

**THE ROLE OF THE RAT MEDIAL PREFRONTAL CORTEX IN COMPLEX DECISION-
MAKING IMPAIRMENTS**

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Abstract

Damage to the medial prefrontal cortex (mPFC) often leads to problems characteristic of addiction, such as impulsivity and insensitivity to future consequences. To learn more about the role of this region, we studied the effects of mPFC lesions in rats on decision making processes related to behavioral addiction. We hypothesized that rodents with mPFC lesions would be less flexible when faced with changing task contingencies resulting in a diminished ability to obtain as much reward as comparable control animals and that this would be due to a deficit in the rats' ability to generate appropriate expected values when presented with multiple choice options. To this end, we designed a rodent decision-making task, the N-Arm Bandit Task, to test these hypotheses. We found that damage to the mPFC decreased the ability of rats to obtain reward after a change in reward contingency and had a modest effect on the likelihood of rats to persevere on ports that were previously rewarding. Finally, we found that PL lesions had a major impact on reward processing in that the reinforcement learning model used to fit the rats' behaviour was unable to meaningfully describe the performance of the PL damaged rats, while the behaviour of the control animals was well described by the model.

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List of Abbreviations

ACC – anterior cingulate cortex
AGI - lateral agranular cingulate area
AH – anterior nucleus of the hypothalamus
AI - agranular insular cortex
AM - anteromedial nucleus of the thalamus
AMG - amygdala
AON - anterior olfactory nucleus
AU2 - secondary auditory cortex
AV – anteroventral nucleus of the thalamus
BAR - Barrington's nucleus
BLA – basolateral amygdala
BMA – basomedial amygdala
BST - bed nucleus of the stria terminalis
CEA – central nucleus of the amygdala
CEM - central medial nucleus of the thalamus
CG1 – cingulate cortex, area 1
CG2 – cingulate cortex, area 2
CL - central lateral nucleus of the thalamus
CLA – claustrum
CM - central medial nucleus of the thalamus
COA – cortical nucleus of the amygdala
CS - conditioned stimulus
CSF - cerebrospinal fluid
DA - dopamine
DBh - horizontal limb of the diagonal band of Broca
dlPFC – dorsolateral prefrontal cortex
DM – dorsomedial nucleus of the hypothalamus
dmStr - dorsomedial striatum

EC - entorhinal cortex
ECT - ectorhinal cortex
ET – exploratory trial
FEF - frontal eye fields
fmi - forceps minor of the corpus callosum
FPC – frontopolar cortex
FR2 - medial agranular region
GABA - γ -aminobutyric acid
GP - globus pallidus
HF – hippocampus
HRA – high reward arm
IGT – Iowa Gambling Task
IL - infralimbic cortex
IP - interpeduncular nucleus
IPS – intraparietal sulcus
LA - lateral amygdala
LC - locus coeruleus
LDT - lateral dorsal tegmental nucleus
LH - lateral habenula
LHy – lateral nucleus of the hypothalamus
LM - lateral mammillary nucleus
LO – lateral orbitofrontal cortex
LPO - lateral preoptic nucleus of the hypothalamus
LRA – low reward arm
M - motor cortex
M2 - secondary motor cortex
MA - magnocellular preoptic nucleus of the hypothalamus
MD – mediodorsal nuclei of the thalamus
MEA – medial nucleus of the thalamus

MHy – medial nucleus of the hypothalamus
MO - medial orbitofrontal cortex
mPFC – medial prefrontal cortex
MRA – medium reward arm
NAc – nucleus accumbens
NAcC - nucleus accumbens core
NAcS - nucleus accumbens shell
NA/DARI - noradrenaline/dopamine reuptake inhibitor
NI - nucleus incertus
NTS – solitary nucleus of the medulla
OFC – orbitofrontal cortex
OT - olfactory tubercle
PAG - periaqueductal gray
PB – parabrachial nucleus of the medulla
PC – paracentral nucleus of the thalamus
PET - positron emission tomography
PF – parafascicular nucleus of the thalamus
PFC - prefrontal cortex
PFx - perifornical nucleus of the hypothalamus
PG – pathological gambling
PGN – paragigantocellular nucleus
PGs – pathological gamblers
PH - posterior hypothalamus
PIR - piriform nucleus
PL – prelimbic cortex
PM - premammillary nucleus of the hypothalamus
PMC - premotor cortex
PO – preoptic nucleus of the hypothalamus
PPC - posterior parietal cortex

PPT - pedunculo pontine tegmental nucleus
PRC - perirhinal cortex
PT – paratenial nucleus of the thalamus
PV – paraventricular nucleus of the thalamus
PVH – paraventricular nucleus of the hypothalamus
RDT – reward driven trial
RE – nucleus reuniens of the thalamus
RF - reticular formation
RH – rhomboid nucleus of the thalamus
rIGT – rodent Iowa Gambling Task
RN - raphe nucleus
R-O - response-outcome
RSP - retrosplenial cortex
sAA - salivary cortisol and alpha-amylase concentrations
SC - superior colliculus
SCR – skin conductance response
SEM – standard error of the mean
SEP - septum
SI - substantia innominata
SLN - supralemniscal nucleus
SMA - supplementary motor area
SN - substantia nigra
SNc - substantia nigra pars compacta
SNM - solitary nucleus of the medulla
SNr - substantia nigra pars reticulata
S-R - stimulus-response
SS - somatosensory cortex
SS2 - secondary somatosensory cortex
SSRI – selective serotonin reuptake inhibitor

STG – superior temporal gyrus
STN - subthalamic nucleus
Str – striatum
SUB – subiculum
SUM - supramammillary nuclei of the hypothalamus
TC - temporal cortex
TP - temporal pole
TR - amygdalo-piriform transition zone
TT - taenia tectum
V - visual cortex
V2 - secondary visual cortex
vIPFC - ventrolateral prefrontal cortex
VM - ventral medial nucleus of the thalamus
vmPFC – ventromedial prefrontal cortex
VP - ventral pallidum
VO - ventral orbitofrontal cortex
vPFC – ventral prefrontal cortex
VR – variable ratio
vStr – ventral striatum
VTA - ventral tegmental area
ZI - zona incerta

The Role of the Rat Medial Prefrontal Cortex in Complex Decision-Making Impairments

Chapter 1: Introduction and Overview

Pathological gambling (PG) is classified as a mental illness whereby individuals will continue to engage in gambling behaviours despite accumulating costs, often involving the inability to maintain healthy relationships or stable finances, difficulties at work, and, in extreme cases, criminal behaviours such as theft in order to pay back debts and maintain their gambling habits. Additionally, PGs often display an inability or unwillingness to forgo immediate gratification even when it will lead to seriously unfavourable consequences in the future. In this way, the problems experienced by individuals with gambling addiction closely resemble many of the same problems experienced by individuals suffering from chemical dependence. The following document will explore many of the neurological underpinnings known to be associated with gambling and other addictions. Chapter 2 begins with an overview of the anatomical connections of regions that appear to be particularly dysfunctional in PGs. Then, the role of one of the principle neurotransmitter related to the addictive process, dopamine, is discussed and the characteristics of games of chance and their impact on dopamine-mediated learning and motivational processes are examined. Afterwards, several theoretical models related to the role of dopamine in reward learning and development of addiction are discussed. Then the findings from several studies investigating the effectiveness of pharmacological treatment on PG severity are reviewed. Finally, the Somatic Marker hypothesis and the different roles that regions in the prefrontal cortex play in behavioural flexibility are explored. Chapter 3 focuses on the role of the medial prefrontal cortex in poor decision-making and how processing impairment in this area can lead to the inflexible behaviour observed in pathological gamblers.

The majority of the chapter is devoted to our investigation of the role of prelimbic cortex in the ability of rats to flexibly adjust their behaviors in response to changing task demands using a variant of the N-arm bandit task, including the methodology used, results of our study, and discussion of our findings. Chapter 4 concentrates on the integration of several areas of research into a theoretical framework for the development of gambling addiction. The addictive process is described from the inheritance of vulnerabilities to addiction to compulsive/habitual behaviours as a result of long term problem gambling. The chapter then closes with overall conclusions and final remarks.

Chapter 2: The Neurobiological Substrates of Gambling Addiction

2.1 Prefrontal Cortex and Striatum Anatomical Connections

Medial prefrontal cortical (mPFC) and striatal (Str) regions are heavily involved in goal-directed learning and dysfunction in these regions has been strongly implicated in behavioural and chemical addiction (de Greck et al., 2010; Gottheil, Winters, Neighbors, Grant, & el-Guebaly, 2007; Grant, Brewer, & Potenza, 2006; Tanabe, et al., 2007; Vanderschuren, di Ciano, & Everitt, 2005). The mPFC projects heavily to the Str and is also interconnected with virtually every other part of the central nervous system; however different regions within the mPFC exhibit differences in afferent and efferent projections and a concomitant segregation of function.

Medial prefrontal cortex (mPFC) regions follow a graded dorsoventral topographical organization (see Appendix A for a thorough discussion). Dorsal regions (dorsal prelimbic cortex and anterior cingulate cortex) primarily receive information from motor and sensory areas concerned with the external environment and send processed information back to output structures that effect change in the external environment as well as basal ganglia and limbic areas concerned with learning from prior experience in order to guide this behaviour. Likewise, ventral regions (ventral prelimbic cortex and infralimbic cortex extending into the orbitofrontal cortex) primarily receive information from visceromotor and sensory areas concerned with the internal environment and preferentially send processed information to output structures that effect change within the body in addition to basal ganglia and limbic areas concerned with learning from prior experience in order to guide these changes (Gruber & McDonald, 2012;

Heidbreder & Groenewegen, 2003; Hoover & Vertes, 2007; Klein, et al., 2010; Kolb, 1990; Kondo & Witter, 2014; Selemon & Goldman-Rakic, 1985).

The striatum appears to be topographically organized in a similar way; with more dorsal areas receiving information from PFC, sensory and motor association areas concerned with the external environment, and ventral areas receiving input from PFC and limbic regions concerned with the internal environment (Chikama, McFarland, Amaral, & Haber, 1997; et al., 2000; Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012; Goto & Grace, 2008; Groenewegen, Wright, Beijer, & Voorn, 1999).

2.2 The Role of Dopamine in Decision-Making

Research into the function of dopamine (DA) in the brain indicate that it is involved in reinforcement and learning (Schultz, 1997), and that abnormal dopaminergic functioning is implicated in the development of neurological and psychiatric disorders such as Parkinson's disease, Huntington's chorea, Tourette's syndrome, addiction, and schizophrenia (Surmeier, Ding, Day, Wang, & Shen, 2007; Surmeier, Song, & Yan, 1996). Originally, it was hypothesized that DA in the striatum carried a hedonic pleasure signal in response to primary reward because of increases in striatal DA levels observed after cocaine administration, but careful study of dopaminergic activity in the striatum cast doubt on this original supposition (Kringelbach & Berridge, 2012). Namely, researchers discovered that the consumption of food was not impaired after nucleus accumbens (NAc) or striatal dopamine depletion using the neurotoxin 6-hydroxydopamine (6-OHDA) or after the introduction of dopamine antagonists even though cocaine self-administration was severely limited (Aberman & Salamone, 1999; Salamone, Wisniecki, Carlson, & Correa, 2001); rather, the consumption of food and basic Pavlovian

approach and avoidance appeared to rely on hind brain and mid brain nuclei. So DA antagonists did not impair appetite to consume food but did impair motivation to engage in goal-directed behaviours in order to obtain food or drug-rewards (Salamone & Correa, 2002). The role that DA plays in reward and learning became clearer after a series of experiments yielded results indicating that the absence of an expected reward decreased DA efflux while presentation of an unexpected reward increased DA efflux (Schultz, 1997; Schultz, Dayan, & Montague, 1997; Schultz, 1998). Importantly, it was also discovered that DA neurons respond initially to a primary reward, then shift to firing in response to cues that predict the reward – the conditioned stimulus (CS) - and no longer fire when the reward is delivered (Day, Roitman, Wightman, & Carelli, 2007; Mirenowicz & Schultz, 1994; Takikawa, Kawagoe, & Hikosaka, 2004). Furthermore, it was also noted that a delay in the reception of reward after the (CS) presentation resulted in a corresponding DA signal depression during the period of time when reward was expected followed by a robust signal increase upon the unexpected presentation of the reward (Richardson & Gratton, 1996). Given that these studies determined that dopaminergic neuron firing is more clearly related to unpredictability, it was now hypothesized that dopaminergic neuronal projections - which are generated in the ventral tegmental area (VTA) and innervate PFC and basal ganglia structures - carry a reward prediction error signal (or teaching signal) regarding the difference in expected reward and the actual amount of reward received (Cromwell & Schultz, 2003; Hollerman & Schultz, 1998; Kawagoe, Takikawa, & Hikosaka, 1998; Mirenowicz & Schultz, 1994). This allows experience to alter the strength of medium spiny neuron synaptic connections within the striatum that ultimately biases the animal to choose one action over another (Jocham, Klein & Ullsperger, 2011; Schultz, 1997;

Surmeier, Plotkin, & Shen, 2009). Hence, this teaching signal is used to generate and maintain/update associations between rewards and actions that lead to the reward, and then ultimately connects those actions to environmental cues that are predictive of those rewards.

However, the role that DA played in learning became more complicated when experiments utilizing aversive rather than appetitive stimuli yielded comparable results; this indicated that the teaching signal supplied by the VTA, rather than being limited to reward prediction error, also seems to encode errors in predicting negative outcomes. That is, increases in dopamine were related to a cue that predicted mild foot-shock and presentation of the cue after foot-shock or alone with no consequence produced no increase in dopamine levels (Young, Joseph, & Gray, 1993). This was unexpected considering that the prevailing DA theory at the time was that DA was released only in response to cues that predicted reward and that decreases in DA levels were supposed to indicate the response to an aversive cue. More recent research has indicated that separate populations of dopamine neurons (that are spatially segregated) encode appetitive and aversive events, while some respond to both (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Matsumoto & Hikosaka, 2009). Thus, changes in DA efflux within the PFC and striatum relate information concerning a general difference between expectation and outcome. Moreover, this error prediction signal appears to have the effect of motivating behaviour toward (in the case of reward) or away (in the case of punishment) from these sources of unpredicted outcome – and eventually towards or away from the cues that predict the outcome. In support of this idea are results from several experiments that have found that dopamine depletion or antagonism in the NAc (or damage to the NAc) affects responding on: (1) fixed ratio schedules that are require high (but not low) amounts of operant

responding in order to obtain a reward (Aberman & Salamone, 1999; McCullough, Cousins, & Salamone, 1993), (2) fixed interval schedules that involve a large amount of time (but not a small amount) elapsing between reinforcements, (3) variable ratio (VR) schedules (where the amount of operant responding required to obtain a reward is varied), and (4) variable interval schedules (where the time elapse required to gain reward is variable; Nicola, 2007).

Additionally, several experimenters found that as rats advanced through a progressive ratio schedule (i.e. the amount of operant responding required to receive reward increases as the session progresses), responding became more sensitive to dopamine antagonism (i.e. ratio strain; Aberman & Salamone, 1999; Nicola & Deadwyler, 2000; Salamone, et al., 2001). In all of these experiments, interfering with the ability of presynaptic DA to effect change in postsynaptic neurons resulted in a decrease in conditioned responding. What all of these schedules have in common is the increasing amount of unpredictability associated with the amount of work required or the amount of time that is required to pass in order to obtain reinforcement. And thus manipulation of DA when performing these tasks affects the amount of work (i.e. either physical work or, in the case of delay, work in the sense of sustained attention) that participants are willing to do in order to obtain the reward – with increases in DA resulting in increased motivation to work and decreases resulted in decreased motivation to work for unpredictable outcomes.

The findings of these studies are of particular import to PG. Gambling games employ specifically designed variable ratio schedules which engender consistent fluctuations in phasic DA release, particularly in the NAc. Generally speaking the payoffs should not be so frequent that it becomes easy to predict how often a person is likely to win (e.g. coin tossing), but also

not be so infrequent that the player loses interest (Linnet et al., 2012). In order for a person to be persuaded to gamble on very remote odds, generally the payoff has to be very large (e.g. national lotteries). The release of DA in the NAc has been linked to an increased motivation to engage in goal-directed behaviours related to the source of the tonic fluctuation (Kringelbach & Berridge, 2012; Anselme, 2013). Moreover, it appears that reducing the time between action and outcome increases the strength of this effect, which may help explain why games characterized by a more immediate outcome are more frequent amongst PGs (da Silva Lobo, 2009). Generally, the closer in time an action is to an unexpected but associated reward, the more reinforcing the effect (Balsam, Drew, & Gallistel, 2010). Therefore, an individual can learn the association between the two more rapidly. Additionally, the closer in proximity a conditioned stimulus is to a reinforcer, the larger the DA efflux (Bermudez & Schultz, 2014). In PGs, this increased reinforcing effect due to close proximity of action and outcome likely increases the motivation to gamble compared to games with delayed outcome (e.g. lotteries).

2.3 Incentive Salience Model

A prominent theory of the role of DA in learning and addiction was proposed by Robinson and Berridge in 1993. The Incentive Salience theory (also referred to as Incentive-Sensitization theory) of addiction posits that all drugs of abuse possess the ability to effect mesotelencephalic dopaminergic neurotransmission. They proposed that increases in DA release linked to the consumption of a drug imbue related actions and contextual cues with motivational properties, making them attractive to the consumer and evoking Pavlovian approach behaviours. If consumed over a long period of time, these cues and actions become sensitized to the point that they will elicit such intense drug cravings that some individuals are

unable to inhibit their responses to these cues, even at great cost to themselves or those around them.

Within this framework of addiction, Robinson and Berridge (1993) noted that, although highly correlated, there is a dissociation between wanting to gain a reward and liking the reward, and that DA neurotransmission appears to be an essential component of the former. A study by Berridge, Venier, & Robinson (1989) yielded findings indicating that rats were able to experience hedonic pleasure in the absence of dopamine neurotransmission. After injections of 6-OHDA (a neurotoxin that selectively destroys dopaminergic and noradrenergic neurons resulting in a dramatic *decrease* of extracellular dopamine levels) into the substantia nigra of rats, the authors observed no change in taste reactivity to different sweet and bitter solutions in the treatment group compared to control animals. That is, rats that received 6-OHDA lesions displayed similar rhythmic or lateral tongue protrusions in response to pleasantly tasting solutions (a response that indicates “liking”) and gapes in response to unpalatable taste solutions (indicating “disliking”) when compared to the responses of the control animals. In agreement with this finding, genetically altered dopamine transporter knockdown mice (DAT KD; which has the effect of chronically *increasing* extracellular dopamine levels) resulted in an increased motivation to obtain reward (“wanting”), but did not increase the enjoyment of the reward (“liking”). Specifically, DAT KD mice had higher breakpoints when tested on a PR reward schedule (i.e. they were willing to make more instrumental responses in order to receive reward than control animals; Cagniard, Balsam, Brunner, & Zhuang, 2006), were found to consume more water and food reward, and were more focused on obtaining a goal on a runway task (i.e. they left the starting area more quickly, stopped less often on the runway,

were less distractible, had more direct pathways to the goal, and required less trials to learn the task compared to control animals). However, consistent with the idea that “liking” was not affected, these mice did not display a change in taste reactivity (rhythmic or lateral tongue protrusions) when they were observed while consuming the reward (Peciña, Cagniard, Berridge, Aldridge, & Zhuang, 2003).

