effects. On a neurobiological level, some studies have suggested a dopaminergic basis for their effects (e.g. Poy et al., 2004; Bucker & Theeuwes, 2014)—an idea that will be discussed in in the following section.

1.3.2 Striatal Dopamine

The neurobiological basis of trait impulsivity is an extremely complex area of investigation, due to both the heterogeneity of impulsive traits—and the complexity of the neural systems themselves (Dalley et al., 2011; Bari & Robbins, 2013). On the most basic level, converging lines of evidence support that abnormalities in prefrontal cortex function play a major role in impulsivity (Casey et al., 2011; Houghton & Tipper, 1996; Leshem, 2016a; Bari & Robbins, 2013). This is not surprising considering that the prefrontal cortex is the primary region implicated in self-control or 'willpower' in general (Crockett et al., 2013).

Furthermore, there is growing evidence that abnormalities in the striatum—as well as frontostriatal connections—are important (see Dalley & Robbins, 2017, for a recent review). As discussed previously (1.2.1), striatal dopamine signalling is heavily implicated in the modulation of frontostriatal connections (Cools & D'Esposito, 2011). Indeed, striatal dopamine is thought to play a major role in trait impulsivity—the evidence of which will be outlined below.

Firstly, working memory capacity is positively related to striatal dopamine levels (Cools et al., 2008); and high trait impulsivity has been related to reduced working memory capacity in humans (Hinson, Jameson & Whitney, 2003; Klingberg, Forssberg & Westerberg, 2002; Westerberg, Hirvikoski, Forssberg & Klingberg, 2004), and non-human primates (James et al., 2007). Similarly, spontaneous eye blink rates are positively related to striatal dopamine signalling (Colzato, Slagter et al., 2008), and are lower in high-impulsives (Korponay et al., 2017).

Additionally, Costa et al. (2013) found that higher trait impulsivity was related to greater dopamine transporter availability using PET imaging. Dopamine transporters are responsible for the removal of extracellular striatal dopamine, hence higher numbers of transporters are related to lower striatal dopamine levels (Fuke et al., 2001). As such, these studies indicate that impulsive individuals have relatively low striatal dopamine levels.

Further support for this claim comes from striatal dopamine manipulations.

Firstly, two studies found that motor impulsivity was increased following dietary tyrosine depletion—which is the amino acid precursor of dopamine (Ramdani et al., 2014; Mehta, Gumaste, Montgomery, McTavish & Grasby, 2005). The effect of the depletion was most apparent in the striatum (Ramdani et al., 2014), and the extent of striatal depletion was positively related to the severity of impulsivity (Mehta, Gumaste et al., 2005). Secondly, Cools, Sheridan, Jacobs and D'Esposito (2007) found that by administering a D2 agonist, attention flexibility was improved in high- but not low-impulsive individuals—indicating that low-impulsives began with low baseline striatal dopamine levels (Cools et al., 2007). (See section 1.2.1 for the discussion of inverted-U effects of striatal dopamine).

However, it should be noted that there is also evidence for relatively high levels of striatal dopamine in trait impulsivity—but only when the dopamine system is stimulated. For instance, Buckholtz et al. (2010) found that higher impulsivity was related to fewer D2 autoreceptors receptors in the striatum; indicating lower baseline striatal dopamine levels (Groman et al., 2014). However, the number of D2 receptors was inversely related to striatal dopamine release following the administration of *d*-amphetamine (Buckholtz et al., 2010). D2 autoreceptors function to inhibit dopamine release in the striatum (Viaro, Calcagno, Marti, Borrelli & Morari, 2013). Therefore, having fewer produces a greater dopaminergic response following stimulation (Usiello, Baik & Dierich, 2000; Viaro et al., 2013).

Taken together, this evidence indicates that high impulsivity is related to lower baseline striatal dopamine levels[4]. As such, it is proposed that trait impulsivity may be utilised as an indirect measure of striatal dopamine levels to explore the role of striatal dopamine in IOR. Furthermore, ERPs could be utilised to compare the specific effects of direct pharmacological manipulations with trait impulsivity (see section 1.2.2 for a discussion of how ERPs can be used to investigate the role of dopamine in IOR).

1.4 Thesis Aims

The primary aim of this thesis is to investigate the role of striatal dopamine in attentional inhibition, as measured by IOR. Previous studies have investigated this role by observing IOR in certain neurological disorders, different baseline striatal

[4]It is unlikely that lower striatal dopamine is the *cause* of impulsivity. Indeed, this would not fit with high levels of impulsivity in Schizophrenia (Abi-Dargham et al., 2000), and low levels in Parkinson's disease (Ayano, 2016b). Furthermore, increasing striatal dopamine levels can exacerbate the impulsive symptoms of ADHD (Evenden, 1999), and cause impulse control disorders in Parkinson's disease (Napier et al., 2015). As such, the neurobiological causes of trait impulsivity remain under considerable debate (Dalley & Robbins, 2017)—and are not the focus of this thesis.

dopamine levels, and using pharmacological manipulations (1.2.1). However, there are several methodological issues associated with these studies, including with IOR task design, and the specificity of striatal dopamine observations/manipulations. Furthermore, studies have largely been behavioural, therefore it is unclear which IOR processing stages are affected by striatal dopamine signalling.

Therefore, the studies conducted in this thesis will (1) employ IOR paradigms designed to circumvent confounds, (2) manipulate striatal dopamine using the most selective means available, and (3) utilise ERPs to further investigate behavioural effects.

Additionally, trait impulsivity has been identified as an indirect measure of baseline striatal dopamine (1.3.2), and will therefore be utilised to complement these investigations. This will also contribute to the presently inconsistent literature surrounding trait impulsivity and IOR (1.3.1). Finally—due to the use of ERPs in this thesis—different analysis approaches for measuring ERPs in IOR will be investigated. This may also contribute to understanding the mechanisms underlying IOR (1.2.2).

To meet these aims, this thesis comprises four standalone journal articles (Chapters 3-6), each written to be submitted for publication in peer-reviewed journals. The studies were designed, conducted, analysed, and interpreted by Grace Whitaker, under the supervision of Wael El-Deredy, Ellen Poliakoff, and Joanna Neill. All three supervisors advised in several stages of the development of these studies, and the thesis as a whole. The chapters comprising the thesis are outlined below.

Chapter 2 discusses the main methods utilised in this thesis, addressing details which are not addressed in the individual methods sections of articles.

Chapter 3 is a behavioural investigation of the IOR-impulsivity relationship. The investigation is divided into three studies: Study 1 utilises a cue-target IOR paradigm, with equal numbers of cued and uncued trials, and the BIS-11 as a measure of trait impulsivity. Additionally, levels of inattention are controlled for using measures of ADHD. Study 2 utilises a target-target IOR task with balanced sensory stimulation across the display, also using the BIS-11 and equal numbers of cued and uncued trials. Study 3 investigates the effect of increased motivational state on the IOR-impulsivity relationship. Note that Study 3 was not included in the original aims of the thesis, as it was conducted to investigate an unexpected finding from the ERP study of IOR and impulsivity (see below).

Chapter 4 is an ERP study of the IOR-impulsivity relationship, conducted in order to ascertain which stages of processing may be responsible for behavioural

effects. Results may be later compared with direct pharmacological manipulations of striatal dopamine to help draw conclusions regarding the role of striatal dopamine in IOR.

Chapter 5 is an article which highlights issues with the traditional analysis of ERPs in IOR. In order to demonstrate these issues, an ERP study of IOR mechanisms is replicated, and additional analyses applied to the data.

Chapter 6 is a study investigating the effects of direct pharmacological manipulations of striatal dopamine on IOR. A target-target IOR task is utilised, with balanced sensory stimulation across the display. Drugs which increase and decrease striatal dopamine are administered, and spontaneous EBR is used as an outcome measure of the manipulation. ERPs are measured to investigate the effects of drugs on processing stages (and to compare with Chapter 4).

Finally, **Chapter 7** is a general discussion which evaluates the findings of the thesis in relation to the thesis aims, and in the context of previous literature.

Chapter 2

General Methods

Each of the study chapters contains their own standalone methods sections. However, this chapter provides a more detailed evaluation and justification of the key methods, and how they were selected.

2.1 IOR Task Design

Tasks which measure IOR can take many forms (see section 1.1.1 of the introduction). In order to circumvent certain proposed confounds apparent in other designs, the studies in this thesis utilise an IOR task with two key features: (1) A continuous stream of targets (target-target paradigm). This is to avoid participants needing to inhibit their response to a cue—as would be the case in a more traditional cue-target paradigm (Poliakoff et al., 2003). (2) Targets presented alongside visually-matched non-targets. This is to prevent the unbalanced sensory refraction at cued locations, thought to predisposes sensory modulations (McDonald et al., 2008).

The task utilised by McDonald et al. (2008) fitted the above criteria (study described in 1.1.2)[1]. It was also designed to measure sensory (P1/N1) and selective attention (N2pc) ERPs, making it particularly useful for the purposes of this thesis. However—due to the measurement of ERPs—the task included 1,080 trials, making the task duration around 25-30 minutes. This is unnecessarily long for a behavioural IOR study, as is required for some of the studies in this thesis. A version if the task was piloted to ensure that IOR would still be apparent following adaptation for a behavioural study.

The task was identical to that employed by McDonald et al. (2008), but the number of trials reduced to around 150. Coloured discs flashed on the screen in pairs, and were either pink, green, or blue. Participants were allocated one of these

[1]This task does not afford apparent motion, as the optimal interstimulus interval for apparent motion is 60ms, and anything above 200-300ms is seen as 'successive' (i.e. no movement). This has been shown with circle stimuli flashing for the same duration as in this task (Steinman, Pizlo & Pizlo, 2000).

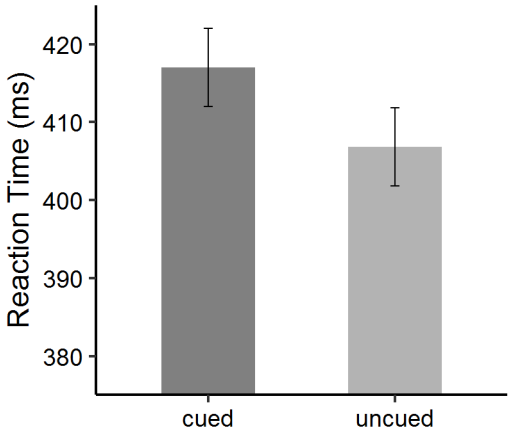

Figure 2.1: Mean reaction times to targets in cued and uncued trials of the target-target inhibition of return pilot study. Error bars represent standard error.

colours as their target, and were asked to press an arrow key to report if their target appeared on the left or the right of the screen.

Longer RTs were observed in the cued condition compared to the uncued condition (i.e. IOR). However, this difference was not statistically significant (paired t-test, two-tailed; $t(20) = 1.706$, $p = 0.10$); see Figure 2.1. The seven participants who were allocated the blue disc as their target reported the colour being "paler" than the other discs. In the remaining fourteen individuals who were allocated the pink or green discs, the IOR effect was significant using the same analysis; $t(13) = 2.499$, $p = .027$, $d = .667$. As such, in subsequent studies a photometer (Oetjen & Ziefle, 2009) was utilised to measure the exact luminance of each of the coloured discs, to ensure balanced sensory stimulation across the screen (McDonald et al., 2008).

Results of the pilot study also suggested that fourteen participants were sufficient to elicit a moderate IOR effect ($d = .667$). Power analysis using the R package 'pwr' (Champely, 2015) determined that at least thirty-six participants are required per experimental condition to achieve 80% chance of obtaining a statistically significant IOR effect. For EEG experiments with an order of magnitude more trials, the number of participants is expected to be much lower: McDonald et al. (2008) found statistically signifcant behavioural and ERP effects with fourteen participants. However, the researchers do not report effect sizes or sufficient information to calculate them. Furthermore, in order to measure individual differences in IOR between different impulsivity levels, more participants would be required. As such, sample sizes are frequently based on previous literature in the studies in this thesis. Sample size is addresed individually for studies in the relevant sections of chapters.

2.2 Electroencephalography (EEG)

The neurotransmission of synchronously active neurons in the brain produces field potential changes, which propagate through the brain, skull and scalp. Here, they can be recorded as voltage oscillations by an array of surface electrodes within milliseconds of their conception—a method termed electroencephalography (EEG). This technique offers the most direct measurements of brain activity, unrivalled by the likes of fMRI or PET (Hillyard & Anllo-Vento, 1998; Luck, Woodman & Vogel, 2000).

However, surface voltage oscillations carry little/ambiguous information regarding their generators' location, known as the 'inverse problem' (Michel et al., 2004; Pascual-Marqui, 1999). As such, EEG is most reliably utilised to measure ERPs, which are components of EEG that relate to a specific event (e.g. stimulus presentation). They are produced by averaging multiple EEG waveforms of the same event, such that the resulting 'clean' waveform omits event-irrelevant neural activity (Luck et al., 2000). The differences in latency, amplitude, and scalp topography of ERPs can be compared across conditions and individuals to reveal differences in processing not apparent in behaviour (Luck et al., 2000). The following ERPs are of interest due to their potential utility to explore the processes underlying IOR (see 1.2.2). Furthermore, the features of the IOR paradigm outlined above makes their measurement possible.

The P1 and the N1 are the first positive and negative deflections in an EEG waveform following visual stimulus presentation in an individual's area of focus (Kiss, Van Velzen & Eimer, 2008). They typically appear within 80 and 110 milliseconds of stimulus presentation at posterior electrode sites (Hillyard & Anllo-Vento, 1998). Their amplitudes are larger when stimuli are more salient, irrespective of whether the stimulus is a target or a distractor (Mangun & Hillyard, 1987)—indicating that they reflect early sensory gating of stimuli. If an individual is provided with a cue as to where a stimulus will be presented, P1 and N1 amplitudes are enhanced compared to no cues (Mangun & Hillyard, 1991). Therefore P1/N1 may be said to reflect sensory orienting/gating of stimuli (Luck & Gold, 2008).

While the P1/N1 components occur before stimuli are selected, the N2 posterior-contralateral (N2pc) represents the moment of target selection from a visual search array (Luck & Hillyard, 1994). The component is a more negative deflection recorded from posterior electrodes contralateral to the visual field of selected stimuli, and appears between 200 and 350 milliseconds after target appearance; see Figure 2.2 (Luck & Hillyard, 1994). The N2pc is preferentially activated for targets over distractors, and remains unchanged by top-down orienting information (Kiss

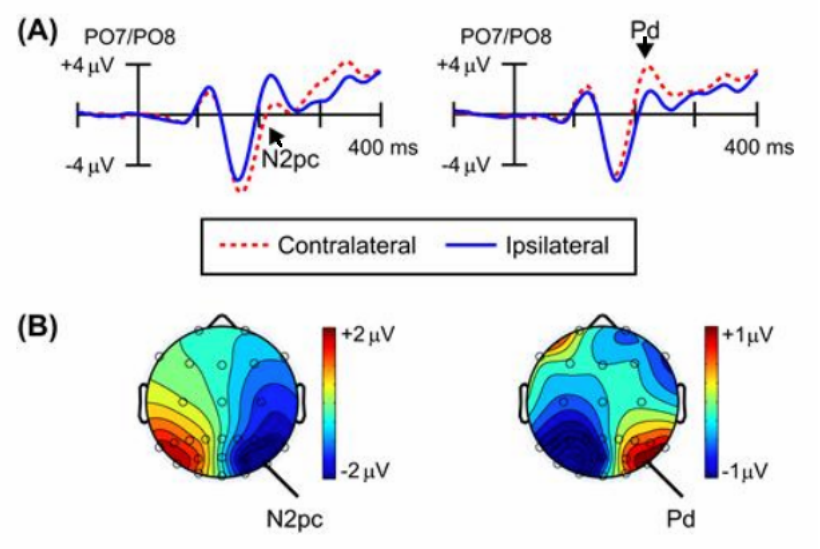

Figure 2.2: (A) Example ERP waveforms of the N2pc (left) and Pd (right). Dotted red lines denote waveforms averaged from posterior electrodes of the hemisphere contralateral to the visual field in which the stimulus was presented, whereas solid blue lines are averaged from electrodes ipsilateral to the stimulus. (B) Example EEG topographical maps for the N2pc (left) and Pd (right). Figure adapted from Mangun (2013).

et al., 2008). These features have led to the wide acceptance of the N2pc as a marker of the covert deployment of selective attention (Luck, 2011).

The positive deflection (Pd) is proposed to reflect attentional suppression (Hickey, Di Lollo & McDonald, 2009). The Pd shares many characteristics with the N2pc, and is sometimes referred to as its 'mirror image'; they share the same scalp topography, latency and amplitude (see Figure 2.2) (Hickey et al., 2009). However, the Pd has the opposite positive polarity, and is elicited by stimuli that individuals are actively suppressing (Hickey et al., 2009). Further observations reveal that after a target has been attended and processing of it is complete, the initial N2pc is followed by a Pd (N2pc-Pd sequence) (Sawaki et al., 2012). Hence the Pd is thought to reflect the termination of attention (Sawaki et al., 2012).

2.3 The Barratt Impulsiveness Scale

The Barratt Impulsiveness Scale (BIS) is the most widely utilised measure of trait impulsivity in the literature (Patton & Stanford, 1995). The questionnaire consists of 30 statements which identify certain features and habits of individuals' daily functioning relating to impulsivity (see Appendix A)(Stanford et al., 2009). For each item, recipients rate if the statement is true for them either rarely/never, occasionally, often, or almost always/always (Stanford et al., 2009).

Table 2.1: Factors of the Barratt Impulsiveness Scale, 11th edition.

2nd Order Factors	1st Order Factors	Example Statement
Attentional	Attention	I concentrate easily.*
	Cognitive Instability	I often have extraneous thoughts when thinking.
Motor	Motor	I act on the spur of the moment.
	Perseverance	I can only think about one thing at a time.
Nonplanning	Self-Control	I plan tasks carefully.*
	Cognitive Complexity	I am more interested in the present than the future.

* = item is reverse-scored

Researchers often only report the combined BIS score to provide an overall measure of trait impulsivity (e.g. Buckholtz et al., 2010). However, one of the main advantages of the BIS is its measurement of the heterogeneity of impulsivity, by discerning several separable sub-traits (Stanford et al., 2009). The most recent version of the BIS (11th edition; BIS-11) identifies six first-order traits, which relate to three second-order traits (Stanford et al., 2009) (see Table 2.1). These were developed from principal component analysis of the BIS-10, which only included the three first-order factors (Patton & Stanford, 1995). The BIS-11 has high test-retest reliability and strong internal consistency (Spearman's rho = .83, and Cronbach's alpha = .83, respectively) (Stanford et al., 2009).

Furthermore, the BIS-11 is particularly useful in this thesis for its extensive links to striatal dopamine. For instance, it has been used to relate trait impulsivity to striatal dopamine transporters (Costa et al., 2013); baseline D2 receptors, and their response to *d*-amphetamine (Buckholtz et al., 2010); changes in frontostriatal signalling (Cools et al., 2007); and spontaneous EBR (Korponay et al., 2017). Therefore, the BIS-11 may provide an indirect means of measuring striatal dopamine signalling.

2.4 Striatal Dopamine Manipulations

The most important considerations for manipulating dopamine in this thesis were safety/tolerability, and selectivity to striatal dopamine. Furthermore—for the sake of comparability—it was desirable that dopamine signalling was increased and decreased in an equivalent manner. D2 receptor agonists and antagonists meet these criteria. For instance, D2 receptors are distinctly more concentrated in the striatum of the brain compared to other brain regions (Jackson & Westlind-Danielsson, 1994); and drugs which stimulate or block postsynaptic D2 receptors increase and decrease striatal dopamine signalling, respectively (Honey et al., 2003; Mehta, Hinton, Montgomery, Bantick & Grasby, 2005).

Regarding safety—D2 receptor drugs are frequently administered to treat various

neurological disorders (Ayano, 2016a); meaning that they have been extensively tested in humans, and tolerability is well documented. There are a number of D2-targeting drugs presently prescribed in the UK which could be utilised in this thesis—which are addressed below.

2.4.1 D2 Agonist

Bromocriptine is one of the most widely-prescribed D2 agonists for the treatment of Parkinson's disease (Ayano, 2016b; Deleu, Northway & Hanssens, 2002). It is a potent D2/D3 agonist, but also weakly binds to D1-like, serotonergic, and adrenergic receptors (Deleu et al., 2002). The drug *ropinirole* is another D2 agonist with a similar binding profile to bromocriptine, also used to treat Parkinson's disease (Deleu et al., 2002; Gerlach et al., 2003). However, ropinirole has a much higher affinity for D2 receptors (Gerlach et al., 2003), and may be better tolerated than bromocriptine—showing less than half the instances of adverse effects in Parkinson's disease patients (Korczyn et al., 1999; Deleu et al., 2002). Finally, the Parkinson's disease treatment *cabergoline* has comparable tolerability with ropinirole, but has a considerably higher affinity for D2 receptors (Gerlach et al., 2003). The stronger affinity to D2 by cabergoline—as well as its tolerability—makes it the most ideal choice for the purposes of this thesis. Furthermore, cabergoline provides a novel approach to manipulating striatal dopamine, as no previous studies have investigated the effects of cabergoline on IOR (see Rokem et al., 2012, for an IOR study using bromocriptine).

D2 agonists can stimulate presynaptic autoreceptors in low dosages, meaning that they may have an inhibitory effect on dopamine signalling in the striatum (Frank & O'Reilly, 2006). Therefore, a relatively high dose was chosen to avoid presynaptic effects. The typical starting dosage of patients with Parkinson's disease is between 0.5-1mg per day, depending on the severity of symptoms (Del Dotto & Bonuccelli, 2003). In healthy participants, previous studies have safely administered a single dose of 1.25mg, and have observed significant effects on cognition (e.g. Nandam, Hester & Wagner, 2013; Frank & O'Reilly, 2006). As such, a dose of 1.25mg was chosen for the study in this thesis.

2.4.2 D2 Antagonist

The D2 antagonist *haloperidol* is the most frequently prescribed antipsychotic for the treatment of Schizophrenia (Ayano, 2016a; Chung et al., 2012; Sapir et al., 2007). It binds to several serotonergic and adrenergic receptors, but has strongest affinity for D2 and D3 receptors (Frank & O'Reilly, 2006). However, *sulpiride* as a newer antipsychotic D2 antagonist—and has significantly higher affinity and selectivity for

D2 receptors; and produces fewer side-effects compared to haloperidol (Tardieu, Micallef, Gentile & Blin, 2003). There is some indirect evidence that haloperidol decreases dopamine signalling in the striatum to a greater extent than sulpiride (Imazu, Kobayashi & Shohmori, 1989; Akaike, Sasa & Takaori, 1983)—making it unclear which may be the most effective. Related to the structure of sulpiride, the antipsychotic *amisulpride* has higher affinity for D2 receptors than haloperidol—but comparable affinity compared to sulpiride (Tardieu et al., 2003). Furthermore, amisulpride has been shown to produce fewer side-effects than both haloperidol and sulpiride (Tardieu et al., 2003; Delcker, Schoon, Oczkowski & Gaertner, 1990)—making it the best candidate for studying IOR in humans.

To avoid the aforementioned presynaptic effects on D2 receptors (Herrera-Estrella et al., 2005), a relatively high dose of 400mg was chosen for the study in this thesis (Chung et al., 2012; Perrault, Depoortere, Morel, Sanger & Scatton, 1997). Furthermore, other studies have used this dosage to observe effects on cognition in healthy volunteers, with little to no adverse reactions (Chung et al., 2012; Park et al., 2012; Barrett, Bell, Watson & King, 2004).

2.4.3 Spontaneous Eye Blink Rate

As mentioned, stimulation of presynaptic versus postsynaptic D2 receptors has opposing effects on dopamine signalling (Frank & O'Reilly, 2006). This can also be baseline-dependent, as presynaptic receptors may be preferentially activated in the presence of high baseline striatal dopamine levels (Rokem et al., 2012). Therefore—to target postsynaptic D2 receptors—we administer relatively high dosages of a D2 agonist and antagonist (see above). Furthermore, we recruit medium-impulsive individuals, thought to have non-extreme levels of striatal dopamine (Buckholtz et al., 2010).

As an added precaution, spontaneous eye blink rates (EBRs) are employed to measure the outcome of manipulations on striatal dopamine (Jongkees & Colzato, 2016). EBRs are positively correlated with striatal dopamine levels: Patients with Schizophrenia show higher blink rates (Kleinman et al., 1984), and individuals with Parkinson's disease show lower rates (Karson, 1983). Individuals with a history of cocaine abuse (Colzato, van den Wildenberg & Hommel, 2008), and high trait-impulsive individuals (Korponay et al., 2017) also show reduced EBRs. Additionally, individuals genetically predisposed to higher striatal dopamine levels (DAT1 genotype, 1.2.2) show higher EBRs (Colzato, van den Wildenberg, Van der Does & Hommel, 2010). EBRs may also predict cognitive functions thought to rely on striatal dopamine signalling, including cognitive flexibility (see Jongkees & Colzato, 2016, for an extensive review).

More direct evidence comes from PET imaging, showing that the availability of D2 receptors in the striatum is positively correlated with EBRs (Groman et al., 2014). Furthermore, pharmacological manipulations to increase and decrease striatal dopamine have been shown to increase and decrease EBRs, respectively (Kleven & Koek, 1996; Blin, Masson, Azulay, Fondarai & Serratrice, 1990).

