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Dopamine and the affective-cognitive gradient in the human striatum studied with multimodal brain imaging

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To Pia

In memory of Sture and Caje

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List of publications

This doctoral thesis is based on the following publications:

Study 1:

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Study 2:

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Study 3:

Grill, F., Guitart-Massip, M., Johansson, J., Stiernman, L., Axelsson, J., Nyberg, L., & Rieckmann, A. Human in vivo Evidence for Striatal Dopamine Release in Response to Reward-Prediction Errors during Reversal Learning. *Manuscript*.

Additional publications not included in the thesis:

Jonasson, L., **Grill, F.**, Hahn, A., Rischka, L., Lanzenberger, R., Lundmark, V. P., Riklund, K., Axelsson, J., & Rieckmann, A. (2021). Dissociations between glucose metabolism and blood oxygenation in the human default mode network revealed by simultaneous PET-fMRI. *PNAS*, *118*(27). https://doi.org/10.1073/pnas.2021913118

Pedale, T., Fontan, A., **Grill, F.**, Bergström, F., & Eriksson, J. (2022). Non-conscious information can be identified as task-relevant but not prioritized in working memory. *Cerebral Cortex*

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Preface

This is a story mainly surrounding a structure in the brain called the striatum, the neurochemical dopamine, and human behavior. The story is told from the perspective of cognitive neuroscience. The underlying idea of cognitive neuroscience is to observe brain function while someone (or something e.g., a mouse) performs various behaviors. In the latter half of the 20th century, non-invasive techniques were invented to measure brain activity. This unlocked a new world of possible discoveries relating to the brain's electrical potentials, blood flow and neurochemical information. Positron emission tomography (PET) and magnetic resonance imaging (MRI) are the two brain imaging methods used in this thesis. Importantly, a combination of the two methods were used to acquire simultaneous information regarding neurochemical and hemodynamic processes. Even though there are commonalities between the studies, there are some fundamental differences: data from study 1 is from a large scale openly available dataset, data from study 2 was collected in Umeå on a small sample before I began my PhD studies, and data from study 3 was collected in Umeå during my PhD studies. Due to these differences, I have opted for describing the general methods in the main text while keeping the details of the methods contained in the summary of each study. The presentation of the studies includes some results that are not part of the publications but are relevant for the thesis. Each study is followed by a brief discussion specific to that study, the results are then discussed in a broader context in the main text. I would also like to make a disclaimer regarding the presented data analyses: several additional analyses have been done on the data due to exploratory reasons but also due to the steep learning curve of neuroimaging methods (not everything goes as planned) and are not presented in the thesis. Study 1 and study 2 described in this thesis have previously been published in peer-reviewed journals under a Creative Commons Attribution License (CC-BY).

Abstract

Both dopamine and the dopamine rich brain area, striatum, have been linked to behaviors related to incentives, motor action, and associative processing. Most of the cortex sends projections to the striatum, these connections have been described as a gradient organization representing a repertoire of functional behaviors. Although considerable research efforts have been made on the functions of dopamine, it is still unclear how and when it is released in the striatum in humans and what role it has for everyday behavior.

The overarching aim of this thesis is to contribute to our understanding of the role of striatal dopamine release during human behaviors relating to incentive, motor, and associative processing. Using a combination of multimodal brain imaging (positron emission tomography and functional magnetic resonance imaging) as well as cognitive modelling this thesis investigates: how a reproducible striatal response to incentives can be divided into behaviorally relevant components relating to affective and cognitive processes, how striatal dopamine release during motor action represent several component processes of behavior, and also provides evidence that striatal dopamine is released during reward prediction errors in humans. The results are consistent with an affective-cognitive gradient in the striatum and suggest that dopamine release into the striatal gradient might facilitate the integration of component processes into complex representations of behavior. The results of this thesis are based on healthy young individuals, however, aberrant dopamine signaling is a hallmark of several psychiatric and neurological diseases making it crucial to further understand the healthy dopamine system.

Sammanfattning på svenska

Denna avhandling handlar om ett område i hjärnan som kallas striatum, signalsubstansen dopamin, och beteenden som utförs av människor. Under loppet av en dag utförs en bred repertoar av komplexa beteendesekvenser. Även om flera av dessa beteenden verkar konceptuellt åtskilda (som mellan motorrörelser och belöningar) så har de några fundamentala likheter: de är associerade med dopamin och är representerade i striatum. Trots stort fokus på forskning om dopamin så är det fortfarande oklart hur dopamin påverkar alldagliga normala beteenden. Genom multimodal hjärnavbildning undersöks här dopaminfrisättning genom positronemissionstomografi och neurala representationer av beteenden genom magnetresonanstomografi. Det övergripande syftet med denna avhandling är att bidra till vår förståelse angående dopaminfrisättning i striatum vid beteenden relaterade till belönings-, motoriska-, och associativa-processer. Tre studier är beskrivna och diskuteras i avhandlingen:

- Studie 1 undersöker neurala representationer av belöningar som täcker delar av en funktionell gradient i striatum och hur denna representation relaterar till tidigare beskrivna modeller angående hur dopamin frisätts.
- Studie 2 undersöker frisättning av dopamin vid en motorisk uppgift och relaterar dopaminfrisättningen till neurala representationer av motoriska processer lokaliserade i striatum.
- Studie 3 syftar till att observera frisättning av dopamin när man råkar ut för prediktionsfel angående belöningar och att relatera denna dopaminfrisättning till neurala representationer och beteende parametrar angående associativt lärande.

Tillsammans visar fynden att striatum bearbetar information angående belönings-, motoriska-, och associativa-processer på ett sätt som är förenligt med en tidigare beskriven funktionell gradient. Vi visar även för första gången i människor att dopamin frisätts i striatum vid prediktionsfel vilket tidigare bara har setts i djurstudier. Alla fynd är från unga friska individer men har potentiell klinisk relevans då abnorm dopaminfunktion är ett signum för flera psykiatriska och neurologiska sjukdomar.

Abbreviations

ACC – Anterior Cingulate Cortex

BOLD – Blood Oxygen Level Dependent

BP – Binding Potential

DOF – Degrees Of Freedom

CS – Conditioned Stimulus

CSF – CerebroSpinal Fluid

D1-5 – Dopamine receptors 1 to 5

DLPFC – Dorso Lateral Prefrontal Cortex

fMRI – functional Magnetic Resonance Imaging

GLM – General Linear Model

HCP – Human Connectome Project

HRF – Hemodynamic Response Function

ITI – Inter Trial Interval

lp-ntPET – linear parametric neurotransmitter PET

MRI – Magnetic Resonance Imaging

PET – Positron Emisson Tomography

ROI – Region Of Interest

RPE – Reward Prediction Error

SN – Substantia Nigra

TAC – Time Activity Curve

US – Unconditioned Stimulus

VS – Ventral Striatum

VTA – Ventral Tegmental Area

Introduction

During our everyday life we continuously execute complex behavioral sequences, often without even noticing it. Waking up, walking to the fridge, deciding what to make for breakfast, making the breakfast, and eating while watching the morning news on TV. This is how most of my days start, and I imagine that most people would have a similar account for their morning routines. All parts of the routine involve a tightly orchestrated execution of simple actions that come together into a complex expression of behavior. After waking up, walking to the fridge requires some motor planning and motor execution, which can be thought of as component processes of general motor function. Deciding what to have for breakfast has its own hierarchy of processes; to make an inventory of what is in the fridge requires working memory which has its own component processes involving maintaining current information in memory and manipulating said information (will the combination of these ingredients make a tasty sandwich?). Through experience, I know that this particular toast, with butter, and cheese will make a tasty breakfast and I make the decision to create the meal. But *how* do I know that *this* particular sandwich will taste satisfactory? To make such a decision, one would have to generalize from previous occasions where a very similar sandwich has been satisfactory. Such generalization has its own component processes involving reinforcement and memory encoding. This morning, something was off with the sandwich, the cheese was fine, but the bread was stale. The sandwich tasted worse than I predicted which will slightly reduce the probability of me making the same sandwich in the future. I watch the news, which requires external attention, simultaneously eating my sandwich.

Interestingly, all the component processes laid out above have (at least) one thing in common: they have all been associated with the neurotransmitter dopamine. Motor function (Albin et al., 1989; Calabresi et al., 2014; DeLong, 1990), working memory (Cools & D'Esposito, 2011; McNab & Klingberg, 2008), attention (Anderson et al., 2016), decision making (Deserno et al., 2015), and incentives (Jonasson et al., 2014; Joutsa et al., 2012; Pappata et al., 2002) all have a link to dopamine. Additionally, several of these component processes are represented in the most dopamine rich area of the brain, the striatum. Together, the striatum and dopaminergic functions might signify an interface between various component processes (Aarts et al., 2011) and an integrative link to complex behavior.

In this thesis, the neural correlates of behavioral component processes represented in the striatum and their relation to dopamine are investigated.

Reward related behaviors

A fundamental aspect of interacting with the environment is to produce behaviors that generate rewards and minimize punishments. Rewards and punishments are thus incentives (with opposite valence) that lead to approach/avoidance behaviors which are reinforced depending on the outcome of the behavior. Incentives (or reinforcers) are divided into two classes, primary and secondary. Primary incentives include stimuli that are biologically important such as food, water, sleep, and sex. Humans have through exposure developed a pseudo permanent secondary reinforcer in the form of monetary incentives, that is, pairing a neutral stimulus such as money with a primary reinforcer creates a secondary reinforcer that represents a primary reinforcer. Such association between stimuli is known as conditioning where an unconditioned stimulus (US; e.g., food) gets paired with a neutral stimulus which over time becomes a conditioned stimulus (CS; i.e. secondary reinforcer). The associations can be created in a passive sense through classical conditioning which was discovered and formalized in a series of now famous experiments published in 1897 by Ivan Pavlov. As the story goes, Pavlov was investigating the physiology of digestion in dogs by measuring the volume of saliva produced while in the presence of food. He soon noticed that the dogs started to salivate when in the presence of the technician that usually fed them. What Pavlov soon realized was that the mere anticipation of food caused the dogs to salivate; an experiment was set up where a neutral stimulus (e.g., a bell) rung prior to food delivery. Indeed, after a few repetitions, the dogs had associated the neutral stimulus with the primary reinforcer, the previously neutral stimulus was now a secondary reinforcer. As research on conditioning progressed, it became clear that it could be used to increase or decrease the likelihood of behaviors to occur by using punishments as well, which became known as operant conditioning (or instrumental learning). A reinforcer thus entails more than just the reward or punishment by itself, it involves associations of preceding behaviors which themselves can be more or less complex, requiring motor skills, working memory, attention, and motivation. In this thesis, part of study 1 investigates if a highly reproducible reward response in the striatum could be dissociated into components representing such behaviors in a simple task where participants were rewarded or punished while making choices.

A breakthrough in the field of conditioning came in 1972 when Robert Rescorla and Allan Wagner formalized a mathematical model describing the associative strength between a CS and US as a result of conditioning trials. This lead to the idea that associative learning does not happen due to two events co-occurring but happens due to the unexpectedness of the co-occurrence relative to the current associative strength between the events. What is described is known as a reward prediction error (RPE), i.e., if a reward was unexpected, a positive RPE occurs which increases the associative strength between the reward and preceding event; if a reward was expected but omitted, a negative RPE occurs which instead decreases the associative strength of the events. Using Pavlov's dogs as an example, the equation:

$$V_{t+1} = V_t + \alpha(R_t - V_t)$$

where V_t is the associated value of the bell at time t, R_t is the food reward at time t ($R_t - V_t$ is the RPE), and α is a parameter bound between 0 and 1 that is describing the sensitivity to RPE (commonly known as learning rate), is able to capture the associated value of the bell for each iteration with surprising accuracy. Let's go through this equation a couple of iterations to see what is happening to V_t. The first time the bell is rung there is no associated value so $V_t = 0$. For simplicity, let's fix $\alpha = 0.5$, and every time food is delivered $R = 1$. This first iteration will update $V_{t+1} = 0.5$, the associative value of the bell has thus increased for the next trial due to the occurrence of a RPE. In the next iteration $V_{t+1} = 0.75$, if the iterations continue like this $V_t \rightarrow 1$, the RPE is then resolved, and the bell is now fully predicting the upcoming reward. This process also works if rewards are omitted which then decreases the associative value of the bell due to negative RPE. Such an equation is the quintessential idea of cognitive modelling where a behavioral phenomenon is described as a mathematical model. Since the conception of the Rescorla-Wagner model the field of *reinforcement learning* has been active and successful in developing more intricate models with parameters describing diverse cognitive phenomenon to explain behaviors and to solve computer science problems. In this thesis, study 3 makes use of cognitive modeling, specifically, reinforcement learning to investigate the hypothesis that RPEs release dopamine to the human striatum.

In 1997, Wolfram Schultz used electrophysical recordings to investigate the firing of midbrain dopaminergic neurons when non-human primates were exposed to rewards in a similar fashion as Pavlov did with his dogs. Some stimulus was presented to the animal and short thereafter a reward in the form of a drop of fruit juice was delivered. Before any associative learning had occurred, a marked increase in the neuronal population's firing rate was observed directly after the reward was received. After a couple of trials, this increased firing rate in relation to the reward was gone, instead the neurons were firing in relation to the stimulus that preceded the reward. If the reward was omitted, a decrease in firing rate was observed at the time where the reward was predicted to be received, together, the firing of dopaminergic neurons was consistent with RPEs. The findings have been corroborated by direct measures of dopamine concentrations in the rodent striatum (Clark et al., 2009; Hart et al., 2014), and recently by widefield-two-photon imaging (Hamid et al., 2021), showing a complex spatial and temporal dynamic of striatal dopamine release during operant and classical conditioning.

Cognitive control and reversal learning

Cognitive control is a broad behavioral construct that involves several component processes. It refers to the intentional selection of appropriate behaviors based on the current environmental demands and the simultaneous suppression of inappropriate or habitual behaviors (Miller & Cohen, 2001). It is apparent that cognitive control requires attention (for intentional decisions), associative processing (to realize what is appropriate/inappropriate) and working memory (to maintain and manipulate current information for goal-directed behavior). Note that these cognitive constructs have its own component processes that can be interrelated to each other (Nyberg & Eriksson, 2016), e.g., attention can be seen as a component process of working memory (Eriksson et al., 2015). Cognitive control is regarded as a top-down process which means that some inner goal influences stimuli perception and selection (Melloni et al., 2012), as opposed to bottom-up processes where external stimuli instead influence the inner goal. Studies on cognitive control have shown that humans are reluctant to engage cognitive control unless the value of doing so is greater than to avoid it (Dixon & Christoff, 2012), implying that the process is associated with some internal cost. It has been theorized that, in an environment where the average reward rate is high, there is a diminishing need for cognitive control (the current behavior is appropriate and yielding rewards). If suddenly the average reward rate decreases (the current behavior is inappropriate), which can be seen as a cost related to the current behavior, there is a heightened necessity for cognitive control in an attempt to modify the current behavior to match the previously high reward rate (Westbrook et al., 2021).

Reversal learning refers to the unlearning and relearning of stimulus-outcome associations when some environmental shift has changed the value of previously learned stimulus-outcomes. The Wisconsin Card Sorting Test is a classic example of potential reversal learning. In the test, participants are presented with cards that have e.g., three stimulus dimensions: shapes, the color of shapes, and the number of shapes. Participants are instructed to match the cards that are given to them but not how to match and are only told if they were correct (which can imply a reward) or incorrect (which can imply a punishment). By trial and error, the participants learn that matching by the color of the shape is the correct rule and can now exploit this information. If the rule suddenly changes, the current behavior will yield incorrect matches, the participant must now unlearn and relearn a new rule, which constitutes reversal learning. The task as explained above is fairly simple but becomes significantly harder if the rule is applied probabilistically, that is, the rule is only valid some percentage of the time. Under the reinforcement learning framework, probabilistic reversal learning is used to investigate decision flexibility (Gagne et al., 2020; Vinckier et al., 2016; Waegeman et al., 2014). To successfully reverse a response rule, it must be detected that the current response results in more incorrect than correct matches and a new rule should be learned. Sorting by the previously correct rule after a rule change signifies perseverance errors and are, by definition, in a paradigm where correct responses are rewarded, negative RPEs. As described in the previous section, RPEs has been confidently linked with dopamine in rodents and non-human primates. In humans, there is evidence that drugs that act on the dopamine system influence RPE sensitivity such that increasing dopamine signaling increases the sensitivity to RPEs (Chowdhury et al., 2013; Cook et al., 2019; Rutledge et al., 2009).

