Dopamine/Serotonin interactions in reward-related behavior: Focus on the Iowa Gambling Task

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1. Introduction

Throughout the day we engage in numerous actions to provide ourselves with objects we want or to prevent interaction with things we do not want. That is, we act both to obtain positive events and to prevent experience of negative events. Often, behavioral actions are made in response to certain cues from the environment that have proven to result in a good outcome before or that warn us for objects that may be harmful or disliked. In a constantly changing environment however, cues are frequently changing and actions that result in a favorable outcome today may not do so tomorrow. Therefore, a constant adjustment of behavior in order to adapt to the demands of the ever changing environment is a vital component of survival. Adaptive behavior involves several actions. Depending upon the ultimate goal that an agent wants to obtain, particular actions have to be selected and performed, whereas other, non-relevant actions have to be inhibited (Ridderinkhof et al, 2004). The agent also has to monitor the results of its actions and to be able to adjust actions when the preferred goals are not obtained. Cognitive control comprises all of these components (Ridderinkhof et al, 2004). The different aspects of cognitive control may be regulated by different neural areas; however, all areas are located within the prefrontal cortex (PFC) (Ridderinkhof et al, 2004).

1.1 Modeling real life behavior

Associative learning behavior has been extensively modeled in laboratory settings. Classical and operant conditioning paradigms study (simple forms of) associative learning. In addition, several tasks have been developed to study the effect of the amount of effort an agent has to exert to obtain a reward or the varying delay at which a reward is delivered on the relative value of the reward for the agent. Also, chance learning and decision making can be modeled, for example: rewards can be delivered with a certain probability or subjects can be made to choose between different types or magnitudes of rewards. Often, however, the different components that make up behavior are separated and tasks modeling these behaviors do not measure behavior as a whole. For example, standard classical and operant conditioning paradigms, in which an agent learns to associate a stimulus cue with a forthcoming reward, do not take into account the long term effects a behavior may have. In addition, these paradigms generally focus on either reward or punishment, whereas a mixed situation may increase the validity of the test as a model for decision making and adaptive behavior.

The Iowa Gambling Task (IGT) is a tool to study decision making behavior. Subjects choose cards from four decks; choosing a card will result in gain or loss of money and subjects are instructed to gain as much money as possible at the end of the task. However, subjects are not informed of the length of the task. Two decks result in immediate high gains, but in the long run result in substantial losses, whereas the other two decks provide moderate immediate gains however, choosing from these two latter decks will provide a positive balance in the long run. These latter decks thus constitute the preferred choice, when regarding the long term goal of gaining as much money as possible. Although subjects may develop an idea or estimation of the relative risk of choosing a deck, when performing the task subjects generally do not calculate the gain and losses provided by a

deck (Bechara et al, 1994). Because subjects are not able to calculate or keep track of their previous gains and losses their choices for a particular deck are based on estimations of the relative gain of the decks (Brand et al, 2006).

1.2 Neural substrates for decision making relevant for the IGT

The orbitofrontal cortex (OFC) and amygdala are important neural structures for ambiguous decision making (Brand et al, 2006). Initially, subjects explore the available options, switching to the option generating the best long term outcome in the second half of the task. It has been suggested that the reward system, with dopamine as its major neurotransmitter is particularly important during the early stages of the task, whereas the self control system, with serotonin as the main neurotransmitter, controls behavior during the second half of the task (van den Bos et al, 2006). Choosing immediate rewards during the first stages of the task may be considered as impulsive behavior, whereas choosing for the 'delayed' reward (or long term positive balance) reflects self-control (Bizot et al, 1999). Brand et al (2006) suggest that decision making during the first half of the IGT is characterized by ambiguous decision making (i.e. subjects choose cards from a certain deck but they have no idea what the consequence of their choice is, they do not yet have an estimation of the gains/losses that can follow from choosing a particular deck), while behavior in the second half may be determined by risk taking (i.e. subjects generally have formed an estimation/hunch of the magnitude of gains/losses that follow after a certain deck, but may vary in their preference for high risk/immediate high reward or lower risk/immediate low reward decks) and certainty about an expected outcome. The dorsolateral prefrontal cortex (dlPFC) may be more involved in risky decisions and may therefore be more active during the later part of the IGT, although the OFC/ventromedialPFC (vmPFC) are most likely also still involved (Brand et al, 2006). The involvement of dopamine and serotonin in the IGT may not be an all-or-none phenomenon. It is likely that dopamine and serotonin are both present through the tasks, but that one system may be dominant over the other system and vice versa during the different stages of the task. For example, the balance between serotonin and dopamine may determine whether approach behavior or behavioral inhibition is observed (Daw et al, 2002). During the IGT, the balance between serotonin and dopamine determines whether a short or long term beneficial choice is made.

Patients suffering from vmPFC damage continue choosing cards from the disadvantageous decks even in the second half of the IGT when healthy subjects switch to cards from advantageous decks, i.e.: patients prefer immediate large rewards over a delayed positive outcome (Bechara et al, 1994), eventhough they may be aware that the decks they are choosing are disadvantageous (Bechara et al, 1997). Rather than an altered sensitivity to reward or punishment, these patients appear to be unable to consider future consequences of their behavior; instead, they are always choosing immediate options, whether or not it provides them with a positive or negative outcome (Bechara et al, 1994). Damage to the amygdala can also result in impaired decision making (Bechara et al, 1999). The amygdala is an important structure for assigning affective value to certain stimuli. Damage to the amygdala interferes with the affective value of a situation that

people usually experience and influences the behavior people would normally show in response to the situation (Bechara et al, 1999).
Exposure to outcomes after choosing from different decks will result in expectations of the outcomes that result from choosing a particular deck. Both wins and losses are components in this expected value (Rogers et al, 2003). When exploring the different decks during the first phase of the IGT, subjects will encounter both gains and losses and this will help them to develop expectancies concerning the values of the different decks and to develop a strategy that can be followed when performing the task. The expected value of a reward depends on both the magnitude of the reward and the probability at which the reward is delivered (Knutson et al, 2005). The different components of expected reward value also appear to have different neural substrates. Activation of the nucleus accumbens (NAC) is related to the magnitude of the reward whereas the mPFC is associated with the probability at which a reward is delivered and may integrate the two components that make up the expected value (Knutson et al, 2005). Also, cortical areas (anterior cingulated cortex - ACC) may monitor the performance and make corrections (mPFC) so that the probability of obtaining future rewards is maximized (Knutson et al, 2005). Blair et al (2006) observed differential activation of the ACC and vmPFC during choices of 'good' and 'bad' options. The ACC showed increased activation when choosing between two 'bad' options, suggesting it may be involved in strategies diminishing punishment (Blair et al, 2006). The ACC may be an important structure integrating good and bad outcomes and selecting an appropriate response to execute (Blair et al, 2006). The vmPFC was activated by choices between 'good'options (Blair et al, 2006). However, rather than coding the expected value for the upcoming reward (i.e. the reward that follows the stimulus that has been chosen by the subject), the activation in the vmPFC appears to be related to the total amount of reinforcement in a trial (i.e. reinforcemental of the chosen stimulus + reinforcement that could have been obtained by choosing the other stimulus) (Blair et al, 2006).

In the IGT subjects have to deal with immediate rewards (i.e. the immediate gains that can be obtained with a chosen card) and delayed reward (i.e. a positive balance at the end of the task). McClure et al, (2004) used functional magnetic resonance imaging (fMRI) to see whether immediate or delayed rewards would result in activation of distinct neural structures. The relative value of a reward may vary depending on the time at which it is delivered (McClure et al, 2004). When animals chose an immediate reward activation was observed in the NAC, medial OFC, mPFC, posterior cingulate cortex and left posterior hippocampus while intraparietal cortex, right dorsolateral pfc, right ventrolateral pfc and right lateral OFC were activated independent of the delay (McClure et al, 2004).

In conclusion, both subcortical and cortical substrates are involved in decision making during the IGT. A cortico-striatal circuit, encompassing the NAC, amygdala and several areas of the PFC subserves this behavior. Within this circuit, the different components are more or less involved with the different components that are involved in the task. Whereas the subcortical areas may be more involved in coding reward magnitude and assigning affect to certain stimuli, the cortical areas appear to be more important for coding stimulus-reward contingencies and adapting behavior when following a long term

strategy. Ventral and medial PFC areas and their associated dopaminergic circuitry are more involved in the first half of the IGT, when subjects show no clear preference for a particular deck but choose cards from decks randomly. (Dorso)lateral PFC areas and their associated serotonergic circuitry appear to be more important during the later stages of the IGT, when subjects have formed preferences for certain decks over others. In this thesis, I will describe how dopamine and serotonin may interact during the IGT. First, the dopaminergic and serotonergic pathways and their known involvements will be described. This will be followed by a brief description of experimental evidence suggesting how these neurotransmitter pathways may interact. Then, I will describe the sites where interactions take place and the functional effects of these interactions. To conclude, some suggestions concerning the dopamine/serotonin interactions during the IGT will be made in addition to some suggestions for further research. As both humam and animals experiments concerning decision making will be described and the PFC is an important structure invovled in decsion making, I will start with a short overview of PFC comparative anatomy between human and rodents

1.3 Comparing human and rodent PFC

Within the PFC, different areas can be found. The different subdivisions of the PFC differ in their cortical and subcortical connections and in their expression of certain receptor subtypes. Therefore, besides anatomical differentiation, functional differentiation of different areas within the PFC may be observed.
The PFC is important for cognition, planning and execution of actions (Schoenbaum et al, 1998). Functionally, the PFC can be divided in motor areas, areas regulating emotional behavior – medial (pre-and infralimbic cortex) and orbital prefrontal cortex – and a part that is involved in cognition, the lateral prefrontal cortex (Fuster, 2001). Three subdivisions within the PFC are found in humans, non-human primates and rats (Uylings et al, 2003): 1. a region around the OFC involved in emotional and social behavior, 2. a dorsolateral region for working memory, 3. the ACC region important for visceromotor behavior (Uylings et al, 2003). In rats, the frontal cortical area 2, dorsal anterior cingulate area and prelimbic cortex are thought to be similar in function to the dorsolateral prefrontal cortex in humans (Uylings et al, 2003). Dalley et al (2004) describe the components of the three subdivisions in the rodent PFC as follows: the medial PFC (mPFC) is further divided in a dorsal part (precentral and anterior cingulate cortex) and a ventral part (prelimbic, infralimbic and medial orbital cortex). The dorsal and ventral agranular insular cortex and lateral orbital cortex make up the lateral PFC and the ventral orbital and ventral lateral orbital cortex make up the ventral PFC (Dalley et al, 2004). In this thesis, I will refer mostly to the mPFC (comprising precentral, anterior cingulated, pre- and infralimbic and medial orbital cortices).
The PFC has extensive reciprocal connections with several subcortical structures, such as the thalamus, the amygdala, dorsal and ventral striatum and the brainstem in addition to connections between the subdivisions of the PFC itself and other cortical areas, that may each subserve slightly different functions (Dalley, 2004; Fuster, 2001; Uylings, 2003). In fact, different subdivisions within the PFC are part of distinct parallel circuits between thalamus, basal ganglia and PFC (Uylings et al, 2003). In addition, the PFC is innervated and projects back to cholinergic and monoaminergic neurotransmitter systems (Dalley et al, 2004). Each of the three subdivisions of the PFC is hypothesized to contribute a part to

