Berkeley
Pharma Tech
Journal of Medicine

Traumatic Brain Injury-Induced Parkinson's Disease:

An Analysis of the Potential Correlation

By: Bhavana Sreepad, Maliha Khan, Rochelle Shtutin, Sofia Piedrafita-Ortiz, Tejaswini Govindaraman, Neha Ramachandran, Danielle McMillion, Ariana Samimi and Diego Sandoval

Correspondence:
bhavana.sreepad@gmail.com

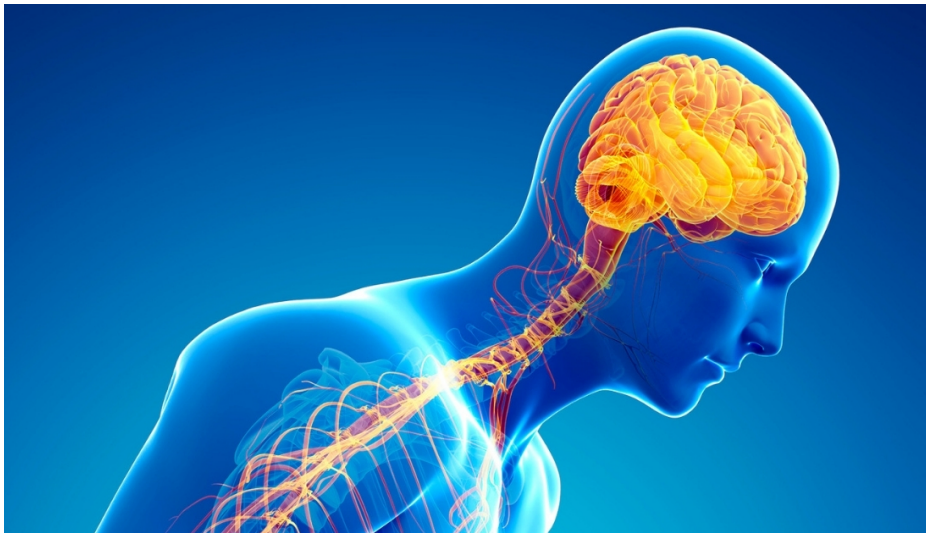


Image Credits: N/C

Keywords:
Parkinson's Disease
Traumatic Brain Injury
Alpha-synuclein
Tyrosine hydroxylase
Dopamine

Abstract

Research findings on the correlation between Traumatic Brain Injury (TBI) and the onset of Parkinson's Disease (PD) are inconclusive. With PD affecting thousands of individuals, it is imperative to determine a potential causal link. The purpose of this literature review is to under-stand the validity and extent of the relationship between TBI and PD by examining population demographics, biological, sociological, and cognitive factors, as well as therapeutic treatments. Previous research has found that the incidence of TBI can occur during the prodromal period of PD, which is the period when symptoms of the disease begin to show, though the directionality of the correlation between TBI and the onset of PD requires a more in-depth investigation. Other findings include the over-accumulation of alpha-synuclein in the substantia nigra—a protein that regulates vesicle trafficking—which is prominent in both patients with TBI and those with PD. The presence of Tyrosine Hydroxylase from TBI has also been proven to contribute to the decrease in dopamine seen in PD. Hippocampal damage is present in patients who experience either PD or TBI, which leads to cognitive decline. These findings indicate a positive correlation between TBI and the subsequent onset of PD, and confirm the need for additional research to develop new therapies for PD.

Submitted July 7, 2021
Accepted August 28, 2021
Published December 17, 2021

Introduction

Parkinson's disease (PD) affects movement and is the second most common progressive neurodegenerative disorder after Alzheimer's disease. Symptoms include slow movement, rigidity, shuffling gait, postural instability, and imbalance [1]. This neuronal imbalance is followed by the degeneration of dopamine neurons in the substantia nigra of the basal ganglia tissue in the brain, and the development of Lewy bodies, which interfere with brain activity [2]. PD was first described by James Parkinson in 1817 [3]. The cause of neurodegeneration associated with PD has not been scientifically proven and, only a small percentage of PD diagnoses are attributed to genetic factors. However, PD has been explored in association with non-genetic risk factors such as traumatic brain injury. Traumatic brain injury (TBI) typically results from blunt external force to the skull, which may result in cognitive and behavioral disruptions that could lead to brain pathologies [4]. Current research remains divided regarding the strength of the correlation between TBI and the onset of PD. As such, this review analyzes population demographics, biological and cognitive factors to elucidate the nature of this correlation.

