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Suicide in Parkinson's disease: The role of dopamine deficiency

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Abstract

Parkinson's disease is the second most common neurodegenerative disease markedly lowering the quality of life. Suicidal ideation is elevated in Parkinson's disease, and affected patients may be at the higher risk for suicide, especially after Deep Brain Stimulation (DBS). Lower quality of life does not show to be enough to explain this increased risk for suicidality. A number of major risk factors for suicide overlap with some of the most common non-motor symptoms preceding or accompanying Parkinson's disease. This thesis explores these overlapping factors - notably depression, impulsivity, problems with executive function, and an unbalanced HPA axis - and demonstrates that dopamine is an essential part of the mechanisms in each of the forementioned factors. Thus, dopamine plays a crucial role in suicide in Parkinson's disease, and possibly among other populations as well.

Introduction

Suicide is one of the leading causes of mortality in the world – it is constantly listed among the top 15 causes of death globally; in Italy, it is the 12th leading cause of death, with more than 4000 people losing their lives to suicide every year (Ritchie et al., 2015). Age-wise, the older population is at the highest risk of suicide (Ritchie et al., 2015). Death by suicide is extremely complex. It includes a wide range of risk and protective factors that interact with the personal vulnerability for suicidal behavior. In some populations, such as among patients diagnosed with certain psychiatric disorders like mood disorders, substance use disorders, personality disorders, or psychosis, the rate of suicide is peculiarly high (O'Connor & Nock, 2014; Turecki et al., 2019). Another group of patients especially vulnerable to suicide are patients diagnosed with neurodegenerative disorders, such as Parkinson's disease (PD) (Erlangsen et al., 2020).

Parkinson's disease is a progressive neurodegenerative disease essentially affecting the basal ganglia and causing motor impairments that mainly manifest as bradykinesia, rigidity, tremor, and postural imbalance (PD). It is the second most common neurodegenerative disease primarily affecting the older population (over the age of 60), although cases of early onset (around the age of 40 and even earlier) are also present (Balestrino & Schapira, 2020). Besides motor impairment, a wide range of non-motor symptoms accompanying and even preceding the motor symptoms is also present, markedly lowering the quality of life of PD patients, sometimes even more than motor impairment itself (Chaudhuri et al., 2011).

Suicidal ideation is significantly increased in patients with PD, with many studies demonstrating that suicide rates among this population are also elevated (Chen et al., 2021; Lee et al., 2016). Part

of the reason behind increased suicidality is a significantly lower quality of life that stems from both motor and non-motor symptoms. However, lowered quality of life is not enough to explain increased suicidality in PD patients. For example, increased suicide rates among PD patients are reported after patients are put on DA medication such as L-dopa, and especially after surgical treatment for PD such as deep brain stimulation (DBS), after motor symptoms are drastically improved and the quality of life should be substantially enhanced (Du et al., 2020; Giannini et al., 2019). The majority of the most common risk factors for suicide overlap with the most common non-motor symptoms of PD. Some of these non-motor symptoms, as previously mentioned, emerge well before the first onset of motor symptoms and the diagnosis of PD and before the quality of life is significantly diminished. Thus, some other factors besides the lower quality of life are at play when it comes to elevated suicidal ideation and suicidal behavior in PD patients. Interestingly, dopamine alterations are underlying the overlapping factors between suicide and PD. Thus, the hypothesis is that dopamine (and its alterations in both directions – deficit and excess) plays a crucial role in suicide in PD. Furthermore, through the lens of PD, we may be able to understand possible crucial mechanisms dopamine plays in suicide in general, which may improve risk estimation and suicide prevention both in PD patients and in other populations.

In this thesis, the overlap between risk factors for suicide and non-motor symptoms of PD, all of which have an underlying dopamine mechanism influencing them, will be explored. Firstly, a general overview of suicide will be given, with some terminological clarifications provided, as will be used in this thesis. Secondly, the most common risk factors for suicidal behavior and suicide will be explored, bounded into two relevant groups: psychiatric disorders and neurocognitive factors. Furthermore, the neurobiology of suicide will be discussed, with an emphasis on the role of neurotransmitters (serotonin, norepinephrine, and especially dopamine) and hypothalamic-

pituitary-adrenal axis (HPA axis). This will be followed by a chapter about Parkinson's disease – its clinical manifestations, pathophysiology, treatment, and, most importantly, the most common non-motor symptoms preceding or accompanying PD. Lastly, research on suicide in PD will be presented, including a discussion about the possible underlying mechanisms that lead to it, with a special focus on the dopaminergic system that contributes to it.

To set the ground for understanding the main notions and arguments throughout this thesis, three main concepts will be presented as part of this introduction: A) *The Diathesis-stress model,* that should provide the framework of thinking about suicidality and, feasibly, PD as well; B) *General overview of the dopaminergic system,* since it will pervade throughout each following chapter; and C) *Functional anatomy of the basal ganglia,* aiming to help in understanding the pathophysiology of PD and the rationale behind its treatment, which will be an important part of the discussion about suicide in PD.

No research so far has encompassed both risk factors for suicide in general and common non-motor symptoms of PD to explain suicidality in PD through the role of dopamine. The goal of this thesis is to provide a new perspective on suicide and the role of dopamine in it, hopefully inspiring future research and informing clinical practice and so contribute to a better suicide risk assessment, interventions, and prevention of suicide in PD patients.

A) Diathesis-stress model

Mann (1999) proposed a diathesis-stress model of suicide, that is now widely accepted and most commonly used as a theoretical framework and explanatory model of suicidal behavior. According to Mann's diathesis-stress model, suicidal behavior is a result of an interaction between a *diathesis* – a predisposition for suicidal behavior – and a *stressor*, which is a trigger for suicidal behavior. As it is often observed in individuals who experience suicidal thoughts or engage in suicidal behavior, stress is frequently a trigger that precedes such events (Brodsky & Mann, 2002). However, not all levels of stress will have the same impact on all individuals; in other words, not all people will develop suicidal thoughts or engage in suicidal behaviors, even when exposed to extreme levels of stress. The difference between individuals who develop and who do not develop suicidal behavior when encounter different levels of stress is explained by the diathesis-stress model of suicidality - there are some predisposing factors in individuals (diathesis) that create vulnerability for developing suicidal behaviors when stress occurs. Such predisposing factors have an additive effect and interact with each other, and can also contribute to the appearance of precipitating factors (van Heeringen, 2012). Some factors that comprise diathesis include genetics, early life adversity, personality traits, cognitive deficits, etc. (Turecki et al., 2019). Stressors or precipitating factors that act as triggers for suicidal behavior are considered state-related, and may include current psychiatric disorders such as depression, schizophrenia, or bipolar disorder, acute substance intoxication, personal stressors (familial, social, financial), etc. (Turecki et al., 2019). For example, although the majority of suicides are done by people diagnosed with a depressive episode, the majority of people who suffer from depression never attempt nor complete suicide.

Thus, what differentiates depressed individuals who attempt suicide from those who don't is their diathesis to suicidal behavior. Van Heeringen (2012) summarizes it: "If the diathesis is absent, there is no effect of stress so that even severe stress will not lead to the development of the disorder. When the diathesis is present, the expression of the disorder will be conditional on the degree of stress: as stress increases so does the risk for the disorder in persons who possess the diathesis".

B) An overview of the dopaminergic system

Dopamine is a catecholamine (a family of molecules that also includes epinephrine and norepinephrine) that has a modulatory role in the central nervous system. It is involved in a number of important functions such as, broadly speaking, voluntary movement, reward and pleasure, motivation, and executive functions, as well as some lower-level functions such as lactation and nausea. There are around 400,000 dopaminergic neurons in the central nervous system, with their bodies located mainly in two important nuclei – ventral tegmental area (VTA) and substantia nigra – and their axons projecting vastly throughout many areas of the brain. Dopamine is operating through four major dopaminergic pathways in the central nervous system, each of them having a relatively distinctive structure and functions. Those are: nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathways.

The nigrostriatal pathway contains the largest proportion of dopamine in the central nervous system. This pathway is comprised of basal ganglia projections that go from the substantia nigra to the dorsal striatum. Substantia nigra is a nucleus located in the ventral mesencephalon,

and got its name thanks to its dark color that comes from high levels of neuromelanin, a pigment produced by dopamine neurons located in this area. Substantia nigra consists of two parts – pars compacta and pars reticulata. Dopamine in this pathway is mainly produced in *pars compacta*, where dopaminergic neurons are densely packed and send projections to the striatum, supplying it with dopamine. Degeneration of dopaminergic neurons in this area is the ruling pathology underlying Parkinson's disease, and will be discussed in more detail in the next chapter. Caudate nucleus and putamen of the dorsal striatum, one of the main input areas of the basal ganglia, receive signals from substantia nigra pars compacta (as well as from thalamus and cerebral cortex) and further send signals through direct and indirect pathways to the motor cortex. Thus, nigrostriatal pathway is mainly involved in motor planning and voluntary movement. It is responsible for the coordination of movement by initiating action and, at the same time, inhibiting opposing or unnecessary movement, producing a smooth, fluid, purposeful motion as a result (Iversen et al., 2009). Additionally, along with further elaborated mesolimbic and mesocortical dopamine pathways, nigrostriatal pathway is also, in part, involved in cognition, motivation, and reward systems (Wise, 2009).

The mesolimbic pathway is the major dopamine pathway associated with the most common thought-of function when it comes to dopamine – pleasure and reward. Mesolimbic pathway begins in the Ventral tegmental area (VTA) of the midbrain, another principal dopamine-producing area, and sends its projections to the nucleus accumbens, the major component of the ventral striatum. The VTA region is also the origin of dopaminergic projections to other structures in the brain, particularly the hippocampus, cingulate gyrus, amygdala, and the olfactory bulb. The most prominent and most widely studied function of the mesolimbic pathway is its role in the reward system. Mesolimbic pathway is associated with (mutually intertwined) reward, motivation, and

pleasure. Most simply put, this pathway has been thought to regulate dopamine release in response to rewarding stimuli or anticipation of rewarding stimuli, thus reinforcing reward-seeking behavior (Klein et al., 2019).

Another dopaminergic pathway considered to be an integral part of the reward system is the mesocortical pathway. Mesocortical pathway also begins in the VTA but projects to the cerebral cortex, more precisely, frontal cortices, including prefrontal, orbitofrontal, and cingulate cortices, as well as sensory and motor cortices. Mesocortical pathway is involved in a wide range of functions that extensively overlap with mesolimbic pathway, of which the most prominent is the reward processing. Since VTA projects, among other areas in the cerebral cortex, to frontal cortices, which are responsible for emotion processing and cognition, this pathway is involved in motivation-driven goal-oriented behavior, decision-making, learning, and executive functions. Together, mesolimbic and mesocortical pathways form a so-called mesocorticolimbic system (Klein et al., 2019).

Alterations in the mesocorticolimbic system are heavily involved in the pathophysiology of addiction, attention deficit hyperactivity disorder (ADHD), positive (mesolimbic pathway) and negative (mesocortical pathway) symptoms of schizophrenia, and depression, as well as in determination of some personality traits, including sensation seeking, extraversion, and impulsivity (Alcaro et al., 2007). Although the activity of DA neurons from VTA (and also, in part, from substantia nigra), has long been believed to correlate with pleasure and approach-oriented behavior, the picture is far more complex. Numerous studies pointed toward reasoning that the role of dopamine, when it comes to reward, is wider than regulating positive reward-related experiences, and that it, instead, has a broader function that could be described as encoding

motivation-related stimuli, either positive or negative, and regulating both appetite-motivated as well as aversion-avoiding behaviors. This conclusion has been drawn from different studies which demonstrated that dopamine levels don't change only during rewarding experiences, but also in situations where experiencing something estimated either positive or negative, as well as in exposure to the aversive stimuli (Verharen et al., 2020). For example, in studies that involved reward prediction error (RPE), which is the difference between expected reward and obtained reward, the activity levels of dopamine neurons consistently correlated with RPE. Thus, when the received reward was greater than the expected, there was an increase in firing of dopamine neurons, whereas when the expected and received reward were the same, the rate of DA neurons firing remained the same. When the obtained reward was smaller compared to the predicted reward, as well as when the organism unexpectedly faced an aversive stimulus, DA neurons firing was decreased. Interestingly, the rate of DA neurons firing did not decrease when an expected punishment was received, but instead, stayed the same (Schultz, 2016). Other studies show how DA levels may even increase in certain areas of the brain in response to exposure to aversive stimuli (Brooks & Berns, 2013). Thus, dopamine signaling is involved in encoding information about environmental stimuli associated with positive and negative experiences, hence helping the brain learn and direct behavior to maximize the chances of obtaining a reward and avoiding aversive experience.

Finally, the fourth distinctive dopaminergic pathway is called the tuberoinfundibular pathway. It starts in the arcuate and periventricular nuclei of the hypothalamus, and projects to the median eminence of the hypothalamus. Here, dopamine is produced by neurons in the arcuate nucleus and released into the hypophyseal portal system, an area that connects the hypothalamus with the pituitary gland, to influence the release of hormones from the anterior pituitary. The main

function of dopamine in tuberoinfundibular pathway is the inhibition of prolactin release. This is why one of the side effects of some antipsychotics may be hyperprolactinemia that can manifest as gynecomastia – the lower amount of dopamine as an effect of antipsychotics may not be able to inhibit prolactin production (Iversen et al., 2009).

Chemically, dopamine is produced from L-phenylalanine, which is converted into L-tyrosine by the enzyme called phenylalanine hydroxylase. Then, L-tyrosine is converted into L-DOPA, the main precursor of dopamine, by the enzyme tyrosine hydroxylase. Finally, L-DOPA gets converted into dopamine by the enzyme aromatic L-amino acid decarboxylase. Dopamine is present in food, as well as in our bodies. However, to operate in the CNS, dopamine has to be produced in the brain because it cannot be absorbed from the bloodstream since its molecules are too big to pass the blood-brain barrier. This is why medication for Parkinson's disease that is used to increase the levels of dopamine in the brain, contain L-dopa, which is small enough to pass the blood-brain barrier and then gets converted into dopamine once it reaches the brain (Iversen et al., 2009).

Dopamine exerts action upon binding to its G protein-coupled receptors. There are five types of them – D1, D2, D3, D4, D5 – which are subdivided into two groups – D1-like and D2-like - based on their function. The effect of the activation of D1-like family of dopamine receptors (D1 and D5) can be excitatory or inhibitory. On the other hand, dopamine binding onto receptors in D2-like family (D2, D3, D4) has an inhibitory effect. Most simply put, D1-like receptors activate the enzyme adenylate cyclase, thus increasing intracellular levels of cyclic adenosine monophosphate (cAMP), a derivate of adenosine triphosphate (ATP) and an important

intracellular second messenger. D2-like receptors inhibit adenylate cyclase, thus decreasing the levels of cAMP in the neuron (Ledonne & Mercuri, 2017).

Dopamine release into the synaptic vesicles has two "patterns" of activity – tonic and phasic release. Phasic dopamine release is activated by action potentials and it leads to a fast and transient increase in the amount of dopamine in the synaptic cleft. After binding to DA receptors, dopamine is quickly removed from the synaptic cleft by the reuptake mechanism. Phasic activation is often called "burst spike firing", and it is thought to be triggered by unexpected rewards or anticipation of a reward. However, dopamine can be released also without presynaptic action potentials, but instead, by other mechanisms such as neurotransmitter reuptake or certain metabolic processes in neurons. Such spontaneous-like dopamine release is lower in intensity, and it is called tonic release. The amount of extracellular dopamine depends on this kind of activity. It has been suggested that tonic activation may be related to learning related to avoiding aversive stimuli and obtaining rewards, since research showed a transient suppression of tonic firing in DA neurons in response to aversive stimuli or when an expected reward was not received (Goto et al., 2007).

Dopamine is broken down by enzymes monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT), and the final product is homovanillic acid (HVA), which is further removed from the body through kidneys and urine. HVA can be found in blood and cerebrospinal fluid. It is commonly used in research to measure the amount of dopamine in the system, and it is considered a potential biomarker for different neuropathologies. For example, it has been shown that the amounts of HVA in Parkinson's disease and Alzheimer's disease may be correlated with disease progression (Klein et al., 2019).

Dopamine is, as we can see, a modulatory neurotransmitter that plays an array of important roles in different processes of the brain, including movement, motivation, reward, cognition, learning… Thus, disruptions in dopaminergic pathways often comprise the hallmark of the pathophysiology of different neurological and psychiatric conditions, including depression, substance use disorders, schizophrenia, ADHD, etc., and, very prominently and at the same time significant for this thesis, Parkinson's disease and suicide.

C) Functional anatomy of the basal ganglia

Basal ganglia are a group of subcortical structures primarily responsible for motor control, and is an integral part of the extrapyramidal system. Impairments in these structures are the main pathology behind Parkinson's disease, but also other neurodegenerative diseases characterized by voluntary movement problems, such as Huntington's chorea. However, the functions of basal ganglia are not limited to motor control – they also include high-order limbic-related and cognitive-related processing (Smith, 2012).