the execution of goal-directed actions. While the anterior cingulate area (part of the mPFC) is suggested in motivational aspects of goal-directed behavior (most likely through connections with the amygdala), the OFC prevents the disturbance of ongoing behaviors and may also be involved in the coding of expectations about outcomes following responses that are made to obtain the outcome, the lateral PFC is thought to be involved in temporal aspects of goal-directed behavior (Fuster, 2001; Schoenbaum et al, 1998). Together with the basolateral amygdala, the OFC shows activation during the period between a behavioral action and an anticipated reward following this action, indicating a role for these structures in the acquisition of goal-directed behavior, when associations between behavioral actions and benefits resulting from actions are made (Schoenbaum et al, 1998). The dlPFC may be more involved in choosing actions relevant for a particular task whilst the ventromedial part of the PFC may be more important for decisions influenced by affect or emotion (Ridderinkhof et al, 2004). In addition, the ventromedial PFC might monitor several reinforcements that are coupled to different stimuli (Blair et al, 2006). It is possible then, that besides monitoring of the chosen stimuli and the associated outcome, alternatives are considered as well (Blair et al, 2006). Of course, experience with the different stimuli and their associated outcomes would be necessary for this type of monitoring.

2. Dopamine and Serotonin projection pathways and function

2.1 Dopamine – reward learning

Dopamine is heavily associated with the brain reward system. Although some issues regarding the precise role of dopamine in the reward system remain debated, the phasic dopamine signal has been established as being important during reward related behavior. Cell bodies of the mesolimbic/-cortical dopamine pathway are located in the VTA and project to the NAC, PFC and amygdala (among others) (Schultz, 2002).
However, besides dopamine, several other neurotransmitters may be able to influence activity within the reward system (see figure 1). The mesolimbic dopamine system is connected with several other neural systems. Dopamine cells in the VTA receive cholinergic input from the pedunculo-pontine tegmental nucleus (PPTg), located in the brainstem (Wise, 2002). Glutamatergic input arises from the medial and occipital prefrontal cortex as well as the amygdala, hippocampus and thalamus (Kelley et al, 2003; Schultz 2002; Wise, 2002). Both the VTA and the NAC receive glutamatergic innervation from the mPFC, which also innervates the PPTg (Wise, 2002). Indeed, it is the converging input of both dopamine and glutamate on medium spiny neurons in the striatum, acting through D1 and NMDA receptors respectively, that is thought to be essential for neural plasticity during reinforcement learning (Schultz, 2002; Kelley et al, 2003).
Medium spiny neurons are abundantly present throughout the striatum (Jog et al, 1999). The medium spiny neurons within the NAC contain dopaminergic synpases are the main output neurons of the mesolimbic dopamine system and may therefore constitute the final relay station within the reward circuitry (Wise, 2002). Glutamate neurotransmission is implicated in neural plasticity and (long-term) changes in connectivity between neurons. Thus, the converging input of dopamine and glutamate on medium spiny neurons in the nucleus accumbens may result in changes in second messenger cascades (Kelley et al, 2003), resulting in strengthening of the synapse when the input from cortical (glutamate) and subcortical (dopamine) structures arrives within a limited time-span (Schultz, 2002). Both dopamine and glutamate are essential during the early phases of an instrumental learning task, where a cue signals that a reward is available once a particular behavioral action is made (Kelley et al, 1997; Smith-Roe & Kelley, 2000).
The mesolimbic dopamine system receives GABAergic input from striatl and prefrontal regions (Wise, 2002). In addition, the output neurons of the NAC, projecting to the ventral pallidum (VP) and substantia nigra (SN)/VTA are GABAergic (Wise, 2002). Furthermore, GABAergic projections from the VP innervate the VTA and from the VTA arise GABA projections to the PPTg (Wise, 2002). The interactions decribed above allow the possibility of different manners in which the reward system can be activated. It is known for example, that different kinds of drugs of abuse all activate the mesolimbic dopamine system; however, they may do so in different manners (see Wise, 2002). Thus, activation of the dopamine system during the IGT may come from two sources. First, the rewards obtained during the task may directly activate VTA neurons, increasing phasic dopamine release. Second, serotonergic input to the DA cell body regions or projections areas may indirectly activate the dopamine system (see below (ch. 4, 5) for more elaborate description)

A role for dopamine in mediating approach behavior during classical conditioning has been shown extensively (Di Ciano et al, 2001; Parkinson et al, 2002). Therefore, dopaminergic transmission during the early stages of the IGT may regulate approach towards the different decks, exploring all available options. In line with the suggestion that dopamine may be less important during the second half of the task is the finding that dopamine is more important during the learning phase of a task than to maintain performance (Choi et al, 2005; Phillips et al, 2003).

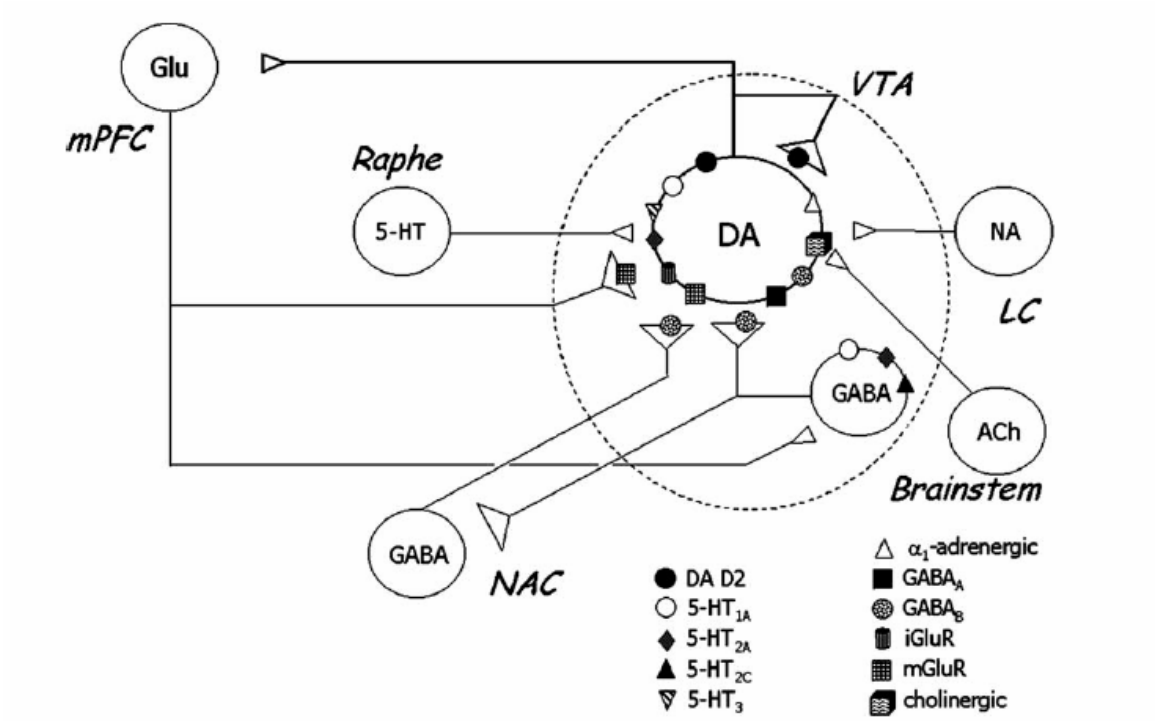

Figure 1. Schematic representation of neurotransmitters influencing activity of dopamine neurons in the mesolimbic dopamine pathway (VTA). The VTA receives cholinergic input from the pedunculopontine tegmental nucleus in the brainstem. Glutamatergic input arises from prefrontal areas as well as amygdala, hippocampus and thalamus. Serotonergic projections from the raphe nuclei in the brainstem innervate the VTA. In addition, GABAergic input from striatal areas may influence dopaminergic activity in the VTA (Figure copied from Adell & Artigas, 2004).

Different timescales at which dopamine can be active is another factor to consider when investigating the influence of dopamine on behavior. The extracellular dopamine concentration is relatively stable; although dopamine is continuously released, simultaneous uptake from the extracellular space leaves the concentration relatively constant (Wightman & Robinson, 2002).Transients increases in dopamine concentration may result from burst firing of dopamine neurons, however, this increase rapidly disappears following reuptake of dopamine in the neurons (Wightman & Robinson, 2002). The tonic dopamine concentration enables global processes in movement, cognition and motivation, whereas the rapid dopamine signaling provides a learning signal (Schultz, 2002). Learning of new responses may be particularly mediated by phasic dopamine activity while tonic dopamine activity is sufficient for maintaining learned behaviors throughout a task (Parkinson et al, 2002). This suggestion was

supported by studies using intracranial self stimulation where an association was found between transient DA release and acquisition of self stimulation; once behavioral responses were acquired phasic DA activity was no longer needed for performance (Wightman & Robinson, 2002). The tonic and phasic dopamine release may be regulated by two separate inputs to the VTA (Floresco et al, 2003). Floresco et al (2003) studied the influence of two afferent pathways to the VTA on dopamine burst firing and population activity. Activation of the hippocampal-NAC-VP pathway, via reduction of GABAergic input to the ventral pallidum resulted in an increase in population activity of VTA dopamine neurons (Floresco et al, 2003). This increase in population activity resulted in a heightened extracellular dopamine concentration in the NAC (Floresco, 2003). Therefore, it appears that apart from burst firing, increased tonic firing activity can also result in an increased dopamine level in the projection areas. Stimuluation of the second VTA afferent, the projection from the pedunculopontine tegmental nucleus (PPTg) by increasing the excitatory input to the PPTg resulted in an increase in burst firing without affecting the population activity. In contrast to the observations after stimulation of the NAC-VP pathway, the extracellular dopamine concentration was not found to be altered (Floresco et al, 2003). In addition, input from the amygdala can modulate activity in the mesocorticolimbic dopamine pathway (Phillips, Ahn & Howland, 2003). Glutamatergic projections to the NAC arise in the basolateral amygdala (BLA) (Phillips, Ahn & Howland, 2003). The BLA also projects the mPFC (Phillips, Ahn & Howland, 2003). Therefore, the BLA may influence release of dopamine directly in the terminal fields (NAC and mPFC), but may also be able to influence VTA activity, via input to the mPFC (which in turn projects back to the VTA). The VTA is also innervated by GABAergic neurons from the central nucleus of the amygdala (Phillips, Ahn & Howland, 2003).