Dopamine

Dopamine is a catecholamine neurotransmitter discovered by Dr. Arvid Carlsson in the 1950s which later awarded him the Nobel Prize in 2000 for Medicine/Physiology. In a series of experiments Carlsson and colleagues found that the acute effect of loss of motor control in animals treated with reserpine was reversed when given injections of a precursor to dopamine (Carlsson et al., 1957). From that moment on, dopamine would be associated with motor function and dysfunction. Reserpine was used in psychiatry as a sedative, also, two other drugs, chlorpromazine and haloperidol were found to alleviate symptoms of psychosis but were often accompanied by side effects resembling parkinsonism. Together, these findings would associate dopamine with psychiatric diseases such as schizophrenia (Howes & Kapur, 2009). A set of experiments performed on rodents in the 1970s found that rodents would willingly and repeatedly self-stimulate certain areas of the brain with electricity. These areas were comprised of dopamine neurons and the dopaminergic system, now placing dopamine as the central neurotransmitter in motivation and incentive behaviors, as well as addiction (Nutt et al., 2015).

What does dopamine do?

Dopamine is one of the most well studied neurotransmitters, however, it is still a bit of a mystery what role dopamine plays for everyday behavior. We know it is modulating a neuron's potential for firing, that is, depending on what receptor dopamine binds to it either increases or decreases a neuron's potential for firing. There are five known dopamine receptors D1, D2, D3, D4, and D5. These receptors are usually classified as either D1-type (D1 and D5) which increases a neurons potential for firing, or D2-type (D2, D3, D4) which decreases a neuron's potential for firing. Dopamine neurons have been shown to fire in patterns that are consistent with RPEs (Schultz et al., 1997), but have also been shown to fire in response to salient[1] stimuli (H. Matsumoto et al., 2016; M. Matsumoto & Hikosaka, 2009; Schultz, 2016). As mentioned, dopamine has been related to a wide range of behaviors and it is tantalizing to think that its function is something that is common across the behavioral repertoire. An early proposal for the role of catecholamines (such as dopamine) was that they may increase the signal-to-noise ratio in neural responses (Clark et al., 1987). A recent perspective regarding the function of dopamine is that it provides a dynamic estimate regarding if it is worth expending some limited internal resource, such as attention, time, and even energy (Berke, 2018). Another perspective is that dopamine is associated with signaling and computing different forms of uncertainty relating to one's environment (Gershman & Uchida, 2019). However, a unifying account regarding the role of dopamine in behavior is still debated.

Where is dopamine?

Although the effect of dopamine is widespread in the brain, the actual neurons producing and releasing dopamine are confined to relatively small areas of the midbrain, the substantia nigra pars compacta/pars reticulata (SNc/SNr or SN) and the ventral tegmental area (VTA). From here, dopaminergic neurons project to the brain through three major pathways, the nigrostriatal (SN to striatum), mesolimbic (VTA to striatum), and mesocortical (VTA to cortex) pathway. Dopamine

[1] Salient meaning the strength of some stimulus dimension e.g., something being louder.

receptors are found on neurons throughout the brain (except in the cerebellum where an insignificant number of receptors are found which is important and convenient for reasons laid out in the PET chapter of this text). However, the striatum sticks out due to 5 to 10 times higher density of dopamine receptors (depending on receptor type) compared to other areas of the brain (Hall et al., 1994).

Striatum

The striatum is a subcortical structure, part of the basal ganglia, consisting of three major anatomical divisions, the caudate, the putamen, and the nucleus accumbens (Figure 1). Both its structure and function seem to have been preserved through vertebrate evolution over 560 million years (Grillner et al., 2013). The striatum was initially associated with planning and execution of motor behaviors, it has however become increasingly clear that its role extends beyond motor function to domains involving, affective, and associative processing. Most of the cortex has axonal projections to the striatum, instead of dividing the structure into anatomical subdivisions, the striatum can be divided into functional compartments (Figure 1) relating to which areas of the cortex has projections to which areas of the striatum (Tziortzi et al., 2014). This generally leads to a tripartite division where a sensorimotor domain is assigned to posterior dorsal parts of the striatum, an associative domain assigned to anterior dorsal parts, and an affective/limbic domain to the most ventral parts. An important finding elucidated by cognitive

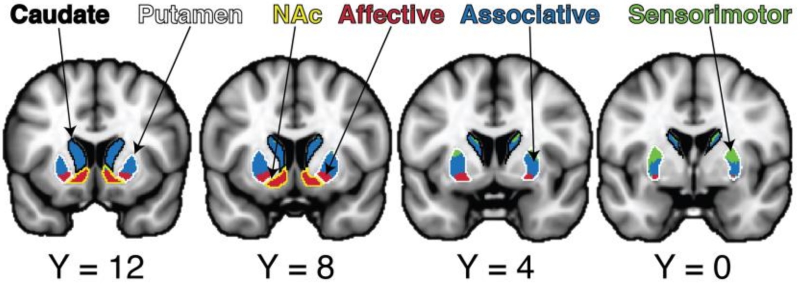
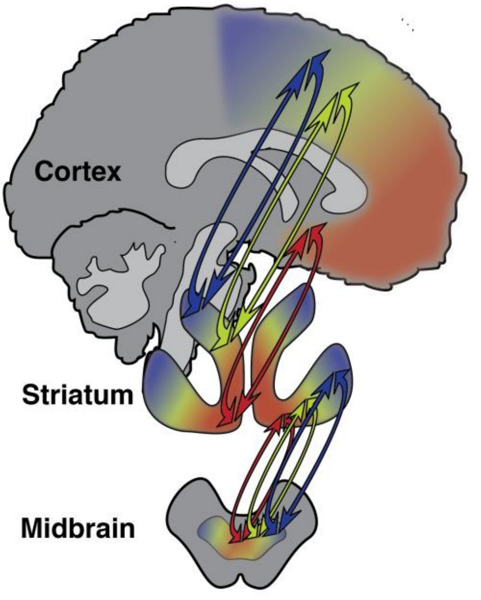


Figure 1. Anatomical and functional division of the striatum. Colored outlines depict the major anatomical divisions: Black = Caudate, White = Putamen, Yellow = Nucleus Accumbens. Colored fills (Tziortzi et al. 2014) depict major functional divisions: Red = Affective, Blue = Associative, Green = Sensorimotor.

Figure 2. Gradient organization of cortico-striatal-cortico as well as striatal-midbrain-striatal looping connections. The ventral striatum has reciprocal connections with the ventromedial prefrontal cortex and ventral tegmental area (red). The dorsomedial striatum has reciprocal connection with the dorsal prefrontal cortex and the medial substantia nigra (yellow). The dorsolateral striatum has reciprocal connections with sensorimotor cortex and lateral substantia nigra (blue). This general organization is a depiction of what is referred to as the gradient organization of striatum in the text. Adapted from Haber and Knutson (2010) with permission from Springer Nature.



neuroscience is that the brain is organized and operates through distributed regions forming interconnected networks supporting behaviors related to the external and internal environment (Yeo et al., 2011). The striatum has been shown to be involved in the majority of these networks (Choi et al., 2012). Cortico-striatal tracing studies have shown that neighboring cortical areas projecting to the striatum share some striatal space, making discrete functional divisions as described above, an oversimplification of the anatomical reality (Haber & Knutson, 2010). Instead, the arrangement of cortico-striatal projections is better described as a topographical gradient[2] (Figure 2). This cortico-striatal gradient has been recovered in humans using neuroimaging data (Marquand et al., 2017). Thus, the striatum seems to be organized with smooth continuous transitions from one functional domain to another. The most ventral part of the striatum represents behaviors related to what can be described as motivation (incentives, rewards). Moving dorsally, the striatum represents more cognitive behaviors such as working memory, attention, and associative processing. The most dorsolateral posterior part represents behaviors relating to motor action which include locomotion

[2] Topographical meaning the distribution of features, here location in the cortical space, and gradient meaning a gradual increase or decrease of that feature when passing from one point to another.

and even speech production (D'esposito & Alexander, 1995). As can be seen from the account above, describing spatial-functional relationships in cognitive neuroscience often imply discrete boundaries, but with a gradient organization one must imagine "fuzzy" boundaries where two (or more) functional domains are represented.

Dopaminergic projections from the midbrain to the striatum can also be characterized as a gradient-like organization. The VTA projects to the ventral striatum, the medial SN projects more dorsally, and the lateral SN projects to the dorsolateral striatum. Additionally, the striatum projects to the midbrain to form reciprocal connections between the areas, forming striato-midbrain-striatal connections that are looping through the two structures (Haber & Knutson, 2010). Through these open loops, it has been shown that the ventral striatum can influence motor processing in the dorsal striatum (Aoki et al., 2019), creating an interface between affective and motor processing. Most of the striatum is morphologically homogenous[3]. It is estimated that over 95% are GABAergic (i.e., sending inhibitory signals) medium spiny neurons that project from the striatum (Graveland & Difiglia, 1985), the rest are either cholinergic or GABAergic interneurons acting locally in the striatum. Together, these neurons form a repeated circuitry that covers the striatum and filters, modulates, amplifies, and transforms information related to motor and cognitive behaviors (Burke et al., 2017).

Motor processing

A prominent polysynaptic circuit model of the striatum and basal ganglia is the Go/No-Go model of motor functions involving the direct and indirect pathway. The direct pathway is postulated to promote movement, whereas the indirect pathway inhibits movement. Both pathways include complex excitatory and inhibitory signaling involving the cortex, striatum pallidum, the subthalamic nucleus, and thalamus forming cortico-striatal-thalamo-cortical loops. Of note is that a distinction is made regarding dopaminergic modulation in the pathways, the direct pathway is modulated by dopamine binding to D1 receptors, and the indirect pathway is modulated by D2 receptors (Albin et al., 1989; Calabresi et al., 2014; DeLong, 1990). This model has led to the hypothesis that the striatum and its extended circuit act as an action selection gate where desirable movements are facilitated while undesirable movements are attenuated. A large corpus of neuroimaging studies shows that the putamen exhibit a robust response to motor processing (Witt et al., 2008)

[3] Striatal structures cannot be divided based on the form of neural populations, i.e., given a random tissue sample from the striatum it cannot be decided if it is from the caudate or putamen.

as well as dopamine release (Badgaiyan et al., 2003; Goerendt et al., 2003). Interestingly, dopamine release in response to motor processing has also been observed in striatal regions that are not traditionally related to motor functions (Badgaiyan et al., 2003; Goerendt et al., 2003). In study 2, a motor task was used as a test bed for concurrent functional magnetic imaging responses and dopamine release (fMRI).

Incentive processing

The ventral striatum has been integrally linked with incentive processing and motivated behavior across mammalian species (Haber & Knutson, 2010; Ikemoto & Panksepp, 1999; Salgado & Kaplitt, 2015). Using neuroimaging in humans it has been shown that metabolic activity as well as *Blood-Oxygen-Level-Dependent* (BOLD) responses increase in the ventral striatum when exposed to both primary and secondary positive reinforcers (Knutson & Greer, 2008; Künig et al., 2000; Small et al., 2001; Wang et al., 2016). Importantly, using BOLD fMRI, a differential ventral striatum response is often observed between rewards and punishments such that negative reinforcers instead show a decreased BOLD response. Using [11C]Raclopride *positron emission tomography* (PET) imaging, increased dopamine has been observed in the striatum in response to pharmacological reinforcers (Leyton et al., 2002; Volkow et al., 1999). The increased dopamine in the ventral striatum between control and pharmacological scans using amphetamine has shown to strongly correlate with feelings of euphoria (Drevets et al., 2001). Interestingly, the prediction or anticipation of an upcoming reinforcer has also shown to increase dopamine in the ventral striatum to the same level as actually receiving the reinforcer (Boileau et al., 2007).

Associative processing

Associative processing or associative learning is largely divided into two types: Pavlovian/classical conditioning and operant/instrumental conditioning (described in more detail in Introduction: Reward related behaviors). The case of predicting an upcoming reinforcer (increasing striatal dopamine levels) described previously (Boileau et al., 2007) can be thought of as classical conditioning since no response or action is needed from the subject to form an association. In contrast, operant conditioning requires some goal-directed response from the subject that in turn leads to some reinforcement. A dissociable role for ventral and dorsal striatum has been found using fMRI BOLD imaging where the dorsal striatum responds to operant conditioning but not classical conditioning, while the ventral striatum responds to both (O'Doherty et al., 2004). Additionally, in rodents, lesions in the dorsal striatum impair goal-directed learning (Yin et al., 2005). This indicates that for successful goal-directed actions, both the ventral and dorsal striatum are needed.

Hippocampus and dopamine neurons

An influential model regarding dopamine release has proposed a polysynaptic functional loop between the hippocampus and VTA controlling the readiness of dopaminergic neurons to fire (Grace, 2016; Lisman & Grace, 2005). In this model, the hippocampus acts as a novelty detector, matching learned representations with sensory reality to conclude if the sensory reality is expected or novel. If novelty is detected, the hippocampus sends an excitatory signal to the ventral striatum. The ventral striatum sends an inhibitory signal to the ventral pallidum, inhibiting the tonic inhibition the ventral pallidum exerts over the VTA. This inhibition of tonic inhibition results in a disinhibition of the dopaminergic neurons, making them ready to release dopamine in response to novel stimuli (Figure 3). It should be noted that the model is debated since there is a lack of evidence for such disinhibition of dopamine neurons in non-sedated animals (Berke, 2018; Mohebi et al., 2019). Given the putative role of hippocampus in “releasing the breaks” of dopaminergic neurons, it can be expected that it responds to reinforcement learning tasks. The hippocampus has been shown to respond to reward cues (Adcock et al., 2006), and indeed to RPEs (Dickerson et al., 2011; Foerde & Shohamy, 2011). Additionally, a recent experiment has shown that, apart from processing RPEs, the hippocampus was involved in guiding the balance between exploration and exploitation behaviors (Dombrovski et al., 2020), both key components of reinforcement learning. The putative role of hippocampus as a novelty detector might thus be too narrow and might extend to surprise detection (Barto et al., 2013) or even salience detection.