As participants will be wearing an EEG cap during the study, frontal electrodes can be utilised to measure the electrical activity produced by eye blinks (Korponay et al., 2017). The number of blinks can be quantified using independent component analysis of continuous EEG recordings (Delorme & Makeig, 2004). Independent component analysis is a statistical tool which extracts the activity associated with an independent 'generator'—in this case, the specific pattern of activity produced by eye muscles when blinking (Jung et al., 2000; Delorme & Makeig, 2004). Finally, time of day can affect EBR (Barbato et al., 2000). As such, EBRs will be measured at the same time of day for each participant and session.

Chapter 3

An Investigation of Trait Impulsivity, Inhibition of Return, and Motivational State

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Abstract

Trait impulsivity is associated with impaired inhibitory control abilities. Such impairments can negatively impact individuals' lives, resulting in increased likelihood to engage in unwanted or risky behaviours. In order to better understand and treat high trait impulsivity, it is essential to better understand how inhibitory mechanisms are disrupted. This study investigates how impulsivity is associated with inhibition of return (IOR); a low-level inhibitory control mechanism in which the attention system is inhibited from re-attending to spatial locations. Previous research into the IOR-impulsivity relationship is unclear, and there is evidence that motivational states may play a role. Therefore, we measured individuals' trait impulsivity levels and IOR responses under neutral conditions, or with reward incentives to increase motivational state. Our initial findings are consistent with the current understanding of inhibitory control—that inhibitory mechanisms are impeded for higher trait impulsivity (reduced IOR). Therefore, our findings extend research into trait impulsivity; finding that under neutral circumstances, IOR is smaller in more impulsive individuals. However, future work is necessary to establish how motivational states may affect the IOR-impulsivity relationship.

3.1 Introduction

Trait impulsivity is an aspect of human personality, with high levels related to the preference for novel stimuli, immediate rewards and an inability to inhibit certain thoughts and responses (Bari & Robbins, 2013). As a consequence, individuals with high impulsivity are more likely to engage in risky behaviours including substance abuse, gambling, violence, and criminality (Moeller, Barratt, Dougherty, Schmitz & Swann, 2001). In order to better understand trait impulsivity and the negative behaviours associated with it, researchers have investigated inhibitory mechanisms and how they are disrupted.

The relationship between impulsivity and unconscious cognitive inhibition is often overlooked, such as in the earliest stages of processing when stimuli are selected by the attention system. IOR is one such inhibitory mechanism, and is the focus of this study. Differences in early attention allocation contribute to higher processes that ultimately lead to behaviour (Murray, Nobre & Stokes, 2011; Vanrullen & Thorpe, 2001). Therefore, investigating the relationship between IOR and impulsivity may improve our understanding of higher/behavioural inhibitory mechanisms associated with this personality trait.

IOR is a phenomenon first reported by Posner and Cohen (1984), and is the observation that the attention system is biased away from recently attended to locations (i.e. attention prioritised toward 'new' stimuli over 'old'). Tasks that elicit IOR typically involve participants being cued to attend to a spatial location by a sudden stimulus onset, such as a light flash, followed by target presentation either within the same cued area, or in a novel uncued area (cue-target paradigm) (Klein, 2000). Participants report when they have detected the target by pressing a button, giving a measure of RT to the target. Cued and uncued trials are balanced such that the cue does not predict target location. Attention is captured by the cue, and then returned to a central point by a disengagement cue, such as a central light flash. Attention is slower to return to the cued location compared to the uncued location, i.e. inhibited from returning (Posner & Cohen, 1984; Klein, 2000). The inhibitory effect has been found to last for as long as 4.8 seconds (Poliakoff et al., 2002), acting over a spatial gradient strongest at the cued location itself (Samuel & Kat, 2003). There is some evidence to suggest that IOR is an adaptive attentional mechanism, serving to facilitate visual search by biasing attention away from locations that have already been inspected (Klein & Macinnes, 1999; Tipper et al., 1991).

Some studies have attempted to explore the relationship between IOR and impulsivity with conflicting results. Avila (1995) and Poy et al. (2004) found that higher impulsivity was related to an increased IOR magnitude (i.e. larger differences in RTs

between cued and uncued trials). The authors concluded that higher impulsivity is related to greater ability to shift visual attention (Poy et al., 2004). However, both of these studies utilised IOR tasks with significantly more cued than uncued trials, making the cue predictive of target location. With predictive cues, it is strategic to allocate and maintain attention at the cued location, such that individuals may be slower to disengage their attention from the cue (Berger, Henik & Rafal, 2005; Tipper & Kingstone, 2005). This means that differences in IOR magnitude observed with such tasks could be caused by use of the predictive cue; causing altered speed of disengagement, or alterations in the inhibitory mechanism generating IOR. It may be argued that their results reflected the effect of expectation violation, with impulsive participants prioritising stimuli at novel/unpredicted spatial locations (due to impulsive individuals' preference for novelty, Eysenck & Eysenck, 1977)

Similarly, Bucker and Theeuwes (2014) found a positive relationship between impulsivity and IOR. However their study focused on the effect of motivational state; when motivated by higher compared to lower reward incentives, impulsivity was related to an increased IOR effect. The authors argue that motivation increases recruitment of resources for cognitive inhibition mechanisms, which is more pronounced for individuals sensitive to reward (Bucker & Theeuwes, 2014). However, they did not observe a significant difference in RTs between cued and uncued trials in the low-reward condition (i.e. no IOR effect). Therefore, the relationship between impulsivity and IOR in more neutral contexts remains unclear. Additionally, the study measured a narrow subset of impulsivity relating to an individual's propensity to seek reward (the BAS-Drive, Carver & White, 1994). Their findings nevertheless suggest that motivational state influences the relationship between impulsivity and IOR magnitude.

In contrast to the research discussed above, Li et al. (2003) observed that impulsivity was related to reduced IOR magnitude. They attributed their findings to reduced function of inhibitory mechanisms. However, the study measured impulsivity in children with combined-type ADHD, making it difficult to assess the separate contributions of inattention and impulsivity symptoms (Wolraich, Hannah, Pinnock, Baumgaertel & Brown, 1996). Another study did account for ADHD subtypes, and found that IOR was more negatively affected in those with the combined type than the inattentive type (Adams et al., 2008). However, there is some evidence that inattention symptoms contribute more strongly to deficits in response inhibition than hyperactive/impulsive symptoms (Chhabildas, Pennington & Willcutt, 2001; Geurts, Verté, Oosterlaan, Roeyers & Sergeant, 2005). Hence accounting for inattention may be of importance when investigating the relationship between impulsivity and IOR.

Another critical issue that may confound the previous work in this area is the use of the typical cue-target IOR paradigm. As previously described, in cue-target paradigms, participants observe a lateralised visual cue before the target is presented (Klein, 2000). Visual stimulation of the lateralised space by the cue causes a temporary sensory refraction over the cued location, which can slow responses to the target there (McDonald et al., 2008). Furthermore, cue-target tasks require participants to suppress their response to the cue, forming a similar motoric refractory period (Coward et al., 2004; Poliakoff et al., 2002). To circumvent such effects, target-target IOR paradigms present continuous streams of targets that do not require cue suppression (Coward et al., 2004; Maylor & Hockey, 1985; Poliakoff et al., 2002). Additionally, presenting non-targets in parallel with matched visual features ensures that sensory refractory periods are balanced across the stimulus display (McDonald et al., 2008). Hence target-target IOR paradigms (with parallel, visually matched non-target) are argued to more accurately access the attentional inhibitory mechanisms of IOR.

In summary, previous research offers contradictory claims about the effect of impulsivity on IOR. Higher impulsivity could increase IOR magnitude due to increased preference for novelty, or through an ability to shift attention through space (Avila, 1995; Poy et al., 2004). Alternatively, higher impulsivity may reduce IOR magnitude due to impaired inhibitory processes (Li et al., 2003). Importantly, the relationship between IOR magnitude and impulsivity may be modulated by motivational state (Bucker & Theeuwes, 2014). In order to address these confounds, our study investigates the relationship between impulsivity and IOR addressing limitations of previous studies; such as, predictive cues, sensory/motoric refractory periods, and motivational state. To achieve this, we utilise two IOR paradigms with balanced numbers of cued and uncued trials. Study 1 used a cue-target task, accounting for inattention factors; Study 2 used an alternative IOR paradigm, thought to access attentional IOR mechanisms (i.e. a target-target task, with targets presented alongside visually-matched non-targets); and Study 3 used the same target-task, modified to induce a higher motivational state using reward incentives.

3.2 Study 1: Cue-target IOR

The aim of Study 1 was to explore the relationship between impulsivity and IOR using a cue-target paradigm. As inattention symptoms have been related to inhibition issues (Chhabildas et al., 2001; Geurts et al., 2005), the study employed questionnaires and task-based measures of both inattention and impulsivity. Cued and uncued trials were balanced such that the cue did not indicate target location,

preventing top-down expectations from affecting disengagement from cued locations (Bucker & Theeuwes, 2014; Lupiáñez et al., 2006). The task was designed to match (visually and temporally) the target-target tasks employed in Studies 2 and 3 (based on McDonald et al., 2008).

3.2.1 Materials and Methods

Participants

No previous studies have utilised the IOR paradigm or impulsivity measures employed here to measure the IOR-impulsivity relationship, thus obscuring a power analysis to ascertain an appropriate sample size. The aforementioned previous studies of individual differences and IOR exhibited a range of sample sizes, from n = 11 in Li et al. (2003) to n = 96 in Poy et al. (2004), and do not report effect sizes. As such, the average sample size of the four most relevant studies in the literature was calculated to provide a minimum number of 58 participants (Avila, 1995; Bucker & Theeuwes, 2014; Li et al., 2003; Poy et al., 2004).

Seventy-two participants (6 left-handed; 42 female; mean 22 years; standard deviation 3.9 years) were recruited via online advertisements and posters placed around the University of Manchester campus. Participants had normal or corrected-to-normal vision and were not colour-blind. The experiment was completed in a single thirty-minute session wherein informed consent was obtained. Participants received a financial reward (or the equivalent course credits for University of Manchester undergraduate psychology students). The study was approved by The University Research Ethics Committee of The University of Manchester, UK (ref. 14194).

Personality measures

To measure aspects of trait inattention and impulsivity, each participant completed the Conners' Adult ADHD Rating Scale–Self-Report, Long Format (Conners, Erhardt & Sparrow, 1998; Conners, Erhardt & Sparrow, 1999); and the Conners' Continuous Performance Test, third edition (Conners, 2014). The former is a 66-item self-report questionnaire providing measures of inattention, hyperactivity, impulsivity, self-concept problems and diagnostic evaluation of such factors. The latter is a computer-based task requiring key press responses to a continuous stream of single letters appearing on a monitor. Participants were instructed to rapidly respond to all letters apart from the intermittent letter 'X', for which they were told to withhold from responding. Performance in this task provides measures of impulsivity, sustained and selective attention (Conners, 2014). Participants also completed the Barratt Impulsivity Scale (BIS-11, Patton & Stanford, 1995), a 30-item

self-report questionnaire providing a measure of several impulsivity factors, namely: attention, cognitive instability, motor, perseverance, self-control, and cognitive complexity.

Inhibition of Return task

Following the personality measures, participants completed a computer-based IOR task. The task was coded using PsychoPy software (Peirce, 2007), and displayed on a 12.1" LED monitor, at a viewing distance of approximately 50cm. Participants were instructed to focus on a white fixation cross in the centre of the black screen throughout trials (see Figure 3.1A). Each trial consisted of an uninformative cue stimulus flashing for 100ms (grey disc) positioned 4 degrees below, and either 6 degrees to the left or right of fixation. Participants were instructed not to respond to the cue, and that its location was unrelated to that of the target. After a stimulus onset asynchrony of 900/1100/1300ms (randomised), a coloured disc would flash for 100ms either in the same location as the previous cue (cued trial), or on the opposite side of the screen (uncued trial). Participants were assigned a target colour (pink, green or blue) counterbalanced across participants. They were instructed to respond to their target coloured disc as quickly as possible by pressing the spacebar, ignoring the appearance of non-target coloured discs (catch trials). Left and right response hand was counterbalanced across participants. 400-600ms after the cue, the fixation cross flashed from white to the target colour for 100ms, which served to terminate participants' attention from a lateralised position. The target-detection screen then appeared another 400-600ms later. Participants completed a practice block of 9 trials at half speed and 18 trials at full speed. If participants were comfortable with the practice, they continued to complete 180 trials separated into four 60-second blocks with breaks in-between. Cued, uncued, and catch trial targets appeared equally on the left and right screen locations, and were randomised. Cued, uncued, or catch trials comprised roughly one third of the total number of trials each.

3.2.2 Results

One participant was removed from the analysis for having an incorrect response rate more than three times higher than the interquartile range. For the remaining participants, incorrect responses to catch trials comprised a mean of 2.1% (SD=1.9). RTs underwent an outlier removal process (Selst & Jolicoeur, 1994), which removed an average of 1.5% (SD=0.6) of trials from each participants' responses. The means of remaining RTs were calculated for each trial type and participant. Using a paired t-test, these values indicated the presence of IOR, as participants were

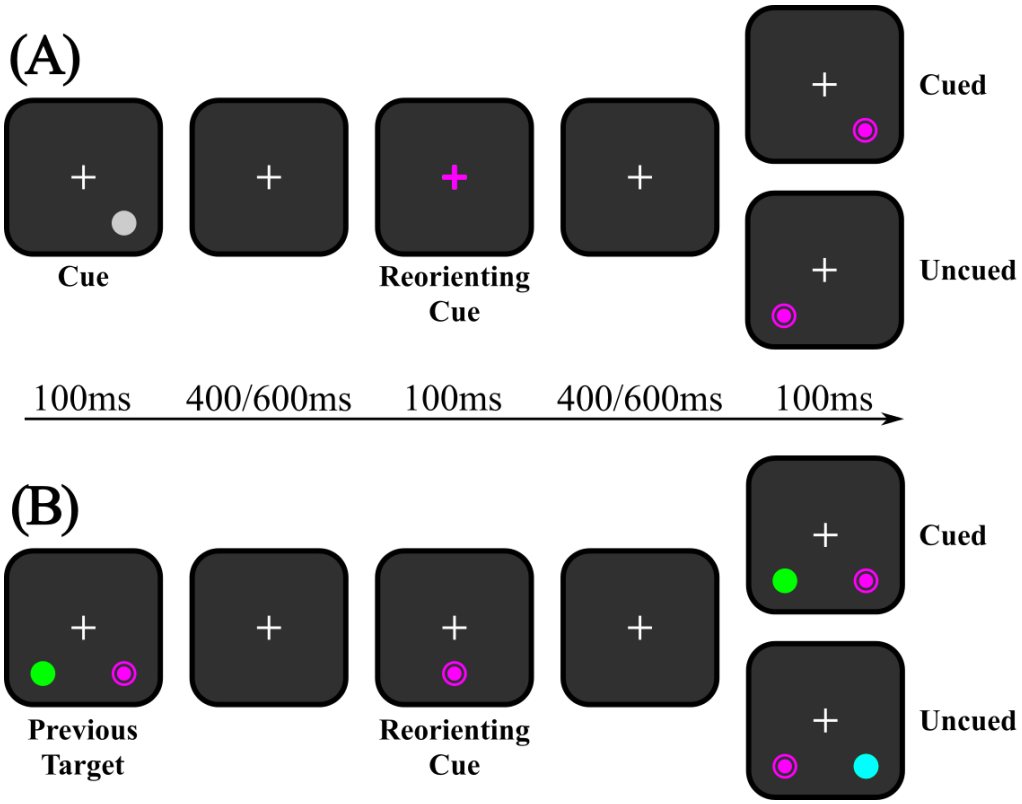

Figure 3.1: Diagram depicting the time-course of stimulus displays in inhibition of return task versions used in in the present studies. (A) The cue-target version of Study 1, and (B), the target-target version of Studies 2 and 3. In these examples, the target is marked by an embossed edge. In cued trials, the target appears in the same location as the previous cue or target, in contrast to the opposite location in uncued trials.

significantly slower responding to targets in the cued location (M=379, SD=.037) compared to the uncued location (M=356, SD=.034); $t(70) = 12.36$, $p < .001$; $d = 1.491$. Percentage of errors in cued trials (M=1.97, SD=4.6) and uncued trials (M=1.92, SD=5.0) were not significantly different using a paried t-test; $t(70) = .123$, $p < .903$, $d = .014$. Therefore a speed-accuracy trade-off in responses was not apparent.

IOR magnitude was ascertained for each participant by subtracting their mean RT to uncued targets from their mean RT to cued targets, such that a larger value indicated higher IOR magnitude. Stepwise multiple linear regression analysis was employed to explore the relationship between IOR magnitude and impulsivity, whilst controlling for inattention levels. The best predictor of the dependent variable (IOR magnitude) was the 'Cognitive Instability' factor of impulsivity (from the BIS-11): $F(1, 69) = 9.076$, $p = .004$; $R^2 = .116$. Scores in this aspect of impulsivity were negatively related to IOR magnitude; see Figure 3.2. All other impulsivity and

Table 3.1: Variables entered into the stepwise linear regression model predicting inhibition of return magnitude. All but 'Cognitive Instability' were excluded.

Measure Type	Variable Name and Order	*p*
Impulsivity	BIS Attention	.957
	BIS Cognitive Instability	.004*
	BIS Motor	.500
	BIS Perseverance	.248
	BIS Self Control	.924
	BIS Cognitive Complexity	.908
	CPT Commissions	.867
Inattention	CPT Sensitivity Index	.277
	CPT Omissions	.299
	CAARS Inattention	.319

*regression coefficient $p < .05$ included in the model, BIS = barratt impulsiveness scale, CPT = continuous performance test, CAARS = conners adult ADHD rating Scale

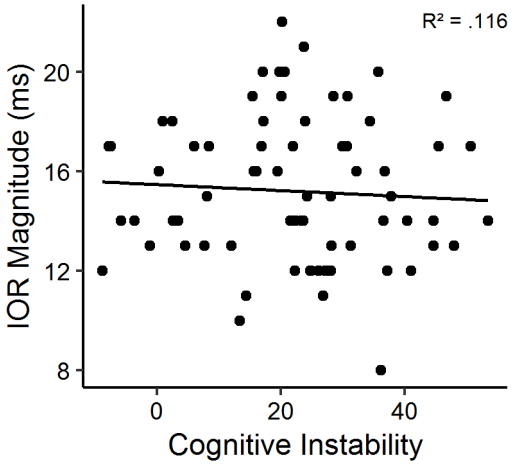

Figure 3.2: The negative relationship between inhibition of return (IOR) magnitude (cued minus uncued reaction times; RTs) as a function of the Cognitive Instability sub-factor of the Barratt Impulsiveness Scale (BIS-11).

inattention measures were excluded from the model. See Table 3.1 for the excluded variables, and the order which they were entered into the model.

3.2.3 Study 1 Discussion

Here we demonstrate that, independent of trait inattention level, higher trait impulsivity was associated with a reduced magnitude of IOR. This supports previous research in children with ADHD (Li et al., 2003; Adams et al., 2008), and extends them to observe the relationship in a healthy adult population. Our findings con-

tradict those of Avila (1995) and Poy et al. (2004), who found that impulsivity was related to increased IOR magnitude.

3.3 Study 2: Target-target IOR (neutral)

Study 2 aimed to replicate the findings of Study 1, but in a different population, and using a target-target paradigm with targets presented in parallel with visually matched non-targets (Coward et al., 2004; Poliakoff et al., 2002). The task was a near replication of that employed by McDonald et al. (2008) in their EEG study, designed to circumvent motoric and sensory refractory period confounds. However, the numbers of trials were reduced appropriately for a behavioural IOR study, and a black instead of white background used to reduce potential eye strain. Trait impulsivity was measured via the BIS-11, as it emerged as the key measure from Study 1, and is the most widely utilised impulsivity scale in the literature (Stanford et al., 2009).

3.3.1 Materials and Methods

Participants

Due to the notion that target-target IOR tasks may produce IOR effects half the size of cue-target tasks (Poliakoff et al., 2003), a power analysis was conducted using an effect size half of that observed in Study 1 (d = .746) to determine sample size (Champely, 2015). The calculation determined that 28 is a sufficient number of participants to elicit a significant IOR response with 80% certainty (p =< .05).

Fifty-seven participants (30 female; mean 28 years old; standard deviation 16.3 years) were recruited opportunistically from visitors at two University of Manchester open days. Participants had normal or corrected-to-normal vision and were not colour-blind. Informed consent was obtained and the experiment completed in a single 10-minute session. The study was approved by The University Research Ethics Committee of The University of Manchester, UK (ref. 14194).

Stimuli and Procedure

To measure trait impulsivity, participants answered the BIS-11 (see Study 1 methods; 3.2.1). Each then completed a target-target IOR task. The task was coded and displayed using the same apparatus described for Study 1. Participants were assigned a target coloured disc (pink, green or blue). Each trial contained pairs of such coloured discs appearing on the screen for 100ms 4 degrees below and 6 degrees to the left and right of fixation. No two discs in a pair were the same colour. The

timing of stimulus display presentations is outlined in Figure 3.1B. The participant was instructed to maintain focus on the central cross throughout, and identify if their target circle was on the left or right of the screen by pressing left and right buttons (*b* and *n* keys, respectively) on a keyboard, with their dominant hand. The target disc was present in two-thirds of trials and the remaining third served as catch trials. Whether the target appeared on the same or opposite side of the screen as the previous trial dictated if the trial was deemed as cued or uncued, respectively. The possible different combinations of disc colours were represented equally and randomised such that cued and uncued trials occurred equally on the left and the right of the screen. Between trials, the target disc was presented for 100ms in the centre of the screen. This served to re-centralise the participant's attention and acted as a reminder of the target colour. After a practice block consisting of 12 trials, participants completed a total of 152 trials separated into four blocks with breaks in-between each.

3.3.2 Results

Each of the participants' error rates were within the accepted three times the interquartile range. Incorrect responses comprised a mean of 7.7% (SD=7.2). IOR data was subject to the same analysis outlined for Study 1. The outlier removal procedure removed an average of 1.2% (SD=0.6) of trials from each participants' responses. IOR was successfully elicited by the task, as participants were significantly slower in responding to targets in the cued location (M=366, SD=.048) compared to the uncued location (M=340, SD=.065); $t(56) = 8.304$, $p < .001$; $d = 1.287$. Percentage of errors in cued trials (M=4.95, SD=6.5) and uncued trials (M=4.83, SD=5.8) were not significantly different using a t-test; $t(56) = .176$, $p < .861$, $d = .023$. Therefore a speed-accuracy trade-off was not apparent in responses.

As it was expected that results would follow the same direction as the cue-target task in Study 1, a one-tailed Pearson's r analysis was utilised, demonstrating that higher impulsivity was related to lower IOR magnitude, with the following BIS-11 factors: 'Attention' ($r(55) = -.26$, $p =< .05$; one-tailed) and 'Perseverance' ($r(55) = -.23$, $p =< .05$; one-tailed; Figure 3.3A).

3.3.3 Study 2 Discussion

The results of Study 2 indicate that higher impulsivity is related to smaller IOR magnitude, supporting the findings of Study 1. The present study also extends Study 1 and previous findings by the use of a target-target paradigm, with targets presented alongside matched non-targets. This demonstrates that the observed

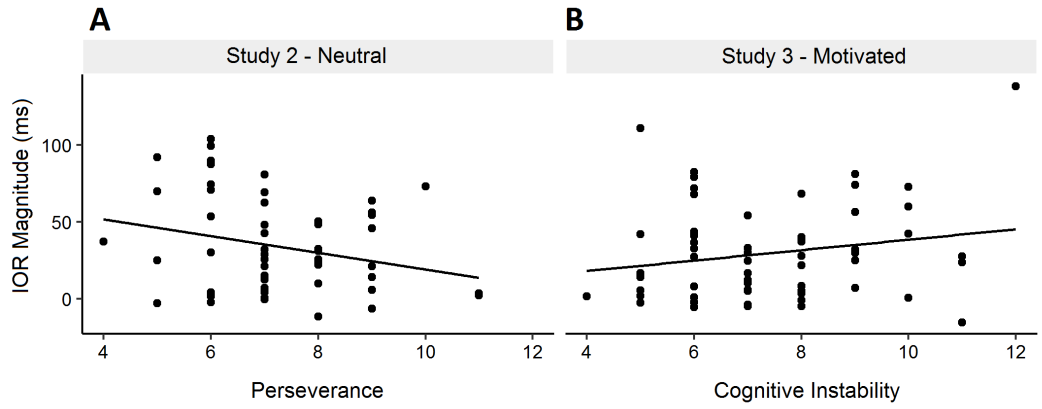

Figure 3.3: Target-target IOR magnitude as a function of impulsivity. Study 2 (A) employed a neutral version of the task, reproducing the results of Study 1. Impulsivity level is participants' scores in 'Perseverance' of the BIS-11. Study 3 (B), included reward incentives to increase motivational state. Impulsivity level is participants' scores in 'Cognitive Instability' of the BIS-11.

relationship is not caused by the sensory and motoric confounds associated with cue-target tasks (Coward et al., 2004; McDonald et al., 2008; Poliakoff et al., 2002). As in Study 1, the results contrast the findings of Avila (1995) and Poy et al. (2004), and show that impulsivity is related to decreased IOR magnitude.

