The role of medial prefrontal cortex in cognition, aging and Parkinson disease

Lia de Oliveira Jereissati [1], **Luiz Aldir da Silva** [2], **Tiago Antoniol** [2], **Alexandre Almeida da Silva** [1], **Vitor Olímpio Coimbra** [1], **Amanda Rebouças Bezerra de Menezes** [1], **Gabriel Felipe Gomes** [3], **Stéfani Lara Galvão** [3], **Roger Wilson Gonçalves de Oliveira** [4], **Nayla Lima dos Santos** [1], **Pamella Mendes Martiniano da Silva Cardoso** [5], **Luciano Barroso de Albuquerque Filho** [1], **Camilla Costa Sallem** [1], **Rafaella Iughetti da Costa** [1], **Lara Maria Fujita Vieira Lima** [1], **Micael Porto Portela Lima** [1], **Júlio César Claudino dos Santos** [1, 2, 6, 7, *]

[1] Faculdade de Medicina, Centro Universitário Christus, UNICHRISTUS, Fortaleza, CE, Brasil.
[2] Christian Business School, Orlando, Estados Unidos.
[3] Centro Universitário Barão de Mauá, CUBM, Ribeirão Preto, SP, Brasil.
[4] Centro Universitário Fametro, Manaus, AM, Brasil.
[5] Universidade Federal da Paraíba, João Pessoa, PB, Brasil.
[6] Laboratório de Neurociências, Departamento de Neurologia e Neurocirurgia, Universidade Federal de São Paulo, São Paulo, SP, Brasil.
[7] Programa de Pós-Graduação em Ciências Morfofuncionais, Universidade Federal do Ceará, Fortaleza, Ceará, Brasil.

* Correspondência: julio.santos@alu.ufc.br.

Abstract: The prefrontal cortex (PFC) is a vital center for executive control, influencing cognition, emotion, memory, and sociability. Specifically, the medial prefrontal cortex (mPFC), a part of the PFC, monitors actions toward goals, aids decision-making, and regulates cognitive control. It assesses outcomes relative to expected rewards, selects appropriate behavior based on continuous performance analysis, and facilitates strategic adaptation in response to adverse results. Unfortunately, these cognitive functions decline with age due to changes in neuroplasticity, especially in neurodegenerative disorders like Parkinson's Disease (PD) and Alzheimer's Disease (AD). Neurodegenerative diseases disrupt normal brain activity, leading to tissue atrophy and cognitive impairment caused by degeneration and neuronal death. PD is the second most common neurodegenerative disease globally, characterized by a decline in neurotransmitters and dopaminergic neuron death in the substantia nigra, along with the presence of Lewy bodies. Recognizing these factors as risk factors for PD development is crucial. This article examines how aging affects cognitive activities regulated by the mPFC, a pivotal region for critical cognitive functions. Through a narrative review of literature published between 2010 and 2022 in the Medline (Pubmed) database, the study explores the topics of "cognition and Parkinson's disease," "prefrontal cortex," and "cognition and aging." By applying predetermined criteria, the review selects the most relevant articles to provide a comprehensive understanding of cognitive deficits mediated by the mPFC in both healthy and pathological aging.

Keywords: Prefrontal cortex; Cognitive deficits; Aging; Parkinson's Disease.

1. Introduction

The prefrontal cortex (PFC) is a neocortical area that, along the evolutionary process, was more developed in human beings and in primates [1]. The PFC is responsible for transmitting and receiving information originated from various encephalic regions and

presents itself as the center of human personality, an area that plays an important part in cognition, emotion, memory, and sociability of an individual, besides being able to suppress undesired actions [2, 3]. The damage of this region, caused by cerebrovascular accident, trauma, neurodegeneration, as well as the aging process, leads to a decline in the cognitive process4. The medial prefrontal cortex (mPFC) associated to the mediodorsal thalamus, hippocampus, and nucleus accumbens (NAc) are regions that perform a control of the cognitive domains, such as memory, attention, language, motivation and executive functions [2, 5]. One of many functions of the mPFC is selecting the convenient behavior in adequate timing, aiming to generate a procedural harmony of when and how to act in a determined situation, in other words, a temporal control of the action, besides also acting in the adaptive behavior in daily uncertain environments [6]. Thus, the cognitive functions cited above are compromised as the age increases. In part, this occurs due to the modifications in the neuroplasticity process in the aged brain [7]. These alterations are observed, mainly, in neurodegenerative pathologies, such as Parkinson's disease (PD) and Alzheimer's disease (AD), generating more significant motor and cognitive dysfunctions in the individuals [2].

Aging is a natural process, caused by numerous complex factors that manifest a progressive decline of normal physiological functions as time goes on. This phenomenon increases the probability of developing various diseases, such as cancer, metabolic disorders, and neurodegenerative diseases (ND) [8]. As years go on, it is expected that the elderly population, in other words, above 65 years-old, present some cognitive decline due to the aging process or to some associated dementia [9]. Thus, it is important to report that dysfunctions in the communication between neurons, the increase of oxidative stress and of neuroinflammation, the altered intracellular signalization, as well as the decreased neurogenesis and modified synaptic neuroplasticity, are the main factors to generate a significant compromise in the cognitive domains [7].

Neurodegenerative diseases are defined as illnesses that mitigate normal brain activity, being commonly accompanied by nervous tissue atrophy, as well as the cognition decrease, that get worse with the progression and chronification of the diseases [10]. These pathologies, in general, are not curable and are debilitating, having consequently the degeneration and neuronal death, manifesting itself through bradykinesia, resting tremor, intestinal dysfunction and sleepiness [11]. Parkinson's disease is considered the second most prevalent neurodegenerative disease after Alzheimer's disease. It is estimated that PD is present in 0,3% of the general population, males being two times more susceptible to develop this pathology when compared to women [12], and its incidence varies from 5/100.000 to more than 35/100.000 new cases a year, besides increasing from 5 to 10 times in the sixth until the ninth life decade, which proves the impact of aging as a risk factor to develop these diseases [13]. Additionally, PD is characterized by a modification in the neurotransmitters with the deterioration of substantia nigra, which represents the death of dopaminergic neurons, associated with the presence of Lewy bodies [11, 14]. For many decades, the association between aging and Parkinson's disease has been recognized by the scientific community; therefore, aging is characterized as a risk factor to develop PDDP [15].

Therefore, it is evident that the medial prefrontal cortex is very damaged in neurodegenerative diseases because these pathologies alter the brain activity and are associated, intrinsically, to the aging process of the population. It is fundamental to understand the role of this region in the cognitive functions that are altered in the senescence and in Parkinson's disease, so that the studies related to this problem are perfected. Thus, the aim of the present study is to substantiate a literature review about the role of the medial prefrontal cortex in the cognitive processes, aging and Parkinson's disease, and the benefits of the non-pharmacological treatment, in other words, exercise, in this condition.

2. Methodology

A gathering of scientific literature was done, in the PubMed database, in the years from 2010 to 2022, about Parkinson, aging and cognitive decline of the medial prefrontal cortex. In the PubMed database, 321 articles were found using the association of the descriptors "cognition [mesh terms] and parkinson disease [mesh terms]", besides "prefrontal cortex and cognition and aging" in the years from 2010 to 2022, using the filters "Review e Systematic Review", of which 64 articles were selected after their title was read (Figure 1). The second exclusion criterion was the reading of the abstracts, of which 33 were selected according with the theme that will be addressed. The exclusion criteria were titles that were not associated with aging, Parkinson's disease and prefrontal cortex, articles published in another language that wasn´t English and studies that were published outside of the period from 2010 to 2022.