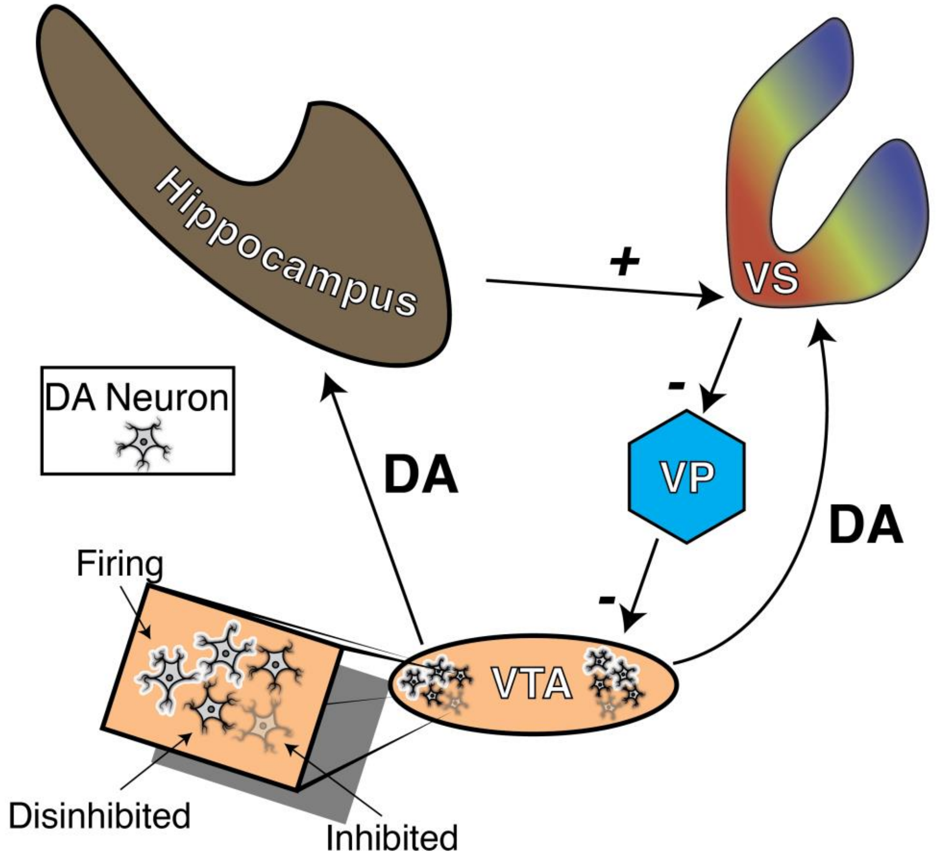


Figure 3. Model of dopamine release developed by Lisman and Grace (2005). The hippocampus acts as a salience detector (e.g., novelty salience) by matching learned representations with sensory reality. If salient events are detected it sends a glutamatergic, excitatory, signal to the ventral striatum. Neurons projecting from the striatum are GABAergic and therefore inhibits its targets. The ventral striatum targets the ventral pallidum which exerts tonic inhibition over the ventral tegmental area. The excitatory signal from the hippocampus thus inhibits the tonic inhibition that is put on the dopaminergic neurons in the ventral tegmental area, resulting in disinhibited neurons that are ready to fire. DA = dopamine; VS = ventral striatum; VP = ventral pallidum; VTA = ventral tegmental area.

Aims

The overarching aim of this thesis is to contribute to our understanding of the role of striatal dopamine release during behaviors relating to incentive, motor, and associative processing.

Study 1. Given the ventral striatum's gradient like cortical connections, connection to hippocampus and the dopaminergic midbrain, as well as its highly reproducible response to incentives – this study aimed to specify which component of incentive processing relate to the hippocampus.

Study 2. Dopamine release has previously been observed in the striatum in areas associated with motor processing but also in areas related to cognitive processing. Using multimodal brain imaging – this study aimed to disentangle if such diverse dopamine release was directly or indirectly related to motor processing.

Study 3. Striatal dopamine signaling has convincingly been shown to be related to reward prediction errors in non-human primates and rodents, but striatal dopamine release during reward prediction errors has never been observed in humans. Using multimodal brain imaging and cognitive modelling – the study aimed to observe dopamine release in the human striatum during reward prediction errors as well as relate it to neural correlates and behavioral parameters associated with reinforcement learning.

Materials and Methods

On the brain imaging side of the methods, two modalities were utilized: PET and MRI. There are some basic commonalities between the two methods, but also some stark differences. Technically, both modalities make use of electromagnetic radiation to collect its images, however as we shall see, in very different ways. A common feature between them is that both are based on tomography (i.e., acquiring images in slices) meaning that the smallest spatial element of the collected data is a voxel (a three-dimensional pixel). Both modalities can make use of time-resolved data, meaning that functional processes can be tracked over time. Around here is where the commonalities stop and the differences begin, which will be explored in more detail below. Due to the commonalities and differences between the modalities, there are some obvious synergistic information that can be extracted from the simultaneous use of both.

PET

PET is a (minimally) invasive imaging technique due to the requirement of injecting individuals with radioactive isotopes. The method is however very useful due to its chemical specificity. A drug binding to some target in the body can be labeled with a radioactive isotope (together radio ligand) and the basic idea is that the radio ligand accumulates at its targets, causing the target areas to be more radioactive than its surrounding. When the isotope decays it emits a positron which does not have to travel very far until it encounters an electron, causing an annihilation event. The annihilation produces two gamma rays (high energy photons) which are ejected from the event in a line 180° from each other. These photons are then detected by sensors put in a ring around the PET scanner which, through coincidence pairs, infers the timepoint and location of the annihilation. The data is then reconstructed into images where each voxel of the image at each timepoint has a quantitative radioactivity count. Although the decay-annihilation cycle essentially occurs continuously, to get reasonable statistics for every image-frame the reconstruction averages the radioactivity counts often over minutes, reducing the temporal resolution of the data.

The radio ligand used in these studies was the D2 receptor antagonist [11C]Raclopride. It is a well validated ligand which can reliably measure striatal D2 receptor availability. Importantly for our experiments, its relatively low receptor binding affinity compared to endogenous

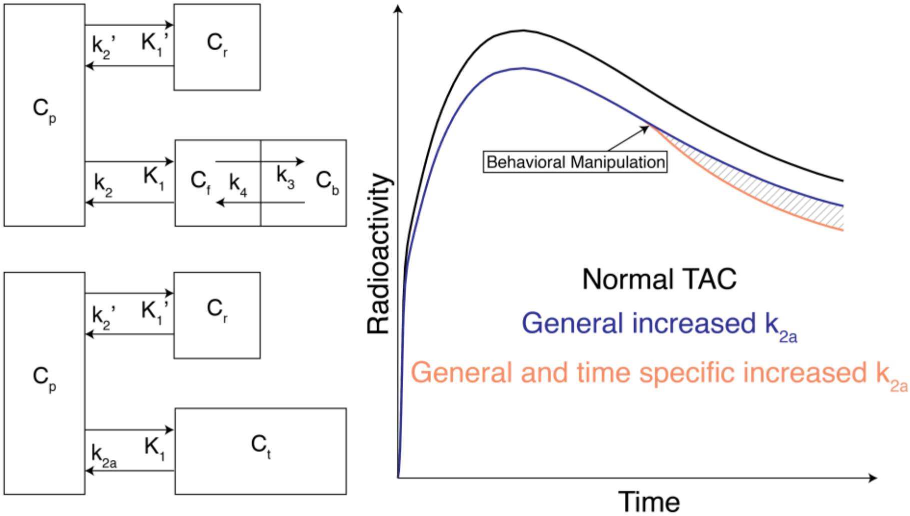


Figure 4. Left is a depiction of compartmental models used to estimate pharmacokinetic parameters from the PET data. On the top is the full reference tissue compartmental model (C_p = blood compartment, C_r = reference region here cerebellum, C_f = freely bound to tissue compartment, C_b = bound to receptor compartment, arrows depict flow rate parameters to and from the various compartments). On the bottom is the simplified reference tissue model where C_f and C_b are combined to a single tissue compartment and flow rate parameters k_2, k_3, and k_4 are combined to k_{2a}. Right is a cartoon of the time activity curve of some region where the ligand binds to a receptor (e.g., striatum in the case of [11C]Raclopride). Black curve depicts the radioactivity over time during a resting condition. Blue curve depicts the radioactivity over time during an active condition. Orange depicts the radioactivity over time during an active condition and a behavioral manipulation that releases endogenous neurotransmitters and displaces the ligands bound to receptors.

dopamine enables it to be displaced from the receptor it binds to. Thus, [11C]Raclopride and endogenous dopamine are in competition for receptor occupancy. In areas where the concentration of endogenous dopamine increases from one moment to the next, one would then expect a decrease in radioactivity counts at that moment. It has been proposed that 80% of D2 receptors are accessible by [11C]Raclopride, since at any given moment it has been estimated that around 20% of the receptors are occupied by endogenous dopamine. To make things more complicated, D2 receptors have been shown to exist in a high and low affinity state each with a distribution of 50%. [11C]Raclopride can bind to both affinity states while endogenous dopamine has preferential binding to the high affinity state. Thus, only 30% of D2 receptors have the potential for competition between [11C]Raclopride and endogenous dopamine (Caravaggio et al., 2019).

Binding potential

There are several ways to analyze PET data which also depends on the ligand used. As mentioned before, the raw reconstructed PET data consists of voxels containing moment to moment radioactivity counts. Plotting a voxel's radioactivity counts over time is referred to as a time activity curve (TAC). One can imagine how the blood supply distributes the ligand throughout the brain and at sites where the ligand binds, there is a higher radioactivity count. However, we know that in a single voxel there are several kinds of compartments e.g., blood vessels, various kinds of brain cells, and receptors that will all influence the TAC. The compartment we are most interested in is the radioactivity associated with the receptors, but this is now confounded by the other compartments. Pharmacokinetic modelling is used to estimate what part of the radioactivity count is related to which compartment. A theoretically simple, but practically complicated, way of getting information regarding the blood compartment is to continuously sample arterial blood from participants and measure its radioactive content while the PET scan is ongoing. In the case of [11C]Raclopride, one can use the fact that the cerebellum has a negligible amount of D2 receptors and use this region as a reference tissue to gain insight about the compartment dynamics in other areas of the brain, such as the striatum. In the studies using PET, we utilize the simplified reference tissue model (SRTM) to estimate the static binding potential (BP) which is a measure of receptor availability that [11C]Raclopride can bind to (Lammertsma & Hume, 1996). BP is defined as the ratio between the influx rate from the tissue compartment (k_3) to the binding compartment and the outflux rate between the binding compartment and tissue compartment (k_4). However, using SRTM, as the name suggest, simplifies the model by combining the free and specific binding compartments, reducing the number of parameters to be estimated (k_2, k_3 and k_4 now collectively called k_{2a}; Figure 4), and instead makes BP its own parameter to be estimated, which has been validated to produce robust BP estimates using [11C]Raclopride (Lammertsma & Hume, 1996). The model can be modified further by linearizing the parameters and doing a first pass estimation of k_2' which is then fixed for subsequent estimations (Endres et al., 2011; Ichise et al., 2003). It should be noted that a difference in magnitude between the BP in two voxels can stem from different sources. If the BP is lower in one voxel compared to another, it either means that there are less receptors for [11C]Raclopride to bind to, or there is more dopamine occupying the receptors which is blocking [11C]Raclopride binding.

lp-ntPET

In study 2 and 3, the dynamics of BP are probed further using linear parametric neurotransmitter PET (lp-ntPET; Normandin et al., 2012). When endogenous dopamine is released due to some challenge, a portion of [11C]Raclopride that is bound to D2 receptors are knocked away which increases the outflow rate (k_{2a}) and thus lowers the BP. The increased outflow rate can be estimated from the TAC by finding the best least-squares solution from a library of basis-functions that span a portion of the space of k_{2a} increases (Figure 4) yielding dynamic BP curves. The percentage of dopamine occupancy can then be calculated accordingly:

$$Occupancy(\%) = \frac{baseline\ BP - post\ challange\ BP}{baseline\ BP} \times 100$$

This approach accounts for inter-individual and inter-regional differences of [11C]Raclopride displacement which is important since individual and regional differences in dopamine release to behavioral manipulations are unknown. Using lp-ntPET on the voxelwise level can identify areas that exhibit dopamine release Using lp-ntPET on the level of regions of interest (ROI), the dynamics of dopamine release can be estimated.

MRI and fMRI

A popular non-invasive way of imaging the brain while it is performing some task is functional magnetic resonance imaging (fMRI) using the BOLD contrast (Ogawa et al., 1990). As suggested in its name, fMRI is dealing with a resonance phenomenon. A resonance phenomenon is for example when a singer is able to hit the correct resonance frequency of a wine glass to make it vibrate and shatter. Instead of sound waves and large object resonance, we are looking at a quantum phenomenon where electromagnetic radiation at the correct frequency excites proton nuclei to a higher energy level. When the nuclei then go back to their ground state, they emit radiation which is observed and converted into images. Different tissue types have different amounts of proton nuclei resulting in different signal contrast between the tissues. The structural images used in all studies are T1w contrast images.

The BOLD contrast additionally makes use of differences in the magnetic properties of oxygenated and deoxygenated hemoglobin. The fact that deoxygenated hemoglobin is paramagnetic is at the center of the BOLD contrast; increased concentrations of deoxyhemoglobin disturb the magnetic field causing a lower signal. Neuronal activity has certain metabolic demands, such as oxygen consumption. Neurons with increased activity therefore consume more oxygen (Logothetis et al., 2001). The metabolic consumption of neurons also causes changes in blood supply to an area, a phenomenon known as neurovascular coupling. Hence, when neurons consume oxygen, signals inform the vasculature to increase the supply of arterial blood which increases the amount of oxygenated blood. Counter to the paramagnetic properties of deoxygenated blood, oxygenated blood is diamagnetic which does not disturb the magnetic field. Importantly, the rush of fresh blood to active neurons is much greater than the oxygen that is consumed which results in an oversupply of oxygenated hemoglobin. What is important to point out is that we are *not* measuring neuronal activity directly, but instead the indirect effects that the neuronal activity has on the vascular system in the immediate vicinity.

These vascular changes can be described by the hemodynamic response function (HRF). Compared to neural activity that fire at the millisecond time scale, the HRF is slow and the peak of the HRF does not occur until around 6 to 12 sec after a stimulus onset (Logothetis et al., 2001) making it an important aspect to consider when designing experiments. An advantage with the BOLD contrast is that it is relatively quick to acquire; an image of the whole brain can be collected every couple of seconds enabling time-resolved sampling of the HRF.

fMRI analysis

Two main techniques were used in this thesis to analyze the fMRI data: mass-univariate general linear models (GLM) for the task data (Friston et al., 1994) in all three studies and BOLD timeseries correlations to estimate functional connectivity during resting state (Lowe et al., 2000) in study 1 and study 2. With GLM, the idea is that the timing of the experiment events are known which can be translated into predictor variables also known as regressors. The regressors are then used to explain the time-resolved BOLD data in each voxel, yielding parametric maps describing how well the regressor fit the data. In study 1 and 2, the time series of peak voxels representing a good fit of regressors were extracted from the resting state data and correlated with the rest of the brain to identify areas that rise and fall with the extracted time series, indicating a functional coupling between the areas (functional connectivity).

Multimodal Brain Imaging

The term multimodal brain imaging refers to the collection and use of two or more modalities containing unique information from the same participant. By that definition, all three studies contained in this thesis utlize multimodal brain imaging: study 1 uses task and resting state BOLD fMRI, study 2 uses task and resting state BOLD fMRI as well as [11C]Raclopride PET, and study 3 uses task BOLD fMRI as well as [11C]Raclopride PET. However, only study 2 and 3 utlize simultaneous collection of two modalities: task BOLD fMRI and [11C]Raclopride PET (from now refered to as hybrid imaging). As reviewed previously, the two modalities probe different aspects of brain function at different temporal resolutions. With BOLD fMRI, hemodynamic signals are measured at a timescale of 1 to 4 sec, with [11C]Raclopride PET the ligands receptor binding can be estimated at a timescale of 1 to 2 min. The benefits of hybrid imaging have previously been described as 3 levels (Mulert & Lemieux, 2010):

1. *Spatial integration*. At this level the fact that the modalities were collected simultaniously is used to make sure that the images are in the same space.
2. *Asymetric integration*. This level refers to the use of one metod to inform or interpret the information of the other method, e.g. using the superior temporal resolution of fMRI to understand or interpret PET information.
3. *Symmetric integration*. At the higest level, hybrid brain imaging is fully integrated to create or inform biophysical models.

At best, most hybrid imaging studies can be described as level 2 on the scale of modality integration (Chen et al., 2018).

The general method of hybrid PET/MR imaging and the use of functional PET during behavioral paradigms have advanced in recent years, allowing new questions to be answered from the data. With novel paradigms, basic questions regarding the metabolic demands of the brain during visual processing (Rischka et al., 2018) as well as during working memory (Jonasson et al., 2021) using hybrid PET/MRI have been investigated. The relationship between neurovascular responses and dopamine receptor occupancies has been investigated showing that D2 receptor antagonists are associated with spatially specific and temporally related increases in cerebral blood volume (Sander et al., 2013). Dopamine release in the amygdala has been associated with concurrent fMRI BOLD response to fear conditioning (Frick et al., 2021). The difference in striatal dopaminergic markers between healthy controls and depressed patients has been used to inform alterations in brain network coupling between the groups (Hamilton et al., 2018). In this thesis, hybrid and multimodal brain imaging was used to investigate striatal dopamine release and concurrent BOLD response during motor, incentive, and associative processing.