3.4 Study 3: Target-target IOR (motivated)

The aim of Study 3 was to extend the findings of Studies 1 and 2 by investigating how reward-induced motivation may affect the IOR-impulsivity relationship. Previous findings suggest that motivation increases the IOR effect, and more for impulsive individuals than for those who are less impulsive (Bucker & Theeuwes, 2014). However, Bucker and Theeuwes (2014) focused on IOR accuracy scores, and were unsuccessful in eliciting IOR in the low-motivation condition—meaning that no comparison could be made between high versus low-motivation task versions. Therefore, in Study 3 we measured the relationship between impulsivity and IOR magnitude (rather than accuracy), which could then be compared to our motivationally-neutral Study 2 results. Furthermore, our study aims to address the sensory and motoric refractory period confounds of previous research by using a target-target IOR paradigm with targets presented alongside matched non-targets (Coward et al., 2004; McDonald et al., 2008; Poliakoff et al., 2002).

3.4.1 Materials and Methods

Participants

Using the effect size of the IOR response from Study 2, it was determined that at least 10 participants would be required to achieve a statistically significant effect (p =< .05) with 80% certainty (Champely, 2015).

Sixty-four participants (30 female; mean 27 years old; standard deviation 14.6 years) were recruited opportunistically from visitors at two University of Manchester open days. Participants had normal or corrected-to-normal vision and were not colour-blind. Informed consent was obtained and the experiment completed in a single 10-minute session. The study was approved by The University Research Ethics Committee of The University of Manchester, UK (ref. 14194).

Stimuli and Procedure

Participants completed the BIS-11 to measure trait impulsivity, followed by the Target-target task outlined in Study 2 Materials and Methods, 3.3.1. Adaptations were made to the task to increase reward-induced motivation: Participants were informed that they could win Amazon (online shopping) vouchers (£10, £20 or £30) if they were in the top three participants for speed and accuracy in the task. A public leader-board displayed the most recent top three scoring participants, and participants received feedback on their speed and accuracy following each of the four task blocks.

3.4.2 Results

Five participants were removed from the analysis for having incorrect response rates more than three times higher than the interquartile range. For remaining participants, incorrect responses comprised a mean of 4.4% (SD=3.8). RT data were subject to the same analysis process outlined for Studies 1 and 2. The outlier removal procedure removed an average of 1.1% (SD=0.6) of trials from each participants' responses. IOR was successfully elicited by the task, as participants responded significantly more slowly to targets in the cued location (M=375, SD=.057) compared to the uncued location (M=345, SD=.042); $t(58) = 7.236$, $p < .001$; $d = 1.053$. Using a paired t-test of percentage error rates, participants made more errors in cued trials (M=4.82, SD=8.2) compared to uncued trials (M=3.12, SD=5.3); $t(58) = 2.590$, $p < .05$; $d = 0.337$. Therefore the RT IOR effect was not the result of a speed-accuracy trade-off.

As it was unclear how motivation may affect the IOR-impulsivity relationship with this task, two-tailed Pearson's r correlation analyses were utilised, demonstrating

no significant relationship between impulsivity (scores from the BIS-11) and IOR magnitude (figure 3.3B; 'Cognitive Instability'; $r(57) = .194$, $p = .142$; two-tailed).

In order to statistically test for an interaction between the IOR-impulsivity relationship in a neutral versus motivated context, regression slopes were compared using univariate analysis of variance. Each of the three significant IOR-impulsivity correlates from Studies 1 and 2 were included separately as covariates. However, the slopes of the IOR-impulsivity relationship were determined to be homogenous between motivation levels for all three covariates: cognitive instability, $F(1,116) = 2.439$, $p = .121$, $\eta_p^2 = .021$; attention, $F(1,116) = 1.337$, $p = .250$, $\eta_p^2 = .012$; perseverance, $F(1,116) = 1.099$, $p = .297$, $\eta_p^2 = .010$.

3.4.3 Study 3 Discussion

Study 3 indicated that when motivated by reward incentives, the previously observed negative relationship between IOR and impulsivity was not observed. This partly supports findings from Bucker and Theeuwes (2014), as they observed increased IOR accuracy scores for more impulsive individuals when participants were motivated. However, the relationship between impulsivity and IOR magnitude did not alter significantly as a function of motivational state between Study 2 and 3, making it difficult to draw conclusions regarding the effect of motivation.

3.5 General Discussion

We aimed to investigate the relationship between impulsivity and IOR magnitude, and how this relationship is affected by motivation. Our findings demonstrate that higher trait impulsivity is related to a reduced IOR magnitude. The same relationship was found using both cue-target and target-target IOR tasks (Studies 1 & 2, respectively). Furthermore, the relationship between impulsivity and IOR magnitude was not apparent when participants were motivated by reward (Study 3).

The results of Study 1 indicate that high trait impulsivity is associated with reduced cognitive inhibition in IOR, extending the findings of patients with ADHD (Li et al., 2003; Adams et al., 2008) to a healthy adult population, and accounting for the potential confounding factor of trait inattention level (Chhabildas et al., 2001; Geurts et al., 2005). Study 2 used a target-target, rather than a cue-target IOR paradigm—thus avoiding two factors that could exaggerate true attentional IOR; a motoric refractory period caused by cue suppression (Coward et al., 2004; Poliakoff et al., 2002), and a sensory refractory period caused by a visually unbalanced stimulus display (McDonald et al., 2008). Results were not specific to one form of IOR task,

as we observe the same relationship between impulsivity and IOR magnitude across both the cue-target and target-target paradigms.

Our results are in contrast with Avila (1995) and Poy et al. (2004), who found that impulsivity was related to increased IOR magnitude. An explanation for the discrepancy between these studies and ours could be their use of predictive cues. If the cue is more likely to predict target location, highly impulsive individuals may find uncued trials more salient compared to less impulsive individuals (Eysenck & Eysenck, 1977; Whiteside & Lynam, 2001). This could speed RTs to uncued targets and accentuate apparent IOR magnitude. Therefore, the number of cued and uncued trials should be balanced in cue-target IOR studies (as in our Study 1).

Our data indicate that the over-prioritisation of novel stimuli often observed with trait impulsivity (Eysenck & Eysenck, 1977; Whiteside & Lynam, 2001) may not affect IOR magnitude. An explanation for this finding may be that uncued locations are not actively considered novel in IOR, and are therefore not over-prioritised by impulsive individuals. Alternatively, reduced ability to inhibit cued locations may override preference for novelty—thus reducing IOR magnitude overall. Brain imaging methodologies such as EEG may be useful to examine the selection and inhibition stages involved in an attempt to resolve this issue. For example, electrophysiological markers could be measured to observe potential delays or reductions in selective attention to uncued locations in high versus low impulsive individuals (Luck, 2011; Luck & Hillyard, 1994).

Impulsivity is a multifaceted construct, with aspects that are behaviourally and neurobiologically distinct (Robbins, 2002; Robinson et al., 2007). Hence we utilised both behavioural and self-report impulsivity measures in Study 1, and persisted with the multi-dimensional BIS-11 (Patton & Stanford, 1995) for Studies 2 and 3. The impulsivity factor most strongly relating to IOR magnitude was the same in Studies 1 and 3 (from the BIS-11; 'Cognitive Instability'). However, the impulsivity factors that best predicted IOR magnitude were different in Studies 1 and 2 ('Attention' & 'Perseverance' from the BIS-11 for Study 2). This highlights the importance of accounting for the heterogeneity of impulsivity when exploring inhibitory mechanisms, and suggests future studies to explore the different impulsivity factors contributing to this relationship.

Study 3 indicates that when individuals are motivated, impulsivity is not related to IOR magnitude. This may suggest that reward-induced motivation recovers the reduced inhibition abilities observed in high trait impulsivity, as also suggested by Bucker and Theeuwes (2014). However, it should be noted that there was no statistically significant difference in the IOR-impulsivity relationship as a function of motavional state, making it difficult to draw conclusions from the comparison

between Studies 2 and 3. In future work, a repeated-measures design may provide a more powerful basis for comparison to explore the effect of motivation on the IOR-impulsivity relationship. Furthermore, it is possible that a higher motivational state than that induced in Study 3 would reproduce the pattern found by Bucker and Theeuwes (2014), that IOR and impulsivity are positively related following reward-induced motivation.

Additionally, it cannot be ruled out that the lack of IOR-impulsivity relationship observed in Study 3 may be due to a lack of statistical power. The designs of these studies were unprecedented, making it difficult to ascertain an appropriate number of participants. Future research must demonstrate that the IOR-impulsivity relationship alters as a function of motivational state with sufficent statistical power to draw more firm conclusons from these studies.

In summary, our findings are consistent with previous work demonstrating that inhibitory mechanisms are reduced when trait impulsivity is high (Bari & Robbins, 2013). We extend the more extensive literature on higher-level cognitive inhibition by investigating IOR; a low-level, rapid form (Klein, 2000). Finally, we find that the disinhibition commonly associated with trait impulsivity may not be fixed, but instead may be ameliorated by increased motivational state. However, this requires further investigation to substantiate, including a more powerful experimental design (between-subjects) and higher numbers of participants.

3.6 Power Analysis

After conducting these studies, *a priori* power analyses were conducted to attempt to determine the sample size appropriate to find a statistically significant IOR-impulsivity relationship ($p =< .05$). For Study 2, the analysis was conducted using the strongest IOR correlate from Study 1 (BIS-11, cognitive instability, $r = .23$). This indicated that 145 participants would be necessary to observe a relationship with 80% certainty using, 'pwr' in R (Champely, 2015). Similarly, the strongest impulsivity correlate of IOR from Study 2 determined the sample size appropriate to find a statistically significant relationship in Study 3 (BIS-11, attention, $r = .26$). This indicated that 113 participants would be necessary to observe a significant relationship with 80% certainty.

The original participant number of 58 was selected to fit with previous literature (as discussed). Furthermore, Study 2 found a similarly strong IOR-impulsivity relationship to Study 1, indicating that Study 3 should have been sufficiently powered to detect the same magnitude of relationship. Nevertheless, the article does not

make claims about the IOR-impulsivity relationship without acknowledging the limitation of sample size.

Chapter 4

An ERP Study of the Relationship between Trait Impulsivity and Attentional Inhibition

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Abstract

IOR is a an attentional inhibitory mechanism proposed to prevent the unnecessary re-inspection of attended stimuli—thus aiding processes such as visual search. High trait impulsivity is associated with impairments in inhibition, including in Inhibition of Return (IOR). Therefore, we aimed to gain a deeper understanding of the IOR-impulsivity relationship. To achieve this, we compared the key stages of cognitive processing in IOR between high- and low-impulsive individuals using electroencephalography (EEG). Contrary to previous research, our results showed that higher impulsivity was related to stronger IOR responses at the beginning of the task, but not at the end. EEG findings indicated that the stronger IOR response may have been related to an increased ability to shift attention between stimuli. We postulate that these unexpected results were caused by the novelty of participating in an EEG experiment, which affected the psychological states of participants. These results indicate that impulsive individuals can show exceptional attentional inhibition under certain circumstances. Furthermore, findings highlight the importance of accounting for changes in psychological state associated with the experience of brain imaging.

4.1 Introduction

High trait impulsivity is a feature of personality associated with impaired inhibitory control abilities (Bari & Robbins, 2013), which predispose individuals to engage in risky or unwanted behaviours (Moeller et al., 2001). Less well understood are potential impairments in cognitive inhibition, which may negatively impact the efficient processing of stimuli (Moeller et al., 2001; Bari & Robbins, 2013). For example, highly impulsive individuals may struggle to inhibit thoughts (Gay, Rochat, Billieux, D'Acremont & Van der Linden, 2008), switch attention (Cepeda, Cepeda & Kramer, 2000), or suppress distracting stimuli (Sanbonmatsu, Strayer, Medeiros-Ward & Watson, 2013). The present study investigates trait impulsivity in IOR—a form of attentional inhibition in which attention is inhibited from returning to previously attended stimuli (Posner & Cohen, 1984).

IOR is typically elicited using target-detection paradigms; targets are presented either at the same location as a previous target (cued trial), or in a novel location (uncued trial). IOR is then measured as the delayed response to cued trials compared to uncued trials (Posner & Cohen, 1984; Lupiáñez et al., 2006).

In a previous behavioural study, we found that high trait impulsivity was related to reduced IOR, unless individuals were motivated by rewards (see Chapter 3). IOR is thought to optimise the processing of stimuli by reducing unnecessary re-inspections (Klein & Macinnes, 1999; Wang & Klein, 2010). Therefore reduced IOR magnitude may represent an important processing inefficiency associated with trait impulsivity. In the present study, we aim to gain a deeper understanding of the IOR-impulsivity relationship using ERPs.

Researchers have used ERPs to investigate impulsivity and some forms of inhibition. For instance, the Stroop task requires individuals to inhibit a written colour in order to report the discordant colour of the word itself (Lansbergen, Kenemans & Van Engeland, 2007); West (2003) found that high-impulsive individuals made more errors in the Stroop task, which were reflected in topographical differences of the 'sustained potential' marker of attention control. Another task requires individuals to respond to a continuous stream of stimuli (go trials), but withhold their response from rarer stimuli (no-go trials) (Yechiam et al., 2006). Several studies demonstrated that high-impulsive individuals made more errors, reflected in reduced *P3* amplitudes to no-go stimuli (Ruchsow et al., 2008; Schmüser et al., 2016; Zhou, Yuan, Yao, Li & Cheng, 2010; Kamarajan & Porjesz, 2012). As P3 is considered a marker of attentional resource allocation (Ruchsow et al., 2008), the results may reflect reduced cognitive resource allocation for inhibition compared to less impulsive individuals.

Taken together, the EEG studies discussed above indicate that disinhibition

emerges from disrupted attentional processes. However, these studies investigated attentional processes which are more voluntary than IOR. It remains unclear how attention may differ in such a reflexive, low-level form of inhibition (Tipper & Kingstone, 2005). Furthermore, IOR is related to different attentional ERP components.

The *P1* component is the first positive deflection of an ERP waveform occurring around 100ms following a visual stimulus presentation (Kiss et al., 2008). Its amplitude is larger when stimuli are more salient, irrespective of whether a target or distracter (Mangun & Hillyard, 1987). This indicates that the P1 reflects early sensory orienting towards stimuli. In contrast, the N2pc marks the covert deployment of selective attention (Luck, 2011), as it is preferentially activated for targets over distractors (Kiss et al., 2008). The N2pc is the positive difference between electrodes ipsilateral and contralateral to the target, and occurs around 200ms after target presentation (Luck & Hillyard, 1994). Previous EEG studies have found smaller P1 and N2pc amplitudes in cued versus uncued IOR conditions. Therefore, IOR is thought to be the product of both sensory and selective attention modulations (see Martín-Arévalo et al., 2016, for a review).

These ERPs offer a means of identifying how processing inefficiencies may arise in impulsive individuals. For example, it could be that reduced IOR emerges from relatively increased P1 amplitudes for cued targets. This would demonstrate that disinhibition occurs at the earliest possible stage of attention orienting, in the sensory system (Mangun & Hillyard, 1987). On the other hand, disinhibition may emerge from longer N2pc latencies for cued targets. This would demonstrate that disinhibition emerges from delayed deployment of selective attention (Kiss et al., 2008; Luck, 2011).

Furthermore, there is evidence that high-impulsive individuals show abnormalities in attentional disengagement from one stimulus to focus on another (Cepeda et al., 2000; Leshem, 2016b; Winstanley, Eagle & Robbins, 2006). This would be reflected in an EEG component termed *Pd*, a marker which has not previously been measured in IOR studies. Pd marks the disengagement of attention from stimuli once processing of it is complete (Sawaki et al., 2012). It follows the N2pc in sequence, and is a negative difference between signals ipsilateral and contralateral to the target (Hickey et al., 2009).

In summary, there is evidence that IOR is disrupted in high-impulsive individuals (Chapter 3) (Li et al., 2003), which may represent an inefficiency in stimulus processing (Klein & Macinnes, 1999; Wang & Klein, 2010). Therefore, we aim to better understand the IOR-impulsivity relationship by using EEG to measure key attentional events (Martín-Arévalo et al., 2016). We predict that either sensory

orienting (P1), selective attention (N2pc), or attention termination (Pd) may be affected by impulsivity in IOR.

4.2 Method

4.2.1 Participants

The previous ERP study of IOR conducted by McDonald et al. (2008) did not provide sufficient information to conduct a power analysis, but found significant ERP effects with fourteen participants. As this study additionally measures correlates of trait impulsivity with ERPs and IOR, it was determined that at least double the number of participants should be recruited to account for this added complexity. However, it is difficult to establish an appropriate sample size without previous research with a similar design.

Forty-nine Participants were recruited from advertisements around The University of Manchester (3 left-handed; 31 female; mean age 21 years; standard deviation 2.9). Participants had normal or corrected-to-normal vision and were not colour-blind. They received a financial reward for taking part in the study (or the equivalent course credits for University of Manchester undergraduate psychology students). Before participating, individuals completed an online version of the Barratt Impulsivity Scale (BIS-11; Patton & Stanford, 1995). This 30-item self-report questionnaire provided a measure of several impulsivity factors, namely: attention, cognitive instability, motor, perseverance, self-control, and cognitive complexity. The study was approved by The University Research Ethics Committee of The University of Manchester, UK (ref. 14194).

4.2.2 IOR Task

Participants performed a computerised target-target IOR task. The task was adapted from McDonald et al. (2008), using a black rather than white background to reduce potential eye strain. The stimuli were displayed on a 17" LED monitor, and were programmed using PsychoPy software (Peirce, 2007). Participants were assigned a target coloured disc (randomised; pink, green, or blue). Each trial contained pairs of such coloured discs appearing on the screen for 100ms, four degrees below and six degrees to the left and right of a central fixation cross. No two discs in a pair were the same colour. Participants were instructed to maintain focus on the central cross throughout, and identify if their target circle was on the left or right of the screen by pressing left and right buttons (*b* and *n* keys, respectively). Response hand

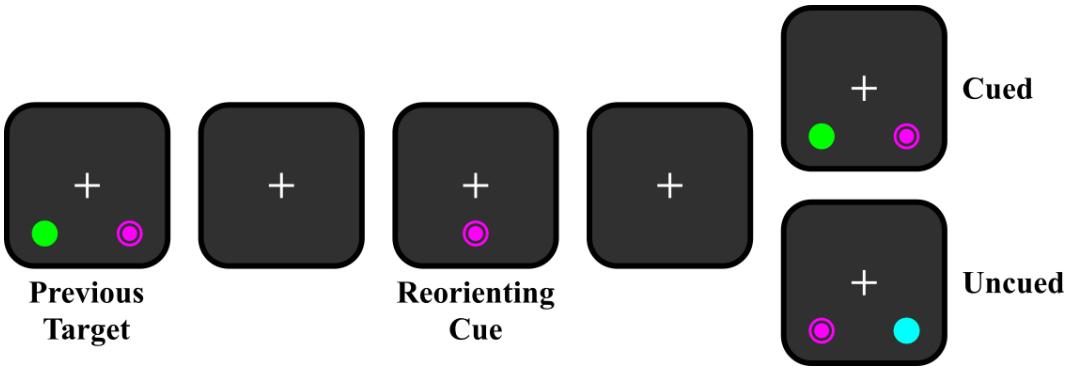

Figure 4.1: The time-course of stimulus displays in the target-target inhibition of return task. Examples of cued and uncued trials wherein the target appears in the same location versus the opposite location to the previous trial, respectively.

was counterbalanced across participants. The target disc was present in two-thirds of trials and the remaining third served as catch trials.

Whether the target appeared on the same or opposite side of the screen as the previous trial determined if the trial was deemed as cued or uncued, respectively. A neutral trial was defined as containing a target, but following a trial without a target. The possible different combinations of disc colours were represented equally and randomised such that cued and uncued trials occurred equally on the left and the right of the screen. Between trials, the target disc was presented for 100ms in the centre of the screen. This served to re-centralise the participant's attention and acted as a reminder of the target colour. See Figure 4.1 for a visual representation of the stimulus displays. After a practice block consisting of 22 trials, participants completed a total of 1,026 trials separated into 27 blocks, each lasting ~45 seconds. The participants' brain activity was recorded via EEG throughout the task.

4.2.3 IOR Analysis

EEG recordings require a much larger number of trials than behavioural studies, making the duration of the task 20-30 minutes (around three times that of a standard behavioural IOR task). There is evidence that motivation fluctuates across task durations (Ralph, Onderwater, Thomson & Smilek, 2017; Thomson, Besner & Smilek, 2015), which could have differential effects on high or low-impulsive individuals (Anderson & Revelle, 1983). To account for this, analyses were performed using values obtained from three equal blocks of trials taken from the first, middle, and final parts of the task (as well as across the whole task duration).

For each participant, the difference between averaged cued and uncued RTs provided a measure of IOR magnitude (cued minus uncued; more positive values

represented a larger IOR response). To confirm the relationship between IOR magnitude and trait impulsivity level, individual IOR magnitudes were correlated with BIS-11 questionnaire scores (across the task and in the three sub-blocks). If the relationship between impulsivity and IOR differed depending on time-point, then time-point would be factored into further analyses.

In order to examine the differences in cued and uncued RTs between high and low-impulsive individuals, a mixed-design ANOVA was employed (with time-point as a factor, if necessary). High vs low-impulsive subgroups of participants were defined using a median split of the BIS-11 impulsivity factor most related to IOR magnitude.

4.2.4 EEG Recording and Analysis

Continuous EEG was recorded using 64 scalp electrodes at a sampling rate of 512Hz, and using the 'ActiveTwo' BioSemi system (BioSemi, Amsterdam, Netherlands) with ActiView acquisition software (BioSemi). Flat-type electrodes were positioned above and below the right eye and at the outer edge of each eye to measure blinks and horizontal eye movements, respectively. Offline, data were re-referenced to an average (whole-scalp) reference. Using SPM12 software (Statistical Parametric Mapping, UCL, England), EEG recordings were pre-processed; firstly, the signals were high-pass and low-pass filtered (with cut-off frequencies of 0.1Hz and 40Hz, respectively) and down-sampled to 200Hz. Epochs were defined as -100ms to 400ms relative to the onset of the target display, and were baseline-corrected relative to the 100ms pre-stimulus time window. Trials contaminated by artefacts (including eye-blinks/movements) were excluded from analyses, detected as a events recorded at any of the electrode channels exceeding 75μV, relative to the pre-stimulus baseline. Incorrect trials (and trials directly following an incorrect response) were excluded from analyses.

The P1, N2pc, and Pd mean latencies and amplitudes were obtained for each participant in each condition (cued, uncued, and neutral). P1 was defined as the first positive peaks of the signal occurring across posterior electrodes contralateral to the target location (electrodes P6/7, PO6/O7, P3/4, PO3/O4). N2pc and Pd were measured at the aforementioned posterior electrode sites, and as the peak difference between signals ipsilateral and contralateral to the target location, occurring in a time window of 160-260ms (N2pc) and 260-400ms (Pd) post stimulus onset. The mean amplitude values of P1, N2pc, and Pd were quantified as the average voltages 10ms, 20ms, and 30ms either side of the ERP peaks, respectively (Luck & Hillyard, 1994; Luck, 2011). ERP latencies were measured as the time of peak ERP amplitude relative to the target onset.

To investigate which ERP(s) may underlie behavioural effects, the same analyses were conducted as for RTs, but for the latencies and amplitudes of each ERP. The same pattern of statistical findings for an ERP would be indicative of its involvement in behavioural effects. Furthermore, correlation analyses were conducted to find which ERP(s) best predicted notable behavioural effects. As ERP analyses were exploratory in nature, correlations and tests of simple effects were Bonferroni adjusted.

4.3 Results

One participant was removed from analyses for having incorrect response rates more than three times higher than the interquartile range. Remaining participants made an average of 4.2% (SD = 3.1) errors. Two participants were removed from analyses as they failed to meet the requirement of at least 20 trials per condition following EEG artefact rejection. Two participants were removed due to the lack of discernible visual-evoked potential in their ERP waveforms, defined as a prominent positive peak between 70-140ms following stimulus presentation (Di Russo, Martínez, Sereno, Pitzalis & Hillyard, 2002). RTs were also subject to an outlier removal procedure for each participant in each condition. (Selst & Jolicoeur, 1994), which removed an average of 2.4% (SD=0.6) of trials from each participants' responses. To ensure that results reflected cuing effects, incorrect trials and those directly following an incorrect trial were not included in behavioural or EEG analyses (cf. Poliakoff et al., 2003).

4.3.1 Behavioural

Average cued RTs were significantly slower (M = 409ms, SD = 38) than uncued RTs (M = 385ms, SD = 37); $t(43) = 9.55$, $p < .001$, $d = 1.44$, two-tailed. This 24ms difference demonstrated that IOR was successfully elicited by the task. Average percentage error rates were significantly higher in cued trials (M = 4.75, SD = 3.2) compared to uncued trials (M = 2.81, SD = 2.6); $t(43) = 5.25$, $p < .001$, $d = .791$, two-tailed. Therefore, a speed-accuracy trade-off was not apparent.