Given this evidence, the theory emerged that increased DA levels induced by the consumption of drugs of abuse causes uncontrollable drug craving “wanting” and seeking behaviours due to increased incentive sensitization in vulnerable individuals (Berridge, 2007). Because games of chance also increase DA release in an analogous fashion, it is likely that gambling addiction shares many of the same features as chemical addiction. Namely, ventral striatal (vStr; a region heavily implicated in reward learning and addiction; Everitt & Robbins, 2005) dopamine manipulation by games of chance appear to affect desire more than hedonic pleasure and the actions and cues associated with gambling likely acquire incentive salience over time in vulnerable individuals, according to this theory.

2.4 Frontostriatal Involvement in Reward Learning and Addiction

Both the mPFC and vStr appear to play major roles in both reward learning and gambling addiction (see section 3.1 for a discussion of results from neuroimaging studies related to PG). Theoretically, the mPFC and vStr act in concert during learning so that an animal is able to maximize reward and avoid punishment. When observed using functional magnetic resonance imaging (fMRI), the mPFC typically displays increases in blood-oxygen-level dependent (BOLD) activity during tasks that involve the processing of uncertain rewards (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005) and decreases in BOLD activity as the tasks are

learned and outcomes become predictable, a pattern which is mirrored in the vStr (Nicola & Malenka, 1998; Nicola & Deadwyler, 2000; Anselme, 2013). One hypothetical interpretation of this activation pattern is that the mPFC and vStr are involved in the processing of information early in learning, when outcome is uncertain, and are an integral part of a larger skill acquisition process linked to survival (Clark, Lawrence, Astley-Jones, & Gray, 2009). Specifically, the vStr is likely involved in goal-directed emotional-motivational processes that promote interaction with sources of unexpected/novel reward, while the mPFC processes complex contextual information that helps guide this motivated behaviour (which is primarily driven by the vStr). That is, when an animal encounters a novel source of reward or punishment in the environment, the vStr drives the motivation to either interact with the source of the reward or to avoid the source of punishment (Flagel et al., 2011; Mirenowicz & Schultz, 1994; 1996; Adriani et al., 2010; McCullough, et al., 1993). This in turn increases the exposure of the animal to sources of reward and provides opportunities for the animal to determine whether there are any stable predictors of reward in the environment (Shizgal & Arvanitogiannis, 2003), whether the animal needs to perform any behaviour(s) to procure the reward, and to practice any skills required to capture the reward (Clark, 2010).

Different stages of the learning and skills acquisition process described above appear to be subserved by different areas of the Str with a shift from more ventral to more dorsal regions of the Str as learning progresses. A major theory concerning this shift suggests that vStr mediates early reward processing (when the relationship between action and outcome is uncertain) and preferentially recruits attentional systems in order to assist in the learning of reward associations; however,

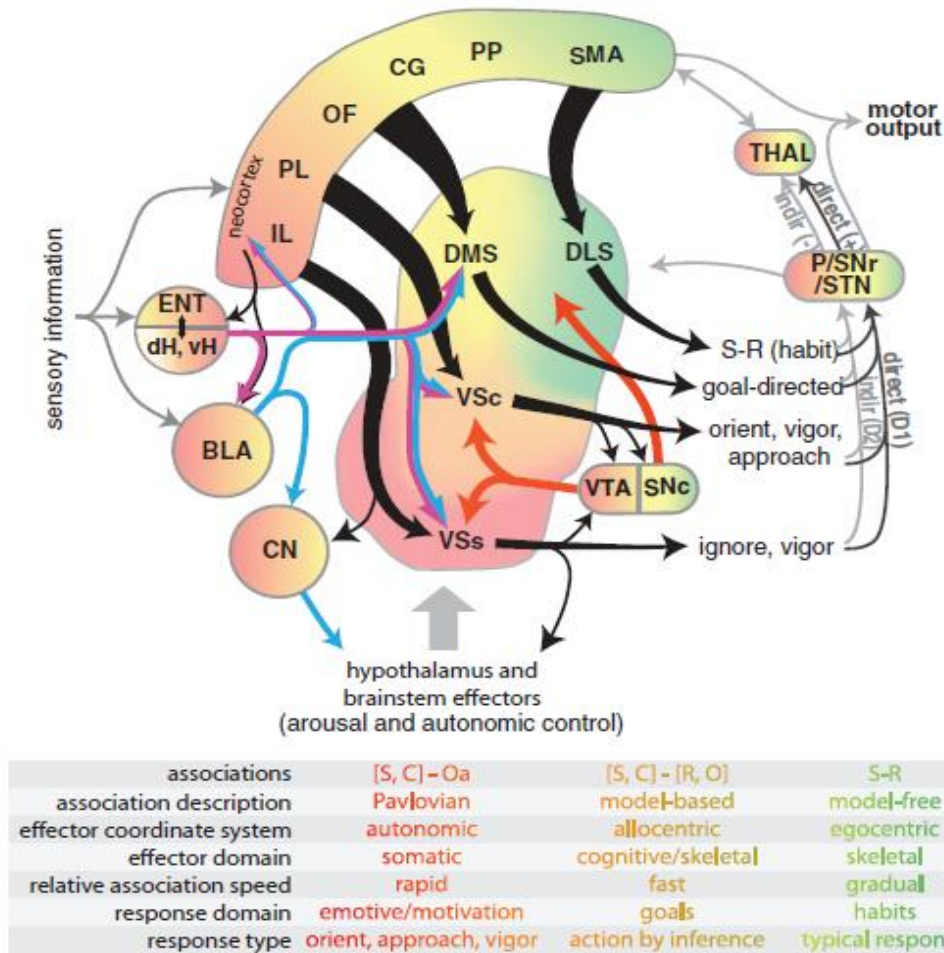


Figure 2.1. From Gruber and McDonald (2012; Figure 1). A schematic illustrating PFC inputs into the Str. Regions are colour-coded to indicate the nature of the information being processed. Red/orange indicates emotional/motivational information, orange/yellow indicates goal-directed information, and yellow/green indicates that habit-related information is processed in these areas. Abbreviations in this figure are as follows: infralimbic cortex (IL); prelimbic cortex (PL); orbitofrontal cortex (OF); anterior cingulate cortex (CG); posterior parietal cortex (PP); supplementary motor area (SMA); thalamus (THAL); pallidum (P); substantia nigra pars reticulata (SNr); substantia nigra pars compacta (SNc); subthalamic nucleus (STN); ventral tegmental area (VTA); nucleus accumbens shell (VSs); nucleus accumbens core (VSc); dorsomedial striatum (DMS), dorsolateral striatum (DLS); central nucleus of the amygdala (CN); basolateral nucleus of the amygdala (BLA); entorhinal cortex (ENT); dorsal hippocampus (dH); ventral hippocampus (vH); stimulus (S); context (C); affective outcome (Oa); response (R); specific outcome (O).

maintaining this attention comes at a price, both in terms of overall energy consumed and in the amount of cognitive resources (i.e. visual/auditory attention, working memory, etc.)

devoted to this specific task which could be used to solve other problems (Gruber & McDonald, 2012). So as the animal learns how to properly engage with the environment in order to gain more reward, the presentation of the reward becomes more predictable and control of those behaviours shifts from vStr to dorsomedial striatum (dmStr) and finally to dlStr (see Figure 2.1; Gruber & McDonald, 2012; van Holst, van den Brink, Veltman, and Goudriaan, 2010). Once under control of posterior regions of the dmStr and the dlStr late in the learning process, the reward associations are thought to become fairly inflexible (whereas they are quite malleable in early stages of learning) and automatic (Yin, Knowlton, & Balleine, 2004; Gerfen & Surmeier, 2011). These associations are characterized by insensitivity to outcome, and behaviours associated with activity in these regions tend to be stereotypical and habit-like (Yin & Knowlton, 2006; Yin, Ostlund, Knowlton, & Balleine, 2005). Not surprisingly, when dopamine (DA) receptors are activated in this area, animals display repetitive stereotypic behaviours (Nicola & Malenka, 1998). In this way, the more resource intensive brain regions utilized in early learning are free to be used to learn something new.

Connectivity studies have lent support to the theory that learning involves a shift from ventral to dorsal areas of the striatum. Haber, Fudge, and McFarland (2000), by means of an analysis of anatomical connectivity of cortical-basal ganglia-thalamic circuits, proposed that the basal ganglia in conjunction with mesencephalic structures form an ascending spiral loop from the shell of the nucleus accumbens (NAcS) to the dorsolateral striatum (dlStr). Specifically the authors found that NAcS sends efferent projections down to the ventral tegmental area (VTA) and substantial nigra pars compacta (SNc), then the medial substantia nigra (SNm; right next to

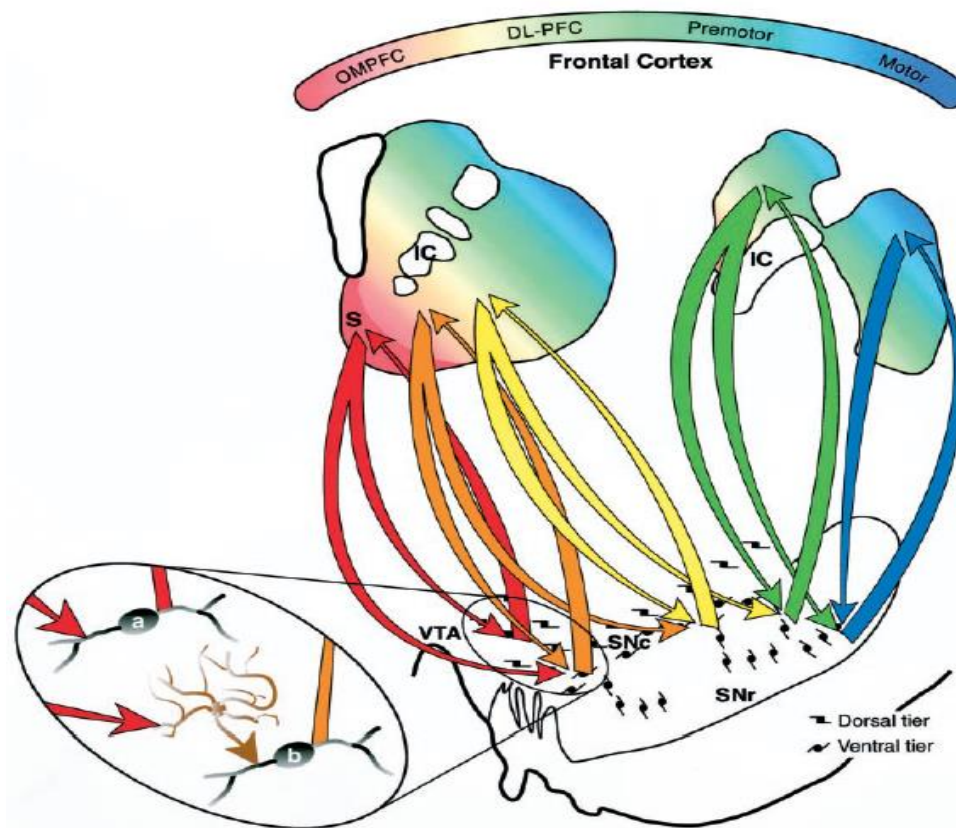


Figure 2.2. From Haber, Fudge and McFarland (2000; Figure 12). An graphical representation of the pathways involved in the ascending striatonigrostriatal loop. Red arrows represent the NAcS to VTA/SNc projections, orange arrows represent the SNc to NAcC to SNm projections, yellow and green arrows represent the SNm to dmStr to SNp, and the blue arrows indicate the SNp to dlStr projections. Cortical input is also colour-coded to indicate connectivity with regions of the striatum. Abbreviations in this figure are as follows: orbitofrontal and medial prefrontal cortex (OMPFC); dorsolateral prefrontal cortex (DL-PFC); nucleus accumbens shell (S); internal capsule (IC); substantia nigra pars reticulata (SNr); substantia nigra pars compacta (SNc); ventral tegmental area (VTA).

the SNc) neurons project back up to the nucleus accumbens core (NAcC) region, which then projects back down into the posterior SN (SNp), and finally the SNp projects back up to the dorsolateral striatum (see Figure 2.2). This ascending loop provides a neurobiological substrate for response-outcome (R-O; this describes the learned association between an action that is performed and a reward that is subsequently obtained) information in the NAc (which

processes unpredictable – DA dependent information) to flow and change via experience into the stimulus-response (S-R; this describes the association between a predictive stimulus and an action that is taken in response to stimulus presentation) associations characteristic of the dlStr (which processes highly predictable information and is relatively insensitive to DA modulation and reward outcome; Everitt, et al., 2008; Gruber & McDonald, 2012; Horvitz, 2008).

Research investigating addiction supports the idea that the vStr is involved in early learning, processes R-O associations and is sensitive to unpredictability, while the dlStr is involved in late learning, processes S-R associations and is unresponsive to deviations in expectation. For example, investigators in one study observed that DA release in the NAc will increase and accumulate in the extracellular space after cocaine administration in drug naive animals, but that DA release is attenuated in animals that had received repeated cocaine exposure prior to testing (Hurd, Weiss, Koob, And, and Ungerstedt, 1989). Furthermore, during early exposure to cocaine, DA release has been shown to increase in the NAcS, NAcC and caudate–putamen after self-administration (i.e. upon reception of reward, but only in the NAcC when cocaine-associated cues were presented unexpectedly); however, after long-term exposure, DA release evoked by a cocaine associated cue only occurred in the dStr (Ito, Dalley, Howes, Robbins, & Everitt, 2000; Ito, Dalley, Robbins, & Everitt, 2002). This shift in behavioural control from vStr/mPFC control early on in reward processing over to dmStr and finally to dlStr control late in reward processing is important in that, theoretically, if functioning in the vStr/mPFC areas is abnormal or disrupted, it stands to reason that behavioural control may become dominated by dlStr mediated activity in situations where vPFC-vStr signalling would

usually dominate behavioural output (e.g. situations where mPFC is needed to update reward associations based on important feedback).

The mPFC has the capacity to change the activity in the vStr and dmStr and may provide contextual information (e.g., based on past experience) to guide future choices. Numerous lines of evidence suggest that context can have a strong influence on decision making. For example, Tinklepaugh (1928), studied monkeys that were trained to discriminatively respond in order to receive reward. Early in the task, favoured food items such as pieces of bananas and grapes were used as rewards for responding correctly; however, later in the task, unbeknownst to the monkeys, Tinklepaugh replaced the preferred food items with a less preferred food item, a piece of lettuce. The monkeys rejected the lettuce reward and became very agitated even though under other circumstances the lettuce would have been readily consumed. This study established that the relative hedonic qualities of the reward can alter the emotional-motivational response; although, more advanced follow-up research was required to establish the means by which this happens. Evidence suggests that the contextual information, such as comparative value, which influences decisions involves dopaminergic activity in both the NAc and mPFC. For example, a study conducted by Ahn and Phillips (1999) found that during a satiety task, both motivation to consume food and DA activity in both the mPFC and vStr (specifically the NAc) were concurrently altered. Specifically, a group of rats were implanted with cannulae in either the mPFC (n=14) or NAc (n=14), and after which were trained on a sensory-specific satiety task. During testing, each rat was placed in a chamber and allowed access to one of two meals (Froot Loops® or Onion Rings®). After a recess, a second meal was presented in which half of the rats were presented with the same meal they had consumed

earlier (same food condition), while the other half received the other meal (different food condition; this was counterbalanced on the second day of testing). *In vivo* microdialysis samples were collected at 10 min intervals during testing over the two testing days. The experimenters observed that all animals exhibited decreased motivation (longer approach times) to consume the food in the same food condition and ate less of the food overall than when they were tested in the different food condition. Moreover, while a robust increase in DA efflux was present during anticipation of food reward in rats whose microdialysis samples were taken from the mPFC, and during food consumption in those rats whose samples were taken from the NAc during second phase of the different food condition; DA levels remained near baseline for both groups of animals in the same food condition. In sum, changes in relative hedonic qualities of these two food rewards was found to be related to changes in extracellular dopamine levels in both the mPFC (during anticipation) and NAc (during consumption). It remains unclear whether the changes in DA level in the mPFC directly influenced the changes in DA level observed in the NAc. However, findings from another study conducted by King, Zigmond, & Finlay (1997), lend support to this idea. The authors observed that after a group of rats underwent mPFC DA depletion using 6-OHDA, basal DA levels in the NAcS increased by 30% compared to control animals. Additionally, the mPFC DA depletion potentiated responses to stress (tail pressure). These findings suggest that DA activity in the mPFC directly affects DA activity in the vStr and thus can effect emotional-motivational processing. It is important to remember that different regions of the mPFC project to separate areas of the Str (see Figure 2.1). Thus the mPFC is likely not only involved in the guidance of emotional-motivational

behaviours, but also that of “goal-directed” behaviours subserved by dorsomedial regions of the striatum (see section 3.1 for a discussion on the role of mPFC in “goal-directed” learning).