The probability with which rewards are delivered – either spontaneously or following a deliberate action to obtain reward – is another factor influencing behavior. Dopamine neurons show increased firing activity between the presentation of a cue stimulus and the presentation of reward (Fiorillo et al, 2003). Firing rates do not reach peak levels seen after cue presentation, but are consistently higher than baseline levels. This sustained activity may reflect uncertainty of the expected outcome, as fully predicted rewards do not result in increased activity (Fiorillo et al, 2003). Human imaging studies have also linked increased dopamine release in both ventral and dorsal striatum to expectation (de la Fuente-Fernandez, 2001; 2002).

2.2 Serotonin – Impulsivity

Serotonin (5-hydroxytryptamin, 5-HT) cell bodies are located in the medial and dorsal raphe nuclei in the brain stem. Serotonin projects throughout the central nervous system (CNS) to cortical, subcortical and spinal targets. Serotonin is released throughout the CNS and its effects may be diverse, depending upon the type of receptor and brain area activated. At present, 14 receptor subtypes are known, spread over 7 families (5-HT_{1-7}) (Barnes & Sharp, 1999). Almost all 5-HT receptors are G-protein coupled metabotropic receptors with the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel (Barnes & Sharp, 1999). In general, 5-HT_1 receptors are coupled to an inhibitory G-protein and cause neural inhibition. 5-HT_2 and 5-HT_3 receptors in contrast, have an excitatory effect (Barnes & Sharp, 1999). In addition, the expression pattern of the

various members of the 5-HT receptor family differs. Two receptors subtypes can function as autoreceptors: the 5-HT_{1A} receptor is located on presynaptic 5-HT neurons (in the medial and dorsal raphe nuclei) and functions as an autoreceptor regulating the amount of 5-HT release from the raphe nuclei (Higgins & Fletcher, 2003). In addition, the 5-HT_{1B} receptors, which show high expression levels in the basal ganglia, can also function as autoreceptors (Barnes & Sharp, 1999). The other receptor subtypes do not regulate the release of 5-HT, but may influence release of other neurotransmitters and are important in the regulation of diverse aspects of behavior.

Serotonin is often associated with impulsive behavior and behavioral flexibility. A reduction in 5-HT levels may predispose an individual for impulsivity. Rather than a unitary phenomenon, impulsivity may be characterized by several components, such as decreased behavioral inhibition, decreased tolerance to delayed rewards, premature responding and non-considerate decision making (Winstanley, in press). More broadly described, impulsivity may be accompanied by inappropriate decision making, favoring immediate outcomes over delayed outcomes. The decisions made may be inappropriate for the given situation and risky. Because different components contribute to impulsivity, impulsive behavior is difficult to model in laboratory settings. Two types of paradigms are used to study impulsive behavior. One type, the 5 choice serial reaction time task, focuses on the motor aspect (premature responding) and measures impulsive action (Winstanley, in press). Behavioral inhibition and tolerance to delayed rewards is generally modeled in a task where subjects have to choose between a small immediate or large delayed reward (Winstanley, in press). Using a combination of tasks measuring motor and psychological aspects of impulsivity can therefore contribute to the mechanisms underlying impulsivity. Of course, the ideal task would model both components at the same time.

Several areas that are involved in reward-related learning (see above) are also implied in impulsive decision making. The NAC together with its connections to the mPFC and anterior cingulate cortex (ACC) form an important part of the neural circuitry underlying choices between immediate and delayed reinforcement (Cardinal et al, 2001). Lesioning the NAC core let rats to choose small immediate rewards over large delayed rewards, whereas lesions of the ACC and mPFC did not affect impulsive choice (Cardinal et al, 2001). The ACC, however, has been implied in reward related learning and motoric impulsivity (rats show premature and over-responding to rewarding stimuli) (Cardinal, 2006) and the mPFC cortex was found to be involved in aligning behavior according to the passage of time (Cardinal et al, 2001). The ACC may also be involved in monitoring the value of the reinforcement over time, thereby influencing the decision whether it is worthwile to perform an action to obtain the reinforcer or not (Kennerly et al, 2006). The BLA, an important afferent to the VTA, is also involved in impulsivity and damage to this structure increases the choice for small immediate rewards over large delayed rewards (Cardinal, 2006).

Central 5-HT neurotransmission may be important for attentional processes in impulsivity (Harrison et al, 1997). For example, while detection of visual stimuli is not impaired after central depletion of 5-HT, animals show an increased number of premature

responses (Harrison, 1997). These animals are unable to focus their attention to the stimulus that is predictive of subsequent reinforcement. Instead, they also respond to distracting stimuli that are irrelevant for the task (Harrison et al, 1997). These results suggest that serotonin is an important mediator for the control of responses. When serotonin is depleted, animals increase their overall responding (Harrison et al, 1997). Harrison et al (1997) suggest that central 5-HT may be particularly important for the control of responses when a reinforcer is anticipated, following the high number of premature responses in lesioned animals. A similar function was assigned to the ACC by Kennerly et al (2006). The anterior cingulate cortex is part of the mPFC and is often regarded as a transition zone between cortical and limbic structures (Ridderinkhof et al, 2004). Therefore, serotonin neurotransmission within this cortical-striatal circuit may be an important regulator of response behavior and monitoring the changing value of the reinforcer over time. Another cortical structure involved in impulsive behavior and control of responses may be the OFC. Clarke et al (2004) suggest an important role for 5-HT neurotransmission within the OFC, as tasks depending on function of the OFC often also need intact 5-HT transmission (Clarke et al, 2004). Indeed, local depletion of 5-HT in the PFC impaired performance, animals showed increased perseveration, on a task that was previously found to be dependent upon OFC functioning (Clarke et al, 2004). The OFC is also implicated in encoding the associations between a cue stimulus and the reinforcer following the stimulus (Schoenbaum et al, 1999).
Although many studies investigating the relation between 5-HT and impulsivity report that decrease of 5-HT neurotransmission may result in increased impulsivity, Dalley et al (2002) found increased 5-HT release in the prelimbic area of the PFC during impulsive behavior. In addition to the heightened 5-HT release, impulsive subjects showed impairment in prefrontal (prelimbic, infralimbic and anterior cingulated cortices) dopamine function (Dalley et al, 2002), suggesting both neurotransmitter systems may be involved in impulsive behavior.

The balance between 5-HT release and re-uptake determines the level of 5-HT in the brain. The 5-HT transporter regulates the extra cellular concentration of 5-HT by reuptake in presynaptic neurons. Both female subjects with the s/s variant of the 5-HT transporter and female $SERT^{+/+}$ rats (as compared to $SERT^{+/-}$ and $SERT^{-/-}$) more often choose from disadvantageous decks in the IGT compared to subjects with l/s or l/l variants (Homberg et al, in press). Interestingly, this disadvantageous choice was most notable in the second half of the test, supporting a role for 5-HT in maintenance of a chosen choice strategy (Homberg et al, in press). Increasing the differences in reward magnitude between the disadvantageous and advantageous deck let subjects to prefer large immediate rewards over the long term goal of gaining as much money as possible (van den Bos et al, 2006). Increasing the reward differences, may result in more activation of the dopamine system when receiving a larger reward. However, 5-HT may also be involved in monitoring reward magnitude as a reduction in central serotonin levels following dietary tryptophan depletion caused impaired discrimination of different reward magnitudes in healthy volunteers, suggesting impaired processing of reward cues (Rogers et al, 2003).

Unlike dopamine, 5-HT has not been implicated in probabilistic decision making and its role in reward related behavior may be confined to decisions concerning delayed reinforcement (Denk et al, 2005). Delayed reinforcement can be regarded as a cost. Although reward is delivered, its value decreases with an increasing delay. Within the IGT, the outcome at a later time (i.e. the preferred long-term goal to gain as much money as possible) has to be considered when choosing cards from a deck. Effort, however, is not modeled in this particular task. Dopamine is involved in decisions concerning effort and delay while 5-HT is only involved in decisions concerning delay (Denk et al, 2005); therefore, the serotonergic system may be the dominant system during the later stages of the IGT when subjects generally make decisions that reflect they are focusing on a future goal.

2.3 Conclusion

In conclusion, it appears that dopamine and serotonin are both modulators in cortico-striatal circuits underlying reward-related and impulsive behavior. Both circuits involve (parts of) the PFC, amygdala and striatal (limbic structures). However, the precise components of the circuits and the function of the neurotransmitter within the circuit may differ. Because of the great overlap in neural circuitry it appears likely that the two neurotransmitter systems are also able to interact with each other and that both serotonin and dopamine may be involved in both types of behavior. However, it is likely that at a certain time, one neurotransmitter system is more involved than the other, and that the balance between dopamine and serotonin release may influence behavior.

3. Experimental evidence suggesting dopamine/serotonin interactions

Several lines of evidence suggest that interactions between dopamine and 5-HT can take place. As shortly described above, the neural circuitry involved in behavior that is modulated by dopamine or 5-HT is highly similar. In addition, pharmacological manipulation of one neurotransmitter system may also affect activity in the other neurotransmitter system via indirect mechanisms. For example, drugs acting on the 5-HT system, may also result in a heightened dopamine release, although the drugs itself does not interact with the dopamine system.

Behavior that depends on dopamine neurotransmission can be attenuated by increased serotonergic activity, whereas reduced release of 5-HT can enhance dopamine dependent behavior, such as reward-related learning (Fletcher et al, 1999). Depletion of 5-HT in striatal and hippocampal regions by administration of 5,7-dihydroxytryptamine resulted in an increase in goal-directed behavior executed to obtain a reward (Fletcher et al, 1999). The lesion did not influence learning of the stimulus-reward association; rather, it appeared that behavior triggered by the stimulus is enhanced in 5-HT-depleted animals (Fletcher et al, 1999). The reduced 5-HT levels may result in a disinhibition of dopamine neurons in the VTA. Activation of the VTA by the stimulus in turn results in increased dopamine release in the NAC and thereby increases behavior to obtain the reward (Fletcher et al, 1999). Although this serotonin/dopamine interaction may not take place directly at the terminals of dopamine neurons, effectively, the dopaminergic reward signal is disrupted (Fletcher et al, 1999). Drugs elevating central 5-HT levels, such as 5-HT agonists and selective inhibitors of 5-HT uptake diminish intake of rewarding stimuli such as food and drugs of abuse, suggesting that the effectiveness of these drugs as reinforcers is reduced (Higgins & Fletcher, 2003). Administration of cocaine results in an elevation of 5-HT release in substrates implicated in the dopamine pathway (e.g. NAC) (Broderick & Phelix, 1997). Broderick and Phelix (1997) suggest that 5-HT neurons may regulate dopamine release.