Structures that form the basal ganglia are: subthalamic nucleus, globus pallidus, substantia nigra, and putamen and caudate nucleus, commonly together referred to as the striatum. *The striatum* is further often divided into the dorsal striatum (which consists of the previously mentioned putamen and caudate nucleus) and ventral striatum (consisting of the olfactory tubercle and the nucleus accumbens), which is not part of the basal ganglia. *Globus pallidus* (GP) has two segments – globus pallidus interna (GPi), one of the main output sites of the basal ganglia,

providing inhibitory signaling, and globus pallidus externa (GPe), serving as a relay for information. *Substantia nigra* is, as previously mentioned, a group of nuclei within the brainstem, encompassing substantia nigra pars compacta (SNpc), the main site of the DA production in the brain with the majority of DA neurons originating here, and substantia nigra pars reticulata (SNpr), involved in regulating motor activity by its GABAergic neurons. The last key structure of the basal ganglia is the *subthalamic nucleus* (STN), an important modulator of basal ganglia output, and one of the main sites of surgical treatment of advanced PD (the other, less commonly targeted area, is GPi) (Smith, 2012). Regarding basal ganglia input and output, the dorsal striatum is the main inpu site of the basal ganglia, receiving information from the cerebral cortex. It also receives afferents from the substantia nigra and thalamus and, as previously said, have an important role in voluntary movement. It is also involved in regulating many aspects of cognition, including executive functions. The main output sites of the basal ganglia are GPi and SN, sending projections to the thalamus, which further carries information back to the cerebral cortex. As previously mentioned, the main role of the basal ganglia is regulating motor control, and it is done so by initiating, inhibiting, or modulating movement through the direct, indirect, and nigrostriatal pathways respectively (Yelnik, 2002).

Direct pathway is excitatory and it regulates initiating motor activity. The signaling "loop" of the direct pathway is: cortex – striatum – GPi and SNpr – thalamus – motor cortex. Glutamatergic projections are sent from the cerebral cortex to the dorsal striatum, exciting it. Further, GABAergic projections are sent from the striatum to the GPi and SNpr, inhibiting their neurons. GPi and SNpr have inhibitory projections to the thalamus. Since GPi and SNpr are inhibited, less GABA is released in the thalamus, releasing disinhibition and sending excitatory signaling to the motor cortex, increasing motor activity (Gerfen & Bolam, 2010).

The indirect pathway's role is to prevent, inhibit, or terminate the motor activity. The order of signaling in the indirect pathway is as follows: cerebral cortex – striatum – GPe – STN – GPi – thalamus – motor cortex. Same as in the direct pathway, the indirect pathway starts with excitatory signaling coming from the cortex to the putamen and caudate of the striatum. However, in this pathway, GABAergic projections are further sent to the GPe, inhibiting it. GPe projects to the STN and releases GABA, inhibiting it. Since STN mostly contains GABA neurons, their inhibition means there will be less GABA released to the next site of the indirect pathway – GPi – which will have the excitation of GPi as a consequence. GPi further projects to the thalamus, where more GABA is released, inhibiting it, which, with its projections back to the motor cortex, inhibits movement (Gerfen & Bolam, 2010).

Lastly, nigrostriatal pathway is involved in the modulation of these pathways, and thus being able to amplify motor activity in both ways - facilitating desired and inhibiting undesired movement. DA neurons from the SNpc project to the D1- like receptors (to remind, these receptors have an excitatory function) in the dorsal striatum within the direct pathway. This way, DA from the SNpc amplifies the activity of the direct pathway, meaning it leads to a significant decrease in the inhibition in the thalamus, which intensifies the "power" of initiating movement. Within the indirect pathway, DA projections are sent from the SNpc to the striatum and DA binds to D2-like receptors (which, to remind, have an inhibitory function). This "added" inhibition from DA heightens the activity of the indirect pathway, inhibiting the thalamus and (unwanted) movement even more (Young et al., 2021).

Damage to these pathways is behind motor manifestations of Parkinson's disease. PD is a progressive neurodegenerative disease marked by neurodegeneration of dopaminergic neurons in the SNpc. This manifests in difficulties initiating or maintaining movement and also in controlling

unwanted movement, in form of bradykinesia, dyskinesia, tremor, and postural imbalance. These symptoms usually manifest after more than 60% of nigrostriatal neurons are degenerated (Dauer & Przedborski, 2003). As a consequence of neurodegeneration in the SNpc, there is DA depletion in the nigrostriatal pathway, which has a crucial role in modulating direct and indirect pathways, thus, inflicting impairments on voluntary movement control. More precisely, in PD, the lack of DA leads to excessive disinhibition of GPi and increased inhibition of the thalamus, which results in problems in initiating and controlling motor activity (Yelnik, 2002). Schematical depictions of functional circuits of the direct, indirect, and nigrostriatal pathways in an unaffected brain and in PD are shown in Figures 1. and 2. PD will be discussed in more detail in Chapter 4. of this thesis.

1. General overview of suicide: epidemiology and terminology

Suicide is a major health concern - it is among the 15 leading causes of death in the world (World Health Organization, 2021). According to the World Health Organization (WHO), around 700.000 people die by suicide every year globally. What makes the problem even more concerning is that this number is likely an underestimate. Due to the stigma surrounding suicide as well as the fact that this act is against the law in some countries, a number of cases of suicide are likely reported as accidents, not as intended acts of self-harm. In Italy, the number of deaths by suicide has been more or less steady for the past 15 years – around 4.500 every year (Ritchie et al., 2015). Figure 3 shows the comparison of suicide rates – the number of deaths per 100.000 people – between Italy, Europe, and the world.

Gender-wise, global suicide rates are significantly higher in men – over twice as high as in women. This difference varies by country and region; however, in recent years, it does not go below the 2:1 ratio for men and women respectively. In Italy, this difference is even more prominent – suicide rates are almost 3 times higher in men than in women. More precisely, annually, there are around 11 deaths by suicide per 100.000 people in men; for women, this number is around 4 deaths per 100.000 people (Figure 4). However, it is important to note that, while rates of completed suicide are, indeed, higher in male than in female population, many reports indicate that the incidence of suicide ideation and suicide attempts does not significantly differ between men and women (Nock et al., 2008) or that it might be even higher in women (Ting et al., 2012; Turecki & Brent, 2016). One of the possible explanations of this paradox is that men, on average,

choose more violent, high-lethality methods of suicide compared to women (Nock et al., 2008; World Health Organization, 2014).

Suicide is the leading cause of death in the young population. However, this does not mean that suicide rates are higher in young people compared to the older population. In fact, age-wise, suicide rates are the highest in the population aged 70 years or older. Suicide is not the leading cause of death in older population because there are other more common causes, such as cardiovascular and respiratory diseases. Generally, global data shows that the older the age group – the higher the risk for suicide is. Figure 5, Figure 6, and Figure 7 show suicide rates by age group in Italy, Europe, and in the World, respectively.

Suicide is a wide term that includes various patterns of cognition and behavior, and this has been a source of frequently inconsistent use of different terms in this area of research. For example, the term suicidal behavior can, for some, mean only concrete, physical action taken in the direction of ending one's own life; however, for others, this term can also include ideas about suicide and making plans to commit it, with or without concrete action that follows it. Similarly, some use the term self-harm to refer to any self-directed injurious behaviors, regardless of the intent, while others use it to refer to specific self-directed injurious behaviors specifically *without* the intent to die (for example, superficial skin cutting, extreme substance abuse, etc.) (Klonsky et al., 2016). Thus, it is crucial to precisely use terminology related to suicide in order to accurately describe and predict different aspects of suicidal behavior and its phenomena, as well as to avoid misunderstandings that can, consequentially, hinder progress in this area of research and practice. Thus, following are some of the definitions of different terms related to suicide, according to the US Center for Disease Control And Prevention (Crosby et al., 2011), as they will be used in this thesis:

- **Suicide** is defined as death caused by self-directed injurious behavior with an intent to die as a result of the behavior.
- A **suicide attempt** is a non-fatal, self-directed, potentially injurious behavior with intent to die as a result of the behavior. A suicide attempt might not result in injury.
- **Suicidal ideation** refers to thinking about, considering, or planning suicide.

Additionally, self-harm, or non-suicidal self-injury (NSSI), as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013) as non-suicidal self-directed violence, or self-injurious behavior with non-suicidal or undetermined intent. It is important to note that although self-harm refers to self-directed violence without suicidal intent, people who engage in such behavior are at a higher risk of suicide and suicide attempts compared to the general population. First, because there are different shared variables between suicidal behaviors and self-harm, such as mood disorders and personality disorders (Hawton et al., 2013), which are known to increase the risk of suicidal behaviors. Second, because self-harm often leads to the habituation to pain and to self-inflicted violence, which increases the risk of actual suicide attempt occurring in the future (Klonsky et al., 2013). Nevertheless, previous acts of self-harm and suicide attempts are predictors of future suicide attempts and suicide (Turecki et al., 2019).

2. Risk factors for suicide

As mentioned in the introduction section A, suicidality is a multi-factorial phenomenon that results from a complex interplay of individual vulnerability for suicide and present risk factors. There is no single factor that can "cause" suicidality; various risk and protective factors are at play, and they depend on the individual. However, research of risk factors associated with suicidality can help us predict possible suicidal behavior and thus be more effective in preventing it. There is now a considerable scope of research that identified significant factors that contribute to the increased risk of suicide. Since discussing them all surpasses the scope of this thesis, three relevant groups of risk factors will be discussed in the following section from the context of the diathesis-stress model: *psychiatric disorders* (most prominently depression, other mood disorders, and substance use disorders) as part of the stress component, and *neurocognitive factors* as part of the diathesis component. Neurobiological factors also comprise the diathesis of suicide, and they will be discussed in the next chapter. Other risk factors, such as genetics, personality traits, early life adversity, gender and socioeconomic factors, are nonetheless important for the understanding of suicide, but will not be discussed as part of this thesis.

2.1. Psychiatric disorders as risk factors for suicide

Psychiatric disorders make up the largest proportion of the background of suicidality. Psychological autopsy studies suggest that more than 90% of completed suicides are done by people who were suffering from a psychiatric disorder (O'Connor & Nock, 2014). This, of course, does not mean that the majority of people who suffer from mental illness would engage in suicidal behavior; only a small proportion of this population would make a suicide attempt or die by suicide (O'Connor and Nock, 2014).

Depression appears to be the prime risk factor for suicide. Major depressive disorder is by far the most prevalent diagnosis among suicide victims. Some studies found that at least 30% of lifetime prevalence of suicide attempts can be attributed to a major depressive episode (Bachmann, 2018; Bernal et al., 2007), and that the severity of depression is a significant correlate of the level of suicidality (Brådvik, 2018). Other authors suggest that major depressive episode, whether it is a part of major depressive disorder, bipolar disorder, or generally any other mood disorder (ICD-10 F3), can be accounted for more than half of all suicide deaths (Turecki & Brent, 2016). Among people who suffer from depressive disorders, suicides are more common in the elderly, especially the ones who experience psychotic symptoms alongside depression (Bachmann, 2018). However, it is important to note that the depression diagnosis only is not merely enough to predict the risk of suicide. Not everyone who experiences suicidal ideation will attempt suicide. Although suicidal ideation is almost always a precedent of a suicide attempt, there is a significantly larger proportion of people who experience suicidal thoughts only, without ever acting on them, than the ones who try to take their own life. According to different authors, such as Klonsky et al. (2016) and Brådvik (2018), depression seems to be a strong predictor of *suicidal ideation;* however, it loses its

predictive power when it comes to suicide attempts or completed suicides. In other words, the diagnosis of Major depression does not have the power to distinguish between those who experience suicidal ideation alone from those who have attempted suicide. This is true for other clinical correlates of suicidality as well – they appear to be strong correlates of suicidal ideation, not suicide attempts. Therefore, it is thought that there are other factors in addition to a psychiatric diagnosis that lead from suicidal ideation to suicide attempts and completed suicides, and addressing them is the key to understanding suicidality and preventing it. What these factors are is still not clear, however, there are some suggestions from research and literature that can help in better understanding of these mechanisms.

One of the key factors that may be responsible for the progression from suicide ideation to suicide attempt may be increased impulsivity (Klonsky et al., 2015). This is a convincing argument considering the fact that substance use disorders (ICD-10 F1) – mostly, but not exclusively, alcohol-related, which is known to increase impulsivity - are the second most common diagnosis among those who attempt or die by suicide (Brådvik, 2018). This is especially prominent in the elderly population, which has higher suicide rates overall, and also the highest proportion of suicide attempts related to alcohol use, alongside depression (Esang & Ahmed, 2018). Around 40% of individuals who seek treatment for substance-related disorders have at least one previous suicide attempt (Yuodelis-Flores & Ries, 2015). Alcohol intoxication is a significant correlate of suicidality in both, chronic use of alcohol (alcohol use disorder) and acute alcohol intoxication (Esang & Ahmed, 2018). It is estimated that at least 40% of suicides are conducted under the influence of alcohol in otherwise non-consuming individuals (Bachmann, 2018). This is not to say that substance abuse alone is responsible for increased suicidality. The relationship between substance use and suicide is far from simple and well-understood because it is intertwined with

other risk factors in a complex way that comprises a picture of comorbidity where it is difficult to untangle whether substance use led to these other risk factors or vice versa, which further complicates the understanding of etiology of suicidality. Substance use disorders are frequently comorbid with other psychiatric disorders, and acute alcohol or other substance intoxication, regardless of dependence, is often contemporaneous with adverse or stressful life events, which are also correlated with increased suicidality (Norström & Rossow, 2016). That stated, there is still substantial evidence that substance use disorders, especially in combination with other psychiatric disorders, notably depression, significantly contribute to increased suicidal behavior. Many authors believe that the mechanism behind this increased risk is that "alcohol-related problems are the most relevant determinant of progression from suicidal ideation to making a suicide attempt" (Bernal et al., 2007). One way of thinking about this mechanism can be in terms of accumulation of diagnoses or, in other words, the additive contribution of comorbidity to the increased risk of suicidal behavior. Another route of explaining the role of alcohol intoxication in elevating the risk of attempting or completing suicide is the effect alcohol has on impulsivity and cognition. This is especially important in the light of the fact that acute alcohol intoxication and alcohol use disorder are separate constructs, but both increase the risk of suicide. Many suicides in individuals with alcohol use disorder are done outside of acute intoxication, which falls under the explanation of comorbidity and additive effect of different risk factors that led both to alcohol use disorder and eventually to suicidality, but there is still a markedly elevated risk of suicide during acute alcohol intoxication, which suggests that there are some mechanisms at play related to alcohol intoxication that may be facilitating the transition from suicidal ideation to suicide attempt (Borges et al., 2017). Pompili et al. (2020) state that "acute and chronic alcohol abuse may impair judgment, weaken impulse control, and interrupt neurotransmitter pathways, leading to suicidal tendencies through

disinhibition". Indeed, numerous studies have consistently confirmed the previous argument, showing that alcohol use, among other effects, impairs "higher functions of the brain" like problem-solving and impulse control (Alfonso-Loeches & Guerri, 2011; Oscar-Berman & Marinković, 2007; Spear, 2018) and also that there is a negative correlation between the level of development of these functions and the risk of suicide (Grover et al., 2009; Joiner, 2005; Reinecke, 2006). Additionally, alcohol intake, in many cases, can amplify feelings of sadness and hopelessness (Boden & Fergusson, 2011), as well as impulsive aggression (Heinz et al., 2011) which can also be turned toward self and have been associated with an increased risk of suicide (Gvion & Apter, 2011; Klonsky et al., 2016). Pompili et al. (2010) summarizes mentioned potential psychological mechanisms through which alcohol consumption may have an effect on suicidality: "A state of intoxication may trigger self-inflicted injuries, not only by increasing impulsivity, but also by promoting depressive thoughts and feelings of hopelessness, while simultaneously removing inhibiting barriers to hurting oneself".

The third most common psychiatric diagnosis among suicide victims after major depression and substance use disorders is schizophrenia. Suicide is the major cause of death in people with schizophrenia, with a lifetime prevalence of suicide at around 5%. The proportion of people with a diagnosis of schizophrenia in attempted or completed suicides is especially high among the inpatient population. In fact, it is the second most common diagnosis in inpatient suicides (20%), and the rate is double compared to outpatients (Brådvik, 2018). As stated earlier, the elderly with the combination of a depressive episode and psychotic symptoms are at a higher risk of suicide, especially the ones who, in addition, have a substance use problem (Brådvik, 2018).

A good proportion of attempted and completed suicides is done by individuals with a diagnosis of a personality disorder, especially the ones from cluster B like the borderline personality

disorder. These disorders are characterized by poor emotional control, impulsivity, and sometimes aggression, which are traits that have all been associated with a heightened risk of suicidal behavior (Turecki & Brent, 2016).

