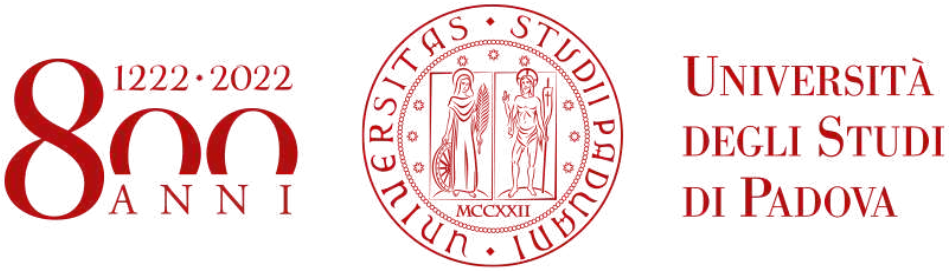

Department of General Psychology

Bachelor's Degree Course in Psychological Science

Final dissertation

The Dopaminergic Role in Healthy and Pathology

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Academic Year 2023/2024

To my sweet mom.

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Abstract

The correct functioning of human beings is affected, among other factors, by the activity neurotransmitters exhibit in the body. The present paper focuses on dopamine: a catecholamine neurotransmitter, acting through distinct pathways in the brain, and binding to different types of receptors. A summary of its main implicational functions in reward, motivation, cognitive functions and movement, along with a brief historical perspective is presented. A further discussion about the most common disorders associated with dysregulation of this molecule is highlighted. The following will be considered: Substance-Related Disorders, Schizophrenia, Attention-Deficit Hyperactivity Disorder, and Parkinson's Disease. Lastly, the focus will move to side effects related to medications involving this molecule.

Chapter 1: Introduction

Human's functioning is subject to many influences in everyday life. The brain is a complex organ, responsible for the coordination of many actions and reactions in the body. Its role is fundamental in many functions at the basis of an organism's survival. These, and other types of information is communicated thanks to the neurons, the brain's specialized cells, and their use of neurochemicals. Neural communication is possible through the the release of ions and chemicals, either involving the propagation of the signal from the presynaptic neuron to the receiving postsynaptic neuron by means of the process of action potential, or by the release of them into extracellular fluid and cerebrospinal fluid (CSF). The latter allows a more distant communication since the released chemicals can be sent to remote locations throughout the body.

Based on their method of action, neurochemicals can be classified into three distinct categories: neurotransmitters, neuromodulators and neurohormones, acting respectively on adjacent neurons, further away through the process of diffusion, and to more distant locations traveling into the bloodstream. There are many distinct ways in which these processes can fail, deeply influencing an individual's development, way of processing, and altering its functioning (e.g. imbalance in the amount of neurochemicals, synapses dysfunction, impairment in signal transmission, speed of communication, genetic mutations ecc.). Based on their composition, they can be classified into three distinct categories: amino acids and amines, made up by small molecules, and peptides, larger molecules constituted by chains of amino acids.

1.1 Definition

Catecholamines are amine types of neurotransmitters containing *catechol* and having the amino acid *tyrosine* as precursor. Neurons responsible for their synthesis are able to convert tyrosine into the compound *L-dihydroxyphenylalanine (L-dopa)* using the enzyme *tyrosine hydroxylase (TH)*. The enzyme *dopa decarboxylase* is responsible for the subsequent conversion of L-dopa into the neurotransmitter *Dopamine (DA)*. Further processing using supplementary enzymes results in the synthesis of *norepinephrine (NE)*, and *epinephrine*, making up the three catecholamines. The complete pathway of synthesis is shown in Figure 1. The main source of variations in the production of these

monoamines is the availability of L-dopa: the more L-dopa there is, the more synthesis of catecholamine can be made.

Dopamine's molecular formula is $C_8H_{11}NO_2$, structurally containing 8 carbon atoms forming a benzene ring characterized by 2 hydroxyl groups (OH), and a carbon chain bound to a terminal aminic group NH_2. Its chemical name is 4-(2-aminoethyl)benzene-1,2-diol, reflecting its nature as catechol in which the hydrogen at position 4 is substituted by a 2-aminoethyl group.

Once released in the synaptic gap, they can be deactivated through the process of reuptake, in which specialized transporters move these molecules back into the sending neuron, where they can either be re-used or broken down and destroyed by the enzyme *monoamine oxidase (MAO)*. In case they are not transported back into the neuron, they are disintegrated by the enzyme *catechol-0-methyl-transferase (COMT)* in the synaptic gap. Dysfunctions in these enzymes can result in excessive availability of these chemicals.

1.2 Receptors

If the chemical does not go through the breakdown process, it is captured by receptors in the postsynaptic neuron. Dopamine, as well as other neurotransmitters, has different subtypes of receptors. Five distinct types of slow metabotropic dopaminergic receptors have been established so far: D1, D2, D3, D4, and D5, which can be further classified into first class (D1 and D5) and second class types (D2, D3 and D4), depending on weather they have excitatory or inhibitory capacities, respectively.

1.3 Pathways in the brain

As other molecules, dopamine can be found mainly in specific regions in the brain in which neurons containing it are more prevalent. They follow "topographically organized anatomical tracts" (Albanese et al., 1986), allowing communication with other brain's structures, and having a subsequent influence on them. Dopaminergic pathways are among the most important in regulating everyday's activities and influencing human choices. They can be categorized based on the route they follow and the main role they assume by operating in these regions, although they seem to employ a more dynamic and interconnected functioning, influencing one another and displaying

co-operation on the implementation of those tasks. So far, research has established the existence of five pathways: the Mesostriatal, the Mesolimbic, the Mesocortical, the Tuberoinfundibular pathways and the Hypothalamospinal tract (Figure 2).

The *Mesostriatal* or *Nigrostriatal pathway* contains the majority of dopamine in the brain. It originates in a structure of the midbrain called substantia nigra, and projects to the dorsal striatum of the basal ganglia, specifically to the caudate nucleus and putamen. These structures of the basal ganglia contribute to the conscious control of motion, and modulates activities involving the planning of purposeful motor movements, as well as motivation of behavior and learning.

The Mesolimbic and Mesocortical pathways both originate from the ventral tegmental area (VTA) of the midbrain and are sometimes uniquely referred to as the "Mesocorticolimbic dopaminergic network". The *Mesolimbic pathway*, informally known as Dopamine Reward circuit, communicates mainly with another structure of the basal ganglia, the nucleus accumbens, located in the ventral striatum, as well as other structures of the limbic system. As the name suggests, this pathway is thought to mediate reward and reinforcement perception, and to have an effect on motivation and emotions. Contrary to the Mesolimbic one, the *Mesocortical pathway* expands its projections to the prefrontal cortex and structures of the cerebral cortex. These areas are responsible, among other activities, for executive functions, surveillance of behavior, planning and cognition.

The last two dopaminergic systems originate from the hypothalamus, the structure implicated in the control of the Autonomic Nervous System. The *Tuberoinfundibular pathway*, also called Second hypothalamic dopaminergic pathway, specifically arises in the arcuate nucleus and projects to the infundibular region of the hypothalamus. This system is responsible for the transmission of dopamine to the pituitary gland: it regulates the release of the hormone prolactin from this gland, therefore, contributing to the monitoring of lactation, breast development and milk production. The *Hypothalamospinal tract,* also known as Paraventricular dopamine system, links the hypothalamus to the thalamus, and it mediates motivated behaviors, allowing some control of aspects such as sex, appetite and thirst.

More clusters of dopaminergic neurons have been shown to exist, but their recognition as proper circuits is not agreed upon researchers; these might include the retinal dopaminergic cells believed to mediate some visual processes, the diencephalon-spinal dopaminergic neurons playing a role on spinal cord sympathetic neurons, and the incerto-hypothalamic system, not possessing yet a clear role.

Chapter 2 : Functions

As briefly described, many are the activities known to be influenced by the action of dopamine; the dopaminergic systems are thought to be involved in a variety of vital functions, and to mediate the correct functioning of some brain structures and behaviors related to them.

2.1 History

Today's knowledge has been gained thanks to scientific research, but had to face some major challenges and debates throughout the course of history, and yet many are expected to emerge. As a matter of facts, the role of dopamine has been a controversial and unclear topic, and, nowadays, there is still no general consensus on some models of dopamine functioning.

Initially, its comprehension was limited to concepts of pleasure only. Early experiments highlighting a possible link were carried out in the 50s, where brain stimulation of animal models was employed as soon as the animal reached a given corner of the environment. Interestingly, in those trials where electrodes stimulating the brain targeted dopaminergic clusters, the animal showed a repetitive goal-directed enhancement in moving towards the location paired with the delivery of electrical shock (James Olds, 1956), demonstrating a learning mediated by the principle of operant conditioning, in which an association was made between the corner of the box and the electrical simulation, a stimulus reinforcing the behavioral reaction at the point of inducing the rat to persistently stay there. This reward-seeking behavior was narrowly attributed to the experience of pleasure and enjoyment, thought to be induced by the electroshock through dopaminergic activation in the brain area stimulated, excluding the implication of a more complicated mechanism, and leading to the inaccurate notion of dopamine as being the "pleasure molecule".

The "Anhedonia hypothesis" is another example of incomplete knowledge believed to be true about dopamine during the course of history. Anhedonia is defined as the inability to enjoy experiences or activities that normally would be pleasurable (American Psychological Association, 2019). Evidence of symptomatic anhedonia in animal models after administration of neuroleptic medications, drugs decreasing dopamine neurotransmission in the brain, led to the partially incorrect assumption of a

major role of dopamine in the association of rewarding stimuli and pleasant experiences, therefore, in the mediation of hedonic properties of reinforcers (Wise et al., 1978).

Criticisms about the accuracy and completeness of these hypotheses arose following new experimental findings, leading to the partial detachment of this dopaminergic-pleasure views, and shifting the focus in its involvement in reward and motivating behavior. A crucial discovery challenging this view was the retention of the pleasurable experience observed in rodents when depleted by dopamine, measured by means of facial expressions and taste-reactivity natural responses, reflecting enjoyment and hedonistic appreciation. (Berridge et al, 1989).

The overall picture of dopamine seems to be much more complex than what was believed. The pleasure and hedonistic hypotheses, however, have not been completely rejected, rather modified through the course of time, combining the dopaminergic implications in pleasure mechanisms with novel understanding of its functions. Credits must be given to them in generating insight in past research, leading to the refinement of this molecule's functional definitions. We now have a much broader comprehension of the complex mechanisms underlying this molecule. Advancement achieved must be attributed mainly to animal research, a cardinal scientific element for the development of public knowledge, especially when considering neurobiological investigation. Furthermore, the development of better neuroimaging techniques to study and stimulate the brain, allowed a better localization of reward and motivation-generating areas in the brain. However, our understanding of this neurochemical today highlights the role of interconnecting structures, working together in elaborated manners to carry out various activities, and still many other scientific advances must be accomplished before asserting a clear and comprehensive knowledge of it.