Studies with experiments related to animal models, even if pertinent to the subject, were excluded. Besides, although the main theme of the present study is not associated with Alzheimer's disease, some studies related to the association between aging and Alzheimer´s were included for addressing cognitive decline in aging. Furthermore, 14 articles were selected through PubMed following a relevance for the synthesis of the present study. Besides these, 15 articles were manually added from the reference list of the eligible articles, totalizing 29 added articles. Finally, 62 original articles in English (including reviews and systematic reviews) remained (Figure 2).
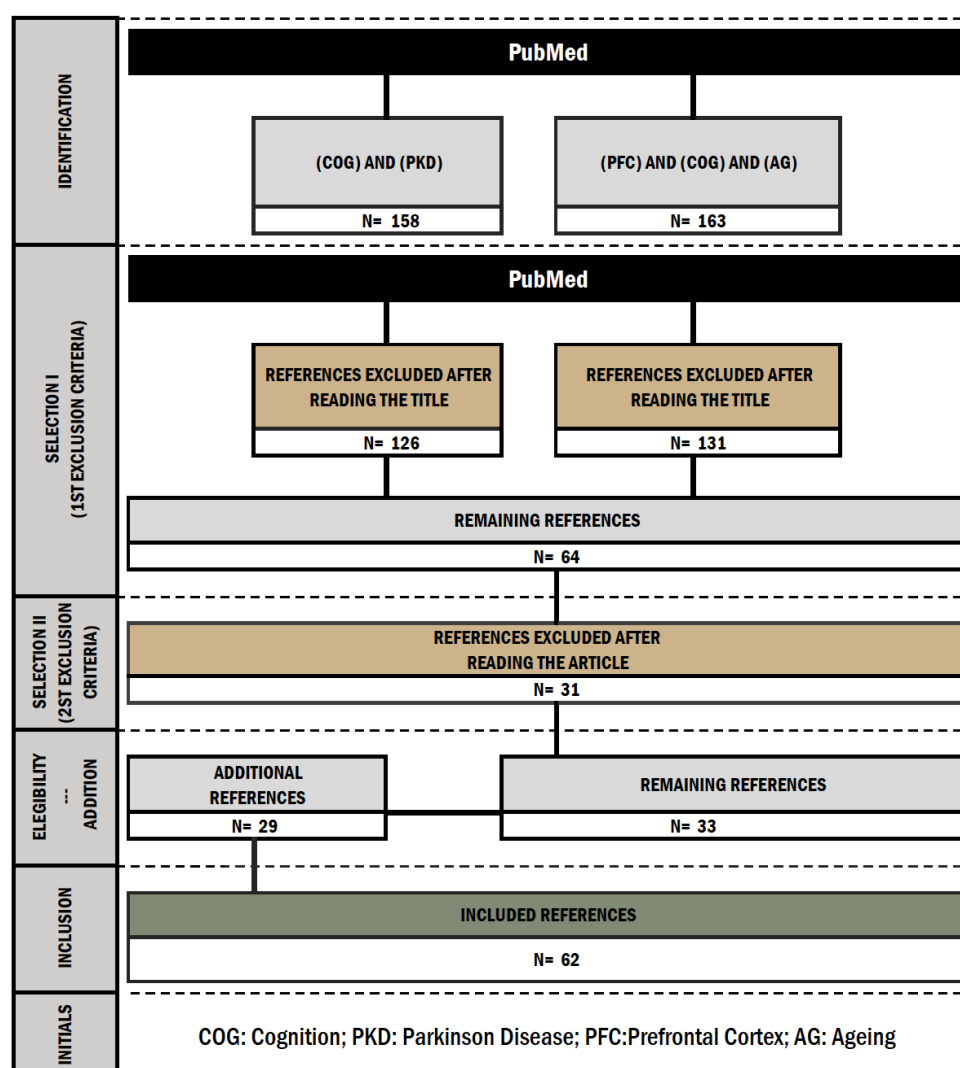

Figure 1. Flowchart of the article selection.

Author/year	Title	Objective	Correlated Disorders	Results/Conclusion
Carlén, 2017	What constitutes the prefrontal cortex?	To review how the prefrontal cortex enables complex behavior and the structure and function of this brain area.	Dysexecutive syndrome	The fundamental function of the prefrontal cortex could be to represent and produce new forms of goal-directed actions.
de Kloet et al., 2021	Bi-directional regulation of cognitive control by distinct prefrontal cortical output neurons to thalamus and striatum	Characterize dorsal medial prefrontal cortex (dmPFC) and ventral medial prefrontal cortex (vmPFC) outputs to distinct thalamic and striatal subdomains.	Cognitive deficits	The study shows that mPFC output pathways targeting anatomically and functionally distinct striatal and thalamic subregions encode bi-directional command of cognitive control.
Zang et al., 2021	Medial prefrontal cortex and the temporal control of action	Review evidence that across species, medial prefrontal lesions impair the temporal control of action.	Parkinson's disease, schizophrenia, and attention-deficit hyperactivity disorder (ADHD)	The study highlights how medial prefrontal regions orchestrate behavior in time, which could inspire novel neuromodulation therapies for human diseases.
Pettigrew et al., 2019	Defining Cognitive Reserve and Implications for Cognitive Aging	Summarize current conceptual models of cognitive reserve (CR) and related concepts and to discuss evidence within the context of aging and Alzheimer's disease.	Alzheimer's disease, mild cognitive impairment	Cognitive reserve, as measured by proxy variables, has beneficial effects on late-life cognitive and clinical outcomes, which might delay the onset of symptoms of cognitive impairment and reduce the risk of MCI/dementia.
Sousa et al., 2021	Impact of cognitive intervention on cognitive symptoms and quality of life in idiopathic Parkinson's disease: a randomized and controlled study	Determine the impact of CT on cognitive and quality of life measures in patients with Parkinson's disease who were seen a hospital neurorehabilitation program.	Parkinson's disease, mild cognitive impairment	Engagement in cognitive activities was associated with better cognitive abilities in Parkinson's Disease–Mild Cognitive Impairment (PD-MCI).
Funahashi et al., 2013	Prefrontal cortex and neural mechanisms of executive function	Use a paired association task to examine the neural correlates of top-down signals in the prefrontal cortex.	Dysexecutive syndrome	The results suggest that prefrontal neurons play significant roles in retrieving associative information of visual stimuli and indicate that pair-selective sample-period activity might be a candidate of the top-down signal.
Parnaudeau et al., 2018	The Mediodorsal Thalamus: An Essential Partner of the Prefrontal Cortex for Cognition	Discuss anatomical, behavioral, and electrophysiological findings from animal studies that provide a new understanding on how mediodorsal prefrontal cortex circuits support higher-order cognitive function.	Schizophrenia	The study suggests that the mediodorsal thalamus may be required for amplifying and sustaining cortical representations under different behavioral conditions
Upright et al., 2021	Prefrontal cortex and cognitive aging in macaque monkeys	Review the cognitive functions mediated by the prefrontal cortex, and their corresponding connections, as well as the evidence for age-related alterations in specific regions of prefrontal cortex.	Alzheimer's disease (AD), mild cognitive impairment	The prefrontal cortex undergoes significant changes in aging and while these changes are across the major divisions, the cognitive dysfunction can be mapped to deficits in specific pre-frontal areas.
Krajcovicova et al., 2019	Gray Matter Changes in Parkinson's and Alzheimer's Disease and Relation to Cognition	Summarize structural MRI findings of gray matter atrophy related to cognitive impairment in Alzheimer's disease and Parkinson's disease.	Alzheimer's disease, Parkinson's disease, cognitive impairment	The hippocampus-to-cortex ratio seems to be the best sMRI biomarker to discriminate between various AD subtypes and predict rate of cognitive decline. PD is clinically far more variable than AD, with heterogeneous underlying brain pathology.
Frouni et al., 2022	Cognition and serotonin in Parkinson's disease	Provide an overview of the pharmacological, clinical and pathological evidence that implicates the serotonergic system in mediating cognition in Parkinson's disease.	Parkinson's disease, dementia	The pathophysiology underlying cognitive impairment in PD is still poorly understood, but there is evidence to support involvements of the cholinergic, dopaminergic, and noradrenergic systems.