Conclusively, psychiatric disorders are the most important risk factors for suicide. They are at the background of almost all suicide attempts and completed suicides, with major depressive episode being the main risk factor for suicidal behavior, followed by substance use disorders, especially alcohol abuse, and schizophrenia. The distribution of psychiatric diagnoses comorbid with suicide attempts and completed suicides differ between inpatients and general population (Bertolote & Fleischmann, 2002), which is shown in Figure 8 and Figure 9 respectively. It may be important to note that it has been speculated that psychiatric disorders are very good predictors of suicidal ideation but not exactly of suicide attempt or completed suicide. Although suicidal ideation is common in psychiatric disorders, especially in the above-mentioned, only a small proportion of these individuals will make a suicide attempt. This implies that there are factors that facilitate the transition from suicidal ideation to suicide attempts. Such factors (some of which will be discussed in the next sections) can include genetics, neurobiological factors such as the availability of different neurotransmitters, personality traits and cognitive patterns such as impulsivity or poor problem-solving skills, stress, environmental factors, etc. Generally, disorders characterized by high levels of anxiety and depression (such as major depressive disorder or post-traumatic stress disorder) and poor impulse control (such as substance use disorders), are strongly associated with a higher risk of suicide through the route of transition from suicidal ideation to suicidal attempt (Turecki et al., 2019). Each diagnosis has an additive power to the increased risk of suicide, which means that people with comorbid psychiatric disorders have a higher risk of suicide, especially when co-occurring with substance abuse (notably, alcohol).

2.2. Neurocognitive risk factors of suicide

Deficits in a range of cognitive functions, including different domains of executive functions, such as attention, working memory, problem-solving, decision-making, as well as impulsivity, have been found to correlate with suicidal behavior.

Impulsivity has long been known as a strong psychological correlate of suicide (Gvion & Apter, 2011; Plutchik & Van Praag, 1989). Although studies that explored the link between impulsivity and suicidality show somewhat inconsistent results - with many researchers demonstrating a moderate to strong relationship between increased impulsivity and risk for suicidal behaviors (Liu et al., 2017; Millner et al., 2020) and others claiming such correlation is rather weak (Anestis et al., 2014; Klonsky et al., 2017) - there is now such an overwhelming body of research on this topic that there is no doubt such correlation, to a certain extent, exists. It may be the case that impulsivity is a factor that contributes to the transition from suicidal ideation to suicide attempt, which has been supported by a study conducted by Auerbach et al. (2017), who demonstrated that impulsivity is a significant predictor of suicidal behaviors, and is uniquely associated with suicide attempts. The results remain consistent even when current psychiatric diagnoses and symptoms are controlled as factors. On contrary, Klonsky et al. (2017) assert opposite results, claiming that impulsivity may be associated with suicidality, but that it does not differ between ideators and attempters. Inconsistency in research results might in part stem from

inconsistency in defining impulsivity among researchers (Anestis et al., 2014), and also from the fact that many of them approach impulsivity with an intuitive stance, treating it as a monolithic phenomenon (J. L. Evenden, 1999). Impulsivity is a multifaceted construct. As a whole, it might be broadly defined as "actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes" (J. L. Evenden, 1999). Within the context of cognitive neuroscience, some authors make a distinction between trait impulsivity, impulsive action, and impulsive choice (J. Evenden, 1999). Similarly, impulsivity may be conceptualized as comprised of: *cognitive or choice impulsivity* (making impulsive choices, for example choosing a proximal but smaller reward instead of waiting for a bigger reward later), *motor impulsivity* (making a motor action without thinking it through, difficulty inhibiting a motor response), and *reflection impulsivity* (making a decision without previously gathering sufficient evidence). This distinction is supported by findings that there are distinctive neural correlates behind each of these constructs (Millner et al., 2020).

Deficits in executive functions have been strongly associated with an increased risk of suicide. The term executive functions refers to a set of top-down cognitive processes needed for effortful guidance of goal-oriented behavior. These mental operations heavily rely on the prefrontal cortex and, in non-routine activities, regularly shape and direct lower-order cognitive processes, such as perceptions and motor actions. Executive functions are what is commonly known as "conscious control of mental activities", such as attention, planning, problem-solving, etc. There is now a general agreement that executive functions broadly consist of three groups of cognitive skills: 1. Inhibition – the ability to suppress automatic or prepotent cognitive and behavioral impulses, which influences selective attention; 2. Working memory – includes monitoring and updating relevant information; 3. Cognitive flexibility – mental set shifting, the ability to switch between

tasks (Bredemeier & Miller, 2015). Executive dysfunction in general, but also deficits in specific aspects of executive functions, have been associated with suicidality, and there are suggestions and evidence that point to the direction of executive dysfunctions being a factor that uniquely contributes to suicide attempts through facilitating the transition from suicidal ideation to suicide attempt (Saffer & Klonsky, 2018). Different studies confirmed this hypothesis, offering convincing evidence in form of finding significant differences between suicide attempters and non-attempters in performance on tasks such as Iowa Gambling Task and Cambridge Gambling Task (decision-making), Stroop task (attention), Reversal Learning (cognitive flexibility), and on different cognitive inhibition tasks (Keilp et al., 2008).

Ho et al. (2018) found that the capacity for general inhibition is what differentiates depressed individuals with suicidal ideation alone from depressed individuals who attempted suicide. More specifically, worse general inhibition skills were found in MDD patients with previous suicide attempts compared to healthy controls and MDD patients without previous attempts. Another, earlier study (Richard-Devantoy et al., 2012), demonstrated similar results on the elderly population – depressed elderly with previous suicide attempts showed significant impairments in all aspects of inhibition compared to depressed elderly without previous suicide attempts, or healthy adults. The effect was significant even when controlled for the severity of depression or suicidal ideation, which suggests that deficits in inhibition might be an independent marker for increased risk of suicide.

Attentional deficits have been consistently found in individuals with previous suicide attempts, especially the ones diagnosed with a depressive episode. The Stroop Test has been frequently used for measuring attention capacity and is a reliable predictor of its deficits. Although depressed individuals perform worse on the Stroop test compared to the general population, greater deficits

are found in depressed suicide attempters than in depressed non-attempters, especially in the interference task, implying that these individuals may have a greater difficulty shifting attention from "compelling but inappropriate" stimuli (Keilp et al., 2008). In their later study, Keip et al. (2013) also found that, compared to healthy controls and individuals with suicide ideation but without previous suicide attempts, past suicide attempters performed worse on tasks related to attention, but also on tasks associated with working memory. Similar results were obtained in depressed suicidal elderly patients. Depressed and suicidal elderly patients showed significantly poorer performance on tests of executive functions, memory, and attention compared to the non-suicidal depressed elderly group. These results were consistent regardless of the severity of depression or physical illness, and could not be explained better by potentially present dementia, substance abuse, medication used, or brain injury (Dombrovski et al., 2008).

Fundamental deficits in executive functions may be increasing the risk of suicidality by contributing to a cognitive approach commonly observed in individuals with suicidal ideation and attempts, which is marked by 'cognitive rigidity' and hopelessness (Carballo et al., 2009). Impairments in general inhibition may be accountable for greater difficulties resisting the urge on acting on thoughts of self-harm when they occur, which may be additionally supported by difficulties in shifting one's attention away from thoughts about self-harm toward healthier coping mechanisms in response to stress. Possible impairments in working memory may contribute to problems in 'updating' or retrieving past information that, in response to stress, would help an individual see the 'bigger picture' and imagine possible future outcomes. Executive function deficits are found in a number of psychiatric disorders associated with an increased risk of suicide, such as depression, schizophrenia, and substance use disorders (Bredemeier & Miller, 2015). Moreover, structural and functional abnormalities in the prefrontal cortex associated with

executive functions, especially attentional control, are overlapping considerably with regions implicated in these disorders (Keilp et al., 2008). These are indirect but convincing arguments that support and explain the link between executive (dis)function and suicidality.

3. Neural correlates of suicide

Although there are many different elements that play important roles in suicide such as environmental, psychological, and social factors, the most critical ones that are considered to be "a final common pathway implicated in suicidal behavior" (Mann, 2003) are neurobiological factors. In this chapter, the role of neurotransmitters and the HPA axis in suicide will be discussed.

3.1. Neurotransmitters

3.1.1. Serotonin and Norepinephrine

Serotonin neurotransmission deficits have been the most extensively studied and the most uniformly reported biological factor that significantly contributes to the etiology of suicidal behavior, as well as of Major depressive disorder (MDD) and other disorders that include a depressive episode (Mann & Currier, 2010). Serotonin (5-HT) is a neurotransmitter that plays a role in many processes, the most prominent being the regulation of mood, emotions, sleep, food intake, and sexual behavior. It is produced by raphe nuclei of the brainstem. The serotonergic innervation to the cerebral cortex comes mostly from dorsal (DRN) and medial (MRN) raphe nuclei. 5-HT is synthesized from the enzyme tryptophan hydroxylase, transported via 5-HT transporter SERT, and regulated by a network of pre- and post-synaptic receptors, of which the most relevant for the further discussion is the 5-HT_{1A} receptor (Bach & Arango, 2012).

Decreased levels of serotonin neurotransmission have been found in both the brainstem and the forebrain serotonergic projection areas of suicide victims (Bach & Arango, 2012). Lower

amounts of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been consistently found in cerebrospinal fluid (CSF) of individuals who attempted suicide, as well as in post-mortem studies of individuals who completed suicide (Carballo et al., 2009). These findings seem to be independent of psychiatric diagnosis (Mann & Currier, 2010). Some studies show that people with levels of 5-HIAA in their CSF below the median had a 4.5 times larger risk to die by suicide than those with CSF 5-HIAA levels above the median (Mann et al., 2006). When compared to patients who did not attempt suicide, patients with previous suicide attempts, particularly those who used violent methods, had significantly lower levels of 5-HIAA in CSF (Jokinen et al., 2009). Paradoxically, in the brain stem, no deficiency in the number of serotonin neurons has been found, or even an increased number of serotonin neurons in raphe nuclei, particularly in DRN and MRN of patients with a history of suicide behavior have been reported (Mann, 2003). Furthermore, there is an increase of tryptophan hydroxylase (TPH), the key enzyme in 5-HT synthesis, in the DRN of suicide victims with a history of depression (Boldrini et al., 2005). This increase in serotonin neurons in the brainstem and an increased immunoreactivity of TPH in DRN is thought to be a compensatory mechanism as part of the homeostatic upregulating response to the decreased neurotransmission of 5-HT (Bach-Mizrachi et al., 2008). Other evidence of the serotonergic system dysfunction include alterations in serotonin receptor functioning, more precisely, upregulation of 5-HT_{1A} receptors in the ventral prefrontal cortex, as well as lower amount of serotonin transporter (SERT) binding sites in the prefrontal cortex and other brain regions of suicide victims (Carballo et al., 2009; Mann, 2003).

Taken together, all this evidence shows the important role the serotonergic system has in regulating mood and behavior in suicide. It has been hypothesized, and in many studies demonstrated, that there is a link between serotonergic dysfunction and increased aggression and

impulsivity, two well-established risk factors associated with suicidal behavior, that also may explain differences in the levels of violence and lethality of suicidal behavior (Glick, 2015). Serotonin is a modulatory neurotransmitter, meaning that serotonergic projections from the raphe nuclei to the prefrontal cortex, orbitofrontal cortex, amygdala, and nucleus accumbens modulate how the person reacts to a stressor, and if there are alterations in the serotonergic system, it can result in alterations in modulation of reactive distress, leading to inappropriate behaviors such as self-injury (Bortolato et al., 2013). In other words, dysregulations of 5-HT production and transmission that leads to a depletion of 5-HT in the brain and alterations in 5-HT homeostasis may contribute, through impaired inhibition, to the increased expression of aggression and impulsivity in response to stress, which are both thought to be associated with suicide attempts. However, it is important to note that this relationship is not simple, that the inverse relationship between the levels of 5-HT and suicidal behavior is not necessarily direct, but that there are many interfering factors that modulate it, which include, for example, environmental factors, gender-related variables, the expression of certain genes, and the interaction with other neurotransmitters (Bortolato et al., 2013; Glick, 2015).

Another neurotransmitter associated with the biology of suicide is norepinephrine. Norepinephrine is a catecholamine neurotransmitter that has an active role in modulating various physiological reactions and behaviors, such as sleep, levels of alertness and focus, attention, memory, decision-making. Overly decreased levels of NE can have a sedating effect, leading to, among other effects, low mood and lack of focus and concentration. Overly increased levels of NE have an excitatory effect, and can result in irritability, anxiety, insomnia, etc. However, the most notable function NE has is the modulation of the stress response (Chandley & Ordway, 2012). NE

is produced by neurons in locus coeruleus (LC), a bundle of nuclei located in the brainstem, near the floor of the fourth ventricle. This area receives afferent projections from numerous regions of the brain such as the hypothalamus, central amygdala, insula, lateral habenula, cerebral cortex, etc. Moreover, the efferent tracts from LC innervate nearly the entire brain. This bundle of afferent and efferent projections creates a mutually influential feedback loop that produces and modulates physiological and behavioral reactions. More precisely, when exposed to stress, LC activates, partly through activation of these stress-sensitive neural circuits, and partly by an increase in the activity of the hypothalamic-pituitary-adrenal (HPA) axis, which will be discussed later in this chapter. As a result, the amount of NE in the brain increases. Prolonged and repeated exposure to stress leads to a depletion of NE in LC as well as in projection areas, simply because "the demand exceeds the supply" (Chandley & Ordway, 2012). This can finally result in psychiatric disorders, such as depression. On the other hand, depression can be a result of disturbances or anomalies in these circuits that can lead to maladaptive reactions to stress and therefore depleted amounts of NE. As Chandley & Ordway (2012) summarize it: "Biological systems that mediate stress may be particularly vulnerable to damage produced by sustained stress, or alternatively, deficiencies in these systems may be pathognomonic and contribute to the underlying vulnerability of a human to develop stress-related disorders such as depression or suicidal behaviors."

As previously suggested, alterations in noradrenergic functions have been associated with depressive episodes and with a greater risk of suicide. A lower number of norepinephrine (NE) neurons in LC has been reported in suicidal patients with Major depressive disorder (van Heeringen, 2003). Moreover, cortical noradrenergic overactivity in the prefrontal cortex of suicide victims has been found – α-adrenergic binding is lower and β-adrenergic binding is higher in this brain region (Carballo et al., 2009). Most simply, activation of α-adrenergic receptors inhibits the

release of NE, while activation of β-adrenergic receptors facilitates NE release. Considering the lower number of norepinephrine neurons in LC, this overactivity of the noradrenergic system leads to the depletion of norepinephrine in the brain (because LC cannot produce enough NE that the noradrenergic system demands in response to stress), ultimately leading to alterations in mood and behavior that can result in depression and suicidal behavior Some studies found that low amounts of NE in the brain are associated with increased levels of hopelessness, one of the critical cognitive correlates of suicide, and that NE levels could even have a potential of predicting suicidal behavior, with greater deficiency carrying the risk of more lethal suicide attempts (Mann & Currier, 2010).

In sum, significantly low levels of serotonin and norepinephrine have both been found in the brains of suicidal individuals, particularly those with a history of depression and suicide attempts, as well as in post mortem studies of suicide victims. Decrease in serotonin levels has been associated with increased impulsivity and reactive aggression, while depletion of norepinephrine is correlated with increased hopelessness and pessimism, both factors appearing as significant components of suicidal behavior (Duica et al., 2020). Mann (2003) gives a useful schematic representation (Figure 10) of the way serotonin and noradrenaline play a role in the diathesis of suicidal behavior and potentially, in presence of stressors, facilitate the transition from suicidal ideation to suicidal attempt.