Serotonin is thought to play a role in impulsive behavior; however, DA may also be an important modulator of impulsive behavior. Lesions of the NAC core impair the choice for a delayed reinforcer, suggesting the involvement of the NAC in tracking the value of a reinforcer when its delivery is delayed (Cardinal et al, 2001). Dopamine and serotonin neurotransmission may be differentially involved in impulsive behavior in separate areas of the PFC. When choosing between a small immediate or large delayed reward, an elevation of 5-HT release in the mPFC was observed, while 5-HT levels in the OFC remained constant (Winstanley et al, 2006). In addition, DOPAC, the metabolite of dopamine was found to be higher in the OFC when animals had to choose between small immediate or large delayed rewards, whereas DOPAC in the mPFC was also elevated for yoked controls that did not make the decision for a reward themselves. This led the authors to suggest a possible role for dopamine in the mPFC signaling reward, whereas dopamine in the OFC may be more important for making choices when a reward is delayed (Winstanley et al, 2006). Basal levels of DA are higher in the mPFC, whilst 5-HT levels are higher in the OFC (Winstanley et al, 2006). Sasaki-Adams and Kelley

(2002) studied dopamine/serotonin interactions in reward-related learning. Rats were trained in a classical conditioning paradigm to associate a stimulus with a food reward. The same stimulus was then used in an instrumental learning task to signal availability of a food reward that could be obtained after performing a lever press. Administration of fluoxetine (a selective serotonin reuptake inhibitor – SSRI) selectively increased responding for the lever that resulted in presentation of the conditioned stimulus, whereas the lever press behavior on the other lever was not altered. In addition, administration of cocaine resulted in an enhancement of increased responding usually seen after cocaine administration (Sasaki-Adams & Kelley, 2001). Direct administration of 5-HT in the nucleus accumbens did not result in a selective increase in lever presses on the conditioned lever. However, a general increase in motor behavior (lever presses on both the conditioned and unconditioned lever) was observed. In contrast, administration of dopamine directly in the NAC resulted in enhanced responding for the lever providing a reward (Sasaki-Adams & Kelley, 2001). Sasaki-Adams & Kelley (2001) propose an indirect interaction between serotonin and dopamine in the nucleus accumbens. The elevated 5-HT levels caused by the chronic administration of fluoxetine may result in an enhancement of dopamine release in the NAC, resulting in the enhanced responding for the conditioned reinforcement (Sasaki-Adams & Kelley, 2001).
Another area where interactions between dopamine and serotonin are likely to take place is the PFC. Serotonin neurotransmission in the mPFC may be particularly involved when behavior is guided by the affective value of a reinforcer. Changing the type of reward (and thereby the affective value of the reward) during reversal learning impaired performance of control animals. This impairment after a change in affective value of the reinforcer was not seen in rats that received a local 5-HT depletion in the mPFC by administration of 5,7-hydroxytryptamine, indicating that serotonin neurotransmission within the mPFC is important for cognitive flexibility when behavior is guided by the affective value of the reinforcer (van der Plasse et al, 2007). After central serotonin depletion, animals are no longer able to correctly process a change in the value of a reinforcer (van der Plasse et al, 2007). Adapting behavior to a changing value of the reinforcer is an important component in goal-directed behavior and these result suggest that serotonin is an important mediator guiding behavior according to the affective value of a reward.

Daw et al (2002) suggest a theoretical model of reinforcement learning that incorporates both dopamine and serotonin. In their model, a distinction is made between tonic and phasic activity of both neurotransmitters. The phasic dopamine signal initially follows delivery of the reward itself; upon learning an association between this reward and a preceding stimulus, the phasic dopamine signal shifts from the time of reward delivery to the time of stimulus presentation. The phasic dopamine signal functions as a learning signal and is composed of a temporal difference error signal (prediction error) and background noise (Daw et al, 2002). The phasic 'reward' signal is always compared to a more tonic average prediction of reward. Daw et al (2002) propose that the tonic prediction of reward is a 5-HT signal, originating in the dorsal raphe nucleus, as a signal reporting the long-term average reward prediction. The roles reverse for aversive learning. A phasic 5-HT signal may function as the learning signal for aversive events

while tonic dopamine functions as an average prediction of punishment (Daw et al, 2002).

4. Anatomical location and functional effects of dopamine/serotonin interactions

When considering the possible interactions between the serotonergic and dopaminergic systems in the brain, one can think of several potential mechanisms of interaction. First, the two systems may influence each other directly. This could be a one way interaction - e.g. 5-HT may be able to influence the release of dopamine or interact with dopamine at dopamine projections sites whilst dopamine does not influence the 5-HT system – or the interaction may be reciprocal. In order for direct interactions to take place, 5-HT receptors should be present on dopaminergic neurons and/or vice versa. The effects then, may differ depending upon the type of receptor that is present and whether the receptors are located pre- or postsynaptically. When the receptor is located directly on the axon of a second neuron releasing a different transmitter (e.g. a 5-HT receptor located on a dopaminergic terminal), the receptor can directly influence the release of the neurotransmitter but will only activate the axon of the second neuron. In contrast, when located on the soma of a second neuron, the receptor is able to influence the activity of the neuron as a whole. In both cases, the receptor is termed a heteroreceptor, i.e. a receptor of a particular neurotransmitter influencing the activity of a neuron releasing a different neurotransmitter (Fink & Göthert, 2007).

Second, indirect interaction between the two neurotransmitter systems may take place. For example, 5-HT receptors may be located on GABAergic interneurons that in turn project to dopamine neurons. Depending on the type of receptor present on the interneuron, activation will result in inhibition or disinhibition of the dopamine neuron; e.g. the presence of 5-HT_1 receptors will inhibit the interneuron, whereas $5\text{-HT}_{2/3}$ receptors will excite the interneuron (Fink & Göhtert, 2007). A similar effect may be observed when 5-HT receptors are located on glutamate neurons that project to dopamine neurons. Of course, for the interneurons to have an effect on the releasing neurons these have to express the appropriate GABA or glutamate receptors (Fink & Göhtert, 2007). This indirect inhibition can take place within a structure, when the interneurons are located in close proximity to the dopamine cell bodies (e.g. a GABAergic interneuron with 5-HT receptors is located within the VTA). Alternatively, the cell body of the interneuron may be located in a brain structure different form the structure it projects to. Also, neural circuits involving 5-HT or dopamine may have a certain overlap in brain areas.
In some cases, the dopamine transporter may be affected by 5-HT, thereby changing the reuptake of dopamine neurons back in to the cytoplasm and an effect on the extracellular dopamine concentration (Fink & Göhtert, 2007). The basal 5-HT levels in the striatum and NAC are suggested to be involved in regulating local DA release through this mechanism (Finke & Göhtert, 2007). Here, I will describe the modulation of dopaminergic neurotransmission by serotonin with relevance to reward-related behavior.

4.1 Serotonin receptors in dopamine pathways

Alex and Pehek (2007) provide an elaborate overview of the presence of different types of 5-HT receptors and their influence on the nigrostriatal, mesolimbic and mesocortical

dopamine systems. The amygdala and striatum, structures of the mesolimbic reward system, are innervated by 5-HT projections from the dorsal raphe (Daw et al, 2002). The medial raphe nuclei do not project to the dopamine system (Daw et al, 2002). 5-HT projections originating in the raphe nuclei are found in the dorsal and ventral striatum, however, interaction with dopaminergic fibers may be more abundant in the ventral striatum (Broderick & Phelix, 1997). In addition, the type of interaction in both stratial areas differs: whereas axodendritic synapses predominate in the dorsal striatum, the majority of 5-HT projections in the ventral striatum synapse on axons (Broderick & Phelix, 1997). Although 20% of the 5-HT innervation in the NAC may be directly to dopaminergic neurons, projections to non-dopamine neurons are also observed (Broderick & Phelix, 1997). The serotonergic input inhibits the mesolimbic reward system (Broderick & Phelix, 1997; Fletcher et al, 1999). In all three major dopamine pathways, modulation by 5-HT is possible (Alex & Pehek, 2007). However, 5-HT receptors differ in their effect on dopamine neurotransmission. While 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3 and 5-HT_4 receptors facilitate dopamine release, stimuluation of the 5-HT_{2C} receptors inhibits release of dopamine (Alex & Pehek, 2007, see also below). Depending upon the type of rewarding stimulus that is used, 5-HT_{1B} receptors may facilitate or disrupt reward related behavior (Higgins & Fletcher, 2003).

4.2 5-HT_3 receptors locally facilitate dopamine release

5-HT_3 receptors are directly coupled to an ion channel. Activation of the receptor upon binding of 5-HT may result in postsynaptic depolarization. Presynaptically localized on axons in limbic and forebrain structures, 5-HT_3 receptors can modulate the release of a variety of neurotransmitters, including dopamine (Grant, 1995). 5-HT_3 receptors are relatively high expressed in the dopamine pathways originating in the VTA and administration of 5-HT_3 agonists in this area results in and increased dopamine release in the NAC. In contrast, its influence on nigrostriatal dopamine release is limited (Grant, 1995). Yet the role of 5-HT_3 receptors in mediation of the dopamine system may be limited to a modulator role in local dopamine release, as 5-HT_3 manipulations do not appear to be sufficient to influence behavior (Grant, 1995). Puig et al (2003) found expression of 5-HT_3 receptors in the mPFC of the rat. Expression was particularly high in the cingulate, prelimbic and infralimbic areas of the mPFC (Puig et al, 2003). The 5-HT_3 receptors were located on GABAergic interneurons in superficial layers of the mPFC (Puig et al, 2003). Therefore, it appears that 5-HT_3 activation may show heterogeneous effects: dopamine release in the NAC may be stimulated, whereas activation of the 5-HT_3 receptors in the mPFC may result in an excitation of inhibitory interneurons, thereby inhibiting the release of dopamine in the mPFC (Puig et al, 2003). However, unlike the inhibition mediated by 5-HT_{2C} receptors (see below), the 5-HT_3 -mediated inhibition may be of short duration (Puig et al, 2003).