Although Str regions appears to be more-or-less sufficient to process the more basic S-R-O associations mentioned earlier in this section, it appears that the mPFC in conjunction with other prefrontal regions are required for more complex reward processing. In particular, the mPFC appears to process signals which combine reward/punishment information with contextual cues over time resulting in the recruitment of behavioural programs tailored to those specific contextual demands (Goudriaan, Oosterlaan, Beurs, & van den Brink, 2004; Heidbreder & Groenewegen, 2003; Kolb, 1990; Euston, Gruber, & McNaughton, 2012). For example, if a dog owner gives his new dog some treats, the dog will learn to associate the owner with the presentation of food rewards and will thus learn to approach the owner with the expectation of forthcoming reward. However, the owner is not likely to produce a treat for the dog every time it approaches him. It generally would not be wise for the dog to simply give up on trying to procure the reward immediately upon reward omission; rather, the dog would be better served to persist in trying to obtain the reward from the owner for a period of time. However, it is also disadvantageous to continue to approach or to behaviourally respond to the owner endlessly. An optimal strategy would be to respond for a period of time, and then disengage in order to seek out other possible rewarding situations. The amount of time spent seeking reward after reward ceases on any particular task appears to be an inherent characteristic, individual to each animal (generally measured by discounting curves of various kinds; Everitt et al., 2008; de Visser et al., 2011; Morrow, Maren, & Robinson, 2011). The mPFC appears to come into play primarily during engagement with these variable reward schedules

(Fukui, et al., 2005; Killcross & Coutureau, 2003). Knowledge acquired at this stage is generally not explicit, even in humans, and theoretically may be experienced more as an emotional biasing of behaviours in response to internal or external environmental cues (Goudriaan, et al., 2004; Conversano et al., 2012; de Visser et al., 2011). Returning to our example, over time the dog may learn that the owner will give him treats more often if he produces certain behaviours for the owner such as sitting on his haunches or laying down on his stomach, and that he is more likely to gain reward in the evening than in the morning, or in the house rather than in the backyard. In other words, the mPFC will enable the dog to learn about the specific instrumental responses and contexts which predict reward. Subsequently, as the rewards become more predictable, activity in both the mPFC and vStr decreases and activity in the dStr increases (Everitt et al., 2008).

In summary, the vStr regions subserve emotional-motivational processing as an individual learns to interact with a novel source of reward, increasing the desire to engage with the reward. As the individual learns how to act in order to obtain the reward, activity shifts to “goal-directed” regions (dmStr). This region subserves processes that allow for skills to be acquired. Regions of the mPFC connect to these areas of the striatum and help guide these processes by modulating activity so that it includes information such as past experience, somatic state, and error detection (see sections 2.2 and 3.1). Finally, late in associative learning, the individual learns to produce the response learned during the skills acquisition phase when a stimulus predictive of reward is presented. This association is mediated by dlStr activity and tends to be “habit”-like.

2.5 Somatic Marker Hypothesis and the Iowa Gambling Task

The neural processes required to make good decisions are complex and involve not only the monitoring, attentional selection, and interpretation of external stimuli, but also similar operations concerning internal stimuli (Bechara, 2005; Lin, Chiu, Cheng, & Hsieh, 2008). Emotion-based signals which are thought to contain information arising from the body (e.g. heart rate, muscle tone, etc.), generally travel through subcortical regions and terminate in cortical structures (primarily the vmPFC, amygdala, insular, and somatosensory cortices) where they modulate complex decision-making processes (de Visser et al., 2011; van Holst, et al., 2010). Damage to the vmPFC is thought to interrupt anticipatory related processing of this information (Bechara, Damasio, Tranel, & Damasio, 1997; Goudriaan, et al, 2004).

The picture that is emerging from biophysiological studies of PGs is that their somatic responses are exaggerated when anticipating gambling but blunted when actually engaging in gambling or risky decisions. For example, Labudda, Wolf, Markowitsch, & Brand (2007) found that when performing the Game of Dice Task, which involves choices involving both risk and reward, patients with PG who made particularly disadvantageous decisions exhibited no increase in salivary cortisol and alpha-amylase concentrations (sAA; an indirect marker of sympathetic nervous system activity), while both healthy control subjects and high performing PG patients did show an increase in sAA concentrations. Likewise, Goudriaan, Oosterlaan, de Beurs, & van den Brink (2006) found that PGs exhibited lower anticipatory skin conductance responses (SCRs) and heart rate decreases compared to normal control subjects before they made risky decisions during the IGT. Furthermore, they found that PGs exhibited a decrease in heart rate after wins while the normal controls experienced a heart rate increase. Further

supporting the idea that PG affects anticipation but not the actual act of gambling, A review paper by Goudriaan, et al. (2004) surveying abnormal physiological markers in PGs, reported that several studies yielded findings that indicated increased heart rate in PGs compared to both control subjects and recreational gamblers when exposed to gambling cues, especially when the cue related to their game of choice. However, when examining gamblers during actual play, a different pattern emerged. In one study, PGs (which were classified as such by the amount of money spent on gambling) exhibited lower blood pressure during slot machine play compared to non-pathological gamblers (Carroll & Huxley, 1994); and although the author of another study found that the heart rates of high frequency gamblers and low frequency gamblers increased from baseline to a similar level during slot machine play, the heart rates of high frequency gamblers returned to baseline more quickly than low frequency gamblers after the gambling session ended (Griffiths, 1993).

One theoretical model that may shed some light on why PGs exhibit abnormal biophysiological responses when gambling or making risky decisions is the Somatic Marker Hypothesis. This theory was proposed by Damasio, Tranel, and Damasio (1991) in an attempt to explain the profound personality changes in a patient following bilateral ablation of the vmPFC to in order to remove a cancerous tumor. After surgery, this patient, EVR, was unable to maintain a job (due to unreliability), and continually made errors in judgment concerning other peoples' social character and what behaviours were socially acceptable; although many other executive functions, such as memory and verbal IQ, remained intact. Additionally, EVR's ability to plan for future events was severely disrupted and would often include peripheral concerns (e.g. what to wear) while internally debating which would paralyze his decision-making

processes, locking him into endless debate. Damasio theorized that EVR was unable to activate somatic states related to reward and punishment, thus disrupting his ability to quickly discern which matters were of import and incorporate those feelings into a timely action.

In an effort to create an experimental task that would tap into the serious decision-making impairments observed in patients with vmPFC damage, such as EVR, Bechara, et al., (1997) designed the Iowa Gambling Task (IGT). In this task, participants are required to make a series of 100 choices from four decks of cards. Each deck offers consistent monetary rewards but also contains probabilistic monetary loss. Two of the decks (A and B) offer large rewards (\$100 per card) but also contain large occasional losses (-\$1250 over ten cards) and so are disadvantageous (i.e., lead to a net loss). The other two decks (C and D) offer smaller rewards (\$50 per card), but smaller probabilistic losses (-\$250 over ten cards) and yield an overall gain in reward if consistently chosen (Bechara, Damasio, Tranel, & Damasio, 2005; Yechiam, Busemeyer, Stout, & Bechara, 2005). Participants are told to try to maximize their profits, but are not made aware of the reward and punishment schedules of the decks and must learn to avoid the risky decks (A and B) and focus on the safe decks (C and D) through trial and error. Bechara, et al., (1997) demonstrated that vmPFC damaged patients are impaired at this task and are drawn to the risky decks (particularly deck B; Hartstra, Oldenburg, Leijenhorst, Rombouts, & Crone, 2010). The authors noticed that healthy control subjects were initially drawn to the risky decks, but then gradually switched over to the safe decks. Moreover, they discovered that after receiving a few losses from the risky decks, healthy participants started to generate skin conductance responses whenever they reached for cards from the risky decks. The vmPFC damaged participants failed to generate such responses.

Bechara (2005) proposed that vmPFC impairment may ultimately impact the balance between the brain's impulsive system (which is controlled by the Str) and the reflective system (which is controlled by the PFC), favouring the former. Importantly, impairments similar to those exhibited by vmPFC patients have also been found when drug addicts and PGs perform the IGT (Tanabe, et al., 2007; Goudriaan et al., 2006). Bechara theorized that the vmPFC functioned as a convergence point for the top-down executive control network and the bottom-up limbic network, and that it is at this point where the two networks battle for control over behaviour. He suggested that dysfunction caused by addiction or trauma in this region would create an imbalance in the relationship between these two networks favouring the bottom-up impulsive network. Because a functional top-down reflective network appears to be necessary to compare present with past events, individuals that cannot integrate this information often exhibit myopia for future consequences (Conversano, et al, 2012, Fukui, et al. 2005, Brogan, Hevey, & Pignatti, 2010; Hoover & Vertes, 2007). Bechara surmised that the critical function disrupted when vmPFC dysfunction is present is the biasing of emotional signals by body states. The SMH posits that the body produces biasing signals in response to reward/punishment outcomes and environmental cues and contexts.

Disruption of somatic signal integration seriously impacts the ability to make timely, situation appropriate decisions. Biasing signals arising from the body generally emerge very quickly after experiencing the rewarding or punishing consequences of interacting with an object, or in response to environmental cues that have been previously linked to rewarding or punishing outcomes. As described earlier (see section 2.4), mesolimbic dopamine signals link outcomes with actions and predictive cues; when this happens, environmental stimuli that are

closely associated in time and space are also linked to the primary S-R-O associations (Everitt et al., 2008). So when a particular environmental situation arises that has been previously linked to an S-R-O association, the brain recruits attentional systems in an effort to monitor the environment for the predictive cue and then can respond accordingly in order to gain reward or avoid punishment. Furthermore, it stands to reason that not only do external environmental stimuli become linked to S-R-O associations, but internal stimuli as well. Like external stimuli, the interaction between the brain and internal somatic signals are bidirectional. For example, experiencing a rewarding outcome can cause the brain to signal an increase in heart rate, while an increase in heart rate (even when artificially induced) can affect changes in brain processes (e.g. alter the perception of a situation, increase the likelihood of one action being taken over another; Christianson, 1992). Within the context of the IGT, Bechara believed that the SCR present in the healthy subjects that participated in the IGT was an indicator of just such a signal and that vmPFC damage in the patient group prevented the R-O information processed in the vmPFC from affecting changes in their bodies (e.g. heart rate, blood pressure, and SCR). Without the input of these somatic markers, the vmPFC damaged patients had serious difficulty keeping track of reward and punishment over time, integrating their internal physiological states with salient environmental cues, and modulating their responses accordingly (Heidbreder & Groenewegen, 2003).

In support of the SMH are findings from anatomical connectivity studies that indicate that the mPFC sends and receives information from regions of the brain that carry information to and from the body. As described in section 2.1 and Appendix A, both the PL and IL regions of the mPFC project massively to mesolimbic structures (particularly the NAc) and are

substantially interconnected with lower visceromotor regions in the brain (e.g. hypothalamus and brainstem nuclei; Hoover & Vertes, 2007; Vertes, 2004), so it stands to reason that dysfunction in the PL or IL regions may result in an inability of the lower visceromotor regions to both engender coordinated somatic activity (e.g. changes in gastric pressure and vascular conductance; Heidbreder & Groenewegen, 2003) in response to learning (mediated by mesocorticolimbic dopamine signalling) and feed somatic information back to the mPFC.

In regard to the poor IGT performance observed in PGs, it is possible that some of the dysfunction is due to a break in communication between the body and brain. Somatic information relating responses to stress (e.g. increased heart rate) or general excitation are not incorporated into the decision-making process and thus may result in an increased tolerance of risk and decreased responses to both punishment and reward. It stands to reason that this breakdown in communication may underlie some of the decision-making impairments and risk-taking behaviours observed in PGs.

2.6 The Dopamine-Deficiency Hypothesis of Addiction

A prominent theory that has been put forth in an attempt to explain why some people are more susceptible than others to the motivational effects of gambling and addictive substances is the dopamine-deficiency hypothesis. This theory states that some individuals have reward systems that are chronically hypodopaminergic, decreasing their ability to become motivated by normal activities (Oberg, Christie, & Tata, 2011; Choi, et al., 2011; Conversano, et al., 2012; Gottheil, et al., 2007). Such individuals would be driven to seek out substances or engage in behaviours that are risky in order to ameliorate the shortage - a kind of homeostatic process (van Holst, et al., 2010; Goudriaan, et al., 2004). Several lines of research lend support

to the dopamine-deficiency theory of addiction. Firstly, researchers have suggested that the decreased activity observed in vStr and PFC in drug and behaviourally addicted individuals reflects this hypodopaminergic state (see section 3.1 for a more detailed discussion of imaging studies). Additionally, several imaging studies using positron emission tomography (PET) have yielded findings that suggest that there is decreased dopamine receptor binding (particularly D_2 and D_3) in the reward systems of people with gambling and other addictions (Tanabe, et al., 2007; van Holst, Goudriaan, Veltman, & van den Brink, 2010). This may indicate that PGs have a reduction in numbers of postsynaptic dopamine receptor sites. Furthermore, reduced $D_{2/3}$ receptor binding has been linked to a general impulsive profile in both rats and humans (Dalley et al., 2007; Everitt et al., 2008; Besson et al., 2010; Boileau et al., 2012).

However, the picture become more complicated when considering that researchers in other studies found that PGs express increased DA receptor binding in the NAc when gambling compared to healthy controls (Joutsa et al., 2012; Linnet, Peterson, Doudet, Gjedde, & Møller, 2010). And perhaps even more intriguing, Linnet, Møller, Peterson, Gjedde, & Doudet (2011) saw similar decreases in receptor binding bilaterally in the ventral striatum of PGs and healthy controls (indicating dopamine release) when performing the Iowa Gambling Task (IGT) compared to baseline; however, while higher levels of DA release were correlated with increased IGT performance in healthy controls, the opposite pattern was observed in the PG group, indicating a possible U-shaped effect of DA on risky decision-making. Additionally, the few studies that have investigated DA metabolite concentrations in cerebrospinal fluid (CSF) have found increased levels of homovanillic acid present in the CSF of both PGs and impulsive individuals indicating that increased levels of DA were present (Chambers & Potenza, 2003;

Conversano, et al., 2012; Cilia et al., 2010; Ibáñez, Blanco, de Castro, Fernandez-Piqueras, Sáiz-Ruiz, 2003).

Genetically driven changes in the activity of enzymes that degrade extracellular DA may help explain some of the inconsistencies related to how abnormal DA levels influence decision-making in PGs. The aforementioned increase in CSF levels of DA metabolites may indicate abnormal activity of certain enzymes that breakdown extracellular DA into homovanillic acid (e.g. MAO, COMT). Indeed, certain manipulations that influence the expression MAO-B in the Str and of COMT in the PFC, and thus influence extracellular DA levels in these regions have been found to effect risky decision-making. Specifically, MAO-B knockout mice (which causes an increase in Str extracellular DA levels) were found to have a significantly more risk-taking behavioural profile compared to wild-type mice (Bortolato, Godar, Davarian, Chen, & Shih, 2009). Similarly, the COMT Met¹⁵⁸Met polymorphism (which is associated with increased extracellular DA levels in the PFC) has been found to increase risky decision-making compared to the COMT Val¹⁵⁸Val polymorphism (Farrell, Tunbridge, Braeutigam, & Harrison, 2012). Both of these studies indicated that increased extracellular dopamine increases risky decision-making, which appears to contradict the finding that increased levels of homovanillic acid are present in the CSF of PGs given that decreased MAO and COMT enzymatic activity should lead to a decrease in the degradation of extracellular DA. However, given that genetically determined baseline levels of MAO and COMT activity related to this impulsive/risk-taking profile are chronic in nature, homeostatic mechanisms may be in play that counteracts the long-term increase in extracellular DA levels, leading to an increase in DA metabolites.

However, this is speculative in nature and further experimentation would be needed to determine if this is the case.

Taken together, the evidence suggests that PGs and other impulsive individuals may be experiencing a rapid turnover of DA in reward related areas rather than a simple dopamine deficiency. Additionally, efficiency of DA in the NAc and PFC may be described as an inverted U-shaped function, that is, synaptic DA concentrations at either extremity may result in decision-making impairments. So, when healthy people gamble, the increase in DA in the NAc leads to better decision-making, whereas the increase in DA levels in PGs leads to sub-optimal decision-making (Linnet, et al., 2011).

2.7 Pharmacological Treatment of PG

Few approaches have been found to be effective in the treatment of gambling addiction. Although, there is some evidence of efficacy using behavioural treatment therapies (Potenza, et al., 2013), I will focus briefly on evidence related to the pharmacological treatment of PG, due to the role that neurochemicals appear to play in the aetiology of the disorder.

Several studies investigating the effects of various pharmacological drugs on PG have been conducted. Most target dopaminergic, serotonergic, and opioidergic systems; however, a few also examined the effects of glutamatergic, γ -aminobutyric acid (GABA)ergic, noradrenergic, anticonvulsant, and mood stabilizers. PG patient groups in various studies prescribed selective serotonin reuptake inhibitor (SSRI) medications escitalopram and fluvoxamine, the noradrenaline/dopamine reuptake inhibitor (NA/DARI) medication bupropion, the opioid antagonist naltrexone, the glutamate antagonist drugs memantine and n-acetylcysteine, the GABA agonist /glutamate antagonist medication acamprosate, and the

anticonvulsant medication carbamazepine, all experienced improvements (Grant & Kim, 2003; Black, Shaw, Forbush, & Allen, 2007; Dannon, Lowengrub, Gonopolski, Musin, & Kotler, 2005; Grant & Potenza, 2006; Dannon, 2004; Dannon, Lowengrub, Musin, Gonopolski, & Kotler, 2005; Lahti, Halme, Pankakoski, Sinclair, & Alho, 2010; Bosco et al., 2012; Grant, Chamberlain, Odlaug, Potenza, & Kim, 2010; Grant, Kim, & Odlaug, 2007; Black, McNeilly, Burke, Shaw, & Allen, 2011; Black, Shaw, & Allen, 2008). Another study found that the GABA agonist /glutamate antagonist medications acamprosate and baclofen were ineffective at treating PG (Dannon, Rosenberg, Schoenfeld, & Kotler, 2011). However, none of the aforementioned studies were placebo-controlled and so considering the wide range of neurochemical targets and the nearly ubiquitous positive outcomes, it stands to reason that the majority of the improvements observed were due to a placebo effect.

A few placebo-controlled, double blind pharmacological studies have been conducted with PG patients testing the effectiveness of the SSRI medication paroxetine, the opioid antagonists naltrexone and nalmefene, the NA/DARI medication bupropion, or the anticonvulsant medication topiramate (Grant et al., 2003; Black et al., 2007; Berlin et al., 2013). Only treatment using the opioid antagonist medications naltrexone and nalmefene resulted in a significant improvement in PGs compared to placebo, however drop-out rates tended to be high (>50%) in most studies (Grant, Odlaug, Potenza, Hollander, & Kim, 2010; Grant, Potenza, Hollander, Kim, & Cunningham-Williams, 2004; Grant et al., 2006; Grant, Kim, & Hartman, 2008). One of the studies investigating the effectiveness of opioid antagonists found that significant improvement over placebo was only observed when the PGs had a family history of alcoholism (Grant, Kim, Hollander, & Potenza, 2008). This is noteworthy because these

medications are primarily used to treat alcohol addiction. Importantly, significant improvements in gambling severity were found in one placebo-controlled study investigating the effectiveness of the mood stabilizer lithium on PGs with comorbid bipolar disorder (Hollander, Pallanti, Allen, Sood, & Baldini Rossi, 2005). The key finding in this study was that the main effect of lithium was to alleviate the symptoms of the comorbid bipolar disorder, which in turn helped to lessen the gambling severity.