3.1.2. Dopamine

Another neurotransmitter that plays a significant role in suicide, especially in combination with the above-mentioned neurotransmitters, is dopamine. The amount of monoamine metabolites in the CSF has been extensively studied as an indicator of different levels of neurotransmitters in the brain and a potential biomarker of different pathological conditions. In suicide, the levels of monoamine metabolites are shown to be lower, and this result is found to be independent of, possibly simultaneously existing, psychiatric conditions. In other words, regardless of a psychiatric diagnosis, lower levels of monoamine metabolites are often found in individuals who attempted or completed suicide (Lindqvist et al., 2011; Mann, 2003; Mann et al., 2001). Besides the most widely studied and most consistently reported lower levels of serotonin metabolite 5-HIAA in the CSF of suicide attempters and suicide victims, lower levels of dopamine metabolite HVA also appear to be a significant factor in suicide. A considerable number of studies have reported lower levels of HVA in the CSF in both depressed and non-depressed suicide attempters compared to depressed or non-depressed individuals without previous suicide attempts, indicating the important role of dopamine in suicide or, more precisely, a possible contribution of dopamine hypoactivity to the increased suicide risk (Pitchot, Hansenne, et al., 2001; Sher et al., 2006). However, research on the relationship between DA levels and suicide shows inconsistent results (Oquendo et al., 2014; Sharma et al., 2021). For example, some studies did not find the correlation between the levels of CSF HVA and suicide to be significant (Mann & Malone, 1997; Jokinen et al., 2009). The most recent meta-analysis conducted by Hoertel et al. (2021) analyzed studies of the CSF levels of monoamine metabolites – particularly 5-HIAA, HVA, and MHPG - in suicide attempters compared to individuals with no history of suicidal behavior and found that CSF levels of 5-HIAA

and HVA were, indeed, significantly lower in suicide attempters than in non-attempters, while the levels of MHPG did not significantly correlate with suicide attempts. The inconsistency in results of different studies of the relationship between HVA and suicide may stem from the fact that the concentrations of HVA in CSF are not independent of 5-HIAA and MHPG; they interact with each other, which may have an influence on research reports (Sharma et al., 2021). Further evidence of an association between lower dopamine and suicidality was provided by a recent study (Prepelita, et al., 2019). The authors unequivocally showed that the blood levels of dopamine significantly negatively correlate with levels of suicide ideation, and that the level of dopamine might be a significant predictor of suicide risk, explaining 64% of the variance in their sample. However, as previously mentioned, dopamine being a predictor of suicide should be taken with a level of cautiousness, because it is not clear whether dopamine can be taken as an independent predictor of suicidality or whether its reductions are an accompanying effect of depression, especially considering the fact that the majority of studies investigating the association between dopamine and suicide risk are conducted on populations diagnosed with depression (Prepelita, et al., 2019). Nonetheless, convincing evidence in favor of the hypothesis that DA is uniquely related to suicide, without a mediating relation to depression, comes from a study by Sher et al. (2006), where they found that the levels of CSF HVA of depressed patients with previous suicide attempts were significantly reduced compared to CSF HVA of depressed patients with no previous suicide attempts. This suggests that CSF HVA levels could be considered as biomarkers of suicidal behavior, or an accompanying factor of the transition from suicidal ideation to suicide attempt. Finally, abnormalities in monoamine oxidase (MAO) activity, the main enzyme involved in the process of degradation of monoamines, including serotonin, dopamine, and norepinephrine, and in the expression of MAO genes, have been frequently reported in depression and suicide, as well

as in both depressed and non-depressed suicide attempters (Oreland et al., 1981; Mann, 2003; Ryding et al., 2008; Carballo et al., 2009).

Other significant studies investigating the relationship between dopamine and suicide include dopamine receptor binding, with a hypothesis that dopamine receptor binding and dopamine transporter might be altered in depression and suicide (Fitzgerald et al., 2017; Meyer et al., 2001; Pitchot, Reggers, et al., 2001; Ryding et al., 2006). A study conducted by Fitzgerald et al. (2017), where they measured the levels of dopamine transporter (DAT), and D1 and D2 receptor binding in the dorsal striatum of suicide victims, postmortem, and compared them with controls, showed that there was a positive correlation between D1 and D2 receptor binding in controls, but not in suicide victims. This may indicate that there is an imbalance in binding between D1 and D2 receptors in suicide which implicates that there is a decreased ability to dynamically regulate D1 and D2 receptor availability. However, it is still not clear whether it represents a unique diathesis for suicide or an aftereffect of MDD (Fitzgerald et al., 2017). Some studies investigated dopamine receptor sensitivity in the context of suicide in MDD by comparing the growth hormone (GH) response to apomorphine, a selective dopaminergic agonist, in depressed suicidal patients with and without previous suicide attempts. What was found is that the mean peak of GH response to dopamine agonist in depressed individuals with previous suicide attempts was significantly lower than the mean GH peak response in the group with no history of suicidal behavior, suggesting lower sensitivity of DA receptors in depressed individuals who engage in suicidal behavior. This data, again, implies the involvement of the dopaminergic system in suicidality, with an emphasis on the role of D2 receptors (Pitchot et al., 1992; Pitchot et al., 2001). Striatal D2 receptor binding appears to be increased in postmortem studies of MDD patients who died by suicide, indicating that DA turnover is decreased in these individuals (Belujon & Grace, 2017).

Dopamine system disruptions have consistently been found in depressive disorders and alcohol use disorder, conditions that are major risk factors for suicide (Carballo et al., 2009). As mentioned earlier, it is considered that more than 60% of all suicides have a background in form of depression-related disorders, such as MDD. Although the role of the serotonergic system is the most prominent and most widely studied in depression, multiple sources of evidence highlight the important role the dopaminergic system has in depression (Belujon & Grace, 2017; Mann, 2003; Pitchot, Reggers, et al., 2001; Yadid & Friedman, 2008). DA circuits in the CNS, especially mesolimbic and mesocortical pathway, and depression have a common link – concentration, motivation, and the ability to experience pleasure are the main regulatory functions of the first and heavily impaired in the second (Dunlop & Nemeroff, 2007). Some depressed patients appear to be resistant to antidepressant drugs that target the serotonergic system (such as SSRIs), or only partially responsive, with anhedonia-related symptoms such as depleted motivation and reward-related cognitive impairments being especially difficult to treat in these patient populations. It has been hypothesized that the reason behind this is that these patients have a peculiarly prominent dopamine function dysregulation that, besides other causes, contributes to their depressive symptoms and that the increase in serotonin provided by SSRIs is not enough to lift the symptoms (Belujon & Grace, 2017). Some authors even propose a consideration of the existence of a subtype of depression that stems primarily from DA dysfunction (Dunlop & Nemeroff, 2007). Augmentation of SSRI treatment with other medication, such as atypical antipsychotics, has been often and successfully used to increase the efficacy of treatment of depression, and such practice has been approved by the United States Food and Drug Administration (Belujon & Grace, 2017). Different animal studies also showed a strong association between depression and DA hypoactivity (Friedman et al., 2008; Kapur & John Mann, 1992; Rincón-Cortés & Grace, 2020; Roth-Deri et

al., 2009). The one that powerfully demonstrates the involvement of the DA system, especially the mesolimbic DA pathway, in the pathophysiology and behavioral expression of depression was done by Tye and colleagues in 2013. Using optogenetics to manipulate dopaminergic neurons in the VTA of mice, they were able to show, in real time, that mice consistently expressed depressive-like behaviors when their dopaminergic neurons were "turned off". Moreover, after mice were exposed to chronic stress for 8-12 weeks and, as a result, started showing depressive-like behaviors (such as learned helplessness behaviors or not engaging in activities that normally induce pleasure), the excitation of their DA neurons in the VTA eliminated these symptoms. In other words, with selective inhibition of DA neurons in the VTA the authors were able to induce multiple behaviors present in depression in mice (or, at least, the same "depressive" symptoms that appear as a result of chronic stress); furthermore, with excitation of these neurons in mice that expressed depressive-like behaviors as a consequence of chronic stress, the symptoms withdrew. What was interesting is that reactions in response to the excitation/inhibition of DA neurons were almost immediate, and also that this effect was present with DA neurons only – glutamate neurons manipulation in the same area had no effect (Tye et al., 2013).

Finally, DA involvement in depression has been considered and studied also because of the unduly high frequency of depression among patients with Parkinson's disease. It is estimated that up to 40% of Parkinson's disease patients experience depression, with symptoms of depression often showing even before any signs of Parkinson's disease (Dunlop & Nemeroff, 2007; Kapur & John Mann, 1992). The relationship between depression and suicide with Parkinson's disease, and the role of dopamine in that picture, will be discussed more extensively in Chapter 4 and Chapter 5 of this thesis.

3.2. Hypothalamic-Pituitary-Adrenal axis (HPA) and suicide

A very important risk factor frequently mentioned in the literature of suicidal behavior and extensively researched in depression and suicide is altered Hypothalamic-Pituitary-Adrenal axis (HPA). HPA axis is a system that controls an organism's response to stress via endocrine activities in the hypothalamus, the anterior pituitary and the adrenal cortex respectively. When the person is exposed to stress, HPA axis activates, stimulating the release of corticotropin releasing factor (CRF) in the paraventricular nucleus (PVN) of the hypothalamus. The release of CRF stimulates the activation of the anterior pituitary gland and the secretion of adrenocorticotropic hormone (ACTH) from that site, which in turn, prompts the release of cortisol by the adrenal cortex. The goal of the activation of the HPA axis is to provide enough energy for the organism to deal with stress, since cortisol mobilizes glucose from the liver and catalyzes the chain of different reactions to increase the chances of survival when an organism is faced with homeostasis disturbances. A healthy HPA axis functions as a so-called negative feedback loop (see Figure 11), which means that cortisol inhibits the release of CRH and ACTH in the hypothalamus and anterior pituitary respectively, therefore downregulating the stress response and prompting the system to return to its homeostatic state (Renoir et al., 2013). The HPA axis is bidirectionally regulated by serotonergic, noradrenergic, and dopaminergic systems. Thus, disturbances in the neurotransmitter systems can lead to altered activity of the HPA axis, and vice versa – the abnormal activity of the HPA axis can disrupt the activity of neurotransmitters. Disturbances of HPA axis activity, most commonly its negative feedback loop, can lead to severe hormonal imbalances and behavioral deficits, and are often present in different psychiatric conditions, such as MDD, bipolar disorder,

anxiety disorder, PTSD, substance use disorders (Renoir et al., 2013), as well as in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Du & Pang, 2015). One of the most consistently replicated biological states found in clinical depression is hyperactivity of the HPA axis (Du & Pang, 2015). Consistent with this finding, antidepressant medications have been shown to alter HPA axis activity (Mason & Pariante, 2006).

HPA axis activity strongly correlates with suicide risk, many studies confirm (Jokinen et al., 2009; Jokinen & Nordström, 2008; Pompili et al., 2010), however, they disagree on whether it is independently or through the association with psychiatric conditions and other risk factors for suicide. One recent study (Berardelli et al., 2020) have found that the HPA axis significantly correlates with increased suicide risk, regardless of the presence or absence of a psychiatric condition. One of the most commonly used methods to investigate the HPA axis activity is the dexamethasone suppression test. Dexamethasone normally provides negative feedback to the pituitary gland, therefore suppressing the release of ACTH, which leads to a suppression of cortisol. However, when there is a hyperactivity of the HPA axis, cortisol levels will not be decreased as in normal HPA axis function after the injection or ingestion of dexamethasone. Numerous studies have found that resistance of cortisol to dexamethasone suppression test is linked to an increased risk of suicide (Alacreu-Crespo et al., 2020; Coryell et al., 2006; Yerevanian et al., 2004). However, there are also some studies that found an opposite effect - a blunted HPA axis response in suicide attempters compared with individuals with no history of suicide (Melhem et al., 2016, 2017). Although there are somewhat conflicting findings and the studies don't universally agree about the HPA axis activity and the levels of cortisol in individuals with a higher risk of suicide, it seems, overall, that the HPA axis hyperactivity and the inability to suppress

cortisol after the administration of dexamethasone, after all, reflects an increased risk for suicide (Mann, 2003). Some authors even claim that this risk is elevated by as much as 14-fold (Coryell & Schlesser, 2001). The link between the HPA axis and suicide is not surprising, considering the involvement of the HPA axis in different psychiatric disorders associated with suicide, such as major depressive disorder, as well as the fact that there is a regulatory bidirectional relationship between the HPA axis and neurotransmitters, particularly dopamine, norepinephrine, and serotonin, all of which play an important role in the neurobiology of suicidality.

4. Parkinson's Disease

4.1. Clinical manifestations, pathophysiology, and treatment of Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disease that most notably manifests as impairments in voluntary movements in form of bradykinesia, rigidity, and tremor. It mainly affects the elderly population (older than the age of 60), however, there are also cases of early onset, with motor symptoms emerging even before the age of 40. It is the second most common neurodegenerative disease after Alzheimer's disease. It affects approximately 1% of population older than 60, and around 0.3% of general population (Samii et al., 2004). Parkinson's disease is mostly considered an idiopathic disease, meaning that the cause of the disease is unknown. However, around 15% of patients diagnosed with Parkinson's disease have a first-degree relative with the same condition, which suggests that there may be some genetic influence and a certain degree of heritability (Samii et al., 2004). The pathophysiological hallmark of Parkinson's disease is the death of dopaminergic neurons in substantia nigra pars compacta (SNpc), meaning impairment in the nigrostriatal dopaminergic pathway and depletion of DA in the brain, particularly basal ganglia, but also in other structures. This ultimately leads to the motor manifestations of the disease – difficulties in voluntary movement control. These symptoms usually appear after around 60% of dopaminergic neurons in SNpc is already dead (Balestrino & Schapira, 2020). The pathophysiology of motor pathways involved in PD is explained in the Introduction's section about Basal ganglia. Also, some loss of dopaminergic neurons, although

much less severe, has been observed in the Ventral Tegmental Area (VTA) of Parkinson's disease patients, indicating that mesolimbic and mesocortical pathways are also affected. The underlying cause that triggers neuronal loss in these areas is still not completely understood (Balestrino & Schapira, 2020). What has been consistently found, as another hallmark of pathology on the cellular level in the brains of Parkinson's disease patients is Lewy body pathology, and it is considered a "biological marker for neurodegeneration in Parkinson's disease" (Kalia & Lang, 2015). More precisely, fragments of abnormally folded α-synuclein, a protein normally present in neurons with functions still ambiguous, accumulate in the neurons of Parkinson's disease patients in form of Lewy bodies, which disrupt the cells' homeostasis and eventually lead to neurodegeneration. What triggers the abnormalities in α-synuclein activities and the formation of α-synuclein aggregates is still under debate and research (Kalia & Lang, 2015). A wide range of non-motor symptoms is present in PD as well, accompanying motor symptoms or even preceding them by several years. Non-motor symptoms of PD include, but are not limited to: depression, anxiety, psychosis, constipation, pain, sleep problems, cognitive decline and executive dysfunctions, problems with impulse control, etc. Some of these symptoms arise as part of the disease itself, while others emerge as a complication of DA therapy (Pfeiffer, 2016). They will be discussed in more detail in the next chapter.

There is currently no cure nor treatment that would stop neurodegeneration in PD. Medicaments for PD are used in the first stages of PD, after the diagnosis is established, and are directed toward symptom management, meaning relieving motor and non-motor symptoms to increase the quality of life. However, in advanced PD the effect of DA replacement therapy may "wear off" and patients may develop a tolerance for medication. Additionally, some PD patients react poorly to DA replacement therapy or it is not enough to relieve their motor symptoms. In

these cases, surgical treatment procedures are recommended (Antonini et al., 2018). Treatment for motor symptoms of PD currently include dopaminergic medication therapy and surgical procedures such as deep brain stimulation (DBS) and Magnetic resonance-guided focused ultrasound thalamotomy (Michael J. Fox Foundation, n.d.).

The most vastly used DA therapy includes DA replacement therapy in form of *Levodopa (L-dopa)*, a precursor of DA that is able to pass the blood-brain barrier and convert to DA in the brain, and *DA agonists*, which mimic the effect of DA in the brain by binding to DA receptors. Medication that is typically used in addition to L-dopa is *Catechol-O-methyltransferase (COMT) inhibitors*, which block COMT from breaking down levodopa in the body, as well as *Decarboxylase inhibitors (carbidopa)*, which assist to lessen the side effects of L-dopa treatment and also help more levodopa to reach the brain. Other DA medications include *Monoamine Oxidase (MAO) inhibitors* that allow available dopamine in the brain to be accessible for a longer period of time by blocking MAO from breaking down DA, as well as *anticholinergic medications* (Antonini et al., 2018; Michael J. Fox Foundation, n.d.).

Surgical options are considered for people who respond poorly to medication and have motor complications in response, or for cases in which some motor symptoms, such as tremor, persist despite medication. *Deep brain stimulation* (DBS) is the most common surgical treatment for PD. Small electrodes are placed in the subthalamic nucleus (STN) or globus pallidus interna (GPi), and continuously deliver high-frequency electrical impulses to these areas through a wire-connected pulse generator – a device placed under the patient's skin – to modulate neural activity. Parameters of electrical signaling, such as frequency, intensity, and pulse width, can then be modulated by a professional as needed to reach desired outcomes in individual PD patients (Antonini et al., 2018). Another surgical option for treating PD is *MR-guided focused ultrasound*

thalamotomy. It is a noninvasive treatment usually chosen by people who, for different reasons and possible complications stemming from their health condition, cannot undergo invasive surgery like DBS. Focused ultrasound aims to the same areas as DBS, however, high-frequency ultrasound beams are directed to STN or GPi unilaterally, to induce ablation in the targeted zone and help reduce tremor (Magara et al., 2014).

Treatment of non-motor disturbances depends on the exact symptoms, thus, can include medication for managing sleep disturbances like *sedatives* (in case of insomnia) or *stimulants* (in case of excessive daytime sleepiness), *pain relievers* or *botulinum toxin injections* for managing pain, *food supplements* or *laxatives* for constipation, *antidepressants*, different forms of *talk therapy* like cognitive behavioral therapy (CBT), *antipsychotics*, etc. (Michael J. Fox Foundation, n.d.).