2.2 Reward

During history, there has been accumulating amount of evidence pointing at the mediation of the catecholamine circuitry in brain reward. Evidence of dopaminergic importance to the rewarding properties were first found in studies where reduction or absence of dopamine induced decreased or no responses when reward-sensitive brain areas were electrically stimulated (Fouriezos et al., 1978), and generated decreased or

complete cessation of self-administration of reward-eliciting drugs (e.g. cocaine, amphetamines) (De Wit & Wise, 1977). The following theoretical implication assumed a direct dopaminergic participation in reward.

A more specific involvement concerns the learning association of stimulus-reward, consequently shaping the individual's engagement in goal-directed behaviors. It has been shown that "the most normally reinforcing stimuli and events fail to reinforce either instrumental behaviour (i.e. actions performed to reach a goal) or associations between rewards and other stimuli when dopamine function is impaired" (Wise, 2004). With damaged dopaminergic functioning, animals fail to associate the pressing of a lever for natural rewarding stimuli that would naturally elicit the behavior (e.g. food, water ecc.) (Wise & Schwartz, 1981). Dopamine seems, in fact, to be a mediator of the stamping-in process of positive reinforcement's acquisition.

During history, however, criticisms and controversies have emerged in relation to the assumption that dopamine directly mediates rewards, by means of observation of more complex mechanisms, not only unique to positive reinforcement, but also including aversive conditioning. Its involvement has been proposed to be more related to the conceptualization of reward prediction. Extensive animal research has shown an enhanced dopaminergic activity clustering at the level of the basal ganglia, particularly in the dorsal striatum, when a reward was predicted rather than received. Dopaminergic cells in monkeys performing a learnt task activated to the instruction signaling the animal to execute the task that will provide the reward, instead of responding to the reward itself as initially shown (Apicella et al., 1992). The primary reward does not produce a response anymore, instead it is substituted by the predictive cue, triggering the animal's behavioral reaction to obtain the reward. Coherently to the "reward prediction hypothesis", dopaminergic activity seems to underlie the anticipation of the possible reward coming from a stimulus, rather than the reward itself. Confirmatory evidence has been recently growing: fMRI highlights an increased dopaminergic activity in anticipation of glucose acquisition in the midbrain and striatum (O'Doherty et al., 2002) and expectation of monetary reward in gambling behavior clustered in the nucleus accumbens (Knutson et al, 2001), further underlying its involvement in projecting possible future outcomes. Predicting processing is adaptive both for pleasant, rewarding stimuli, and aversive stimuli: animals are likely to pursue the former while

avoiding the latter for the best of their survival. Imaging studies showing activity clustered in the ventral striatum after the prediction of a negative event following aversive conditioning (Jensen et al, 2003) highlights this broader application, not only narrowed and limited to positive reinforcements, even though, it is to keep in mind that a general consensus on this functional processing of the striatum is yet not reached.

This hypothesis has been elaborated even more with the introduction of the notion of "reward prediction error", where the error simply represents the mismatch between an expectation and the actual occurrence of the event. The failure in prediction introduces a novel awareness about it, which shapes subsequent forecastings. At the molecular level, dopamine is triggered if a reward is expected, raises if the outcome is better than predictions, and shuts down if expectancy is greater than the outcome. This type of process is adaptive precisely because, through the unexpected reward, the individual is able, firstly, to discriminate among those rewards that are more pleasurable, therefore, worth to be pursued, and secondly, to learn how to better interpret and predict the situation in future events, with the purpose of subsequently modifying the behavior to obtain the best possible reward. Experiments investigating the engagement of single cells support the hypothesis: an initial dopaminergic activity is displayed when the reward is presented with no predictive cue. After pairing of the reward with the predictive cue, however, activation is only shown when the latter is presented, therefore, reflecting an activity linked to the predictive cue rather than simply signaling the appetitive stimulus. Additionally, removing the reward causes the cells to shut down. (Schultz et al., 1992). This indicator exactly seems to underlie the failure in the prediction and expectancy of the reward, and might be a way to alert the organism in order to shape future predictions related to the subject. It is important to note that further experiments also showed a gradual decreased activation in dopamine neurons when the prediction is correctly reached after the pairing of the conditioned stimulus with the reward. It has been suggested that the individual's ability to correctly identify the future outcome mediates this process, and since no error is made in the prediction, the outcome is as expected causing cells to gradually decrease their activity to disengage their attentional effort. The firing of these neurons, therefore, seems to represent an alerting signal to unexpected events, with the aim of capturing attention when different-than-predicted, salient events are presented.

Besides the complex, and, under some aspects, still unclear, rewarding implication, there is no doubt dopamine plays a role in memory formation.

The predictive reinforcing effects of a stimulus acquired by the system seems to be stored in long term memory, and later influence instrumental behavior; reward acquisition following a behavioral response, later evoked by the memory system's retrieval process, stimulates the behavior antecedently paired with the reward even precedently to the reward itself, and, if the reward is different than the one stored, it takes several trials before adapting and changing the learnet association. An example is the mice running and pressing a lever to obtain brain stimulation, subsequently increasing or decreasing the frequency and speed of the behavior based on the new stimulation obtained. This process reflects a gradual adjustment of behavior based on a previously learnt and stored experience initially eliciting the same behavioral response, mediated by the prediction of the same rewarding magnitude, but, later adjusted following the incorporation of the new learning association experienced (Gallistel et al., 1974). These adjustment operations highlight the recollection of previously stored associations, the prediction of reward associated to them, and the integration of these information to present stimulation in order to mediate goal-directed actions, resulting in an increased and decreased motivational load to carry out the behavior, respectively when the stimulation is incremented and reduced. Additional evidence in support of dopaminergic contribution to memory formation comes from studies involving the hippocampus, the main structure implicated in memory, showing that a dopaminergic enhancement positively influences memory processes and block depotentiation, while its reduction impairs them. (Otmakhova & Lisman, 1998). Indeed, dopamine activation has been shown reinforcing and inhibitory effects in the hippocampus; activation of D1 excitatory receptors seems to promote early and late Long Term Potentiation (LTP), the process of synaptic connections' strengthening underlying memory retention, while, conversely, triggering of D2 inhibitory receptors facilitates Long Term Depression (LTD), the weakening of synaptic connections. Dopamine's activation influences the plasticity of the brain by modulating glutamate release on GABAergic neurons controlling how effective rewards predictions are. This plasticity between reward-predicting cues and followed outcome is the key for driving behavior towards

reward seeking or punishment avoidance, therefore, possessing important motivational properties influencing the primate's choices.

More research is being conducted with the aim of clarifying the mediation and contribution of this chemical in the reward processes. Nevertheless, it is clear that stimulus-reward association possess motivational properties increasing the likelihood of instrumental behavior.

2.3 Motivation

Dopamine has indeed shown to support motivated behavior and motivational functioning: suppression and enhancement of dopamine can attenuate and amplify the individual's motivation to act towards a stimulus. Once again, evidence comes from animal research where absence or depletion of dopamine, either due to brain damage or drug administration, induced decreased feeding behavior in animal models, manifested by aphagia (i.e. inability or refusal to swallow) and adipsia (i.e. inappropriately decreased or absent feelings of thirst) (Smith et al., 1972). Supplementary analysis ruling out a possible causal implication involving motor deficits, suggests a decreased motivational effort to carry out such a primary and primital behavior. It seems, indeed, to concern more a decreased willingness to carry out goal-directed behavior, and an apparent apathy underlying a usually naturally-exciting stimulus.

It has been speculated that this molecule influences the behavior-driving effects by mediating the process of motivational importance's attachment during the pairing of a neutral stimulus with a reward. It therefore, shapes how much a stimulus is important and worth being pursued by the individual, consequently shaping the effort put in relation to its reaching. When subsequently presented and retrieved by memory systems, what became the incentive-motivational stimulus, will energize the individual towards specific goal-directed behaviors thanks to this dopaminergic mediation in reward anticipation formation. The role of dopamine here, in fact, seems to be related to the attachment of value to the stimulus that was previously neutral, and to the formation and perception of reward predictability related to it. The "incentive salience hypothesis" conceives dopamine as the chemical responsible for salience attribution, the process of converting neutral stimuli into important incentives, motivating towards action. Research suggests that dopaminergic projections to the nucleus accumbens extending to

the amygdala contribute to the encoding of salient information for the individual (Iversen & Iversen, 2007). This implies that dopamine is able to influence how much the individual perceives a stimulus to be salient, as well as mediating how sensitive one is to pleasant and unpleasant experiences, therefore, impacting orientation of attention. Its contribution in these perceptual processes leads to believe it also plays a role in the emotional response humans have towards salient events.

The Mesolimbic system in particular, seems to indirectly mediate the perceptive experience of future imagination: by placing salience upon a certain resource it indirectly highlights the benefits that could be obtained out of it. It does so, by shifting an individual's attention towards the desired cue, accentuating its recognizability, and by moderating the individuals' view of it through reward anticipation, with the consequence of making it shine in a more favorable light. This enhancing process of the stimulus' significance is likely to motivate behavior towards the acquisition of the latter, with the anticipation of a consequent reward. These mechanisms of action are independent of resources already possessed: dopamine generates reward anticipation and motivates with the purpose of maximizing resources and obtaining more, not considering what the individual already owns, and tricking the mind into a better future perspective. The reward prediction error hypothesis seems to perfectly explain this maximization process by simply supporting the fact that, with each error prediction leading to a better reward, the individual automatically and unconsciously raises up the threshold for the expected reward. Therefore, for dopamine to be triggered in the same way, the consecutive reward must be higher.

Evolutionary speaking, it is understandable to picture dopamine's development and maintenance, precisely for its contribution in boosting resources in case of future need. It has been suggested, in fact, a beneficial and adaptive role for the maturation of dopamine by "promoting behaviors that lead to survival and reproduction" of the individual (Lieberman & Long, 2018). Our ancestors seemed to be captured and moved by an intrinsic incentive to gather resources; it indeed makes sense to think about the development and maintenance of an underlying supportive mechanism, continuously stimulating individuals by allocating their attention towards things and behaviors that enhanced their chances of survival and reproduction. Predictions of behavioral outcomes allow the animal to prepare the right behavioral reactions, and improve future

choices to maximize outputs and minimize losses. Furthermore, the evolutionary progression of this circuit is coherent with its contribution in memory formation, which is likely to function for the purpose of recalling those stimuli that previously led to some rewarding experiences, in order to subsequently reproduce the most adaptive behaviors with the help of the energizing properties that act on the animal to pursue them.