4.3 5-HT_{2C} receptors inhibit dopamine release

Diminished motivation can be observed after administration of 5-HT_{2C} receptor agonists (Higgins & Fletcher, 2003). This type of 5-HT receptor is expressed in both the cell body

region (VTA) and the projection areas (NAC and PFC) of the mesolimbic/-cortical dopamine system (van Bockstaele, 1994, 1996, de Deurwaerdere et al, 2004). Under baseline conditions, 5-HT_{2C} receptors tonically inhibit dopamine neurons in the VTA, allowing a steady state release of dopamine in the projection areas. The administration of 5-HT_{2C} agonists may therefore result in an even stronger inhibition, resulting in reduced dopamine release in the NAC and PFC, causing the reduced motivation. In contrast, a reduced level of central 5-HT can facilitate behavior towards rewarding stimuli (Higgins & Fletcher, 2003) and increase motivation. 5-HT_{2C} knockout mice have been created. These animals lack the tonic inhibitory control of 5-HT_{2C} receptors on dopamine release and are therefore likely to show an elevated intake of rewarding stimuli in addition to enhanced motivation. Strong motor deficiencies may not necessarily be present as the 5-HT_{2C} receptors are more strongly involved in the mesolimbic as compared to the nigrostriatal dopamine system (Higgins & Fletcher, 2003). Indeed, 5-HT_{2C} knockout mice show an increased tendency to self administer cocaine, suggesting they are more sensitive to or more motivated to obtain the reinforcer (Higgins & Fletcher, 2003). However, whenever knockout animals are used, the possibility of adaptation to or compensation for the loss of 5-HT_{2C} receptors should be taken into account.
As 5-HT_{2C} type receptors are intrinsically stimulatory receptors, i.e. coupled to a G_q protein, the tonic inhibitory control is likely to be mediated indirectly via GABA interneurons (Finke & Göhtert, 2007). A reduction in serotonin levels may thus result in a reduction in the tonic inhibition mediated by 5-HT_{2C} activation of GABAergic interneurons (Adell & Artigas, 2004). 5-HT_{2C} receptors are known to reduce firing activity of dopamine neurons in the VTA and decrease DA release in the dopaminergic pathways originating in the VTA (Adell & Artigas, 2004). These receptors may be involved in the basal release of dopamine as well as the phasic dopamine activity (Adell & Artigas, 2004). Direct projections from the raphe nuclei to the VTA are involved in the tonic inhibition via 5-HT_{2C} receptors (Diaz-Martaix et al, 2005). Dremencov et al (2005) found increased 5-HT_{2C} activity, resulting in a reduced dopamine level in the NAC, in the FSL rat, a model for depression (Dremencov et al, 2005). Administration of antidepressant drugs resulted in a facilitation of the 5-HT-induced dopamine release, by diminishing the increased inhibition through 5-HT_{2C} receptors (Dremencov et al, 2005). The lack of 5-HT_{2C} receptor expression on dopaminergic neurons in the VTA, and observed expression of 5-HT_{2C} receptors on GABA neurons is in line with the suggestion that 5-HT_{2C} receptors mediate the inhibitory effects via inhibitory GABAergic interneurons (Eberle-Wang et al, 1997).
Increased burst firing of VTA neurons was observed after administration of a selective 5-HT_{2C} antagonist (Di Matteo et al, 1999). This suggests that 5-HT_{2C} receptors are involved in tonic as well as phasic dopamine release (Di Matteo et al, 1999). In addition, in both NAC and striatum, inhibitory heteroreceptors, most likely of the 5-HT_{1B} type, can directly inhibit dopamine release (Fink & Göhtert, 2007).

4.4 Serotonin/dopamine interactions in the VTA

5-HT_1 receptors
Systemic injection of 5-HT_{1A} agonists resulted in increased firing rate of the majority (75%) of dopaminergic neurons in the VTA (Prisco et al, 1994). It is unlikely, however,

that this effect is mediated by 5-HT_{1A} receptors located within the VTA, as direct administration of a 5-HT_{1A} agonist does not increase firing activity in VTA dopamine neurons (Prisco et al, 1994). More likely, 5-HT_{1A} activity in the mPFC affects firing activity of VTA neurons (see below). Consequently, an indirect projection involving 5-HT_{1A} receptors connecting to the VTA may be able to modify activity of dopaminergic neurons. However, others suggest that 5-HT_{1A} receptors are located on dopaminergic as well as non-dopaminergic neurons in the VTA, suggesting that activation of this receptor can have both excitatory and inhibitory actions on dopamine neurons (Adell & Artigas, 2004). When administered systemically, 5-HT_{1A} agonists excite VTA neurons at a low dose, whereas dopamine neurons are inhibited at a higher dose (Adell & Artigas, 2004). Another possible way in which serotonin can modulate dopamine activity is through the 5-HT_{1A} autoreceptors in the raphe nuclei. Systemic administration of 5-HT_{1A} agonist can activate the 5-HT_{1A} autoreceptors in the raphe nuclei, resulting in a decreased 5-HT release and, consequently, a disinhibition of the tonic inhibition of 5-HT on dopamine neurons (Adell & Artigas, 2004). In contrast, 5-HT_{1C} receptors appear to mediate neuronal activity within the VTA itself; systemic as well as direct administration of 5-HT_{1C} agonists reduced firing activity in the VTA (Prisco et al, 1994). 5-HT_{1C} receptors in the VTA may tonically inhibit the mesolimbic/mesocortical dopamine system (Prisco et al, 1994).

Local administration of 5-HT_{1B} agonist in the NAC or VTA induces elevated dopamine release in the NAC (Yan & Yan, 2001). 5-HT_{1B} receptors are coupled to G_i proteins and have an inhibitory effect. Therefore, the elevation of dopamine release in the NAC is most likely the result of a disinhibition of dopamine release from axons originating in the VTA, as a result of decreased activity of inhibitory interneurons after 5-HT_{1B} activation (Yan & Yan, 2001).

5-HT_2 receptors

The VTA receives glutamatergic projections from the PFC. This glutamatergic input can influence neuronal activity in the VTA via NMDA and AMPDA/Kainate receptors that are located on dopaminergic and non-dopaminergic neurons (Adell & Artigas, 2004). When glutamate receptors are also present on non-dopamine GABA-ergic interneurons, a biphasic action of glutamate on the dopamine system may be seen. However, the glutamatergic input appears to be limited to activation of the dopamine system. The mescortical dopamine system may be tonically excited by PFC glutamatergic input (Adell & Argias, 2004). Although a tonic stimulatory input from the PFC to the VTA may also regulate dopamine release in the mesolimbic pathway, the glutamatergic input appears to be more important for inducing phasic excitation (burst firing) in this pathway (Adell & Artigas, 2004). Interestingly, the excitatory input from the PFC to the VTA appears to be regulated or may be enhanced by 5-HT neurotransmission within the PFC itself (Bortolozzi et al, 2005). Although 5-HT_{2A} receptors within the VTA may locally stimulate dopamine release, the major influence of 5-HT_{2A} activation on the dopaminergic pathway comes from mPFC input (see below).

4.5 Serotonin/dopamine interactions in the mPFC

The medial prefrontal cortex (mPFC) is innervated by dopaminergic fibers originating in the ventral tegmental area (VTA). Stimuluation of the mPFC results in glutamate release in the VTA, thereby stimulating dopaminergic cell bodies in this area (Wise, 2002). Activation of the VTA in turn results in dopamine release in the nucleus accumbens and PFC. The glutamatergic input from the mPFC to the VTA therefore appears to be an important component of the neural circuitry associated with reward (Wise, 2002). The dopaminergic projections to the PFC are important during reward related learning. Within the PFC, release of dopamine may be involved in the formation or strengthening of neural circuits consisting of neurons that were activated by the cue stimulus and neurons that were activated by the reward (Miller, 2000). Within the PFC, the strengthening of these connections may result in a 'cortical map' of the task and its features (Miller, 2000). The posterior part of the mPFC may be the neural substrate where selective strengthening of reward related neural patterns takes place (Ridderinkhof et al, 2004).

5-HT_{1A} receptors

The mPFC is also heavily connected to the serotonergic system. Reciprocal connections have been observed between the mPFC and dorsal raphe nuclei (Matsumoto et al, 1999). Stimuluation of the mPFC appears to exert an opposing effect on the dopamine and serotonin systems. While the dopamine system is activated by the glutamatergic input to the VTA, activation in the serotonergic system is inhibited after stimulation of the mPFC (Celada et al, 2001; Hajós et al, 1998; Varga et al, 2001). Release of 5-HT in the mPFC can mediate an effect through 5-HT_{1A} and 5-HT_{2A} receptors, located on pyramidal neurons in cortical layer V (Celada et al, 2001). While activation of 5-HT_{1A} receptors results in increased 5-HT release in the mPFC, reduced 5-HT release in the mPFC is observed after activation of 5-HT_{2A} receptors (Celada et al, 2001). 5-HT_{1A} receptors located on postsynaptic mPFC neurons, may project back to the dorsal raphe nuclei, providing a feedback signal that influences activity of serotonergic neurons in the dorsal raphe nuclei (Celada et al, 2001). Several studies have observed an inhibitory response of 5-HT neurons in the dorsal raphe after stimulation of the mPFC (Celada et al, 2001; Hajós et al, 1998; Varga et al, 2001). However, not all 5-HT neurons show an inhibitory respons. A small proportion of dorsal raphe 5-HT neurons show activation after electrical stimulation of the mPFC (Celada et al, 2001; Hajós et al, 1998; Varga et al, 2001). There are two possible ways by which the mPFC can inhibit activity of 5-HT neurons. Acitvation of the small portion of 5-HT neurons in the dorsal raphe may result in release of 5-HT. Upon binding to 5-HT_{1A} autoreceptors on 5-HT neurons in the dorsal raphe, this released 5-HT then inhibits 5-HT neurons by inhibitory auto-feedback (Celada, 2001). Another possibility is that the inhibition of 5-HT neurons is mediated by GABAergic interneurons in the dorsal raphe (Celada et al, 2001; Hajós et al, 1998; Varga et al, 2001). For example, increased cortical activation as a result of exposure to cues that are associated to drugs of abuse may result in activation of the GABAergic interneurons in the dorsal raphe nucleus, causing reduced release of 5-HT (Bradberry & Rubino, 2004). Possibly, both direct and indirect mechanisms will contribute to the inhibition of 5-HT release after cortical stimulation.

The effect of activation of 5-HT_{1A} receptors appears to be heterogeneous, depending on the type of neuron and the brain area where the receptor is expressed. Inhibition in the

mPFC may be mediated by direct effects of 5-HT_{1A} stimulation, whereas excitation may result indirectly through GABA interneurons (Santana et al, 2004). 5-HT_{1A} stimulation in the striatum and NAC inhibits basal dopamine release and increased dopamine release following administration of antipsychotic drugs (Ichikawa & Meltzer, 2000). However, prefrontal 5-HT_{1A} activation may also result in activation of the dopaminergic system. Diaz-Mataix et al (2005) injected a 5-HT_{1A} agonist directly in the mPFC and observed an increase in the firing rate of VTA neurons in addition to increased burst firing (Diaz-Mataix et al, 2005). Activation of the mPFC 5-HT_{1A} neurons did not only result in increased firing activity; release of dopamine in the mPFC was enhanced as well. Activation of 5-HT_{1A} receptors may therefore result in heterogeneous actions, with an net excitatory effect of low concentrations of 5-HT_{1A} agonists and a net inhibitory influence on dopaminergic neurons after administration of higher doses of 5-HT_{1A} agonists (Adell & Artigas, 2004; Diaz-Martaix et al, 2005) The excitation of VTA dopaminergic neurons after low doses of a 5-HT_{1A} agonist may result from a disinhibition of excitatory projections from the mPFC as a result of activation of 5-HT_{1A} receptors on GABAergic interneurons (Diaz-Martaix et al, 2005). At higher concentrations of the the 5-HT_{1A} receptors, this effect is overpowered by the direct inhibition of mPFC neurons by 5-HT_{1A} receptors located on the cell bodies of mPFC pyramidal neurons (Diaz-Martaix et al, 2005).