4.2. Common non-motor symptoms of Parkinson's disease

In addition to the typical motor symptoms such as bradykinesia, rigidity, tremor, and postural imbalance, a wide range of non-motor symptoms is characteristic for Parkinson's disease. Unfortunately, these symptoms are often neglected in treatment, although they are the ones that often majorly lower the quality of life of affected patients, in many cases even more than motor symptoms do (Martinez-Martin et al., 2011). A vast majority of PD patients experience non-motor symptoms – more than 98% of PD patients report at least one non-motor symptom, and an average number of non-motor symptoms reported per patient is 6 (Barone et al., 2009). Non-motor manifestations include sleep disorders, constipation and other autonomic problems, olfactory disturbances, gastrointestinal problems, pain, as well as neurocognitive and neuropsychiatric problems such as cognitive decline and dementia, problems with executive functions, depression, and anxiety (Barone et al., 2009; Chaudhuri et al., 2011; Pfeiffer, 2016). It is interesting that Parkinson's disease is characterized by a long preclinical stage, and that many of these symptoms, most notably depression, constipation, olfactory disturbances, and sleep problems (of which the most common one is rapid eye movement behavioral disorder (RBD)), are present even well before the appearance of motor symptoms and the diagnosis of Parkinson's disease is established (Chaudhuri et al., 2011). Figure 12 shows a timeline of non-motor symptoms preceding the clinical diagnosis of Parkinson's disease. Figure 13 depicts the development of pre-motor and motor symptoms in PD, from early stages preceding clinical diagnosis to the advanced stages of the disease.

A large proportion of PD patients – up to 50% - have comorbid depression or significant depression-related symptoms (Lew, 2007; Marsh, 2013). It is also one of the most common premotor symptoms in PD (Marsh, 2013). This fact argues against the hypothesis that depression in PD is merely a consequence of the lower quality of life due to the chronic disease and points toward the conclusion that some biological factors conjoining depression and PD must be at play. The summary Kapur & Mann (1992, p.5) made three decades ago still stands: “The emergence of depression before the onset of motor symptoms of Parkinson's disease, the lack of relation between the severity of Parkinson's disease and depression; and the higher incidence of depression in Parkinson's disease even when compared with patients with equally disabling illnesses argues against a "reactive" etiology of depression in Parkinson's disease”. There may be a genetic link between PD and depression, since the higher incidence of depression and anxiety has been found in unaffected first-degree relatives of PD patients compared to the general population, suggesting a possible “shared familial susceptibility to PD with depression”, however, more research is needed to support this hypothesis (Arabia et al., 2007). Although Parkinson’s disease is characterized majorly by DA depletion due to degeneration of DA neurons in the SNpc (and in other regions), it has been found that serotonergic and noradrenergic systems are also affected. Lewy bodies are found in the neurons of locus coeruleus (primary noradrenergic neurons’ site) and raphe nucleus (primary serotonergic neurons’ site), as well as in the cerebral cortex of PD patients (Lieberman, 2006). However, these changes were smaller compared to studies of major depression (Anderson, 2004). As described earlier, all three systems of neurotransmitters contribute to depression; however, the fact that the major damage to the DA pathways in Parkinson’s disease, in combination with, in comparison, much smaller alterations in noradrenergic and serotonergic systems, so often cooccurs with depression, indicates that DA

plays an important role in the biology of depression. Moreover, besides the nigrostriatal DA pathway that is mainly affected in PD, there is evidence that mesolimbic and mesocortical pathways are impaired as well (Hemmerle et al., 2012). For example, tyrosine hydroxylase is often used to identify dopaminergic neurons in different brain regions – higher activity of this enzyme suggests the presence of DA cells in a certain area. In PD patients, the activity of tyrosine hydroxylase is significantly decreased in their VTA, which puts forward evidence that mesocorticolimbic pathways in these patients are altered (Zhu et al., 2012). This impairment causes dysfunctions in the orbitofrontal cortex and disruptions of the serotonergic system in the dorsal raphe, which is thought to lead to depression in PD (Marsh, 2013). As discussed in the previous chapter, depletion of DA in the mesolimbic and mesocortical pathway have been shown in different studies to correlate with an increased risk for depression. Finally, it has been found that DA agonists may have a significant effect in alleviating depression in PD in many cases (Rektorová et al., 2003; Saleem & Anwar, 2019). Indeed, one interesting study (Kritzinger et al., 2015) found that there may be a different way depression is manifested in PD patients compared to depressed controls. Specifically, depressed PD patients report less "guilt" and "self-hate" compared to depressed controls, but more general dissatisfaction and "inability to feel pleasure", a feature considered to be DA-dependent and associated with the "pleasure and reward" circuits (Kritzinger et al., 2015). This raises the question of whether the clinical picture of depression in PD manifests differently than in major depression alone, which would help in the early diagnosis of the disease.

A range of cognitive decline symptoms have been consistently reported as one of the most common non-motor symptoms accompanying, or often preceding, PD, and being a significant cause of the lower quality of life, caregiver burden, or disability (Aarsland & Kurz, 2010; Biundo

et al., 2016). With the progression of the disease, a substantial proportion of patients – up to 55% - develop Mild cognitive impairment (MCI) or Parkinson's dementia (Caballol et al., 2007). Within 15 to 20 years from the clinical diagnosis of PD, around 83% of patients develop dementia (Aarsland & Kurz, 2010). Regardless of whether dementia is present or not, problems in executive functions are particularly pronounced in PD patients, and are the most consistently found cognitive impairment in PD (Mckinlay et al., 2010), affecting at least 30% of patients (Parker et al., 2013). These problems manifest in slowed thinking, difficulties in planning and problem solving, impairments in working memory and attention, difficulties in set-shifting, and in lowered impulse control (Aarsland & Kurz, 2010; Rowe et al., 2008). Numerous studies have demonstrated and replicated that, compared to age-matched controls, PD patients performed worse on a range of tests that measure executive functions, such as Wisconsin Sorting Card Test, Stroop Test, Tower of London, and Trails Making Test (Dirnberger & Jahanshahi, 2013). A meta-analysis conducted by Kudlicka et al. (2011) that analyzed results of 33 studies of early-staged, unmedicated PD patients on a variety of standard neuropsychological tests of executive functions showed that, indeed, PD patients show significant impairments in executive functions. As mentioned in the Introduction, dopamine has a crucial role in regulating executive functions, mainly through the mesocortical pathway. Indeed, in animal studies, depletion of DA has cognitive deficits as a consequence, manifesting in impairments in working memory, decision making, planning, attention, and set-switching (Schultz, 2007). Treatment of PD with DA treatment, besides improving motor symptoms, very often substantially improve cognitive problems in these patients as well (Kehagia et al., 2012; Rowe et al., 2008). Alterations in the mesocorticolimbic DA pathway probably account for executive function impairments in PD. It has been shown that there are DA deficits in the caudate nucleus and putamen even in the early stages of PD, and only with progression of the

disease ventral striatum becomes more depleted. Dorsal caudate nucleus is heavily connected with dorsal parts of the frontal lobe, including dorsolateral PFC, an area largely responsible for executive functions like planning, attention, decision making, etc. Ventral caudate is more connected to the ventral frontal lobe regions, including ventrolateral PFC, more responsible for, generally speaking, emotional processing, motivation, and reward (Leh et al., 2010). The involvement of mesocortical pathway pathology in executive dysfunction of PD patients has been supported by results showing that, with DA therapy, patients with early Parkinson's disease show improvement on tasks that engage dorsal frontostriatal circuits. On the other hand, their performance stays the same or even worsens on cognitive tasks related to the activity of ventrostriatal circuits, probably because of the 'overdose' with dopamine in this area with treatment, since DA is still not substantially depleted in the ventral striatum and its connections to the ventrolateral PFC are still more or less intact (Cools, 2006; Leh et al., 2010). Thus, alterations in mesocorticolimbic pathways largely account for executive dysfunctions and depression in PD, and the above-described data (impairments in the mesocortical pathway preceding alterations in the mesolimbic pathway) may explain why cognitive impairments and problems in executive functions appear earlier in the course of the disease, and depression and apathy usually, if present, appear closer in time to the onset of motor symptoms. However, it is important to note that DA treatment does not restore all cognitive abilities, which implicates that factors other than DA-related, such as other neurotransmitter systems, might also account for cognitive deficits in these patients (Biundo et al., 2016). Same goes for depression in PD, as explained earlier in this chapter.

Impulsivity and related regulatory behavioral disturbances are also frequent non-motor symptoms accompanying Parkinson's disease. In the Italian cohort, it has been reported that around 28% of PD patients experience some form of abnormal impulsive behavior (Isaias et al.,

2008). Impulse control disorders (ICDs) are characterized by "a loss of voluntary control over impulses, drives, or temptations to engage in excessive hedonic behavior that interferes with daily functioning and is harmful for the patient and others" (Ruitenberg et al., 2018). An interesting study conducted by Djamshidian et al. (2012) compared PD patients with and without ICDs with three groups: substance abusers, pathological gamblers, and healthy, age-matched controls. They found that "all patients with PD made more impulsive and irrational choices than the control group. PD patients who had an ICD showed similar behavior to illicit substance abusers, whereas patients without ICDs more closely resembled pathological gamblers" (Djamshidian et al., 2012). In PD patients, ICDs often manifest as gambling, binge eating, compulsive buying, and hypersexuality (Antonini & Cilia, 2009). These behaviors, as well as other potentially harmful reward-seeking or repetitive behaviors, appear to be a side-effect of DA replacement treatment, mostly DA agonists and especially in higher doses (Weintraub et al., 2015). PD patients under DA agonist therapy have a 2 to 3 times higher chance of developing some form of ICD compared to non-treated patients (Antonini & Cilia, 2009). ICDs in PD patients under DA replacement therapy might be a result of an 'overdose' of DA with DA agonists in the ventral striatum, associated with reward- and punishment-related learning. More precisely, decreased D2 receptor binding and relatively unchanged D1 receptor binding were found in the ventral striatum of PD patients with ICDs compared to PD patients without pathological impulsive behaviors. To remind, D1-like receptors are coupled to excitatory cAMP signaling and are related to reward-based learning, while D2-like receptors are coupled to inhibitory cAMP and are associated with avoidance-based or negative reinforcement learning. The most common DA agonists are more selective to D2-like receptors than to D1-like receptors. It has been hypothesized that DA treatment can lead to overstimulation of D2-like receptors in the relatively spared ventral striatum, which impairs negative reinforcement

learning, while positive effects of the reward experienced through D1-like receptors remain intact (Augustine et al., 2021). Thus, DA treatment, especially DA agonists, can lead to impairments in risk-reward processing by inducing overactivity of reward-seeking circuits and hypoactivity of avoidance-learning circuits, hence inflicting ICDs in PD patients undergoing DA treatment. Figure 14. comprehensively shows how striatal dopamine levels in different DA pathways influence different (dis)functions that appear in PD. It is important to note that DA treatment-induced ICD in PD patients is not a "must" – many PD patients don't develop ICDs as a side effect of DA replacement treatment. It is probable that ICDs are triggered by DA agonist therapy in individuals with amplified trait impulsivity (Isaias et al., 2008), or in already predisposed individuals, for example those with prominent trait novelty seeking, or with a history of substance use disorders (Antonini & Cilia, 2009).

Lastly, unbalanced HPA activity has been consistently found in PD patients (Ibrahimagic et al., 2016; Soares et al., 2019; van Wamelen et al., 2020). This population shows elevated levels of plasma cortisol (Herrero et al., 2015) and is more likely to demonstrate DST non-suppression reaction (Du & Pang, 2015) in comparison with age-matched controls. Lewy body pathology has been found in the adrenal glands and the hypothalamus of PD patients, which has been hypothesized to be the main cause behind the apparent dysregulation of the HPA axis of these patients. However, the exact mechanisms that lead to such dysregulation in PD are still not well understood (Herrero et al., 2015). Since there are significant overlaps between HPA overactivity and PD symptoms, the are some speculations about the causal link between stress and PD, or at least a significant correlation. For example, some studies found that hyperactivity of the HPA axis, inflicted by early psychological stress, is associated with reduced DA synthesis and can intensify DA depletion in the brain (Dallé & Mabandla, 2018). Some authors (Djamshidian & Lees, 2014)

hypothesize that prolonged stress could be a potential trigger for nigrostriatal depletion of DA neurons in susceptible individuals and lead to PD. They describe the relationship between motor functions and stress from different studies, including animal models. For example, elevated glucocorticoid levels in rats can worsen motor performance and lead to neurodegeneration in the SN. Additionally, DA release and turnover in the striatum of rats increases in response to stressful stimuli, and chronic exposure probably "excites striatal dopamine nerve terminals to death through increased oxidative stress" (Djamshidian & Lees, 2014). Moreover, biologically induced stress with corticosterone in animal models has been shown to trigger a neuroinflammatory response and enhance DA neurotoxicity, as well as inflict the appearance of PD-like features (Kelly et al., 2012). Thus, abnormally and chronically high levels of cortisol that reflect the unbalanced HPA axis are associated to DA neurodegeneration found in PD patients, and could be responsible for PD progression (Ibrahimagic et al., 2016). However, since neuroinflammation in the brain, which happens as a result of any neurodegenerative disease including PD, is considered as a biological stress by the organism, it increases the activity of the HPA axis as a response. Hence, it is difficult to determine the initial cause and the consequence in this circle – whether the HPA axis is responsible for DA neuronal loss and worsening the PD symptoms, or whether PD progression leads to chronic and irreversible HPA axis impairments (Ibrahimagic et al., 2016). It is probable that the relationship is mutual, and that stress is a mediator of PD development. Since evidence about the correlation between stressful life events and risk for PD is ambiguous and inconsistent, perhaps susceptibility to psychological and/or psychological stress may be a 'diathesis' factor for the development of PD in case of exposure to chronic stress (van Wamelen et al., 2020). Lastly, dysfunctional activity of the HPA axis has been associated with a higher incidence of depression

in PD patients (Du & Pang, 2015). This is not surprising, considering the fact that dysfunctional HPA axis has been consistently found in depressed patients, as discussed in Chapter 1.

Altogether, non-motor symptoms of PD are frequent, precede and accompany the motor symptoms, and lead to a significant decrease in the quality of life. Many of these symptoms, such as depression, ICDs, and cognitive decline, are in part regulated by DA and probably induced by its alterations, both by DA deficits in some parts of the brain stemming from neurodegeneration of DA neurons, or by DA overstimulation in other parts of the brain instigated from DA medication therapy. They lead to a significant decrease in the quality of life of PD patients, thus calling for more extensive research and, in practice, more detailed assessment and careful management.

5. Suicide in Parkinson's Disease

A considerable feature the majority of PD patients experience is the lower quality of life that stems from motor and, notably, non-motor symptoms, as discussed in the previous chapter. Some of these patients may have an increased risk of suicide. PD is associated with higher suicidality, with some authors estimating a 2-fold increased suicide risk in PD patients compared to the general population (Chen et al., 2021). However, the literature on this topic is inconsistent (Shepard et al., 2019), with some studies demonstrating a strong positive association between PD and suicide (Chen et al., 2021; Lee et al., 2016), and others suggesting that there is no doubt about the existence of increased suicidal ideation in PD – around ¼ of PD patients experience it - but that the correlation between PD and suicide attempt is still in question (Kostić et al., 2010; Nazem et al., 2008). Kummer et al. (2009) found that the rate of suicidal ideation in PD is, indeed, very high, significantly higher compared to the general population, but that suicide attempts are not so common, and that depression is the strongest predictor of suicidal ideation in PD patients. Elevated suicidal ideation in PD patients was confirmed by newer studies (Belvisi et al., 2019) not only compared to age- and sex-matched general population, but also compared to matched patients with chronic medical conditions other than PD, such as psoriasis. Suicidal ideation in PD patients correlated with the presence of motor complications, severity of non-motor symptoms, perceived disability, and the presence of psychiatric disturbances, including depression and psychosis. However, suicidality in PD is only partially, but not fully explained by the lower quality of life and/or higher rates of mental disorders present in this population, thus suggesting that PD in itself,

or some other specific features present with it, may greatly contribute to the suicide risk (Belvisi et al., 2019). One study (Chen et al., 2021) showed that PD patients who died by suicide have a somewhat different 'profile' compared to suicide victims in general population – PD patients were younger at their time of death and more likely to have a diagnosis of mental disorder. However, among PD patients, the severity of PD symptoms, duration of the disease, or severity of comorbid mental disorders, including depression, did not proportionally correlate with an increased suicide risk, suggesting that the lower quality of life and a psychiatric diagnosis do correlate with an elevated suicide risk but are not enough to fully explain a higher rate of suicide among PD patients (Chen et al., 2021). It is important to note that none of these studies included PD patients with ICDs or assessed their cognitive abilities and executive functions, which are all strongly associated with elevated suicide risk, as discussed in Chapter 1., and frequently present in patients with PD, as mentioned in Chapter 4. Additionally, none of the above-mentioned studies included PD patients undergoing DBS. Perhaps increased impulsivity and impairments in executive functions are features that may be important mediators of the suicide risk in PD. As mentioned in Chapter 1., impulsivity is thought to be, by some authors, a factor that facilitates the transition from suicidal ideation to suicide attempt, and the same could be true for PD patients. Support for this hypothesis comes from studies that report a significant correlation between increased risk of completed suicide and higher dosages of L-dopa medication in PD patients (Lee et al., 2016). This relationship was present even when controlled and adjusted for sex, age, and other clinical variables. It is probable that completed suicide in PD patients is a result of increased impulsivity induced by higher levels of DA from DA medication (Lee et al., 2016).