2.4 Cognitive functions

The dopaminergic implication in the frontal cortex, together with the involvement of the basal ganglia, has been proposed to concern mainly the development and the coordination of cognitive functions. The action of the Mesocortical system is likely to play a role in the mediation of the reward seeking and anticipatory mechanisms, by arbitrating conscious control of long-term goals. This seems to be possible thanks to the action of the frontal cortex, entailing structures involved in planning, moderation and control of certain behaviors. It is likely that dopamine cells influence the activity of these structures in order to tune inputs from subcortical networks connecting them to the basal ganglia, combining internal signals, and eventually resulting in coordination and organization of behavior. Evidence of its implication in these organizational and cognitive abilities results from multiple studies: in the prefrontal cortex (PFC) dopamine reduction was associated with failure in behavioral inhibition and organization expressed as motor hyperactivity (Tassin et al., 1978). Lesion involving, more generally, neurons in the Mesocortical pathways seemed to induce a "disconnection syndrome, similar in many ways to that observed after the destruction of the frontal lobe areas" (Nieoullon & Coquerel, 2003), and destruction of dopaminergic neurons clustered to the substantia nigra and striatum resulted in sensory inattention syndrome in baboon animal models (Viallet et al., 1984).

Moreover, the nucleus accumbens' action on the forebrain seems to be related to the evaluation of effort-linked activities, influencing subsequent decisions on which behavior to enact. Animal's achievements can be broadly considered a consequence of their decision process in which an evaluation between the value of a stimulus and the instrumental effort necessary to obtain it is made, and either generates or not the behavioral output required to achieve the stimulus. Again, dopaminergic involvement in this cognitive evaluation emerges from scientific research: mice usually prefer to work

by means of lever pressing to obtain Bioserve pellets as treats, compared to accessible lab chow. However, when given dopamine antagonists (i.e. drugs inhibiting the action of another substance) or a depletion of accumbens neurons occurs, they favor the free availability of chows (Salamone et al., 1991). Given that the rats' ability to direct and perform behavior towards food consumption was intact, these results highlight a decreased effort and willingness to expend and invest energies for the reward. It, therefore, demonstrates that a dopamine reduction due to lesion or depletion can lead to a decreased engagement in effortful tasks, likely to be a consequence of a dysfunctional cost-benefit analysis. Further research investigating lesions attributes to the anterior cingulate cortex (ACC) these effort-related decisional role functions: rats given the choice of a large reward after performing a climbing, or a small reward in exchange of a lower energetic demanding task normally show to prefer the high cost–high reward option, and engage in performance of a effortful behavior in order to obtain a better outcome. When ACC is lesioned however, they only engage in the low cost–low reward option, reflecting a preference to work harder for a better reward, and demonstrating ACC's role in decision making related to evaluation of costs and benefits and effort engagement (Walton et al. 2003).

2.5 Movement

As previously mentioned, another fundamental role of dopamine is carried out by the Nigrostriatal pathway, and it concerns its implication in movement. This circuit is believed to mediate all kinds of motor behavior: simple, complex, with stimulus association and not. The basal ganglia, among other functions, is known to exert a selective control of movement execution, enabling inputs from the cortex to be initiated and sent to the appropriate motor structures in order to implement these commands. Dopaminergic projections from the substantia nigra to the basal ganglia is believed to mediate these inputs reaching the latter, facilitating the implementation of movement. Striatal dopaminergic blockage has been linked to motor impairments exhibited by delayed responses in relation to reaction-time tasks. In contrast, stimulation of those circuits leads to premature responses, suggesting a motor facilitation related to a higher level of motor readiness, likely to impair attentional processes and time estimation. (Baunez et al., 1995). More implicational evidence involves the substantia nigra's

degeneration, shown to result in movements slowness, resembling the symptomatology of Parkinson's disease (Viallet et al., 1984). A particular attention has been given to the D2 receptors implication in the performance of motor movements and sensitivity for sensorimotor integration: rats instructed to perform a task at a given signal showed increased reaction time and, therefore, incorrect responses, when D2 antagonists were administered, conversely to the pre-treatment case with D1 antagonists which resulted in no impairment in performance (Amalric et al., 1993). Further research highlights the akinetic patterns in animal models that, despite adequate motor and muscular capacities, underlie the lack of spontaneous movement not displayed even in relation to such motorial mechanisms aimed at survival (e.g. feeding behavior), following degeneration of Nigrostriatal pathway (Ungerstedt, 1971). This type of experiments also highlight the partial mediation on motivational mechanisms of the circuit; an hypothesis involving the motivation to carry out effort-related motor behavior has, therefore, been proposed to explain the movement deficits observed when dopaminergic reduction in the Nigrostriatal pathway occurs. It seems, in fact, that lesions involving the circuit might interfere with some aspects of motor functioning which allows the initiation and maintenance of instrumental responding, resulting in the failure to organize and complete motor movements.

The multiple hypotheses underlying these activities highlight, once again, the inability to clearly define a specific functional role of each system, rather, they suggest a complex interconnection of these mechanisms to carry out such behaviors.

Chapter 3 : Implication in mental disorders

The implication of dopamine in these structures has been proven by dysfunction or unbalanced activity of dopamine resulting in abnormal behaviors, suggesting, not only a major role of dopamine in these activities, but also its causal implication in some symptomatology and/or progression of psychopathologies. In the present paper the focus will be on some specific neurological and psychiatric disorders thought to mainly involve deficits in the dopaminergic functioning, believed to be causally implicated in the development and maintenance of them. However, it is to be kept in mind that the spectrum is much broader, and several other pathologies not mentioned here seem to display dopaminergic dysfunctions as well. Furthermore, dopamine is unlikely to be the only factor involved in the course of these diseases, indeed, the majority of them is believed to be multifactorial, involving the interaction of biological and environmental features. However, the present paper will focus specifically on the role of this molecule, leaving aside additional factors involved.

3.1 Substance-Related Disorders and Addictive Disorders

"Substance-Related and Addictive disorders" is a broad term to characterize conditions underlying substances and behaviors that have the potential to generate an addictive pattern. Addictive behavior can be defined as a type of behavior based on the pathological need for a substance and/or behavior, characterized by continued, excessive use despite consequences (abuse), and/or physiological need for increasing amounts of the substance to achieve the desired effects (dependence). Addiction is a major concern in today's society; it has recently been experienced an increased need to uncover the mechanical-biological processes underlying it, in order to develop preventive and therapeutic implications possibly saving people's life, nowadays, struggling and dying of this enslaving practice.

Although different drugs and behaviors vary widely in terms of addictive properties, dependence indexes and withdrawal symptoms, what is common among them is the involvement of the molecule dopamine in their use development. The Mesocorticolimbic dopamine pathway is thought to profoundly shape the initiation and maintenance of these behavioral patterns involving "neurobiological changes that cause rewards to be intensely overvalued" (Dingman, 2019). The first association of dopamine

with stimulant substances was made in the 70s followings the “catecholamine (CA) hypothesis” assuming that catecholamine-containing neurons mediate the reinforcing properties of intracranial self-stimulation (ICS) in animals, enhancing the operant behavior related to the discharge of electrical stimulation. This hypothesis resulted following observation of increased rate of lever pressing to obtain ICS, following administration of d-amphetamine and cocaine, catecholamine-increasing substances, reflecting facilitation of the response, while, contrarily, administration of catecholamine-decreasing substances led to a decrease in the behavior. The assumption regarding noradrenergic neurons was later rejected following the emergence of controversial evidence, suggesting a mediation not exclusive to those neurons, but, instead, shifting the focus on the effects of dopaminergic neurons, which, indeed, seemed to play a direct role in reward thresholds related to stimulants use. Later investigation allowed the reaching of a broader comprehension, spreading the implication not only to stimulants substances, but also to abused drugs belonging to different pharmacological classes (e.g. opiates, central depressants, cholinergic agonists) discovered to be involved as well, mainly exhibiting higher dopaminergic clustering in the nucleus accumbens, but also in the dorsal caudate nucleus (Di Chiara & Imperato, 1988). Neuroimaging studies conducted in the 90s revealed associations between stimulant administration and dopamine release, exhibiting magnitudes correlating with the experience of “euphoria” the drug released (Laruelle et al., 1995). It followed the development of subsequent “theories of addiction” implying the involvement of dopamine activation in addictive drugs. Later research, however, showed inconsistent results in the correlation causally implicating dopamine with the experience of “high” of the drug, suggesting a more complex procedure involved. It seems that only stimulants substances act directly by enhancing dopaminergic firing, contrarily to other drugs, that, however, seems to indirectly elevate dopamine levels through the actions of additional receptors (e.g. opioid receptors activating in the ventral tegmental area disinhibiting the dopamine system in the case of opiates), increasing excitation and/or disinhibition from the presynaptic neuron, inhibiting reuptake, and increasing dopamine’s levels at the cytosol(for additional explanations: Wise & Robble, 2020).

Using different mechanisms of actions, illicit drugs act on dopamine to shape and instaurate the habit-formation process. Habit formation can be seen as a complex

learning process involving synaptic changes following the experience of learning, and leading to automaticity. Drugs are believed to be able to shape this process by activating dopaminergic cells which, especially through projections from the nucleus accumbens to the amygdala, have been shown to fire in response to the encoding of salient stimuli, and affecting the memory system by enhancing LTP or LTD, facilitating the conditioned learning. The experience of drug intake will, therefore, be remembered as highly salient, and will influence the subsequent individual's prediction of the rewarding effects related to it. This memory will later motivate and drive behavior towards drug intake, especially when conditioned stimuli associated with the drug-use experience are evoked, further strengthening the conditioned experience and the automaticity of the behavior, promoting habit development.

A hedonistic component has additionally been speculated, supporting the encoding of the learnt habit in the circuit itself: structures of the reward system seem to detect the pleasurable experience related to drug use. This pleasurable experience leads to repeated use, which, coupled with activation and enhancement of the LTP process, contributes to the strengthening of the association and subsequent stimulation of the circuit.

The experience-dependent plasticity of the brain in relation to drug use is not only limited to the strengthening of associations in the memory system; it also implies the extension and the building of new connections. The reward system itself has shown to develop new dendritic connections between neurons following substance use, allowing an amplified and/or stronger signaling, spread to surrounding neurons. The brain's reward system becomes sensitized (i.e. hypersensitive) to drug use and drug-associated stimuli. With its implicational role in salience detection, the establishment of new connections, indeed, reflects a better association and a stronger encoding of those cues associated with drug use, which once presented again, will be more likely to elicit a stronger cue reactivity, resulting in craving of the drug's rewarding effects, and further motivate towards its use. Research confirmed this speculation and further identified the involvement of a complementary system allowing individuals to learn to avoid those cues associated with misrepresentation or unavailability of the drug; participants exhibited anxiety, stress and negative affect in relation to pairing of stimuli predictive of cocaine intake that become aversive when presented without drug consumption (Robbins et al., 1999).