Studies on the Risk Factors for TBI and Parkinson's Disease

TBI is traditionally organized into clinical categories that distinguish the levels of severity and each category's potential to lead to neurodegeneration. Yet, most research serves to analyze the impact on only severe TBI. Insufficient research has been conducted on patients with moderate TBI, proving to be a challenge for researchers [6]. However, through research of mild and severe TBI, it has been determined that the majority of TBI cases in the United States result from falls and motor vehicle accidents.

Researchers analyzed demographics and the causes of injury using registry data from the National Trauma Data Bank (NTDB) between 2007 to 2014 for patients over the age of 18 with mild TBI. It was determined that falls and motor vehicle-related injuries accounted for 43% and 34% of TBI cases, respectively. Furthermore, assessing TBI outcome severities demonstrated that adults in the 45-to-64-year age range had about a two-fold increased risk, while those over 80 years old had nearly a five-fold increased risk of experiencing poor outcomes. Researchers defined poor outcomes as in-hospital mortality, hospice, and long-term care. Similarly, a cross-sectional analysis conducted by Majdan et al. identified 1,375,974

TBI-related hospital discharges and found the most prevalent causes of TBI to be falls and traffic incidents [5]. In recent years, however, there has been a shift from traffic accidents to falls as the most frequent cause of TBI [8].

On the other hand, there are many risk factors associated with the development of PD — one of which is genetic risk. A genome-wide linkage and sequencing study conducted from 2008 to 2017 aimed to identify genes involved in the onset of PD. The researchers first conducted a genome-wide analysis on an Italian family whose members had PD through dominant inheritance. The identified gene was then analyzed and compared in a representative sample of international patients diagnosed with PD. Quadri et al. identified a mutation on LRP10 on chromosome 14 to be involved in the onset of PD. Out of the 11 patients identified with this mutation in the international cohort, 10 had a family history of PD. The LRP10 mutation was also found in the DNA of nine out of 10 relatives of the international cohort. These results suggest that there is a hereditary aspect of the increased risk of developing PD [9].

Other risk factors of PD include the consumption of dairy products, cancer, and exposure to pesticides [7]. Researchers conducting an observational study on nutritional factors and PD found that the higher intake of dairy was associated with an increased risk of PD development, with a larger risk in men compared to women [10]. An increased prevalence of malignant melanoma and skin carcinoma is also associated with a higher risk of PD. An epidemiological study in Denmark found the prevalence of malignant melanoma was 0.57% in PD patients compared to 0.4% in control patients, while skin carcinoma prevalence was 4.24% in PD patients compared to 3.4% in controls [11]. Researchers have found similar patterns of increased relative risk when investigating the effect of pesticides on patients who suffered from PD and/or TBI [12]. A controlled study researched the effects of both TBI and paraquat exposure, which causes damage to the digestive system organs, in patients with PD. Researchers estimated a two-fold increase in the risk of developing PD in patients who experienced TBI, further supporting the correlation between the two diseases. In contrast, when examining the combined effects of both paraquat exposure and TBI, researchers noticed a three-fold risk increase [13]. A study in rats further substantiated these findings by demonstrating that TBI and paraquat exposure led to a loss in dopaminergic neurons and

concurrently increased alpha-synuclein accumulation and inflammation in the brain, which are common characteristics of PD [14].