Using IOR magnitude derived from the full length of the task, no relationships were found between trait impulsivity levels (BIS-11 scores) and IOR magnitude using two-tailed Pearson's *r* correlation analyses. Using the first block, IOR magnitude was positively related with three BIS-11 measures of trait impulsivity (Attention, $r(42) = .381$, $p < .05$; cognitive instability, $r(42) = .300$, $p < .05$; overall BIS-11, $r(42) = .327$, $p < .05$). In the middle block, one trait impulsivity factor remained positively related with IOR magnitude (attention, $r(42) = .389$, $p < .05$). In the final block,

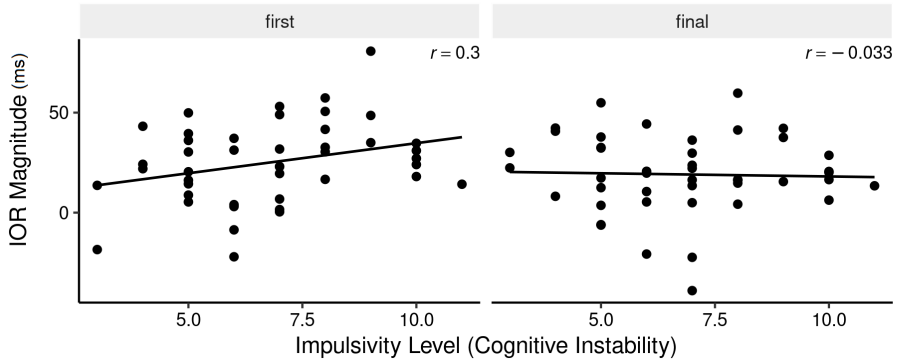

Figure 4.2: The relationship between impulsivity (cognitive instability) and IOR magnitude (cued minus uncued reaction times) reduces over time: The positive correlation between IOR and impulsivity was apparent in the first task block (left scatter plot), but not in the final task block (right scatter plot).

no trait impulsivity measures were associated with IOR magnitude, see Figure 4.2: attention, $r(42) = .249$, $p = .103$; cognitive instability, $r(42) = -.033$, $p = .832$; overall BIS-11, $r(42) = .166$, $p = .281$.

Changes in IOR magnitude (first block-final block) were correlated with impulsivity scores. Larger reductions in IOR magnitude were significantly related to higher trait impulsivity (cognitive instability from the BIS-11; $r = .289$, $p < .05$, one-tailed).

A two-way mixed ANOVA was conducted on IOR magnitude with two independent variables, each with two levels; impulsivity level (low, high), and time-point (first block, final block). The main effects of impulsivity level and time-point were not significant ($p = .229$, $p = .131$, respectively). The interaction was significant; $F(1,42) = 5.35$, $p < .05$, $\eta_p^2 = .113$). Planned test of simple-effects demonstrated that high-impulsive individuals exhibited significantly larger IOR magnitudes (M=31.3ms) than low-impulsive individuals (M=17.5ms) in the first block of the task; $t(42) = 2.35$, $p < .05$, $d = .710$; but not in the final block ($p = .761$).

To investigate which of cued and/or uncued trials gave rise to higher IOR magnitudes for impulsive individuals, a three-way mixed ANOVA was performed on RTs. There were three independent variables, each with two levels; impulsivity level (low, high), condition (cued, uncued), and time-point (first block, final block). The main effect of condition was significant ($p < .001$), demonstrating longer RTs for cued trials compared to uncued trials (i.e. the IOR effect, reported above). The main effect of time-point was significant; $F(1,42) = 20.3$, $p < .001$, $\eta_p^2 = .327$; demonstrating shorter RTs in the final block (M=390) compared to the first (M=405); $t(43) = 4.51$, $p < .001$, $d = .680$. The main effect of impulsivity level was not significant ($p = .678$). All two-way interactions were not significant (time-point

Table 4.1: For high and low-impulsive individuals, mean and standard deviation of percentage incorrect rates of cued and uncued conditions in the first and final blocks of the task.

	Low		High	
Block	Cued	Uncued	Cued	Uncued
First	4.52(3.3)	3.52(3.6)	4.28(3.2)	2.26(1.8)
Final	3.30(2.2)	2.48(2.8)	5.29(3.6)	3.13(2.9)

by impulsivity level, $p = .850$; condition by impulsivity level, $p = .229$; block by condition, $p = .131$). The three-way interaction between impulsivity level, condition, and time-point was significant; $F(1,42) = 5.35$, $p < .05$, $\eta_p^2 = .113$; and is further explored below.

To investigate whether cued versus uncued RTs contributed to higher IOR magnitudes for impulsive individuals, planned t-tests were conducted; neither cued nor uncued trials were significantly different between high and low-impulsive groups ($p = .832$ and $p = .595$, respectively). This indicates that small differences in both cued and uncued trials may contribute to the enhanced IOR magnitudes of impulsive individuals (see Figure 4.3).

In order to establish if the RT effects described above may be the result of a speed-accuracy trade-off, a three-way mixed ANOVA was performed on percentage error rates. As with the RT data above, there were three independent variables, each with two levels; impulsivity level (low, high), condition (cued, uncued), and time-point (first block, final block).

There was a main effect of condition; $F(1,42) = 28.1$, $p < .001$, $\eta_p^2 = .400$; indicating that error rates were higher in cued (4.35) versus uncued (2.84) trials; $t = 5.30$, $p < .001$, $d = .799$; demonstrating that IOR effect is not a trade-off between speed and accuracy (as reported above across task blocks). There was a significant interaction between condition and impulsivity level; $F(1,42) = 4.34$, $p < .05$, $\eta_p^2 = .094$. Exploring this effect, t-tests of simple effects did not reach statistical significance: high versus low-impulsive cued trials, $t = 1.32$, $p = .194$; high versus low-impulsive uncued trials, $t = .503$, $p = .618$. There was no significant three-way interaction; $F(1,42) = .071$, $p < .792$, $\eta_p^2 = .002$. Therefore, the RT effects described above were not the result of a speed-accuracy trade-off. See Table 4.1 for descriptive statistics.

To determine whether cued or uncued RTs changed over time for impulsive individuals, further planned t-tests were conducted; for high-impulsive individuals,

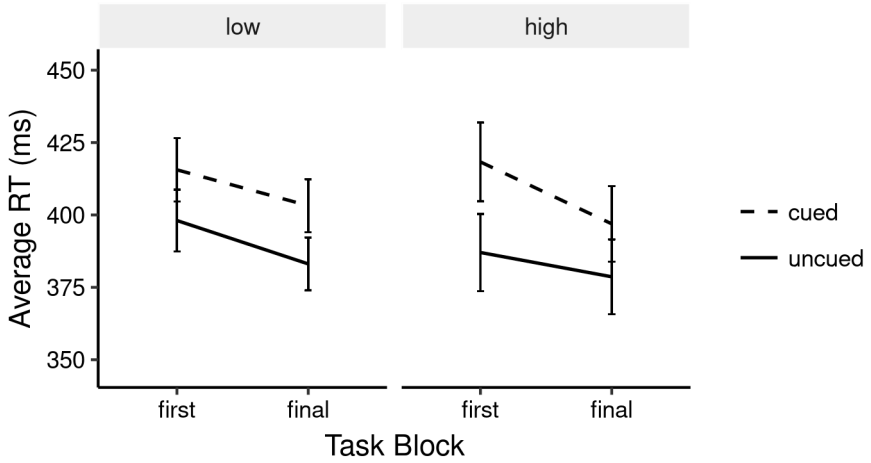

Figure 4.3: For high-impulsive individuals, cued reaction times were significantly faster in the final task block compared to the first. This demonstrates that inhibition reduced over time for high-impulsive individuals.

only cued RTs significantly reduced from the first block (M=418) to the final block (M=397); $t(23) = 5.44$, $p < .001$, $d = 1.11$; see Figure 4.3. This indicated that the speeding of cued RTs leads to the reduction of IOR magnitude in high impulsive individuals (i.e. a reduction in inhibition).

4.3.2 Behavioural Results Summary

Results showed that higher impulsivity was related to greater IOR magnitude at the beginning of the task, but not at the end of the task. We also found that the reduction in IOR over time for high-impulsive individuals was due to the speeding of cued RTs (i.e. reduced inhibition).

4.3.3 EEG

Relating ERPs to Behaviour

See Figure 4.4 for ERP plots for each task condition. We investigated which ERP(s) may underlie behavioural effects using three-way mixed ANOVAs (analogous to the behavioural analyses). However, none of the ERPs showed the same pattern of results as the behavioural interactions between IOR condition, impulsivity level, and time-point (see Table 4.2).

This null result could be due to cued and uncued stimuli being processed differently. Therefore, a more informative approach would be to assess the relationship between ERPs and RTs separately for cued and uncued trials. To compare impulsivity levels, this was conducted separately for high and low-impulsive individuals;

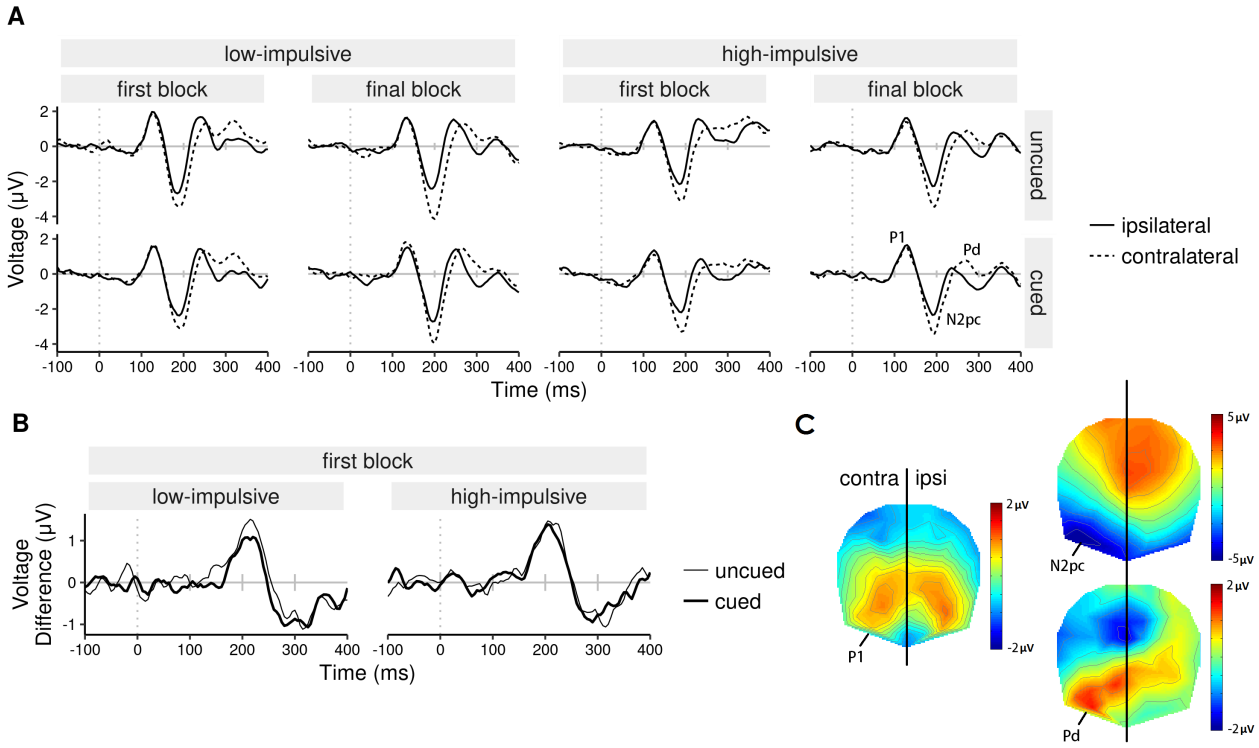

Figure 4.4: (A) Grand average waveforms elicited by visual targets in the inhibition of return task. Waves were averaged from posterior electrodes, separately for electrodes ipsilateral and contralateral to the target location on the screen. (B) Ipsilateral minus contralateral difference waves elicited by targets in the same location as a previous target (cued trial) or in the opposite location (uncued trial). (C) EEG scalp topographies of ERPs. In this example, the target would be on the right side of the screen.

Table 4.2: Results of three-way ANOVAs measuring the effect of task condition (cond.—cued/uncued), time (first/final task block), and impulsivity level (imp.—high/low) on event-related potentials (ERPs).

		Latency			Amplitude		
ERP	Effect	F	η_p^2	p	F	η_p^2	p
P1	cond.	0.603	0.014	0.442	0.006	0.000	0.941
	time	1.950	0.044	0.170	0.856	0.020	0.360
	impulsivity	0.157	0.004	0.694	6.567	0.135	0.014*
	cond. × imp.	0.143	0.003	0.708	1.444	0.033	0.236
	time × imp.	0.570	0.013	0.455	1.244	0.029	0.271
	cond. × time	0.157	0.004	0.694	9.823	0.190	0.003*
	cond. × time × imp.	0.013	0.000	0.910	1.191	0.028	0.281
N2pc	cond.	3.594	0.079	0.065	7.347	0.152	0.010*
	time	1.723	0.039	0.196	0.156	0.004	0.695
	impulsivity	0.109	0.003	0.743	0.318	0.008	0.576
	cond. × imp.	1.474	0.034	0.231	0.463	0.011	0.500
	time × imp.	0.587	0.014	0.448	0.036	0.001	0.850
	cond. × time	1.740	0.040	0.194	1.200	0.028	0.280
	cond. × time × imp.	0.266	0.006	0.609	0.001	0.000	0.976
Pd	cond.	0.495	0.012	0.486	1.279	0.030	0.265
	time	1.343	0.031	0.253	1.606	0.037	0.212
	impulsivity	1.178	0.027	0.284	0.208	0.005	0.657
	cond. × imp.	0.298	0.007	0.588	0.208	0.005	0.651
	time × imp.	0.524	0.012	0.473	0.320	0.008	0.575
	cond. × time	2.546	0.057	0.118	3.178	0.070	0.082
	cond. × time × imp.	0.273	0.006	0.604	0.051	0.001	0.822

degrees of freedom = 1, 42, p = * statistical significance, η_p^2 = partial eta squared measure of effect size.

using correlation analyses, in the first block of the task faster uncued RTs were related to shorter Pd latencies for high-impulsive individuals. This indicates that for high-impulsives, faster responses to uncued targets was related to faster attention termination/disengagement. There were no other ERP correlates of cued or uncued RTs for high- or low-impulsive individuals (see Table 4.3).

Further analyses were focused on cued RT changes over time for high-impulsive individuals. However, there were no significant ERP correlates of changes in cued RTs from the first block to the final block (see Table 4.4).

Other ERP effects

In the aforementioned three-way ANOVA (Table 4.2), the main effect of condition on N2pc amplitude was significant—showing larger uncued (M = 2.44) compared to cued amplitudes (M = 2.07), t(43) = 2.71, $p < .025$, $d = .409$. This demonstrates

Table 4.3: Results of Pearson's r correlation analyses measuring the relationships between event-related potentials (latencies and ampitdues) and behaviour (reaction time), separately for high- and low-impulsive individuals. Numbers represent r-values.

		P1		N2pc		Pd	
		Amp.	Lat.	Amp.	Lat.	Amp.	Lat.
Cued	Low	0.159	0.329	-0.243	-0.309	0.285	0.161
	High	-0.363	0.272	-0.177	0.155	0.369	0.044
Uncued	Low	-0.019	0.242	-0.277	-0.057	0.124	0.473
	High	-0.294	0.253	-0.150	0.065	0.338	0.698*

p <.008. * = statistical significance (Bonferroni adjusted).

Table 4.4: Results of Pearson's r correlation analyses measuring the relationship between the change (Δ) in reaction times (RTs) between the first and final task blocks, and the corresponding changes in event-related potentials (latency and amplitude), for high-impulsive individuals.

	ΔP1		ΔN2pc		ΔPd	
	Lat.	Amp.	Lat.	Amp.	Lat.	Amp.
ΔCued RT	-0.379	-0.284	0.233	-0.436	0.308	-0.058
p-value	0.068	0.179	0.285	0.033	0.143	0.786

p <.008. p* = statistical significance (Bonferroni adjusted).

that selective attention to cued targets was weaker than for uncued targets, reflecting behavioural IOR in general.

Although the interaction between condition and time-point was also significant for P1 amplitude, tests of simple effects did not reach statistical significance. The main effect of impulsivity level on P1 amplitude was significant, showing larger amplitudes in low-impulsive (M = 2.76) compared to high-impulsive participants (M = 1.95); t(42) = 2.56, p < .025, d = 2.40. This indicates stronger sensory orienting to targets in low-impulsive individuals, irrespective of time-point.

4.3.4 EEG Results Summary

Using ANOVAs, no ERP latencies or amplitudes showed the same pattern of effects as behaviour. Instead, further correlational analyses showed that in high-impulsive participants, faster uncued RTs in the first task block were related to faster disengagement of attention from the target.

Additional findings showed modulations in selective attention for cued and uncued targets across all participants and task blocks. This demonstrates that EEG

was successful in measuring the general IOR effect (as seen in McDonald et al., 2008).

Furthermore, sensory orienting was found to be significantly stronger in low-impulsive compared to high-impulsive individuals, irrespective of IOR condition or time-point.

4.4 Discussion

Here we found that the relationship between impulsivity and IOR changed over time; higher impulsivity was related to higher IOR magnitude in the beginning of the task, but not at the end of the task. This finding was unexpected, as we hypothesised that higher impulsivity would be related to *reduced* IOR magnitude, in accordance with previous findings from our lab (Chapter 3).

Previous research indicates that changes in psychological states—such as motivation level—may influence the IOR-impulsivity relationship. For example, reward-induced motivation may recover reduced IOR in impulsive individuals, and enable them to give more accurate responses than less-impulsive individuals (Bucker & Theeuwes, 2014). Anderson and Revelle (1983) found that high-impulsive individuals performed optimally at the beginning and end of a visual search task, but not in the middle of the task. The authors suggested that the novelty of beginning and approaching the end of the task increased the motivational states of impulsive individuals (Anderson & Revelle, 1983).

Therefore, we suggest that the novel circumstance of undergoing EEG increased arousal and motivational states at the beginning of the task—especially in high-impulsive participants. This effect then reduced over time as participants became more familiar with the experiment circumstances. This would explain why the same effect was not apparent in much shorter behavioural studies of IOR.

Indeed, there is evidence that undergoing brain imaging can affect participants' psychological states due to the unusual procedures involved (Duncan & Northoff, 2013; Raz et al., 2005). Previous studies are largely concerned with how fMRI imaging scanners may provoke anxiety (Duncan & Northoff, 2013; Raz et al., 2005)—which may not be relevant for EEG. The present study was not designed to delineate potential anxious versus motivational influences on IOR. However, the two states may be inextricably linked; anxiety increases arousal to motivate individuals to avoid aversive outcomes (Eysenck & Calvo, 1992; Pessoa, 2009). If participants consider poor task performance an aversive outcome, then anxiety may be motivational for the task (Eysenck & Calvo, 1992).

Furthermore, there is some acknowledgement that the lengthy and unusual preparation involved in brain imaging studies can affect motivational state (Raz et al., 2005). EEG studies require several preparation stages focused on participants, including the individual application of 64 electrodes to the scalp. Therefore, individuals may feel more motivated to 'perform well' due to the perceived time and effort focused on their participation (Raz et al., 2005). Furthermore, most individuals have little or no experience with brain imaging procedures, making the circumstances somewhat novel.

Further analyses of our findings showed that the larger IOR magnitudes of high-impulsive individuals was due to both slower cued RTs and faster uncued RTs. This fits with previous findings that motivation 'sharpens' executive functions, and increases attention orienting efficiency (Engelmann & Pessoa, 2007). The sharpening effect may be more apparent in high-impulsive individuals, as they are thought to be more sensitive to motivational factors (Coffey, Gudleski, Saladin & Brady, 2003; Bari & Robbins, 2013; Dalley et al., 2011; Mason et al., 2012; Bucker & Theeuwes, 2014). Furthermore, impulsive individuals made faster cued responses at the end of the task compared to the beginning, thus reducing overall IOR magnitude. This indicates a reduction in inhibition of cued locations over time (Klein, 2000)—which may have been related to reduced motivation.

We propose that these effects may be related to striatal dopamine transmission in the brain; striatal dopamine is thought to affect IOR through its influence on the superior colliculus—a key brain region for the generation of 'inhibitory tags' necessary for IOR (Klein, 2000; Fecteau & Munoz, 2005; Sapir et al., 1999). Motivation is associated with increases dopamine in the striatum of the brain (Ikemoto et al., 2015), and it has been proposed that medium levels produce largest IOR effects (Rokem et al., 2012). High-impulsive individuals are thought to have reduced baseline dopamine signalling in the striatum compared to low-impulsives (Costa et al., 2013; Caplan, Guthrie & Komo, 1996; Cools et al., 2007). Therefore the increase of dopamine caused by motivation may have enhanced IOR for high-impulsives with a low baseline, but decreased IOR for low-impulsives—who would then have excessive dopamine. The effect would then 'wear off' along with the novelty of the circumstances. However, further research is necessary to investigate the direct effects of dopamine signalling on IOR.

We used EEG to further explore the IOR-impulsivity relationship. More generally, the results showed that selective attention was stronger for uncued versus cued targets, irrespective of time or impulsivity level. This reproduces findings from (McDonald et al., 2008), and demonstrates the IOR effect in the brain. We also found that sensory orienting (P1 amplitude) was stronger for low-impulsive

compared to high-impulsive individuals. This indicates that higher impulsivity is related to reduced early sensory orienting, which may reflect general inattention. This fits with other ERP studies which have found delayed/reduced sensory orienting in ADHD (e.g. Karayanidis et al., 2000). However, in this study, the effect was observed for both cued and uncued targets—and is therefore unlikely to be related to the behavioural IOR effects observed.

Nevertheless, no single ERP latency or amplitude showed the same pattern of behavioural effects relating to impulsivity. This result was not entirely unexpected, as cued and uncued targets are likely to be processed differently (Engelmann & Pessoa, 2007), and may be related to multiple stages of processing (Martín-Arévalo et al., 2016; Berlucchi, 2006). Therefore, we also measured the ERP correlates of cued and uncued RTs in the first block of the task, as well as the speeding of cued RTs over time; we discovered that for high-impulsive individuals, uncued RTs at the beginning of the task were related to shorter Pd latencies—indicating faster termination of attention to uncued targets (Sawaki et al., 2012). Increased striatal dopamine levels have been shown to increase the ability to shift attention between stimuli (Nieoullon, 2002). Therefore, this finding may support that impulsive individuals experienced a burst of dopamine at the beginning of the task, increasing their IOR magnitudes.

We found no further ERP correlates of behavioural effects, either for the first block of the tasks, or for the loss of inhibition over time seen in impulsive individuals. These null ERP findings could be attributed to several factors. Firstly, subtle changes in multiple processes may underlie behavioural effects, rather than larger modulations of specific processes. Previous studies indicate that P1 and N2pc are modulated by IOR in general (Martín-Arévalo et al., 2016). However, they may not be sufficiently sensitive to measure individual differences in processing, as in the present study. Furthermore, analyses were conducted by time-point, reducing the number of trials available for EEG analyses, thus reducing statistical power. Lastly, the effects of impulsivity on IOR may be related to other processes beyond those measured in the present study (e.g. in the motoric or higher executive system).

It should be noted that even towards the end of this task, the hypothesised negative IOR-impulsivity relationship was not apparent (as was observed in our aforementioned previous studies). This may reflect that individuals were more motivated at the end of the EEG task than they were during the behavioural tasks. However, it is difficult to draw this conclusion without an objective measure of motivational state to compare between these studies. As such, future work is necessary to demonstrate that the nature of the IOR-impulsivity relationship can indeed reverse due to the effects of motivation.

Nonetheless, these findings indicate that impulsivity may be related to increased inhibition under certain circumstances. This may be related to increased ability to shift attention from uncued stimuli. This has implications for the understanding of impulsivity in general—challenging the idea that high impulsivity is related to immutable deficits in inhibition. Instead, high impulsivity may confer some inhibitory benefits if individuals are sufficiently aroused/motivated (Anderson & Revelle, 1983; Bucker & Theeuwes, 2014).

Chapter 5

Returning to EEG markers of IOR: Sensory Orienting Predicts Selective Attention

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Abstract

Individuals exhibit faster responses to novel stimuli compared to previously-attended stimuli—a phenomenon termed Inhibition of return (IOR). Researchers have used ERPs to investigate the underlying cognitive processes involved in IOR, finding that modulations of sensory orienting are key. Conversely, others show that selective attention may be more important. These inconsistencies are likely to emerge from differences in experimental design. In this article, we highlight that different analysis approaches can also affect the conclusions drawn from ERP studies of IOR, which may impact such debates in the literature. To do so, we replicated a previous study conducted by McDonald et al. (2008), which found that sensory orienting was not involved in IOR. We applied further analyses to measure the relationships between ERPs, and analysed the ERP correlates of behavioural effects. This demonstrated that sensory orienting was related to selective attentional processes in IOR—indicating that IOR involves modulations of both. Therefore, the traditional analysis techniques (i.e. only looking for differences between conditions) may underestimate the involvement of smaller ERP modulations. Instead, a range of analysis techniques should be used, especially exploring the relationships between different ERPs, and their relationships to behaviour.

5.1 Introduction

IOR is an attentional mechanism proposed to aid efficient sampling of stimuli in the environment (Posner & Cohen, 1984; Klein, 2000). In the visual domain, IOR inhibits attention from recently attended spatial locations and objects (Tipper et al., 1991). Hence IOR may facilitate attention-dependent processes such as visual search, by preventing unnecessary re-inspections (Klein & Macinnes, 1999; Tipper et al., 1991). IOR is typically measured as delayed RTs to targets appearing in the same location as a previous target (a cued trial) compared to a novel location (an uncued trial) (Klein, 2000; Lupiáñez et al., 2006).

Event-related potentials (ERPs) have been utilised to discern the underlying mechanisms of IOR, yet the mechanisms remain under debate. This could be due to discrepancies in task designs producing different results, such as the timing of stimuli; the type of response required; the presence of intervening events; and how the stimuli are presented visually (see Martín-Arévalo et al., 2016, for a review). Therefore, when interpreting the results of ERP studies of IOR, methodological differences between tasks should be carefully considered (Martín-Arévalo et al., 2016; Berlucchi, 2006). Building on this, in this paper we demonstrate the importance of considering different data analyses when conducting and interpreting ERP studies of IOR.