5-HT_{1B} receptors

Stimulation of the dorsal raphe nucleus results in elevated 5-HT release in the PFC (Matsumoto et al, 1999). Interestingly, the stimulation of the raphe nuclei also results in an elevation of prefrontal dopamine (Matsumoto et al, 1999). Local administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI) in the PFC also resulted in elevated dopamine release in the PFC (Matsumoto et al, 1999). Matsumoto et al (1999) suggest that activity of serotonin on dopamine nerve terminals via a 5-HT_{1B} mediated pathway influences dopamine release as administration of a 5-$HT_{1B/1D}$ antagonist prevented the release of dopamine in the PFC (Matsumoto et al, 1999). Most likely, this effect is indirect through GABA interneurons, as 5-HT_{1B} is an inhibitory receptor (Matsumoto et al, 1999). Striatal dopamine release can be facilitated by 5-HT_{1B} heteroreceptors located on GABA interneurons, although presynaptically located 5-HT_{1B} heteroreceptors are also able to inhibit dopamine neurons directly and may be involved in direct inhibition of dopamine neurons in the striatum (Fink & Göhtert, 2007). The local increase of 5-HT in the PFC as a result of fluoxetine administration, may therefore effect the local release of dopamine, by influencing dopamine terminals located in the PFC. Also, the heightened 5-HT levels in the PFC may result in an indirect activation of the VTA, thereby increasing the dopaminergic input to the PFC, for example via a 5-HT_{1A} mediated pathway.

5-HT_{2A} receptors

Prefrontal dopamine release can also be modulated by the 5-HT_{2A} receptor. This receptor type is mainly located on the soma or dendrites of dopamine neurons as well as non-dopaminergic neurons in the VTA (Doherty & Pickel, 2000), but is also present in the mPFC (Bortolozzi et al, 2005). The input to dopaminergic dendrites may be more important for the effects of 5-HT on dopamine activity (Doherty & Pickel, 2000). More

than half (50-66%) of the pyramidal neurons in the medialPFC express 5-HT_{2A} receptors (Bortolozzi et al, 2005). In addition, some (20%) GABAergic interneurons within the mPFC also express the 5-HT_{2A} receptor (Bortolozzi et al, 2005). Both direct and indirect projections from the mPFC to the VTA are able to exert influence over VTA firing activity. 5-HT_{2A} receptors are intrinsically stimulatory in nature, however, when coupled to an inhibitory GABA inhibitory interneuron, both 5-HT_{2A} mediated excitation and inhibition of dopaminergic neurons is possible. Therefore, pyramidal neurons in the mPFC can be activated (depolarization) or inhibited (hyperpolarization) when 5-HT_{2A} receptors are activated. The net result then may depend upon the experimental conditions and activation of receptors other than the 5-HT_{2A} receptor in addition to activation of other neurotransmitter systems (Bortolozzi et al, 2005; Adell & Artigas, 2004). Apart from a direct projection pathway from the mPFC to the VTA, two indirect pathways exist. The first projects from the mPFC to the laterodorsal/pedunculopontine tegementum to the VTA; the second travels via the nucleus accumbens and ventral pallidum (Bortolozzi et al, 2005; Adell & Artigas, 2004).
Administration of a 5-$HT_{2A/2C}$ agonist locally in the mPFC resulted in an increase in the total number of spikes fired, increased burst firing and an increase in the percentage of spikes that was fired in bursts, in addition to an elevation of dopamine release in the mPFC (Bortolozzi et al, 2005). In addition, dopamine release induced by K^+ stimulation and administration of 5-$HT_{2A/C}$ agonists can be attenuated by administration of a 5-HT_{2A} antagonist, suggesting that these cortical receptors may potentiate the phasic release of dopamine (Pehek et al, 2001), by phasically exciting VTA dopamine neurons (Adell & Artigas, 2004). After administration of a 5-$_{HT2A/2C}$ agonist, activation of VTA neurons and increased dopamine release in the mPFC was not observed when 5-HT_{2A} activity was selectively blocked suggesting that activation of the 5-HT_{2A} receptors mediates the excitatory input from mPFC to VTA (Bortolozzi et al, 2005). The excitatory effect of mPFC 5-HT_{2A} activation in the mPFC on VTA neurons may be direct or mediated via the indirect pathways described above (Bortolozzi et al, 2005). Back projections from the VTA neurons innervated by the mPFC close the mPFC-VTA circuit (Bortolozzi et al, 2005). Additionally, VTA neurons that do not project back to the mPFC project to several subcortical nuclei, however, the VTA-NAC connections do not appear to be influenced by mPFC 5-HT_{2A} activation (Bortolozzi et al, 2005). Although 5-HT_{2A} receptors are also found within the VTA, the mPFC VTA projections appear to be more important for regulation of neuronal activity, as systemic and local mPFC administration of 5-HT_{2A}-ergic compounds produce similar effects (Bortolozzi et al, 2005). Within the mPFC, 5-HT_{2A} receptors are highly co-localized with 5-HT_{1A} receptors and both receptors may differentially involved in different aspects of mPFC functioning by their opposing actions on the glutamatergic output of the mPFC (Carli et al, 2005). However, VTA neurons may also be influenced by 5-HT_{2A} receptors within the VTA as 5-HT_{2A} receptors can directly activate dopamine release. This facilitation may be limited to conditions when striatal dopamine neurons are already activated (Fink & Göhtert, 2007).

Serotonin can thus have different effects on activity in the mPFC. Depending upon the type of receptor involved the effect may be excitatory or inhibitory. This was nicely illustrated in an electrophysiological study by Puig et al (2005). They studied the involvement of serotonin and GABA in activity of pyramidal neurons in the prefrontal cortex. 5-HT_{1A} and 5-HT_{2A} receptors are often co-expressed on neurons that also stain

positive for glutamate, suggesting their presence on pyramidal neurons in the mPFC (Puig et al, 2005; Santana et al, 2004). Within the mPFC, expression is high in prelimbic and infralimbic areas (Santana et al, 2004). The contrasting effects of stimulation of these receptors can have a heterogenous effect on mPFC functioning (Puig et al, 2005). In addition, the localization of stimulatory as well as inhibitory 5-HT receptors on prefrontal interneurons further complicates the biphasic effects serotonin can have on prefrontal functioning. Electrical stimulation of the raphe nuclei resulted in inhibition, excitation and biphasic responses of mPFC pyramidal neurons (Puig et al, 2005). Although stimulatory 5-HT_{2A} receptors are abundantly present in the mPFC, the main effect of raphe stimulation – hence, the main effect of serotonin released in the mPFC – appears to be inhibitory, as 66% of mPFC pyramidal neurons were inhibited by stimulation of the raphe nuclei (Puig et al, 2005). Figure 2 shows an overview of the connections between the VTA and its projection areas and the serotonin receptors involved in these areas.

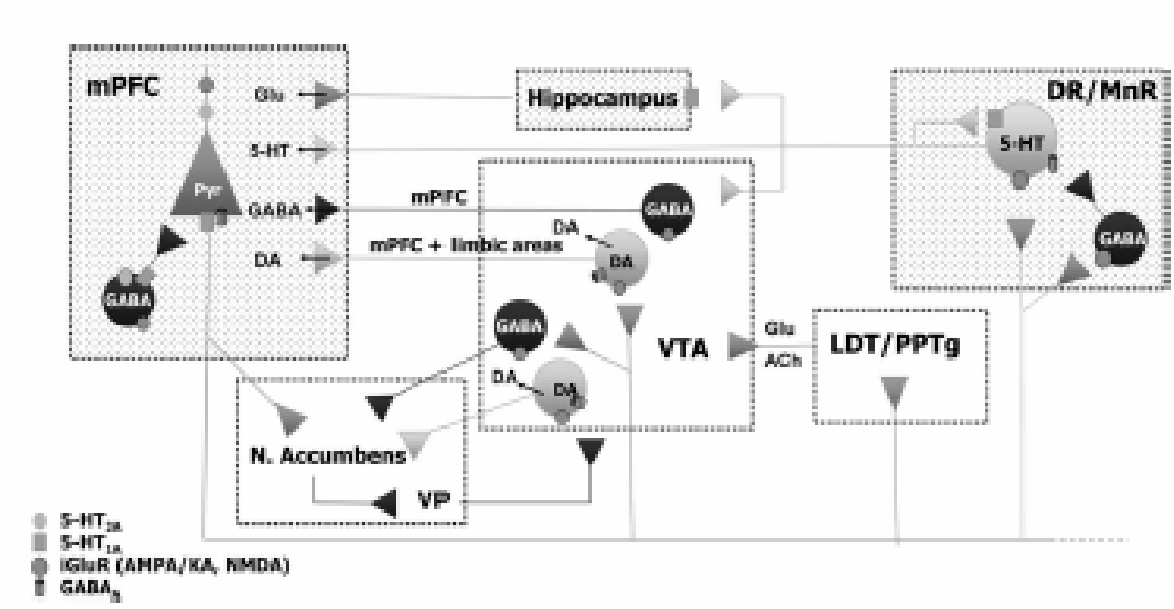

Figure 2. Anatomical and functional connections between the raphe nuclei and mesocortical dopamine system. The raphe nuclei send projections to both VTA and mPFC. Activation of the mPFC results in enhanced dopamine release from the VTA. Direct activation of mPFC pyramidal neurons through 5-HT_{2A} receptors and indirect activation of mPFC pyramidal neurons via 5-HT_{1A} receptors increased VTA activity. The excitatory input from mPFC to VTA may be direct or indirect, via a mPFC-NAC-VP-VTA or mPFC-PPTg-VTA pathway. (Figure from Diaz-martaix et al, 2006).

4.6 Conclusion

Serotonin can influence activity in the dopamine system via several of its receptors, in particular the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors. Moreover, each of the receptors types appears to be able to affect activity in the dopaminergic system in a biphasic manner, both stimulating and inhibiting dopamine release. Almost all receptors can influence the dopamine system directly and indirectly via inhibitory interneurons. Whether the direct or indirect influence is excitatory or inhibitory depends on the

intrinsic characteristics of the particular 5-HT receptor. Serotonin can modulate the dopamine system in the cell body region (VTA) as well as the projection areas of the dopamine system (NAC and mPFC).