Figure 2. Resume of the role of medial prefrontal cortex in cognition, aging and Parkinson disease.

3. Results (Review)

3.1 The role of the medial prefrontal cortex in cognition activity

The right stimulation can evoke different familiar reactions in a fast and automatic way through simple and stereotyped behaviors, known as bottom-up processing. On the other hand, the diversification of behavioral possibilities demands more flexible patterns of interaction between stimulus and answer16. However, this repose flexibilization en-

hances the disorder risks, needing a coordination of attention and decision making [4, 16].

The simultaneous and coordinated operation from the numerous cortical and subcortical structures focused on one aim is known as cognitive control and acts through a top-bottom processing [17] (Figure 3). Cognitive control consists, generally, of maintaining active the representation of relevant stimuli and of the goal, evaluating if the obtained results are adequate to the objective and doing possible necessary adjustments. Thus, in case the given answer is not in agreement with the objective, through cognitive control it is possible to suppress actions or thoughts regulating the behavior [18]. The executive control of behavior, emotions, thoughts, planning and intentionally flexible decision making receives the name of executive functions, acting through the control of the cognitive domain [19]. Generally, cognitive flexibility, inhibiting control, attention, working memory and decision making compose the executive functions [4]. Many structures participate in this processing, but the prefrontal cortex (PFC) is consistently pointed out as the command center of executive control, receiving, and transmitting information from almost every sensorial and motor systems [16]. On the other hand, this group of processes intrinsic to cognitive control are possible due to working memory, which consists in the temporary storage of information and its manipulation through previous knowledge focused on one goal, being essential for learning and problem solution and having PFC as a neural correlate [20].

Besides, some aspects of cognitive control, such as attention and decision making, can be influenced by emotions. In contrast, cognition is also responsible for the regulation of emotional answers [21]. Inserted in this mechanism, PFC acts in the regulation of biogenic amines liberation, such as dopamine, noradrenaline, and serotonin, that generate humor alterations4. Other studies also linked cognitive control and PFC as intrinsically related to social cognition that involves the elaboration of answers adequate to the norms, values, and moral judgements [22]. Therefore, prefrontal lesions or neurodegenerative processes that damage PFC can cause personality changes, as well as in the other functions previously mentioned [23].

A portion of the PFC named medial prefrontal cortex (mPFC) plays a key part in this process of monitoring action focused on one goal. In particular, the anterior cingulate cortex (ACC), a region that integrates the mPFC and regulates the detection of errors and conflict monitoring [24]. The mPFC acts in the strategic adaptation of behavior adjusting to adverse outcomes. Thus, mPFC is central for decision making and cognitive control, monitoring the result in relation to the expected reward and selecting the adequate behavior to the situation through a continuous performance analysis. This flexible monitoring also demands an analysis and temporal adjustment of the action aiming the answer precision and efficiency, modulation consistently associated with the activity of the mPFC [25]. mPFC can be divided in subdivision named dorsomedial prefrontal cortex (dmPFC) which communicates predominantly with neocortical regions; and ventromedial PFC (vmPFC) whose communication predominantly occurs with limbic structures and basal ganglia [21].

Outside this perspective, mPFC is responsible for rescuing long term memories aiming to identify, in past experiences, the most adequate answer to each situation, directing the behavior [26]. Therefore, this task involves selecting a convenient memory and rejecting memories that are irrelevant to the task, which is only possible due to the communication between the mPFC and hippocampus, mainly the ventral hippocampus [27]. The motivation plays a fundamental role in orienting the behavior, in relation to the search for rewards and when possible, errors or conflicts with the goal are identified [24, 26]. Other evidence points out the hippocampus´s role in providing emotional aspects and spatial contexts that project to the mPFC and subsidize the selection of an adequate behavior to the context. On the other hand, the activity of mPFC also acts in the memory consolidation, establishing information that was just obtained and facilitating the learning process. Studies suggest that during periods of greater inactivation, such as during

sleep, the hippocampus is activated again and recreates an acquired memory, which also generates its repetition in cortical structures. This process creates the consolidation of acquired memory [26]. The synchrony between the mediodorsal thalamus and the mPFC is associated to working memory, in which the inhibition of the mediodorsal thalamus makes the action directed to the task more difficult and decreases the efficiency in the selection of adequate behavior, as well as maintaining the representations of the stimulus in the working memory [28] (Figure 3).

Additionally, the association between mPFC and nucleus accumbens is essential to the modulation of the goal-directed behavior, mainly those directed to rewards. The reward anticipation regulated by these structures originates from the comparison of information coming from emotional evaluations in the amygdala and spatial contextualization in the hippocampus and leads to the planning and execution of adequate goal-directed behaviors [29]. Besides, the activation of mPFC acts in the intermediation of the attention allocation, which works through the neglect of irrelevant stimuli and focus on the selected stimuli. Thus, the mPFC is fundamental for the efficiency of the executive functions and its compromise can cause numerous damages in the control of these functions [21].
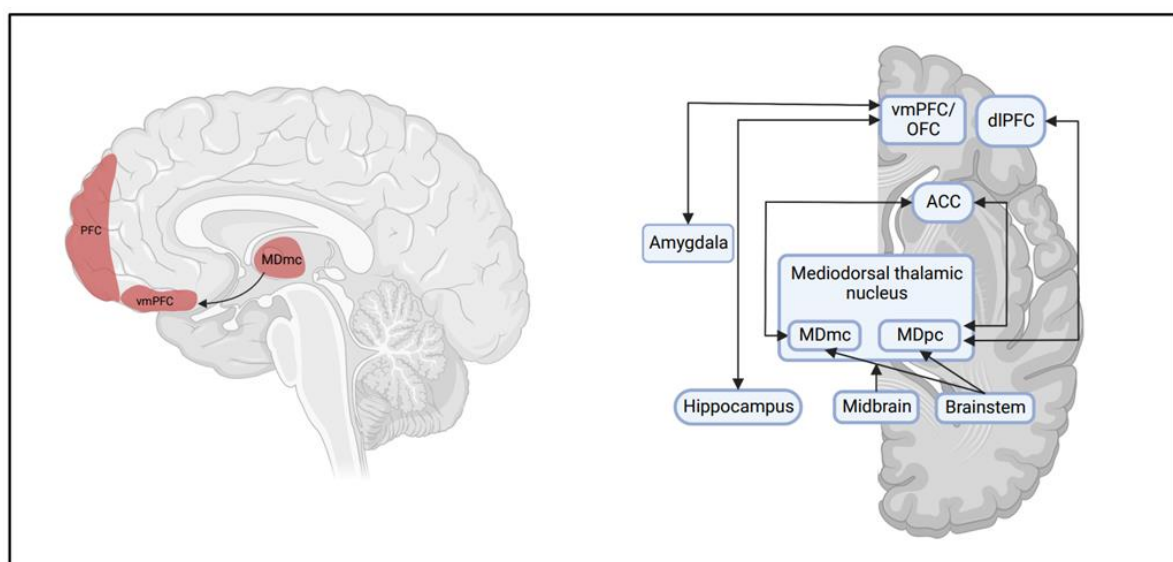