Cognitive Modelling

All models are wrong, but some are useful – Geroge Box

The above quote pertains to the basic truth that reality is messy. Capturing reality through observations will always come with some loss of information. What we can do, is to approximate a real phenomenon through models. The idea with cognitive modelling is to build a model that captures or approximates some cognitive processes. Arguably, the most successful case of this is the Rescorla-Wagner model for reinforcement learning (Rescorla-Wagner, 1972). The equation described in the introduction concerning conditioning is essentially the base model that was fit to the data in study 3. In addition to calculating the trial-by-trial RPE each participant encounters, the weight parameter α which is estimated from the observed data is of particular interest. Each RPE is multiplied by this weight, an α approaching 0 essentially nullifies the RPE meaning that there is no or very little updating of the expected value of a choice, an α approaching 1 takes the whole RPE in account when updating the expected value. In this sense α can be conceptualized as RPE sensitivity. It is equally valid to view α in a more temporal sense where an α approaching 1 only takes the most recent trial information into consideration while a lower α takes more of the trial history into account when updating the choice value. It is easy to see that a high α will represent a stochastic response pattern susceptible to environmental noise while a low α will represent a more rigid response pattern unresponsive to environmental signals. There has been significant development in reinforcement learning models over the past decades with an extensive addition of various parameters that are considering various cognitive processes. A common procedure of fitting these models to behavioral data is to do model comparisons, that is fit several different models and compare their performance against each other to find a model that best approximates the data. The model that best accounted for the data in study 3 included a meta-cognitive level which yielded a trial-by-trial estimate of α by estimating the confidence of the participants choices.

Study 1: Neural Correlates of Reward Processing: Functional Dissociation of Two Components Within the Ventral Striatum

Introduction

Maximizing rewards and minimizing punishments is fundamental to successfully interact with the environment. By definition, such interaction requires the processing and recognition of desirable or aversive stimuli but also involves a repertoire of other behavioral processes. To approach or avoid stimuli motor processes must be engaged; desirable stimuli might not be readily available, to obtain them might require working memory processes to be engaged; to learn what is or is not desirable require associative learning if it is not intrinsically obvious. The striatum is known to process these diverse sets of behaviors in a regionally specific manner such that stimuli related to incentives (rewards and punishments i.e., the valence of a stimulus) are represented in the ventral striatum (VS), associative processing is represented in the anterior dorsomedial striatum, and motor processing is represented in the posterior dorsolateral striatum. However, such discrete functional divisions have proven to be too simplistic, instead, the functional organization of the striatum is better described as a continuous gradient (Haber & Knutson, 2010; Marquand et al., 2017). The canonical VS response to rewards (Sescousse et al., 2013) appears to cover parts of this gradient that is not only related with processing stimuli valence but also related to associative processing. Such a reward response might thus represent a mixture of reward recognition and associative learning of the reward that can be exploited for future decisions.

Reward processing and dopamine functioning has long been closely linked (Schultz, 1992; Wise, 1980). Midbrain dopaminergic neurons project to the striatum and are responsible for the supply of dopamine to the structure. Research on rodents have suggested that, through a polysynaptic pathway, projections from the hippocampus to the VS play an important role in controlling the responsivity of the dopaminergic neurons in a context-dependent manner (Grace, 2012; Lisman & Grace, 2005). In humans it has been shown that the VS and hippocampus are functionally coupled and that the strength of the connection is associated with the density of dopamine D2 receptors in the striatum (Nyberg et al., 2016). In this study, we wanted to further probe the specificity of the relationship between these two areas.

First, we investigated if a canonical VS reward response, that covers parts of an affective-cognitive striatal functional gradient, could be parcellated into meaningful components relating to stimulus valence and associative (more cognitive) properties. Next, we investigated which of these components showed strongest functional coupling to the hippocampus. Indeed, we found that a seemingly homogenous reward response in the VS could be parcellated into an inferior and superior component that was consistent with an affective-cognitive gradient. We then showed that the inferior part of the response had significantly stronger functional coupling to hippocampus than the superior response. The results suggest that stimulus valence rather than cognitive load modulate a hippocampus-VS circuit that has previously been implicated in dopamine functions.

Methods

Participants

Data from 350 participants was acquired from the human connectome project (HCP). The data was then split into a discover sample (N = 175, 92 female, mean age 29.8 [SD = 3.65], mean years of education 14.95 [SD = 1.78]) and a replication sample (N = 175, 91 female, mean age 28.8 [SD = 3.73], mean years of education 14.95 [SD = 1.75]). Participants were excluded if they had been marked by any quality control issue by the HCP consortium. The participant's "mother identification" and "father identification" were unique to ensure that all participants were unrelated. The study was approved by the local ethics committees at Umeå University, Umeå Sweden.

MRI

Time resolved fMRI EPI BOLD images (spatial resolution 2 × 2 × 2 mm, 72 slices, TR = 720 ms, TE = 33.1 ms, flip angle = 52 deg, FOV = 208 × 180 mm, multiband factor = 8) from the HCP gambling task, working memory task, and resting state were downloaded for each participant as well as T1w structural images. Before downloading, the BOLD data was preprocessed through the HCP minimal processing pipeline (Glasser et al., 2013). Briefly, the BOLD data was motion corrected (6 defrees of freedom (DOF) registration to a reference image), phase encoding distortion corrected, registered to the T1w structural image (6 DOF), and registered to the 2mm MNI template space. In addition, preprocessing for the current study was carried out on the task fMRI including additional motion correction, spatial smoothing (FWHM = 4 mm), high-pass temporal filter (0.024 Hz), and prewhitening. The resting state BOLD data underwent a separate preprocessing pipeline that included variance normalization to allow for concatenation of the two acquired runs, regressing out signal from deep white matter, regressing out signal from deep CSF, regressing out the global signal, spatial smoothing (FWHM = 4mm), and band- pass temporal filter (low-pass = 0.1 Hz, high-pass = 0.01 Hz).

Experimental design

The gambling task was adapted from a previous study and involved a simple card-guessing game (Delgado et al., 2000). Participants were shown a card with a question mark and were supposed to indicate whether the unseen number behind the question mark was above or below five. Correct guesses were rewarded with $1 during a feedback screen showing a green upwards pointing arrow. Incorrect guesses were punished with −$0.5 during a feedback screen showing a red downwards pointing arrow. If the number behind the question mark was neither above nor below five, a gray double-headed arrow oriented vertically was shown during the feedback screen. All trials were pseudorandomized meaning that participant output did not change the feedback, or the resulting monetary reward given to them. The trials were arranged in blocks with eight trials in each block. The blocks were either mostly rewarding (6/8 rewarding trials, where 2/8 were either a neutral or punishing trial) or mostly punishing (6/8 punishing trials, where 2/8 were either a neutral or rewarding trial). Each trial lasted for 3.5 sec (question mark presentation and participant input 1.5 sec, feedback 1 sec, and 1 sec intertrial interval (ITI)) resulting in a block duration of 28 sec. Each session consisted of two mostly rewarding and two mostly punishing blocks. A resting condition of 15 sec was interleaved between each block. The duration for each gambling task run was 3 min 22 sec.

The working memory task involved a N-back paradigm with two levels of load, “2-back” and “0-back”. During the 2-back condition, participants were shown a train of stimuli and were asked to indicate whether the current stimulus is the same as the stimulus presented two steps back. During the 0-back condition, a target stimulus was presented, and participants were then shown a train of stimuli and asked to indicate if the current stimulus was the same as the target stimulus presented at the start. Note that the load manipulation deviates from other N-back tasks found in the literature (Callicott et al., 1999; Dahlin et al., 2008; Nevalainen et al., 2015) and could rather be described as a manipulation of working memory updating (2-back) and working memory maintenance (0-back). Each of the two fMRI runs consisted of eight blocks (four 2-back, four 0-back) and within each block one of four possible stimulus categories were presented (faces, places, tools, body parts; the stimulus categories were ignored in this study). At the start of each block, a 2.5 sec cue indicated the load level (and the target if the condition was 0-back). Each block consisted of ten trials, and each trial consisted of a 2.5 sec stimulus presentation and an ITI of 0.5 sec. Each run had four fixation blocks with a duration of 15 sec, positioned after every other block. The duration for each working memory task run was 4 min 52 sec. More information regarding the fMRI tasks are described elsewhere (Barch et al., 2013).

Statistical analysis

fMRI GLM

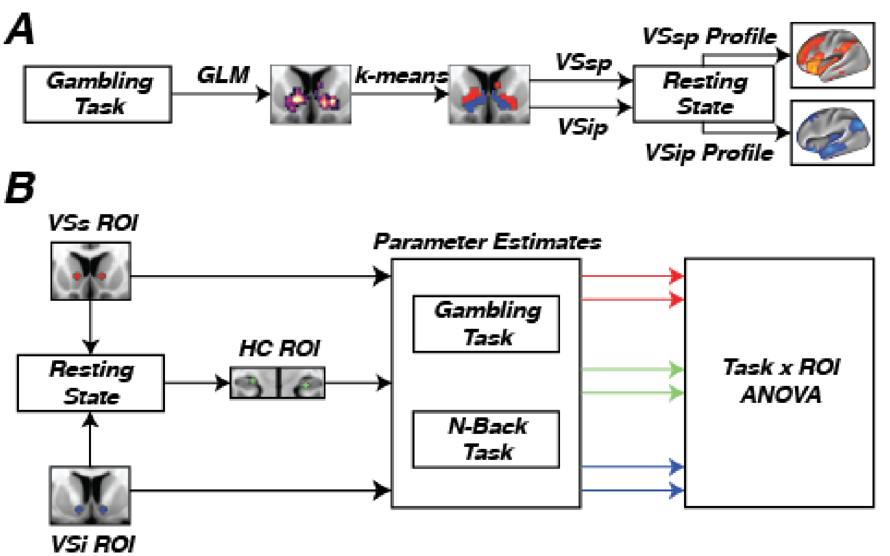
The task data was analyzed using FSL's FEAT (Woolrich et al., 2001). Two regressors were defined: one for the reward blocks and one for the punish blocks. A contrast was then created between the two regressors (reward > punish) to identify the canonical reward response. The individual responses of the two regressors as well as the contrast was then taken to a group level analysis using FSL's randomise (Winkler et al., 2016) with 5000 sign-flip permutations and corrected for multiple comparisons using threshold free cluster enhancement (TFCE; Smith & Nichols, 2009). An identical analysis was performed on the N-back task data with the contrast of interest 2-back > 0-back.

Parcellating the reward response

K-means clustering was used to investigate the hypothesis that the seemingly homogenous VS reward response can be disassociated into component parcels. The k-means algorithm was given each voxel's reward parameter estimate on the group level as one dimension and each voxel's punish parameter estimate as a second dimension (taken from the voxels inside the significant VS reward > punish cluster). The optimal number of clusters was determined using the average silhouette method between k(1 to 5). After each voxel was assigned to a cluster, the data were projected back into volumetric space yielding separable parcels of the initial reward > punish cluster.

Resting state functional connectivity

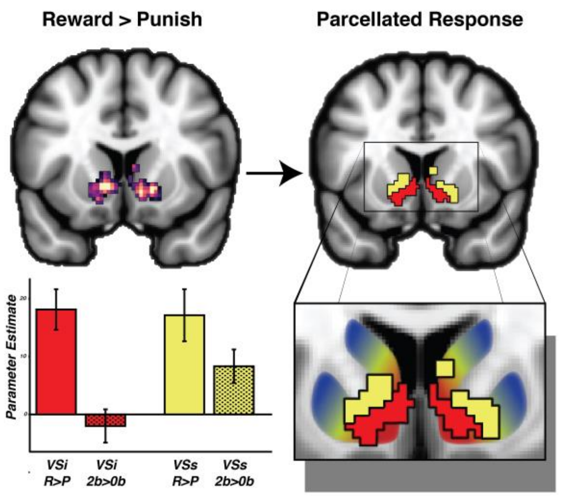
Parcels from the k-means analysis were used as seeds in a functional connectivity analysis. The resulting functional connectivity maps were r-to-z transformed. The individual maps were then entered into a random effects group level analysis using FSL's randomise with 5000 sign-flip permutations and TFCE correction. In order to determine which functional network a parcel mostly corresponded to, dice similarity coefficients were calculated between the 7-network resting-state parcellation (Yeo et al., 2011) and the cortical functional connectivity map for each parcel.



S1-Figure 1. Visual representation of the two analysis pipelines: (a) VS reward response parcellated into VSsp and VSip which show differential resting state profiles; (b) ROI definitions from literature VSs and VSi show differential functional connectivity in the hippocampus (HC ROI), parameter estimates were extracted from the task contrasts and entered into an ANOVA. Figure from Grill et al. (2020).

Region of interest definition

Two regions of interest (ROI) in the VS were defined from descriptions in the literature (Di Martino et al., 2008). The placement of the ROIs corresponded well with the inferior and superior parcels from the k-means clustering and were termed: VS-inferior (VSi) and VS-superior (VSs). The ROIs were used as seeds in a functional connectivity analysis which was used to define ROIs in the hippocampus, as well as to extract parameter estimates from the GLM task contrasts. The logic behind defining regions of interest were twofold: 1) to balance the number of voxels used as seeds in the functional connectivity analysis and later extraction of parameter estimates from areas in close proximity; and 2) to show that the functional dissociation from the k-means analysis corresponds to loci that are commonly used and cited in the literature (Di Martino et al., 2008; Harrison et al., 2009; Nyberg et al., 2016; Sarpal et al., 2015). The analysis pipeline is depicted in S1-Figure 1.



S1-Figure 2. Results of the canonical reward > punish response in the ventral striatum. Using the voxelwise parameter estimates from reward and punish separately the response was parcellated into an inferior (red) and superior (yellow) response. The parcellation fit well with the known gradient-like ventromedial to dorsolateral organization of cortico-striatal connections. Only the superior parcel responded to a working memory load manipulation (2b>0b) suggesting that the area is involved with both incentive and working memory processing. The inferior parcel showed relatively stronger functional connectivity to the hippocampus potentially reflecting a circuit controlling the readiness of midbrain dopaminergic neurons. Figure adapted from Grill et al. (2020).

Results

We replicated previous studies in finding a reward > punish response in the VS (TFCE corrected $p < .0005$, k-voxels = 722). The mean responses for reward and punish for each voxel in the significant cluster was fed into a k-means clustering algorithm which showed an optimal solution for k = 2 clusters, signifying that the seemingly homogeneous contrast could be parcellated into two constituent parts (S1-Figure 2). Transforming the data back to the voxel space revealed an inferior (VSip) and superior (VSsp) division of the VS cluster. The seed based functional connectivity analysis confirmed differential functional coupling profiles to cortical networks between the parcels (S1-Table 1).

Using the *a priori* defined ROIs extracted from the literature showed that both the superior and inferior ROI responded to the reward > punish contrast (VSs, mean = 17.14, CI = [12.64–21.64]; VSi: mean = 18.13, CI = [14.62–21.64]) but only the superior ROI responded to the working memory load contrast 2-back > 0-back (VSs: 2back > 0back, mean = 8.32, CI = [5.42–11.22]; VSi: 2back > 0back, mean = −2.00, CI = [−4.87 to 0.87]).

Contrasting the functional connectivity between VSi and VSs showed greater functional connectivity of VSi in the hippocampus (hippocampus right: x = 24, y = −18, z = −18, t-stat = 3.65; left: x = −22, y = −20, z = −14, t-stat = 4.09). Using these coordinates as a ROI and extracting the contrast parameter estimates showed that hippocampus co-responded to the reward > punish contrast (mean = 10.30, CI = [4.50–16.10]) but not to the 2back > 0back contrast (mean = −22.60, CI = [−27.21 to −17.99]).

S1-Table 1. Dice score coefficients between the parcellated reward > punish response in VS and cortical networks show differential functional coupling.