Demographics

Age and gender have proven to be significant factors in the incidence of TBI and in the development of PD [16, 17]. When researching the demographic data relating to these diseases, studies have been geared towards researching the demographics of TBI and PD individually rather than on their relationship to each other. A study analyzing the characteristics of patients with PD found that the age-adjusted incidence rate of PD was higher in men than in women, at 19.0 per 100,000 persons and 9.9 per 100,000 persons, respectively. Incidence rates and the male to female ratio increased rapidly after 60 years of age. The mean age of diagnosis was 70.5 years for both men and women, yet women were diagnosed over a larger age range (31 to 93 years) than men (38 to 91 years). Further analysis found incidence rates of 0.50 per 100,000 persons in the 30-to-39-year group and 119.01 per 100,000 persons in those over 89, suggesting that the risk of being diagnosed with PD increases dramatically with age. Researchers also sought to distinguish the prevalence of idiopathic PD among different racial groups. Non-Hispanic Whites were found to be diagnosed with PD at an older age than Hispanics and Asians/Pacific Islanders, and a slightly older age than African Americans. When adjusting for age and gender, incidence rates of PD were highest among Hispanics, followed by non-Hispanic Whites, Asians/Pacific Islanders, and African Americans. Pairwise comparisons among different groups found this data to be somewhat statistically significant. Prevalence of PD in the non-Hispanic White cohort compared to the Asian/Pacific Islander cohort was 13.6 and 11.3 per 100,000 persons ($p = 0.07$) respectively, while the non-Hispanic White cohort compared to the African American cohort exhibited incidence rates of 13.6 and 10.2 per 100,000 persons ($p = 0.11$). Researchers also noted that in every group besides the Asian/Pacific Islander cohort, the incidence of PD was higher in men than in women by two-fold [18].

Researchers have found increasing evidence pointing to gender as an important factor in the development and expression of PD [19]. A case study conducted by Haaxma et al. found women to be 2.1 years older than men at their age of symptom onset, the mean ages being 53.4 and 51.3, respectively [20]. At symptom onset, women presented tremors, a symptom of PD, more frequently than men (67% and 48%), regardless of their age of

onset. However, men presenting tremors at the age of onset were, on average, 3.6 years older than women. From this research, it was concluded that gender-based differences in PD patients were significant. Women tended to be older at symptom onset, presented higher striatal dopamine affinity and tremor dominant symptoms, and experienced slower disease progression compared to men. Other studies have shown that women diagnosed with PD tend to present more benign phenotypic symptoms, but later tend to have an increased risk of treatment complications compared to men, further pointing to the biological and phenotypic differences between male and female patients with PD [21]. Reviewing demographic factors relating to TBI reveals similar trends regarding data on the age and gender of patients.

A cross-sectional study analyzed data from the National Hospital Ambulatory Medical Case Survey (NHAMCS) and collected information on demographic characteristics of older patients who sustained mild TBI in the United States. The average age of patients diagnosed with mild TBI was 79.1 years of age, 87.8% of whom were White, and 64.3% of whom were female.

Emergency department (ED) visits were also observed to increase with age. In patients aged between 65 to 74 years old, the rate was 386 per 100,000 persons, while patients 85 years or older had an incidence rate of 1,205 per 100,000 persons. Since the rates for those 85 and older triple the rates for those between 65 to 75 years of age, TBI has been found to be more prominent in older age groups. Researchers found that women visited the ED for TBI at a rate of 706 per 100,000 persons, while men visited at a rate of 516 per 100,000 persons. Another characteristic that researchers investigated was geographic region, finding that visits related to diagnosed TBI were more common than visits related to possible mild TBI in the northeastern and western regions of the United States. The diagnosis of TBI was more prevalent on the west coast and less prevalent in the south and Midwest, compared to the northeast regions of the United States. This data, however, should be interpreted with caution, as some have suggested that the CDC codes for detecting mild TBI have poor sensitivity and mild TBI can be underdiagnosed [22]. A retrospective cohort study analyzed data on older adults from the Ontario Association of Community Care Access Centers (OACCAC) home care database. In this experiment, incidence of TBI among patients of varying education levels, marital status, sex, race, and age groups were observed over a ten-year period from 2003 to

2013. Investigators found that those who had sustained a TBI had an equal sex distribution. Overall, positive associations were found between sustaining TBI and several groups, including males, patients of aboriginal origin, increasing age, education level, being widowed, and having PD [23]. In another study on the medical data of Californian patients 55 years or older who were diagnosed with TBI but not PD, patients with TBI were slightly older, more likely to be male, have higher income, and higher severity scores when compared to patients with non-TBI trauma (NTT) [24].

Moreover, patients with TBI were more likely to be diagnosed sooner with PD than patients with NTT. The average time until PD diagnosis was 3.1 years for TBI patients versus 3.3 years for NTT patients, and 66% of the trauma for both the TBI and NTT group was caused by falls. Patients with PD had an average age of 76 years old, with 59% being female and 68% being white. Data showed that incidence rates of TBI among racial groups was highest among Whites, followed by Hispanics, Asians, and African Americans. Cases of TBI were found to increase with wealth; there were 10,276 incidents of TBI in the lowest quartile, while there were 14,132 cases of TBI in the highest, wealthiest quartile. Researchers also noted that TBI was associated with a 44% increased risk of PD diagnosis after having adjusted for demographic variables (age, sex, race, income, etc.) This data suggested an increased risk of PD associated with TBI compared to NTT. Similarly, researchers found that the risk of being diagnosed with PD increases with the severity and frequency of TBI, providing support to a more causal association [24].