The majority of addictive substances provoke tolerance symptoms. Tolerance is the term referring to the biochemical changes in the body accompanying dependence. This is partially a consequence of their molecular composition which is likely to hijack the reward system by overly activating it, either directly or indirectly. Homeostatic processes in the body seeking to achieve stability and balance in the continuing changing environment, must find a way to inhibit their excessive activation, and restore normal reward functioning. These processes induce neuroadaptation at a cellular, molecular and/or functional level, leading to the establishment of a new set point. The majority of the time they act by modifying receptors' density at the synapses through gene expression, protein synthesis, exchange of receptors with the membrane, or degradation. Receptor changes can be of two types depending on which drug they are adapting to: receptor downregulation (i.e. a decreases in receptor availability), reducing the effects of an agonist drug, and receptor upregulation (i.e. an increases in receptor availability), conversely, reducing the effects of an antagonist drug. Chronic drug intake has, indeed, been shown to lead to a reduction in D2 receptors in the striatum, but also, generally, in dopaminergic release (Volkow et al., 2007). As a consequence, once used again in the same amount, the substance will have a weaker effect, and a general decreased sensitivity to natural reinforcers will be experienced. A higher drug dosage will, therefore, be considered the only reasonable practice able to generate the previously-experienced effects, and the only possible method to activate the reward circuit again. Confirmation of synaptic modification, especially in the Mesolimbic circuit, can be found in brains of drug addicts and obese food-addicts individuals showing a less number of dopaminergic receptors compared to healthy subjects (Baik, 2013), but also in animal models to whom drugs were chronically administered, reflecting the molecular implications involved and the balancing process carried out when excesses are displayed.

Implication of the cortex is suspected as well: reduction of D2 receptors in the striatum subsequently results in reduced activation of orbitofrontal cortex and cingulate gyrus, structures involved respectively in motivation, salience attribution, compulsive behaviors, and inhibitory control and impulsivity (Volkow et al., 2007). Awareness of dopamine's link with executive functions, including the inhibition of behavior and impulse control, suggests a downregulation of the cortico-striatal circuit in addicted

patients, disrupting the ability to delay gratification and control impulses, leading towards a tendency to enact immediate pleasure-seeking behaviors, hence, predisposing the individual to compulsive behaviors. As previously highlighted, the Anterior Cingulate Cortex (ACC) has been shown to profoundly mediate the evaluation of how much effort one should expend on a target reward, thereby influencing cost-benefit analysis and subsequent behavior enacted. It seems plausible to attribute a dysfunctional role to this structure in such disorder: defective activity of the ACC would prevent this executive function to correctly evaluate the situation, allowing the complete dominance of primitive rewards that are generally held back.

Once the habit is established and plasticity has changed the brain's structural anatomy, hedonistic properties are not involved anymore: many times addicts cannot resist the compulsion even if they do not enjoy the use, it is just a matter of craving coming from a biological learnt association, combined to an impaired prefrontal top-down self-regulation favoring compulsive use.

Gambling, the act of playing games of chance for money, is a common phenomenon exhibited by the general population in an adaptive manner most of the time, however, it can assume a pathological facet implying the development of an addiction pattern. Indeed, the Diagnostic and Statistical Manual of Mental Disorders: Volume IV (5th ed.; DSM–5; American Psychiatric Association [APA], 2013) has been recently re-categorized it from an "impulse control disorder (ICD)" (i.e. a disorder characterized by the inability to resist an impulse, urge or drive that is harmful to the person and/or others) to a proper "behavioral addiction" (Non-Substance -Related disorder) where the persistency and/or recurrency of the behavior cannot be avoided, and leads to clinically significant impairment or distress.

As previously introduced, fMRI study investigating the role of gambling highlighted an increased activation of the nucleus accumbens when prediction of the monetary reward was made, rather than when it was actually acquired (Knutson et al, 2001), suggesting a dopaminergic increase related to the prediction of the reward, potentially alternating habit formation. Higher than normal release of dopamine were found in pathological gamblers compared to healthy individuals (Bergh et al., 1997) suggesting the implication of the same mechanisms underlying drug addiction. Moreover, a mesocorticolimbic excessive activation may be implicated in the generation of high

arousal, leading to symptoms such as increased risk taking, inhibited control and impulsivity.

3.2 Schizophrenia

Schizophrenia can be defined as a disorder characterized by an array of diverse symptoms usually involving extreme oddities in perception and thinking, and the possible development of psychosis: a significant loss of contact with reality. Schizophrenic manifestations include: positive symptoms (i.e. excesses in behaviors normally not present in healthy individuals), negative symptoms (i.e. deficits in behaviors that are ordinarily present), disorganized thinking, mainly concerning speech, and grossly disorganized or abnormal motor behavior. Positive symptoms entails delusions (i.e. firmed beliefs held despite contradictory evidence, highlighting cognitive rigidity), and hallucinations (i.e. sensory experiences occurring in the absence of any external stimulation). Negative symptoms are usually categorized based on the nature of the concern: diminished motivation and pleasure include asociality tendencies, anhedonia and avolition (i.e. an apathy-like attitude mainly concerning instrumental behaviors), while reduced expression entails emotional blunting and alogia, respectively, a lack of emotional expressions and poverty of speech.

The “dopamine hypothesis of schizophrenia” is one of the most accepted and believed to underlie the illness. Prevalent in this condition are unbalanced transmissions of dopamine and glutamate signals, thought to generate psychotic and cognitive symptoms (Owen et al., 2016). Initially leading to the idea of a possible dopaminergic association with the disorder was the observation of dopamine agonists and amphetamine-like drugs (i.e. stimulants) causing psychotic-like manifestations and cognitive distortions (Angrist & van Kammen, 1984). The resulting model, therefore, implies a higher-than-normal dopaminergic activity in schizophrenic patients’ brains, exhibiting abnormal features commonly not present in healthy individuals, the positive symptoms. In support of the hypothesis, autopsies of schizophrenic patients’ brain post mortem were performed showing higher dopaminergic levels, although, possibly accounting for the medications taken by those patients. Validating evidence in support further resulted from several brain imaging studies, exhibiting higher than normal amounts of dopamine synthesis, dopaminergic release, and density of D2 receptors in schizophrenic patients with no

history of medications intake (Howes et al., 2012). Moreover, both the prodromal phase, the period preceding the active-stage symptoms, and the onset of psychosis are found to be correlated with elevated dopamine levels.

Additionally, cognitive deficits concerning the evaluation of emphasis and salience on events are thought to mediate attentional experiences, leading to a misplacement of attention on futile and unimportant stimuli. The "hyper-attention syndrome" underlying the overactivation of the dopaminergic systems, therefore, concerns the inability to refrain and fileting irrelevant stimulation, both entailing internal and external stimuli, resulting in an ineffective ability to abstain from those cues, with the consequent development of psychotic manifestations associated with them. Evidence comes from several studies, such as the one performed by Silbersweig and colleagues (1995), demonstrating activity in deep brain structures during hallucinations by means of cerebral blood flow distribution, and further suggesting a specific hallucinatory manifestation based on the unique structural activation of each individual. Projections extending from nucleus accumbens to the amygdala seem to play a role in the hyper-attention syndrome as well: they promote the encoding of saliency information, thus, affecting the pairing process related to important events and the individual's emotional response to them. Dysfunctional role of this system contributes, firstly, to a maladjusted perception of stimulus saliency, and, secondly, to the generation of the emotional negativity disposed in the disease, by underlining some still unspecified deteriorations.

An alternative explanation conceives positive symptoms as a "disorder of internal monitoring", therefore, resulting from a misattribution of internally generating thoughts and acts perceived as external cues. An example might be a self-dialogue erroneously believed to come from the external environment, emerging as auditory hallucinations. Such deficits are attributed to a disconnection between the cortex and limbic structures, which, normally, plan behavior in order to be executed, comparing stored information with intended actions, but, when malfunctioning, provoke such reality distortions. Confirmatory evidence originates from studies where schizophrenic patients abstained from error corrections in a task requiring it, highlighting the lack of internal monitoring (Frith & Done, 1988).

Further discussion about the possible dopaminergic involvement in negative symptoms have brought to the hypothesis of a dysfunctional hypoactive role of this molecule, especially underlying the Mesocortical pathway. This “hypofrontality syndrome” seem to result in decreased dopaminergic signals to medial prefrontal regions of the brain responsible for cognitive functions (executive control, inhibition of behavior, working memory, volitional control and internal monitoring), as well as potentially causing disorganization in speech, thought and behavior, indicators of negative symptoms (Liddle et al., 1992). Neuroimaging techniques support the dysfunctional role of these structures by pointing to the fact that frontal cortices of schizophrenic patients suffer a reduction in white and gray matter, accounting for the symptomatology described, and further involving a decreased volume in caudate nucleus and thalamus.

As a link for the two types of symptoms, it has been suggested that dysfunctions of the prefrontal cortex (causing negative symptoms) might account for the enhanced neurotransmission at the level of the ventral striatum and limbic structures (generating positive symptoms). Supporting evidence has been displayed by studies demonstrating the correlation (Meyer-Lindenberg et al., 2002), although more research is needed to confirm the results.

Further dopaminergic implication is suggested by genetic studies pointing at some candidate genes, likely to influence dopamine activity during neurodevelopment, and by the implication of abnormal motor behavior in the disorder, known to be, at least partially regulated by dopamine.

Some symptoms of the condition can be improved by dopamine antagonists: positive symptoms benefit the use of neuroleptic medications, but it has been shown little or no improvements in negative ones and cognitive impairments. Antipsychotic medications, indeed act on D2 dopamine receptors by occupying them, therefore, not allowing the communication of the signal from pre- to postsynaptic neuron. The overall result is a reduced dopaminergic neurotransmission, likely to benefit the hyperactive syndrome of the disease allowing the individual to normally perceive salience from external stimulation, however, entailing no, or even worsening effects on the inhibitory patterns concerning negative symptoms, promoting cognitive oddities.

3.3 Attention-Deficit Hyperactivity Disorder (ADHD)

The DSM-5 classifies the Attention Deficit Hyperactivity Disorder (ADHD) as a neurodevelopmental disorder, by considering the early onset it generally displays, not excluding, however, its prevalence among adults. This condition is characterized by inattention and/or hyperactivity or impulsivity interfering with everyday's functioning (APA, 2013). Inattentional deficits can include failure in paying attention, lack of persistence, incapacity to sustain the right amount of attention, being easily distracted by external cues, forgetfulness, as well as a possible lack of organization. The hyperactivity slice presupposes an agitated and restless behavior, engagement in excessive motorial behavior, excessive talking and frequently interrupting during conversations. The impulsivity dimension is captured as a failure in the inhibition and/or in the delay of behavioral responses.