	Resting-State Network						
	Visual	Somato-motor	Dorsal Attention	Ventral Attention	Limbic	Frontal Control	Default Mode
VSip	.07	.04	.00	.03	.16	.15	.68
VSsp	.07	.03	.00	.38	.05	.39	.29

Brief Discussion

We confirmed that a canonical reward response in the VS, that covers parts of an affective-cognitive striatal functional gradient, could be parcellated into components relating to stimulus valence and associative (more cognitive) properties. The parcellation was largely congruent with a ventromedial to dorsolateral functional gradient as observed in previous studies (Marquand et al., 2017). The results may reflect an interface between affective processing of incentives and the associative learning of incentives which has been hypothesized to involve striatal dopamine signaling (Aarts et al., 2011). In line, we were able to show that the inferior, affective, component and hippocampus both co-responded to rewards and were functionally coupled which might reflect a functional circuit that provides a salience signal to modulate the readiness of dopamine neurons to fire (Floresco et al., 2001; Grace, 2012; Lisman & Grace, 2005). However, no firm conclusions regarding dopamine signaling can be made from the data since it lacks neurochemically specific information.

Study 2: Dissecting Motor and Cognitive Component Processes of a Finger-Tapping Task with Hybrid Dopamine Positron Emission Tomography and Functional Magnetic Resonance Imaging

Introduction

Interacting with the environment requires some form of motor action whether its moving to approach/avoid some stimulus, grasping, communicating desires through speech production, or in the modern world – communicating through tapping fingers on a keyboard. The striatum is known to process behaviors related to motor action but also behaviors related to motivation and working memory in a spatially and functionally specific manner. The organization of cortico-striatal connections can be described as a functional gradient where motivational and affective behaviors are represented in the most ventral part, cognitive behaviors are represented in the dorsomedial part, and sensorimotor behaviors are represented in the dorsolateral parts. Additionally, striatal dopamine release patterns are involved in motivated behaviors (Ikemoto & Panksepp, 1999), associative learning (Cools et al., 2009; den Ouden et al., 2013), and mediate the execution of desirable movements (Albin et al., 1989; Calabresi et al., 2014; DeLong, 1990). Previous studies on striatal dopamine release in relation to finger tapping have shown that the release is largely consistent with the functional organization of the striatum, observing dopamine release in the putamen (Badgaiyan et al., 2003; Goerendt et al., 2003). However, both these studies report dopamine release in the caudate as well which is unexpected from the point of view of discreet functional boundaries. Both Badgaiyan et al. (2003) and Goerendt et al. (2003) speculated that dopamine release in the putamen was reflective of motor demands, consistent with known anatomical projections to the motor cortex, while the caudate responses may have reflected non-motor processes such as learning or attention, which are likely to occur at different timescales than the transient motor specific aspects of the task. Using fMRI, finger tapping produces a robust BOLD response in the putamen (Witt et al., 2008), but not in other areas of the striatum, creating a discrepancy of findings which can potentially be explained by the temporal resolution between the modalities capturing different aspects of the task.

In this study, we simultaneously collected [11C]Raclopride PET and fMRI to investigate dopamine release and BOLD response in nine human participants while they performed a finger tapping task consisting of long (several minutes) blocks of tapping and blocks of rest. Importantly, the task design permitted us to capture hemodynamic changes specific to the transient component of finger movements at the timescale of seconds using fMRI, while PET was used to identify striatal regions where dopamine release was related to the task at both faster and slower temporal scales. That is, the fMRI analysis was tuned to identify the regions that were more likely related to the fast component of motor activity, while the maps identified by using PET provided an overall spatial dopaminergic activity pattern regardless of task component process. By comparing the statistical spatial maps from both modalities, we hence theorized that signal overlap would reflect striatal dopamine release in response to the transient motor components of the task, while dopamine release without task-specific BOLD response was hypothesized to reflect non-motor components of the task, e.g., motivation or attention. The aim of this study was to test the hypothesis that striatal dopamine release during motor function is associated with motor as well as non-motor processes, in a spatially distinct manner. In order to further understand the nature of non-motor contributions, we used the non-overlapping dopamine release areas as seeds in a resting state functional connectivity analysis to map their functional coupling to cortical systems and thereby constrain the interpretation of their functional contribution.

Methods

Participants

Participants were recruited via ads placed around Umeå University campus, targeting young healthy adults between 20–40 years of age. Exclusion criteria included history of head trauma, current or past diagnosis of neurological or psychiatric illness, drug or alcohol dependence, and use of psychopharmaceuticals or stimulants other than caffeine or nicotine for the past 6 months. Individuals with MR-incompatible metallic implants or objects in their body were excluded. Pregnant or breast-feeding women, as well as individuals having previously undergone PET scanning for research purposes were excluded due to radiation safety reasons. All included participants were right-handed. One participant was excluded due to excessive head motion during the scan. The resulting sample size consisted of 9 healthy young adults (mean age = 24.9, SD = 4.2, range 20–34; mean height = 172.7, SD = 12.9, range 151–196; mean weight = 71.78, SD = 13.1, range 55– 98; 5 females). This study was approved by the Regional Ethics Committee at Umeå University.

Procedure

Imaging was performed on a 3T General Electric Signa PET-MR system with a 15-channel head coil. Behavioral data (button presses) were recorded with an MR-compatible 4-button response pad from Cambridge Research Systems. The data was collected between November 2015 and March 2016.

Upon arrival, participants were informed about the study and signed an informed consent form. An intravenous needle used for infusion was placed in the left arm. Participants were then positioned into the scanner bore where a mirror mounted on the scanner coil directed their gaze toward a screen located behind the scanner. Task instructions were prompted on the screen during the experiment. A T1w structural image was collected, followed by a resting state BOLD sequence. Participants were injected with [11C]Raclopride at the start of the PET scan. Twenty minutes later the task BOLD sequence started.

Experimental Design

The task consisted of sequential finger tapping with the right hand (index, middle, ring, little finger). Participants were told to self-pace their tapping and were visually cued to tap for 10 sec and then rest for 10 sec until they were cued to start tapping again. The embedding of this on-off design within the task periods was chosen to fit the temporal resolution of BOLD response so that the BOLD signal would increase during the tapping event while allowing it to decrease during the rest ITIs. The tapping task was partitioned into blocks with differing number of blocks, duration, and onset times between participants. Note that, since the individual displacement maps were averaged across subjects for the main analysis, the individual differences in design were not of interest to the current study. Nevertheless, since it is unknown how short task blocks may be in [11C]Raclopride displacement studies the dopamine occupancy curves from the different clusters and task versions are presented in S2-Figure 2.

These analyses showed that all task block lengths between 5 and 13 min were able to elicit displacement.

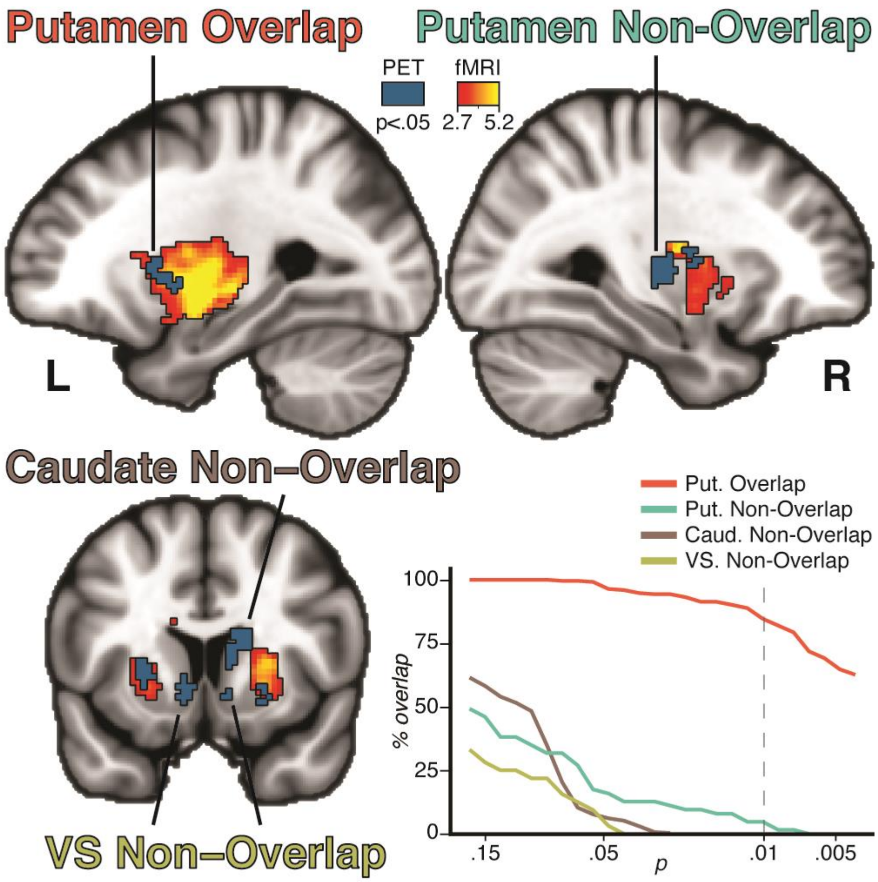
MRI

Structural T1w images were acquired for 7 min 22 sec with the following acquisition parameters: [FOV: 25 × 20 cm^2, matrix: 256 × 256, Slice Thickness: 1 mm, Slices: 180, TE: 3.1 ms, TR: 7,200 ms, Flip Angle: 12, Bandwidth: 244.1 Hz/Pixel]. T1w images were used for segmenting the brain into anatomical compartments using Freesurfer (Fischl, 2012) and normalization to standard MNI space using a preliminary 12 DOF registration with FMRIB's Linear Image Registration Tool (FLIRT) followed by a non-linear registration using FMRIB's Non-linear Image Registration Tool (FNIRT), resulting in 2 mm isotropic voxels.

S2-Table 1. Group level significant [11C]Raclopride displacement clusters and indication if they spatially overlapped with fMRI.

	Location	Number of voxels	Mean t-stat	Peak t-stat	Overlap
Putamen	Left middle-anterior	78	2.63	6.19	YES
	Right anterior	28	2.37	3.26	YES
	Right middle	24	2.90	5.38	YES
	Right posterior	63	3.07	6.07	NO
Caudate	Left anterior	19	2.36	2.87	NO
	Right anterior	106	2.70	7.80	NO
	Right posterior	24	2.63	3.49	NO
VS	Left	27	2.36	3.34	NO
	Right	16	2.55	3.84	NO

All BOLD fMRI data were collected with the same sequence parameters (FOV: 25.6, Matrix: 96 × 96, Slice Thickness: 3.6 mm, TE: 30 ms, TR: 4,000 ms, Flip Angle: 80◦, Acceleration Factor: 2.0). Acquisition of BOLD resting state data started after the T1w image and data was collected for 6 min 40 sec. Acquisition of BOLD task data commenced 20 min after the PET acquisition started and was collected for 40 min.

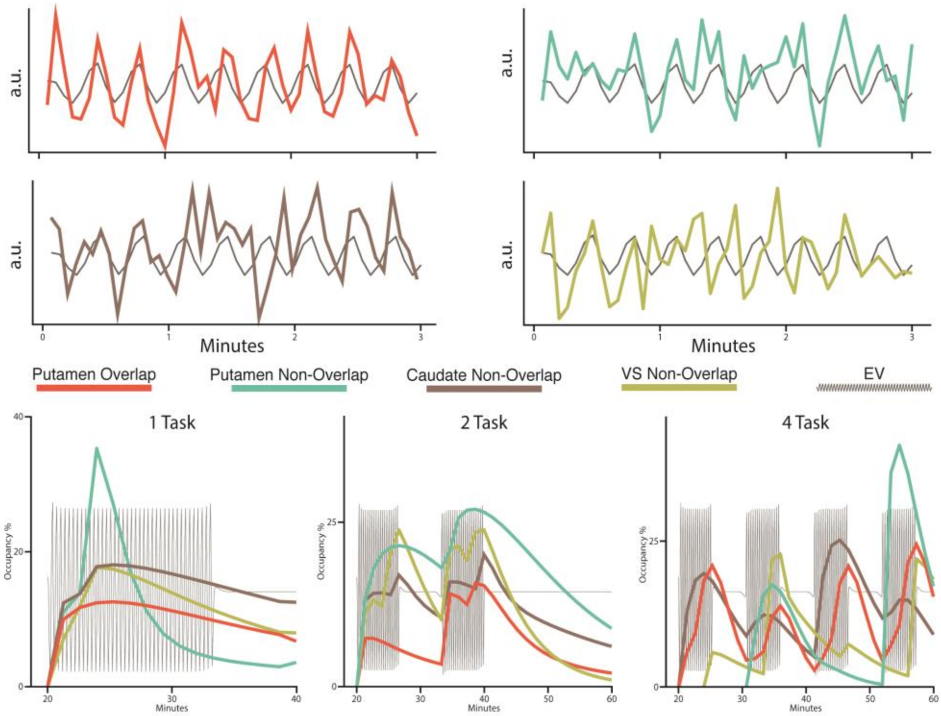


S2-Figure 1. PET and fMRI results from the finger tapping task. Blue clusters represent significant [11C]Raclopride displacement over the group. Red-Yellow represent BOLD response parameter estimates to the contrast tapping > rest. An overlap between modalities could be observed in the anterior putamen while only [11C]Raclopride displacement was observed in the posterior putamen, caudate and ventral striatum. At the bottom right the voxel percentage overlap between the different clusters at various thresholds of the fMRI data is plotted, indicating that the overlap/non-overlap definition was threshold independent. Figure from Grill et al. (2021).

The task data was preprocessed following conventional steps for fMRI as implemented in FSL FEAT. Briefly, this included motion correction by volume-wise rigid body transformation to the first volume, slice timing correction, spatial smoothing (FWHM 5 mm), high pass (50 s) temporal filtering. Single subject task data was analyzed using a GLM with a single on-off regressor of interest describing finger tapping events. The beta estimates from the single subject analysis were taken to a second level group analysis using FSL's randomise function (512 permutations exhaustive combination of permutation; uncorrected p-value) estimating the group mean using a one-sample t-test. The resting state data was motion corrected by volume-wise rigid body transformation to the first volume, slice timing corrected, and 24 motion parameters as well as framewise displacement outliers were regressed out from the data. Minimally preprocessed images were then non-linearly registered to MNI-space using FNIRT. White matter, CSF, and global signal were regressed out and the data was spatially smoothed (FWHM 5 mm) and band pass filtered (high pass 0.01 Hz, low pass 0.1 Hz). Striatal seeds identified from the lp-ntPET analysis were used in a whole brain functional connectivity analysis to provide indications of their connected cortical targets and thereby constrain the interpretation of their functional contribution. For this, each time-series from the striatal seeds were individually correlated (Pearson's correlation) with each voxel's time-series for the whole brain. Individual correlation maps were then Fisher's r-to-z transformed and entered to a second level group analysis. The resulting group t-statistic maps were given a threshold of $t > 2.9$ corresponding to an uncorrected p-value (one-tailed; df = 8) of 0.01 to investigate each seed's strongest functional coupling. The group t-statistics maps were projected to a cortical surface for visualization purposes.