Prevalence of TBI in patients with PD

Contradicting evidence exists regarding the statistical significance of the association between TBI and the risk of developing PD [25]. TBI-related emergency visits have increased in recent years in the United States, with age-adjusted rates showing increases from 534.4 per 100,000 persons in 2007 to 787.1 per 100,000 persons in 2013 [26]. Savica et al. similarly cites an increase in PD incidence in recent decades. With these increasing rates, it becomes even more pertinent to assess whether there is a correlation between PD and TBI [27].

Recent epidemiological studies have cited a lack of correlation between the development of PD and severe head injury. One study analyzed the medical

records of the Danish population 20 years and older who were hospitalized for head trauma from 1981 to 1993. Of the 8769 cases requiring hospitalization, 107 patients developed PD, in which 55 of those cases were male and 52 cases were female. The mean age to sustain the injury was 39.7 for males and 49.2 for females [28]. Regarding the severity of TBI, Raj et al. found that the mean age of sustaining moderate-to-severe TBI (39 years) was less than that of patients diagnosed with mild TBI (46 years) [29]. In a study by Spangenberg et al., the expected number of participants who developed PD without sustaining a severe head injury was 112.14 per 100,000 persons [28]. Due to these results, the study concluded that there was no correlation between PD risk and severe head injury among adults. Similarly, Raj et al. found no significant pattern of correlation between TBI history and PD risk in the adult Finnish population [29].

Conversely, other studies have observed a correlation between PD risk and TBI. A case control study consisting of twins found that head injuries were associated with a three-fold increase in PD, while head injuries with amnesia and loss of consciousness were more strongly associated with the onset of PD. These results suggest that mild-to-moderate closed head injury may increase PD risk. It was also observed that the risk for PD increased with the frequency and severity of the head injury [30]. Similarly, a study by Bower et al. corroborated this as the researchers found that only moderate-severe diagnoses of TBI were correlated with an increased PD risk [31]. Similarly, White et al. found a 2.69-fold and 3.70-fold increase in PD risk in Veterans Affairs healthcare facilities' patients diagnosed with mild TBI and moderate TBI, respectively, indicating a correlation between increased incidence rate and the severity of TBI [32]. Bower et al. and White et al. also observed a possible association between PD risk and TBI in their studies [31, 32].

During our literature review regarding the prevalence and demographics of PD and TBI, some studies noted the possibility of attaining TBI due to PD. In a study conducted in Denmark, patients were found to have a 50% higher risk of developing PD if they sustained a head injury less than 10 years before the diagnosis, and an even higher risk if the TBI was sustained three months prior to PD diagnosis. Due to this lack of correlation over the l0-year study, Rugbjerg et al. concluded that there was no correlation between head injury and PD. In fact, Rugbjerg et al. mentioned the possibility of PD-induced TBI due to PD patients' tendency to have a slower reaction time [33]. Delayed reaction time makes it difficult for PD

patients to break their fall with their arms, resulting in a more severe injury which could lead to TBI. It is possible that head injury in the months preceding PD is not a cause of diagnosis, but rather a consequence due to decreased control of motor function. This could serve as a plausible explanation for the observed association between TBI and the subsequent PD diagnosis in the previous study. This reverse relationship could be mistaken for an association between TBI and increased PD risk and should be researched further to assess the nature and directionality of this association [33].

Cognition

PD and TBI can greatly affect a patient's cognitive function. The association between the two suggests that cognition can be affected from both physical and biological standpoints.