There is a general consensus for theoretical implications concerning catecholaminergic dysregulation in the disorder. Dopamine active transporter (DAT) density has been shown to be enhanced in ADHD patients compared to healthy individuals (Dougherty et al., 1999), suggesting a dopaminergic implication in support of the "low-dopamine hypothesis"; DATs are presynaptic monoamine transporters mediating dopamine reuptake at the synaptic level, allowing to store the molecule back into cytosol. An excessive availability of the transporter might result in a premature deactivation of the molecule, which would fail to reach the receptors in the appropriate amount. The "low-dopamine hypothesis" is further supported by administration of low-dosage dopamine agonists, enhancing its neural transmission and shown to reduce attentional deficits and locomotor activity (Arnsten, 2006).

Performances of the prefrontal cortex related to the suppression of responses to irrelevant stimuli, as well as its size appear to underlie the condition's symptoms. Extensive research proved impaired attention both in animals and humans following lesions of the cortex. As noted, indeed, the frontal cortex plays an important role in many executive functions among which there is inhibitory capacity, the ability to exclude irrelevant stimulation and refrain from action. From research involving ADHD children a supportive pattern emerges: their performance on response inhibition tasks is significantly lower and less accurate compared to the control group, and correlates with fMRI analysis demonstrating abnormalities in the activation of prefrontal cortex,

caudate nucleus and globus pallidus, another structure part of the basal ganglia (Casey et al., 1997). From this conceptualization the "inhibitory control hypothesis" has been originated, assuming a defective role of response inhibition execution: a primary deficit in control inhibition would lead to the inability to refrain from responding to a stimulation. Support for the idea can be found in results of the Stop Signal Paradigm, a task where participants must respond to a "go" stimulus as fast as possible, but withhold the response when an occasional "stop" instruction is presented simultaneously. This paradigm should capture the individual's inhibitory ability by assessing the stop signal reaction time (SSRT) (i.e. the speed of the stopping process) averaged among trials. Longer reaction times reflecting the failure to inhibit incorrect responses, thus, associated with diminished inhibitory capacities, have been prevalent in ADHD subjects, revealing an impulsive pattern due to an impaired stop-signal inhibition (Shachar & Logan,1990).

A distinct branch of speculation to explain the impulsivity symptom has been developed to distantiate from the "inhibitory control hypothesis". The "delay aversion hypothesis" conceptualizes impulsivity as a choice to avoid delay due to an intolerance for waiting, often culminating in the tendency to choose instant gratification over postponed one. ADHD patients often display delay aversion, inability to resist temptation, insufficient capacity to delay gratification, and high levels of stimulation-seeking traits; these are all characteristics likely to generate distorted ideas about reinforcement parameters. Supporting evidence emerges from the "Choice-Delay Tasks" where hyperactive children tend to deliberately choose a smaller reward within a few seconds rather than wait for a bigger one expected at a later time (Sonuga-Barke et al., 1992). Again, dopaminergic implication seems rational by simply accounting for its contribution on cost-benefit analysis, and its decisional role on effort-related behaviors to enact.

Research suggests that both the "inhibitory control" and the "delay aversion" hypotheses are implicated in the disorder and contribute to the symptomatology displayed, but more investigation needs to be carried out in order to assess the causal extent of each of them.

Suspected contribution of low dopamine to the disorder also comes from the knowledge about dopaminergic cognitive involvement in saliency and attentional processes: low dopaminergic neurotransmission seem to be associated with diminished attention

directed to salient stimuli, inevitably leading to a missing out of important information and an easy distractibility pattern. As well as schizophrenic patients, it has been suggested a potential dysfunctional role of the system projecting from nucleus accumbens to the amygdala contributing to the encoding of saliency events. Differently to schizophrenia's emotional symptoms, in the ADHD case the defective activation results mainly in failure to accurately evaluate stimulus saliency in the first place, subsequently impacting the orientation of attention.

Besides describing the disorder as one of the most heritable among the psychiatric ones, genetic studies offer additional documentation supporting dopamine interference by associating several candidate genes likely to be implicated in the disorder with dopamine receptors (Faraone & Mick, 2010).

Symptoms can be improved by low doses of dopamine agonists, enhancing the neural transmission of dopamine. Although hyperactivity is a main symptom of the diseases, and it might seem counterintuitive to administer stimulants for its treatment, curiously enough, in some countries, the use of controlled-dosage of d-amphetamine have shown a great efficacy, highlighting, once again, the complex effects stimulant psychoactive drugs have on the dopaminergic systems.

3.4 Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative movement disorder caused by the accumulation of *α-synuclein (LB)*, involved in the formation of *Lewy bodies*, abnormal protein aggregation within neurons provoking neuronal death. Motor symptoms include bradykinesia (i.e. slowness of movement), akinesia (i.e. inability to voluntarily move muscles), postural instability, impaired reflexive movements, tremors, and rigidity, displayed by increased muscle tone.

The first attribution of dopaminergic responsibility involved in the disorder was made in 1959 by Carlsson, who reported a depression of motor activity following the lack of catecholamines, and, specifically, the possibility to develop a parkinsonian-like syndrome as a consequence of dopamine depletion from the corpus striatum. (Carlsson, 1959). Later on, the understanding of its implication was deepened with the discovery of a dopaminergic neurons' high concentration in the so called Nigrostriatal pathway, extending from midbrain to the striatum (Carlsson et al., 1964), and implicated in the

disorder, especially in the substantia nigra and the basal ganglia's regions of the putamen and caudate nucleus, suffering dopaminergic neuronal death (Hornykiewicz, 1966). More recent considerations support neurodegeneration involving the substantia nigra's dopaminergic neurons. Lesioning baboons' substantia nigra have resulted in motorial deficits mostly correlated with PD's bradykinetic symptoms, exhibited by lengthening of movement time, decrease in reactivity, postural impairments and contralateral disuse syndrome (i.e. non-utilisation of the body half contralateral to the lesion) (Viallet et al., 1984), suggesting an important causal implication of this structure in the symptomatology of the disorder. Moreover, the involvement of the basal ganglia in the execution of motor programs is well established, therefore, its implicated dopaminergic neuronal death can easily account for symptoms of the disease as well.

The most effective treatment is L-dopa therapy, rooting its first trial administration in 1961, and consequent investigation of its use in the following years, till the understanding and acceptance of its dopamine-restoring benefits in the brain. The administration of dopamine itself is not possible since the molecule is not able to cross the blood-brain barrier, whereas L-dopa is, making its discovery a revolutionary tool to increase dopamine in the brain. L-dopa acts by increasing dopamine synthesis in the substantia nigra's remaining cells, and working as a D2 receptor agonist, boosting dopamine transmission. Side effects in the use of L-Dopa alone emerged, but with the combination of additional chemicals they can be avoided or attenuated (for additional information: Fahn, 2008). This therapeutic intervention is beneficial to alleviate symptoms, acting mainly on akinesia and, to a lesser extent, on rigidity; nevertheless, it does not stop the progression of the disease, nor the dopaminergic degeneration of cells, leading to a re-emerge of symptoms and, eventually, a premature end.

Parkinson's disease is likely to involve dopamine-related cognitive deficit as well, although, there is not a general consensus to assure this premise. It seems logical, however, to assume a disorganization of sequential movement planning by comparing dopaminergic's roles with symptoms of the disease. Scientific evidence is mixed, but some studies shed the light on the possibility of a dysfunctional implication in voluntary action planning and strategy arrangement (Nieoullon, 2002), as well as some aspects of memory. Memory impairments seem to be differentially correlated to the clinical severity of the disease, showing a significant dysfunctional implication for those with

more severe clinical symptoms. The cognitive involvement in motor functioning mainly concerns the planning and organizational skills required to initiate and carry out adequate motor movements, and it is thought to be mediated by circuits involving the prefrontal cortex and the striatum. It is not surprising, therefore, that dopaminergic damage to the corpus striatum might result in this inability to coordinate high-level motor planning. Demonstrations of these implications can be found in studies where participants showed increased activation of both frontal region structures and caudate nucleus during a planning task requiring mnemonic abilities and production of motor responses (Owen et al., 1996), supporting the hypothesis that a disruption in projections linking the striatum to the frontal cortex might be, at least partially, responsible for motor deficits in Parkinson's disease.

Chapter 4 : Side effect of drugs

Medication therapy is often used as a partial solution in order to alleviate symptoms of psychiatric disorders. As briefly introduced, all the mentioned diseases might benefit the administration of a particular molecular composition likely to influence dopaminergic neurotransmission, stimulating it in the case of agonists, and inhibiting it in the case of antagonists. However, the problematic implication of these treatment drugs concerns the specificity in the choice of target: their action involves multiple dopaminergic circuits, ruling out the possibility of selectively activating or inhibiting a specific pathway.

4.1 Dopamine Agonists

Treatment involving the use of agonist medications, enhancing dopaminergic neurotransmission, as in the case of Parkinson's disease, have been linked to the risk of developing a range of symptomatology commonly associated with excessive dopaminergic levels. Many are the reports of cases involving behavioral abnormalities following dopaminergic enhancing treatment, for instance, a study involving patients with Parkinson's disease revealed a tendency to meet the diagnostic criteria for an impulse control disorder (ICD) among those receiving dopamine agonists medications (Weintraub et al., 2006). The most common symptoms to emerge is compulsive gambling, but additional ordinary manifestations include hypersexuality, drug use, compulsive shopping, binge-eating, and, in extreme cases, the development of psychotic features, including hallucinations and delusional thinking. The implication of environmental and personal features, such as an impulsive personality and sensation seeking traits, as well as genetic factors, are largely suspected to contribute to the development of these symptoms. However, the use of dopamine agonists is per se a sufficient risk factor.

4.2 Dopamine Antagonists

In the case of dopamine antagonists, drugs inhibiting dopaminergic neurotransmission, the opposite reaction emerges: extrapyramidal side effects often originate leading to drug-induced parkinsonism (DIP). The most common symptoms are tremors and tardive dyskinesia (i.e. slowness in movement), exactly as those exhibited in Parkinson's disease, sometimes contributing to the wrong diagnostic evaluation due to the

misattribution of overlapping symptomatology. What is induced in DIP, however, seems to concern majorly changes in the motor circuit of the basal ganglia following a persistent dopaminergic receptor blockade, not involving dopaminergic depletion in the substantia nigra and striatum, as in the case of PD. The present distinction is the essential differentiation allowing the precise diagnostic assessment. Further reactions of these inhibitory medications might involve weight gain, sedation and hyperprolactinemia (i.e. increased prolactin release) by under-activating the Tuberoinfundibular pathway, possibly causing breast enlargement, galactorrhea, reduced libido and erectile dysfunction.

The most common cause of parkinson-like symptoms is attributed to antipsychotic medications, although they are especially effective in the relief and prevention of relapse of psychotic symptoms, therefore, commonly prescribed when these symptoms are experienced.