PET

Participants were injected with a bolus plus constant infusion of [11C]Raclopride (Kbol = 105 min; Watabe et al., 2000) commencing at start of PET scan. Following the local standard protocol for [11C]Raclopride studies (Jonasson et al., 2014; Nevalainen et al., 2015), 250 MBq was delivered to the participant during the experiment. A 60 min (20 × 60 s, 30 × 80 s) dynamic time-of-flight acquisition and an MR-based attenuation correction was collected. The data was reconstructed to a voxel size of $1.56 \times 1.56 \times 2.78$ mm^3, employing a resolution recovery OSEM algorithm (3 iterations, 28 subsets, 3.0 mm post filter), with decay, randoms, scatter, and attenuation corrections applied. The data were then motion corrected using FSL's mcflirt with mutual information as cost-function to the 25th frame using framewise rigid body alignment, processed using a HYPR filter (Christian et al., 2010), and temporally smoothed using a three-frame Gaussian kernel ([0.25 0.50 0.25]). Linear parametric neurotransmitter PET (lp-ntPET) was used to estimate voxelwise dynamic binding potentials (Johansson et al., 2019; Normandin et al., 2012; Sander et al., 2013). First, multilinear reference tissue modeling with fixed k2' was conducted. An additional time-dependent term was then fitted to the data for each task block to account for [11C]Raclopride displacement. The time-dependent term was defined as the best least-squares solution of a library of gamma functions (Madsen, 1992) with varying α controlling growth and decay rate. This approach



S2-Figure 2. fMRI and PET signals from finger tapping. The top depicts the mean BOLD signal over 3 min of on/off finger tapping. The 3 min on/off events convolved by the HRF are plotted in grey (EV). The putamen overlap BOLD signal show congruency to the EV while the other clusters are incongruent. Bottom depicts the various task structures (1 Task, 2 Task, 4 Task) and the occupancy dynamics estimated by the lp-ntPET model. Figure from Grill et al. (2021) supplementary materials.

takes into account inter-individual as well as inter- regional differences in [11C]Raclopride displacement, adaptive with the unknown shape and onset of dopamine release related to finger tapping. The best solution for each voxel results in individual t-statistics maps of [11C]Raclopride displacement during the tapping task. Individual task timings were considered only in the first-level model. The individual t statistics maps were then taken to a second level analysis using FSL's randomise function (512 permutations exhaustive combination of permutation; uncorrected p-value) which estimated the group mean [11C]Raclopride displacement using a one- sample t-test, independent of each person's individual on- and offsets (which were not of interest to the current analysis). Thus, the final group map provided a statistical map of coherent spatial locations of dopamine release during task as compared to rest.

Modality Overlap

Qualitative assessment of overlap/non-overlap between modalities was performed at an (arbitrary) t-threshold of 2.9 ($p = 0.01$) for the fMRI group map and a p-threshold of 0.05 for the group PET map. To ensure robustness of assessment a voxel overlap percentage count was conducted for stepwise [t(step) = 0.1] increasing t-thresholds [t(min) = 1, t(max) = 3.5]. This analysis was made to confirm that overlap/non-overlap definitions were threshold-independent. Overlapping and non-overlapping clusters were then assigned to their appropriate anatomical region (putamen, caudate, VS). Once overlap/non-overlap and anatomical compartment ROIs were established, the lp-ntPET analysis was performed again on the TACs extracted from the ROIs to confirm [11C]Raclopride displacement for each ROI and individual.

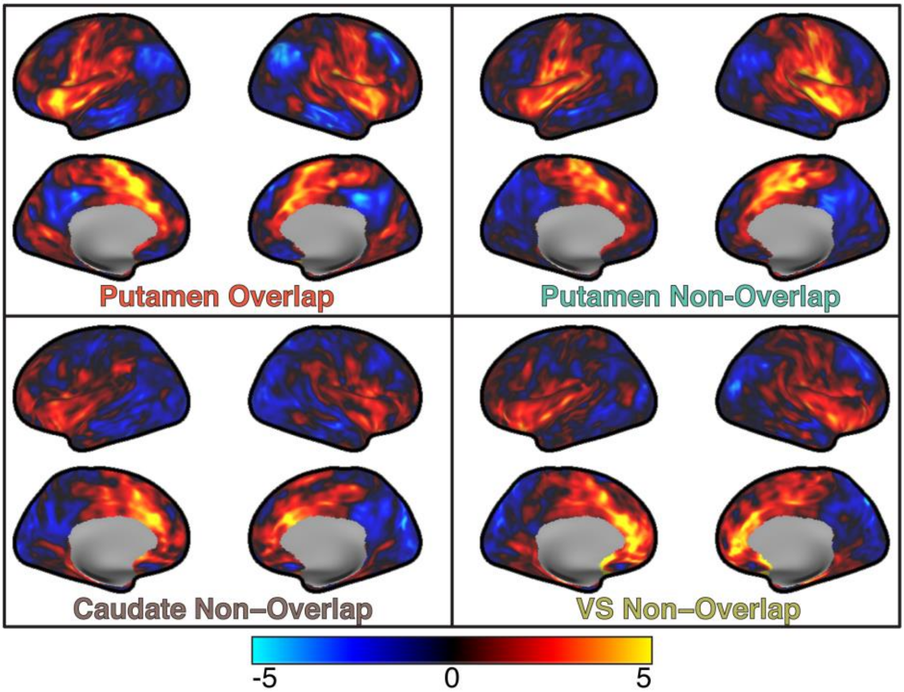
Results

The lp-ntPET analysis showed [11C]Raclopride displacement in several areas of the striatum. Four clusters were observed in the bilateral putamen, three clusters in the bilateral caudate, and two clusters in the bilateral VS. Due to the spatial proximity the clusters were grouped within each anatomically defined for further analysis (S2-Table 1).

The fMRI contrast (tapping > rest) showed a bilateral response in the putamen (left: $p = 0.002$, cluster size 990 voxels, peak t-stat = 8.06; right: $p = 0.002$, cluster size 953 voxels, peak t-stat = 5.25; S2-Figure 1). Modality overlap between [11C]Raclopride displacement and task fMRI response was observed in parts of the putamen (S2-Figure 1). The clusters overlapped well at all thresholds, with 84% of voxels overlapping at an fMRI threshold of p = 0.01. The non-overlapping clusters showed poor

overlap even at lower thresholds, indicating that overlap/non-overlap definitions were fairly threshold-independent. Four general patterns were established: bilateral putamen overlap, ipsilateral putamen non-overlap, caudate non-overlap, and VS non-overlap (S2-Figure 1). An exploratory analysis of the BOLD time course in the non-overlapping clusters showed that non-overlap was not driven by a shifted or negative BOLD signal in relation to the task regressor (S2-Figure 2, top).

The seed-based functional connectivity analysis showed that putamen overlap was functionally coupled to the bilateral motor cortices, supplementary motor area (SMA), anterior cingulate cortex (ACC), and insula. The putamen non-overlap cluster showed generally similar functional coupling as the putamen overlap cluster. The caudate non-overlap cluster showed functional coupling to the ACC. The VS non-overlap cluster showed functional coupling to the medial prefrontal cortex



S2-Figure 3. Cortical functional coupling of all striatal PET clusters separately. Color bar represents t-statistics. Overlapping functional coupling can be seen in the ACC. Figure from Grill et al. (2021), supplementary materials.

and ACC. Overlapping functional coupling between the putamen non-overlap, caudate non- overlap, and VS non-overlap seeds was observed in the ACC (S2-Figure 3).

Brief Discussion

We replicated previous findings that dopamine release is elicited in the putamen and caudate during a non-rewarded finger tapping task. Additionally, we observed dopamine release in the VS, which to our knowledge, has not been reported before during similar tasks. Making use of hybrid imaging, we provide support for the hypothesis that dopamine release observed in the putamen is related to the relatively fast frequency of motor action, while dopamine release observed in the caudate and VS might convey slower sustained task general processes relating to cognitive control and motivation. Resting state functional connectivity with the various dopamine release clusters as seeds was used to explore similarities in cortical functional coupling patterns. A common locus of functional coupling was the ACC which has previously been hypothesized as an integrative area of component processes related to motivation, attention and motor control (Paus, 2001). Our results support an integrative view of ACC and provide evidence that such integration is modulated by striatal dopamine functioning.

Study 3: Human in vivo Evidence for Striatal Dopamine Release in Response to Reward-Prediction Errors during Reversal Learning

Introduction

Learning, unlearning, and relearning action-outcome associations are necessary to optimize rewards and minimize punishments in uncertain environments. Uncertain environments entail noise that should be ignored as well as signals that ought to be acted upon. Making decisions based on noise imply superstitious beliefs regarding the environment; ignoring relevant signals, that should inform decisions, imply erroneously exploiting previously learned behavior. Probabilistic reversal learning paradigms are used to investigate this type of decision flexibility under the reinforcement learning framework. To successfully reverse a behavior, an agent must detect and recognize that the current response strategy results in errors and thus try to learn new action-outcome associations.

Continuing with a choice that was previously rewarded after a reversal has taken place constitutes perseverance errors and are, by definition, reward prediction errors (RPE). RPEs are the canonical teaching signals in action-outcome associations and are believed to guide behavioral reversals (Rescorla & Wagner, 1972; Sutton & Barto, 1998). Human neuroimaging studies have shown that the striatum is involved in processing RPEs (Corlett et al., 2022; Fouragnan et al., 2018), and there is considerable evidence that midbrain dopaminergic neurons fire in a pattern consistent with RPEs (Schultz et al., 1997). Additionally, in animals, it has been shown that dopamine is released in the striatum in response to unexpected outcomes (Clarke et al., 2011; Hamid et al., 2021; Hart et al., 2014). In humans, dopaminergic functions have been related to RPEs (Pessiglione et al., 2006), dopamine medication have been shown to increase RPE sensitivity (Chowdhury et al., 2013; Cook et al., 2019; Cools et al., 2009) and dopaminergic drug administration influence reversal learning performance (Cools et al., 2009). However, *in vivo* evidence for striatal dopamine release in relation to RPEs during reversal learning is still lacking.

In this study we utilized a two forced choice reversal learning paradigm (that fits both PET and fMRI) to elicit trains of RPEs at certain periods. Tracking the most rewarded choice, participants would encounter large RPEs after a phase transition from a stable task environment (where rewards were easily obtained) to a volatile task environment (where rewards were obtained by reversing a previously established response bias). We hypothesized that striatal dopamine release would be observed at this phase transition. [11C]Raclopride PET data and BOLD fMRI data was collected for the whole duration of the task. Making use of cognitive modelling, we explored whether the magnitude of dopamine release correlated with RPE magnitude and RPE sensitivity as could be expected from previous studies. Finally, we further predicted that the spatial loci of dopamine release would overlap with BOLD responses to perseverance errors and RPEs.

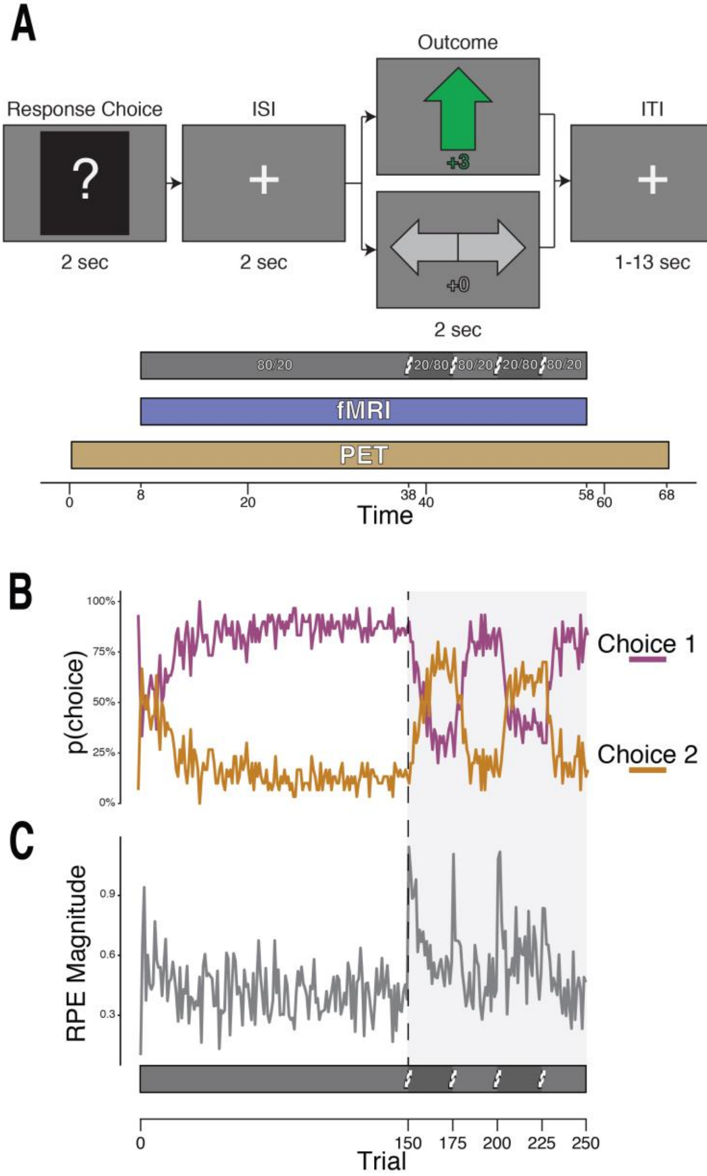
Methods

Participants

Thirty participants (15 female; mean age = 26.13; SD = 4.44, range = 20 – 36) were recruited through ads posted at the campus of Umeå University. Exclusion criteria included current or past diagnosis of neurological or psychiatric illness, claustrophobia, history of head trauma, alcohol or drug dependence, and use of psychopharmaceuticals, drugs, or stimulants other than caffeine or nicotine for the past 6 months. Individuals with MRI-incompatible implants or objects were excluded for MRI safety reasons. Individuals that had previously undergone PET scanning for research purposes as well as pregnant or breast-feeding individuals were excluded for radiation safety reasons. Due to technical reasons, four participants were excluded from the fMRI analysis. This study was approved by the Regional Ethics Committee at Umeå University.

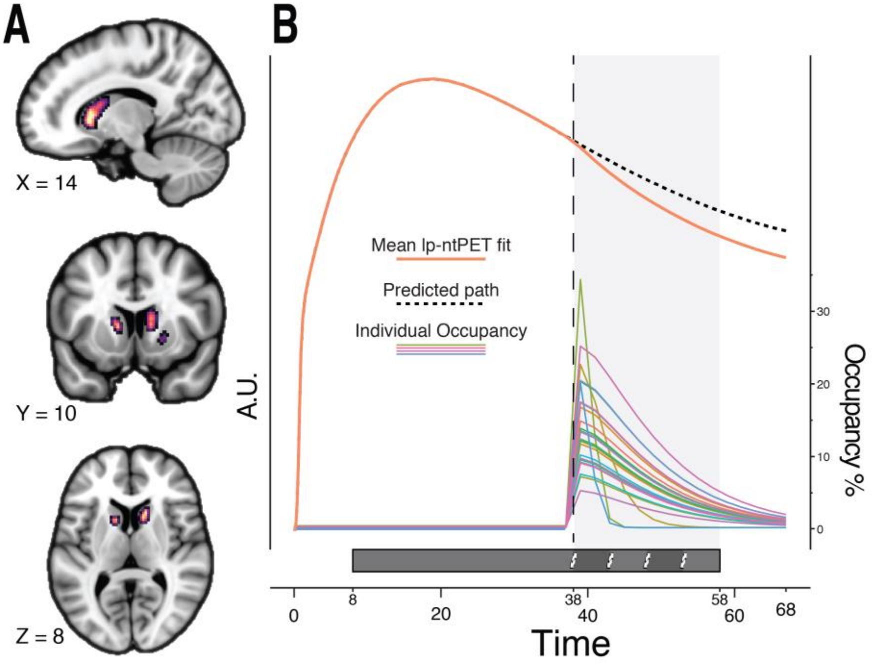
Study Protocol

Participants signed informed consent and were trained on a task resembling the in-scanner task but with random outcomes. After being positioned in the PET/MR scanner they were injected with [11C]Raclopride as the PET scan started. T1w structural images were then acquired as participants observed a fixation cross. Eight min after the PET scan started, the fMRI and behavioral task begun. fMRI and behavioral data were collected for 50 min after which a B_0 filed map



S3-Figure 1. A) depicts a schematic of the task paradigm and experimental procedure. PET and fMRI data was collected during the whole task. B) shows that the reversal manipulation was successful where choice probability for the most rewarded action increased to around 80% during the stable phase and then oscillating back and forth in response to the reversal manipulations. C) using a cognitive model to extract information regarding trial by trial RPEs, we confirm that the behavioral reversals were accompanied by increases in RPE magnitude.

was collected. The PET scan was finished after 68 min, and participants were debriefed regarding task strategies as well as given personality questionnaires to be filled out at home (not used in the current analysis).