Altogether, pharmacological treatment appears to be mostly ineffective in treating PGs other than to provide a placebo effect, which by itself appears to be fairly effective in the short term. There is some evidence that opioid antagonists help to alleviate PG symptom severity, however it may be partially due to the amelioration of comorbid alcohol addiction symptom severity in a similar manner to the effect lithium has on PGs with comorbid bipolar disorder. Therefore, it may be more beneficial to focus on the pharmacological treatment of any comorbid disorders (that are known to respond to medication) that a PG may have rather than trying to treat the PG itself.

2.8 The Role of the PFC in Reversal Learning and Perseveration

Different regions of the PFC are involved in different aspects of modification of behaviour in response to changes in reward and rules. This section will highlight several studies which provide insight into dissociable roles of regions within the PFC in tasks that examine responses to rule or reward changes.

A study by Windmann et al. (2006), found that activity in the medial orbitofrontal cortex (MO) was involved in maintaining a behavioural strategy while activity in the lateral orbitofrontal cortex (LO) was related to the ability to shift from an initially preferred choice

option to an alternative after performing experiments using both the original and inverted versions of the IGT (see section 2.5 for an explanation of the original IGT; the inverted version contains steady losses with occasional gains) in healthy controls.

The OFC and mPFC are both involved in the ability to shift behavioural strategies in response to a change in the cues that predict reward, and damage to either of these regions will produce perseverative behaviours. Rivalan, Coutureau, Fitoussi, & Dellu-Hagedorn, (2011) noted that lesions or drug infusions in the OFC, which alter its normal functioning, impact animals' ability to learn reversal tasks which require the animal to first respond to one set of stimuli in order to gain reward (e.g. press a lever in response to a green light and not respond upon presentation of a red light), then to shift behavior towards another set of stimuli while inhibiting the previously learned behavioural response pattern (e.g. press the lever in response to the red light and inhibit responding upon presentation of the green light); ultimately, the disruption of normal OFC functioning resulted in large increases of perseverative responding, possibly due to its integral role in signaling the value of an outcome (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006). Moreover, while perseverative behaviours are related to OFC dysfunction, mPFC dysfunction (particularly when activity in the PL region is abnormal) also produces perseverative behaviours, but likely because the animals are no longer able to adapt their behaviour in response to both outcome value (i.e. signals from the OFC could no longer influence activity in the PL region) and reward contingency changes (i.e. environmental cue – reward outcome associations could no longer be processed efficiently) after original associations had been established (Seamans, Floresco, & Phillips, 1995).

In summary, different regions of the PFC subserve different aspects of responses to changes in task contingencies, and likely work in conjunction with one another to achieve successful performance and obtainment of reward. The purpose of this section was primarily to provide background and context to role of mPFC in behavioural flexibility that will be discussed in Chapter 3. Additionally, I found during my research that many studies included the OFC when describing changes in mPFC activity during several tasks (e.g. IGT, reversal learning tasks, set-shifting tasks), so it is my hope that this section has helped clarify some of these convolutions.

Chapter 3: The N-Arm Bandit Task

3.1 Introduction and Background

PG can be conceptualized as a deficit in decision-making. The majority of individuals with PG can be characterized as impulsive, risk-seeking, and having a greater preference for strong arousal compared to the general population (Conversano, et al., 2012; Goudriaan, et al., 2006; but see Slutske, Cho, Piasecki, & Martin, 2013). Additionally, PGs have difficulty thinking of future consequences of their actions, instead preferring immediate gratification (Albein-Urios, Martinez-González, Lozano, Clark, & Verdejo-García, 2012; Andrade & Petry, 2012). For example, Alessi and Petry (2003) found that when PGs were tested on a delay discounting paradigm where participants must choose between small immediate rewards or larger delayed rewards; high scores on the South Oaks Gambling Screen (SOGS; a gambling questionnaire which is often used to identify individuals with gambling problems – higher scores indicate higher severity) was the single best predictor of impulsive choice. Furthermore, psychological, neuroimaging, and physiological (see section 2.5) evidence suggests that PGs process reward and punishment differently than healthy persons; a dysfunction that has also been observed in people with chemical addictions (Balodis, et al., 2012; de Greck, et al., 2010; Hewig, et al, 2010; Reynolds, 2006).

PGs consistently show abnormalities in several brain networks, principally in reward learning circuits (see section 2.4 for a discussion on reward learning), when compared to healthy individuals. Specifically, research into neurological dysfunctions in PGs have indicated abnormal activity in ventral Str, PFC (ventromedial, ventrolateral, and dorsolateral, and orbitofrontal), insular, anterior cingulate cortical, and posterior parietal cortical areas. (Potenza,

2013; Iancu, Lowengrub, Dembinsky, Kotler, & Dannon, 2008; de Greck et al., 2010; van Holst, et al., 2010; Dannon et al., 2011; Goudriaan, Ruiter, van den Brink, Oosterlaan, & Veltman, 2010; Clark, 2010; Grant, Brewer, & Potenza, 2006; Hollander, Pallanti, Baldini Rossi, Sood, Baker, & Buchsbaum, 2005). Imaging studies investigating risky decision-making or the anticipation and reception of reward/punishment of PGs compared to healthy control subjects typically produce results indicating that PGs have diminished activity in these regions (particularly the vStr and vmPFC; Tanabe, et al., 2007; Reuter, et al., 2005; but see Linnet et al., 2010). Yet, studies investigating cue reactivity (e.g. images or video of people gambling at a casino) have yielded findings that show the opposite pattern (i.e. increased vStr and vmPFC activity; Reuter et al., 2005; Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005). Although, these findings may appear to be contradictory, this pattern likely reflects the dissociation between “liking” and “wanting”. The increased fMRI BOLD activity induced by the presentation of gambling cues, may reflect the increased desire (“wanting”) to engage in gambling; whereas, the decreased BOLD activity during process of gambling may reflect decreased pleasure (“liking”) experienced by the PGs. Importantly, similar findings have been noted in studies of chemical addiction (see section 2.3; Goudriaan, et al., 2010). Alternatively, it has been suggested that reward networks of PGs may be hypersensitive during those tasks which most closely resemble naturalistic gambling (e.g. participants gamble with their own money, gamblers who prefer slot machines are tested on tasks that use slot machines) and hyposensitive during other decision-making tasks (van Holst, et al., 2010; van Holst, Veltman, Büchel, van den Brink, & Goudriaan, 2012). However, regardless of whether PGs are hyper- or

hyposensitive to reward; there is a clear consensus that they process risk and reward differently compared to healthy individuals.

Because the imaging studies investigating neuropathology in PG have primarily implicated regions involved in reward processing, we decided to focus our research on the mPFC, an area intimately involved in processes related to reward learning. In particular, this region appears to play a key role in the guidance of “goal-directed” learning, which contrasts with the “habit”-like behavioural processing that typically occurs in the later stages of learning. When first attempting to ascertain mPFC function, Corbit and Balleine (2003) ran a series of experiments which examined the effects of damage to the PL region of the mPFC on ‘goal-directed’ action in rats. After receiving either an excitotoxic lesion or sham surgery, the food-deprived rats were trained to press two different levers in order to receive food reward; one lever delivered a sucrose solution while the other delivered food pellets. Once this R-O association was learned, the rats were tested on a satiety/extinction protocol where they were allowed free access to either the sucrose solution or food pellets for 1 h prior to testing. During the extinction testing period, rats were again allowed access to the two levers; however pressing the levers no longer resulted in reward. During this phase the experimenters recorded the number of lever-presses made by each of the animals on both of the levers. They observed that not only did PL damaged rats learn the task more slowly overall, but they also reduced lever-press responding non-selectively during extinction testing. That is, while the control animals more rapidly reduced the number of presses on the lever that previously been known to deliver the food reward that they had access to during the satiation period (e.g. rats that had access to food pellets rapidly stopped pressing the lever that used to deliver food pellets); the

rats with PL lesions reduced responding on both of the levers at the same rate. Importantly, the authors discovered that this effect was specific to extinction; when tested in situations where the levers continued to produce reward when pressed, sham and PL damaged animals responded similarly to specific reward devaluation due to satiation (i.e. both sham and PL damaged rats that were given free access to food pellets before the task pressed the lever that was associated with receiving food pellets less often – and at a similar rate - than the lever that was associated with the sucrose water reward). The authors theorized that while the basic ability to learn and update R-O associations remained intact (although retarded) after injury to the PL region; a specific deficit emerged when multiple R-O associations needed to be held in working memory and used in order to guide behaviour. That is, the PL damaged rats were unable to hold the different R-O associations online in order to predict the specific outcomes of their actions, and subsequently were unable to combine these predicted outcomes with the information related to their specific satiety state. In contrast, the intact animals were able to incorporate the incentive properties of the R-O associations into specific predicted outcomes in an effort to produce the precise behaviours required to reach the goal of obtaining the more valued of the two food rewards; thus actions that led to reception of the devalued reward were more easily extinguished in this group. In sum, the mPFC appears to be necessary for integrating information concerning body states related to past experiences into behaviour, and specifically when that information needs to be held in an online state.

Gambling and other addictions have been linked to dominance of a habit-based brain circuits over goal-directed circuits. As discussed in section 2.4, both the mPFC and dmStr (regions involved in goal-directed learning processes) are sensitive to changes in outcome,

display increases in activity when acquiring and updating R-O associations, and are thought to work together to produce behaviours that lead to goal obtainment. Supporting the relationship between these two regions are the dense anatomical projections from the mPFC (particularly the PL region) to the dmStr (see Appendix A for a full discussion). These “goal-directed” regions contrast with the dlStr, which tends to show increases in activity when S-R associations are utilized, and is thought to be involved in controlling “habit”-like behavioural processes, which are insensitive to changes in outcome. In a seminal paper, Everitt & Robbins (2005) theorized that the change from controlled to compulsive drug use experienced by drug addicts may reflect a shift from dmStr “goal-directed” control of drug-seeking behaviour to dlStr control, resulting in habitual drug-seeking behaviours. Subsequently, this domination of behavioural output by the “habit” system is thought to underlie the perseverative/inflexible kinds of behaviours often observed in drug addicts (Clark, Cools, & Robbins, 2004; Everitt, Dickinson, & Robbins, 2001). Because chemical and behavioural addictions likely share similar neuropathic aetiologies (Gottheil, et al, 2007), it is reasonable to suppose that this theory would also apply to PG.

Many of the cognitive deficits observed in PG may reflect hypo-activity in goal-related regions, including the mPFC. PGs - like drug addicts - frequently exhibit numerous cognitive deficits, particularly on measures of self-control and impulsivity (Potenza, 2013; Leeman & Potenza, 2012). These deficits often manifest in perseverative behaviours which involve the inability to flexibly alter behavioural strategies when reward contingencies change. The inability to maintain an optimal reward strategy supports the suggestion that the “habit” system in PGs is dominant which may be due to an ineffectual “goal-directed” system (possibly due to mPFC

impairment and a resulting inability to incorporate all of the information relevant to reward acquisition and the generation of behavioural responses that reflect the integration of this information). So, even though an individual may be able to initially determine an optimal strategy under one set of conditions, he may be unable to change his behaviour when those conditions are altered – a function that is typically tested using reversal and alternation learning tasks.

Several studies have provided evidence that intact ventral PFC functioning is necessary for an individual to be able to shift behavioural strategies based on changes in reward contingencies. An fMRI study of pathological gambling in humans by de Ruiter et al. (2009) attempted to establish whether ventral frontostriatal dysfunction is associated with the perseverative behaviour commonly observed in PG patients. The authors found that when tested on a reversal learning task in which participants could win or lose money; PG subjects displayed marked impairment in ability to shift behavioural response patterns, a deficit not seen in healthy control subjects. They theorized that this was due to loss of sensitivity to both punishment and reward evidenced by significant decreases in vLPFC activation when money was lost or gained. Another fMRI study investigating reversal learning in PGs was conducted by Dannon, Kushnir, Aizer, Gross-Isseroff, Kotler, & Manor (2011). The researchers observed increased BOLD activity in both lateral and medial PFC regions (particularly in orbitofrontal cortex) during performance of an alternation learning task and that this increase positively correlated with the PGs scores on the SOGS. Finally, an animal study by Seamans, et al. (1995) found that after rats received lesions to the PL region of their mPFC, they exhibited a severely impaired ability to adapt to a change in task rules. The rats ($n = 14$) were initially trained on a

Delayed Spatial Win-Shift paradigm; where rats initially collected food from 4 of the arms on an 8-arm radial maze, and after being removed from the maze for 30 min, were again allowed to forage for food. However, at this time only the other 4 (previously unbaited) arms delivered food reward, thus the rats needed to be able to remember which of the arms had previously been baited and adjust their strategy to exclude those arms when foraging after the 30 min delay. After this training phase, the PL regions of 8 animals were inactivated via a lidocaine injection, while the remaining 6 animals received a saline injection (sparing PL function). After receiving their injection (same-day) the rats were tested on their ability to perform a random foraging task in which 4 of the 8-arms of the radial maze were baited randomly. The experimenters observed that rats with PL inactivations were unable to flexibly adapt to the new rules, and displayed large increases in arm re-entry errors (i.e. perseveration) compared to control animals. These studies highlight the role of the mPFC in reversal learning and the ability to flexibly shift behavioural strategies in response to changes in reward outcome. It then follows that the impaired functioning of this area observed in PGs plays a major role in the impaired behavioural flexibility seen in PGs.

One research area that can possibly shed light on specific functional roles of the mPFC in reward learning and behavioural flexibility is foraging theory. In a foraging environment, an animal must search in order to find food or water. Once discovered, the animal should take advantage of the reward available for some optimal amount of time. If the animal leaves the reward source too soon, it runs the risk of losing that resource to other animals, changes in the weather (e.g. storms or frost), or simply because it is unable to find it again. Alternatively, if the animal continues to exploit that source of food or water for long periods of time, it may

become a target for predators, or it may give up opportunities to find new sources of food or water. This example represents the exploitation/exploration dilemma that animals face when having to decide between gathering resources and gathering information that could lead to more resources. In order for an animal to act optimally in the environment, it must be able to persist in gathering resources when they are available, but also be able to shift into exploratory behavioural strategies when necessary.

To study the neural mechanisms of exploitation/exploration decisions in humans, Daw, O'Doherty, Dayan, Seymour, & Dolan (2006) conducted an fMRI study where 14 healthy participants repeatedly chose between four slots which offered varying rewards in a simulated "Four-arm Bandit" Task. The subjects had to sample the four choices in order to determine which offered the best reward. Over time the amount of reward offered by each arm changed gradually so that an arm with a high pay off initially would gradually decrease in value and vice-versa. The participants had to balance the need to occasionally choose arms where payout was uncertain (exploration) with choosing the slot they thought at that time had the highest payoff (exploitation) in order to figure out which arm was best overall. In addition to recording fMRI BOLD activity during exploration and exploitation phases of the task, the experimenters also fit several reinforcement learning models (RL) to the participants' performance with the intention of better understanding the internal mathematical processes taking place and the potential roles of certain brain regions in these processes.

Reinforcement learning describes the problem of how an agent adjusts its behaviour in the external world in order to maximize reward. RL models are computer algorithms which seek to solve this problem. Most rely on a training signal which is the difference between expected

and actual reward (i.e. an error prediction signal; see section 2.2 for a discussion on the possible role of dopamine as an error prediction signal). The equations used in the computational model include a basic action-outcome reinforcement learning equation (1); where $Q(c)_{t+1}$ represents the predicted value of the choice (c) reward for the next trial (t+1), $Q(c)_t$ equals the expected value of the choice (c) for trial (t), r_t represents the actual reward received on the trial (t), and α represents the learning rate parameter, and a softmax probabilistic decision rule (2); where $P(c_t)$ equals the probability of selecting choice (c) on trial (t), $Q(c)_t$ again equals the calculated value of the choice (c) for trial (t), and β represents the inverse temperature parameter which determines the randomness of the choice.

$$Q(c)_{t+1} = Q(c)_t + \alpha(r_t - Q(c)_t) \quad (1)$$

$$P(c_t) = \frac{\exp(\beta \cdot Q(c)_t)}{\sum(\exp(\beta \cdot Q(c)_t))} \quad (2)$$

The α value (which varies between a range of 0 and 1) determines to what extent the newly acquired information will override the old information. An agent with an α value of 0 will not learn anything, while a value of 1 would make the agent consider only the last trial (and thus totally disregard all previous information). Both extremes are hazardous in the real world, where an animal with a very low $\alpha \rightarrow 0$ would not be able to retain any information and could never adapt its behaviour to exploit a reward source, and an animal with a very high $\alpha \rightarrow 1$ could not adapt its behaviour to probabilistic information derived over time. For example, woodpeckers often have to peck a tree many times to obtain an insect hidden within. These birds would likely peck at a tree until the number of times pecked per insect gained becomes

too high (represented by a standard discounting curve) and would abandon that tree in search for one with potentially more insects within it. A wood pecker with a learning rate where $\alpha \rightarrow 1$, would peck the tree as long as it is receiving insects and conclude that the tree always offers rewards when pecked (high expected value), but upon the first peck where no reward was obtained the bird may conclude that the tree offers no reward (zero expected value) and would fly away to try another tree.

The β value represents the propensity of an agent to choose the option with the highest represented value ($Q(c)_t$). If the inverse temperature is low ($\beta \rightarrow 0^+$), all actions have nearly the same probability (i.e. the agent would produce random behaviours); thus the larger the inverse temperature becomes, the more expected values affect the probability (i.e. when the inverse temperature is very high [$\beta \rightarrow \infty$], the probability that the agent will choose the option with the highest expected reward approaches 1). For example, a participant playing the “4-arm Bandit” Task who had a very low β value would display a fairly random pattern of selection; whereas a participant with a β value $\rightarrow \infty$ would persist at whichever particular arm he thought contained the highest expected value and would never explore any of the other options, unless the value of the arm he was persisting at was devalued to the point where the other arms contained a higher expected reward; at which point he would immediately switch to persisting at which ever other arm had the highest expected value (i.e. a “winner take all” kind of scenario).

After computational analysis, Daw, et al. (2006) determined that the “softmax” decision rule, detailed above, best described the subjects’ performance. In this model, decisions to explore and the choice of which suboptimal arm from which to choose are determined probabilistically on the basis of the choices’ relative expected values. This differs from the

simpler ϵ -greedy RL model (which they also fit to participants' behaviour) in which the option with the highest represented value is chosen almost all of the time, but occasionally (with probability ϵ) selects a random alternative choice. For this reason, we decided to use the "softmax" decision rule in conjunction with the action-outcome reinforcement learning equation to model the behaviours of the animals in our experiment.