Figure 3: Medial prefrontal cortex (mPFC) in executive functions control. The mPFC is divided in vmPFC and dlPFC, involved in the control of cognitive flexibility, inhibition control, attention, working memory and decision making. Abbreviations: ACC, anterior cingulate cortex; MDmc, magnocellular subdivision of the mediodorsal thalamic nucleus; MDpc, parvocellular subdivision of the mediodorsal thalamic nucleus; OFC, orbitofrontal cortex; PFC, prefrontal cortex; VMPFC, ventromedial prefrontal cortex.

3.2 The relationship between medial prefrontal cortex and the aging process

The aging process is constantly accompanied by numerous neuroanatomical and neurophysiological modifications [30]. Therefore, many of the cognitive deficiencies that accompany the healthy aging process are explained by alterations in the medial prefrontal cortex, which plays a critical part in the cognitive decline in aging, including cognitive flexibility and attention [4]. Studies show that even in healthy aging there is a decrease in the connections of the mPFC with other cortical and subcortical areas leading to decline [31]. Corroborating with these findings, a study performed in rodents demonstrates the deterioration of the cognitive function during normal aging, in which occurs a reduction in the velocity information processing when compared to younger rats [32].

In this context, evidence demonstrates notorious deficits related to age in a series of cognitive functions mediated by the medial prefrontal cortex. This data is reinforced by

findings in neurophysiological experiments in elder non-human primates, which presented damage in the working memory with reduced processing velocity [30].

Another important relation that should be highlighted is the decrease in volume and thickness of gray matter in the mPFC, besides alterations in the pathways of the white matter in healthy elders, in a way that the elderly with less volume of gray matter presented increased cognitive repercussion, impacting in the distraction and in the neural suppression of irrelevant information, affecting memory. Similar results were found in elders with decrease of the white matter's integrity [33]. Thus, studies evidenced that any structural or functional alterations in mPFC can lead to loss of the normal function [2].

3.3 Aging neurodegenerative-associated disorders involving the medial prefrontal cortex

Neurodegenerative diseases (ND) are diseases of common cause and crescent morbidity worldwide, mainly in elderly people, and are responsible for and atrophy of the brain tissue leading to a decreased cognition capacity, diminishing the normal brain function that tends to worsen with the chronicity of the condition [10, 12]. In addition to that, phenotypes of neuroimage associated with aging, integrity of the white matter tract, quantitative decrease of neurons in the prefrontal cortex (PFC) [34] are correlated with aging, which is inherently connected to a deterioration of the cognitive function associated with a greater hypermetabolic activity [4]. Thus, considering that one of the main functions of the medial prefrontal cortex (mPFC) is orienting the actions in time, having decision-making as its central utility, since deciding which will be the moment of choice is as important as selecting the appropriate actions in the context; in truth, the right action at the wrong time usually will lead to terrible outcomes. Therefore, when these alterations associated with neurodegeneration, vascular accidents or traumas occur in mPFC can be observed mainly by deterioration of the executive function (defining goals, memorizing, planning, and executing activities), besides also affecting the decision-making process, which was evidenced by functional changes in working memory and cognitive flexibility6. It is valid to highlight that the cited deficits are more accentuated and rapidly progressive in the presence of ND, but aging itself is already responsible for some of these alterations [30]. Amongst them is the deficiency of cognitive control, causing depletion of sustained and selective attention, inhibitory control, working memory and multitasking skills. Additionally, the arithmetic, the comprehension, the perception of emotions and the emotional control, despite being associated with the PFC, do not present decline associated with age. Therefore, cognitive decline is not present in all elderly people [35]. Thus, studies provide evidence that neurodegenerative disorders alter the mPFC's function in a pathologic way, them being Alzheimer's disease, Huntignton's disease and Parkinson's disease4.

Alzheimer's disease (AD) represents from 60% to 80% of all the dementia cases in the world, being the most common manifestation of neurodegeneration and, corresponding to about 24 million people globally. This prevalence is directly proportional to aging, leading to an increase superior to 15 times when our observed sample is between the age gap of 65 to 85 years old. In addition to this statistic, a north American study in which the prevalence reaches 50% in people with more than 85 years old. In the face of this data, it is easy to understand why AD is considered a disease of elderly people [12]. In a physiologic approach, there is deposition of extracellular plaques of beta-amyloid peptide and formation of intracellular neurofibrillary tangles in the brain cortex, these alterations will be clinically perceived as severe cognitive deficits, emotional depression, and progressive motor dysfunction, besides loss of working memory, spatial memory and anterograde memory [2].

Since the mPFC is responsible for working memory, its association with AD is clear. Finally, it is worth mentioning that the hippocampus, a subcortical region of the brain with close relation to the PFC, is responsible for learning, memory consolidation, affective behaviors, and mood regulation. It is believed that neurobiological alterations ob-

served in the aged hippocampus, including increase in oxidative stress and neuroinflammation, altered intracellular signalization and gene expression, as well as reduced neurogenesis and synaptic plasticity, are associated with the cognitive decline related to the age. This region being one of the first sites of action of AD, probably the most documented and known characteristic of the disease is its visualized hippocampal atrophy, mainly in magnetic resonances. Since the typical AD, in which there is memory compromise, represents about 60% of all cases and its main characteristic is the medial temporal lobe atrophy (MTA) along with the atrophy of other temporal regions and atrophy of the posterior cingulate/ precuneus. It is also important to highlight that this alteration can be used to differentiate prodrome phases of AD in healthy individuals, as well as excluding other diagnoses [36] (table 01). Thus, when taking into consideration its communication with the PFC it is demonstrated that AD is a neurodegenerative disorder related to aging [10].

Parkinson's disease (PD) is one of the most common neurodegenerative diseases, standing only behind AD [12, 14].   Its prevalence is of 0,3% in the general population, ~1% in elderly people above 60 years-old and ~3% in elders 80 years-old or above (8 to 18 people from 100.000 per year), being most common in men (1,5 to 2 times greater than women) with medium age of 60 years and life expectancy of 15 years after the diagnosis [12]. This age association comes from the lack of dopamine and motor and non-motor deficits of the disease, besides environmental and genetic factors, such as mitochondrial dysfunction, oxidative stress, protein aggregation, damaged autophagy and neuroinflammation, which influence the risk of PD [13].