Generally speaking, side effects are likely to contribute to poor adherence to the treatment, resulting in a worsening of the initial symptoms related to the pathology. In both cases a preventive approach should be followed: analysis of external factors and characteristics likely to increase the risk for side effects should be assessed, and a unique individual-based dosage should be implemented. Medication reduction strategies and psychotherapy are also highly recommended in case disturbances persist.

Side effects of agonists and antagonists highlight, once again, the complexity and functional broadness of the dopaminergic circuits.

Conclusion

Dopamine is clearly not the only factor to be considered when thinking about the functioning of an individual: an uncountable number of variables are involved in profoundly influencing one's existence. Each of us is differently shaped by personal history and experiences lived, personality traits and unique personal characteristics, biology in all its complexity (e.g. genetics, functioning, structural abnormalities, ecc.), which actively interact with innate and acquired risk and preventive factors for the development of psychopathologies. The specific combination of these countless variables is hard to predict, and it is what distinguishes each individual in a unique and exceptional way from others, contributing to the onset and progression of pathologies.

Even though biology is just a tiny piece of the puzzle, it, nevertheless, deserves the recognition and appreciation of the role it plays; we can attribute a considerable importance to the role of this molecule, among others, in the correct functioning of each individual. Historical discussions, disagreements, the multiple views and proposed explanations of dopamine's mechanisms highlight the complexity of this system, entailing essential structures functionally interconnected in highly specific and adaptive ways, and distributed among spread-out pathways throughout all the brain surface, reaching a multitude of regions involved in different functional aspects of living.

Since its discovery, dopamine has correctly been associated with the functioning of brain reward. Although the discussion on the exact role and mechanism of action of this molecule in relation to rewarding properties and/or reward prediction is still open, the awareness of its role in other domains is well established. In many cases, however, the precise operational mechanisms are still partially to be defined. Experiences shaped by dopaminergic activation are learnt, stored in long-term memory and retrieved to mediate goal-directed behavior. It is, therefore, undeniable the contribution of stimulus-reward association to increase the likelihood of instrumental behavior, by possessing these crucial motivational properties. Many dopaminergic mechanisms are thought to shape motivational properties: the establishment of incentive-motivational value of stimuli during initial conditioning, dopamine's responsibility for salience attribution impacting future orientation of attention, its role in maximizing resources, and its contribution in the coordination of various cognitive functions (impulse control, behavioral inhibition, and evaluation of effort-linked activities). Its well-established implication in motor

activities and motor functioning not only represents the energetic aspect of motivated behavior, but it also links neurodegenerative pathologies to its mechanisms of action.

Indeed, any abnormality in its mechanisms of action clearly has an effect on behavior resulting in atypical conduct, and most likely in the development of pathologies. Irregularities might comprehend a variety of dimensions: overactivation, underactivation, dysfunction in degradation, secretion, synthesis, availability problems, ecc. There are innumerable combinations where these systems can fail to provide necessary and sufficient amounts of this chemical. Any irregularity can give rise to mental conditions, among which we can find Substance-Related Disorders, Schizophrenia, Attention-Deficit Hyperactivity Disorder, and Parkinson's Disease, as the most common to involve dopaminergic deficits. Substance-Related Disorders and Schizophrenia exhibit hyperactivity of dopaminergic mesolimbic circuit, and hypofrontality generating cognitive inaccuracies. The latter is displayed in ADHD patients as well, combined with a decreased functioning of other dopaminergic systems, while, PD involves a disruption of dopaminergic cells mainly concerning the Nigrostriatal pathway. Future research should take into account a possible dysfunctional role of dopamine in a variety of other conditions, among which we can find Bipolar Disorder and Autism Spectrum Disorders, involving cognitive oddities potentially affected by dopaminergic's performance.

Dopamine research has, indeed, had a great impact in the clinical and therapeutic implications for the psychiatric field. However, despite the recent advances made in research on the topic, we must be aware of the limitations of the current literature. The advances achieved must be attributed mainly to the range of new neurochemical and pharmacological tools for the study of single neurons and their function, and experiments on animal models allowing to assess uncommon behaviors under different conditions. Even though credits must be acknowledged to them, these methods are far from complete; new techniques in neuroscience are promising, but further refinement needs to be achieved. Animal research is often time-consuming, expensive and hard to unequivocally generalize. We must be careful to extrapolate conclusions to apply to human beings, based on animal models. Iminent research should focus on methods to test on individuals the same hypotheses proved to be true on animals, both ensuring to correctly follow ethical guidelines. Although not perfect, animal research and animal

models provide a fundamental contribution in the generation of insight and knowledge about neurochemicals' means of working.

Another key limitation is the multitude of models prevalent in most domains of dopamine research. Confusion about the accuracy and precision of each hypothesis is prevalent, and a general consensus is far from achieved. However, these various speculations all contribute to the establishment of paradigms supplying models and motivating towards further investigation.

In my personal opinion, the biggest limitation concerns the use of medications: as seen with agonist and antagonist medications, normalizing dopaminergic functioning can benefit those circuits which are suffering from under- or overstimulation. The challenge here is to be able to refine a treatment method able to selectively involve a specific circuit, without necessarily implicating the others. I fully believe, research should strongly focus on the improvement of current methods and the development of alternative techniques able to implement this partial activation. Pharmacological solutions could be elaborate and refined, but innovative methods are arising as well, potentially opening new trajectories towards this achievement. Advances in the genetic field are promising: optogenetics is a recent technique in which genetic information concerning a specific neuronal population is modified in order to track its activation by means of light stimuli. Through this one, and other procedures, future empirical work will allow to precisely localize a given activation, test it under multiple conditions, and clarify the biological and molecular mechanisms involved with this and other neurotransmitters. The knowledge acquired from these observations will be fundamental for a better comprehension of disorders, and likely to generate therapeutic insight to reverse, cure or at least relieve symptoms of these conditions, with the aim of improving patients' quality of life.

As we have seen, the dopaminergic picture is far more wide than it seems. Albeit, this molecule only represents a tiny portion of the immense neuronal population in the Central Nervous System, through its spread transmission, functional implication and broad modes of activation has been proven to deeply affect an individual's functioning, profoundly shape human's existence and, possibly, change its course of evolution.

Bibliography

Albanese, A., Altavista, M. C., & Rossi, P. (1986). Organization of central nervous system dopaminergic pathways. Journal of neural transmission. Supplementum, 22, 3–17.

Amalric, M., Berhow, M., Polis, I., & Koob, G. F. (1993). Selective effects of low-dose D2 dopamine receptor antagonism in a reaction-time task in rats. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 8(3), 195–200. https://doi.org/10.1038/npp.1993.21

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

American Psychological Association. (n.d.). Apa Dictionary of Psychology. American Psychological Association. Retrieved April 24, 2023, from https://dictionary.apa.org/anhedonia

Anden, N. E., Carlsson, A., Dahlstroem, A., Fuxe, K., Hillarp, N. A., & Larsson, K. (1964). Demonstration and mapping out of Nigro-neostriatal dopamine neurons. Life sciences (1962), 3, 523–530. https://doi.org/10.1016/0024-3205(64)90161-4

Angrist, B., & Van Kammen, D. (1984). CNS stimulants as tools in the study of schizophrenia. Trends in Neurosciences, 7(10), 388–390. https://doi.org/10.1016/s0166-2236(84)80062-4

Apicella, P., Scarnati, E., Ljungberg, T., & Schultz, W. (1992). Neuronal activity in monkey striatum related to the expectation of predictable environmental events. Journal of neurophysiology, 68(3), 945–960. https://doi.org/10.1152/jn.1992.68.3.945

Arnsten A. F. (2006). Stimulants: Therapeutic actions in ADHD. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 31(11), 2376–2383. https://doi.org/10.1038/sj.npp.1301164

Baik J. H. (2013). Dopamine signaling in food addiction: role of dopamine D2 receptors. BMB reports, 46(11), 519–526. https://doi.org/10.5483/bmbrep.2013.46.11.207

Baunez, C., Nieoullon, A., & Amalric, M. (1995). Dopamine and complex sensorimotor integration: further studies in a conditioned motor task in the rat. Neuroscience, 65(2), 375–384. https://doi.org/10.1016/0306-4522(94)00498-t

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2020). Neuroscience: Exploring the brain. Jones & Bartlett Learning.

Bergh, C., Eklund, T., Södersten, P., & Nordin, C. (1997). Altered dopamine function in pathological gambling. Psychological medicine, 27(2), 473–475. https://doi.org/10.1017/s0033291796003789

Berridge, K. C., Venier, I. L., & Robinson, T. E. (1989). Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and anhedonia hypotheses of dopamine function. Behavioral neuroscience, 103(1), 36–45. https://doi.org/10.1037//0735-7044.103.1.36

Carlsson A. (1959). The occurrence, distribution and physiological role of catecholamines in the nervous system. Pharmacological reviews, 11(2, Part 2), 490–493.

Casey, B. J., Castellanos, F. X., Giedd, J. N., Marsh, W. L., Hamburger, S. D., Schubert, A. B., Vauss, Y. C., Vaituzis, A. C., Dickstein, D. P., Sarfatti, S. E., & Rapoport, J. L. (1997). Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 36(3), 374–383. https://doi.org/10.1097/00004583-199703000-00016

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nature reviews. Neuroscience, 3(8), 617–628. https://doi.org/10.1038/nrn896

Clark, L., Averbeck, B., Payer, D., Sescousse, G., Winstanley, C. A., & Xue, G. (2013). Pathological choice: the neuroscience of gambling and gambling addiction. The Journal of neuroscience : the official journal of the Society for Neuroscience, 33(45), 17617–17623. https://doi.org/10.1523/JNEUROSCI.3231-13.2013

Daubner, S. C., Le, T., & Wang, S. (2011). Tyrosine hydroxylase and regulation of dopamine synthesis. Archives of biochemistry and biophysics, 508(1), 1–12. https://doi.org/10.1016/j.abb.2010.12.017

De Wit, H., & Wise, R. A. (1977). Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine or phenoxybenzamine. Canadian journal of psychology, 31(4), 195–203. https://doi.org/10.1037/h0081662

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proceedings of the National Academy of Sciences of the United States of America, 85(14), 5274–5278. https://doi.org/10.1073/pnas.85.14.5274

Dingman, M. (2022). Your brain, explained: What neuroscience reveals about your brain and its quirks. Nicholas Brealey Publishing.