Evidence in this direction is also provided by reports of increased rates of suicides, suicide attempts, or suicidal ideation in PD patients after Deep brain stimulation (DBS) treatment

(Burkhard et al., 2004; Costanza et al., 2021; Du et al., 2020; Giannini et al., 2019). DBS is a surgical treatment used particularly for advanced PD, and also in cases of medication-induced complications or medication-resistant PD. Electrical impulses are delivered through thin electrodes to either Subthalamic nucleus (STN) or Globus pallidus internus (GPi), this way interrupting pathological signaling in these areas. DBS very effectively alleviates motor symptoms of PD and, sometimes, non-motor symptoms as well (Tarsy et al., 2008). However, there are frequent reports of DBS worsening non-motor symptoms and inducing adverse mood and cognitive side effects (Antonini & Cilia, 2009). For example, although DBS can have an alleviating effect on depression in some PD patients, it is it may induce or worsen symptoms of depression and anxiety in others (Castrioto et al., 2014; Couto et al., 2014). Voon et al. (2008) report that up to approximately 25% of PD patients may experience transient or chronic depressive episodes after DBS treatment, even after significant improvement of motor symptoms. Strutt et al. (2012) found that the incidence of depression among PD patients rose from 12% pre-treatment to even 56% of patients meeting criteria for at least mild depression following STN DBS. These effects seem to be more prominent after STN DBS than GPi DBS. Although STN DBS is more frequently used than GPi DBS, there is evidence that GPi DBS may produce fewer or less severe non-motor side effects, especially when it comes to depression and anxiety, while retaining the same efficacy for improving motor symptoms as STN DBS (Negida et al., 2018; Liu et al., 2014; Marsh, 2013). There are several possible explanations for the increased number of cases with depressive symptoms following STN DBS. STN is centrally located within the basal ganglia, and besides its main role in regulating motor activity (and disruptions within its signaling manifesting as motor symptoms of PD), it is also involved in associative and limbic circuits, particularly ventromedial associative and medial limbic parts of these circuits. STN is also innervated with a network of 5-

HT fibers, and they can modulate each other's activity (Tan et al., 2011). It has been demonstrated in animal models that STN DBS can inhibit 5-HT neuronal activity in the dorsal raphe nucleus (Temel et al., 2009) as well as reduced 5-HT release in the dorsal striatum, medial prefrontal cortex, and hippocampus (Tan et al., 2011). Moreover, high-frequency STN stimulation in rodent models of PD induced depressive-like behaviors, which were reversible with SSRIs (Temel et al., 2007) Such findings suggest the involvement of 5-HT in the neurobiological mechanisms behind DBS post-operative depression in PD patients, which are also supported by reports of SSRIs being effective in reducing DBS-following depressive symptoms in human studies (Tan et al., 2011). An additional explanation may be related to the possible occurrence of "dopamine withdrawal syndrome" as a result of the significant decrease in dopaminergic medication after STN-DBS, characterized by a range of autonomic and neuropsychological withdrawal symptoms, including depression and anxiety (Castrioto et al., 2014). Finally, incorrect electrode placement, inappropriate parameters of the stimulation, or a spread of the stimulation field to the surrounding circuits could also be associated with DBS-related mood changes (Marsh, 2013).

Another frequently reported side effect of STN DBS in PD is decreased impulse control, as well impairments in executive functions (Combs et al., 2015). An increased number of cases of pathological gambling behaviors, hypersexuality, or impulsive aggressive behaviors emerged after STN DBS of PD patients, and these behaviors were able to diminish after discontinuation of stimulation or changing the parameters (Smeding, Goudriaan, et al., 2007; Soulas et al., 2008). STN DBS in PD patients showed to possibly negatively impact decision-making processes leading to premature, impulsive decisions (Frank et al., 2007). PD patients also tend to show premature responses in the Stroop's interference task after DBS more prominently than pre-operatively, suggesting declines in frontal lobe functions (Soulas et al., 2008). Newer studies show that the

effect on inhibitory control may depend on the location of DBS stimulation - stimulation of the ventral parts of the STN may lead to impairments while stimulation of the dorsal parts of the STN may lead to improvements of inhibitory control – and on the degree of "conflict" in the decision-making situations, with greater ambiguity corresponding to heightened impulsivity after STN DBS (Scherrer et al., 2020). Combs et al. (2015) demonstrated that PD patients who underwent STN DBS show greater than expected impairments in overall cognition, including verbal fluency, memory, attention, psychomotor speed, and executive functions. Again, these effects show to be slightly more prominent after STN DBS than after GPi DBS (Combs et al., 2015). Inhibition-related and executive functions impairments following STN DBS are not so surprising, considering the role of STN in basal ganglia. In PD, abnormal STN signaling induces motor, cognitive, and emotional inhibition. STN DBS interrupts this abnormal signaling, alleviating motor symptoms. However, it can lead to the reversal of such inhibition, which can manifest as excessive motor, emotional, and behavioral disinhibition (Castrioto et al., 2014). These effects are reversible and may be a result of inappropriately set DBS parameters; with proper adjustments, these impairments should diminish (Smeding, Munckhof, et al., 2007). It is important to note, though, that DBS does not have an exclusively negative effect on impulse control; in many cases, DBS can improve cognitive abilities and reduce ICDs (Razmkon et al., 2021; Witt et al., 2008).

Some of the adverse side effects that emerge as side effects of DBS in PD patients may increase the risk of suicide after the procedure. It is estimated that, among patients who underwent STN DBS, 0.4%-1% may complete suicide while 0.9%-2% may attempt suicide (Soulas et al., 2008; Voon et al., 2008). A recent meta-analysis by Costanza et al. (2021) estimates these rates to be even higher after both GPi and STN DBS – up to 6.1% for suicide attempts and 4.6% for completed suicides. The risk of suicide is estimated to be the highest in the first post-operative

year (Burkhard et al., 2004). The suicide risk following DBS has been linked to post-operative depression, anxiety, and history of impulse control disorders, and younger age of onset (Du et al., 2020; Voon et al., 2008). However, these factors are not enough to entirely explain elevated suicide rates in PD patients after DBS. With these factors explaining around 51% of the variance (Voon et al., 2008), a big proportion of possible explanations behind increased rates of suicides in PD following DBS is left to debate. Still, it is important to have in mind that *depression*, probably induced by a combination of disrupted 5-HT signaling from STN modulation and dopamine withdrawal from reduction of medication, as well as impairments in *executive functions* and emotional and behavioral *disinhibition* induced by excessive "inhibition release" of STN, can significantly increase the risk of suicide in PD patients after DBS treatment, especially STN DBS. This calls for more extensive research on this topic in the future, but also for more careful and detailed pre-DBS screening and post-DBS evaluation, to minimize the risk for suicide. Patients undergoing DBS, especially the ones with a history of ICDs or depression, but also those without such history (since these symptoms can emerge for the first time as a side effect of DBS) should be attentively assessed, followed, and managed, with these risks in mind. Other risk factors, such as being single, or young age at onset, should also be taken into account.

Discussion

Parkinson's disease is a neurodegenerative disorder affecting the older population and significantly lowering the quality of life because of both motor and non-motor symptoms. The most common motor symptoms include bradykinesia, rigidity, tremor, and postural imbalance. The most common non-motor symptoms discussed in this thesis include depression, impulsivity, and cognitive decline including problems with executive functions.

Suicidal ideation is markedly elevated in patients suffering from PD, with an increased risk to die by suicide (Chen et al., 2021). This may partly be a result of the lower quality of life; however, it is definitely not enough to explain an elevated risk for suicide. Many major risk factors of suicide overlap with the most common non-motor symptoms present in PD. Throughout this thesis, it was demonstrated that these overlapping factors have dopamine alterations as their main background, which may be putting PD patients at a higher risk for suicide.

Psychiatric disorders are the most important risk factor for suicide – it is estimated that even 90% of individuals who died by suicide were diagnosed with a psychiatric condition (O'Connor and Nock, 2014). Out of psychiatric disorders, major depressive disorder is by far the most common among suicide attempters and completed suicides. A major depressive episode, as part of any disorder, can be accounted for around 50% of all suicides (Turecki & Brent, 2016). The second most common diagnosis among individuals who engage in suicidal behavior are substance use disorder, especially alcohol-related. Part of the reason why this diagnosis is so common among this population is because it is often comorbid with psychiatric disorders, such as depression, however, another part lays in the fact that some substances, such as alcohol, lead to disinhibition of behavior, which can lead to decreased impulse control and, possibly, suicide

attempt. Indeed, it is estimated that at least 40% of suicides are done under the influence of alcohol (Bachmann, 2018). Some authors, as mentioned in Chapter 2, propose that psychiatric disorders are good predictors of suicidal ideation, but not exactly that good in estimating the risk of suicide attempt, and that there are some factors that facilitate the transition from suicidal ideation to suicide attempt, such as environmental factors, genetics, neurobiological factors, personality traits, and cognitive factors, including impulsivity and problems with executive functions (Turecki et al., 2019). Thus, alcohol use and alcohol dependence may be a factor that contributes to the facilitation of transition from suicide ideation to suicide attempt through disinhibition.

There is a negative correlation between the level of development of "higher functions of the brain" and the risk of suicide (Grover et al., 2009; Spear, 2018). Deficits in executive functions such as problem-solving-, attention-, and working memory-related deficits have been correlated with suicidality, and may be uniquely associated with suicide attempts (Saffer & Klonsky, 2018). Another important risk factor possibly uniquely associated with suicide attempts and considered to be the facilitator of the transition from suicidal ideation to suicide attempt is impulse control (Gvion & Apter, 2011). Decreased capacity for general inhibition and impulse control, together with problems with executive functions, may be contributing to cognitive rigidity and inability to "see the bigger picture" in times of stress, as well as lead to disinhibited behaviors when it comes to acting on thoughts of self-harm (Carballo et al., 2009).

Disruptions of different neurotransmitter systems, as well as alterations in the function of the HPA axis, are associated with suicidal behaviors. Decreased serotonin and norepinephrine neurotransmission have been consistently found in different parts of the brain of suicide victims and those who attempted suicide, independently of a psychiatric diagnosis (Mann & Currier, 2010). As explained in Chapter 3: "Decrease in serotonin levels have been associated with

increased impulsivity and reactive aggression, while depletion of norepinephrine is correlated with increased hopelessness and pessimism, both factors appearing as significant components of suicidal behavior" (Duica et al., 2020). Lower levels of dopamine are associated with an increased risk of suicide as well. This relationship is partly through the route of depression - besides disrupted 5-HT system, hypoactivity of DA signaling have been found in depression (Friedman et al., 2008), and medication that influences DA levels can be effective for treatment of depression in patients who appear to be resistant or semi-resistant to antidepressants that target serotonergic system, such as SSRIs (Belujon & Grace, 2017). Moreover, some studies suggest a more direct link between DA levels and suicide and demonstrate a unique relationship between dopamine and suicide attempts (Pitchot et al., 2001).

Finally, unbalanced HPA-axis, more precisely, hyperactivity of the HPA-axis has been consistently found in psychiatric disorders such as depression, anxiety, substance use disorders, etc., and is strongly correlated with suicide risk (Pompili et al., 2010). This correlation may be independent of any psychiatric condition (Berardelli et al., 2020) or it may be through the presence of them (Du & Pang, 2015), but it nonetheless exists and is an important risk factor for suicidal behavior. The HPA axis is bidirectionally linked to serotonergic, noradrenergic, and dopaminergic systems. Disturbances in either of these systems can inflict disruptions of the others, leading to a range of cognitive, emotional, and behavioral consequences, including, with other factors involved of course, suicidal behaviors.

PD is characterized by a long pre-clinical state, with many non-motor symptoms emerging well before the manifestation of first motor symptoms. One of such non-motor symptoms is depression. It is one of the most common non-motor symptoms preceding and accompanying PD,

with up to 50% of patients reporting depression-related symptoms (Lew, 2007). Such an increased incidence of depression in this population may partly be an effect of the lower quality of life that often comes with the disease, but its emergence before the quality of life is affected, the lack of consistent correlation between the severity of disability and depression, and found familial susceptibility of PD patients and their relatives to depression, argue in favor of the biological etiology of depression in this case (Kapur & Mann 1992; Arabia et al., 2007). DA depletion plays a role in the biology of depression in PD. Lewy body pathology is found in locus coeruleus and raphe nucleus of PD patients, suggesting that serotonergic and noradrenergic systems are disrupted (Lieberman, 2006). Furthermore, PD pathology does not affect the nigrostriatal pathway exclusively - mesocorticolimbic pathways become gradually depleted of DA and impaired, eventually manifesting as apathy and "decreased ability to feel pleasure" (Kritzinger et al., 2015). Expectedly, unbalanced HPA-axis activity is markedly and consistently present in PD pathology (van Wamelen et al., 2020). Such dysregulation may be a part of depression-related symptomatology accompanying PD, however, there is convincing evidence that, in PD, it may be caused by DA depletion that imposes (prolonged) stress on the organism which results in the dysregulation of the HPA-axis in PD patients (Ibrahimagic et al., 2016). Vice versa may be true as well – prolonged stress could trigger neurodegeneration of DA neurons in the SN or lead to DA neuronal death through increased oxidative stress (Djamshidian & Lees, 2014). Whatever the direction is, an unbalanced HPA-axis may be a part of the diathesis for PD, as well as for suicide.

Problems with executive functions are another very common non-motor symptom of PD, affecting at least 30% of patients (Parker et al., 2013). As mentioned in Chapter 4, these problems manifest as "slowed thinking, difficulties in planning and problem solving, impairments in working memory and attention, difficulties in set-shifting, and in lowered impulse control"

(Aarsland & Kurz, 2010; Rowe et al., 2008). Depletion of DA in the mesocorticolimbic pathways, again, makes up a large proportion of the background of these impairments in PD patients. It seems that dorsal caudate, which is heavily connected with dorsolateral PFC and other parts of the frontal lobe responsible for executive functions, gets depleted of DA earlier than ventral caudate, which is connected more to the ventrolateral PFC and other regions more responsible for emotional processing, motivation, and reward (Leh et al., 2010). This may explain why first symptoms of cognitive deterioration and problems with executive functions often emerge earlier in time compared to depression during the preclinical stage of PD.

DA treatment, especially treatment including DA agonists, can help in reducing motor symptoms and also alleviating many non-motor symptoms of PD. However, one complication that can emerge as a side-effect of DA therapy is increased impulsivity and ICDs (Antonini & Cilia, 2009). ICDs in these patients may be a result of an 'overdose' of DA, inflicted by DA medication, in the mesolimbic pathway, responsible for reward-seeking and avoidance-learning behaviors, hence impairing risk-reward processing (Augustine et al., 2021). Thus, PD patients under DA medication tend to show more impulsive behaviors, one of the important risk factors for suicide.

Lastly, an increased incidence of suicides has been reported after DBS, especially STN DBS (Giannini et al., 2019). This is surprising, considering the fact that the motor impairments markedly improve and the quality of life significantly increases in PD patients after this surgical intervention. STN DBS can alleviate non-motor symptoms in some patients, but also can bring adverse mood and cognitive effects in others (Tarsy et al., 2008; Antonini & Cilia, 2009). Increased incidence of depression after STN DBS can be a result of a possibly inhibited 5-HT activity as a result of hyperactive STN, which is demonstrated in different animal models and reversible with SSRIs (Temel et al., 2007), in combination with dopamine withdrawal syndrome possible to occur

after STN DBS when the dose of the DA medication is drastically lowered (Castrioto et al., 2014). Increased impulsivity, impairments of executive functions, and other cognition-related problems can also occur in PD patients following STN DBS (Combs et al., 2015). This is probably the effect of the "reversal of STN inhibition", meaning that stimulation of STN, instead of leading to its optimal functioning, can sometimes lead to its disinhibition that manifests in emotional, behavioral, and cognitive domains (Castrioto et al., 2014). As discussed in Chapter 5, the mechanism by which DBS may increase the suicidal risk in PD patients is that: "*depression*, probably induced by a combination of disrupted 5-HT signaling from STN modulation and dopamine withdrawal from reduction of medication, as well as impairments in *executive functions* and emotional and behavioral *disinhibition* induced by excessive "inhibition release" of STN, can significantly increase the risk of suicide".