The contribution of an ERP component to IOR is usually determined by showing a significant difference between cued and uncued conditions using ANOVAs (Tang et al., 2015; Satel et al., 2014; Jones & Forster, 2012; Hoffmann & Wascher, 2012; Tian, Klein, Satel, Xu & Yao, 2011; Prime & Jolicœur, 2009; Prime & Ward, 2004; McDonald, Ward & Kiehl, 1999; Prime & Ward, 2006; Wascher & Tipper, 2004). However, see Jones and Forster (2013) and Satel et al. (2013) for the use of correlational analyses alongside ANOVAs. Although this approach has undoubtedly provided useful insights, it may underestimate the involvement of functionally relevant ERPs. We highlight how this may be the case using a previous study as an example.

McDonald et al. (2008) aimed to isolate an electrophysiological marker of selective attention (the N2pc) from earlier sensory/perceptual ERPs (P1/N1) in an IOR task; they balanced sensory stimulation across the visual display, as opposed to presenting singleton stimuli. This was to avoid task-irrelevant P1/N1 modulations at lateralised locations. Their results demonstrated significant differences between conditions for the N2pc, but not P1 or N1. This was taken as evidence that the IOR effect is due to modulations in selective attention, independent of sensory/perceptual effects.

However, these electrophysiological markers form part of a continuous chain of attentional events, meaning that earlier sensory processes may influence later ones (Kiss et al., 2008; Woodman, 2010). Hence, it is possible that P1/N1 contributed to the formation of the N2pc, but only the N2pc reached statistical significance. Therefore, to verify if sensory ERPs are related to selective attention in IOR, it may be pertinent to analyse the relationships between them.

Furthermore, the previously-cited ERP studies of IOR employ separate ANOVAs for different ERPs, as well as their latencies and amplitudes. In other words, the differences between conditions can only be found within a given ERP, without allowing for the possibility of combinations of effects. This may be an issue considering that cued and uncued trials are likely to be processed differently; for instance, cued trials involve inhibition, whereas uncued trials do not (Engelmann & Pessoa, 2007). Therefore analyses should address the potential differences between the processing of cued and uncued targets.

To illustrate and explore these points, we replicated the study conducted by McDonald et al. (2008), but extended the analyses to measure relationships between ERPs, and investigated correlates of cued and uncued targets independently. We predicted that markers of sensory orienting may be related to selective attention, and that the processing of cued and uncued targets may be related to different and/or several ERPs.

5.2 Methods

Note that these data are the same as those analysed in Chapter 4 of this thesis, but collapsed across impulsivity level and task block.

5.2.1 Participants

The minimum sample size was selected to be in line with that of (McDonald et al., 2008). The researchers do not provide adequate information to calculate statistical power.

Forty-nine participants (mean age = 21 years, SD = 2.9; 31 female; 3 left-handed) took part in the study. They had normal or corrected-to-normal vision, were not colour blind, and reported no neurological conditions. Participants gave written informed consent to take part. The study was approved by The University Research Ethics Committee of The University of Manchester, UK (ref. 14194).

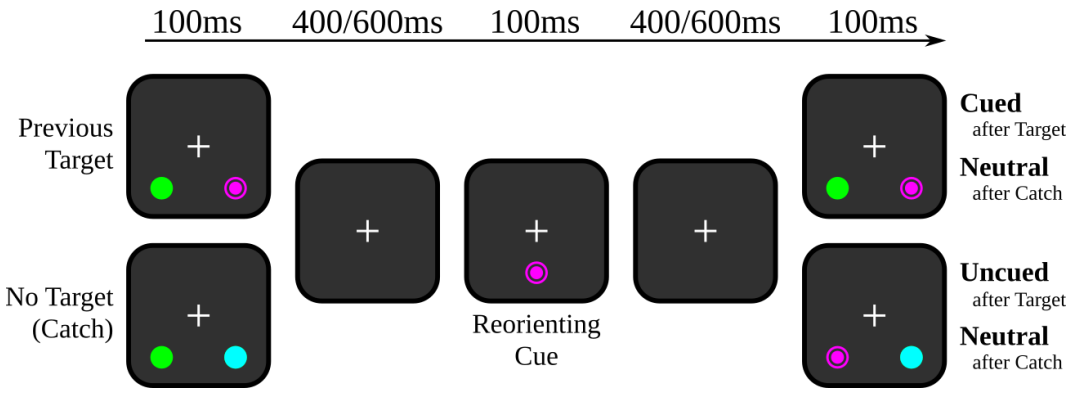

Figure 5.1: Diagram depicting the time-course of stimulus displays from the inhibition of return (IOR) task. In this example, the (pink) target is marked by an embossed edge. In cued trials, the target appears on the same side as the previous target, whereas it appears on the opposite side for uncued trials. In neutral trials, the target is preceded by a catch trial (no target present). IOR magnitude is defined as the difference between cued and uncued RTs.

5.2.2 IOR task

The study was a near replication of that employed by McDonald et al. (2008). The task was displayed using a 17" LED monitor at a viewing distance of 55cm, and was programmed using PsychoPy software (Peirce, 2007). A black, rather than white, background was utilised to prevent potential eye strain (hence the fixation cross was white). Coloured discs of different colours were presented in pairs, four degrees below and six degrees to the left and right of fixation. Discs were either pink, green, or blue, and were matched in luminance. These flashed for 100ms on the screen, and participants identified if their allocated target colour was on the left or the right side of the screen using arrows on a keyboard (*b* and *n* keys of a standard English keyboard, respectively). Participants used their index and middle finger of their left or right hand (counterbalanced between participants). The next stimulus pair appeared after 900, 1100, or 1300ms (randomised). In between the presentation of pairs, a target-coloured circle was presented for 100ms in the centre of the screen, underneath the fixation cross. This served to re-orient participants attention away from lateralised locations before the next stimuli appeared.

The combinations of coloured discs and their locations were presented in equal number, such that two-thirds of pairs contained a target disc. In the absence of the target colour, participants were not to respond (catch trial). Targets which appeared directly after a previous target in the same or opposite location were deemed as cued or uncued trials, respectively. Targets following catch trials were considered neutral trials. Cued, uncued, and neutral trials were presented in equal number, hence the

location of a previous targets did not predict the location of the next target. See Figure 5.1 for example trials including the timings of stimulus displays.

After completing 22 practice trials, participants were presented with a total of 1,026 trials separated in to 27 blocks (each block lasting ~45 seconds). Between blocks of trials, participants had self-paced short breaks, and were provided with a longer break half way through the task. The task was completed in 20-30 minutes, including breaks.

5.2.3 EEG Recording

During the IOR task, continuous EEG was recorded using 64 scalp electrodes mounted on an elasticated cap (international 10-20 system). Data were sampled at 512Hz using the BioSemi ActiveTwo system (BioSemi, Amsterdam, Netherlands). To measure vertical and horizontal eye movements, four electrodes were positioned above and below the right eye, and at the outer edges of each eye.

EEG signals were processed off-line using SPM12 software (Statistical Parametric Mapping, University College London). Recordings were down-sampled to 200Hz, re-referenced to the average of scalp electrodes, and high- and low-pass filtered at 0.1Hz and 40Hz, respectively. Data were segmented into epochs between -100 and 400ms, and baseline corrected from -100 to 0ms, relative the onset of the target display. Trials containing artefacts (any event at any electrode site exceeding 75μV) were removed from analyses, including at eye electrodes.

For each participant, epochs were averaged separately for each condition (cued, neutral, and uncued) and target location (left and right). ERPs were derived from posterior electrodes sites (P6/7, PO6/O7, P3/4, PO3/O4).

P1 and N1 were defined as the first positive and negative peaks of average waveforms from electrodes contralateral to the target side. The N2pc was defined as the peak positive difference between averaged waveforms ipsilateral and contralateral to the target location, occurring in a time window of 160-260ms following stimulus presentation. ERP amplitudes were measured as the average voltage in a window of 10ms for the P1, 10ms for the N1, and 20ms for the N2pc, around voltage peaks (cf. Luck, 2005). ERP latencies were measured as the time of peak ERP amplitude relative to the target onset time.

5.3 Results

Five participants' data were omitted from analyses: One participant had a high number of incorrect responses (3 times the interquartile range). Two participants

had ERPs that lacked discernible visual-evoked potentials, defined as a positive peak at posterior electrodes 70-140ms following stimulus presentation (Di Russo et al., 2002). Two participants did not meet the requirement of having at least 20 trials per condition following EEG artefact rejection.

The remaining participants made an average of 4.2% (SD = 3.1) errors. To ensure that results reflected cuing effects, incorrect trials, and those directly following an incorrect trial, were not included in analyses (cf. Poliakoff et al., 2003). Furthermore, RTs underwent an outlier removal procedure for each participant and condition (cf. Selst & Jolicoeur, 1994), which removed an average of 2.4% (SD=0.6) of trials. No participants' mean RTs or ERP latencies and amplitudes were above 1.5 times the interquartile range.

5.3.1 Replicating Previous Findings: ANOVAs

Figure 5.2 shows ERPs elicited by cued, neutral, and uncued targets. Note that the timing and topography of the N1 in our study was closer to that of the N2 observed in McDonald et al. (2008). Therefore, for comparison purposes, we focused analyses on P1 and N2pc ERPs, as they showed very similar latencies and topographies as in McDonald et al. (2008).

The ANOVA analyses (see Table 5.1) replicated the pattern of findings in McDonald et al. (2008). Relevant main effects and interactions were explored using paired t-tests (Bonferroni adjusted). For behavioural effects, uncued RTs (M = 385ms) were significantly faster than cued RTs (M = 409ms; $t(43) = 9.73$, $p < .001$, $d = 1.47$, two-tailed), and neutral RTs (M = 395ms; $t(43) = 3.04$, $p = .004$, $d = .458$). Cued RTs were significantly slower than neutral RTs ($t(43) = 4.43$, $p < 001$, $d = .668$); see Figure 5.3A. For the N2pc, uncued amplitudes (M = 2.15μV) were significantly larger than in cued (M = 1.76μV; $t(43) = 3.60$, $p = .001$, $d = .543$), but not neutral trials (M = 1.99μV; $t(43) = 1.93$, $p = .060$, $d = .291$); see Figure 5.3B.

Average percentage error rates were significantly higher in cued trials (M = 4.75, SD = 3.2) compared to uncued trials (M = 2.81, SD = 2.6); $t(43) = 5.25$, $p < .001$, $d = .791$, two-tailed. Therefore, a speed-accuracy trade-off was not apparent.

5.3.2 Relating Sensory and Attentional ERPs

As described above, results of ANOVAs revealed that N2pc amplitude was modulated by IOR. In order to test the hypothesis that early sensory processes may be related to this selective attention effect, we measured the relationship between P1 (latency and amplitude) and N2pc amplitude.

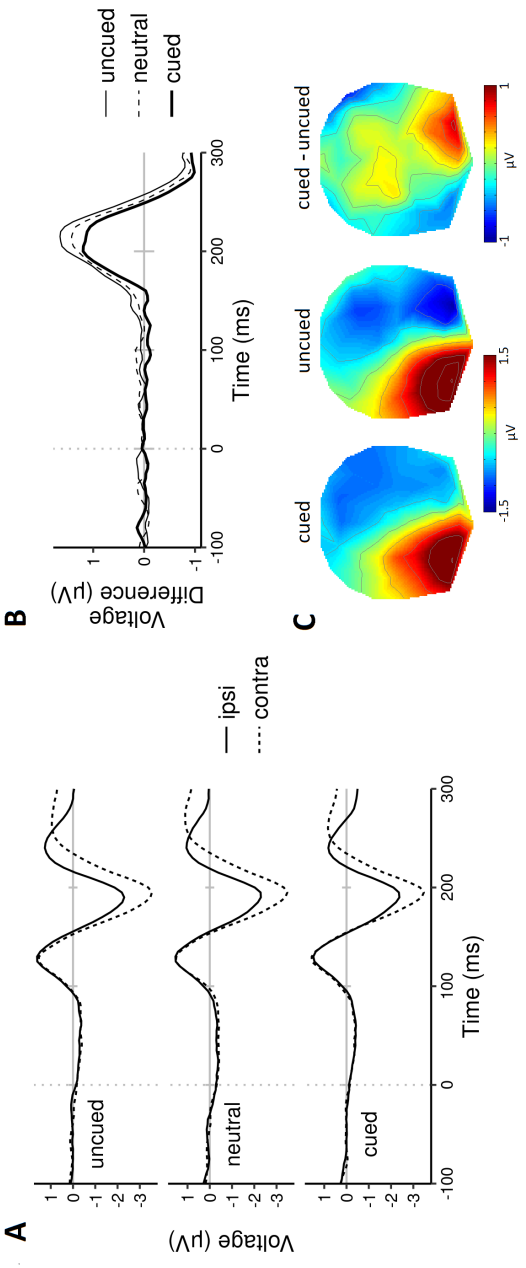

Figure 5.2: (A) Grand average ERPs from posterior electrodes elicited by targets in the same (cued) or opposite (uncued) location as the previous target, or following a non-target display (neutral trial). The first positive peaks of the contralateral wave is the P1 component. (B) The N2pc is the difference between the ipsilateral minus contralateral signals in each condition. The N2pc was larger in uncued trials compared to cued trials. (C) Scalp topographies of the grand average N2pc waveforms (200-220ms), corresponding to the waveforms in B. Cued and uncued topographies are calculated from target-left minus target-right differences.

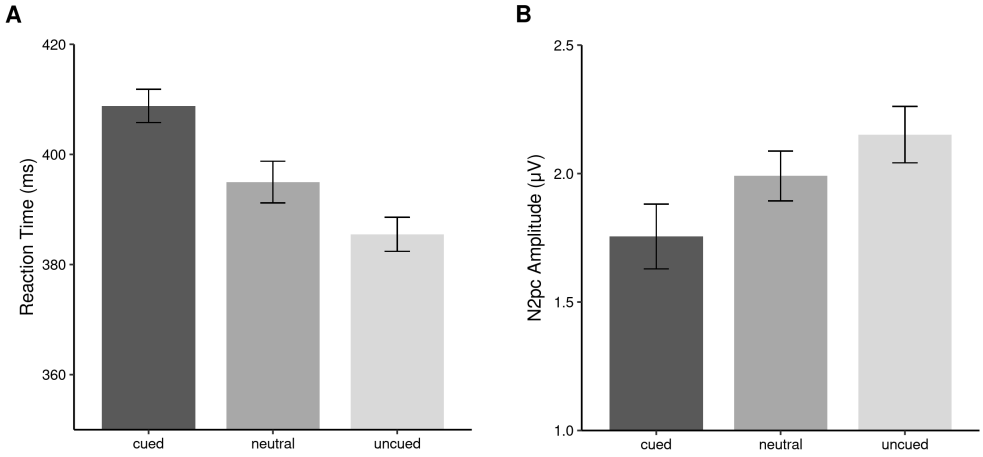

Figure 5.3: Inhibition of Return of reaction times (RTs) and N2pc amplitudes. (A) Faster uncued versus cued RTs; (B) larger uncued versus cued N2pc amplitudes. Error bars represent within-subject 95% confidence-intervals (cf. Cousineau, 2005).

Table 5.1: ANOVA results with reaction time (RT) and event-related potential (ERP) latencies and amplitudes as dependent variables. Condition had three levels (cued, neutral, and uncued) and target location had two levels (left and right).

			Latency			Amplitude		
Measure	Effect	*df*	F	η_p^2	*p*	F	η_p^2	*p*
RT	condition	2, 86	32.69	0.432	0.000*	-	-	-
	location	1, 43	18.89	0.305	0.000*	-	-	-
	cond. × loc.	2, 86	15.16	0.261	0.000*	-	-	-
P1	condition	2, 86	0.211	0.005	0.810	0.434	0.010	0.650
	location	1, 43	5.534	0.114	0.023	5.288	0.110	0.026*
	cond. × loc.	2, 86	0.449	0.010	0.640	1.055	0.024	0.353
N2pc	condition	2, 86	1.187	0.027	0.310	8.141	0.159	0.001*
	location	1, 43	0.053	0.001	0.819	4.562	0.096	0.038*
	cond. × loc.	2, 86	0.468	0.011	0.628	2.645	0.058	0.077

df = degrees of freedom, *p* = * statistical significance, η_p^2 = partial eta squared measure of effect size.

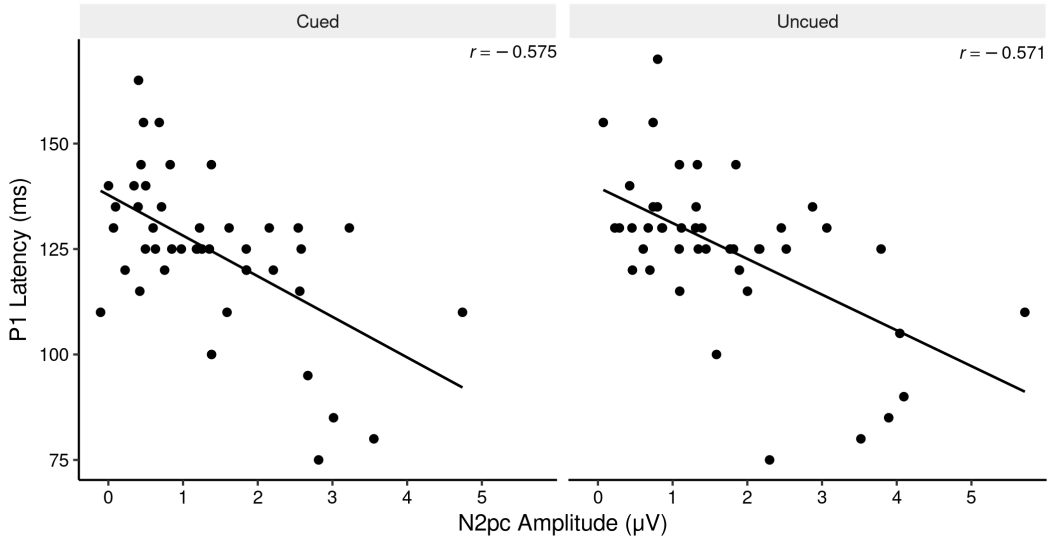

Figure 5.4: Early sensory processes are related to selective attention processes in the inhibition of return task (IOR). Scatter plots show the significant negative relationship between P1 latency and N2pc amplitude for both cued and uncued IOR conditions; earlier sensory orienting to the target is related to greater selective attention

Using separate Pearson's *r* correlation analyses for cued and uncued trial types, the P1 latency was negatively correlated with the N2pc amplitude for both cued trials ($r(42) = -.575$, $p < .001$, two-tailed) and uncued trials ($r(42) = -.571$, $p < .001$, two-tailed); see Figure 5.4. The Bonferroni-adjusted alpha value was $p < .025$. There were no statistically significant relationships between N2pc amplitude and P1 amplitude for cued ($p = .430$) or uncued ($p = .094$) trials.

5.3.3 Correlates of Cued and Uncued RTs

To observe the potentially multifaceted relationship between ERPs and behaviour, we used two-tailed Pearson's *r* correlation analyses with RTs, P1, and N2pc latencies and amplitudes as factors (separately for cued and uncued trial types). As such, the Bonferroni-adjusted alpha value was $p < .008$. Shorter N2pc latencies were related to faster uncued RTs; see Table 5.2. There were no significant ERP correlates of cued RTs. These results indicate that the timing of selective attention is related to behaviour (RTs) for uncued targets, but not for cued targets.

Table 5.2: Event-related potential (ERP) correlates of cued and uncued reaction times (RTs).

ERP		Cued RT		Uncued RT	
		r	*p*	*r*	*p*
P1	latency	0.260	0.088	0.326	0.031
	amplitude	0.070	0.654	-.005	0.972
N2pc	latency	0.198	0.198	0.492	0.001*
	amplitude	-.220	0.151	-.055	0.722

r = Pearson's correlation coefficient, *p** = statistical significance.

5.4 Discussion

In accordance with McDonald et al. (2008), our results suggest that IOR is related to selective attention (N2pc), rather than sensory orienting (P1) modulations. However, our additional analyses showed that faster sensory orienting was related to greater selective attention to targets (shorter P1 latency related to larger N2pc amplitude).

Two main implications emerge from this additional finding. Firstly, sensory processes may be involved in IOR, even when sensory stimulation is balanced across the display. This contributes to the long-standing debate surrounding whether IOR arises from the inhibition of sensory versus attentional mechanisms (Prime & Ward, 2004; McDonald, Ward & Kiehl, 1999). Our findings indicate that IOR originates from *both*—as argued by Berlucchi (2006) and originally by Posner and Cohen (1984).

Secondly, these findings indicate that the common approach to investigating IOR using ERPs may not be sensitive enough to detect smaller ERP modulations. It appears that the IOR task design by McDonald et al. (2008) reduced P1 effects enough to nullify significance in an ANOVA, but not to abolish them completely. Though the authors do admit that their analyses cannot completely rule out the involvement of other ERPs, they make no further investigations.

We also performed additional analyses to identify ERP correlates of cued and uncued targets independently. These indicated that faster selective attention to uncued targets was related to faster RTs (Kiss et al., 2008). This extends the typical ANOVA findings to show that IOR may be related to more than just N2pc amplitudes. The same effect was not apparent for cued RTs, which supports the notion that cued and uncued targets are processed differently, and should be analysed as such (Engelmann & Pessoa, 2007).

It should be noted that in the present study, the N1 ERP more closely resembled the N2 observed by McDonald et al. (2008). Therefore, we did not compare N1

ERPs between the two studies. This could be attributed to small variations in the size of the stimuli on the screen (Luck & Hillyard, 1994). However, this does not necessarily affect the comparability of the P1 and N2pc between tasks, as their latencies and topographies were very similar to those observed in McDonald et al. (2008). Furthermore, the tasks were identical in the key design features specified by McDonald et al. (2008) (i.e. balanced sensory stimulation).

Together, these findings indicate that IOR cannot necessarily be attributed to the modulation of a single ERP, but to more complex interactions of multiple processing stages. This has implications for EEG researchers investigating IOR itself, or investigating individual differences in IOR processes (e.g. psychological disorders). In their review, Martín-Arévalo et al. (2016) highlight how methodological differences between IOR tasks can yield different results. We expand on this idea, proposing that the choice of analysis technique is an equally important consideration.

In summary, we found that by only investigating cued versus uncued differences, ERP studies of IOR may oversimplify the processes involved. Therefore—guided by clear hypotheses—a range of analyses should be employed, such as investigating relationships between ERPs and behaviour and analysing cued and uncued targets separately.

Chapter 6

Striatal Dopamine in Attentional Inhibition: Too Much, Too Little, or Just Enough

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Abstract

Inhibition of Return (IOR) is a mechanism which biases the attention system away from previously-inspected stimuli—and is therefore thought to improve stimulus sampling efficiency from the environment. There is some evidence that 'too much' or 'too little' dopamine in the striatum of the brain is detrimental for IOR. However, there have been no IOR studies of the direct effects of dopamine depletion on healthy individuals, or the effect of both dopamine increases and decreases in the same individuals. Therefore, in the present study, we administered a selective D2 agonist and antagonist to the same healthy participants (cabergoline and amisulpride, respectively), and measured their IOR responses. We further investigated the effects of dopamine manipulations on the underlying cognitive processes of IOR using event-related potentials. Results showed that both increased and decreased striatal dopamine reduced the IOR effect relative to placebo. We propose that the drugs may have altered frontostriatal connections, causing extremes in attentional flexibility and stability to interfere with IOR. These results provide evidence for an 'inverted-U' relationship between striatal dopamine levels and IOR. More broadly, findings may help to improve the specificity of dopaminergic treatments for neuropsychological disorders.

6.1 Introduction

The ability to inhibit attention to irrelevant stimuli in the environment is crucial, as our brains receive more information than they can process (Awh, Armstrong & Moore, 2006; Bari & Robbins, 2013; MacLeod, 2007). The importance of this ability is highlighted by disorders in which it is disrupted, resulting in unwanted or inefficient cognitive processes—such as in Schizophrenia (Gut-Fayand et al., 2001), Parkinson's disease (Bronnick et al., 2006) and high trait impulsivity (Nigg, 2001). It is thought that the neurotransmitter dopamine is key for inhibitory processes (Chambers, Garavan & Bellgrove, 2009; Bari & Robbins, 2013). Hence in the present study, we investigate the role of dopamine in attentional inhibition in the form of IOR—a mechanism for the prioritisation of novel stimuli by the attention system (Klein, 2000; Lupiáñez et al., 2006).

IOR was first observed by Posner and Cohen (1984) as the delayed response to visual targets appearing in the same location as a previous cue, compared to a novel location. The effect is apparent for specific objects, even when moved in space (Tipper et al., 1991), acts over a spatial gradient strongest at the cued location itself (Samuel & Kat, 2003), and is significantly weaker when the initial context is altered (Klein & Macinnes, 1999). These features have led researchers to consider IOR as an adaptive mechanism, facilitating visual search by biasing attention away from locations that have already been inspected (Klein, 2000; Klein & Macinnes, 1999; Tipper et al., 1991).

Since its conception, researchers have studied the neural substrates of IOR, and have established a central role of the midbrain superior colliculus (Rafal et al., 1988; Sapir et al., 1999; Dorris et al., 2002). The superior colliculus is thought to generate inhibitory 'tags', which are then transmitted to frontal cortical brain regions to be maintained (Klein, 2000; Fecteau & Munoz, 2005). The superior colliculus is functionally linked to the basal ganglia in the striatum of the brain, wherein dopamine is generated (Ikemoto et al., 2015). As such, striatal dopamine signalling has been found to have functional relevance for IOR (Rokem et al., 2012; Colzato, van den Wildenberg, van Wouwe, Pannebakker & Hommel, 2009).