Finally, it is important to note that when analyzing the fMRI data, Daw, et al., found that: activity in the medial orbital region was correlated with the magnitude of the reward received (r_t), activity in medial and lateral orbital regions - extending into the vmPFC - was related to the probability assigned by the model to the action actually chosen on a given trial ($P(c)_t$), and vStr as well as dStr activity were correlated with the prediction error (i.e. the difference between the expected reward and the actual reward received ($r_t - Q(c)_t$)). Furthermore, right anterior frontopolar cortex (FPC) and intraparietal sulcus (IPS) were significantly more active during exploratory than exploitative trials; whereas, no regions were significantly more active during exploitative trials compared to exploratory trials (although as mentioned above, striatal and mPFC activity were increased compared to baseline activity during exploitative trials). Therefore, based on the finding that vmPFC activity was related to the ($P(c)_t$) values assigned by the softmax RL model, we concluded that the processing related to such activity needs to incorporate information relating to both the learning rate (α) and inverse temperature (β) parameters described above.

Taking into consideration all of the aforementioned research, that is, PGs frequently exhibit mPFC dysfunction, which likely relates to problems with perseveration, and that mPFC activity relates to the value assigned to a chosen action; we predicted that, if a reinforcement

learning model were fit to rats' behaviour, the learning rate and inverse temperature (randomness) parameters would also be abnormal. Therefore, we designed a novel rodent experiment based on the "4-arm Bandit" design used in the Daw, et al. (2006) study, in which rats were required to adaptively respond to changing task contingencies in order to maximize food reward. Rodent subjects were randomly selected to receive either an excitotoxic lesion in the mPFC region of their brain or a sham surgery before training on our task. Based on the findings of previous studies discussed earlier, we chose to specifically damage the PL region of the mPFC. As mentioned earlier, the PL region is associated with shifting behavioural strategies in response to changing task demands, and damage to this region has been found to produce perseverative behaviours in rats (Seamans, et al., 1995). Additionally, based on evidence from neuroconnectivity studies (see Appendix A); the PL region appears to be expressly placed to influence activity the "goal-directed" regions of the striatum. Thus, we theorized that damage to the PL region would chiefly affect the ability of the rats to engage in "goal-directed" behaviours in response to reward devaluation. Our experiment endeavored to answer several questions: (1) are intact PL regions of the mPFC necessary for animals to make optimal decisions in changing environments? (2) Are PL regions involved the ability of animals to switch behavioural strategies and would this inability of the animals to flexibly adapt manifest in increased rates of perseverative responding? (3) If so, does it come at the expense of the ability to engage in exploratory behaviour? And finally, (4) if a "softmax" RL model was fit to the task-related behaviour of animals with PL damage, would differences in learning rate (α) and/or choice randomness (β) be present when compared to intact animals?

We hypothesized that, because damage to a rats PL region would likely disrupt its ability

to properly generate expected values for each of the choice options; when compared with intact animals, rats with PL damage would: (1) not be able to procure as much food reward as intact animals evidenced by control animals returning to maximum reward consumption more quickly than PL damaged animals after a change in reward location; (2) PL damaged animals would display more perseverative-type behaviour, indicated by a propensity to sample from the same choice arm for many trials after reward devaluation, and that this would come at the expense of the number of trials determined to be exploratory compared to intact animals; and finally that (3) because the general ability of the rats to generate appropriate expected values would become compromised, the “softmax” RL model would be unable to accurately describe the choice patterns of PL damaged rats resulting in much more variable values of alpha and beta across animals. This contrasts with the healthy controls, whose behaviours should be well described by the “softmax” RL model, and so we therefore expect that both the α and β values predicted by the model should be more tightly clustered in healthy animals.

It is our hope that a better understanding of how mPFC dysfunction affects decision-making abilities in rats will help us explain how the abnormalities observed in mPFC activity in PGs may influence the tendency of this group of individuals to make poor life decisions, and that this understanding will provide a foundation from which to work in the attempt to ameliorate such deficits in future research.

3.2 Materials and Methods

3.2.1 Subjects

Subjects were male Long–Evans rats ($n = 26$; all rats from Charles River Laboratories); 3 animals were excluded from analysis, one due to poor performance during pre-training, and

two due to incomplete bilateral lesions discovered upon histological analysis of brain tissue, bringing the total to $n = 23$. Animals weighed 380–450 g and were $\sim 3.5 - 4.5$ months old ($\bar{x} = 130.6$ days; $SD = 11.5$ days) at the start of the experiment. Animals were singly housed in a temperature-controlled colony room under a 12h reverse light cycle (lights off at 10:00 A.M.). Testing took place between 11:00 A.M. and 6:00 P.M. four to six days per week. Water was available *ad libitum*. Animals were food restricted to $\sim 85\%$ of their free-feeding weight and maintained on an at-need amount of standard rat chow per day to maintain their 85% weight, available at the end of each day after all behavioural testing was completed (i.e. all rats within a cohort were fed at the same time after clean-up). All experiments were performed in accordance with the ordinances set by Canadian Council of Animal Care, and experimental protocols were approved by the Animal Care Committee of the University of Lethbridge.

3.2.2 Surgery

Subjects were randomly assigned to receive either bilateral lesions of the prelimbic region of the mPFC ($n = 10$) or sham surgeries ($n = 13$) for which a craniotomy was performed and the injection needle was lowered to the appropriate stereotaxic coordinates. Animals were injected with 0.03 mg/kg buprenorphine (concentration: 0.3mg/mL, 10x diluted), 30 min prior to being anesthetized with 1-3% isoflurane (2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane) (Abbott Laboratories, Abbott Park, IL) and then secured in a stereotaxic frame. Lesions were performed by infusing the excitotoxin N-methyl-D-aspartate (NMDA, 15mg/mL) into the area of interest. Infusions of the NMDA were made manually using a 33 gauge stainless steel injector (Hamilton Company USA, Reno, NV). The location of infusion sites and rates of infusions were based on previous studies (Birrell & Brown, 2000). The coordinates (Paxinos &

Watson, 2007) and rates of infusion for prelimbic lesions were as follows: site 1: anterior–posterior (AP), +3.5; medial-lateral (ML), ± 0.75 ; dorsoventral (DV), -3.3, three 0.1 μ l infusions over 2 min each and a final 0.1 μ l infusion over 4 min for a total of 0.4 μ l over 10 min; site 2: AP, +2.5; ML, ± 0.75 ; DV, -3.2, three 0.1 μ l infusions over 2 min each and a final 0.1 μ l infusion over 4 min for a total of 0.4 μ l over 10 min. The AP coordinate was taken from bregma, the ML coordinate from location of the central sinus, and the DV coordinate from the surface of the dura. After removing the injector, the craniotomy was filled with gel foam and a topical antibiotic was applied after suturing to prevent infection. All rats were treated with 1mg/kg Metacam (meloxicam, concentration: 5mg/mL) for three days post-surgery at 24 h intervals. Animals remained in their home cages for at least 9 days following surgery to allow the animals to recover. During this time, food was available *ad libitum* for 5 days after which the rats were food restricted; water was available *ad libitum* for the entire duration. All animals included within this study recovered well post-surgery.

3.2.3 Behavioral Apparatus

Behavioral testing took place on a six arm radial maze (see Figure 3.1) which was built in-house. Each arm contained a food port at the end of the arm that dispensed a liquid food reward (i.e. liquid chocolate Ensure® in our task). The food well in each port was attached via surgical tubing to a syringe which was mounted to the back wall of each arm at a consistent height (128 cm). The syringes contained a reservoir of liquid Ensure® which would pass via the surgical tubing through a solenoid valve and into the food well. The valve remained closed until the rat nose poked an available port at which time the valve would open for a set amount of time (i.e. 300 ms, 750 ms, or 1200 ms). Every port was fitted with a stimulus LED light to cue

port availability and a horizontal infrared sensor beam that was used to detect rodent nose pokes into the food well. Custom-written Labview software on a standard Windows-based computer in an adjacent control room was used for both data collection and to control the maze. Video was recorded and fed into the control room using a ceiling mounted video camera which utilized Cheetah software (Neuralynx, Inc., Bozeman, MT) for video data collection.

3.2.4 Experimental Design

A timeline of the experimental procedure is available in Table 3.1. To assess the role of the prelimbic region in the ability of rats to flexibly shift their behaviour in response to changing environmental demands, the performance of animals that received prelimbic lesions was compared to animals that received sham surgery prior to N-arm Bandit Task training.

3.2.5 Behavioral Testing

3.2.5.1 Prior testing.

All animals were participants in a suite of studies investigating the role of mPFC in behavioural shifting and had been exposed to a discrimination task prior to testing on the N-arm Bandit Task when they were ~60 days old (9-17 days after surgery [\bar{x} = 11.7 days]). Briefly, this three part study required rats to detect a food reward (i.e. round shaped toasted oat cereal) that was hidden within one of two scented bowls covered either by corncob bedding material or silica sand. The location of the food reward was cued either by the scent in the bowl (e.g. coffee vs. blueberry) or by the digging media (e.g. corn cob vs. sand). In the first part of the experiment, the rat learned by trial-and-error which scented cue accurately predicted the location of the food reward (e.g. blueberry). In the second part of the experiment the scent which predicted reward was reversed (inter-dimensional shift) and the rat now had to respond

| Stage | Type | Number of Days | Objective |
|-----------------------------|-------------|--|---|
| 1. Explore | Pretraining | 1 | Familiarize the rat with the maze. |
| 2. Light Reward Association | Pretraining | To Criteria – Rat must obtain 100 rewards within 20 minutes or complete ten 20 min sessions. | Train the rat to associate a lit LED light with reward availability. |
| 3. Task Training | Training | 21 | Rat learns task contingencies – some ports deliver more food than others and the location of this port is not stable over time. He learns that he must explore in order to find the best one. |
| 4. N-Arm Bandit Task | Testing | 16 | Rat must obtain as much reward as possible within the 20 minute sessions by exploiting the high reward port once he has found it, disengage from that port once it becomes devalued, and search for the new location of the high reward port. |

Table 3.1. N-Arm Bandit Training Schedule. Total sessions performed by each rat ranged from 41 – 48 (\bar{x} = 45.3) days depending upon the amount of time taken in Stage 2 pretraining.

to the other scent (e.g. coffee). In the final part of the experiment, the odour no longer predicted food reward location, rather the type of digging media (corncob vs. sand) now cued reward location (extra-dimensional shift). Again, via trial-and-error, the rats had to determine which digging media was linked to reward location.

3.2.5.2 Habituation and pre-training.

Each animal was given a small amount of chocolate Ensure® one or two days before pretraining began to allow the rat to overcome their neophobia. Animals were habituated to the radial maze one at a time in a single pre-training session (18-59 days post-surgery [\bar{x} = 30.7 days]), during which all six ports were illuminated. Each port delivered 750 ms of food reward when nose-poked. Animals were then trained to make a nose-poke response into a single illuminated port (i.e. light-reward association training). The spatial location of the stimulus light varied randomly between trials across arms. Each session contained 150 trials and lasted approximately 20 min. Rats were moved onto the training stage either after they had completed 150 trials within a 20 min pre-training session or after completing ten pre-training sessions. Twenty rats achieved 150 trials within 20min and three rats (1 lesion; 2 sham) had to be forced onto the training phase after ten sessions.

3.2.5.3 Training.

Animals were then trained over 21 sessions to flexibly seek out the port that offered the most reward. Each session lasted 20 min for all training sessions and all rats. Three of the six arms were assigned to be choice arms (arms 1, 2, and 3) and one arm was designated as the base arm (base 5; see Figure 3.1). The two remaining arms were unlit and unrewarded. During the piloting stage for this task, we found three choice arms to be optimal for testing rodent switching performance; four arms appeared to overtax the rats' ability to distinguish between the choices causing most of the pilot animals to ignore several of the choice arms.

Animals were always placed in the centre of the maze at the beginning of each session (for all experimental phases) facing away from the base arm. Each trial required the animal to

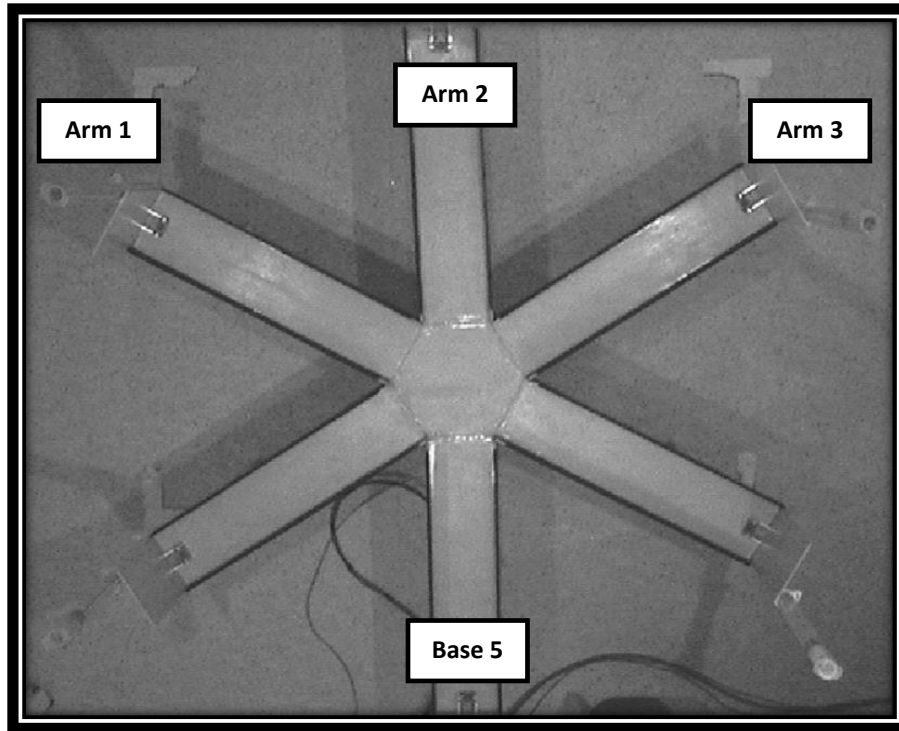


Figure 3.1. N-arm Bandit Task maze. The task was conducted using a six-arm radial maze. Arms 1, 2, and 3, served as choice arms, while Base 5 served as the return to base arm. Arms 0 and 4 were not lit and did not deliver any reward.

first nose poke the port at the end of the base arm; collect the 300 ms reward there, then turn around and travel to the middle of the maze (i.e. the decision zone). At this point the rat could freely choose one of the three choice arms to travel down from which he collected his reward.

Each port offered a different amount of food (300 ms, 750 ms, or 1200 ms) and time-out punishment (20 s, 10 s, or 0 s). The high reward arm (HRA) always offered a large amount (1200 ms) of reward with no (0s) time-out, the medium reward arm (MRA) offered a moderate amount (750 ms) of reward and a moderate (10 s) time-out, and finally the low reward arm (LRA) offered a small amount (300 ms) of food reward and a large (20 s) time out. Through trial-and-error the rat determined which of the three choice ports offered the most food per unit time and began to persist at that arm. Once the animal had chosen the HRA ten times in a

row, the experimenter would initiate a new trial block in which the locations of the HRA, MRA, and LRA were switched – this was done the HRA, arm 2 the MRA, and arm 3 the LRA; after the rat had chosen arm 1 ten times in a row, the reward locations would switch and arm 1 would now be the MRA, arm 2 the LRA, and arm 3 the HRA. New HRA, MRA, and LRA locations were chosen pseudo-randomly in that every arm had to change food amount (i.e. one arm could not continue to offer the same amount of reward and punishment for multiple trial blocks). At this point, the rat had all three arms, the experimenter helped train the rats manually to explore the different options. This involved the experimenter coming into the testing room and leading the rat to the HRA with her hand ~4-5 times and exiting the room. Care was taken to ensure that all rats received similar amounts of intervention and most of the interventions took place during the first half of training and were tapered off in the latter half. No interventions were allowed during the testing phase. This succeeded in increasing the rats' overall propensity to search more of the ports more quickly after a switch, and consequently allowed for more switches to take place per session. After the 21 training sessions were completed, the rats were moved onto testing.

3.2.5.4 The N-arm Bandit Task.

The design of the N-arm Bandit Task is similar to the training phase described above in that rats had to attempt to obtain the largest amount of food reward possible by being able to persist at the HRA and then flexibly adapt to a change in HRA location when the arm becomes devalued after a switch. The main differences in this stage were that switches were no longer tailored to rodent performance and experimenter interventions were not permitted. Sessions are set up in such a way that switches occur automatically after $35 (\pm 5)$ trials. This block size

was determined in our piloting experiments to be long enough for the rats' to determine that a switch had taken place, explore other options, and persist at the preferred arm for a number of trials, while also providing several switch events per session (providing more switch data for analysis). The timing of each switch was varied (i.e. between trials 30 and 40 of each block), so that the rats would not be able to predict exactly when a switch was going to occur. Each rat completed 16 days of testing and each session was 20 min in length. Rats completed as many trials as possible in each session within the allotted 20 min time limit.