In sum, it seems that PD patients are (at least) at a triple risk of suicide:

- The majority of PD patients belong to the *elderly population*. The risk for suicide increases with age, and the elderly are the age group at the highest risk of suicide.
- *DA depletion*, characteristic for PD, is associated with depression and with executive functions problems. Both of these are important risk factors for suicide, and also common non-motor symptoms of PD. Additionally, DA depletion is associated with HPA-axis disturbances, which has been consistently found in PD patients, as well as in suicide victims.
- DA medication therapy can result in a *DA 'overdose'* of certain areas of the brain, resulting in increased impulsivity, known as one of the major risk factors for suicide, or an element

that facilitates the transition from suicidal ideation (which is increased in PD patients) to suicide attempt. Additionally, adverse mood and cognitive side-effects sometimes emerge following STN DBS, caused by overstimulation and, thus, disinhibition of STN, resulting in increased depression, impulsivity, or executive dysfunctions in some patients, hence increasing the risk for suicide.

In conclusion, PD patients are at an increased risk for suicide, and an inadequate DA amount – in both directions - plays an important role: deficits of DA can have depression or cognitive problems as a result, while excess of DA produced by DA agonists and other DA medication, as well as possible side effects of STN DBS, can increase impulsivity and impair executive functions. This is especially important in the context of the age of these patients, as well as the fact that their quality of life may be significantly decreased due to the clinical manifestations of the disease. In such circumstances, depression, cognitive rigidity and impaired decision-making can contribute to elevated suicidality, with increased impulsivity possibly facilitating the transition from suicidal ideation to suicide attempt. It is important to remember, though, in the light of the diathesis-stress model, that suicide is a combination of previous susceptibility or diathesis, and a current stressor that interacts with it. In PD patients, unbalanced HPA axis and previous increased trait impulsiveness may comprise the diathesis for suicide, while stressors may be the clinical diagnosis and its manifestations, depression, acute stress that comes with the burden of the disease, etc. Presence of any of these 'stressors' may not lead to suicide of course, however, if the diathesis is also present, it is important to closely follow these patients in order to timely provide adequate preventative intervention.

It is incredibly important to have optimal ways of assessing suicide risk in PD patients and to follow them carefully after the diagnosis is made and during the established therapy, with a special focus on the above-mentioned risk factors. Additionally, the increased incidence of suicides after STN DBS calls for future research in order to illuminate the possible link between DBS and suicide, and also for careful pre-operative screening and post-operative follow-up. Pre-screening should include the information about previous psychiatric disorders, as well as, if possible, the assessment of cognitive functions with a special focus on executive functions, as well as the presence of impulsivity, apathy, or issues with anger and/or irritability. The first year following DBS should be marked by a careful and consistent follow-up, with a special focus on depression or depressive-like symptoms, impulsivity, executive functions, as well as assessments of suicidal ideation, with a timely adjustment of medication and DBS parameters. Some form of psychotherapy, such as cognitive-behavioral therapy, or PD support groups, may also be recommended, to help the patient adjust and cope with changes that come with (still) incurable neurodegenerative disease. The aim of this thesis was to provide a new perspective on the role of DA in suicidality, with a focus on PD, in hopes to contribute to a better understanding of suicidality in this population, but also in general, and possibly contribute to better preventative measures.

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Appendix

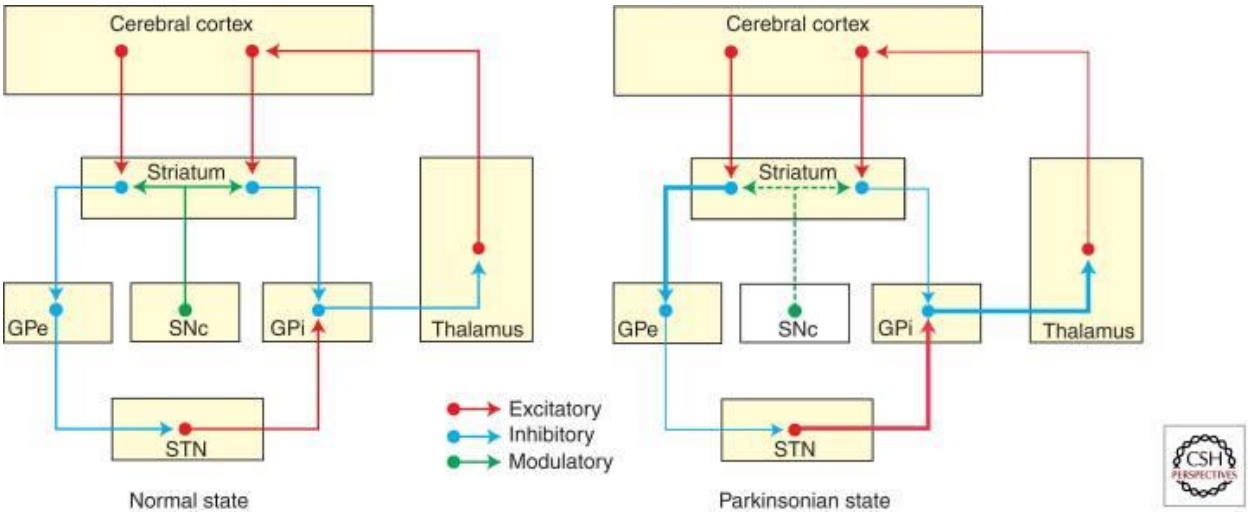

Figure 1. Schematic representation of the motor pathways in a normal state and in a Parkinsonian state. Thickness of arrows represents the functional state of the projection – thicker for hyperactive and thinner for hypoactive circuits. Source: Lanciego et al., 2012.

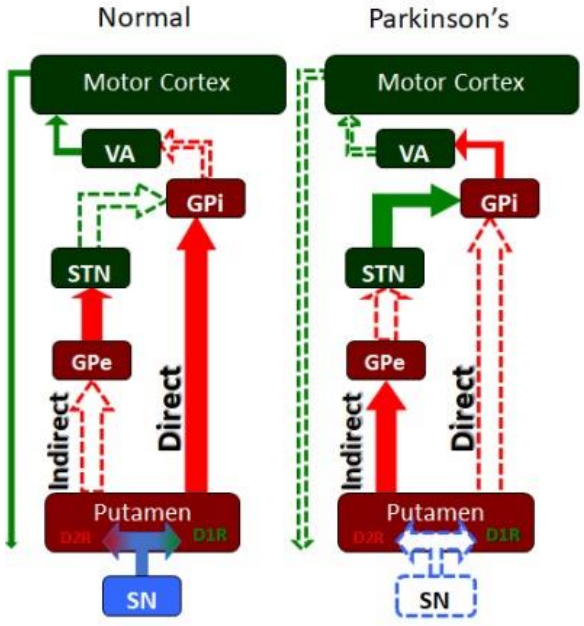

Figure 2. Schematic representation of the motor pathways in an unaffected brain and in PD brain. Source: Young et al., 2021.

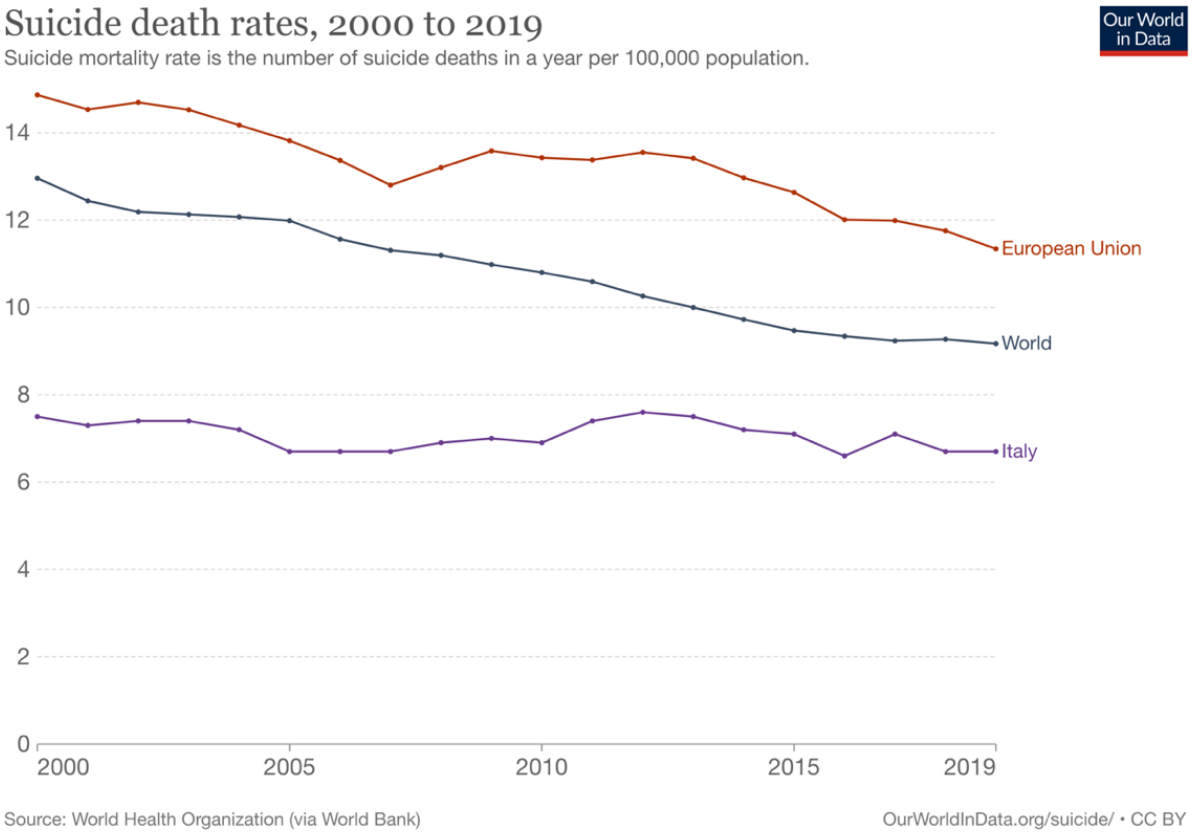

Figure 3: Suicide rates in Europe vs. Italy vs. World, 2000-2019
Source: www.ourworldindata.org/suicide

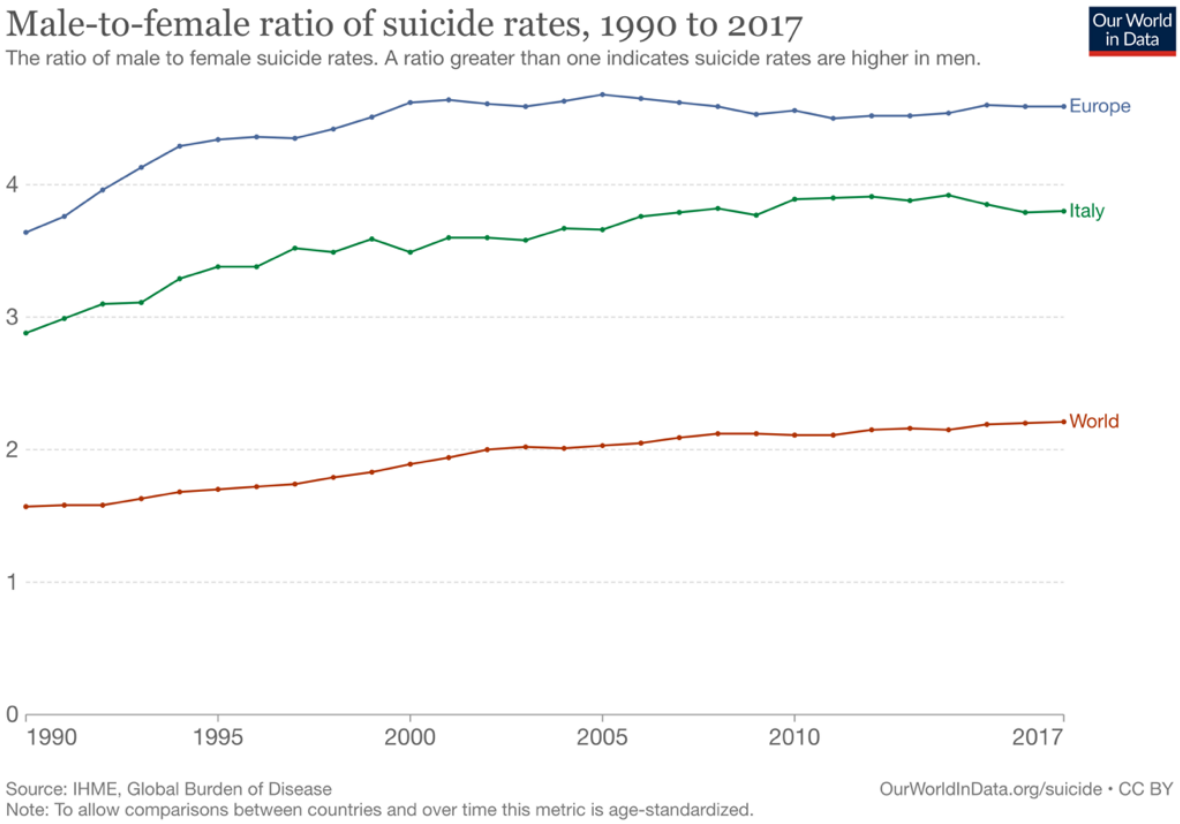

Figure 4: Suicide rates ratio comparison between men and women:
World vs. Europe vs. Italy
Source: www.ourworldindata.org/suicide

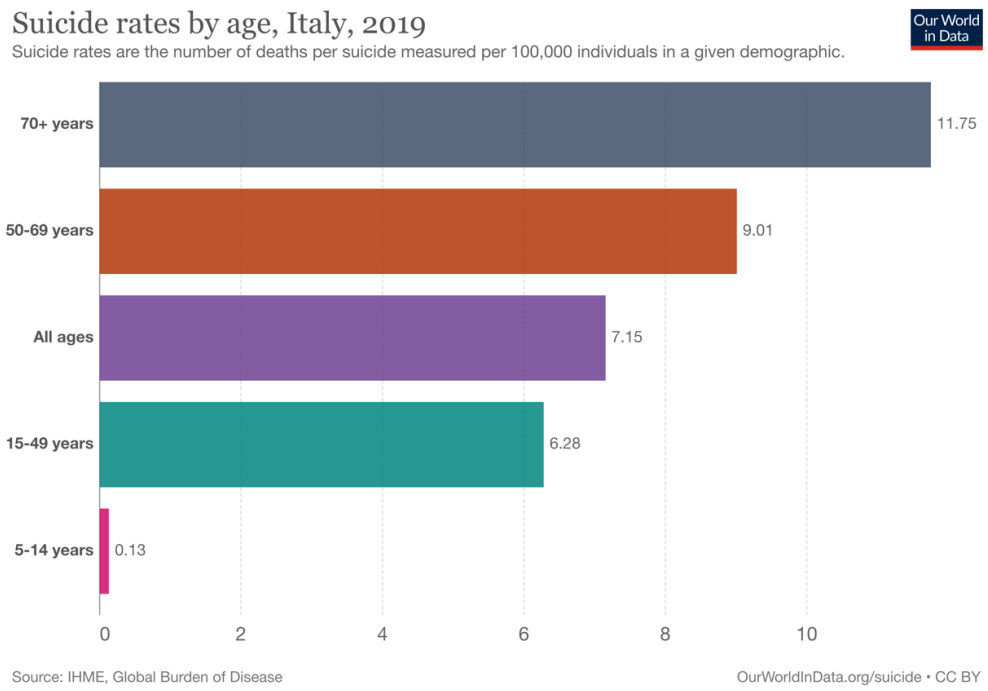

Figure 5: Suicide rates in different age groups in Italy, 2019
Source: www.ourworldindata.org/suicide

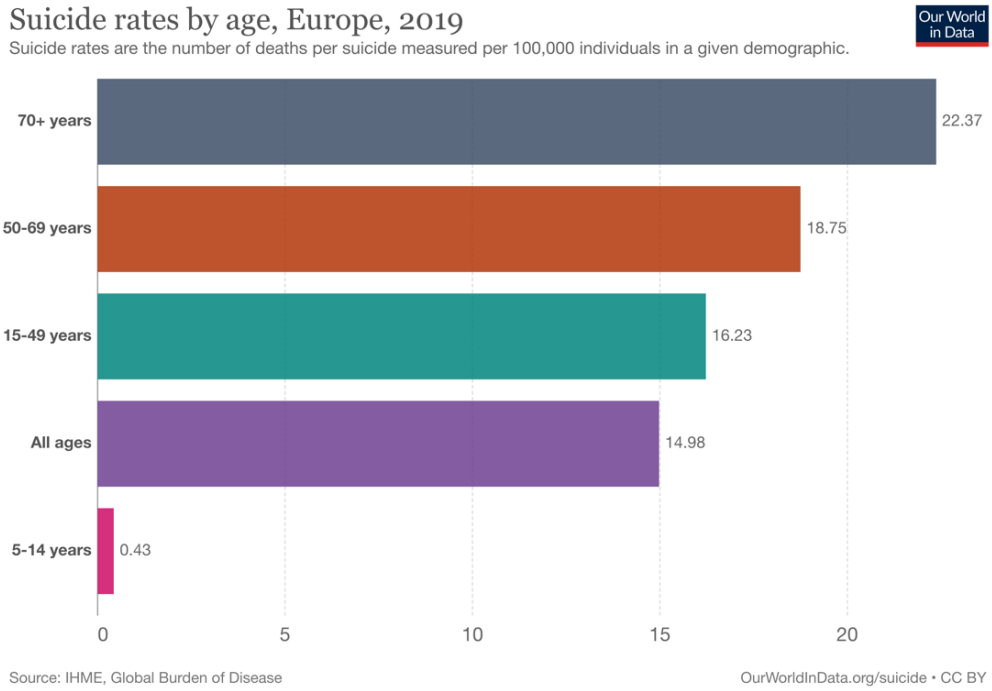

Figure 6: Suicide rates in different age groups in Europe, 2019
Source: www.ourworldindata.org/suicide