Under basal conditions, phasic and tonic dopamine activity is under tonic inhibitory control of the 5-HT system via 5-HT_{2C} receptors. The inhibition is indirect, mediated through GABAergic interneurons. 5-HT_{2A} receptors may locally inhibit dopamine release in the mPFC via inhibitory interneurons, although the inhibition through 5-HT_{2C} receptors is more pronounced. In addition, dopamine neurons can be directly inhibited via 5-HT_{1A} receptors. Tonic inhibition does not mean that dopamine activity is abolished altogether, but ensures a steady-state dopamine concentration in the extracellular space. Release of dopamine (particularly in the NAC) is locally facilitated by 5-HT_3 receptors, although dopamine release mediated by this type of receptor is not sufficient to influence behavior. 5-HT_{1A} and 5-HT_{2A} receptors are abundantly expressed in the mPFC. Activation of the 5-HT_{1A} receptors can activate or inhibit the dopamine system, depending upon the concentration of serotonin that is present in the extracellular space. Low doses of 5-HT_{1A} agonists can stimulate the dopamine pathway, whereas activity is inhibited at high concentrations. As the 5-HT_{1A} receptors is intrinsically inhibiting, the stimulating effects is most likely the result of a disinhibition of dopamine neurons. 5-HT_{2A} receptors within the VTA stimulate dopamine release, although the 5-HT_{2A} mediated input from the mPFC appears to be more important for the stimulatory effect of the mesolimbic dopamine pathway. The cortical activity can selectively potentiate phasic dopamine release, thought to be an important component of reward-related learning.

5. Dopamine/Serotonin interactions in the Iowa Gambling Task

As described above, dopamine may be an important transmitter during the early stages of decision making in the Iowa Gambling Task whereas serotonin may be more important during later stages of the task (Van den Bos et al, 2006). Although neurotransmitter release during the different stages of the IGT has not been monitored so far, several predictions can be made regarding neurotransmitter release in the task on basis of the findings described above. These predictions will be based on an animal model of the IGT. Of course, imaging techniques (e.g. fMRI, PET) may be used to obtain more knowledge on the brain areas activated during several stages of the task and changes in dopamine concentrations may be made visible in a PET scan using a labeled radioligand that binds specifically to dopamine receptors (e.g. see Koepp et al, 1998; Zald et al, 2004). However, real-time measurements of neural firing activity or rapid changes in *in vivo* neurotransmitter release are as yet impossible to measure in human subjects. As these techniques are available in animal studies, at the present stage, monitoring neural activity in addition to release of neurotransmitter and the influence of pharmacological manipulations on these aspects in a rodent version of the IGT may provide a larger insight in the mechanisms influencing decision making behavior. Ideally then, the rodent version of the task will contain similar components (e.g. reward, punishment, uncertainty about an outcome, monitoring of a future goal) as the human version of the task. A difficulty in the animal model may be the concept of a future goal that agents have to keep in mind when choosing different decks. However, an important factor in reinforcement learning theory is that animals will behave in a way to optimize the number of rewards they receive (Balleine & Dickinson, 1998). Hence for the animals, the long term goal is to gain as much reward as possible, although the animal is not consciously aware of this goal.

5.1 Dopamine release during the IGT

First, several predictions can be made concerning dopamine release during the IGT. Both tonic and phasic dopamine may be important during the IGT. In the early stages of the task, phasic dopamine peaks in the NAC and mPFC – resulting from increased burst firing of dopamine neurons in the VTA - may be present in response to obtained rewards. At this time, the rewards are fully unpredicted and will therefore evoke a clear dopamine transient. The availability of a new set of stimuli to choose from (‘the cue’) or the moment subjects choose a card from a particular deck will not result in a phasic dopamine peak at this stage, as subjects have not yet associated the different decks with positive or negative outcomes (Bechara et al, 1994, 1997). The transient increase in dopamine firing activity and the subsequent phasic elevation in extracellular dopamine concentration is hypothesized to code a learning signal (Daw et al, 2002). Schultz (1998, 2002) argues for the phasic dopamine signal as a reward prediction error. The signal reflects the result of a comparison between a prediction and the following reward: a positive signal (dopamine release) is seen when a reward delivered unexpectedly, no signal is observed when the reward is fully predicted, and a decrease in signal (reduction in firing activity) is observed when a predicted reward is not delivered (Schultz, 1998,

2002). However, others (e.g. see Berridge & Robinson, 1998; Horvitz, 2000; Ikemoto & Panksepp, 1999) have argued for a broader range of dopamine functioning. Instead of functioning as a feedback signal representing the current value of the reward, dopamine may function as a general reinforcement signal, involved in learning behavioral actions directed towards novel stimuli (Redgrave & Gurney, 2006). Interestingly, some authors (e.g. Horvitz, 2000) have observed transient dopamine activity in response to novel events that were not rewarding and could even be classified as aversive. As subjects are faced with positive and negative events during the IGT, this task may provide interesting data regarding the different responses of dopamine neurons and/or transient increases in extracellular dopamine concentration to positive and negative events.

Continuing with the task, between trials 10-50, subjects continue choosing cards from various decks and, in general, do not yet show knowledge of the advantageous or disadvantageous decks (pre-hunch period, Bechara et al, 1997). In a well constructed animal model of the task, animals will show similar behavior and at the end of the pre-hunch period, small dopamine peaks may start to arise at the moment when subjects choose an advantageous deck/stimulus. The shift in the phasic dopamine response from the time of reward delivery to the time of reward has been shown in electrophysiological and in vivo voltammetry studies in monkeys and rats (Schultz et al, 1998, 2002; Pan et al, 2005; Day et al, 2007). Moreover, increased dopamine release at the time that a response is initiated suggests a role for nucleus accumbens dopamine in the onset of goal-directed behavior (Roitman et al, 2004). In classical conditioning paradigms, the dopamine transient to the cue starts to arise after 20 or 30 trials. Although animals may not yet have established a stable stimulus-reward association at this stage in the task, the stimulus is a reliable predictor of the forthcoming reward. In the IGT, however, the uncertainty as to whether the chosen option really leads to a reward is much larger. Thus, the uncertainty of the cue may result in a later development of the dopamine transient at the time of the cue; the dopamine transient may be smaller or completely absent.

From trial 50-90, human subjects generally have a distinct preference for certain decks, they ‘like’ the advantageous decks and ‘dislike’ the advantageous decks. However, they may not yet be able to specifically state the reason for these preferences. Bechara et al (1997) term this stage the ‘hunch’ stage. During this stage, animals performing a gambling task – provided that they go through similar stages (prehunch, hunch etc) as human subjects do – may show transient dopamine peaks at the time at which a stimulus has to be chosen/is chosen *and* at the time of reward delivery. In addition, a sustained elevation of dopamine may be apparent in between the two phasic peaks, reflecting uncertainty or expectation about an outcome ((Fiorillo et al, 2003; de la Fuente-Fernandez, 2001, 2002).

In the last phase of the task, the conceptual phase (Bechara et al, 1997), subjects are able to state which decks are result in good outcomes and which decks result in bad outcomes and why (Bechara et al, 1997). In the animal models, rats may show a clear preference for a particular stimulus. The transient dopamine signal then may be solely present during the time of stimulus presentation or the time at which subjects choose a particular stimulus. However, *in vivo* studies measuring dopamine firing activiy and extracellular dopamine concentrations need to be performed in order to support the suggestion of a dopamine transient during the presence of a new set of stimuli to choose from.

In addition to phasic dopamine activity, tonic dopamine may also influence behavior during the IGT. During early stages of the task, subjects show explorative behavior. They choose cards from all four decks in order to gain knowledge about the properties of the different decks. Dopamine neurotransmission is known to be involved in explorative behavior and approach behavior towards rewards (Di Ciano et al, 2001; Parkinson et al, 2002). Continuing explorative behavior after the first few losses have been encountered is important to get an understanding of the functioning of the task and the best strategy to follow in order to reach the long term goal. Therefore, tonic dopamine activity may be involved in explorative behavior during the early stage of the IGT, as well as in expectancy/uncertainty about the outcome that will be delivered after choosing a particular stimulus. Once knowledge about the task has accumulated, and a strategy to complete the task is chosen, this dopaminergic component may loose its influence.

5.2 Serotonergic interaction with dopamine during the IGT

In the following section I will propose a possible course of serotoninergic influence on dopamine activity during the IGT. As desribed above, 5-HT interacts with dopamine neurotransmission in cell body areas as well as projection areas and can exert both an inhibitory and excitatory effect on dopamine neural activity and release. The net result of 5-HT input to the dopamine system may therefore depend upon the population of receptors that is activated and the brain areas that are most strongly activated.

The default situation may be a direct, tonic inhibition of dopamine neurons via 5-HT_{1C} receptors and an indirect tonic inhibition via 5-HT_{2C} receptors located on GABAergic interneurons. Tonic inhibition of dopamine neurons by 5-HT_{2C} receptors occurs in the cell body region (VTA) as well as the projection areas. Facilitation of dopamine release occurs through 5-HT_3 receptors located in the VTA and PFC. However, this concerns a small, local facilitatory effect, not influencing behavior.

Starting with the task, tonic as well as phasic dopamine release (following uncertainty about rewards/approach behavior towards rewards and experiencing rewards respectively) increases. During this stage, the tonic inhibitory control of serotonin on dopamine is (temporarily) diminished or completely absent. Dopamine neurons in the VTA are excited following the received rewards. The excitation of dopaminergic cell bodies in the VTA results in an elevation of dopamine release in the NAC and mPFC. Increased dopamine release in the mPFC may result in activation of these areas, resulting in a decrease of 5-HT release from the raphe nuclei (Celada et al, 2001; Hajós et al, 1998; Varga et al, 2001) and increased activity of VTA neurons via the glutamatergic input to this area (Adell & Artigas, 2004). The tonic inhibition of dopamine neurons by serotonin is then removed. Dopamine phasic activity bursts through the tonic serotonergic inhibition. However, although serotonin release from the raphe nuclei may be reduced following mPFC stimulation, serotonin neurotransmission may still be able to influence dopamine release. Direct activation of phasic dopamine release may occur through 5-HT_{2A} receptors located in the VTA. In addition, 5-HT_{2A} receptors located on glutamatergic interneurons in the mPFC can cause an enhancement of VTA burst firing activity and a selective potentiation of phasic dopamine release. This may occur via direct glutamatergic projections from the mPFC to the VTA and/or via indirect projections (via the mPFC-NAC-Ventral Pallidum-VTA and/or mPFC-Pedunculopontine

tegmental nucleus-VTA pathways). In addition, 5-HT_{1A} receptors in both the VTA and mPFC may also be involved in the activation of the dopamine system. This activation may be particularly apparent when release of 5-HT