3.2.6 Data analysis

The main measures analyzed included (1) switch performance, (2) behavioural breakdown, as well as parameter estimates from fitting a reinforcement learning model, (3) α and (4) β values (see Equations 1 and 2 in section 3.1). The rate of recovery after a switch (switch performance) was determined by dividing the trials after every switch into three sets of 10 trials (we chose thirty trials because every block had at least thirty trials contained within it). We then calculated the average amount of reward obtained by each rat within each of the three trial sets. This measure provided information on whether PL lesions affected the rate at which rats were able to adjust to devaluation of a choice arm. The behavioural breakdown was determined using a simple algorithm; if the rat chose the HRA then the trial was designated a reward-driven trial (RDT), if the rat did not choose the HRA and the arm chosen was the same arm as the rat chose on the previous trial it was designated as a perseverative trial (PT), lastly if the rat did not choose the HRA and the arm chosen was not the same arm as the rat chose on the previous trial then it was named an exploratory trial (ET) (see Figure 3.2). Every trial over

the 16 testing sessions was designated as a RDT, PT, or an ET and the percentage of the total amount of trials was calculated for each type. In this way we were able to determine whether

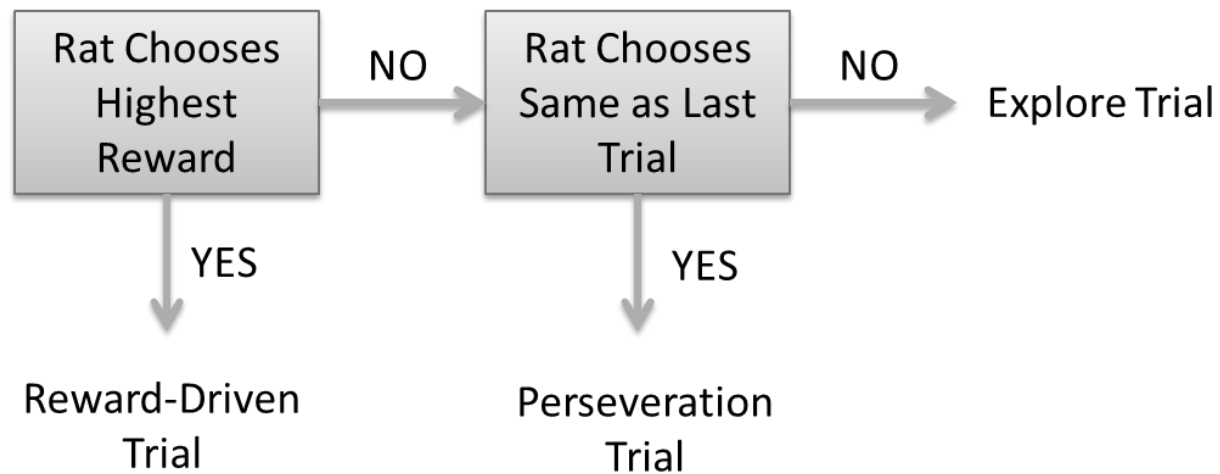


Figure 3.2. Choice breakdown algorithm. Every trial performed by every rat was designated as either a reward-driven trial (RDT), a perseverative trial (PT), or an exploratory trial (ET).

potential group differences in choice type could be explained by an inability to break away from interacting with previously rewarding stimuli in search of something new (and potentially better). Finally, the α and β values were calculated by fitting a softmax reinforcement learning model to the choice data. For all choices from each rat, the “likelihood” was computed as the sum of the log of the probabilities of all choices. A non-linear optimization routine (fminsearch in Matlab, the Mathworks, Natick, MA) was then used to minimize the negative log likelihood, yielding the optimal values of α and β for that animal (Daw, et al., 2006). Group comparisons of these variables may help explain whether group differences in the ability to maximize reward were due to differences in overall learning rates (α) or randomness of choices (β).

3.3 Results

3.3.1 Histology and Lesion analysis

Following completion of behavioral testing, animals were sacrificed via an overdose of 100 mg/kg sodium pentobarbital, then transcardially perfused with 1x phosphate-buffered saline (PBS) and 4% paraformaldehyde (PFA). The brains were removed and postfixed in 4% PFA for 24 h before being stored in a 30% sucrose solution. Brains were sliced into 40 µm sections with a cryostat (Leica Biosystems Nussloch GmbH [Nussloch, Baden-Württemberg, Germany]) throughout the area of interest and stained with 0.5% Cresyl violet.

3.3.2 Data Analysis

Sections were imaged using a parallel microscope (Nanozoomer, Hamamatsu Photonics K. K. [Hamamatsu, Honshu, Japan]). The extent of the lesions were determined and mapped onto standardized sections of the rat brain (Paxinos & Watson, 1998). Superimposed images illustrating the extent of the lesions for all lesion animals are provided in Figure 3.3. Damage was fairly extensive and principally affected the PL region for all lesion animals. Lesions extended somewhat into the infralimbic cortex (IL), medial orbital cortex (MO), and the anterior portions of both the secondary motor cortex (M2) and cingulate cortex (CG1) in most rats. Slight damage to the ventral orbital cortex (VO), the cingulate cortex (CG2), was observed in a minority of animals. As mentioned earlier in section 3.2.1, two animals were excluded from analysis because the lesions were either incomplete or unilateral.

Data were analyzed using a mixed method analysis of variance (ANOVA) for switch performance and independent *t*-tests for the behavioural breakdown choice arm bias, as well

as α and β values. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using IBM SPSS Statistics (version 20).

3.3.2.1 Effects of PL lesions on switch performance.

A mixed design ANOVA was used to determine whether the amount of reward obtained significantly differed between the first ([Lesion: $\bar{x} = 776.12$, SD = 63.99]; [Control: $\bar{x} = 806.71$, SD = 32.7]), second ([Lesion: $\bar{x} = 870.12$, SD = 121.99]; [Control: $\bar{x} = 934.35$, SD = 37.36]), and third ([Lesion: $\bar{x} = 907.95$, SD = 117.14]; [Control: $\bar{x} = 992.57$, SD = 51.5]) set of ten trials after a switch and also, whether the amount of reward obtained by the rats differed as a consequence of receiving PL lesions. The between-subjects factor was treatment (lesion vs. sham) and the within-subjects factors was trial set (three levels, Trials 1-10, Trials 11-20, and Trials 21-30).

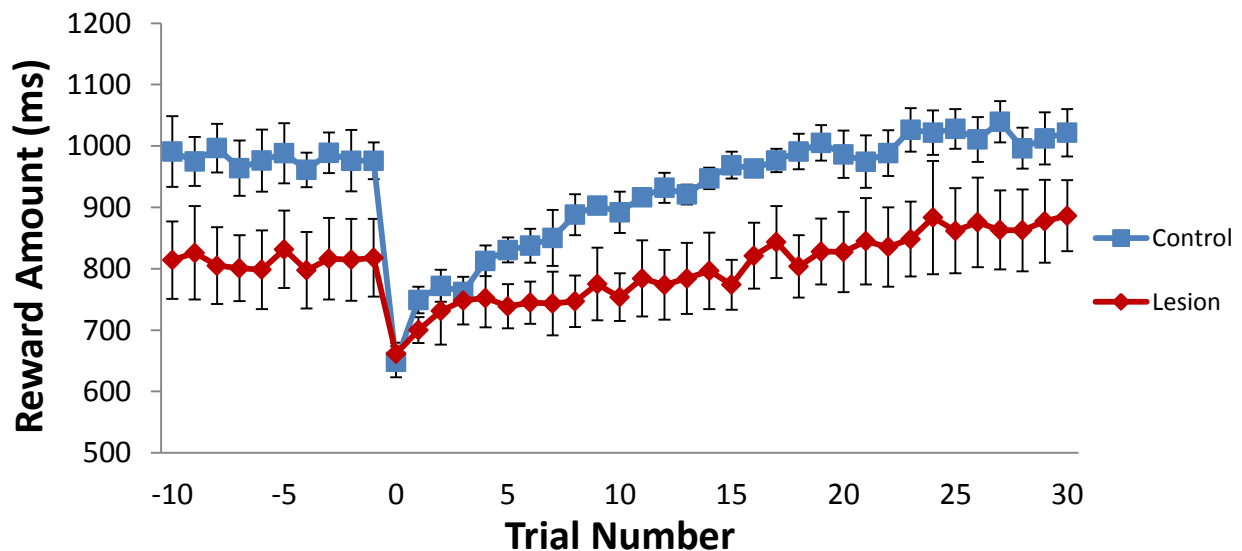


Figure 3.4. Effects of PL damage on switch performance. Control animals maintained an overall higher level of average reward acquisition prior to and after a switch, although this was found to be marginally non-significant. Acquisition of reward in lesion animals increased significantly more slowly across time compared to control animals. Error bars represent the standard error of the mean (SEM).

There were no covariates and no significant skewness or kurtosis was present. A graphical representation of these results is shown in Figure 3.4. The between subjects effect of Treatment was not statistically significant, $F(1, 21) = 4.03$, $p = 0.058$, although there was evidence that the effect of PL lesion on reward acquisition trended towards significance. A larger sample size with more statistical power may be able to confirm whether this null finding was the result of a Type II error. The within subjects effect of Trial Set was statistically significant, $F(1.39, 29.27) = 157.16$, $p < 0.001$ (Greenhouse-Geisser corrected), which simply indicates that the rats were able to learn and adapt to the new reward locations over time. The most interesting result emerged from the interaction effect of Treatment x Trial Set, $F(1.39, 29.27) = 4.42$, $p = 0.033$ (Greenhouse-Geisser corrected). This significant result suggests that the acquisition of reward in lesion animals increased more slowly across time compared to control animals.

3.3.2.2 Effects of PL lesions on reward-driven choices, perseveration and exploration.

T-tests were conducted to establish whether the percentage of RDTs, PT, and ETs observed in animals given PL lesions ([RDT: $\bar{x} = 0.46$, $SD = 0.12$]; [PT: $\bar{x} = 0.35$, $SD = 0.19$]; [ET: $\bar{x} = 0.19$, $SD = 0.11$]) differed significantly from the percentage of RDTs, PT, and ETs observed in control animals ([RDT: $\bar{x} = 0.52$, $SD = 0.06$]; [PT: $\bar{x} = 0.26$, $SD = 0.11$]; [ET: $\bar{x} = 0.22$, $SD = 0.07$]). No significant skewness or kurtosis was present. The *t* statistic was not significant for any of the three behaviours: RDT: $t(21) = -1.65$, $p = 0.113$ (2 tailed, equal variance assumed); PT: $t(21) = 1.49$, $p = .152$ (2 tailed, equal variance assumed); ET: $t(21) = -0.75$, $p = .462$ (2 tailed, equal variance assumed), indicating that PL lesions did not significantly alter the distribution of RDTs, PT, and ETs. Results are illustrated in Figure 3.5.

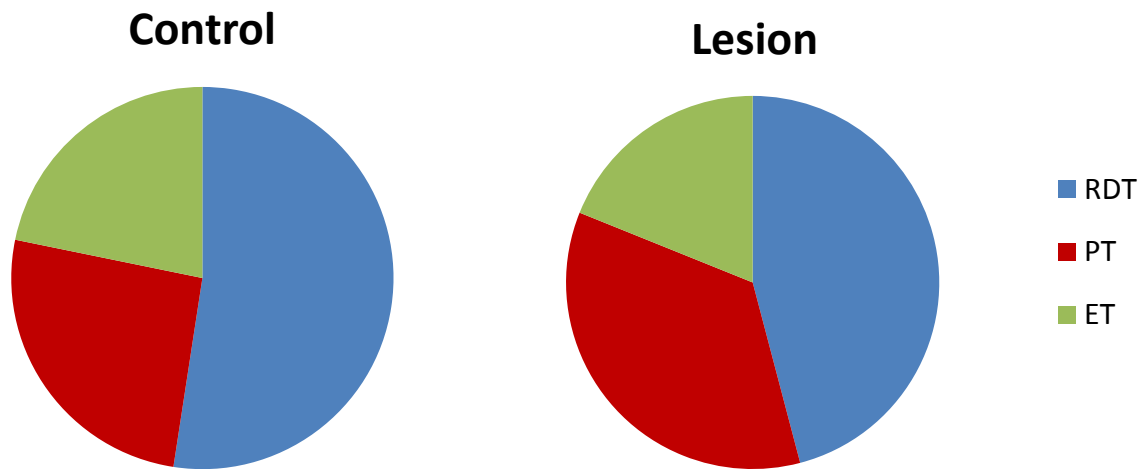


Figure 3.5. Breakdown of choice behaviour. Each pie chart represents 100% of trials completed by the testing animals in each experimental group. The charts are broken down by the type of trial assigned by the algorithm illustrated in Figure 3.2. Blue represents reward driven trials, red represents exploratory trials, and green represents perseverative trials. No significant group differences were found during statistical analysis, although a trend towards increased perseveration in the lesion group was present.

3.3.2.3 Effects of PL lesions on choice arm bias.

After initial analysis of group differences in the proportions of reward-driven trials, perseverative trials, and exploratory trials, we determined that some of the perseverative trials may have been categorized as reward-driven trials due to the algorithm used to parse the trials. Each choice arm offered the high reward for approximately one third of all of the trials; so if a rat was perseverating at one of the arms, he would obtain the high reward approximately one third of the time and those trials would have been classified as reward-driven trials, obfuscating the underlying decision-making process taking place for that rat. With this in mind, we conducted a more sensitive analysis of perseveration for each of the treatment groups. A percentage was calculated for each choice arm that indicated how often each arm offered the

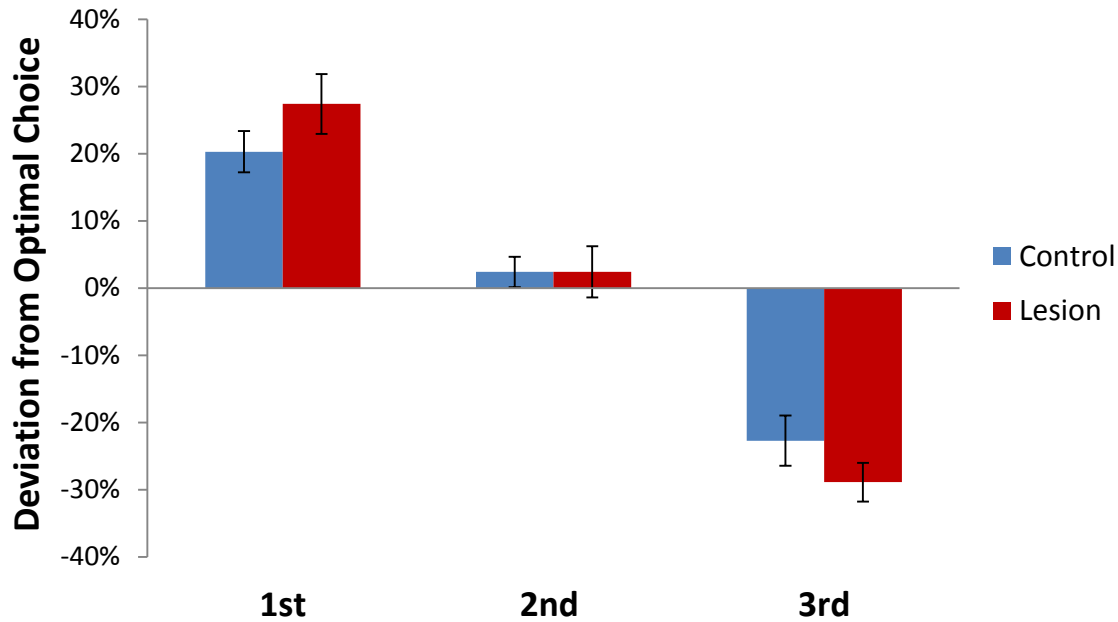


Figure 3.6. Effects of PL damage on choice arm bias. Each column represents the difference between the number of high reward trials offered by a choice arm and the number of trials the animals actually chose that arm. The graph is broken down by choice arm preference for each animal within each treatment group. Columns in the 1st section represent the choice arm that the rats chose from the most and thus had the highest preference for, columns in the 2nd section represent the rats' second highest preference, and columns in the 3rd section represent the magnitude of avoidance for the least preferred choice arm. Large positive deviations from zero in the section labeled 1st, particularly in conjunction with large negative deviations from zero in the section labeled 3rd, indicate that large amounts of perseveration were present. Error bars represent the SEM.

high reward for each rat. Then a percentage was calculated for each choice arm that indicated how often each rat chose each arm; then the difference between the two was calculated for each animal (deviation from optimal choice). Using this deviation measure, we collated the data for each treatment group according to choice arm preference (i.e. the largest positive deviation for each rat was designated the 1st preference, the middle deviation was designated the 2nd preference, and the lowest was designated the 3rd preference). The spatial location of the preferred choice arm differed for each rat (i.e. some rats preferred choice arm 1 while others preferred choice arm 3). This gave us a more sensitive measure of perseveration in that it

clearly showed whether an animal was interacting primarily with only one choice arm. Results are illustrated in Figure 3.6.

Statistical analyses were then performed to determine whether the PL lesion group had an increased tendency to prefer one of the choice arms (at the expense of the others) compared to the control group. *T*-tests were conducted to establish whether the deviation from optimal choice for the 1st preference, 2nd preference, and 3rd preference calculated for animals given PL lesions ([1st: \bar{x} = 0.27, SD = 0.14]; [2nd: \bar{x} = 0.02, SD = 0.12]; [3rd: \bar{x} = -0.29, SD = 0.09]) differed significantly from the deviation from optimal choice for the 1st preference, 2nd preference, and 3rd preference calculated for control animals ([1st: \bar{x} = 0.20, SD = 0.11]; [2nd: \bar{x} = 0.02, SD = 0.08]; [3rd: \bar{x} = -0.23, SD = 0.13]). No significant skewness or kurtosis was present. The *t* statistic was not significant for any of the three categories: 1st: $t(21) = -1.36, p = 0.188$ (2 tailed, equal variance assumed); 2nd: $t(21) = -0.005, p = .996$ (2 tailed, equal variance assumed); 3rd: $t(21) = 1.31, p = .205$ (2 tailed, equal variance not assumed), indicating that PL lesions did not significantly alter the rodents' bias towards one choice arm, although again a trend towards more perseveration in the lesion group was present.

3.3.2.4 Effects of PL lesions on α and β values.

T-tests were employed to determine whether α and β values obtained from animals receiving PL lesions ([α : \bar{x} = 0.26, SD = 0.38]; [β : \bar{x} = 14.61, SD = 15.34]) differed significantly from α and β values obtained from control animals ([α : \bar{x} = 0.19, SD = 0.09]; [β : \bar{x} = 5.92, SD = 2.37]). No significant skewness or kurtosis was present. The *t* statistic was not significant for either α or β values: α : $t(9.83) = 0.52, p = 0.617$ (2 tailed, equal variance not assumed); β : $t(9.33) = 1.78, p = 0.108$ (2 tailed, equal variance not assumed), indicating that PL lesions did not

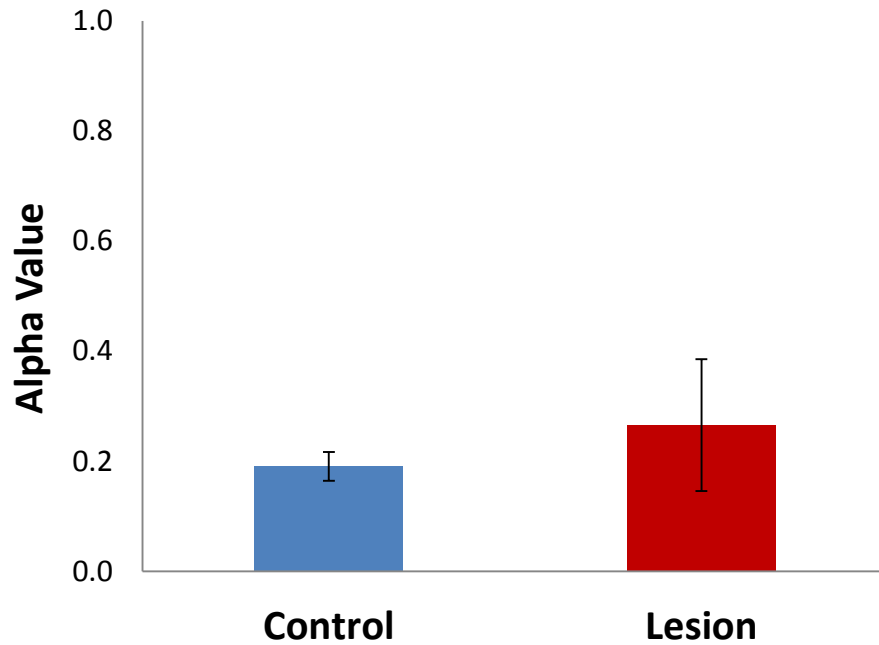


Figure 3.7. Effect of PL lesions on learning rate (α). Comparison of learning rate in lesion versus control animals. Lesion animals did not have a significantly different α values compared to control animals. Error bars represent the SEM.