Cognitive dysfunction in PD and in TBI

Cognitive dysfunction appears as a common symptom among those diagnosed with PD, and numerous studies have examined the extent to which cognition is affected by PD. In one study, 115 participants newly diagnosed with PD and 70 healthy control participants were given a neuropsychological assessment, which included tests for psychomotor speed, memory, language, attention, and executive and visuospatial functions. PD patients performed significantly worse than healthy controls for most of the cognitive measures. The results indicated that PD patients were cognitively impaired due to their dysfunctional performance on at least three neuropsychological tests. 24% of PD patients were determined to be cognitively impaired, whereas only 4% of healthy controls were cognitively impaired. The deficits in PD patients appeared in memory and executive functions. Apparent deficits may be misrepresented by the type of test given, as the tests may have favored assessment of immediate memory rather than cognitive dysfunction as a whole [34]. Further analysis is warranted to discern factors such as TBI and falls that may have contributed to performance.

Another study consisted of a population-based, case-control examination of cognitive function in early PD patients. The study consisted of 46 patients who were 65 years or older that presented PD within five years. All these patients were enrolled in the Neurological Disorders in

Central Spain (NEDICES) and matched with 138 controls for comparison. The Mini-Mental State Examination, a cognitive ability examination of the elderly, was administered and PD patients performed worse ($p = 0.04$) than controls. Subjective memory complaints were observed in 58.7% of PD patients compared to 37% in controls ($p = 0.010$). Results indicated that PD patients who were diagnosed within the last five years did not perform well on global cognition tests, verbal fluency tests, and memory tests. Additionally, 16 of the 46 PD patients with early PD were previously undiagnosed [35].

In addition, a study following cognitive change for five years in newly diagnosed patients was done to explore the extent of cognitive dysfunction in PD patients. At zero, three, and five years, a sample of PD patients ($n = 59$) and a sample of healthy controls ($n = 40$) were given neuropsychological assessments in which six cognitive domains were tested. In all the domains except the assessment of attention, patients with PD showed a greater decline than the healthy controls over time. Individually, 53% of PD patients showed a greater decline in cognition than controls. Overall, cognitive impairment with varying levels of severity seems to be prevalent among PD patients, with memory and psychomotor speed being the most affected [36]. Similarly, patients with TBI commonly exhibit cognitive impairment.

Furthermore, studies have researched areas of the brain in which cognitive impairment occurs in patients with PD. One study assessed the areas in which brain atrophy occurred in PD patients who also had Mild Cognitive Impairment (MCI), a cognitive impairment that does not interfere with daily activities. In comparison to PD patients without cognitive impairment, PD patients with cognitive impairment had hippocampal atrophy, a potential biomarker for initial cognitive decline in patients with PD [37]. As with PD, cognitive dysfunction in patients appears to be a common characteristic among patients with TBI. To better understand the association between cognitive dysfunction and TBI, a study was conducted in 2008 to investigate cognitive impairments ten years after participants experienced TBI (time range of initial injury was limited to the years of 1992 and 1995). 60 TBI participants were gathered and compared to a group of 43 demographically similar participants. These groups underwent a series of tests that measured functions such as attention, processing speed, memory, and executive function. Results showed that the group of patients who had a TBI 10 years prior scored significantly lower than the control

group on the Symbol Digit Modalities Test and the Digit Symbol Coding subtest, both of which measured information processing speed. These results strongly suggest that patients who suffered a TBI may experience long-term cognitive dysfunction [38].

In addition to long-term effects, there appears to be a short-term effect on cognitive function in TBI patients as well. A study from the University of Texas at Dallas in 2016 examined whether a history of TBI was associated with an increased risk of earlier onset of mild cognitive impairment (MCI). 3,187 subjects with MCI and 3,244 normal-cognition subjects were selected from the National Alzheimer's Coordinating Center database and categorized based on severity and demographics. The results demonstrated that patients with MCI were diagnosed 2.3 years earlier in the TBI positive group than the subjects without TBI, showing TBI as a potential risk factor for MCI. Limitations are vast, as this association could be due to other factors such as gender or mental state. However, this opens the door for further studies to discover whether TBI and MCI can be associated with an increased risk of neurodegenerative diseases such as PD [39].

TBI and PD Cognition Studies

Cognitive impairment is a shared characteristic among patients with TBI and PD. Further exploration of cognitive impairment in recent studies has shown that there may be greater cognitive impairment in PD patients who experienced TBI, compared to PD patients who have not experienced TBI. Hence, there is a great need to investigate the role of TBI in inducing or exacerbating PD.