S3-Figure 2. A) The significant displacement cluster at group level was contained to the associative striatum. B) Extracting the TAC of the cluster from each participant revealed that displacement had occurred for all participants as seen by the individual occupancy curves. For illustration purposes the mean lp-ntPET fit over all participants is plotted against the mean path the fit would have taken if no displacement was observed.

Behavioral task

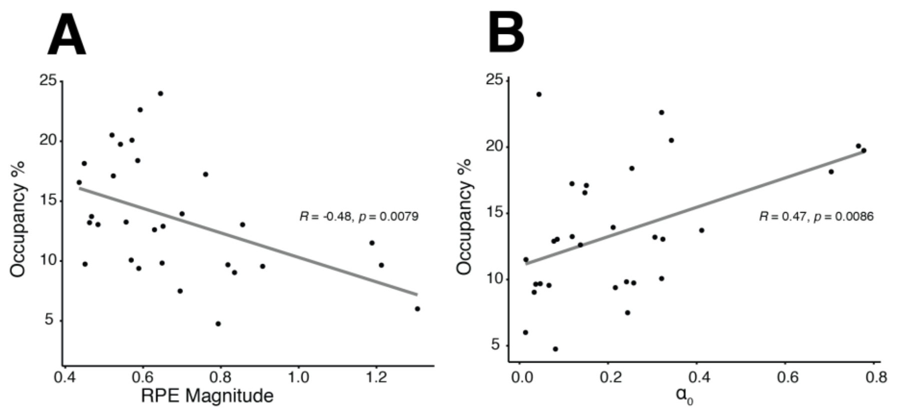
Participants performed a two-forced-choice reversal learning task. Participants were presented with a black card containing a question mark for 2 sec and instructed that there was a number behind the card between 1 and 9. During the question mark presentation they were instructed to indicate with their index finger if they believed the number behind the card to be above 5 and indicate with their middle finger if they believed it was below 5. The question mark was followed by a fixation cross displayed for 2 sec which was followed by the outcome presented for 2 sec. If they guessed correctly, the outcome displayed a green arrow pointing upwards along with a text that showed the amount won ("+3"). If they were incorrect, the outcome displayed a gray double arrow pointing to the left and right and a text indicating that nothing was won ("+0"). The total amount of accumulated rewards was displayed during each outcome presentation. An ITI consisting of a white fixation cross then followed with varying duration. The ITI durations were between 1 – 13 sec and distributed in a pseudorandomized way so that 25 trials took 5 min to complete. Each participant completed 250 trials of the task (S3-Figure 1A).

Unbeknownst to the participants, there was no number hidden behind the question mark. Instead, there was a probabilistic reward contingency relating to if they answered with their index or middle finger. During the first 150 trials, responding with the index finger was associated with 80% chance to be rewarded, while responding with the middle finger was rewarded 20% of the time (stable phase). At trial 151 the reward contingencies switched and continued to switch every 25 trials for 100 trials (volatile phase). Participants were instructed that they would get to keep the accumulated rewards as extra payment (max 600 SEK).

PET

Participants were injected with a bolus of [11C]Raclopride commencing at start of PET scan. Following the local standard protocol for [11C]Raclopride studies (Grill et al., 2021; Jonasson et al., 2014b; Nevalainen et al., 2015) 250 MBq was delivered to the participant during the experiment. A 68 min (6x10 s, 6x20 s, 6x40 s, 9x60 s, 26x120 s) dynamic time-of-flight acquisition and an MR-based attenuation correction was collected. The data were reconstructed to a voxel size of 1.56 x 1.56 x 2.78 mm^3, employing a resolution recovery OSEM algorithm (3 iterations, 28 subsets, 3.0 mm post filter), with decay, randoms, scatter, and attenuation corrections applied. The data were then motion corrected using FSL´s mcflirt with mutual information as cost function to the 25th frame using framewise rigid body alignment, processed using a HYPR filter (Christian et al., 2010), and temporally smoothed using a three-frame gaussian kernel ([0.25 0.50 0.25]).

Lp-ntPET was used to estimate dynamic BP from voxelwise TACs in the striatum (Grill et al., 2021; Johansson et al., 2019; Normandin et al., 2012; Sander et al., 2013). First, multilinear reference tissue modeling with fixed k2' was conducted. An additional time-dependent term was then fitted to the data around the critical transition period between the stable and volatile phases (allowing the function to be fitted 2 min before and 6 min after the critical transition) to account for [11C]Raclopride displacement. The lp-ntPET analysis was then performed identical to study 2. The individual t statistics maps were then normalized to MNI152 space and taken to a second level analysis using FSL's randomise function (5000 permutations; voxel-wise FWE corrected p-value) which estimated the group mean [11C]Raclopride displacement using a one-sample t-test. Thus, the final group map provided a statistical map of coherent spatial locations of [11C]Raclopride displacement, interpreted as dopamine release, during the critical transition from stable to volatile phase of the task. In a next step, the significant [11C]Raclopride displacement cluster was used as an ROI to extract individual TACs for which the lp-ntPET model was fitted again to estimate dopamine occupancy. This two-step approach is done to reduce the noise inherent in the single voxel TACs. For visualization purposes, a predicted path of the TACs was also calculated using parameters R1 and BP estimated from the lp-ntPET analysis, yielding a fit that leaves out the compensatory functions.



S3-Figure 3. A) Significant negative association between RPE magnitude 20 trials and peak dopamine occupancy. B) Significant positive association between RPE sensitivity and peak dopamine occupancy.

MRI

Structural T1w images were acquired during 7 min 22 sec with the following acquisition parameters: [FOV: 25 × 20 cm², matrix: 256 × 256, Slice Thickness: 1 mm, Slices: 180, TE: 3.1 ms, TR: 7,200 ms, Flip Angle: 12, Bandwidth: 244.1 Hz/Pixel]. T1w images were used for segmenting the brain into anatomical compartments using Freesurfer (Fischl, 2012) and normalization to standard MNI space using a preliminary 12 DOF registration with FMRIB's Linear Image Registration Tool (FLIRT) followed by a non-linear registration using FMRIB's Non-linear Image Registration Tool (FNIRT), resulting in 2 mm isotropic voxels.

The BOLD fMRI data was acquired for 50 min with the following parameters: [FOV: 25.6, Matrix: 96 × 96, Slice Thickness: 3.6 mm, TE: 30 ms, TR: 4,000 ms, Flip Angle: 90°, Acceleration Factor: 2.0, resulting in a voxel size of 1.95 x 1.95 x 3.9 mm^3]. The fMRI data was preprocessed following conventional steps for fMRI as implemented in FSL FEAT. Registration of functional data to the structural image was carried out using a boundary based registration algorithm (Greve & Fischl, 2009). The structural image was registered to standard MNI152 space using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001) and was further refined using FNIRT nonlinear registration. Preprocessing was applied accordingly: motion correction using MCFLIRT (Jenkinson et al., 2002), B_0 unwarping, slice-timing correction, non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 8 mm, grand mean intensity normalization of the entire 4D-dataset by a single multiplicative factor, and high pass temporal filtering of 0.04 hz.

Due to the slow TR, it was not possible to disentangle the HRF from the question mark part of a trial from the feedback part of the trial. Events were therefore defined as single whole trials (6 sec). The first contrast of interest concerned the perseverance errors after the first reversal and was defined as error trials within 20 trials after the reversal versus rewarded correct response 20 trials before the reversal (postR1pError > preR1RCR). This contrast was confined to a ROI defined from the PET data. The next analysis investigated BOLD correlates to RPE. Reward, neutral and RPEs at each trial were entered as regressors in a whole brain GLM. The parameter estimates from the contrast reward > neutral and the RPE covariate were extracted from the ROI defined from the PET data and compared using a paired samples t-test.

Computational modelling of behavior

Akin to previous studies (de Boer et al., 2019; Gagne et al., 2020) a base reinforcement learning model (Rescorla & Wagner, 1972; Sutton & Barto, 1998) was fit to the data. The first model included an equation for action probability according to a softmax rule:

$$P(A)_t = \frac{\exp{(\beta \times V(A)_t)}}{\exp(\beta \times V(A)_t) + \exp{(\beta \times V(B)_t)}}$$

where $P(A)_t$ is the probability of choosing A at time t, $V(A)_t$ is the value of choice A at time t, $V(B)_t$ is the value of choice B at time t, and β is a free parameter to be estimated from the data. As well as an equation for value updating:

$$V(A)_{t+1} = V(A)_t + \alpha(R_t - V(A)_t)$$

Where R_t is the reward [0,1] at time t, and α is a free parameter to be estimated from the data. This model was then built upon, including more parameters which were compared against each other using a likelihood ratio test to assess which model best accounted for the data. The first iteration estimated separate α and β for the stable and volatile phase. The second iteration estimated separate α for positive and negative outcomes. The third iteration included meta-cognitive parameters dynamically controlling α based on choice confidence.

Results

The average choice probability over the group confirmed that the reversal manipulation was effective, with decreased probability to the correct choice at reversals (S3-Figure 1B). The mean (M = 5.47 trials) and the standard deviation (SD = 6.45 trials) of the perseverance error for the first reversal showed that there were large individual differences in how quickly individuals were able to unlearn and relearn the action-outcome association. On the group level, spikes in RPE magnitude were seen at the reversal transitions (S3-Figure 1C). The mean RPE magnitude over 20 trials after the first reversal was significantly associated with the number of perseverance errors ($F(1,28) = 46.85$, $p < .001$, $R^2 = 0.63$) such that 0.1 increase in RPE magnitude prolonged perseverance errors with 1.26 trials.

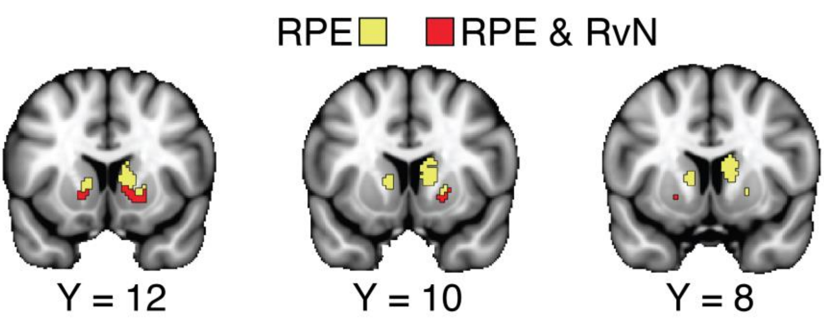
Significant [11C]Raclopride displacement, interpreted as dopamine release, was observed in the associative striatum (peak coordinate = xyz[14,16,6], t-stat = 9.85, k-voxels = 451, $p < .05$, FWE corrected; S3-Figure 2A). The dopamine release was confirmed to occur at the transition between the stable and volatile phase (S3-Figure 2B). Using parameters from the cognitive model, we observed significant associations with peak dopamine occupancy and RPE magnitude ($r(26) = -.48$, $p = .008$) as well as with RPE sensitivity ($r(26) = 0.47$, $p = 0.009$; S3-Figure 3).

Using the significant dopamine release cluster as a ROI we found significant BOLD signal differences using the contrast postR1pError > preR1RCR (TFCE corrected $p < .05$, (peak $t(25) = 3.07$, k-voxels = 105)).

The GLM model including RPE as covariate confirmed that the dopamine release cluster was more related to RPE than the reward > neutral contrast ($t(25) = 2.84$, $p = .009$, mean difference = 8.33).

Brief Discussion

Using multimodal hybrid PET and fMRI together with cognitive modelling we were able to show striatal dopamine release in relation to RPEs during reversal learning. Using fMRI, we were able to confirm a BOLD response difference to perseverance errors during the phase transition that was temporally and spatially congruent with the site of dopamine release. Additionally, we saw that the neural representation of RPEs covered the dopamine release cluster and that the ventral part of the cluster overlapped with the neural representation of rewards, consistent with an affective-cognitive striatal gradient (S3-Figure 4). We confirmed that the variance observed in the magnitude of peak dopamine occupancy was behaviorally relevant through associations with RPE magnitude and RPE sensitivity. As evident from these correlations, although RPE magnitude and RPE sensitivity are related to each other, the observed dopamine release was related to several behavioral processes. It is possible that RPEs signal some secondary higher order cognitive process to be engaged such as cognitive control. The interpretation is compatible with opportunity-cost models that assert an increased cognitive control demand as the average reward rate decreases.



S3-Figure 4. Significant BOLD response to the trial-by-trial covariate of RPE and contrast reward > neutral (TFCE corrected, $p < .05$) inside the dopamine release cluster. The covariate RPE covered all voxels in the cluster (yellow) but overlapped with the reward > neutral contrast in the inferior part (red). MNI-coordinates.

Discussion

This thesis investigates the link between dopamine and various component processes of behavior relating to incentive, associative, and motor functions in healthy young adults using a combination of simultaneously collected fMRI and PET. In two independent studies, using PET, striatal dopamine release was observed during motor processing and during reversal learning. Using fMRI, we were able to constrain the interpretation of the dopamine release as well as relate it to neural representations of behavioral processes. The simultaneous collection and combination of neuroimaging data is a unique aspect of this thesis as it allows for distinctive behavioral paradigms such as reversal learning that could not be performed if the data was collected at separate occasions. In a separate study, we identified a functional network involving the hippocampus and ventral striatum that responded to incentive processing, areas that have been suggested to control midbrain dopaminergic neurons readiness for firing. Below, the results are discussed in a broader context of dopamine signaling, clinical relevance, and methodological considerations.

The functional gradient in striatum

All studies presented in the thesis show results that are consistent with the notion that component processes of behavior are represented in the striatum according to a functional gradient. Most prominent is the result in study 1 where a simple reward response in the ventral striatum could be parcellated into two separate components, where only one of the components responded to an increase in working memory load. Congruent with this finding, we observed a partial overlap between the neural representation of RPEs and reward in a striatal cluster that exhibited dopamine release during reversal learning. The neural representation of rewards is reflecting a bottom-up process, RPEs can be seen as being intermediate between bottom-up and top-down processes since, by definition, the bottom-up stimulus valance must be matched to some internal value expectation for an error to occur. This error is then used to update future top-down expectations. The site of dopamine release during reversal learning might thus represent an interface between bottom-up and top-down behavioral processes. The results from study 2 can be viewed as component processes of motor functions that are represented in the striatal gradient and are influencing motor action. Although not proven here, rodent literature has suggested that open loops in the cortico-striatal-midbrain gradient organization allows for motivational control over motor output (Aoki et al., 2019). Such open loops might partly explain the dopamine release observed in the ventral striatum and caudate during motor functions. Echoing this type of functional domain influence is the finding of overlapping functional couplings in the ACC when using the dopamine release clusters as seeds. The ACC is a target of the meso-cortical dopamine system and has previously been theorized to be an interface where motor control, motivation and cognitive processes meet (Paus, 2001). The dopamine release observed in study 2 and the three-way functional coupling to ACC might signify an integration of component processes during the execution of motor functions.

In study 3 we observed dopamine release which after a *post hoc* control analysis was shown to be specific to the caudate. Comparing the locus of the dopamine release cluster with previous parcellations concerning cortical functional networks (Choi et al., 2012; Yeo et al., 2011), the cluster cover parts of several networks relating to attention and frontal control. From fMRI BOLD imaging during rest, we know that these networks are dynamically oscillating from one network being “active” to another due to the covariance structure of their associated time series. We also know that some of these networks are “task positive” i.e., engaged when external attention on the environment is required, while others are “task negative”, i.e., engaged when internal attention (such as autobiographical thought) is required. Additionally, it has been hypothesized that some of these networks sit as an intermediate between task positive and task negative and act as a circuit breaker to redirect attention (Corbetta & Shulman, 2002; Menon & D’Esposito, 2022). It is possible that the dopamine release observed in study 3 acts to facilitate such redirection of attention, however, due to the quite slow relaxation time of the occupancy curves it is also possible that the dopamine release facilitates the sustain of task positive network engagement.