Converging lines of evidence support that higher levels of dopamine are beneficial for IOR. For example, administration of the dopamine agonist *d*-amphetamine increases the IOR response (Fillmore et al., 2005); Parkinson's disease patients show reduced IOR (Poliakoff et al., 2003), and have reduced dopamine levels in the striatum due to the loss of dopamine-generating neurons in the basal ganglia (Ikemoto et al., 2015). Additionally, carriers of the 9-repeat allele of the dopamine

transporter gene DAT1 have higher striatal dopamine levels than non-carriers, and show greater IOR responses (Colzato, Pratt & Hommel, 2010).

Furthermore, D2 receptors strongly implicate striatal dopamine in IOR, as D2 receptors are most abundant in the striatum of the brain (Cools & D'Esposito, 2011). For example, individuals with a history of cocaine abuse (Colzato & Hommel, 2009) and high trait-impulsivity (Bucker & Theeuwes, 2014) both have fewer D2 receptors, and show reduced IOR responses.

Other evidence suggests that the relationship between dopamine and IOR is not linear. For instance, patients with Schizophrenia exhibit delayed or blunted IOR responses, putatively caused by excessive D2 signalling (Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2007). Furthermore, Rokem et al. (2012) estimated baseline dopamine levels from DAT1 genotype, and administered the D2 agonist bromocriptine. They found that those with low baseline dopamine levels showed increased IOR on the drug, whereas those with a high baseline showed decreases (Rokem et al., 2012). Therefore, intermediate levels of striatal dopamine may be optimal for the IOR response. This non-linear relationship—termed an *inverted-U* function—has been observed for dopamine in other faculties, such as working memory and cognitive control (Mattay et al., 2000; Cools & D'Esposito, 2011).

However, the evidence for inverted-U effects of dopamine in IOR remains incomplete. Firstly, the effect of reduced striatal dopamine signalling on IOR has only been inferred from Parkinson's disease patients (Poliakoff et al., 2003). Parkinson's disease neuropathology originates in the anterior olfactory nuclei and lower brainstem regions, before affecting the dopaminergic neurons of the substantia nigra in the basal ganglia, and beyond (Ayano, 2016b). Therefore any effects of Parkinson's disease on IOR cannot be solely attributed to reductions in striatal dopamine. Furthermore, IOR was studied in Parkinson's disease patients taking various forms of dopaminergic medication, and suffering different degrees of motoric dysfunction (Poliakoff et al., 2003)—which may have contributed to effects.

Secondly, the dopamine agonists used in previous studies (*d*-amphetamine and bromocriptine) have non-selective effects on dopaminergic, adrenergic, and serotonergic systems (Millan et al., 2002; Heal et al., 2013). Consequently, their effects on IOR may (at least in part) be the result of non-striatal dopamine, or other neurotransmitters.

Therefore in the present study, we investigate the direct, causal effects of both increased and decreased dopamine signalling on IOR. To target the striatum, we utilise drugs with a high affinity for D2 receptors—the agonist *cabergoline*, commonly

used in the treatment of Parkinsin's disease and prolactinoma (Gerlach et al., 2003; Nunes, El Dib, Boguszewski & Nogueira, 2011; Odin et al., 2006); and the antagonist *amisulpride*, a second-generation atypical antipsychotic medication (Di Giovanni, Di Mascio, Di Matteo & Esposito, 1998; Correll, Leucht & Kane, 2004).

To gain a deeper understanding of cognitive processes underlying IOR, researchers use ERPs from EEG. For example, it has been shown that the ERP P1 is smaller for cued targets compared to uncued (McDonald, Ward & Kiehl, 1999; Satel et al., 2013). Other studies (including from our own lab; Chapter 5) have shown smaller N2pc amplitudes for cued compared to uncued targets (McDonald et al., 2008). As P1 and N2pc are considered markers of sensory orienting and selective attention, respectively (Kiss et al., 2008)—IOR has been attributed to modulations in both. (see Martín-Arévalo et al., 2016, for a review).

How might striatal dopamine modulations affect these IOR processes? ERP studies of patients with Schizophrenia show that high levels of striatal dopamine can negatively affect attentional suppression of stimuli (Clementz, Geyer & Braff, 1997; Ward et al., 1996). However, this was observed through reductions in P50 amplitudes in an acoustic prepulse inhibition task, hence it is difficult to extrapolate these findings to IOR (Clementz et al., 1997; Ward et al., 1996). Additionally, patients with Schizophrenia show reduced sensory orienting (P1) to novel stimuli during an auditory oddball task (Ward et al., 1991). This indicates that excessive dopamine may reduce sensory processing of novel stimuli, resulting in reduced P1 amplitudes for uncued targets.

Regarding reduced dopamine, administration of the D2 antagonist *haloperidol* reduced the magnitude of selective attention ERPs to auditory tones (Ahveninen & Ka, 2000). Therefore, reduced striatal dopamine signalling may cause reductions in N2pc amplitudes in an IOR task. However, it is unclear how cued and uncued targets may be differently affected. Furthermore, other studies have shown that dopamine modulations affect the switching of attention from one stimulus to another (Agnoli, Mainolfi, Invernizzi & Carli, 2013). In an IOR task, attention switching could be measured via the *Pd*—an ERP which reflects the termination of attention, allowing attention to be switched (Sawaki et al., 2012; Eimer, 2009).

These studies indicate that striatal dopamine modulations are likely to affect sensory orienting, selective attention, and/or attention termination in IOR. However, it is unclear precisely how stages would be affected, and if cued and uncued targets would be affected differently. Therefore, in the present study, we use a combination of dopamine manipulations and EEG imaging to measure IOR in healthy individuals. The ERPs P1, N2pc, and Pd are used to investigate three key stages of attentional

processing in IOR. This allows us to observe the *direct* effects of striatal dopamine on the main processing stages.

Spontaneous EBRs can be used as an indirect measure of striatal dopamine (i.e. individuals blink more when striatal dopamine levels are higher) (Jongkees & Colzato, 2016). This has been shown for baseline dopamine levels (Kowal, Colzato & Hommel, 2011; Agostino et al., 2008; Zhang, Mou et al., 2015), and the effects of pharmacological manipulations (Depue, Luciana, Arbisi, Collins & Leon, 1994; Blin et al., 1990; Kleven & Koek, 1996). However, studies measuring the effect of *reduced* dopamine on EBR have mostly been conducted in patients with Schizophrenia (Karson, Freed, Kleinman & Bigelow, 1981; Adamson, 1994; Kleinman et al., 1984; Mackert, Woyth, Flechtner & Frick, 1988). Therefore, the value of measuring EBR in the present study is twofold—as a non-invasive outcome measure of striatal dopamine manipulations, and to demonstrate the effect of a highly D2-selective antagonist on EBR in healthy individuals.

In summary, there is evidence that dopamine is important for IOR. However, questions remain regarding (1) the direct effect of decreased dopamine, (2) the specificity of striatal involvement, and (3) the processing stages involved. The present study aims to investigate these issues by measuring IOR with (1) a dopamine antagonist (as well as agonist), (2) drugs with a high affinity for D2 receptors, and (3) EEG brain imaging. Furthermore, spontaneous EBR will be employed as a novel outcome measure for these pharmacological manipulations.

We hypothesise that the size of the IOR response may show an inverted-U relationship (greatest IOR in the placebo condition), or increase linearly with striatal dopamine level (greatest IOR in the agonist condition, smallest IOR in the antagonist condition). Certain stages of processing may be affected by dopamine modulations, i.e. sensory orienting (P1), selective attention (N2pc), and/or attention termination (Pd).

6.2 Method

6.2.1 Design

A double-blind, placebo-controlled, repeated-measures, triple-crossover design was employed. Across three visits—each separated by at least one week—participants were orally administered either cabergoline (1.25mg), amisulpride (400mg), or placebo (inactive sugar pill). Each visit consisted of identical procedures, outlined in the procedures section (6.2.4).

The study was approved by the University of Manchester Research Ethics

Committee, and was further approved by the UK Health Research Authority for the use of a National Health Service site (Salford Royal Hospital).

6.2.2 Recruitment and Screening

Individuals were recruited via university email announcements, public study participation websites, and printed posters around the University of Manchester. In order to avoid recruiting individuals extremely high or low in trait impulsivity, prospective participants completed an online version of the Barratt Impulsiveness Scale (BIS-11, Patton & Stanford, 1995). Participants were then further health-screened in person by a clinician. See supplementary materials (6.5) for further details of the screening procedures.

The sample size was established using a power analysis based on the effect size of a previous study from our lab, which identified clear behavioural and ERP effects using the same task (Chapter 5, $d = 1.38$). The analysis was conducted using the R package 'pwr' (Champely, 2015), and calculated that a minimum of 9 participants would be necessary to obtain a significant IOR effect with 80% certainty ($p < .05$). However, the present study utilises three dopamine manipulation conditions. Therefore, the value was multiplied by three to give a minimum of 27 participants. There have only been two previous dopamine manipulation studies of IOR: Rokem et al. (2012), which had 21 participants; and Fillmore and Vogel-Sprott (2000), which had 14. However, neither of these studies reported effect sizes, utilised a target-target paradigm, measured EEG, or included three within-subjects conditions. As such, a more detailed power analysis could not be conducted.

6.2.3 Participants

Thirty-one participants were deemed eligible to participate in the full study (2 left-handed; 16 female; mean age 22.4 years; standard deviation 3.2 years). All participants gave written informed consent, and received financial compensation for their participation.

6.2.4 Procedures

Behavioural

Both of the active drugs reach peak plasma levels around two hours following oral administration (Mauri et al., 2014; Del Dotto & Bonuccelli, 2003). Therefore, following drug administration, participants remained in a neutral environment for

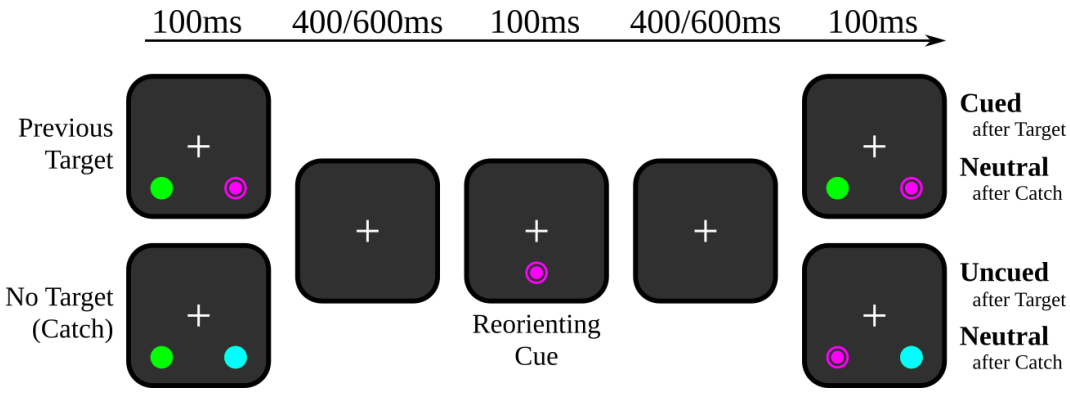

Figure 6.1: Schematic diagram of example trials from the inhibition of return task; the (pink) target is marked by an embossed edge. In the first display, participants identify if the target is on the left or the right of the screen, followed by an attention re-orienting target flash. The next target then appears either in the same location as the previous target (cued trial) or the opposite location (uncued trial). In neutral trials, the target is preceded by a catch trial (no target present).

two hours before testing procedures began. During this time, EEG scalp electrodes were connected.

Spontaneous eye blinks were then measured for nine minutes. During this time, participants were asked to rest (without closing their eyes) whilst the EEG electrodes recorded their 'resting activity'. Participants then completed the computerised IOR task described below.

The IOR task was adapted from McDonald et al. (2008). It was programmed using PsychoPy software (Peirce, 2007) and presented using a 17" LED monitor. Pairs of coloured discs were presented sequentially on a black screen, four degrees below and six degrees to the left and right of a central fixation cross, at a viewing distance of 55cm. Participants were instructed to maintain fixation at the central cross throughout the task. Discs were either pink, green, or blue, and were visually matched in size and luminance. Following the presentation of disc pairs, a single target-coloured disc was presented beneath the fixation cross. This served to disengage the participants attention from a lateralised location (McDonald et al., 2008). See Figure 6.1 for a schematic diagram depicting the timings of stimulus presentations.

Participants were assigned a target disc colour and were asked to identify if the target appeared on the left or right side of the screen using their index and middle finger of their dominant hand (left and right keys were *b* and *n* keys of a standard English keyboard). The target colour remained consistent during the visit, but was counterbalanced across study visits. Possible combinations of colour pairs were presented in equal numbers, hence two thirds of trials contained a target disc.

Coloured discs were presented equally often on the left or the right side of the screen. Participants were instructed not to respond in the absence of the target colour (catch trials). If the target disc appeared in the same or opposite location to a directly preceding target, the trial was considered cued or uncued, respectively (Figure 6.1). Cued and uncued trials were represented equally such that the target location did not predict that of a subsequent trial. After completing 22 practice trials, participants were presented with a total of 1,026 trials separated in to 27 blocks (each lasting for ~45 seconds). Between blocks of trials, participants took self-paced short breaks, and were provided with a longer break half way through the task. The task was completed in 20-30 minutes including explanation, practice, and breaks.

Electrophysiological

EEG was recorded using sixty-four *Easycap* scalp electrodes (easycap.de), at a sampling rate of 1000Hz, and amplified by a *Brainvision BrainAmp DC plus MR* amplifier. Before ERP extractions, EEG recordings were preprocessed off-line; electrodes were re-referenced to a whole-scalp reference, low-pass filtered at 40Hz, downsampled to 200Hz, and then high-pass filtered at 0.1Hz. ERP epochs were then defined as -100ms to 400ms relative to the onset of the target display, were averaged, and baseline-corrected relative to the 100ms pre-stimulus time window. Trials contaminated by artefacts (including eye-blinks/movements) were excluded from analyses, detected as a events recorded at any of the electrode channels exceeding 75μV relative to the pre-stimulus baseline. Incorrect trials (and trials directly following an incorrect response) were excluded from analyses.

Average P1, N2pc, and Pd mean latencies and amplitudes were obtained for each participant in each condition (cued, uncued, and neutral) and for each target location (left and right). P1 and was defined as the first positive peaks of the signal, occurring across posterior electrodes contralateral to the target location (electrodes P6/7, PO6/O7, P3/4, PO3/O4). N2pc and Pd were measured at the aforementioned posterior electrode sites, and as the peak difference between signals ipsilateral and contralateral to the target location, occurring in a time window of 160-260ms (N2pc) and 260-400ms (Pd) post stimulus onset. The mean amplitude values of P1, N2pc, and Pd were quantified as the average voltages 10ms, 20ms, and 30ms either side of the ERP peaks, respectively (Luck & Hillyard, 1994). ERP latencies were measured as the time of peak ERP amplitude relative to the target onset.

6.2.5 Analyses

Blink rate

Using frontal EEG electrodes, individual blinks were quantified using independent component analysis of continuous EEG recordings downsampled to 200Hz and filtered offline. A value of blinks-per-minute was calculated for each participant and visit (i.e. EBR). Contrast analyses were employed to test for the predicted linear relationship between dopamine manipulation and EBR.

Behavioural

For each dopamine manipulation (agonist, antagonist, placebo) the presence of IOR was established by a positive value for mean cued minus uncued responses. For each participant and each dopamine manipulation, a value of IOR magnitude was calculated as mean cued minus mean uncued RTs, such that a larger value represented a greater IOR response.

To assess the impact of dopamine manipulation on IOR magnitude, within-subjects contrast analyses were conducted to test for a linear relationship between dopamine and IOR (highest IOR in the agonist condition, lowest in the antagonist condition), versus a polynomial relationship. If a polynomial relationship was found, a further ANOVA was conducted to establish the nature of the relationship (i.e. inverted-U).

To further analyse how the dopamine manipulations affected mean cued and uncued RTs, a two-way repeated-measures ANOVA compared RTs in the different dopamine manipulations (agonist, antagonist, and placebo), and IOR task conditions (cued, uncued). For multiple pairwise comparisons, alpha values were Bonferroni adjusted.

Electrophysiological

ERP analyses followed that of RT data, using separate analyses for the latency and amplitude of each ERP (N2pc, P1, and Pd); to identify the potential involvement of ERPs in behavioural the effects, cued minus uncued ERP latencies and amplitudes were calculated (as in behavioural IOR magnitude). Contrast analyses were conducted to find linear versus curvilinear relationships between dopamine manipulation and ERP latency/amplitude (depending on the pattern seen in behavioural results). Cued and uncued ERP latencies and amplitudes were separately explored using two-way repeated-measures ANOVAs. For multiple pairwise comparisons, alpha values were Bonferroni adjusted.

Further analyses were guided by behavioural findings, using linear regression analyses to find which ERP(s) best related to notable behavioural effects. Cued and uncued trials were treated separately to account for potential differences in their processing.

6.3 Results

One participant experienced an adverse reaction to amisulpride, and consequently withdrew before completing the study. Another participant withdrew before completing all three sessions. Therefore the remaining data from these two participants were not included in analyses.

6.3.1 Eye blink rate

One participant showed an EBR rate more than 1.5 times higher than the interquartile range for the antagonist group, and was therefore removed from the EBR analysis. There was a significant linear relationship between dopamine level and EBR; lowest, medium, and highest EBR rates were found in the antagonist, placebo, and agonist conditions, respectively; $F(1, 27) = 7.242$, $p < .05$, $\eta p^2 = .211$; see Figure 6.2. There was no significant curvilinear relationship between EBR and dopamine manipulation ($p = .926$). This demonstrates that in the present study, amisulpride and cabergoline decreased and increased striatal dopamine, respectively.

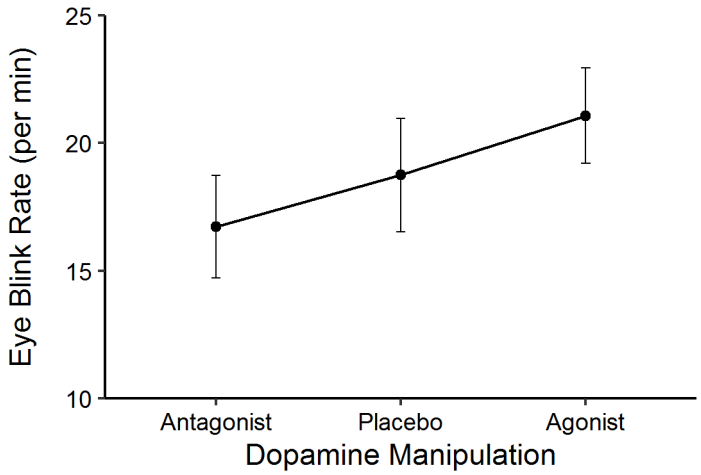

Figure 6.2: Striatal dopamine reduction using a D2 antagonist (amisulpride) reduced spontaneous eye blink rates, whereas a dopamine agonist (cabergoline) increased EBRs, relative to placebo. Hence dopamine level is positively related to EBR using these drugs. Error bars represent within-subject 95% confidence-intervals (cf. Cousineau, 2005).

6.3.2 Behavioural

One participants' placebo IOR scores were not saved due to computer error. Therefore, their data were not included in further analyses. The remaining twenty-eight participants had a mean incorrect response rate of 3.7% (SD = 1.5). RTs underwent an outlier removal procedure (cf. Selst & Jolicoeur, 1994), which removed an average of 2.2% (SD=0.7) of trials from each participants responses in each visit. All three conditions produced positive differences between mean cued minus uncued values.

Using a three-way ANOVA, there was a significant main effect of drug on IOR task condition; $F(2,54) = 5.92$, $p < .05$, $\eta p^2 = .180$. Tests of simple effects demonstrate that both the agonist (M =344ms; $t(27) = 3.30$, $p = .003$, $d = .624$) and antagonist (M = 342ms; $t(27) = 2.65$, $p = .013$, $d = .501$) significantly decreased RTs compared to placebo (M = 354ms). There was no significant difference between agonist and antagonist RTs ($p = .644$). The main effect of IOR condition was significant; $F(1, 27) = 27.70$, $p < .001$, $\eta p^2 = .506$. Tests of simple effects revealed that across dopamine manipulations, cued RTs (M = 356ms) were significantly slower than uncued RTs (M = 337ms); $t(27) = 5.26$, $p < .001$, $d = .994$ (i.e. the IOR effect).

The interaction between dopamine manipulation and IOR condition was significant; $F(2, 54) = 6.29$, $p <.05$, $\eta p^2 = .189$. Planned tests of simple effects determined that cued RTs were significantly faster in the agonist (M = 353; $t(27) = 3.94$, $p = .001$, $d = .745$) and antagonist (M = 349; $t(27) = 3.33$, $p = .003$, $d = .629$) manipulations compared to placebo (M = 366ms). There was no significant difference between agonist and antagonist cued RTs ($p = .415$). There were no significant differences in uncued RTs between dopamine manipulations: Agonist vs. placebo, $p = .025$ (Bonferroni adjusted $p < .017$); antagonist vs. placebo, $p = .090$; agonist vs. antagonist, $p = .950$. See Figure 6.3.

In order to assess the possibility of a speed-accuracy trade-off, a repeated measures ANOVA was conducted using percentage accuracy rates for the different IOR conditions (cued and uncued) and dopamine manipulations (agonist, antagonist, and placebo). See Table 6.1 for descriptive statistics. None of the main effects or the interaction were significant (see Table 6.2). As such, no speed-accuracy trade-off was apparent.

Cued minus uncued RTs provided a measure of IOR magnitude. There was a significant quadratic relationship between IOR magnitude and dopamine manipulation; $F(1, 27) = 8.59$, $p = .007$, $\eta p^2 = .241$. There was no linear relationship between variables ($p = .138$). To investigate the non-linear effect of dopamine manipulation on IOR magnitude, a one-way ANOVA was utilised with three levels; antagonist,

Table 6.1: Mean percentage incorrect rates and standard deviations (SDs) for all conditions.

	Cued		Uncued	
	Mean	SD	Mean	SD
Antagonist	4.30	2.1	3.90	2.7
Placebo	5.06	4.2	3.44	2.4
Agonist	4.18	2.2	3.69	2.1

Table 6.2: Results of ANOVA comparing percentage incorrect rates for each inhibition of return condition and dopamine manipulation.

	df	F	*p*	η_p^2
Drug	2,54	0.170	.844	.006
Condition	1,27	3.465	.074	.114
Drug × Cond.	2,54	1.815	.173	.063

df = degrees of freedom, η_p^2 = partial eta squared

agonist, and placebo. The main effect was significant; F(2,54) = 6.29, p = .003, ηp^2 = .189. T-tests of simple effects identified that the dopamine agonist (M = 17.9); t(27) = 2.37, p = .025, d = .448; and antagonist (M = 14.9); t(27) = 2.96, p = .006, d = .559. both showed smaller IOR magnitudes compared to placebo (M = 22.9). Therefore, results demonstrate an inverted-U relationship between dopamine level and IOR magnitude.

A one-way ANOVA was performed to test the effect of dopamine manipulations on mean RTs in neutral trials. This was to establish if there was a significant shift in participant's baseline RTs which should be accounted for when interpreting the above findings. However, neutral RTs did not differ between placebo (M = 353, SD = 35), agonist (M = 351, SD =37), and antagonist (M = 352, SD = 37); F(2,54) = .107, p = .899, ηp^2 = .004.

6.3.3 ERPs

The data from three more participants were omitted from ERP analyses (as well as the aforementioned three participants). This was due to the lack of discernible visual-evoked potential in averaged waveforms, defined as a prominent positive peak at posterior electrodes between 70-140ms following stimulus presentation (cf. Di Russo et al., 2002).

For the remaining twenty-five participants, see Figure 6.4 for ERPs obtained

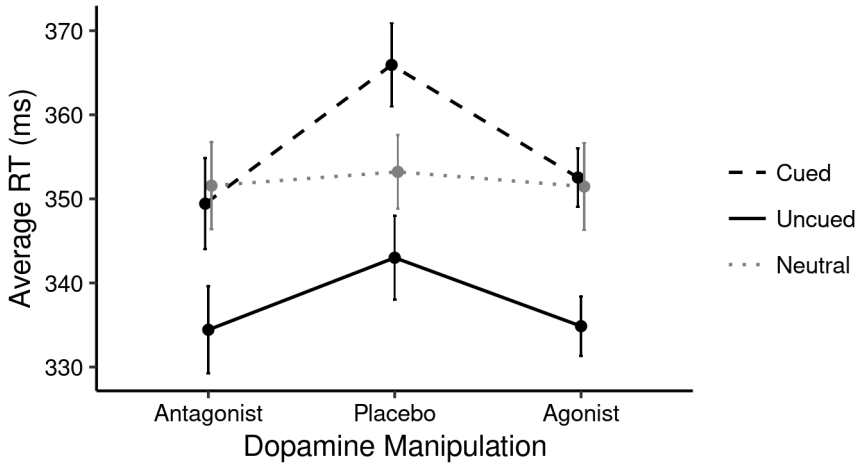

Figure 6.3: Changes in striatal dopamine (increase and decrease with D2 agonist and antagonist, respectively) reduce cued reaction times; the reduction in inhibition of return magnitude seen for both drugs is primarily due to the speeding of cued RTs relative to placebo. Neutral trials do not differ between conditions. Error bars represent within-subject 95% confidence-intervals (cf. Cousineau, 2005).