A research team at UCSF conducted a study to investigate the relationship between head injury and PD phenotype. Data collected from 267 patients in the Parkinson's Progression Markers Initiative (PPMI), it was found that individuals who experienced head injury prior to being diagnosed with PD had higher non-motor symptoms. PD patients with any report of head injury received a mean score of 7.73 on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale, where lower scores indicate milder symptoms. By comparison, PD patients with no history of head injury had a mean score of 6.19 on the same scale ($p = 0.035$). Those with severe head injury had scores of 8.29, and those without a head injury report had a score of 6.19 ($p = 0.051$). Additionally, motor symptoms were

higher in those who had a severe head injury (score of 8.35) on the MDS assessment, whereas patients without a head injury history had a score of: 6.19 (p = 0.042) [40].

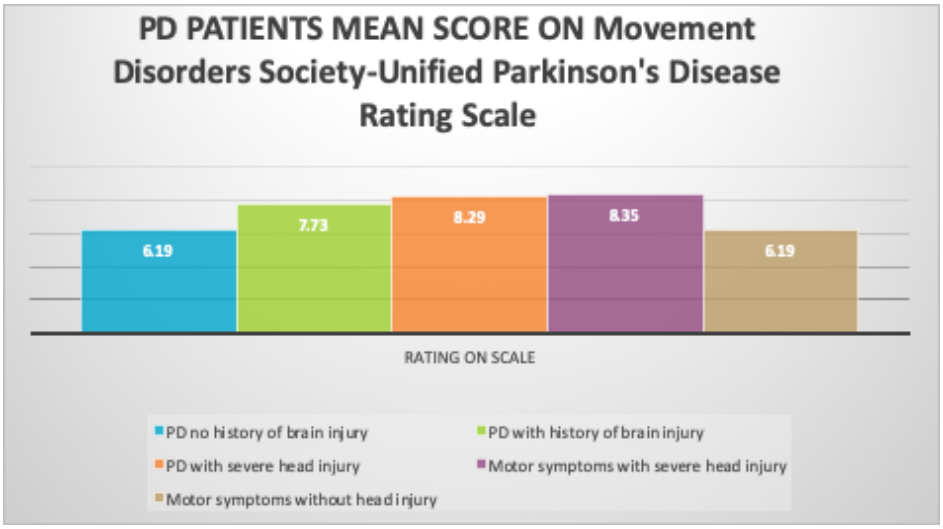


Figure 1*: PD with severe head injury has the highest score (8.29) on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale.*

A separate longitudinal study took place over two years and consisted of cognitive testing on PD patients with and without a history of TBI. The study found that patients with a history of TBI faced more significant cognitive decline over the two years**.** After taking the Mattis Dementia Rating Scale test, which measures attention, initiation-perseveration, construction, memory, and conceptualization, PD patients without TBI had improved scores after two years, whereas PD patients with TBI had a decline in scores. However, both faced a similar decrease in motor function and a similar increase in depressive symptoms. The PD group with a history of TBI fare worse in both memory and initiation/preservation subscales [41]. This study demonstrated a potential correlation between TBI and PD symptoms. Another cross-sectional cohort study was conducted to investigate whether a patient's history of TBI could be associated with PD and cognitive, motor, and neuropsychiatric symptoms. 120 patients between the ages of 60 to 85 were assessed for demographic data, neuropsychological tests, motor evaluation, neuropsychiatric questionnaires, and a brain injury screening questionnaire. Of the 120 patients, 69 had PD and 51 were healthy controls. Results from this study concluded there was a significant negative correlation between the number of TBIs in PD patients and mean z-scores for global cognition ($r_s(69) = -0.338$, $p = 0.004$) [42].

Neurodegeneration in PD and TBI and its Effects on Cognition

The effects of TBI on the brain may increase the severity of cognitive impairment by exacerbating the neurodegeneration present in PD. Weintraub et al. [37] conducted a study to assess regions in which brain atrophy occurred in patients with PD with normal cognition, PD with mild cognitive impairment, and dementia-level cognitive decline. 84 PD patients (61 PD normal cognition, 12 PD mild cognitive impaired, and 11 dementia-level cognitive impaired) and 23 healthy controls were assessed using magnetic resonance imaging of the brain. Results indicated that individuals who had PD and normal cognition did not have significant brain atrophy compared to the healthy controls. When comparing the PD patients with normal cognition and patients with mild cognitive impairment, PD patients with mild cognitive impairment demonstrated hippocampal atrophy ($\beta = -0.37$; $P = .001$), and PD patients with dementia had hippocampal ($\beta = -0.32$; $P = .004$) and medial temporal lobe atrophy ($\beta = -0.36$; $P = .003$) [37]. PD patients with mild cognitive impairment had a similar pattern to the patients with both dementia and PD. A correlation between memory-encoding performance and hippocampal volume was found in the PD groups not exhibiting dementia. From this study, it was concluded that hippocampal atrophy may serve as a biomarker of initial cognitive decline in PD [37].