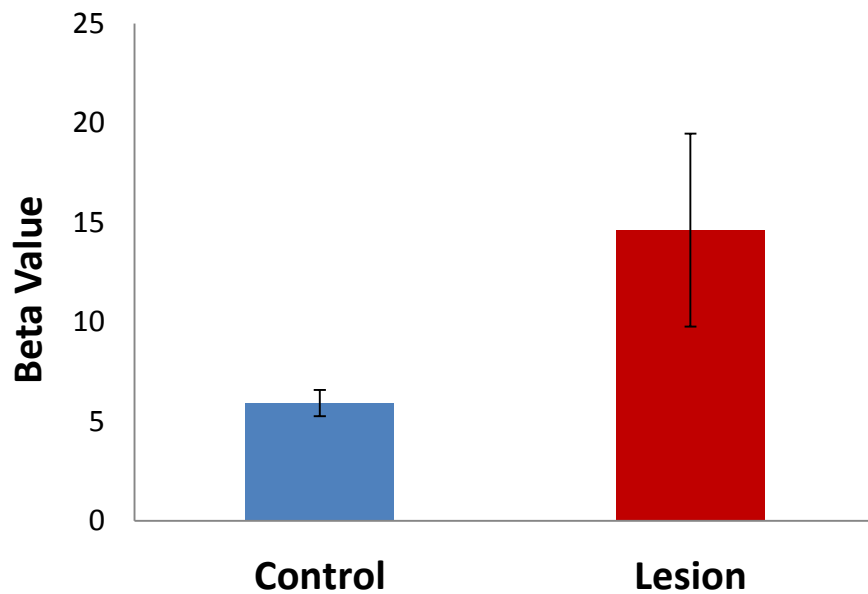


Figure 3.8. Effect of PL lesions on inverse temperature (β). Comparison of inverse temperature values in lesion versus control animals. Lesion animals did not display significantly different β values compared to control animals. Error bars represent the SEM.

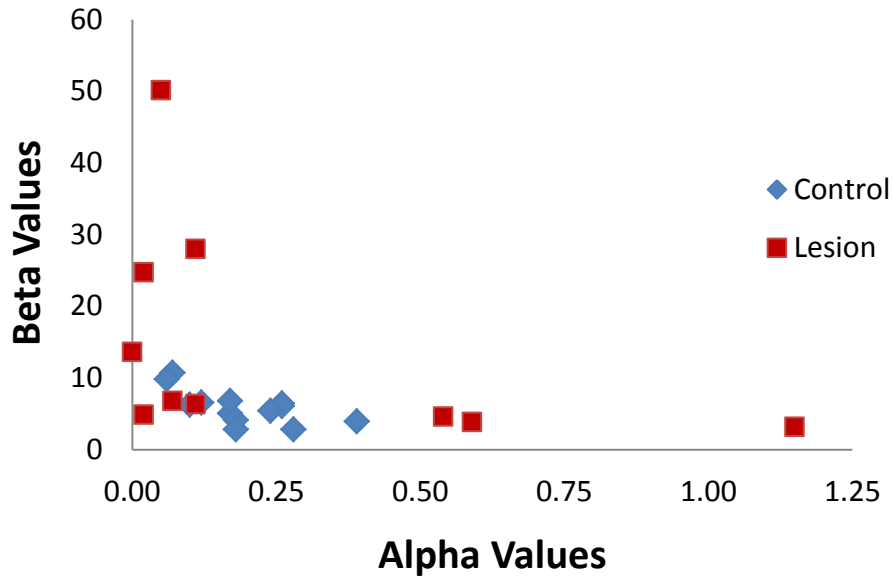


Figure 3.9. Distribution of α and β values. A scatter plot illustrating the distribution of α and β values for individual animals categorized by surgical treatment. Values obtained from control animals tend to cluster together in the bottom left hand corner, while values obtained from PL damaged animals are widely distributed.

significantly alter either learning rate or temperature. Results are illustrated in Figures 3.7, 3.8, and 3.9.

3.4 Discussion

Results of the experiment indicate that in rats, damage to the PL region of the mPFC does alter the ability of rats to adjust to changing task requirements in order to obtain reward. Specifically, rats with mPFC lesions were slower to switch to a high reward arm after a switch in reward contingencies. However, this effect was not striking, as the difference in the overall amount of reward obtained did not reach significance, although a trend toward significance was present. Furthermore, we did not find any statistically significant differences between groups when investigating changes in the proportion of reward-driven trials, perseverative

trials, exploratory trials , choice arm bias, or in the learning rates (α) or inverse temperature (β) values predicted by the “softmax” RL model.

Although the statistical analyses did not indicate an overall change in either learning rate or randomness of choices in animals that received PL lesions, important dissimilarities were present (see Figure 3.9). Most tellingly, when examining how well the softmax RL model fit the rats’ behavioural data, obvious group differences were present. While behaviours in control animals were described quite well by the softmax RL model, it tended to break down when trying to describe those behaviours present in rats that received PL lesions. For, example, several lesion animals were assigned very extreme values for both learning rate and temperature parameters, in one instance assigning an α value of 1.15 for one of the lesion animals, which is an impossible number considering that α values range between 0 and 1. Likewise, several lesion animals were assigned very large β values (25, 28 and 50) when most animals were assigned values between 3 and 10. This finding suggests that the RL model is not providing a good description of lesioned animals performance. Hence, a genuine difference in decision related neural processing may exist. This difference in neural processing may have manifested in the increased variance observed in both the α and β values calculated by the model for PL damaged rats.

Similarly, statistical analyses indicated no differences in the distribution of decisions. A closer inspection of the way choice trials were parsed was undertaken in ordered to further explore why this was the case. We found that the algorithm used to parse the trials into three categories (RDT, PT, and ET) designates all choices that yielded a high reward as a reward-driven trial, implying that every time a rat obtained a high reward outcome, that outcome was a

result of a calculated decision by the rat to choose that arm because it represented the best chance of obtaining a good reward. However, if the rat was perseverating at one of the choice arms because his behaviour had become inflexible, the rat would be able to procure high rewards simply because the arm the rat was perseverating at happened to be the HRA, which was the case during approximately one third of the trial blocks. Therefore, in all those trials where the animal was receiving high rewards, a RDT labels were assigned when in fact PT labels may have been more accurate descriptors. A more accurate measure of perseveration was designed to calculate the percentage of trials in which each arm was the HRA arm for each animal, and then to determine the percentage of trials in which each rat chose each arm. For example, if each arm offered the highest reward one third of the time, high performing rats should have their choices spread evenly over the three choice arms (~ 33% time spent at each arm); however, if the rat was perseverating heavily, then the amount of rewards obtained should be skewed heavily in the direction of the preferred arm. As indicated in the Figure 3.6, the PL lesion group exhibited no obvious increase in perseveration compared to control, although a trend in this direction was present. Therefore, we conclude that damage to rats' PL region does not lead to considerable increases in stereotyped behaviours in our task. This finding opposes the theory that dysfunction of the mPFC may result in a shift of behavioural control from frontostriatal to dorsostratial regions resulting in a prevalence of habitual actions.

Interestingly, both groups displayed similar rates of exploration (each group devoted about 20% of their total choices to exploration) implying that PL damage does not impact the propensity of an animal to occasionally choose a non-optimal arm in order to obtain information rather than reward. This may reflect the finding in the Daw, et al. (2006) paper that

exploratory decisions, at least in humans, appear to be correlated with increases in activity in the anterior FPC and IPS. So damage to the PL region may not affect this particular process. However, considering that rats lack a region homologous to the human FPC, exploratory processes are likely subserved by other areas. The finding that both groups devoted ~20% of their choices to exploration may not reflect rates of exploration in other operant settings. This task likely exaggerated the rats' innate propensity to explore in that an unusual degree of behavioural flexibility was required in order to perform this task well. As mentioned in the Materials and Methods section (section 3.2.5.3), all rats were extensively trained to increase behavioural flexibility in order to gain more switch data per session. Therefore, it is reasonable to speculate that this training may have increased the rats' overall inclination to explore considering that, in this kind of task (i.e. a non-binary task where reward is not stable across time), exploration is essential to the ability of rats to optimize reward over time. In binary tasks, the rats need only to learn two behavioural strategies and then inhibit one or the other depending on reward feedback, while this task requires rats to rapidly forage anew after each switch. Although humans performing this task may employ a strategy based on a process of elimination, we did not see any evidence that rats were able to make use of this kind of strategy as rats generally had to sample from several of the arms multiple times before settling into an exploitative strategy after a switch. It may be of use to determine in future analyses; whether groups differed in when exploratory behaviours were observed in relation to a switch. It is possible that although control animals explore at the same rate as PL damaged animals, they may cluster their exploratory trials close to the switch whereas animals with PL lesions explore more evenly throughout the trial block.

That being said, in keeping with other studies which indicate that PL lesions do not affect either the acquisition or reversal learning of discrimination tests requiring extradimensional shifts, but rather disrupts learning when rats are required to inhibit one strategy and intradimensionally shift to using a new strategy (Ragozzino, 2007); the rats that received PL lesions in our study may have been equally as likely as control rats to explore other arms in response to a switch but then quickly reverted back to their old exploitation strategies. On the other hand, our examination of differences in perseveration yielded insignificant differences between the two treatment groups, so it is unlikely that this type of behavioural strategy was taking place or at least it wasn't taking place more so in the PL lesion group.

The idea that the extensive training may have increased the rats' propensity to explore also raises the possibility that such a regimen may have ameliorated some of the deficits produced by the PL lesions. It is well known that, although not universal, partial function can generally be recovered after a brain region has been damaged, particularly when rigorous rehabilitative therapy is undertaken (Ward & Cohen, 2004; Schlaug, Marchina, & Norton, 2009). For example, Johansen-Berg et al. (2002) found that after undergoing a movement therapy program that combined constraint therapy and graded exercises, patients that had lost motor function after a stroke were able to recover some movement in the hand affected. Patients' brains were imaged using fMRI and a correlation between patient recovery and increases in activity in the premotor cortex and secondary somatosensory cortex was revealed. Furthermore, a meta-analysis of twenty studies involving 2686 stroke patients conducted by Kwakkel, et al. (2004) revealed that, although not overwhelming, a reliable increase in motor function was observed in stroke patients that underwent augmented exercise therapy. They

also found that recovery of function was heavily dependent upon prolonged therapy (at least 16 hours) in order to reach significance and importantly, only therapy programs employed within the first 6 months after a stroke yielded significant findings, whereas those after 6 months did not. So considering that our rodent subjects not only underwent extensive flexibility training in preparation for the task, but were also trained in an post-surgical odour discrimination task (described in section 3.2.5.1; although extradimensional in regard to our task, still included an element of reversal learning) prior to participation in the N-arm Bandit task; a rehabilitative effect similar to that described above may be influencing our results. However, because no PL damaged rats were assigned to run the task without flexibly training, it cannot be confirmed that the neuroplastic changes observed are in excess of recovery that may occur without any intervention. Additionally, the large amount of time that elapsed between surgery and testing (~1.5 - 3 months) may have allowed for considerable cortical reorganization to take place in and around the damaged area. In support of this idea, Wishaw and Oddie (1989) found that after rats received either sham surgery, unilateral medial frontal or bilateral frontal cortex lesions, behaviours related to foraging (i.e. the way rats chose to consume newly discovered food) were seriously impacted in a time-dependent fashion (see Figure 3.10). That interest to see whether group comparisons of behavioural testing data accrued closer to the time of surgery would reveal more definitive differences between treatment groups. Similarly, it would be prudent to also determine the effects of post-training PL inactivation or temporary inactivations on N-arm Bandit task performance as differences in rodent performance on goal-directed tasks, as a result of when mPFC inactivation occurred in relation to training (pre vs.

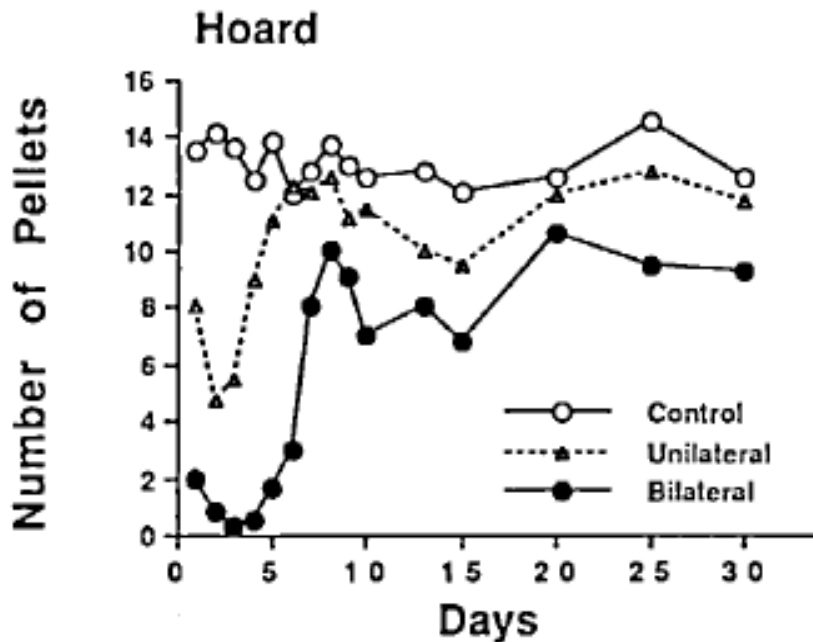


Figure 3.10. From Wishaw and Oddie (1989; Figure 3). The number of food pellets per day that rats with control, unilateral medial frontal or bilateral frontal cortical lesions chose to hoard, rather than eat immediately is displayed above. Frontal cortical lesions appear to effect foraging behaviour in a time dependent manner with the largest change in behaviour observed within 5 days post-surgery.

post), have been reported (Ostlund & Balleine, 2005).

Finally, it is quite likely that the ability to detect differences between the two groups was seriously limited by the small number of animals that participated in the task, particularly because large amounts of individual variation were present (especially in lesion animals). Therefore, it would be beneficial to replicate this study with more animals in order to either confirm the present finding that PL lesions influence the rate of recovery after a change in task contingency and engenders an increase in behavioural variance (in virtually all of the factors measured), but otherwise have no statistically significant effects or provide evidence that supports a specific directional effect (particularly on measures of perseveration).

3.5 Conclusion

Taken together, evidence from our task supports the idea that mPFC dysfunction impairs the ability of rats to make optimal decisions in complex environments. However, the effect appears to be modest and limited to the rate at which an agent is able to adapt to changes in reward outcome and precludes an overall inability to make carefully planned decisions, and modify behaviours accordingly. So in consideration of the serious decision-making problems present in PG individuals, the role of mPFC dysfunction is likely secondary to dysfunction observed in other areas, particularly the striatum. Furthermore, the evidence obtained from our study does not support the idea that mPFC dysfunction, at least in isolation, increases the ability of the dStr to dominate behavioural output. However, the effect of a potential interaction between mPFC dysfunction and other impairment regions (e.g. vStr) on dStr behavioural dominance cannot be ruled out. Importantly, the “softmax” RL model was able to describe the control animals’ behaviour quite well, whereas it tended to break down when describing the behaviours of the lesion animals. This could indicate that; even though the lesion group was able to adapt to changing task contingencies, the processes by which they were able to do this may be quite different than those employed by healthy animals. Finally, although obvious differences in the variance of learning rates and decision randomness were present in animals that received PL lesions, this did not statistically alter the groups’ overall ability to maximize reward when compared to healthy animals (although this measure was also more variable in the PL group compared to controls). It is then possible that in humans with mPFC impairment, this increased variance in learning rate and temperature may manifest in goal-directed behaviours that are more variable/less predictable.

Chapter 4: Pathological Gambling as a Behavioural Manifestation of Abnormal Reward

Learning

4.1 Synthesis and Discussion

PG is a multifaceted disorder characterized by impulsivity and excessive risk taking which involves impairments in long term decision-making, flexible behaviour, and somatic feedback. These impairments appear to be related to abnormal informational processing in the mPFC and Str regions. I have surmised that due to some trait vulnerabilities obtained via specific combinations of genetic polymorphisms, trauma, or exposure to certain pathogens or substances, some individuals possess a brain that is sensitive to the addictive effects of some games of chance. These individuals generally are characterized as having novelty-seeking, risk-taking, and impulsive personality profiles and appear to process risk and reward differently than the majority of people. Particularity they appear to have shifted basal levels of extracellular DA which influences processes related to reward learning and increases susceptibility to the reinforcing and motivating effects of probabilistic reward (other neurochemicals are certainly involved, but DA appears to be especially important in the aetiology of addiction). Although the exact mechanism remains unclear (but may involve homeostatic regulatory mechanisms to compensate for altered tonic levels of extracellular DA), this change in reward processing appears to render these individuals insensitive to common, everyday rewards. And in compensation they seek out situations that are risky, and offer a chance at obtaining large unexpected reward, which elicit large phasic increases in extracellular DA. Games of chance offer this type of experience consistently.

These large fluctuations in phasic dopamine experienced while gambling would further increase the individuals' motivation to gamble, tapping into a learning mechanism that mediates a processes of acquisition of skills in order to obtain sources of reward. In normal circumstances, the unpredicted reward would invoke emotional-motivational processes that would facilitate the learning of motor skills and recognition of predictive stimuli that would increase the likelihood of obtaining the reward over time. Once the associations between the motor responses and predictive stimuli are established and reward becomes predictable, emotional-motivation subsides. However, in games of chance increases in probability of outcome can never be established, and so although the associations between the motor responses and predictive stimuli are still being established, the emotional-motivational input does not disengage.