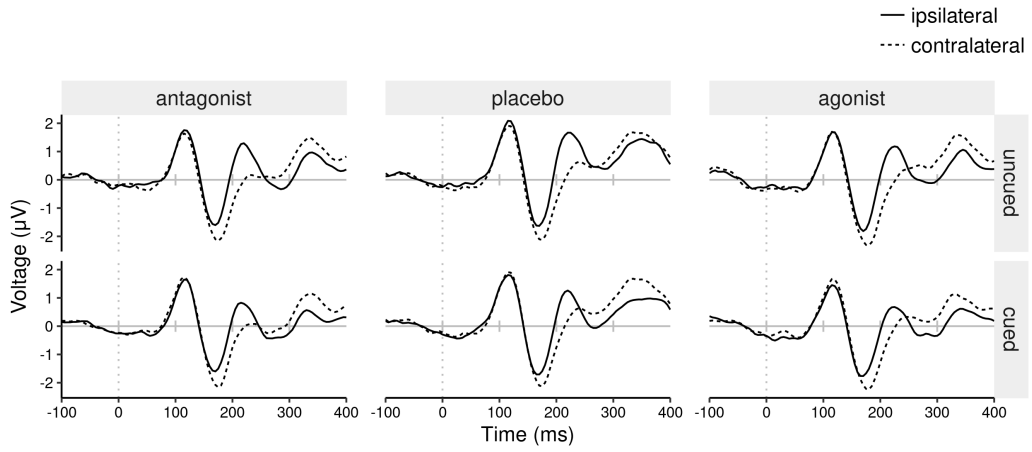

Figure 6.4: Event-related potential (ERP) waveforms elicited by target displays of the inhibition of return (IOR) task. Signals were averaged from posterior electrode sites (P6/7, PO6/O7, P3/4, PO3/O4) contralateral and ipsilateral to the target location for each dopamine manipulation and task condition. No single ERP shows significant differences between dopamine manipulations. P1 was derived from the contralateral waveform, the N2pc and Pd were derived from the ipsilateral minus contralateral waveforms.

Table 6.3: Contrast analyses of the relationship between dopamine manipulation (antagonist, placebo, agonist) and event-related potentials (ERPs).

ERP		Contrast	F	*p*
N2pc	amplitude	Linear	0.709	0.408
		Quadratic	0.086	0.771
N2pc	latency	Linear	0.002	0.964
		Quadratic	0.069	0.795
P1	amplitude	Linear	0.058	0.812
		Quadratic	0.232	0.634
P1	latency	Linear	2.667	0.116
		Quadratic	0.540	0.469
Pd	amplitude	Linear	1.191	0.286
		Quadratic	1.347	0.257
Pd	latency	Linear	1.622	0.215
		Quadratic	1.692	0.206

degrees of freedom = 1,24

for each task condition. No cued minus uncued ERP latency or amplitude showed significant quadratic relationships with dopamine manipulation (see Table 6.3).

See Table 6.4 for results of two-way ANOVAs; the significant main effect of IOR condition on N2pc amplitude was further explored using pairwise comparisons. N2pc amplitude was significantly larger in the uncued IOR condition (M = 1.63μV) compared to the cued condition (M = 1.30μV); $t(24) = 2.86$, $p = .009$, $d = .540$; see Figure 6.5. This demonstrates that selective attention was stronger for uncued targets compared to cued targets.

No other main effects or interactions reached statistical significance. These null ANOVA results may indicate that the effects of the drugs on IOR may be different for cued versus uncued ERPs, or involve more than a single ERP latency/amplitude.

As behavioural results demonstrated that cued RTs changed significantly under both drugs, further analyses focused on cued responses; the *agonist effect* was quantified as mean cued placebo RTs minus cued agonist RTs for each participant. The *antagonist effect* was quantified as mean cued placebo RTs minus cued antagonist RTs for each participant. Agonist and antagonist effects were also quantified in the same manner for each ERPs latencies and amplitudes.

One participant showed a behavioural antagonist effect more than 1.5 times lower than the interquartile range, and therefore their data were not included in

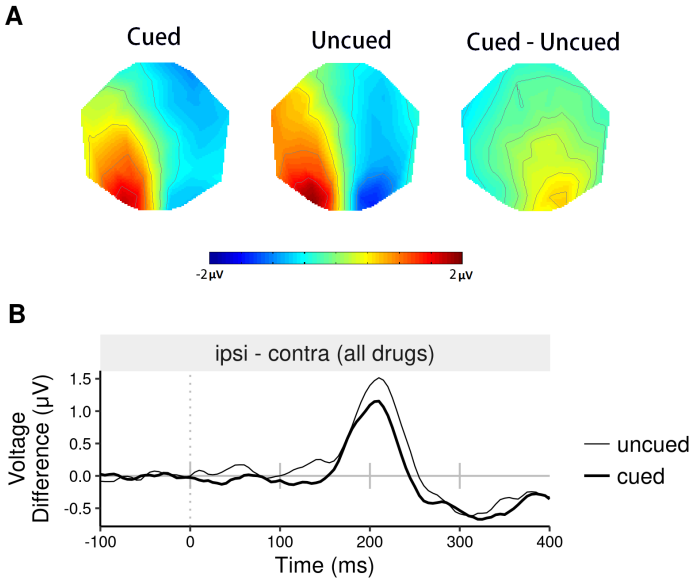

Figure 6.5: The N2pc was significantly larger in uncued versus cued IOR trials. Graph shows N2pc difference waves from cued and uncued IOR task conditions, averaged across dopamine manipulations. (A) Topographical maps of the N2pc, obtained from left-side minus right-side target locations for cued and uncued trials. (B) ERP plots of N2pc difference waves derived from electrodes ipsilateral minus contralateral to the target.

analyses of the antagonist effect. No outliers were identified for the behavioural agonist effect.

The behavioural agonist effect was related to changes in N2pc amplitude; $F(1, 24) = 9.709$, $p = .005$, $R^2 = .297$. All other ERPs were excluded from the model. This indicated that faster cued RTs in the agonist condition were related to larger N2pc amplitudes relative to placebo (see Figure 6.6). No ERPs were significant predictors of the antagonist effect.

Table 6.4: ANOVA results analysing the effect of dopamine drug condition (antagonist, placebo, agonist) and inhibition of return task condition (cued, uncued) on event-related potential (ERP) latencies and amplitudes.

ERP		Effect	*df*	F	η_p^2	*p*
N2pc	amplitude	drug	2, 48	0.234	0.010	0.792
		condition	1, 24	8.162	0.254	0.009*
		drug × condition	2, 48	0.377	0.015	0.688
N2pc	latency	drug	2, 48	1.180	0.047	0.316
		condition	1, 24	0.923	0.037	0.346
		drug × condition	2, 48	0.032	0.001	0.968
P1	amplitude	drug	2, 48	0.700	0.028	0.502
		condition	1, 24	0.107	0.004	0.747
		drug × condition	2, 48	0.142	0.006	0.868
P1	latency	drug	2, 48	0.953	0.040	0.393
		condition	1, 24	0.162	0.007	0.691
		drug × condition	2, 48	1.647	0.067	0.204
Pd	amplitude	drug	2, 48	0.207	0.009	0.814
		condition	1, 24	0.158	0.007	0.695
		drug × condition	2, 48	1.257	0.050	0.294
Pd	latency	drug	2, 48	1.859	0.072	0.167
		condition	1, 24	1.356	0.053	0.256
		drug × condition	2, 48	1.649	0.064	0.203

df = degrees of freedom, *p* = * statistical significance <.05, η_p^2 = partial eta squared measure of effect size.

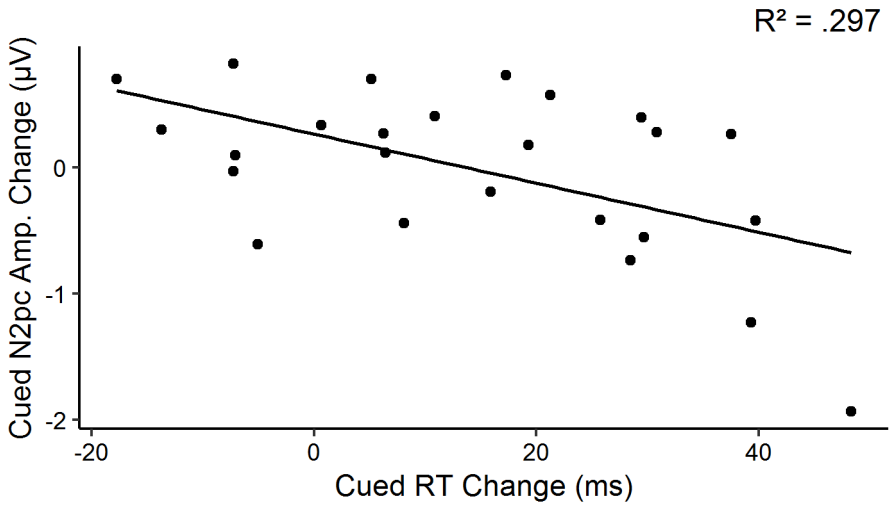

Figure 6.6: Faster reaction times to cued targets were related to larger N2pc amplitudes following D2 agonist administration, indicating increased selective attention to cued locations.

6.4 Discussion

In this study, we investigated the role of striatal dopamine in the attentional mechanism IOR. To achieve this, we manipulated striatal dopamine signalling pharmacologically, and measured the effects on behaviour and cognitive processes using ERPs. EBR was used to verify the effects of drugs on striatal dopamine.

6.4.1 Spontaneous EBR

EBR was highest in the D2 agonist condition, and lowest in the D2 antagonist condition. EBR rates are thought to be directly linked to striatal dopamine levels (Karson, 1983; Kleven & Koek, 1996; Kowal et al., 2011; Agostino et al., 2008; Zhang, Mou et al., 2015). Therefore, our results indicate that the D2 agonist and antagonist successfully increased and decreased striatal dopamine, respectively (relative to placebo).

6.4.2 Behavioural Effects

Our results show that both the D2 agonist and antagonist reduced the IOR effect, relative to placebo. This supports an inverted-U function of striatal dopamine in IOR, with intermediate levels of dopamine producing optimal effects. Furthermore, we demonstrate the particular involvement of striatal dopamine signalling, by the use of highly D2-selective drugs—cabergoline and amisulpride (Odin et al., 2006; Correll et al., 2004).

This is in line with previous findings that over or under-signalling of striatal dopamine reduces IOR, such as in individuals with a history of cocaine abuse (Colzato & Hommel, 2009); patients with Schizophrenia (Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2007); and Parkinson's disease patients (Poliakoff et al., 2003). The results are also consistent with Rokem et al. (2012), who found that the D2 agonist bromocriptine reduced or increased IOR in those with a high or low baseline of striatal dopamine level, respectively.

The present study extends previous findings by showing the direct effects of reduced dopamine signalling on IOR, thus demonstrating three points of the inverted-U within the same participant group. Furthermore, we analysed the effects of drugs on cued versus uncued trials separately and found that both the D2 agonist and antagonist reduced cued RTs compared to placebo.

There was no statistically significant effect of the drugs on uncued RTs. However, it should be noted that the effect of the agonist on uncued RTs approached statistical significance. Indeed, it is possible that uncued RTs were prevented from

speeding further due to the limitations of human response speeds (i.e. a floor effect). Consequently, it is difficult to conclude if too much or too little striatal dopamine may solely reduce *inhibition* of previously-attended visual locations, or speed cued and uncued RTs alike. In order to investigate this potential floor effect, a slower IOR task may be utilised to produce slower mean RTs, thus providing greater scope to observe changes in response speeds to uncued targets.

6.4.3 ERP Effects

In general, we found larger N2pc amplitudes for uncued versus cued targets, irrespective of dopamine manipulation. This reproduces findings in other studies using the same task (McDonald et al., 2008), and demonstrates that selective attention is modulated alongside the behavioural IOR response.

However, striatal dopamine manipulations did not significantly affect the difference between cued and uncued N2pc amplitudes or latencies, or that of P1 and Pd. This indicates that drugs may have affected cued and uncued target processing differently, and/or affected multiple stages of processing in IOR.

Therefore, to account for such complexity, we investigated the potential relationships between how drugs affected RTs and cognitive processes. We found that faster RTs to cued targets in the D2 agonist condition were related to increased N2pc amplitudes. In other words, increased striatal dopamine was related to increased selective attention to cued targets (Kiss et al., 2008). This suggests that the D2 agonist reduced inhibition of cued targets, allowing attention to be captured more strongly—thus speeding RTs and reducing overall IOR.

There were no ERP correlates of the behavioural D2 antagonist effect. This could be attributed to several factors. For instance, other decision-making or motoric processes may have contributed to the behavioural effects (which were outside of the measures taken in the present study). Furthermore, the drug may have subtle effects on several processing stages, rather than larger effects on certain stages—making identification of effects more difficult.

Nevertheless, these findings indicate that both drugs had similar effects on behaviour (i.e. faster cued RTs)—yet their effects on cognitive processes may have differed; the agonist effect was related to changes in selective attention, whereas the antagonist effect was not. Below, we outline potential neurobiological explanations for how excessive or insufficient dopamine may affect the processing of cued targets.

6.4.4 Neurobiological Explanations

Dopamine is proposed to have different—even competing—roles in the striatum of the brain versus the prefrontal cortex (Cools & D'Esposito, 2011); Prefrontal cortex stimulation via D1 receptors stabilises attention and provides resistance to distraction, whereas striatal D2 encourages cognitive flexibility (Durstewitz, Seamans & Sejnowski, 2000; van Holstein et al., 2011). The relative balance of prefrontal cortex versus striatal dopamine signalling is mediated by reciprocal frontostriatal connections (Morris et al., 2016; Alexander, DeLong & Strick, 1986). This allows individuals to both maintain stable task goals, whilst preserving the ability to shift attention and update strategies (Cools et al., 2008; Cools & D'Esposito, 2011).

IOR may be considered a mechanisms of flexibility, as it promotes the inspection of novel stimuli in the environment (Klein, 2000; Colzato, Pratt & Hommel, 2010). Hence decreased striatal dopamine signalling by the D2 antagonist amisulpride may reduce IOR by biasing the frontostriatal system away from flexibility. A more stable system may emphasise the maintenance of inhibitory tags for IOR, preventing attention disengagement. Attention disengagement is thought to be key for the IOR effect (Klein, 2000), and a lack of disengagement may result in more facilitation effects of the cued location (Colzato, Pratt & Hommel, 2010). Alternatively, a reduction in striatal signalling may negatively impact inhibitory tag formation, as striatal dopamine signals are thought to be important for the superior colliculus to produce such tags (Ikemoto et al., 2015; Klein, 2000).

If higher versus lower striatal dopamine is supposedly beneficial for IOR, how could a D2 agonist *reduce* the IOR response? It may be that IOR requires a balance between stability and flexibility, mediated by frontostriatal circuitry. Indeed, such a balance appears to be necessary for several other cognitive functions such as working memory and cognitive control (Cools & D'Esposito, 2011). A large increase in striatal dopamine signalling caused by cabergoline may promote an overly-flexible state, blocking prefrontal cortex activity (Meyer-Lindenberg et al., 2005). The prefrontal cortex may then be unable to maintain inhibitory tags, which would produce faster cued RTs. This would allow for stronger selective attention at the cued location, as we found in our results via N2pc amplitude.

In summary, we postulate that cabergoline and amisulpride may shift the balance between attention flexibility and stability. In the present study, this may have interfered with inhibitory tag formation and maintenance by the superior colliculus and the prefrontal cortex, respectively (thus speeding cued RTs to reduce IOR magnitude). However, in order to clarify the role of dopaminergic frontostriatal connections, future research should directly manipulate dopamine in the prefrontal

cortex. Additionally, further research is needed to establish how ERP modulations relate to inhibitory tag formation and the proposed fontostriatal balance in IOR.

6.4.5 Broader Implications

Previous research has shown that striatal dopamine is important for inhibitory abilities (Cools & D'Esposito, 2011), but none in such a rapid, reflexive form as IOR. Furthermore, some researchers believe that IOR may improve visual search efficiency by reducing unnecessary re-inspections of stimuli (Klein, 2000). Therefore, the effects of dopamine manipulations on IOR may extend to higher processes such as visual search. It may be reasonable to assume that visual search would be negatively affected by both over- and under-signalling of dopamine, as both drugs reduced RTs to cued locations. However, the drugs were likely to have affected IOR via different mechanisms, such as by promoting attention stability versus flexibility. Therefore, future research must relate these IOR findings to real-world functions such as visual search.

Furthermore, investigating the specific roles of dopamine signalling in attention may aid in the treatment of attentional disorders. For instance, dopamine-increasing treatments for Parkinson's disease have unwanted, debilitating effects on attention and impulsivity (Weintraub et al., 2010). This is thought to be caused by non-selective effects of dopamine drugs on different brain systems, as well as individual differences in patients' dopamine systems (Napier et al., 2015; Weintraub et al., 2006). Furthermore, individuals with different subtypes of ADHD respond differently to dopaminergic medications, with some showing reduce inhibitory abilities following medication and others showing increased abilities (Swanson et al., 2007). Therefore, better understanding the role of dopamine in specific brain regions and receptors may aid in producing treatments with improved selectivity.

6.4.6 Conclusion

In the present study, both excessive or insufficient dopamine signalling in the striatum negatively affected IOR; supporting an inverted-U relationship between dopamine level and IOR. We propose that these effects emerged from shifts in the balance between attention flexibility and stability, mediated by dopaminergic fronto-striatal connections. Such findings have implications for IOR itself, demonstrating the importance of striatal dopamine for attentional inhibition. However, there may also be wider implications for the treatment of dopaminergic disorders.

6.5 Supplementary Material

6.5.1 Impulsivity Screening

In previous studies from our lab, the BIS-11 subscale 'cognitive instability' had the most prominent relationship with IOR (Chapters 3 and 4). Therefore, individuals were only recruited if their cognitive instability score fell within one standard deviation of the mean score identified by Stanford et al. (2009) (based on a population of 1,577 healthy adults). Furthermore, participants were only recruited if their overall BIS-11 scores were within 1.5 standard deviations of the aforementioned large sample (Stanford et al., 2009). 162 individuals completed the online impulsivity questionnaire.

The final thirty-one participants had a mean overall BIS-11 impulsivity score of 54.9 (SD = 4.0), and a mean cognitive instability subscale score of 5.9 (SD = 1.2).

6.5.2 Health Screening

Thirty-one individuals attended further health-screening by a clinician. All were deemed fully eligible to participate in the study.

It was required that participants were non-smokers with normal or corrected-to-normal vision, were not colour blind, and were fluent in the English language. It was also required that they had none of the following: History of significant head injuries or seizures, diagnosis of any neurological or psychiatric condition, history of drug or alcohol abuse, use of psychotropic medication within the past six months, use of dopaminergic drug within the past month (or lifetime use exceeding three months), or history of heart problems. It was required that females were not pregnant or trying to conceive.

As amisulpride can cause small changes in heart function (prolongation of the QTc interval) (Täubel et al., 2017), a clinician ensured that heart rate, blood pressure, and electrocardiogram measures were within a healthy range. Clinicians also and took a brief medical history focusing on cardiac abnormalities. Participants' general practitioners were informed of the study, and were asked to notify the research team of any potential concerns.

6.5.3 Precautions and Aftercare

To avoid possible drug interactions, participants were asked to refrain from taking prescription or non-prescription medications for the duration of the study, with the exception of the contraceptive pill and paracetamol (unless discussed with a

study clinician). They were also asked to refrain from consuming alcohol 24 hours prior to participation days, and to consume their typical amounts of caffeine on participation days.

At the end of each visit, participants received a 'contact card' (see Appendix B), stating that the carrier had participated in a research study involving dopamine agonists and antagonists. The card also included contact phone numbers for members of the research team, as well as the participant's unique identification number for emergency unblinding. Participants were instructed to call one of these number if they experienced any unusual sensations after their visit.

6.5.4 Proportional IOR

As the active drugs both significantly improved RTs across task conditions, proportional IOR scores were calculated for each participant and each visit. This was to ensure that the observed differences IOR magnitudes were not caused by drugs generally speeding responses, thus reducing the relative difference between cued and uncued RTs. Proportional IOR was calculated as IOR magnitudes divided by average RTs across conditions for each participant and visit, hence providing IOR as a percentage of overall RT. Proportional IOR scores were then analysed using a two-way mixed-design ANOVA with dopamine manipulation as a within-subjects variable (agonist, antagonist, placebo), and visit order as a between-subjects variable. The main effect of dopamine manipulation was significant $F(2, 46) = 9.04$, $p < .001$. Planned pairwise comparisons demonstrated significantly smaller proportional IOR magnitudes in the agonist (M = 2.8%) and antagonist (M = 2.3%) manipulations, versus placebo (M = 4.1%); $p < .05$. There was no significant difference between agonist and antagonist proportional IOR scores ($p = .216$). The main effect of visit order and the interaction between visit order and dopamine manipulation were not significant ($p = .093$ & $p = .508$, respectively). These findings perfectly replicated the pattern of results found with non-proportional IOR.

Chapter 7

General Discussion

The primary aim of this thesis was to investigate the role of striatal dopamine in attentional inhibition. To achieve this, IOR was investigated behaviourally and using EEG. The role of dopamine was firstly explored indirectly using trait impulsivity (Chapters 3 & 4), and secondly by direct pharmacological manipulations (Chapter 6). Additionally, methodological issues surrounding the measurement of ERPs in IOR were investigated (Chapter 5).

7.1 Summary of Experimental Work

Chapter 3 describes three behavioural studies which investigated the relationship between trait impulsivity and IOR. In the first study, IOR was measured using a cue-target paradigm, with lateralised cues followed by lateralised targets. Trait impulsivity was measured using the Conner's ADHD rating scale, Continuous Performance Test, and BIS-11. Results showed that higher trait impulsivity was associated with smaller IOR magnitudes, irrespective of inattention or ADHD levels. This indicated that highly impulsive individuals exhibit reduced levels of attentional inhibition in IOR.

In the second study, IOR was measured using a target-target IOR paradigm, with targets presented alongside visually-matched non-targets. This circumvented potential confounds, such as motoric and sensory refractory periods thought to exaggerate the apparent magnitude of IOR. Impulsivity was measured using the BIS-11. The results demonstrated a negative relationship between IOR and impulsivity, supporting the results of the first study.

Chapter 4 describes an EEG study which investigated the IOR-impulsivity relationship in more depth. ERPs provided measures of three key processing stages in IOR—sensory orienting (P1), selective attention (N2pc), and attention termination (Pd). However, the behavioural results unexpectedly showed that higher impulsivity was related to increased IOR at the beginning of the task. This finding was attributed to changes in motivational states due to the novel circumstances of brain imaging itself.

Consequently, a third behavioural study was conducted to test the hypothesis that motivation may change the IOR-impulsivity relationship (Study 3, Chapter 3). The study was in the same format as Study 2 in Chapter 3, but with the addition of reward incentives and feedback on performance to increase motivational states. Results demonstrated no relationship between impulsivity and IOR magnitude when motivation was increased—supporting that 'motivation matters' in the IOR-impulsivity relationship. The ERP findings in Chapter 4 were largely inconclusive using the standard approach of analysing the difference between cued and uncued conditions (further discussed below).

Chapter 5 critically evaluated the standard analysis approaches to measuring ERPs in IOR. In the chapter, it was proposed that relationships between ERPs and behaviour should be measured to allow for the involvement of several ERPs. Furthermore, it was suggested that the ERP correlates of cued and uncued trials may be different, and that smaller ERP modulations may be related to larger ones. To illustrate and explore these ideas, the same data from Chapter 4 was re-analysed to replicate the study conducted by McDonald et al. (2008), and additional correlation analyses were performed. Contrary to the conclusions drawn by McDonald et al. (2008), the additional analyses showed that sensory orienting may be involved in the IOR response.

Finally, Chapter 6 describes a study in which dopamine was manipulated directly using the D2 agonist and antagonist *cabergoline* and *amisulpride*, respectively. Their effects on IOR were measured behaviourally and using ERPs. Furthermore, spontaneous EBR was used to confirm that the agonist and antagonist increased and decreased striatal dopamine, respectively. Results demonstrated an inverted-U relationship between striatal dopamine level and IOR magnitude, with both drugs reducing IOR compared to placebo.

How these findings may contribute to our understanding of dopamine in attentional inhibition—as well as impulsivity and IOR themselves—is discussed in the following sections.