Its pathology acts through the presence of aggregates of alpha-synuclein in the brain, containing Lewy Bodies in the brain's substantia nigra, causing synucleinopathy and the loss of dopaminergic neurons in the par's compacta [13-14, 37], leading to a motor control disorder and some complications, such as the deterioration of cognitive functions in 40% of cases, being a risk factor for dementia. Some of these cognitive alterations are executive function, visuospatial abilities, and attention deficits [11]. This deterioration could be, in part, by the alpha-synuclein spreading from substantia nigra pars compacta to cortical structures, affecting, among other areas, the mPFC, progressing according to a Braak stages (Figure 4).
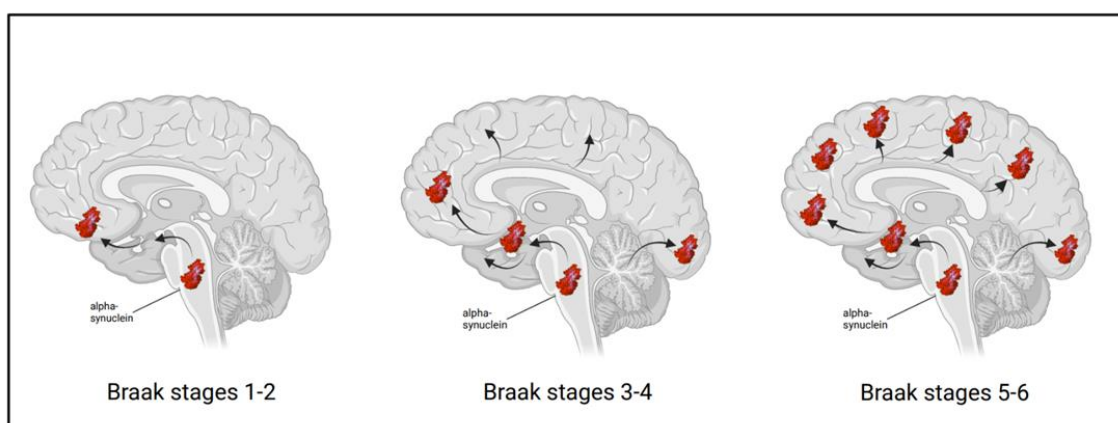

Figure 4: Alpha-synuclein prion-like spreading. From substantia nigra pars compacta to cortical structures, this misfolded protein causes neurodegeneration that, in chronic cases, may lead to cognitive functions impairment.

Previously, it was believed that intellect maintained itself unaltered in PD, but recent studies already demonstrated the prevalence of deficit and all kinds of cognitive dysfunctions in the disease [37]. Thus, cognitive compromise in PD still has its physiology as an incognito in current medicine, but the most accepted theories are that alterations in the cholinergic, dopaminergic, and noradrenergic systems exist. Furthermore, the

cognitive reduction affects 80% of patients with PD38, with a higher prevalence in patients with greater age and disease time [12]. Example of that is: 19-38% of patients present dementia with a PD diagnosis of 10 years, which increases to 75% with additional 10 years of PD and, posteriorly, to 83% when patients have had PD for 20 years [12]. Thus, the clinical evolution to dementia can be observed in manifestations such as working memory and executive function deficiencies [38].

Finally, it is valid to highlight that there is a strong correlation between the neuropathology of neurodegeneration and the gray matter's atrophy, being considered a cardinal sign. Accordingly, we emphasize that this article addressed the main neurodegenerative diseases: AD and PD. The first presents prominent medial temporal lobe atrophy (MTA) as a typical manifestation from the early stages of the disease, which has been considered a useful biomarker in the pre-dementia states of AD that can diagnose and be used as support. On the other hand, PD has a more heterogeneous pathophysiology, resulting in numerous clinical manifestations. Therefore, the atrophy pattern was still not established in a conclusive way for this disease, but recent studies identified specific atrophy patterns in the initial phase that can predict the malignant prognosis of PD, including cognitive decline. Thus, new methodologic approaches showed that the appearance of cognitive deficits in the pathology can be associated with atrophy of areas of cortical projection in the prefrontal and posterior cortical regions due to the loss of cholinergic nuclei in the prosencephalon [36].

3.4 Genetic Physiology of Parkinson's Disease

The advance in research demonstrated that the genetic scope was essential to better the comprehension of Parkinson's disease. From numerous investigated genes, the most well studied include *LRRK2*, *SNCA*, *VPS35*, *Parkin* and *PINK1*. Thus, the mechanisms of each cited gene interfere in the development of Parkinson's disease [39]. However, it is known that 5 to 10% of PD cases are related to genetic mutations, being *LRRK-2* the most frequently altered gene [40] and the most frequent cause in idiopathic PD cases, even covering specific ethnic groups, given that in a sample of 248 affected patients from families with autosomal dominant parkinsonism, 7 were identified for transporting a *LRRK-2* (G2019S) heterozygotic alteration, where such patients are from the United States, Norway, Ireland and Poland [41-43]. Furthermore, in models of patients with sporadic Parkinson's disease from the same populations, additional six patients with *LRRK2* G2019S were identified, and no alteration was found in individual control41. Besides, in another great study, it was discovered that the frequency of mutations was of 1% amongst the sporadic patients and 4% amongst the familial PD patients, but with the greatest frequency of mutation amongst the Arabic and Ashkenazi–North African populations: 39% and 38% amongst the arabic people from the north of Africa, and 10% and 28% between the Ashkenazi jews with sporadic and familial PD, respectively [44, 45].

In this context, *LRRK-2* contains numerous functional domains, including the I2020T kinase domain, which has shown to have divergent effects, some increasing activity 46, whilst others ended up demonstrating its decrease47, since the *LRRK-2* superexpression promotes neuronal toxicity, causing cell death, shortening of dendrites and, consequently, neurodegeneration [48-50]. However, it is worth mentioning that such degenerative consequences were softened with chemical inhibitors of *LRRK-2* or with inactive kinase mutations that were inserted47. Furthermore, the substrates of *LRRK-2* phosphorylation (except autophosphorylation) were also unknown until recently, however, Rab GTPases (Rab5 and Rab7) substrates were identified not long ago, which affect signaling cascades, degradation and endosomal traffic [51]. Sequentially, abnormal morphologies and mitochondrial functions were observed amongst the *LRRK-2* alterations, as well as an abnormal accumulation in autophagic vacuoles, which are believed to be bind through the 5'AMP-activated protein kinase (AMPK) [51]. Additionally, the intensified activities of LRRK-2 increase the PD risk since the amplification of the kinase ac-

tivity has been associated with nigrostriatal degeneration and with the formation of Lewy bodies.

Secondly, when referring to the alpha-synuclein gene (*SNCA*), the pathogenicity mechanism is still not totally clear, since the PD associated with *SNCA* demonstrates an effect of gene dosage suspected of function gain. Thus, it was recently showed that an increase in the number of *SNCA* copies leads to elevated levels of mRNA and wild-type *SNCA* protein [52] and that such ampliation in the quantity of copies has been associated with an earlier beginning of the disease, a more severe phenotype with some atypical characteristics, including myoclonus, and a faster progression than in the duplication [53]. Besides, a case of gene triplication reported by Singleton et al. had a notorious clinical course because of its early beginning and a postmortem examination notable for a prominently cortical and subcortical pathology [54]. Duplications were also reported in numerous ADPD families [55] as well as in sporadic PD [56, 57] in which the reported phenotypes include prominent psychiatric symptoms, including visual hallucinations [55]. Thus, although the alteration in the *SNCA* gene is rare, the abnormal conglomerates of alpha-synuclein protein are present in all the PD patients, in which such gene is the main component of the Lewy bodies, the pathologic mark of Parkinson's disease [58].