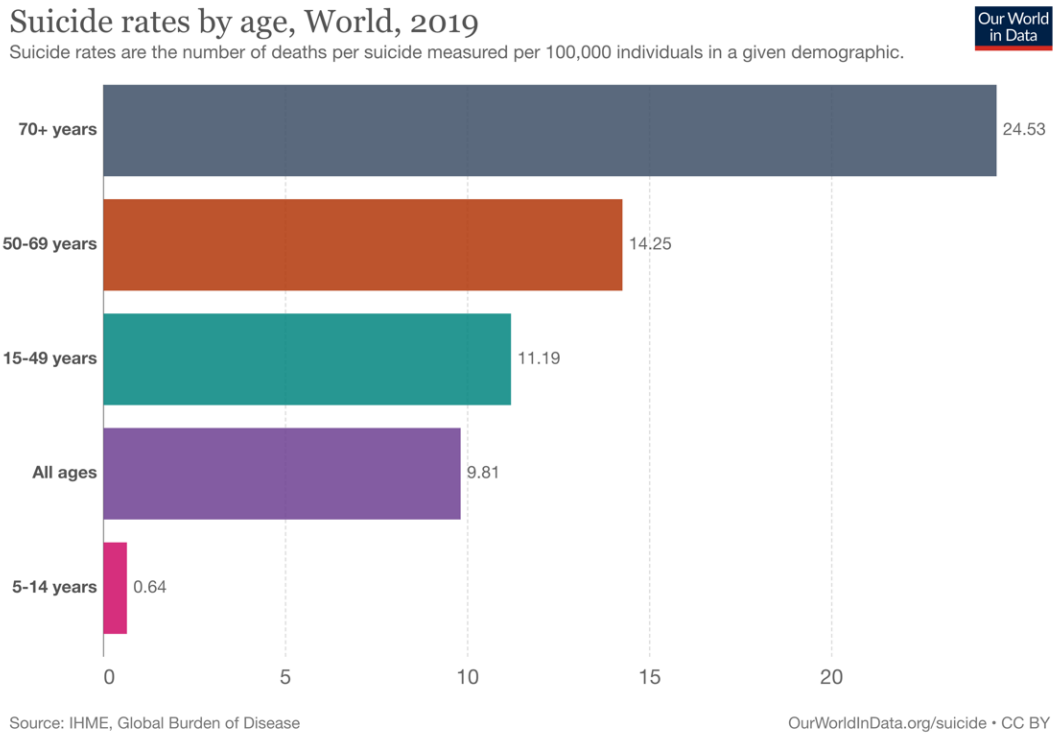

Figure 7: Suicide rates in different age groups in the World, 2019
Source: www.ourworldindata.org/suicide

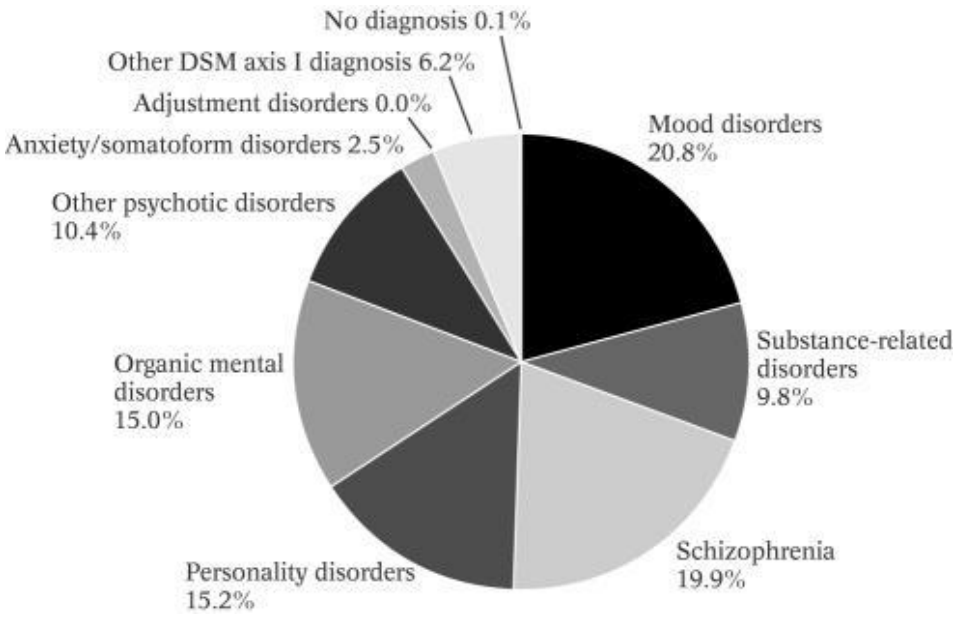

Figure 8: Distribution of psychiatric diagnoses in inpatients who attempted or completed suicide
Source: Bertolote & Fleischmann, 2002

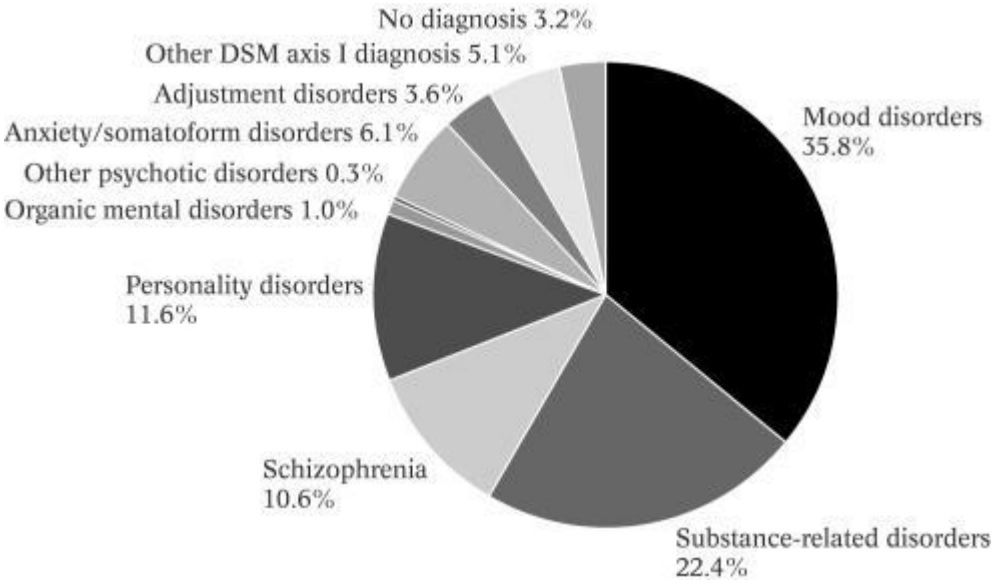

Figure 9: Distribution of psychiatric diagnoses in general population of individuals who attempted or completed suicide.
Source: Bertolote & Fleischmann, 2002

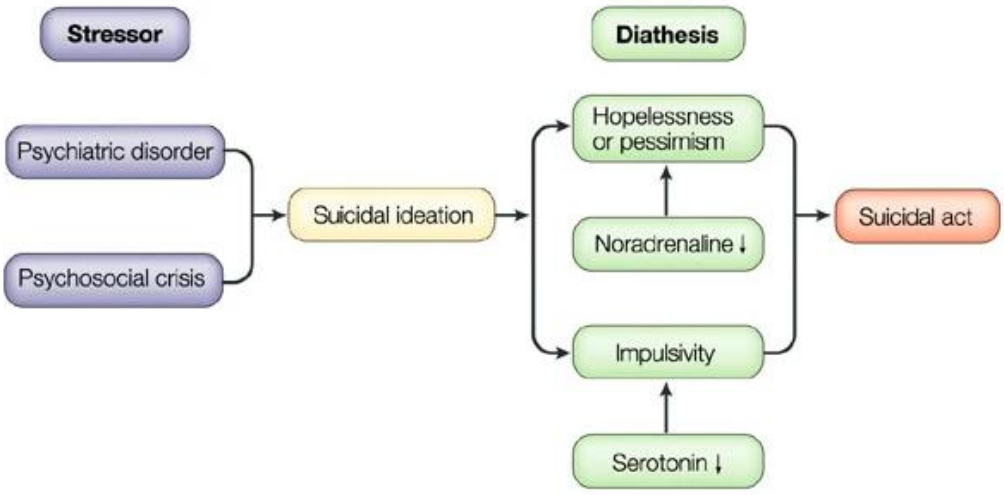

Figure 10: Serotonin and Noradrenaline role in the diathesis of suicidal behavior.
Source: Mann, 2003

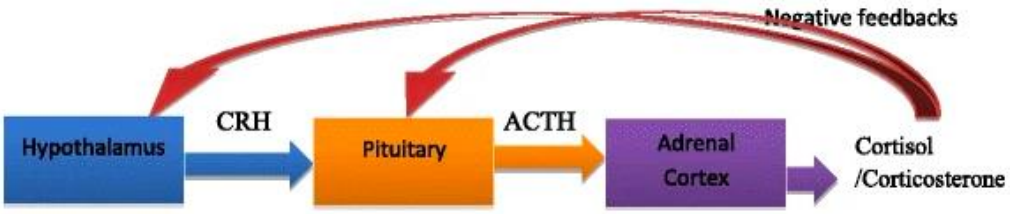

Figure 11: HPA axis feedback loop
Source: Dale & Mabandla, 2018

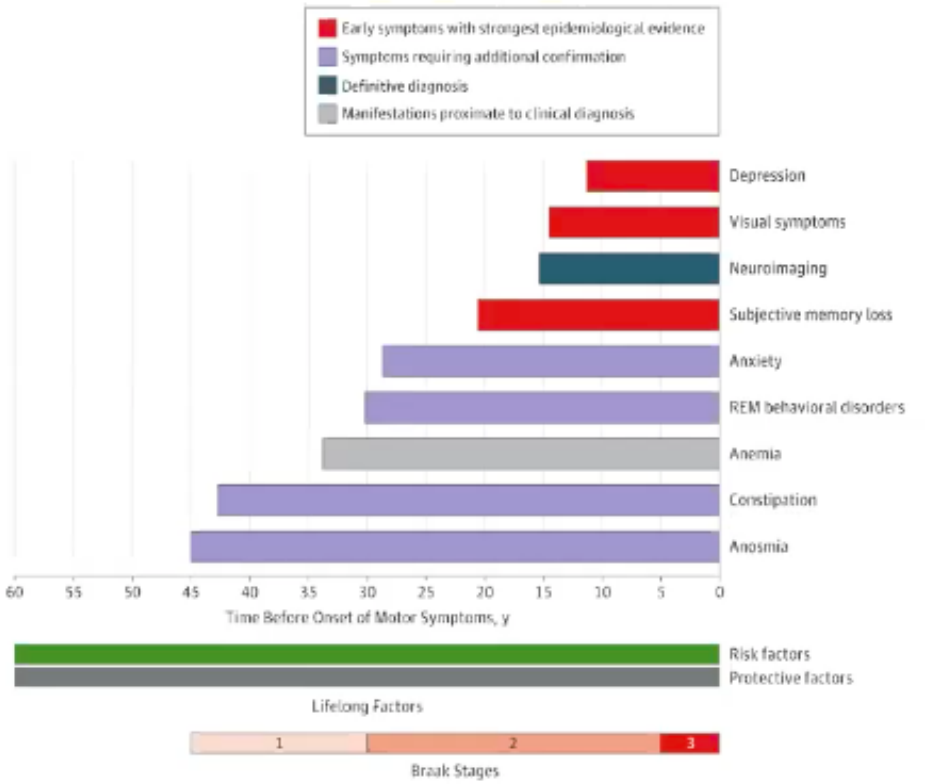

Figure 12. Graphical representation of timeline of premotor symptoms preceding the clinical diagnosis of Parkinson's disease. Source: Savica et al., 2018

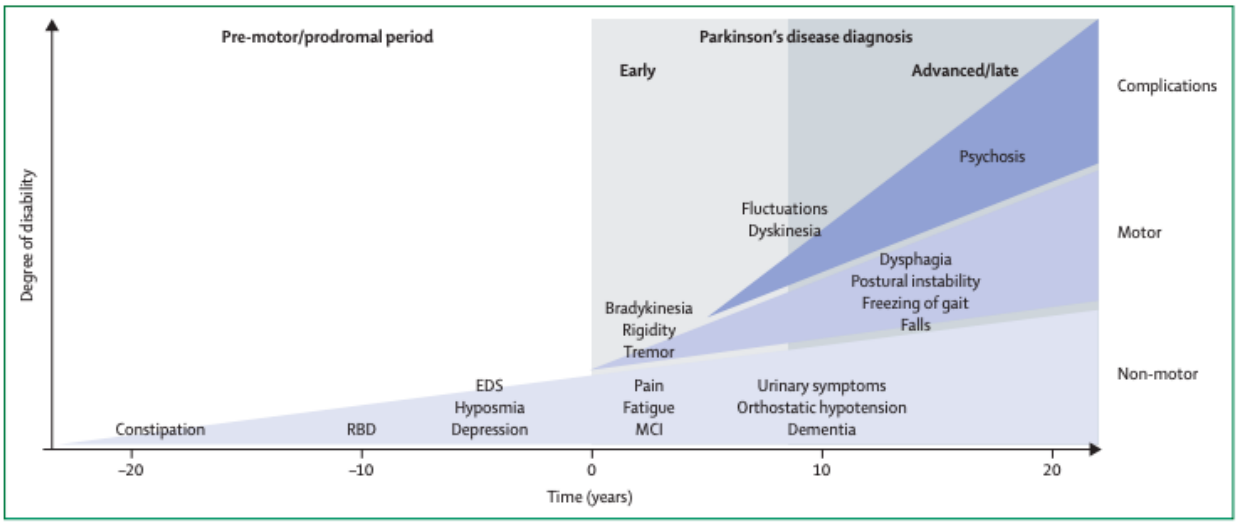

Figure 13. Time course of Parkinson's disease progression. Source: Kalia & Lang, 2015

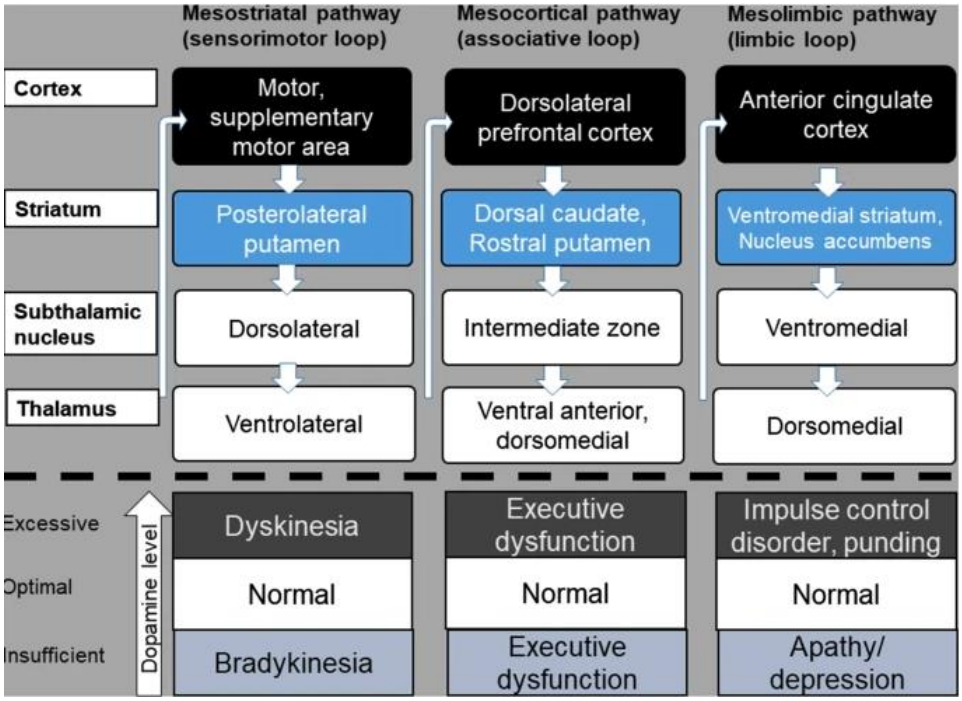

Figure 14. Parallel functions of DA pathways and their relation to the striatal dopamine level. Source: Hirano, 2021