Dougherty, D. D., Bonab, A. A., Spencer, T. J., Rauch, S. L., Madras, B. K., & Fischman, A. J. (1999). Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet (London, England), 354(9196), 2132–2133. https://doi.org/10.1016/S0140-6736(99)04030-1

Fahn S. (2008). The history of dopamine and levodopa in the treatment of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society, 23 Suppl 3, S497–S508. https://doi.org/10.1002/mds.22028

Faraone, S. V., & Mick, E. (2010). Molecular genetics of attention deficit hyperactivity disorder. The Psychiatric clinics of North America, 33(1), 159–180. https://doi.org/10.1016/j.psc.2009.12.004

Fibiger H. C. (1978). Drugs and reinforcement mechanisms: a critical review of the catecholamine theory. Annual review of pharmacology and toxicology, 18, 37–56. https://doi.org/10.1146/annurev.pa.18.040178.000345

Fouriezos, G., Hansson, P., & Wise, R. A. (1978). Neuroleptic-induced attenuation of brain stimulation reward in rats. Journal of comparative and physiological psychology, 92(4), 661–671. https://doi.org/10.1037/h0077500

Freberg, L. A. (2019). Discovering behavioral neuroscience: An introduction to biological psychology. Cengage.

Frith, C. D., & Done, D. J. (1988). Towards a neuropsychology of schizophrenia. The British journal of psychiatry : the journal of mental science, 153, 437–443. https://doi.org/10.1192/bjp.153.4.437

Gallistel, C. R., Stellar, J. R., & Bubis, E. (1974). Parametric analysis of brain stimulation reward in the rat: I. The transient process and the memory-containing process. Journal of Comparative and Physiological Psychology, 87(5), 848–859. https://doi.org/10.1037/h0037220

Hooley, J. M., Butcher, J. N., Nock, M., & Mineka, S. (2018). Abnormal psychology. Pearson Education South Asia Pte Ltd.

Hornykiewicz O. (1966). Dopamine (3-hydroxytyramine) and brain function. Pharmacological reviews, 18(2), 925–964. In O. Hornykiewicz (Ed.), Dopamine and the functioning of extrapyramidal centers: special aspects (pp. 949-956).

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur, S. (2012). The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Archives of general psychiatry, 69(8), 776–786. https://doi.org/10.1001/archgenpsychiatry.2012.169

Hurley, M. J., & Jenner, P. (2006). What has been learnt from study of dopamine receptors in Parkinson's disease?. Pharmacology & therapeutics, 111(3), 715–728. https://doi.org/10.1016/j.pharmthera.2005.12.001. M. J. Hurley & P. Jenner (Eds.), *Introduction* (pp. 716).

Iversen, S. D., & Iversen, L. L. (2007). Dopamine: 50 years in perspective. Trends in neurosciences, 30(5), 188–193. https://doi.org/10.1016/j.tins.2007.03.002

Jensen, J., McIntosh, A. R., Crawley, A. P., Mikulis, D. J., Remington, G., & Kapur, S. (2003). Direct activation of the ventral striatum in anticipation of aversive stimuli. Neuron, 40(6), 1251–1257. https://doi.org/10.1016/s0896-6273(03)00724-4

Klein, M. O., Battagello, D. S., Cardoso, A. R., Hauser, D. N., Bittencourt, J. C., & Correa, R. G. (2019). Dopamine: Functions, Signaling, and Association with Neurological Diseases. Cellular and molecular neurobiology, 39(1), 31–59. https://doi.org/10.1007/s10571-018-0632-3

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport, 12(17), 3683–3687. https://doi.org/10.1097/00001756-200112040-00016

Laruelle, M., Abi-Dargham, A., van Dyck, C. H., Rosenblatt, W., Zea-Ponce, Y., Zoghbi, S. S., Baldwin, R. M., Charney, D. S., Hoffer, P. B., & Kung, H. F. (1995).

SPECT imaging of striatal dopamine release after amphetamine challenge. Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 36(7), 1182–1190.

Levy, F., & Swanson, J. M. (2001). Timing, space and ADHD: the dopamine theory revisited. The Australian and New Zealand journal of psychiatry, 35(4), 504–511. https://doi.org/10.1046/j.1440-1614.2001.00923.x

Lieberman, D. Z. (2019). The molecule of more: How a single Chemical in your brain drives love, sex and creativity - and will determine the fate of the human race. BenBella Books.

Liddle, P. F., Friston, K. J., Frith, C. D., Hirsch, S. R., Jones, T., & Frackowiak, R. S. (1992). Patterns of cerebral blood flow in schizophrenia. The British journal of psychiatry : the journal of mental science, 160, 179–186. https://doi.org/10.1192/bjp.160.2.179

Meyer-Lindenberg, A., Miletich, R. S., Kohn, P. D., Esposito, G., Carson, R. E., Quarantelli, M., Weinberger, D. R., & Berman, K. F. (2002). Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nature neuroscience, 5(3), 267–271. https://doi.org/10.1038/nn804

Mogenson, G. J., Jones, D. L., & Yim, C. Y. (1980). From motivation to action: functional interface between the limbic system and the motor system. Progress in neurobiology, 14(2-3), 69–97. https://doi.org/10.1016/0301-0082(80)90018-0

Negus, S. S., Selley, D. E., & Sim-Selley, L. J. (1970, January 1). Pharmacodynamic tolerance. SpringerLink. https://link.springer.com/referenceworkentry/10.1007/978-3-540-68706-1_272

Nieoullon A. (2002). Dopamine and the regulation of cognition and attention. Progress in neurobiology, 67(1), 53–83. https://doi.org/10.1016/s0301-0082(02)00011-4

Nieoullon, A., & Coquerel, A. (2003). Dopamine: a key regulator to adapt action, emotion, motivation and cognition. Current opinion in neurology, 16 Suppl 2, S3–S9.

Nummenmaa, L., Seppälä, K., & Putkinen, V. (2020). Molecular imaging of the human emotion circuit.

O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural responses during anticipation of a primary taste reward. Neuron, 33(5), 815–826. https://doi.org/10.1016/s0896-6273(02)00603-7

O'Sullivan, S. S., Evans, A. H., & Lees, A. J. (2009). Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. CNS drugs, 23(2), 157–170. https://doi.org/10.2165/00023210-200923020-00005

Olds, J. (1956). Pleasure Centers in the Brain. Scientific American, 195(4), 105–117. http://www.jstor.org/stable/24941787

Otmakhova, N. A., & Lisman, J. E. (1998). D1/D5 dopamine receptors inhibit depotentiation at CA1 synapses via cAMP-dependent mechanism. The Journal of neuroscience : the official journal of the Society for Neuroscience, 18(4), 1270–1279. https://doi.org/10.1523/JNEUROSCI.18-04-01270.1998

Owen, A. M., Doyon, J., Petrides, M., & Evans, A. C. (1996). Planning and spatial working memory: a positron emission tomography study in humans. The European journal of neuroscience, 8(2), 353–364. https://doi.org/10.1111/j.1460-9568.1996.tb01219.x

Owen, M. J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. Lancet (London, England), 388(10039), 86–97. https://doi.org/10.1016/S0140-6736(15)01121-6

Phan, K. L., Taylor, S. F., Welsh, R. C., Ho, S. H., Britton, J. C., & Liberzon, I. (2004). Neural correlates of individual ratings of emotional salience: a trial-related fMRI study. NeuroImage, 21(2), 768–780. https://doi.org/10.1016/j.neuroimage.2003.09.072

Pietrzykowski, A. Z., & Treistman, S. N. (2008). The molecular basis of tolerance. Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism, 31(4), 298–309.

Robbins, S. J., Ehrman, R. N., Childress, A. R., Cornish, J. W., & O'Brien, C. (2000). Mood state and recent cocaine use are not associated with levels of cocaine cue reactivity. Drug and Alcohol Dependence, 59(1), 33–42. https://doi.org/10.1016/s0376-8716(99)00103-9

Robinson, T. E., & Berridge, K. C. (2000). The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction (Abingdon, England), 95 Suppl 2, S91–S117. https://doi.org/10.1080/09652140050111681

Robinson, T. E., & Berridge, K. C. (2003). Addiction. Annual review of psychology, 54, 25–53. https://doi.org/10.1146/annurev.psych.54.101601.145237

Salamone, J. D., & Correa, M. (2002). Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. Behavioural brain research, 137(1-2), 3–25. https://doi.org/10.1016/s0166-4328(02)00282-6

Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology, 191(3), 461–482. https://doi.org/10.1007/s00213-006-0668-9

Salamone, J. D., Steinpreis, R. E., McCullough, L. D., Smith, P., Grebel, D., & Mahan, K. (1991). Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. Psychopharmacology, 104(4), 515–521. https://doi.org/10.1007/BF02245659

Seeman, P., Weinshenker, D., Quirion, R., Srivastava, L. K., Bhardwaj, S. K., Grandy, D. K., Premont, R. T., Sotnikova, T. D., Boksa, P., El-Ghundi, M., O'dowd, B. F., George, S. R., Perreault, M. L., Männistö, P. T., Robinson, S., Palmiter, R. D., & Tallerico, T. (2005). Dopamine supersensitivity correlates with D2High states, implying many paths to psychosis. Proceedings of the National Academy of Sciences of the United States of America, 102(9), 3513–3518. https://doi.org/10.1073/pnas.0409766102

Schachar, R., & Logan, G. D. (1990). Impulsivity and inhibitory control in normal development and childhood psychopathology. Developmental Psychology, 26(5), 710–720. https://doi.org/10.1037/0012-1649.26.5.710

Schultz W. (2017). Reward prediction error. Current biology : CB, 27(10), R369–R371. https://doi.org/10.1016/j.cub.2017.02.064

Schultz, W., Apicella, P., Scarnati, E., & Ljungberg, T. (1992). Neuronal activity in monkey ventral striatum related to the expectation of reward. The Journal of neuroscience : the official journal of the Society for Neuroscience, 12(12), 4595–4610. https://doi.org/10.1523/JNEUROSCI.12-12-04595.1992

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. Science (New York, N.Y.), 275(5306), 1593–1599. https://doi.org/10.1126/science.275.5306.1593

Shin, H. W., & Chung, S. J. (2012). Drug-induced parkinsonism. Journal of clinical neurology (Seoul, Korea), 8(1), 15–21. https://doi.org/10.3988/jcn.2012.8.1.15

Silbersweig, D. A., Stern, E., Frith, C., Cahill, C., Holmes, A., Grootoonk, S., Seaward, J., McKenna, P., Chua, S. E., & Schnorr, L. (1995). A functional neuroanatomy of hallucinations in schizophrenia. Nature, 378(6553), 176–179. https://doi.org/10.1038/378176a0

Smith, G. P., Storhmayer, A. J., & Reis, D. J. (1972). Effect of lateral hypothalamic injections of 6-hydroxydopamine on food and water intake in rats. Nature: New biology, 235(53), 27–29. https://doi.org/10.1038/newbio235027a0

Solanto, M. V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G. D., Wigal, T., Hechtman, L., Hinshaw, S., & Turkel, E. (2001). The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. Journal of abnormal child psychology, 29(3), 215–228. https://doi.org/10.1023/a:1010329714819

Sonuga-Barke, E. J., Taylor, E., Sembi, S., & Smith, J. (1992). Hyperactivity and delay aversion--I. The effect of delay on choice. Journal of child psychology and psychiatry, and allied disciplines, 33(2), 387–398. https://doi.org/10.1111/j.1469-7610.1992.tb00874.x