Finally, it is valid to highlight the PARKIN gene, whose pathogenicity mechanism is also not totally clear. Parkin is an E3 ubiquitin ligase protein, which catalyzes the ubiquitin transference to its specific target protein. Therefore, numerous target proteins with highly variable functions were suggested as possible Parkin substrates, where a role in the protein goal for proteasomal degradation was proposed [59]. Besides, *PARKIN* also triggers a job with the *PINK1* gene in the control of organelle quality through the activation of mitophagy in the context of mitochondrial damage60. The pre-exposed *PINK1* gene is a serine/ threonine kinase, which also contains critical regulatory locations, where its mutations are the second most common cause of ARPD after Parkin, with some superposition with the Parkin phenotype. Its locus was identified for the first time in a Sicilian family (Marsala kindred) with four members affected by early beginning PD, with course notorious for slow progression and a sustained response to Levodopa. Sequentially, as suggested for the first time by Valente et al. through cell culture studies, PINK1 is localized in mitochondria imported to the segmentation pathway61 and its alterations lead to a complete loss of kinase activity and are associated with an early beginning PD [62].Thus, PINK1 works in a more prominent way along with Parkin in the mitophagy activation, accumulating in the external mitochondrial membrane in the context of mitochondrial damage [62].

4. Conclusion

Through the advances in medicine, there was an increase in life expectancy and in the elderly population. In parallel, the prevalence of diseases related to age that led to cognitive decline increased, amongst them Parkinson's disease. In this review, we discussed how aging affects cognitive functions mediated by the medial prefrontal cortex, which has a key role in a series of critical cognitive functions. Thus, this study will contribute to a better characterization of cognitive deficits mediated by the mPFC in the healthy and pathologic aging process.

Conflicts of Interest: The authors declare no conflicts of interest and no specific funding sources for this work.

Supplementary Materials: None.

References

1. Carlén M. What constitutes the prefrontal cortex? Science. 2017 Oct 27;358(6362):478-482. doi: 10.1126/science.aan8868. PMID: 29074767.

2. Xu P, Chen A, Li Y, Xing X, Lu H. Medial prefrontal cortex in neurological diseases. Physiol Genomics. 2019 Sep 1;51(9):432-442. doi: 10.1152/physiolgenomics.00006.2019. Epub 2019 Aug 2. PMID: 31373533; PMCID: PMC6766703.

3. de Kloet SF, Bruinsma B, Terra H, Heistek TS, Passchier EMJ, van den Berg AR, Luchicchi A, Min R, Pattij T, Mansvelder HD. Bi-directional regulation of cognitive control by distinct prefrontal cortical output neurons to thalamus and striatum. Nat Commun. 2021 Mar 31;12(1):1994. doi: 10.1038/s41467-021-22260-7. PMID: 33790281; PMCID: PMC8012364.

4. Jobson DD, Hase Y, Clarkson AN, Kalaria RN. The role of the medial prefrontal cortex in cognition, ageing and dementia. Brain Commun. 2021 Jun 11;3(3):fcab125. doi: 10.1093/braincomms/fcab125. PMID: 34222873; PMCID: PMC8249104.

5. Ferguson BR, Gao WJ. Thalamic Control of Cognition and Social Behavior Via Regulation of Gamma-Aminobutyric Acidergic Signaling and Excitation/Inhibition Balance in the Medial Prefrontal Cortex. Biol Psychiatry. 2018 Apr 15;83(8):657-669. doi: 10.1016/j.biopsych.2017.11.033. Epub 2017 Dec 7. PMID: 29373121; PMCID: PMC5862785.

6. Zhang Q, Weber MA, Narayanan NS. Medial prefrontal cortex and the temporal control of action. Int Rev Neurobiol. 2021;158:421-441. doi: 10.1016/bs.irn.2020.11.004. Epub 2020 Dec 15. PMID: 33785154; PMCID: PMC8875599.

7. Bettio LEB, Rajendran L, Gil-Mohapel J. The effects of aging in the hippocampus and cognitive decline. Neurosci Biobehav Rev. 2017 Aug;79:66-86. doi: 10.1016/j.neubiorev.2017.04.030. Epub 2017 May 2. PMID: 28476525.

8. Pal S, Tyler JK. Epigenetics and aging. Sci Adv. 2016 Jul 29;2(7):e1600584. doi: 10.1126/sciadv.1600584. PMID: 27482540; PMCID: PMC4966880.

9. Pettigrew C, Soldan A. Defining Cognitive Reserve and Implications for Cognitive Aging. Curr Neurol Neurosci Rep. 2019 Jan 9;19(1):1. doi: 10.1007/s11910-019-0917-z. PMID: 30627880; PMCID: PMC7812665.

10. Toledo ARL, Monroy GR, Salazar FE, Lee JY, Jain S, Yadav H, Borlongan CV. Gut-Brain Axis as a Pathological and Therapeutic Target for Neurodegenerative Disorders. Int J Mol Sci. 2022 Jan 21;23(3):1184. doi: 10.3390/ijms23031184. PMID: 35163103; PMCID: PMC8834995.

11. Sousa NMF, Neri ACM, Brandi IV, Brucki SMD. Impact of cognitive intervention on cognitive symptoms and quality of life in idiopathic Parkinson's disease: a randomized and controlled study. Dement. Neuropsychol. 2021;15(1):51-59

12. Erkkinen MG, Kim MO, Geschwind MD. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. Cold Spring Harb Perspect Biol. 2018 Apr 2;10(4):a033118. doi: 10.1101/cshperspect.a033118. PMID: 28716886; PMCID: PMC5880171.

13. Simon DK, Tanner CM, Brundin P. Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. Clin Geriatr Med. 2020 Feb;36(1):1-12. doi: 10.1016/j.cger.2019.08.002. Epub 2019 Aug 24. PMID: 31733690; PMCID: PMC6905381.

14. Moustafa SA, Mohamed S, Dawood A, Azar J, Elmorsy E, Rizk NAM, Salama M. Gut brain axis: an insight into microbiota role in Parkinson's disease. Metab Brain Dis. 2021.

15. Barbosa ENB, Charchat-Fichman H. Systematic review of neuropsychological instruments used in subthalamic nucleus deep brain stimulation in Parkinson's disease patients. Dement. Neuropsychol. 2019;13(2):162-171

16. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167-202. doi: 10.1146/annurev.neuro.24.1.167. PMID: 11283309.

17. Funahashi S, Andreau JM. Prefrontal cortex and neural mechanisms of executive function. J Physiol Paris. 2013 Dec;107(6):471-82. doi: 10.1016/j.jphysparis.2013.05.001. Epub 2013 May 15. PMID: 23684970.

18. Widge AS, Heilbronner SR, Hayden BY. Prefrontal cortex and cognitive control: new insights from human electrophysiology. F1000Research, 2019, 8, F1000 Faculty Rev-1696. https://doi.org/10.12688/f1000research.20044.1

19. Yuan P, Raz N. Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. Neurosci Biobehav Rev. 2014 May;42:180-92. doi: 10.1016/j.neubiorev.2014.02.005. Epub 2014 Feb 23. PMID: 24568942; PMCID: PMC4011981.

20. Funahashi S. Working Memory in the Prefrontal Cortex. Brain Sci. 2017 Apr 27;7(5):49. doi: 10.3390/brainsci7050049. PMID: 28448453; PMCID: PMC5447931.

21. Ray RD; Zald DH. Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. Neuroscience and biobehavioral reviews. 2012, 36(1), 479–501. https://doi.org/10.1016/j.neubiorev.2011.08.005.