On its own, the effect of gambling on reward systems does not appear to be sufficient to cause individuals to cross the threshold into addiction. This appears to require a concomitant impairment in PFC function, particularly impairment in the mPFC. Crucially, those individuals described earlier that have risk-seeking, impulsive personality profiles, generally also exhibit impaired mPFC functioning. Unsurprisingly, the relationship between mPFC impairment and impulsive decision-making is supported by numerous studies (Ding, et al., 2014; George & Koob, 2010; Qiu, et al., 2013). The mPFC processes information related to the expectation and anticipation of a reward, combining input containing information from all sensory modalities, somatic states, and memory of past events. This highly processed contextual information is transmitted to the Str which then selects the appropriate action to obtain the reward. Importantly, only by tracking and processing reward data over time, can actions be shaped to

optimize reward in the future (non-proximal). However, when the mPFC is impaired this processing appears to become distorted. That is, the mPFC is no longer able to provide the Str with accurate information regarding expectation of reward over time and makes it difficult for the mPFC (and other related PFC regions) to enact situation-appropriate inhibitory control over the striatum. This shifts the decision-making process in the direction of acting upon opportunities for immediate reward, even when there is serious risk of long term loss of reward or punishment; which ultimately effects the individuals' ability to make appropriate life choices.

The convergence of compromised long-term decision-making abilities, increased impulsivity, and a source of unpredictable reward that engenders large fluctuations of DA (e.g. gambling or drugs of abuse) in individuals with abnormal tonic DA levels (e.g. due to genetic inheritance) are much more likely to pass the threshold into a state of addiction. In this state, actions and predictive cues associated with the source of the large fluctuations in DA (e.g. the lights and sounds of a slot machine) may become imbued with incentive salience. Although simply conjecture at this point, I think it also stands to reason that the repeated pairings of unpredictable rewards with different environmental and contextual cues increases the generalization of situations and cues that have the ability to invoke a craving state. This increases the desire to gamble and due to the decreased ability of mPFC to inhibit these actions in favour of alternative ones, the individuals decide to gamble. Finally, after many many experiences like this, the control of behaviour shifts from "goal-directed" regions of the striatum to "habit" related regions. At this point, responses to cues start to become subconscious/automatic and thus very difficult to control. It is at this point where PGs are likely to exhibit perseverative behaviours when exposed to changes in reward outcome.

4.2 Conclusions

Damage to the mPFC appears to disrupt complex decision-making processes involving the updating of reward histories with new data concerning unexpected reward or punishment (particularly when there are protracted delays between response and outcome), and coordinating external goal-directed learning processes with internal goal-directed processes in order to direct behaviours in uncertain environments. Intact mPFC functioning is especially important in situations where behaviour must be altered in response to a shift in reward patterns and no concurrent change in environmental cues is apparent. That is, when fixed responses to environmental cues have been previously established, and the animal must alter its behaviour even though the same cues are in place. The inability to inhibit these old behavioural responses to the environmental cue manifests in perseverative patterns of response, which are common in both mPFC damaged humans and animals. PL damaged rats were unable to adjust as quickly as control animals after encountering similar shifts in rewards patterns in our task. Additionally, we found that this impairment in reward obtainment was connected to an obvious change in reward processing reflected in the breakdown of the ability of the “softmax” RL model to meaningfully describe the behaviours of PL lesioned rats. Otherwise the effect of PL damage was modest. Initial and follow-up analysis of perseverative behaviour indicates that PL lesions only modestly affect the ability of rats to flexibly modify their behaviour on our task. Thus, our data does not strongly support the idea that dysfunction in PFC regions leads to a hijacking of behaviour by dorsal areas of the striatum. However, due to the extensive pre-training of our animals, the possibility exists that perseverative biases in lesioned animals were masked by training-induced adaptations.

Abnormal dopaminergic processing in the mPFC likely plays a significant role in the impaired decision-making processes underlying PG. However, the precise nature of how gambling addiction interacts with DA-mediated learning and how it effects long-term changes in mPFC dopaminergic neurotransmission remains elusive. Considering that the efficacy of PG treatment is, so far, quite modest; it is important to increase our knowledge base concerning the genesis, progression, and maintenance of these neurological processing impairments. Therefore, it is our intention that the information gathered from our studies concerning the role of the mPFC in optimal decision-making will be used to increase the understanding of PG neuropathology and inform other research going forward.

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Appendix A

A.1 Afferent and Efferent Projections of the Medial Prefrontal Cortex and Striatum

This section will review and aggregate the findings of several connectivity studies aimed at delineating the anatomical underpinnings of prefrontal cortex (PFC) and Str function. For the sake of brevity, only the connectivity of core regions in the mPFC, namely the anterior cingulate cortex (ACC), prelimbic (PL), and infralimbic (IL) regions will be discussed in depth – major and moderate, but not weak, connections will be reported. The afferent and efferent projections of other regions of interest; namely, the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC; in primates), and Str regions, will be described briefly focusing only on major connections. For the purposes of this discussion, connections to and from the medial agranular region (FR2) and frontal eye fields (FEF) will be combined with ACC and dlPFC projections respectively. Most studies reviewed investigated afferent and efferent projections in rats, so the following overview of connectivity will refer to the rat brain unless specifically stated otherwise.

A.1.1 dlPFC afferent and efferent projections

In primates, the dlPFC receives input chiefly from PFC regions and sensory association cortices. Specifically, significant afferent connections can be observed coming from: frontopolar cortex (FPC), dlPFC, ACC, OFC, somatosensory cortex (SS), visual cortex (V), superior temporal gyrus (STG), and posterior parietal cortex (PPC). Outgoing dlPFC projections terminate primarily in PFC regions, Str, and in temporal cortex; expressly the FPC, dlPFC, ACC, OFC, dorsomedial striatum (dmStr), temporal pole (TP), and STG (Selemon & Goldman-Rakic, 1985; Kolb, 1990).

A.1.2 ACC afferent and efferent projections

The ACC receives input from other PFC regions, sensory and motor association regions, caudal cingulate areas, the claustrum (CLA), limbic regions, the basal ganglia, the basal forebrain, thalamic and hypothalamic nuclei, and mesencephalic regions. Specifically afferent projections can be observed coming from: FPC (primate), dlPFC (primate), ACC, PL, IL, OFC, supplementary motor area (SMA), secondary somatosensory cortex (SS2), agranular insular cortex (AI), PPC, secondary auditory cortex (AU2), secondary visual cortex (V2), lateral agranular cingulate area (AGI), retrosplenial cortex (RSP), CLA, the basolateral (BLA) and basomedial (BMA) nuclei of the amygdala, the hippocampus (HF), subiculum (SUB), perirhinal cortex (PRC), entorhinal cortex (EC), ectorhinal cortex (ECT), ventral pallidum (VP), bed nucleus of the stria terminalis (BST) and substantia innominata (SI) of the basal forebrain, (paraventricular (PV), rhomboid (RH), reuniens (RE), paratenial (PT), paracentral (PC), central medial (CM), anteromedial (AM), ventral medial (VM), central lateral (CL)) nuclei of the thalamus, lateral preoptic (LPO) and magnocellular preoptic (MA) nuclei of the hypothalamus, taenia tectum (TT), and ventral tegmental area (VTA; Selemon & Goldman-Rakic, 1985; Heidbreder & Groenewegen, 2003; Kolb, 1990; Hoover & Vertes, 2007).

ACC efferent projections terminate in PFC regions, sensory and motor regions, Str, caudal cingulate areas, CLA, limbic regions, thalamus, hypothalamus, as well as portions of the mesencephalon and metencephalon. Specifically, when injections are made in ACC anterograde labeling is present in: FPC (primates), ACC, PL, IL, OFC, premotor cortex (PMC), motor cortex (M), SS, V, temporal cortex (TC), AI, dmStr, ventral striatum (nucleus accumbens core (NAcC)), AGI, RSP, CLA, amygdala nuclei (BLA and BMA), PRC, thalamic nuclei (PV, RH, PT, RE, AM, and

anteroventral (AV)), zona incerta (ZI), posterior hypothalamus (PH), superior colliculus (SC), periaqueductal gray (PAG), and the reticular formation (RF). Efferent projections to ACC, dmStr, RE, AM and AV are particularly massive (Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012; Heidbreder & Groenewegen, 2003; Kolb, 1990).

A.1.3 PL afferent and efferent projections.

The PL region receives input from other PFC regions, gustatory and olfactory areas, caudal cingulate areas, CLA, limbic regions, the basal forebrain, thalamic and hypothalamic nuclei, as well as portions of the mesencephalon and metencephalon. Specifically, anterograde tracing studies have shown PL efferents to: FPC (primate), ACC, PL, IL, OFC, AI, endopiriform nucleus (EN), RSP, CLA, amygdala nuclei, (BLA, BMA, and cortical (COA)) nuclei of the amygdala, amygdalo-piriform transition zone (TR), PRC, EC, ECT, lateral mammillary nucleus (LM) of the mammillary bodies, horizontal limb of the diagonal band of Broca (DBh), thalamic nuclei (PV, RH, RE, PT, CM, and CL), PH and supramammillary nuclei (SUM) of the hypothalamus, VTA, pedunculo-pontine tegmental nucleus (PPT), interpeduncular nucleus (IP), PAG, locus coeruleus (LC), and raphe nucleus (RN; Selemon & Goldman-Rakic, 1985; Heidbreder & Groenewegen, 2003; Kolb, 1990; Hoover & Vertes, 2007).

The PL sends efferent projections to PFC regions, Str, gustatory and olfactory areas, CLA, limbic regions, the basal forebrain, lateral habenula (LH), thalamic and hypothalamic nuclei, as well as portions of the mesencephalon, metencephalon, and medulla. Specifically, after injections in PL, anterograde labeling has been shown in: FPC, ACC, PL, IL, OFC, dmStr, NAcC, nucleus accumbens shell (NAcS), AI, anterior olfactory nucleus (AON), olfactory tubercle (OT), piriform nucleus (PIR), TT, CLA, PRC, EC, (BLA and central (CEA)) amygdala nuclei, septum (SEP),

DBh, BST, SI, LH, (PV, RH, RE, PT, AM, central medial (CEM) and parafascicular (PF)) thalamic nuclei, (lateral (LHy) and premammillary (PM)) nuclei of the hypothalamus, subthalamic nucleus (STN), substantia nigra pars compacta (SNc), VTA, lateral dorsal tegmental nucleus (LDT), IP, PAG, LC, RN, suprallemniscal nucleus (SLN), and the solitary nucleus of the medulla (SNM). Efferent projections to PL, IL, dmStr, NAcC, PT, and RE are particularly massive (Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012; Heidbreder & Groenewegen, 2003; Kolb, 1990; Vertes, 2004).

A.1.4 IL afferent and efferent projections

The IL region receives input from other PFC regions, gustatory and olfactory areas, CLA, limbic regions, the basal forebrain, thalamic and hypothalamic nuclei, as well as portions of the mesencephalon and metencephalon. Specifically, tracing studies have shown that IL receives input from: ACC, PL, IL, OFC, AI, AON, PIR, TT, CLA, amygdala nuclei, (BLA, BMA, and COA) nuclei of the amygdala, TR, HF, SUB, PRC, EC, ECT, SEP, DBh, SI, thalamic nuclei (PV, RH, RE, PT), (SUM, LHy, and medial (MHy)) nuclei of the hypothalamus, VTA, LDT, PAG, LC, RN, and nucleus incertus (NI; Selemon & Goldman-Rakic, 1985; Heidbreder & Groenewegen, 2003; Kolb, 1990; Hoover & Vertes, 2007).

IL efferent projections terminate in PFC regions, Str, gustatory and olfactory areas, limbic regions, the basal forebrain, thalamic and hypothalamic nuclei, as well as portions of the mesencephalon, and metencephalon. Specifically, the IL region projects to: FPC, ACC, PL, IL, OFC, NAcC, NAcS, AI, EN, AON, OT, PIR, TT, EC, (BLA, BMA, CEA, and medial (MEA)) amygdala nuclei, SEP, DBh, BST, SI, (PV, RH, RE, PT, AM, CEM, PF) thalamic nuclei, ZI, (LHy, SUM, PH, paraventricular (PVH), preoptic (PO), anterior (AH), dorsomedial (DM), and perifornical (PFx))

nuclei of the hypothalamus, SNc, VTA, LDT, IP, PAG, LC, RN, (SNM, solitary (NTS), parabrachial (PB), Barrington's (BAR), paragigantocellular (PGN)) nuclei of the medulla. Efferent projections to PL, IL, NAcS, OT, PT, and RE are particularly massive (Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012; Heidbreder & Groenewegen, 2003; Kolb, 1990; Vertes, 2004).

A.1.5 OFC afferent and efferent projections

In primates, OFC receives input from PFC regions (FPC, dlPFC, ACC, PL, IL, OFC), all sensory association cortices, CLA, limbic regions (amygdala (AMG) and HF), and SNM. Outgoing OFC projections terminate in PFC regions (FPC, dlPFC, ACC, PL, IL, OFC), Str, (dmStr, NAcC), AI, lateral amygdala (LA), PRC, EC, SUB, HF, mediodorsal thalamic nuclei (MD), PH, LDT, and PAG. Efferent projections to dlPFC, ACC, dmStr, AI, LA, SUB, HF, MD, PH, and PAG are particularly large (Selemon & Goldman-Rakic, 1985; Klein, et al., 2010; Gruber & McDonald, 2012; Kondo & Witter, 2014; Kolb, 1990).

A.1.6 dlStr afferent and efferent projections

The dlStr receives input primarily from motor and sensory association cortices (most heavily from motor) and projects principally to the globus pallidus (GP), substantia nigra pars reticulata (SNr), and the STN (Chikama, McFarland, Amaral, & Haber, 1997; Haber, et al., 2000; Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012).

A.1.7.dmStr afferent and efferent projections

The dmStr receives input primarily from motor and sensory association cortices (most heavily from sensory), PFC regions (dlPFC, ACC, PL, and OFC), BLA, HF, EC, and PPC. In turn, the dmStr sends projections principally to the GP, SNr, and the STN (Chikama, et al., 1997; Haber et al., 2000; Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012).

A.1.8 NAcC afferent and efferent projections

NAcC efferent projection originated primarily from PFC regions (dlPFC, ACC, PL, IL, and OFC), AI, BLA, HF, EC and STG. The NAcC projected principally to the GP, SNr, and the STN (Chikama, et al., 1997; Haber et al., 2000; Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012; Goto & Grace, 2008; Groenewegen, et al., 1999).

A.1.9 NAcS afferent and efferent projections

The NAcS received input primarily from PFC regions (PL and IL), AI, BLA, HF, EC, and STG; while projecting principally to the GP, SNr, and the STN (Chikama, et al., 1997; Haber et al., 2000; Selemon & Goldman-Rakic, 1985; Gruber & McDonald, 2012; Goto & Grace, 2008; Groenewegen, et al., 1999).

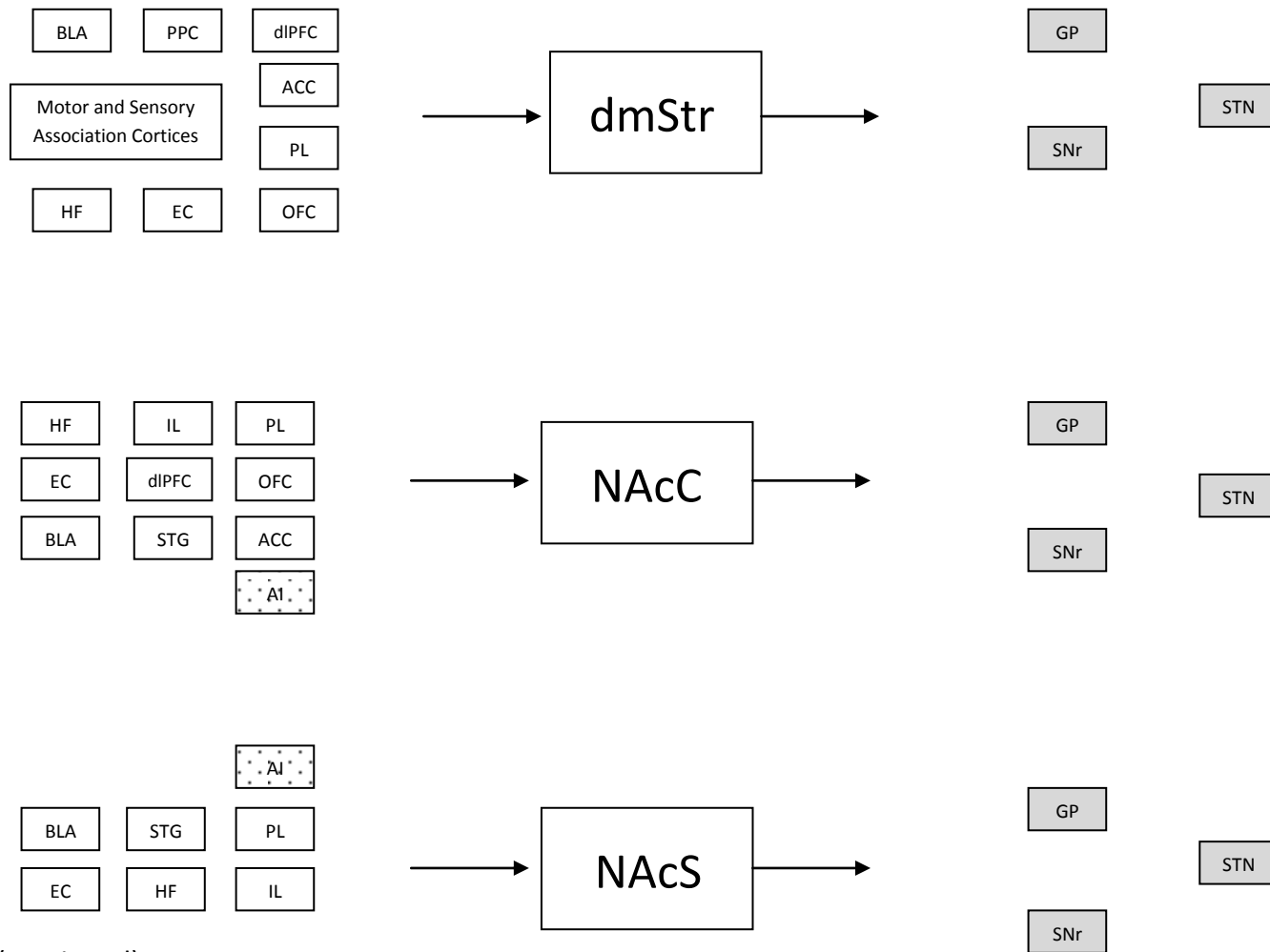


Figure A1 (continued).