The relationship between hippocampus and striatum

Study 1 was guided by a model that positions the hippocampus (through a polysynaptic pathway) as controlling the readiness of midbrain dopaminergic neurons to fire (Grace, 2016; Lisman & Grace, 2005). We were able to identify a hippocampal-striatal functional network responding to incentives that could be a candidate human analogue for the model which has been recognized previously in relation to rewarded memory formation (Adcock et al., 2006). The functional network was identified by creating regions of interest from the task data and then examining the strength of resting state functional connectivity between two regions. Further research could investigate how the functional network is modulated by relevant task load. Additionally, recent methodological developments of functional connectivity measures have elucidated more complex patterns of functional couplings than just straight correlation estimates. Indeed, the intricate topographical cortico-striatal gradient has been observed using resting state functional connectivity “connectopic mapping” (Marquand et al., 2017). The method was initially developed to recover different modes of connectivity that are evident in e.g., the visual cortex (Haak et al., 2018). Interestingly, a second mode of cortico-striatal connectivity has been observed and has shown to be spatially sensitive to dopaminergic markers, even able to track Parkinson’s symptom severity and individual sensitivity to dopaminergic medication (Oldehinkel et al., 2022). Given the intricate anatomical organization of the hippocampus and its known functional coupling to striatum, it could be expected that different connectivity modes between the two structures may be observed. Such hippocampal-striatal connectivity modes might prove to be more sensitive to dopaminergic markers than direct functional connectivity strengths which indeed have shown to be associated with D2 receptor availability and episodic memory (Nyberg et al., 2016).

A hallmark of hippocampal processing is in relation to long term memory formation as evident from patient H.M. who, after a bilateral medial temporal lobectomy, was not able to form new memories but able to remember things from before the operation (Scoville & Milner, 1957). Interestingly, H.M. was able to implicitly acquire new motor skills (Squire, 2009), a process likely to involve striatal dopaminergic signaling due to its observed impairment in Parkinson’s disease (for review see Rieckmann & Bäckman, 2009). This presents a certain challenge for the proposed model, but it should be noted that striatal dopamine release has been observed without dopaminergic neurons in the midbrain changing their firing patterns and it has been shown that striatal cholinergic interneurons can rapidly control dopamine release locally (Cachope et al., 2012; Liu et al., 2022; Threlfell et al., 2012). To resolve if the dopamine release observed in study 3 was related to the proposed model further studies are needed that pharmacologically disrupts hippocampal processing or even studies on patients with medial temporal lobectomy.

Dopamine: uncertainty or resource allocation estimate?

The dopamine release observed in study 3 was confirmed to be related to RPEs. In the study negative RPEs were manipulated which has previously been associated with a brief pause in dopamine neurons firing (Schultz et al., 1997). However, dopamine neurons have also been shown to respond to motivationally salient stimuli (Bromberg-Martin et al., 2010; H. Matsumoto et al., 2016; M. Matsumoto & Hikosaka, 2009; Schultz, 2016). Salience is likely part of the observed dopamine release as the motivational salience to neutral outcomes was indirectly manipulated when they transformed from environmental noise to relevant signal during the phase transition. The association with RPE magnitude indicates a state-like attribute to the dopamine release while the association with RPE sensitivity indicates a trait-like attribute. It is likely that fairly low-level processes as RPEs and motivational salience signal secondary, higher level, processes e.g., cognitive control. For 30 minutes, the participants were habituated to respond in a certain way in which rewards were plentiful. After the initial learning, once the habituation has been established, the task should be very easy to perform. During this period, it can be assumed that cognitive control demands are low for most participants since the response is now more or less automatic. During the contextual shift, participants encounter a train of RPEs that are likely to signal the need for increased levels of cognitive control (Westbrook et al., 2021). Indeed, to be able to keep up the past reward frequency a behavioral reversal must take place which requires external attention for error detection and working memory processes to explore new actions.

Before the phase transition, participants' actions can be conceptualized as model-free since the actions are informed by retrospective performance which becomes habitual. After the phase transition, before the new reward contingency is learned, participants actions can be conceptualized as model-based since actions are now goal-directed to modify decisions towards keeping up with the previous reward frequency. The observed dopamine release can thus, in addition to RPEs and motivational saliency be related to increased cognitive control as well as a change from model-free to model-based actions. This interpretation is consistent with the view of dopamine acting as a signal regarding the value of expending some limited internal resource (Berke, 2018), that is, dopamine release during the context transition indicates that the benefits of increased cognitive control outweighs the cost (Westbrook et al., 2021). The volatile context can be described as a manipulation of increased uncertainty compared to the stable context since the reversals were unpredictable by the participants. By definition, RPEs signal a mismatch between predicted and actual outcome which stems from being uncertain about a stimulus true value. During the phase transition, choice uncertainty can be expected to increase (or its inverse choice confidence decreases). The observed dopamine release is thus also consistent with the view that dopamine signals environmental uncertainty (Gershman & Uchida, 2019).

As opposed to study 3, study 2 does not manipulate environmental uncertainty. In study 2, there is a passive control condition consisting of resting between the motor action condition. When transitioning from rest to task, it can be expected that several component processes beyond motor actions are engaged due to increased attentional and motivational demands. The dopamine release observed in study 2 is hard to reconcile as being related to environmental uncertainty (Gershman & Uchida, 2019) but is consistent with the view of dopamine signaling the value of expending some limited internal resource (Berke, 2018). Together, study 2 and study 3 favor the theory of a unifying account of dopamine as signaling a dynamic estimate regarding if it is worth expending some limited internal resource, such as cognitive control. But as always with dopamine, uncertainty is never out of the question.

Given the evolutionary old origin of the striatum it can be expected to perform some basal computation related to behavior. The success of theories relating to the direct/indirect pathway has led to speculations that the striatum (and extended basal ganglia) resolves selection problems. A selection problem arises whenever two or more competing signals seek simultaneous access to some restricted resource (Redgrave et al., 1999). Given the vast problem space one is continuously faced with when acting in the environment, having a dedicated system for resolving selection problems is likely advantageous. A meta-level of the selection problem occurs with the recruitment of either model-free or model-based modes of decision-making. It has been proposed that the settlement regarding which of the two types that is deployed is made by an estimation of the relative uncertainty associated with a mode's resulting actions (Daw et al., 2005). That is, a decision-making mode is selected based on the accuracy of the action performed in the current situation. A case for dopaminergic signaling of uncertainty can thus not be ruled out.

It is apparent that environmental uncertainty, action uncertainty, and resource allocation are highly correlated, making it complicated to disentangle a unifying role of dopamine.

Behavioral relevance of neuroimaging measures

In study 1, a ventral striatal reward response was parcellated into two separate components. The ventral striatum is a region with relatively low signal-to-noise ratio concerning fMRI partly due to its proximity to tissue boundaries (Choi et al., 2012). Parcellations in this area might thus stem from a signal intensity gradient. Apart from the resemblance to anatomical organization and its differential network coupling, the two-component parcellation in study 1 seem to contain behaviorally relevant attributes. In unpublished work, the participants from the HCP were clustered into four groups based on their fluid and crystalized intelligence scores. One group that stood out against the others was characterized by normal crystallized but low fluid intelligence. Comparing the reward versus punish response of this group against the others showed a blunted reward response in the affective component, including hippocampus, but a normal response in the associative component, indicating behavioral relevance of the parcellation.

Due to low power, the lp-ntPET estimate in study 2 was mainly used as a spatial localizer regarding where dopamine release was observed, but it is possible that different dimensions of the dopamine release carry behaviorally relevant information. A negative correlation between motor response frequency and release magnitude specific to the overlapping cluster in the putamen was observed (df(*6*), putamen overlap: $r = -.85, p = .015$; putamen non-overlap: $r = -.29, p = .53$), however due to low DOF, interpretations regarding the association should be done with caution. The *post hoc* correlation does nevertheless indicate that there is behaviorally relevant variance that can be extracted from the magnitude of dopamine release as estimated with lp-ntPET. With increased power in study 3, we were able to observe a significant association between peak dopamine occupancy and the magnitude of RPEs during the transition between the stable and volatile task environment, indicating dopamine release related state changes. We also observed a significant association between peak dopamine occupancy and RPE sensitivity as estimated over the whole task, indicating a trait like quality to the observed dopamine release (S3-Figure 3).

Clinical Significance

Although this thesis only includes data from presumably healthy young adults, the studies can potentially be translated into clinically relevant tests and biomarkers. In study 1, a simple ventral striatal reward response was parcellated into two separate components representing affective and cognitive processing. Such a distinction is interesting considering the blunted reward response commonly observed in depressed individuals (Ng et al., 2019). In depression, it is possible that one of the two reward processing components, or both, show a diminished response depending on expression and severity of symptoms.

The dopamine hypothesis of schizophrenia asserts that part of the disease expression is related to hyper-dopaminergic function (Howes & Kapur, 2009). Using static PET measures and comparisons between patient and control groups, the results regarding the dopamine hypothesis has been largely inconsistent. However, single scan PET paradigms investigating the reactivity of the dopamine system in psychiatric and neurological disorders have to this day hardly been utilized. In this regard, the work in this thesis acts as a proof of concept that dopamine release can be estimated during a single PET scan in relation to a behavioral task and that the estimation contains relevant variance for individual difference measures.

A hallmark of Parkinson's disease is the degradation of the dopamine system, specifically cell death of dopaminergic neurons in the midbrain. The progression of Parkinson's disease is not fully understood but the cardinal symptom is motor dysfunction, however cognitive deficits are observed as well. In study 2, we investigated striatal dopamine release related to motor processing where we observed responses across the striatal gradient. Comparing the dopaminergic reactivity in various parts of the striatal gradient within Parkinson's patients could potentially elucidate the temporal order of disease progression i.e., in what part of the gradient the reactivity is altered compared to other regions.

A strong correlation between the magnitude of dopamine release and RPE sensitivity (learning rate) was observed in study 3. A simple reversal learning task could then act as a proxy for the reactivity of striatal dopamine during reversal learning. The measure would need to be replicated in a larger sample and validated over different age groups for this statement to be reliable. However, due to the costs and limited availability of PET imaging, finding a behavioral proxy of dopamine release would enable a broader research community to relate their findings to dopaminergic signaling.

Methodological considerations

The dopamine release observed in study 2 was much more spatially distributed than what was observed in study 3 even though the task was simpler. Given the increased task complexity in study 3, one could possibly expect the dopamine release pattern to be comparatively more spatially distributed. A difference in statistical power undoubtably plays a role, however, differences in experimental control are likely more important. In study 3, there is an active control condition consisting of the stable context. The control condition thus includes finger movements for responses, getting rewarded and non-rewarded feedback, and cognitive control demands (although as argued above less than for the volatile context). The observed dopamine release is then what is over and above the release that could be expected from the processes engaged during the control condition. To get more specific dopamine release related to motor action, an active baseline should be utilized where participants are attentionally engaged with the task without performing any motor actions.

The behavioral task paradigms during the PET/MR acquisition were tuned to take both modalities into account. The exceedingly long blocks used in study 2 are a bit unusual from the fMRI perspective but were needed for a more reliable signal from the PET data. It is difficult to capture slow brain processes that evolve over minutes, which are putatively captured using PET, with fMRI. On the other hand, fMRI is able to capture transient events at the timescale of seconds which PET cannot. The temporal resolution of the two modalities is thus complementary to each other which we utilized in study 2 where we interpreted overlapping PET and fMRI signals as dopamine release related to transient events. One aim with study 2 was to push the temporal resolution of the PET paradigm resulting in a dynamic, time varying, BP estimate over the resting and active blocks. We were able to estimate such dynamics for several blocks in some participants (S2-Figure 3), however, the reliability of the estimates needs to be investigated further. In the study, we instead used the spatial information from the PET signal together with the knowledge that the signal has a slower temporal dynamic and fMRI's sensitivity to transient events to infer if the dopamine release was related to transient or more continuous processes. In study 3, all participants performed the same task paradigm which seems to have led to a more reliable estimate of dopamine release during the first behavioral manipulation. When designing the experiment, we opted for pushing the temporal resolution of the dynamic PET signal even further using behavioral reversals every fifth minute without a resting condition.

Analyzing the data reveald that dopamine release was only able to be estimated starting from the first manipulation. This can be interpreted as there being something special happening during the first manipulation (i.e. transitioning from a stable to volatile environment) that is not present in the consecutive manipulations or that it is a methodological artifact due to the temporal resolution. If it is a methodological artifact, the consecutive manipulations could still be expected to influence the estimated function which would be expressed as an attenuated decay of the occupancy curve.

Dopamine can be expected to influence the BOLD signal depending on the type of receptor it binds to. Dopamine binding to D1 receptors is expected to increase cerebral blood flow (Knutson & Gibbs, 2007) while dopamine binding to D2 receptors instead decreases cerebral blood flow (Choi et al. 2006; Sander et al. 2013). While the observed [11C]Raclopride displacement is indicative of local dopamine release it is assumed that dopamine binds to both D1 and D2 receptors thus confounding any dissociable, receptor specific, contribution to the BOLD signal. On the other hand, altered cerebral blood volume and flow could potentially influence [11C]Raclopride delivery. Pharmacokinetic modelling of PET data involves estimating ligand flow-rate parameters between specific compartments which depends on the delivery of the ligand from the blood to tissue. During a behavioral activation task altered delivery between compartments could be expected in regions where a concurrent BOLD response is observed, potentially biasing the PET modelling. However, it has been shown that [11C]Raclopride receptor binding can be assessed independently of altered delivery (Sander et al., 2019). Similar results have also been observed for different ligands (Holthoff et al., 1991; Smart et al., 2020). This is an important consideration when investigating behavioral effects using dynamic PET imaging since both the reference and target region can be expected to be involved in processing the investigated behavior.

Limitations

The polysynaptic efferent/afferent connections and neurochemical signaling relating to the striatum are complex. Several important connections and brain areas have been largely ignored in this thesis, although highly relevant, they are out of the scope and boundary of the current investigation. As an example, the striatum's interactions with thalamus are undoubtedly more significant than let on in the introductory text. Similarly, there are several modulatory neurotransmitters not studied or reported on in this thesis that are interreacting with dopamine in the cortico-striatal loops such as serotonin and acetylcholine.

The dopamine signal examined in this thesis is measured at a low temporal resolution. The actual dynamic of the signal is likely to act at a faster timescale. Several debates regarding the timescale of dopaminergic signals can be found in the literature regarding the difference between tonic and phasic signals, with some arguing that tonic signals are a methodological artifact created by specific sampling frequencies (Berke, 2018; Mohebi et al., 2019). The observed dopamine release in these studies could either stem from a change in tonic release or from a cumulative change in phasic release. The results from study 2 do however indicate that the observed dopamine release is related to, at least, two different timescales in a spatially specific manner during the task.

Conclusions and future avenues of research

This thesis includes three studies investigating component processes of behavior represented in the striatum relating to incentive, motor, and associative processing. Study 1 contributes to our understanding of the heterogeneity contained even within a single cluster identified by a simple contrast between behavioral conditions. Such differentiation of a single response is likely to be expressed in areas of the brain that are inherently organized in a gradient like manner and could potentially be investigated in future studies that utilize task contrasts. Additionally, study 1 contributes to our understanding of hippocampal-striatal connectivity by identifying a functional network that co-responds to incentive processing. Study 2 investigates striatal BOLD correlates and dopamine release in response to finger tapping. Striatal BOLD correlates and dopamine release have been observed previously in separate studies. To my knowledge, this is the first time these aspects have been investigated concurrently in a single study. Using the simultaneously collected data we were able to identify dopamine release clusters that were directly or indirectly related to the behavioral manipulation of finger tapping. The results can be used to generate novel hypotheses regarding dopaminergic signaling in neurodegenerative diseases affecting motor processing e.g., Parkinson’s disease. Study 3 contributes to our knowledge regarding the dopaminergic basis of striatal RPEs, which has not directly been shown before. The results open an avenue for investigating the reactivity of the dopaminergic system in response to cognitive tasks during psychiatric diseases, neurological diseases, and aging.

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