7.2 Trait Impulsivity and IOR

The studies described in this thesis indicate that the relationship between trait impulsivity and IOR may depend on motivational sate. More specifically—when the circumstances are motivating, higher impulsivity is related to larger IOR magnitudes; when the circumstances are neutral or less motivating, higher impulsivity is related to smaller IOR magnitudes. This conclusion is gleaned from both the purposeful manipulation of motivation (Chapter 3, Study 3); and the inadvertent increase

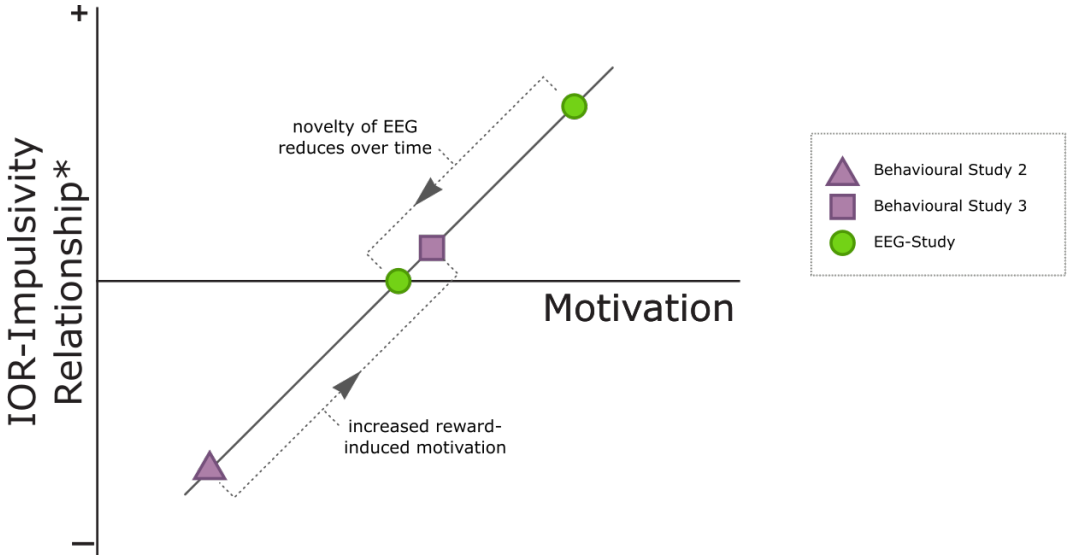

Figure 7.1: Summary of the IOR-impulsivity relationship findings in this thesis: During the EEG study in Chapter 4, participants began in a highly motivated state (positive relationship). Over the course of the task, participants became less motivated (neutral relationship). In Chapter 3 Study 2, participants did not experience any motivation-inducing influences (negative relationship). In Chapter 3 Study 3, additional motivating factors were included outside of the task, and the IOR-impulsivity relationship was slightly positive (x-axis is the proposed motivational state of participants, y-axis is the observed IOR-impulsivity relationship).

in motivation caused by EEG (Chapter 4). Figure 7.1 shows a schematic graph representing the different IOR-impulsivity relationships observed across the studies in this thesis.

These findings contribute to literature surrounding impulsivity as a whole, as researchers usually only investigate the conscious aspects of disinhibition (Enticott et al., 2006; Leshem, 2016a; Bari & Robbins, 2013). Furthermore, they indicate that motivational states may change over the time-course of experiments, differently affecting high- and low-impulsive individuals. To our knowledge, only one other study has reported motivational state changes over time differently affecting high- and low-impulsive individuals; Anderson and Revelle (1983) found that at the beginning of the task, high-impulsives outperformed low-impulsives on a visual search task, but showed worse performance as the task became less novel. This has implications for research into trait impulsivity in general, indicating that if cognitive tasks are long and/or unstimulating, then the attentional inhibitory abilities of impulsive individuals may be misunderstood.

The idea that higher trait impulsivity can be beneficial for cognitive processes is not new; there is a large body of literature surrounding functional versus dysfunctional impulsivity (Colzato, van den Wildenberg, Van der Does & Hommel, 2010;

Dickman, 1990; Claes, Vertommen & Braspenning, 2000; Smillie & Jackson, 2006). Functional impulsivity is related to behaviours such as grasping fleeting opportunities (Dickman, 2000; Colzato, van den Wildenberg, Van der Does & Hommel, 2010). However, the findings in this thesis demonstrate that even dysfunctional impulsivity (as is measured by the BIS-11, Mobini, Grant, Kass & Yeomans, 2007) can be advantageous for attentional inhibition. This may have implications for how dysfunctional impulsivity is perceived and treated—indicating that impulsivity may be less problematic under conditions of high motivation.

Previous studies have shown that increasing motivation can improve the performance of individuals with ADHD (Slusarek, Velling, Bunk & Eggers, 2001; Prins, Dovis, Ponsioen, ten Brink & van der Oord, 2011; Uebel et al., 2010). However, inattention plays a key role in ADHD, which may account for the ameliorating effects of motivation. Furthermore, these studies only demonstrate how impulsive individuals may approach 'normal' levels of performance, rather than how impulsive individuals may even surpass their less-impulsive counterparts.

How may motivational state affect the IOR-impulsivity relationship? Increased motivation is strongly associated with increased dopamine levels in the striatum of the brain (see Ikemoto et al., 2015, for an extensive review)—especially the motivation to 'exert effort' in a task (Salamone & Correa, 2012). Up to a certain point, increased striatal dopamine is thought to increase the magnitude of IOR (Rokem et al., 2012). Therefore, it follows that in motivating circumstances, high-impulsive individuals would exhibit larger IOR magnitudes than when unmotivated. Conversely, low-impulsive individuals have been shown to have higher baseline levels of striatal dopamine (Buckholtz et al., 2010; Costa et al., 2013). Therefore, increased motivation in low-impulsive may produce excessive levels of dopamine in the striatum, negatively influencing IOR. (Note that the relationship between dopamine and IOR is discussed in more detail in the next section of this chapter; 7.3).

This explanation fits with the findings of Dickman (2000), who showed that high-impulsives performed better in a visual search task than low-impulsives when 'energetic arousal' was increased. Energetic arousal is described as a form of alertness and engagement in the task, analogous to motivation. However, Dickman (2000) did not discuss potential neurobiological bases for his findings.

An important consideration when interpreting these findings is the different manner in which the studies altered motivational states: In Chapter 3, motivational states were increased using financial and social reward incentives in the form of prizes and a public scoreboard. Both of these factors are well known to increase motivational states (Ryan & Deci, 2000; Deci, Koestner & Ryan, 1999). However,

in the EEG study (Chapter 4), increased motivation was inferred *post hoc*. The stimulating effects of novelty—such as from brain imaging—are thought to be intertwined with motivational states (Bromberg-Martin et al., 2010; Düzel, Bunzeck, Guitart-Masip & Düzel, 2010). However, it is uncertain how directly comparable these mechanisms may be.

As highlighted by *a priori* power analysis, the experiments exploring the IOR-impulsivity relationship may have been underpowered. As such, it is difficult to interpret null findings. This issue is more prominent in the behavioural study (Chapter 3). Future research is necessary to draw more firm conclusions, including more participants based on the effect sizes in previous studies, improved experimental design (i.e. within-subjects), and demonstrating statistically that the IOR-impulsivity relationship alters as a function of impulsivity (e.g. showing heterogeneity of regression).

A more general criticism of this work is the use of the unitary term *impulsivity* throughout. Here, impulsivity generally refers to participants' scores in the BIS-11 questionnaire (Patton & Stanford, 1995). Although the BIS-11 is one of the most widely used measures of trait impulsivity, and accounts for its heterogeneity to a certain degree (Stanford et al., 2009)—there are other possible ways to measure/subdivide impulsivity (e.g. manual response tasks, Bari & Robbins, 2013). Furthermore, the IOR-impulsivity relationships observed in these studies relate largely to the sub-factor 'cognitive instability' of the BIS-11. Cognitive instability is an attentional form of impulsivity relating to having 'intrusive thoughts' (Reise, Moore, Sabb, Brown & London, 2013; Stanford et al., 2009). Therefore, future work is necessary to establish if these patterns of results are apparent in other forms of trait impulsivity, and if not—why.

In conclusion, these studies demonstrate that higher impulsivity is related to smaller magnitude of IOR, but only in the absence of motivating factors. When individuals are motivated, high-impulsives show larger IOR magnitudes than low-impulsives. However, further research is necessary to demonstrate how this may impact higher-level processes, such as visual search. The effects of impulsivity and motivation on IOR are likely to be underpinned by dopamine—an idea which will be discussed in the following section.

7.3 Striatal Dopamine and IOR

The studies described in this thesis indicate that medium levels of striatal dopamine are optimal for the IOR response. This was inferred from studies of trait impulsivity in Chapters 3 and 4, as well as direct pharmacological manipulations in Chapter 6.

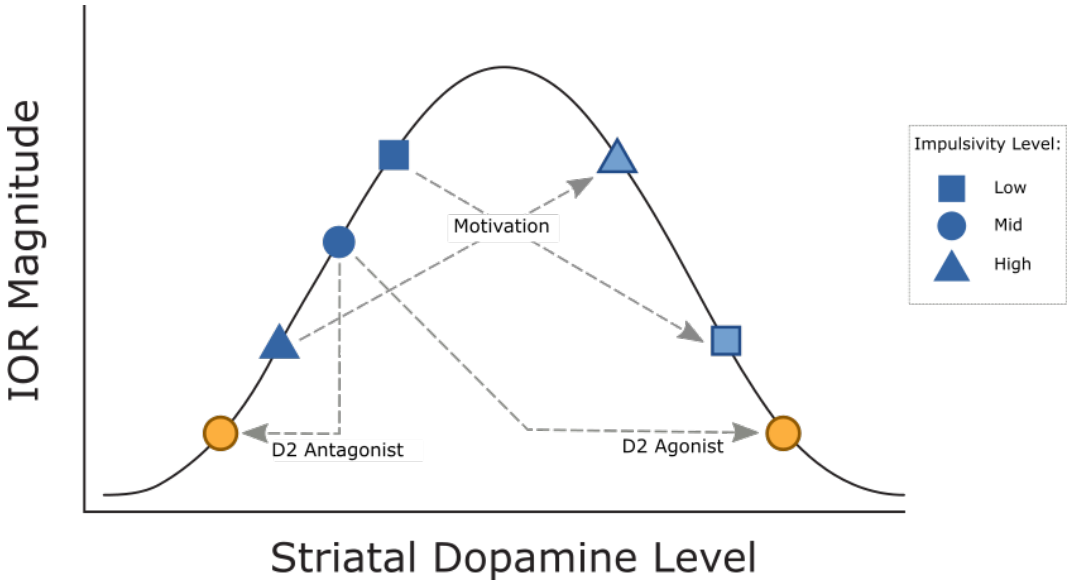

Figure 7.2: The proposed relationships between striatal dopamine level and inhibition of return (IOR) magnitude observed in the studies of this thesis. Motivation is proposed to have increased IOR magnitude in high-impulsives, but decreased IOR magnitude in low-impulsives. Medium-impulsive individuals showed a reduction in IOR following both D2 agonist and antagonist administration. Medium levels of striatal dopamine are proposed to produce the greatest IOR response.

See Figure 7.2 for a schematic graph depicting the proposed inverted-U relationship between striatal dopamine level and IOR, as indicated by these studies.

Across these studies, the IOR effect remained apparent, irrespective of striatal dopamine level. This is in line with findings from patients with Schizophrenia and Parkinson's disease; as they usually show blunted—but not abolished IOR responses (e.g. Poliakoff et al., 2003; Gouzoulis-Mayfrank et al., 2007). Therefore, the IOR effect appears to be robust even when striatal dopamine levels are pathologically high or low. This indicates that striatal dopamine has a *modulatory* role in IOR, but may not be crucial for its emergence.

Nevertheless, such modulations may not be trivial, as IOR is thought to promote the efficient sampling of information from the environment (Klein & Macinnes, 1999; Klein, 2000). Indeed, patients with Parkinson's disease and Schizophrenia shown impairments in visual search and attentional control in general (Uc et al., 2006; Lee et al., 2010; Gold, Fuller, Robinson, Braun & Luck, 2007; Luck & Gold, 2008). However, it unclear to what extent the modulation of IOR observed in these studies may directly relate to such processes.

There have been several other investigations regarding the role of striatal dopamine in IOR; see Figure 7.3 for a schematic graph summarising how their findings may relate. Notably, Rokem et al. (2012) was the only study to demonstrate opposing

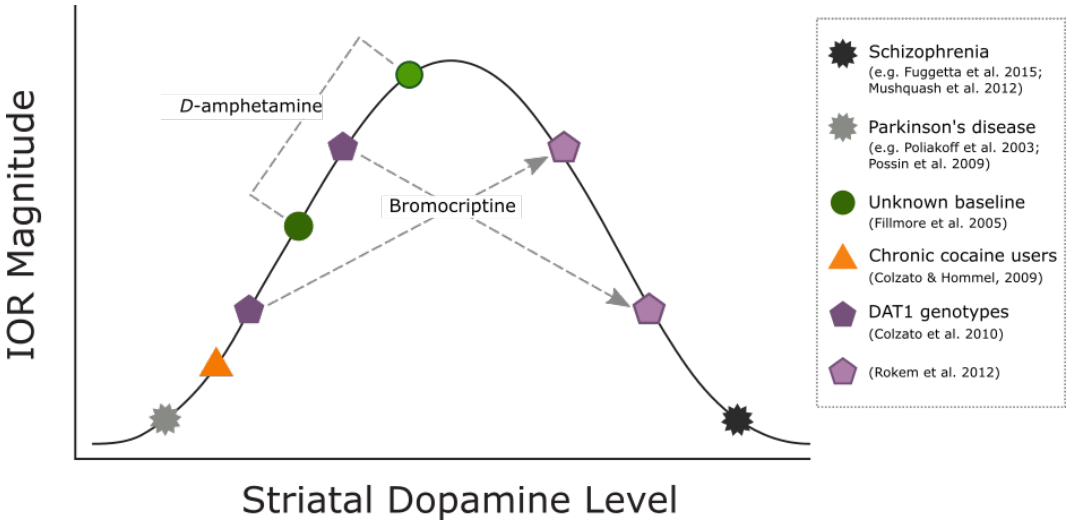

Figure 7.3: Previous studies which have investigated the role of striatal dopamine in inhibition of return (IOR). The findings follow an inverted-U relationship, as is observed in this thesis: the D2 agonist bromocriptine increased IOR magnitudes in individuals with low baseline stiratal dopamine levels, but decreased IOR magnitudes in those with a high baseline. Individuals with Parkinson's disease or Schizophrenia have opposing striatal dopamine levels, yet both show reduced IOR magnitudes.

effects of increased dopamine on IOR. They achieved this by administering the D2 agonist *bromocroptine* to individuals with different baseline striatal dopamine levels (measured via DAT1 genotype). Their study parallels the impulsivity work in this thesis, as instead of DAT1 genotype and the effect of bromocriptine—trait impulsivity and the effect of motivational state was measured. Both investigations show that the effect of striatal dopamine on IOR is baseline-dependent.

How does striatal dopamine signalling influence IOR? Several lines of evidence support that a balance between attention flexibility and stability is important (i.e. dopamine in the prefrontal cortex and striatum, respectively). Dopaminergic signals from the striatum influence the superior colliculus, which is responsible for inhibitory tag formation (Ikemoto et al., 2015; Klein, 2000); whereas the prefrontal cortex is thought to be involved in the maintenance of inhibitory tags (Fecteau & Munoz, 2005; Klein, 2000). Therefore, a system which has 'too much' striatal dopamine may be overly-flexible, enabling rapid attention switching and formation of inhibitory tags, but a lack of tag maintenance. Conversely, 'too little' dopamine would promote an overly rigid attention system, wherein attention is not disengaged—and therefore inhibitory tags are not formed. Both of these circumstances would result in faster responses to cued stimuli, as observed in these studies. This explanation is in line with Cools et al. (2007), who observed that high-impulsive individuals exhibited increased attention flexibility following D2

agonist administration—improving their performance in a working memory task. However, the same drug decreased the performance of low-impulsive individuals (Cools et al., 2007).

One limitation of this work is the difficulty in assessing if motivation, impulsivity, and dopaminergic drugs affected IOR via the same mechanisms. It was hoped that EEG imaging would allow for more in-depth comparison between factors. For example, ERPs could discern if high impulsivity and dopamine depletion affected the same cognitive processes of IOR. However, the EEG findings were largely inconclusive, preventing such comparisons (as discussed in 7.4).

It should also be considered that motivation and impulsivity have complex neurobiological bases beyond striatal dopamine. For instance, dopamine signalling in parietal and prefrontal cortices is important for encoding the value of rewards in motivated states (Locke & Braver, 2008; Wise, 2004; Winstanley et al., 2010); and trait impulsivity has been linked with abnormal dopamine signalling in the prefrontal cortex (Bymaster et al., 2002; Robinson et al., 2007). Therefore, the conclusions regarding dopamine in the striatum specifically should be approached with some degree of caution. Additionally, the prefrontal cortex emerges as a clear target for future research regarding the role of dopamine in IOR.

Furthermore, D2-selective drugs may have important effects beyond striatal dopamine signalling; D2 receptors are substantially more abundant in the striatum, but are also present in several other brain regions, including the prefrontal cortex (Ayano, 2016a; Beaulieu & Gainetdinov, 2011). D2 receptor activation by cabergoline and amisulpride has also been shown to affect other neurotransmitters, including γ-Aminobutyric acid, serotonin, and noradrenaline (Del Dotto & Bonuccelli, 2003; Schoemaker et al., 1997). Nevertheless, these drugs offered the most selective means of manipulating striatal dopamine presently available for human research, and their effects on striatal dopamine are well established (Correll et al., 2004; Odin et al., 2006).

A final limitation of this research is the difficulty in attributing real-world advantages to higher or lower IOR magnitudes. Previous studies indicate that smaller differences between cued and uncued RTs may reflect processing inefficiency (Wang & Klein, 2010). However, faster responses in either cued or uncued trials could be considered optimal for the IOR tasks in these studies—as participants were only required to correctly identify the location of their target. Therefore, future research must investigate how changes in IOR magnitude directly relate to other attentional inhibitory processes.

In conclusion, these findings indicate that striatal dopamine has a modulatory

role in attentional inhibition in the form of IOR. Medium levels of striatal dopamine produce larger IOR effects, which may enable the most efficient sampling of stimuli from the environment. However, further research is necessary to relate IOR magnitudes to other attentional abilities.

7.4 EEG and IOR

It was hypothesised that ERPs would provide a deeper insight into the role of dopamine in IOR by identifying which processing stages were affected by different levels of dopamine. Furthermore, ERPs were measured to compare the effects of direct pharmacological manipulations with indirect observations from trait impulsivity. However, there were very few significant ERP effects using the standard analysis approaches (i.e. ANOVAs), and additional correlational and regression analyses. Therefore, it was not possible to gain the anticipated insights using ERPs.

There are several potential explanations for these null findings, which are not mutually exclusive. Firstly, we cannot rule out that other processing stages were affected outside of those measured in these experiment (although the choice of ERPs was largely guided by the literature; 1.2.2). Secondly, the effects of impulsivity and dopamine manipulations may have been too subtle to measure and/or were spread across several processing stages. This is especially relevant for the EEG study of impulsivity, as analyses were focused on sub-sets of trials—thus reducing statistical power (Chapter 4). Indeed, there was difficulty in calculating sample sizes taking into account individual differences in ERP modulations due to the lack of comparable studies in the literature.

Thirdly, IOR itself is a complex process, as it emerges from the relative balance of facilitation and inhibition of cued stimuli, which are neurally distinct processes (Berlucchi, 2006). Furthermore, IOR is defined as the difference between cued and uncued conditions, also thought to be processed differently (Engelmann & Pessoa, 2007; Berlucchi, 2006). Therefore, it seems likely that the complexities involved at various levels prevented larger, more distinct ERP effects. As such, there may be scope for using more advanced computational/statistical tools to capture the intricacies of dopaminergic effects on IOR processes.

Nevertheless, EEG findings were not entirely inconclusive; across conditions, N2pc amplitudes were significantly larger in uncued versus cued trials. This replicated McDonald et al. (2008), and confirmed that the ERP measures were—at least in part—an accurate reflection of behavioural effects. Furthermore, by applying additional correlation analyses to these data, it was possible to contribute to debates regarding the basis of IOR; we found a relationship between P1 and the N2pc in

both cued and uncued trials. This suggests that IOR is likely to emerge from both sensory and selective attention modulations (Chapter 5).

In conclusion, ERPs were measured to investigate the role of striatal dopamine in IOR. In this respect, the ERP findings were largely inconclusive. However, they served to highlight that IOR is more than just the compound difference between cued and uncued conditions—and is likely underpinned by more than one aspect of cognitive processing.

7.5 Final Conclusions

In this thesis, two lines of investigation support the hypothesis that medium levels of striatal dopamine produce greatest attentional inhibition; firstly, the effects of motivation on high- versus low-impulsive individuals; and secondly, the effects of direct pharmacological manipulations of striatal dopamine. However, neither excessive nor insufficient dopamine levels seem to abolish the IOR effect, indicating that dopamine has a modulatory role in attentional inhibition. This firmly positions IOR alongside other cognitive mechanisms which show inverted-U relationships with dopamine, such as working memory, reversal learning, attention switching, and goal maintenance (Cools & D'Esposito, 2011; Cools et al., 2009; Wallace, Vytlacil, Nomura, Gibbs & D'Esposito, 2011; Cools et al., 2007).

Other aspects of neurobiology may be more crucial for IOR than dopamine in the striatum, such as the superior colliculus, fontal eye fields, prefrontal cortex, and frontostriatal pathways (Lepsien & Pollmann, 2002; Mayer et al., 2004; Sapir et al., 1999; Fecteau & Munoz, 2005). However, dopamine signalling is instrumental in the function of these brain regions (Bromberg-Martin et al., 2010); and better understanding of dopamine has practical applications. For instance, tonic striatal dopamine levels vary substantially between healthy individuals based on genotypes (Colzato, van den Wildenberg, Van der Does & Hommel, 2010; van Holstein et al., 2011; Stock, Arning, Epplen & Beste, 2014; Rokem et al., 2012), and personality traits (Cools et al., 2007; Buckholtz et al., 2010; Depue & Collins, 1999). Furthermore, phasic striatal dopamine levels can change rapidly in response to stimuli (Salamone & Correa, 2012). Additionally, striatal dopamine levels are relatively easy to manipulate (Bromberg-Martin et al., 2010; Grace, 1991; Bäckman et al., 2011), and have a role in several neurological disorders (Li et al., 2006; Ayano, 2016a; Nasrallah, 2008; Georgiev et al., 2015). Therefore, understanding more about the role of striatal dopamine in IOR has practical applications, and potentially far-reaching implications.

Dopaminergic systems are as nuanced as the functions they modulate. As such,

researchers have long since abandoned the broad strokes approach to measuring the role of dopamine in cognition. Therefore, more specific, targeted approaches—such as the one in this thesis—are important to build our understanding of dopamine in cognition as a whole.

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Barratt Impulsiveness Scale (11th Edition)

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	①	②	③	④
2	I do things without thinking.	①	②	③	④
3	I make-up my mind quickly.	①	②	③	④
4	I am happy-go-lucky.	①	②	③	④
5	I don't "pay attention."	①	②	③	④
6	I have "racing" thoughts.	①	②	③	④
7	I plan trips well ahead of time.	①	②	③	④
8	I am self controlled.	①	②	③	④
9	I concentrate easily.	①	②	③	④
10	I save regularly.	①	②	③	④
11	I "squirm" at plays or lectures.	①	②	③	④
12	I am a careful thinker.	①	②	③	④
13	I plan for job security.	①	②	③	④
14	I say things without thinking.	①	②	③	④
15	I like to think about complex problems.	①	②	③	④
16	I change jobs.	①	②	③	④
17	I act "on impulse."	①	②	③	④
18	I get easily bored when solving thought problems.	①	②	③	④
19	I act on the spur of the moment.	①	②	③	④
20	I am a steady thinker.	①	②	③	④
21	I change residences.	①	②	③	④
22	I buy things on impulse.	①	②	③	④
23	I can only think about one thing at a time.	①	②	③	④
24	I change hobbies.	①	②	③	④
25	I spend or charge more than I earn.	①	②	③	④
26	I often have extraneous thoughts when thinking.	①	②	③	④
27	I am more interested in the present than the future.	①	②	③	④
28	I am restless at the theater or lectures.	①	②	③	④
29	I like puzzles.	①	②	③	④
30	I am future oriented.	①	②	③	④

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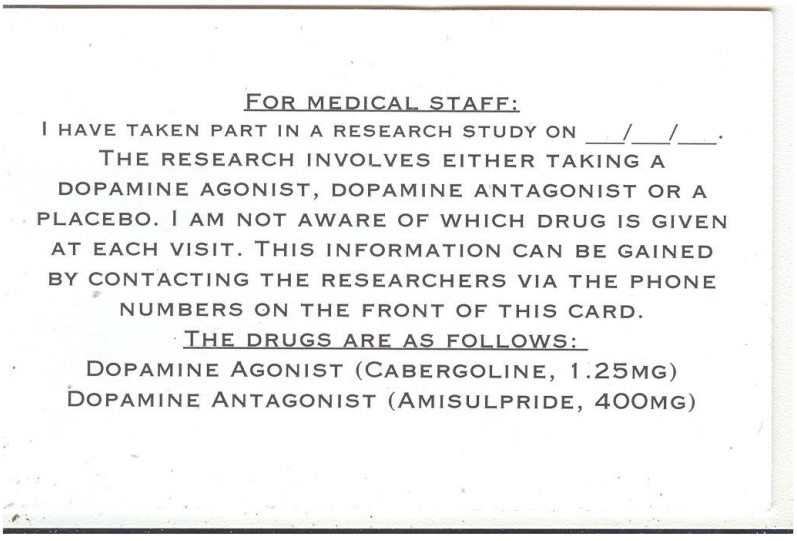
0771 7153918

Sarah Martin
0771 2479217

Please carry this card for 24 hours after your visit


FOR MEDICAL STAFF:

I HAVE TAKEN PART IN A RESEARCH STUDY ON ___/___/___.
THE RESEARCH INVOLVES EITHER TAKING A DOPAMINE AGONIST, DOPAMINE ANTAGONIST OR A PLACEBO. I AM NOT AWARE OF WHICH DRUG IS GIVEN AT EACH VISIT. THIS INFORMATION CAN BE GAINED BY CONTACTING THE RESEARCHERS VIA THE PHONE NUMBERS ON THE FRONT OF THIS CARD.

THE DRUGS ARE AS FOLLOWS:

DOPAMINE AGONIST (CABERGOLINE, 1.25MG)
DOPAMINE ANTAGONIST (AMISULPRIDE, 400MG)