22. Forbes CE, Grafman J. The role of the human prefrontal cortex in social cognition and moral judgment. Annu Rev Neurosci. 2010;33:299-324. doi: 10.1146/annurev-neuro-060909-153230. PMID: 20350167.

23. Chow TW. Personality in frontal lobe disorders. Curr Psychiatry Rep. 2000 Oct;2(5):446-51. doi: 10.1007/s11920-000-0031-5. PMID: 11122995; PMCID: PMC5786154.

24. Gehring WJ, Fencsik DE. Functions of the medial frontal cortex in the processing of conflict and errors. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2001, 21(23), 9430–9437. https://doi.org/10.1523/JNEUROSCI.21-23-09430.2001.

25. Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. Science. 2004 Oct 15;306(5695):443-7. doi: 10.1126/science.1100301. PMID: 15486290.

26. Euston DR, Gruber AJ, McNaughton BL. The role of medial prefrontal cortex in memory and decision making. Neuron. 2012 Dec 20;76(6):1057-70. doi: 10.1016/j.neuron.2012.12.002. PMID: 23259943; PMCID: PMC3562704.

27. Morici JF, Weisstaub NV, Zold CL. Hippocampal-medial prefrontal cortex network dynamics predict performance during retrieval in a context-guided object memory task. Proc Natl Acad Sci U S A. 2022 May 17;119(20):e2203024119. doi: 10.1073/pnas.2203024119. Epub 2022 May 13. PMID: 35561217; PMCID: PMC9171913.

28. Parnaudeau S, Bolkan SS, Kellendonk C. The Mediodorsal Thalamus: An Essential Partner of the Prefrontal Cortex for Cognition. Biol Psychiatry. 2018 Apr 15;83(8):648-656. doi: 10.1016/j.biopsych.2017.11.008. Epub 2017 Nov 15. PMID: 29275841; PMCID: PMC5862748.

29. Miyazaki K, Miyazaki KW, Matsumoto G. Different representation of forthcoming reward in nucleus accumbens and medial prefrontal cortex. Neuroreport, 2004, 15(4), 721–726. https://doi.org/10.1097/00001756-200403220-00030.

30. Upright NA, Baxter MG. Prefrontal cortex and cognitive aging in macaque monkeys. Am J Primatol. 2021 Nov;83(11):e23250. doi: 10.1002/ajp.23250. Epub 2021 Mar 9. PMID: 33687098.

31. Vidal-Piñeiro D, Valls-Pedret C, Fernández-Cabello S, Arenaza-Urquijo EM, Sala-Llonch R, Solana E, Bargalló N, Junqué C, Ros E, Bartrés-Faz D. Decreased Default Mode Network connectivity correlates with age-associated structural and cognitive changes. Front Aging Neurosci. 2014 Sep 25;6:256. doi: 10.3389/fnagi.2014.00256. PMID: 25309433; PMCID: PMC4174767.

32. Houlton J, Zhou LYY, Barwick D, Gowing EK, Clarkson AN. Stroke Induces a BDNF-Dependent Improvement in Cognitive Flexibility in Aged Mice. Neural Plast. 2019 May 5;2019:1460890. doi: 10.1155/2019/1460890. PMID: 31191635; PMCID: PMC6525942.

33. Chadick JZ, Zanto TP, Gazzaley A. Structural and functional differences in medial prefrontal cortex underlie distractibility and suppression deficits in ageing. Nat Commun. 2014 Jun 30;5:4223. doi: 10.1038/ncomms5223. PMID: 24979364; PMCID: PMC4088291.

34. Guevara EE, Hopkins WD, Hof PR, Ely JJ, Bradley BJ, Sherwood CC. Epigenetic ageing of the prefrontal cortex and cerebellum in humans and chimpanzees. Epigenetics. 2022 Jun 2:1-12. doi: 10.1080/15592294.2022.2080993. Epub ahead of print. PMID: 35603816.

35. Zanto TP, Gazzaley A. Aging of the frontal lobe. Handb Clin Neurol. 2019;163:369-389. doi: 10.1016/B978-0-12-804281-6.00020-3. PMID: 31590742.

36. Krajcovicova L, Klobusiakova P, Rektorova I. Gray Matter Changes in Parkinson's and Alzheimer's Disease and Relation to Cognition. Curr Neurol Neurosci Rep. 2019 Nov 13;19(11):85. doi: 10.1007/s11910-019-1006-z. PMID: 31720859; PMCID: PMC6854046.

37. Ding W, Ding LJ, Li FF, Han Y, Mu L. Neurodegeneration and cognition in Parkinson's disease: a review. Eur Rev Med Pharmacol Sci. 2015 Jun;19(12):2275-81. PMID: 26166654.

38. Frouni I, Kwan C, Belliveau S, Huot P. Cognition and serotonin in Parkinson's disease. Prog Brain Res. 2022;269(1):373-403. doi: 10.1016/bs.pbr.2022.01.013. Epub 2022 Feb 4. PMID: 35248202.

39. Kim CY, Alcalay RN. Genetic Forms of Parkinson's Disease. Semin Neurol. 2017 Apr;37(2):135-146. doi: 10.1055/s-0037-1601567. Epub 2017 May 16. PMID: 28511254.

40. Bandres-Ciga S, Diez-Fairen M, Kim JJ, Singleton AB. Genetics of Parkinson's disease: An introspection of its journey towards precision medicine. Neurobiol Dis. 2020 Apr;137:104782. doi: 10.1016/j.nbd.2020.104782. Epub 2020 Jan 25. PMID: 31991247; PMCID: PMC7064061.

41. Kachergus J, Mata IF, Hulihan M, Taylor JP, Lincoln S, Aasly J, Gibson JM, Ross OA, Lynch T, Wiley J, Payami H, Nutt J, Maraganore DM, Czyzewski K, Styczynska M, Wszolek ZK, Farrer MJ, Toft M. Identification of a novel LRRK2 mutation linked to autosomal dominant parkinsonism: evidence of a common founder across European populations. Am J Hum Genet. 2005 Apr;76(4):672-80. doi: 10.1086/429256. Epub 2005 Feb 22. PMID: 15726496; PMCID: PMC1199304.

42. Infante J, Rodríguez E, Combarros O, Mateo I, Fontalba A, Pascual J, Oterino A, Polo JM, Leno C, Berciano J. LRRK2 G2019S is a common mutation in Spanish patients with late-onset Parkinson's disease. Neurosci Lett. 2006 Mar 13;395(3):224-6. doi: 10.1016/j.neulet.2005.10.083. Epub 2005 Nov 18. PMID: 16298482.

43. Aasly JO, Toft M, Fernandez-Mata I, Kachergus J, Hulihan M, White LR, Farrer M. Clinical features of LRRK2-associated Parkinson's disease in central Norway. Ann Neurol. 2005 May;57(5):762-5. doi: 10.1002/ana.20456. PMID: 15852371.

44. Tan EK, Shen H, Tan LC, Farrer M, Yew K, Chua E, Jamora RD, Puvan K, Puong KY, Zhao Y, Pavanni R, Wong MC, Yih Y, Skipper L, Liu JJ. The G2019S LRRK2 mutation is uncommon in an Asian cohort of Parkinson's disease patients. Neurosci Lett. 2005 Aug 26;384(3):327-9. doi: 10.1016/j.neulet.2005.04.103. PMID: 15955629.