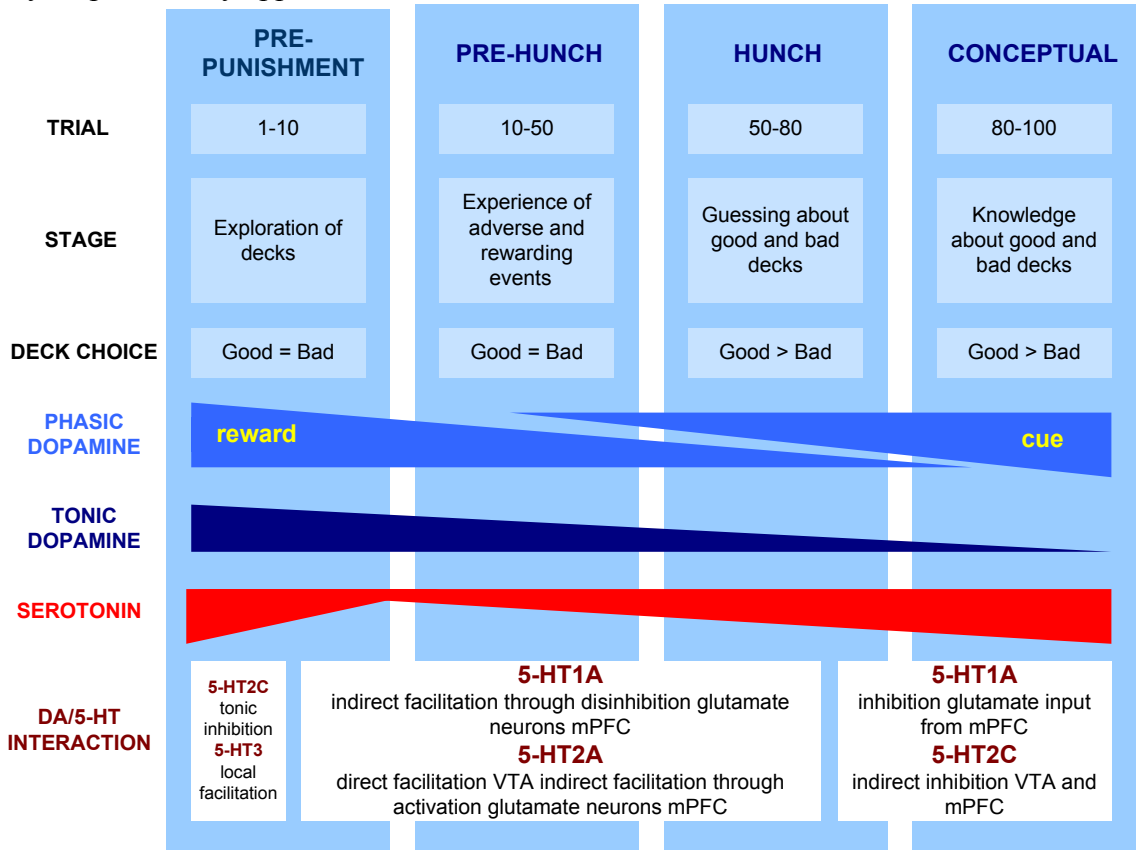

Figure 3. Proposed choice behavior and activity of dopamine and serotonin and their interactions during the IGT. Dopamine transients are expected to follow encounters with rewards from the beginning onwards. At the end of the pre-hunch period, a dopamine transient to the cue/moment of deck chosen may develop, that becomes stronger when the task progresses. At the same time, the transient to the reward will diminish. Tonic dopamine activity mediates explorative behavior during the beginning of the task, when all decks are chosen. Explorative behavior is important for developing representations of the decks and should continue even after encountering the first losses. Tonic dopamine may also code uncertainty during the cue/reward interval. Activation of the mesolimbic/-cortical dopamine system stimulates the mPFC, resulting in decreased firing activity of the raphe nuclei and decreased 5-HT release. This resolves the tonic inhibition of 5-HT on dopamine activity. During the early and middle stages of the IGT, low 5-HT levels may potentiate tonic and phasic dopamine release via 5-HT_{1A} and 5-HT_{2A} receptors. When dopamine activity diminishes, the activation of the mPFC diminishes, resulting in increased activity of the dorsal raphe and elevated 5-HT levels. The glutamatergic input to the VTA is inhibited directly by 5-HT_{1A} receptors and indirectly via 5-HT_{2C} receptors. In addition, indirect tonic inhibition by 5-HT_{2C} receptors in the VTA and mPFC and local facilitation of dopamine release by 5-HT_3 receptors is restored, ensuring static extracellular dopamine levels.

from the raphe is reduced, as 5-HT_{1A} agonists have been observed to activate dopamine neurons at low doses only (Adell & Artigas, 2004). The 5-HT_{1A} mediated activation has to be an indirect activation by inhibiting the activity of GABAergic interneurons as

activation of the 5-HT_{1A} receptors generally causes neural inhibition. The serotonergic input may not be essential for the increase in dopamine activity seen early in the task, nevertheless, it seems likely that dopaminergic activity is potentiated by the 5-HT input. The 5-HT_{2A} and 5-HT_{1A} input to the dopamine system, therefore, may overrule the tonic inhibition of dopamine release by 5-HT_{1B} and 5-HT_{2C} receptors. However, the increased activation of the dopamine system may not last throughout the gambling task. Van den Bos et al (2006) suggest an enhancement of serotonergic tone during the second half of the task. If activation of dopamine neurons will decrease when the task progresses, the dopamine mediated activation of the mPFC is likely to diminish. This dopamine-mediated stimulation of the mPFC in turn, may result in an increase of 5-HT release from the dorsal raphe. Increased serotonin release in the mPFC then further inhibits mPFC activity (Puig et al, 2005), further decreasing the excitatory input form the mPFC to the VTA. An elevation in serotonin levels may then result in restoration of the inhibition of dopamine activity via 5-HT_{1A} and 5-HT_{2C} receptors. Figure 3 depicts the proposed action of dopamine and serotonin in the IGT.

5.3 Future research

Following the suggested interactions at different times in the IGT, several suggestions for future research can be made. First of all, both dopamine and serotonin neural activity and release should be monitored throughout the IGT. For both dopamine and serotonin, firing activity of neurons in areas where the cell bodies are located (i.e. VTA and raphe nuclei) may provide comparative information of the activity of these two systems during several stages of the task. Both rapid and slower changes in extracellular dopamine concentration can be measured with *in vivo* voltammetry and microdialysis respectively. For serotonin, however, signaling of rapid (msec) changes in neurotransmitter concentration is as yet impossible. Nonetheless, microdialysis allows monitoring changes on a minute timescale. Studies using electrophysiology and monitoring of neurotransmitter release provide a general background of the involvement of both systems during the IGT. A more detailed picture can be obtained by using selective pharmacology in different stages of the task. If indeed different 5-HT receptors are modulating dopamine release during different stages of the task, selective pharmacology should be able to block or enhance these effects, causing altered dopamine release and altered behavior. It may be most interesting then, to selectively target the 5-HT_{1A} and 5-HT_{2A} receptors in the mPFC, as these 5-HT receptor subtypes appear to be most involved in potentiating tonic and phasic dopamine release and the 5-HT mediated input from the mPFC appears to be more important for regulation of VTA activity than the local effect of 5-HT_{1A} and 5-HT_{2A} receptors stimulation within the VTA.

If 5-HT_{1A} and 5-HT_{2A} manipulation in the mPFC indeed results in altered dopamine release and behavior during the IGT a further interesting approach may also be to look at 5-HT influence on dopamine release in different areas within the mPFC during different stages of learning. Reinforcement learning theories generally distinguish goal-directed and habitual behavior. When behavior is goal-directed, an agent performs an action in order to obtain a goal. However, when the value of the goal changes, for example by devaluating a rewarding outcome, the agents will cease the performance of the action

(Balleine & Dickinson, 1998). In contrast, habitual behavior will be performed regardless of the current value of the outcome (Balleine & Dickinson, 1998). Habitual behavior involves less cognitive effort, leaving mental capacity for other tasks. However, when a situation in the environment changes habitual actions may no longer result in a positive outcome. Therefore, changing between goal-directed and habitual behavior may be the best adaptive strategy.

Cortico-striatal circuits are involved in both types of learning. Yet the subdivisions of the cortex and striatum involved differ between goal-directed and habitual learning. Moreover, dopamine may be differentially involved in both types of learning. Goal directed behaviors are mediated by a prefrontal-ventral striatal-amygdalar circuit. Combined dopaminergic and glutamatergic input to the NAC is essential for learning of goal-directed learning (Smith-Roe & Kelley, 2000). Besides dopamine and glutamate neurotransmission in the NAC, glutamate transmission and protein kinase A (PKA) in the mPFC and basolateral amygdala are essential for acquisition of goal-directed behavior, suggesting plasticity in the network as a whole is needed for acquisition of this type of behavior (Kelley et al, 2003). In addition, dopamine in the ventromedial PFC may be an important mediator adjusting goal-directed behavior to the present value of reward (Hitchcott et al, 2007). Dopamine in the ventral striatum may not be essential for performance of goal-directed behavior (e.g. Phillips et al, 2003; Choi et al, 2005). In addition, glutamate transmission in the dorsomedial striatum may be a critical substrate for the performance of goal-directed actions (Yin et al, 2005ab). The dorsolateral striatum, in contrast, appears to be an essential neural substrate for habitual behavior (Yin et al, 2004). Separate regions within the mPFC are also differentially involved during goal-directed and habitual behavior. The prelimbic cortex is important during acquisition of goal-directed behavior and is thought to be an important mediator during the formation of action-outcome associations (Killcross & Coutureau, 2003). The infralimbic cortex is active in the phase when behavior can change from being goal-directed to being habitual (Coutureau & Killcross, 2003). Dopamine transmission in the mesolimbic system appears to have a modulating function during goal-directed behavior whereas the nigrostriatal dopamine system is more important for habitual learning.

Extended training can render goal-directed behavior insensitive to the current value of the reinforcer, i.e. the behavior is habitual (Balleine & Dickinson, 1998). It is possible that a similar shift in neural circuits takes place during the Iowa Gambling Task. For example, early in the task, dopamine from the mesolimbic system in the prelimbic-ventral striatal circuit may be important, whereas nigrostriatal dopamine in the dorsal striatum can be observed during the end stage of the task. In between, dopamine release in the infralimbic cortex may be altered. Alternatively, infralimbic input to the mesolimbic dopamine system may result in an inhibition of the mesolmibic dopamine system during the second half of the task. Both 5-HT_{1A} and 5-HT_{2A} receptors are expressed in the prelimbic and infralimbic cortex (Santana et al, 2004). Modulation of 5-HT_{1A} and 5-HT_{2A} receptor activity within the prelimbic cortex then may have effects on dopamine/behavior particularly during the beginning of the task whereas activation of these receptors in the infralimbic cortex may be present halfway or at the end of the task. However, more research will be needed to elucidate the specific neural correlates and the role of dopamine/serotonin interactions in the IGT.

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