Tassin, J., Stinus, L., Simon, H., Blanc, G., Thierry, A., Moal, M. L., Cardo, B., & Glowinski, J. (1978). Relationship between the locomotor hyperactivity induced by A10 lesions and the destruction of the frontocortical dopaminergic innervation in the rat. Brain Research, 141(2), 267–281. https://doi.org/10.1016/0006-8993(78)90197-x

Ungerstedt U. (1971). Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta physiologica Scandinavica. Supplementum, 367, 95–122. https://doi.org/10.1111/j.1365-201x.1971.tb11001.x

Viallet, F., Trouche, E., Nieoullon, A., Beaubaton, D., & Legallet, E. (1984). Unilateral electrolytic and 6-ohda lesions of the substantia nigra in baboons: Behavioural and Biochemical Data. Advances in Behavioral Biology, 373–391. https://doi.org/10.1007/978-1-4684-1212-3_19

Volkow, N. D., Fowler, J. S., Wang, G. J., Swanson, J. M., & Telang, F. (2007). Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Archives of neurology, 64(11), 1575–1579. https://doi.org/10.1001/archneur.64.11.1575

Walton, M. E., Bannerman, D. M., Alterescu, K., & Rushworth, M. F. (2003). Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. The Journal of neuroscience : the official journal of the Society for Neuroscience, 23(16), 6475–6479. https://doi.org/10.1523/JNEUROSCI.23-16-06475.2003

Weintraub, D., Siderowf, A. D., Potenza, M. N., Goveas, J., Morales, K. H., Duda, J. E., Moberg, P. J., & Stern, M. B. (2006). Association of dopamine agonist use with impulse control disorders in Parkinson disease. Archives of neurology, 63(7), 969–973. https://doi.org/10.1001/archneur.63.7.969

Wise, R. A. (1982). Neuroleptics and operant behavior: The anhedonia hypothesis. Behavioral and Brain Sciences, 5(1), 39–53. https://doi.org/10.1017/s0140525x00010372

Wise, R. A. (2004). Dopamine, learning and motivation. Nature reviews. Neuroscience, 5(6), 483–494. https://doi.org/10.1038/nrn1406

Wise, R. A. (2008). Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotoxicity research, 14(2-3), 169–183. https://doi.org/10.1007/BF03033808

Wise, R. A., & Schwartz, H. V. (1981). Pimozide attenuates acquisition of lever-pressing for food in rats. Pharmacology, biochemistry, and behavior, 15(4), 655–656. https://doi.org/10.1016/0091-3057(81)90225-2

Wise, R. A., Spindler, J., deWit, H., & Gerberg, G. J. (1978). Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food. Science (New York, N.Y.), 201(4352), 262–264. https://doi.org/10.1126/science.566469

Wise, R. A., & Robble, M. A. (2020). Dopamine and Addiction. Annual review of psychology, 71, 79–106. https://doi.org/10.1146/annurev-psych-010418-103337

Attachments

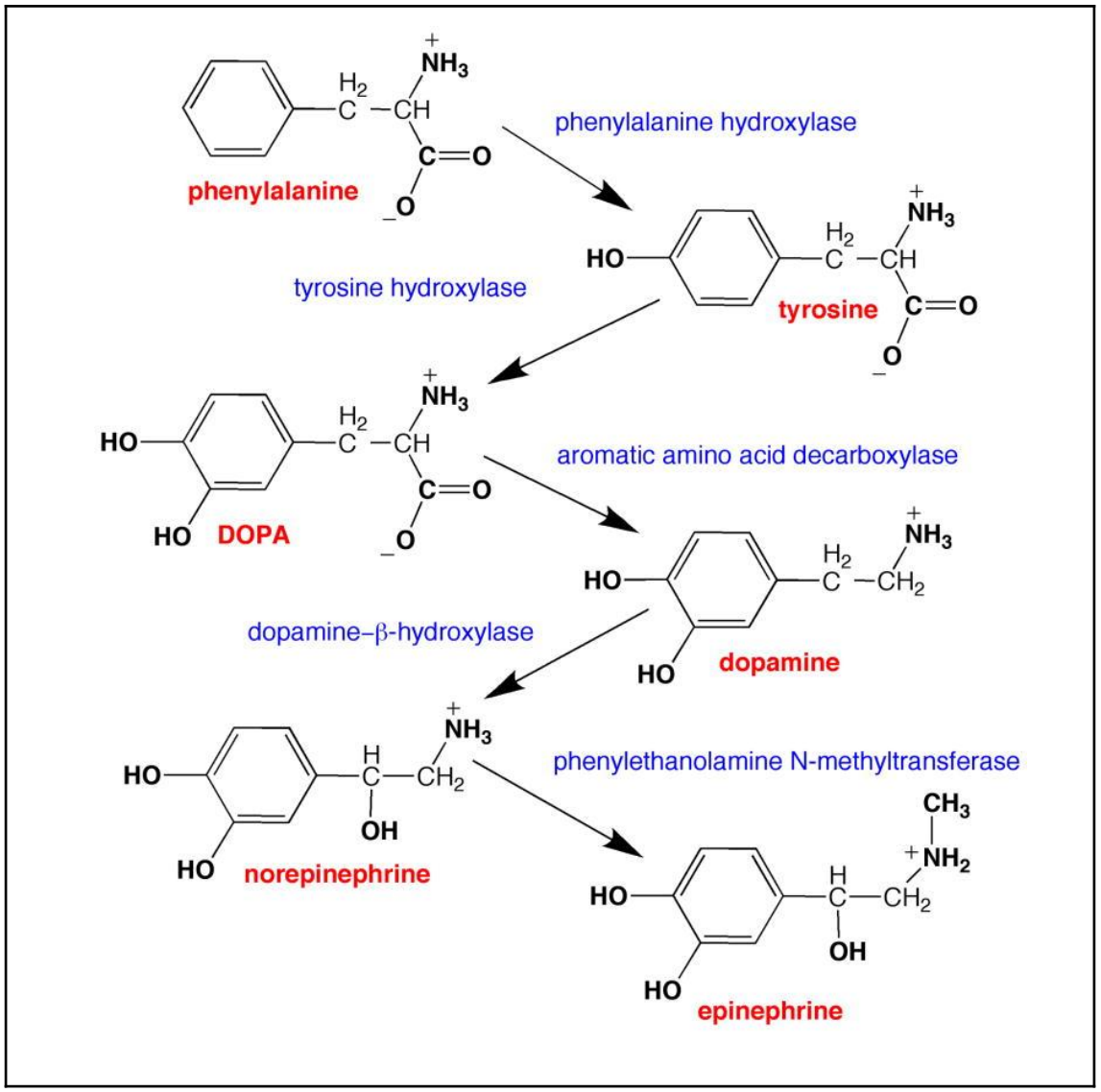

Figure 1.

The pathway for catecholamine neurotransmitters, starting from Phenylalanine, converted by phenylalanine hydroxylase into tyrosine, further transformed by tyrosine hydroxylase (TH) in L-dopa. Dopa decarboxylase is responsible for the subsequent conversion of L-dopa into Dopamine (DA) and dopamine-β-hydroxylase hydroxylates transforms dopamine to norepinephrine, methylated to epinephrine by phenylethanolamine N-methyltransferase.

Retrieved from: Daubner et al., 2011

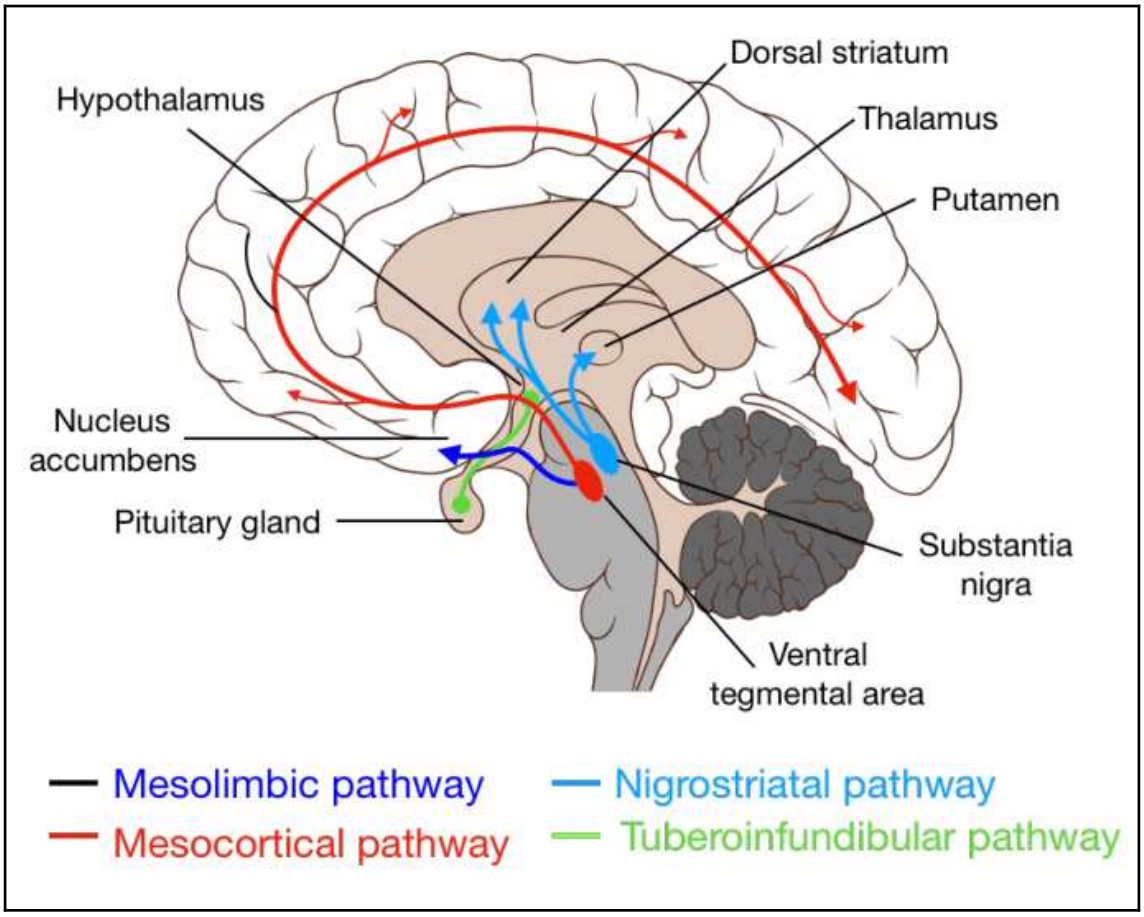

Figure 2.

Four of the main dopaminergic pathways in the brain: the Mesostriatal, the Mesolimbic, the Mesocortical, and the Tuberoinfundibular pathways.

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