45. Di Fonzo A, Rohé CF, Ferreira J, Chien HF, Vacca L, Stocchi F, Guedes L, Fabrizio E, Manfredi M, Vanacore N, Goldwurm S, Breedveld G, Sampaio C, Meco G, Barbosa E, Oostra BA, Bonifati V; Italian Parkinson Genetics Network. A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson's disease. Lancet. 2005 Jan 29-Feb 4;365(9457):412-5. doi: 10.1016/S0140-6736(05)17829-5. PMID: 15680456.

46. West AB, Moore DJ, Biskup S, Bugayenko A, Smith WW, Ross CA, Dawson VL, Dawson TM. Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. Proc Natl Acad Sci U S A. 2005 Nov 15;102(46):16842-7. doi: 10.1073/pnas.0507360102. Epub 2005 Nov 3. PMID: 16269541; PMCID: PMC1283829.

47. Jaleel M, Nichols RJ, Deak M, Campbell DG, Gillardon F, Knebel A, Alessi DR. LRRK2 phosphorylates moesin at threonine-558: characterization of how Parkinson's disease mutants affect kinase activity. Biochem J. 2007 Jul 15;405(2):307-17. doi: 10.1042/BJ20070209. PMID: 17447891; PMCID: PMC1904520.

48. Stafa K, Trancikova A, Webber PJ, Glauser L, West AB, Moore DJ. GTPase activity and neuronal toxicity of Parkinson's disease-associated LRRK2 is regulated by ArfGAP1. PLoS Genet. 2012;8(2):e1002526. doi: 10.1371/journal.pgen.1002526. Epub 2012 Feb 9. PMID: 22363216; PMCID: PMC3280333.

49. Dusonchet J, Li H, Guillily M, Liu M, Stafa K, Derada Troletti C, Boon JY, Saha S, Glauser L, Mamais A, Citro A, Youmans KL, Liu L, Schneider BL, Aebischer P, Yue Z, Bandopadhyay R, Glicksman MA, Moore DJ, Collins JJ, Wolozin B. A Parkinson's disease gene regulatory network identifies the signaling protein RGS2 as a modulator of LRRK2 activity and neuronal toxicity. Hum Mol Genet. 2014 Sep 15;23(18):4887-905. doi: 10.1093/hmg/ddu202. Epub 2014 May 2. PMID: 24794857; PMCID: PMC4140468.

50. Smith WW, Pei Z, Jiang H, Dawson VL, Dawson TM, Ross CA. Kinase activity of mutant LRRK2 mediates neuronal toxicity. Nat Neurosci. 2006 Oct;9(10):1231-3. doi: 10.1038/nn1776. Epub 2006 Sep 17. PMID: 16980962.

51. Rosenbusch KE, Kortholt A. Activation Mechanism of LRRK2 and Its Cellular Functions in Parkinson's Disease. Parkinsons Dis. 2016;2016:7351985. doi: 10.1155/2016/7351985. Epub 2016 May 12. PMID: 27293958; PMCID: PMC4880697.

52. Cronin KD, Ge D, Manninger P, Linnertz C, Rossoshek A, Orrison BM, Bernard DJ, El-Agnaf OM, Schlossmacher MG, Nussbaum RL, Chiba-Falek O. Expansion of the Parkinson disease-associated SNCA-Rep1 allele upregulates human alpha-synuclein in transgenic mouse brain. Hum Mol Genet. 2009 Sep 1;18(17):3274-85. doi: 10.1093/hmg/ddp265. Epub 2009 Jun 4. PMID: 19498036; PMCID: PMC2722989.

53. Kasten M, Klein C. The many faces of alpha-synuclein mutations. Mov Disord. 2013 Jun;28(6):697-701. doi: 10.1002/mds.25499. Epub 2013 May 14. PMID: 23674458.

54. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. alpha-Synuclein locus triplication causes Parkinson's disease. Science. 2003 Oct 31;302(5646):841. doi: 10.1126/science.1090278. PMID: 14593171.Nishioka K, Ross OA, Ishii K, Kachergus JM, Ishiwata K, Kitagawa M, Kono S, Obi T, Mizoguchi K, Inoue Y, Imai H, Takanashi M, Mizuno Y, Farrer MJ, Hattori N. Expanding the clinical phenotype of SNCA duplication carriers. Mov Disord. 2009 Sep 15;24(12):1811-9. doi: 10.1002/mds.22682. PMID: 19562770.

55. Ahn TB, Kim SY, Kim JY, Park SS, Lee DS, Min HJ, Kim YK, Kim SE, Kim JM, Kim HJ, Cho J, Jeon BS. alpha-Synuclein gene duplication is present in sporadic Parkinson disease. Neurology. 2008 Jan 1;70(1):43-9. doi: 10.1212/01.wnl.0000271080.53272.c7. Epub 2007 Jul 11. PMID: 17625105.

56. Ibáñez P, Bonnet AM, Débarges B, Lohmann E, Tison F, Pollak P, Agid Y, Dürr A, Brice A. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet. 2004 Sep 25-Oct 1;364(9440):1169-71. doi: 10.1016/S0140-6736(04)17104-3. PMID: 15451225.

57. Maraganore DM, de Andrade M, Elbaz A, Farrer MJ, Ioannidis JP, Krüger R, Rocca WA, Schneider NK, Lesnick TG, Lincoln SJ, Hulihan MM, Aasly JO, Ashizawa T, Chartier-Harlin MC, Checkoway H, Ferrarese C, Hadjigeorgiou G, Hattori N, Kawakami H, Lambert JC, Lynch T, Mellick GD, Papapetropoulos S, Parsian A, Quattrone A, Riess O, Tan EK, Van Broeckhoven C; Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium. Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. JAMA. 2006 Aug 9;296(6):661-70. doi: 10.1001/jama.296.6.661. PMID: 16896109.

58. Li X, Gehring K. Structural studies of parkin and sacsin: Mitochondrial dynamics in neurodegenerative diseases. Mov Disord. 2015 Oct;30(12):1610-9. doi: 10.1002/mds.26357. Epub 2015 Sep 11. PMID: 26359782.

59. Inzelberg R, Cohen OS, Aharon-Peretz J, Schlesinger I, Gershoni-Baruch R, Djaldetti R, Nitsan Z, Ephraty L, Tunkel O, Kozlova E, Inzelberg L, Kaplan N, Fixler Mehr T, Mory A, Dagan E, Schechtman E, Friedman E, Hassin-Baer S. The LRRK2 G2019S mutation is associated with Parkinson disease and concomitant non-skin cancers. Neurology. 2012 Mar 13;78(11):781-6. doi: 10.1212/WNL.0b013e318249f673. Epub 2012 Feb 8. PMID: 22323743.

60. Valente EM, Bentivoglio AR, Dixon PH, Ferraris A, Ialongo T, Frontali M, Albanese A, Wood NW. Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35-p36. Am J Hum Genet. 2001 Apr;68(4):895-900. doi: 10.1086/319522. Epub 2001 Mar 7. PMID: 11254447; PMCID: PMC1275643.

61. Truban D, Hou X, Caulfield TR, Fiesel FC, Springer W. PINK1, Parkin, and Mitochondrial Quality Control: What can we Learn about Parkinson's Disease Pathobiology? J Parkinsons Dis. 2017;7(1):13-29. doi: 10.3233/JPD-160989. PMID: 27911343; PMCID: PMC5302033.