PD patients with mild cognitive impairment also showed a faster rate of cortical thinning. According to the Montreal Cognitive Assessment, significant thinning of the temporal and medial occipital lobe was correlated with a decline in cognitive function [43]. To understand the genetic nature of cognitive impairment, researchers from North China University conducted an experiment to analyze the dysregulated expression of microRNA144 (miRNA) and its role in the pathogenesis of TBI in a rat model TBI. According to the researchers, miR-144 overexpression was a common characteristic of neurological diseases, as MiR-144 could alter gene expression in the hippocampus. After analyzing the miR-144 gene in TBI patients and TBI in rats in vivo and in vitro, researchers found that the inhibition of the gene led to a better neurological outcome after TBI in vivo and improved cognitive deficits. The researchers also found that overexpression of the miR-144 gene led to an inhibition of the ADAM10 expression, which can modulate beta-amyloid formation, a common

protein involved in the development of cognitive deficits. These results demonstrate the potential relationship between cognitive deficits in TBI and gene expression in the brain, which could lead to neurological diseases such as PD [44].

Previous research has investigated areas of the brain responsible for cognitive dysfunction commonly observed in TBI, PD, depression, and dementia. After analyzing magnetic resonance imaging (MRI) data from participants, researchers found frontoparietal and fronto-occipital networks and temporoparietal, inferior frontal cortices were the primary systems responsible for information processing speed and stimulus-driven attention of the brain [45].

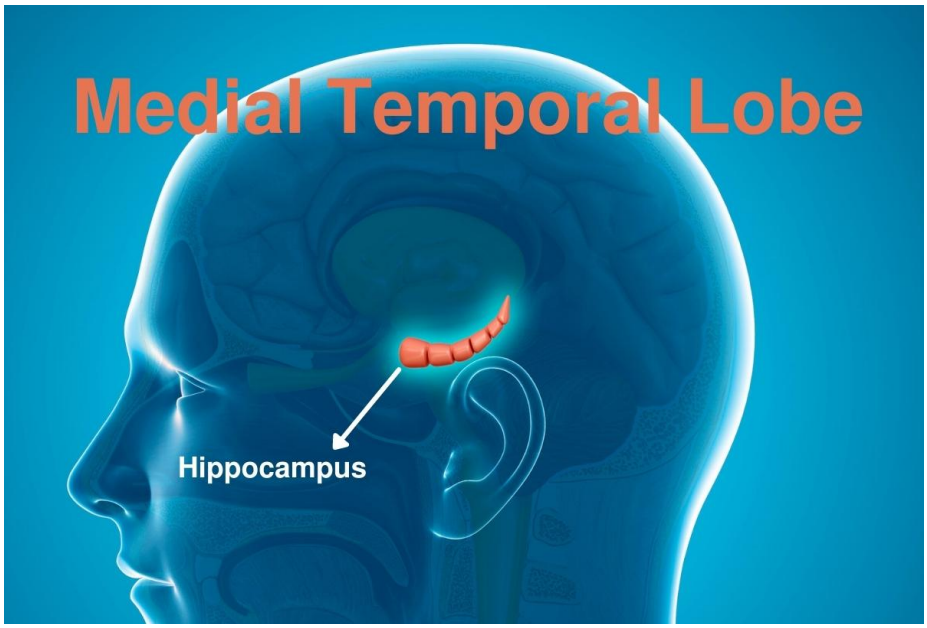


***Figure 2**: The medial temporal lobe, highlighting the hippocampal area affected by TBI and PD.*

Biological Factors

Current literature has largely focused on the role of biological molecules such as alpha-synuclein, a presynaptic neuronal protein that regulates the trafficking of synaptic vesicles and the release of neurotransmitters, and enzymes such as tyrosine hydroxylase. Additionally, biological phenomena such as oxidative stress and neuroinflammation are possible conditions that may contribute to the loss of dopaminergic neurons.

Alpha-Synuclein

The neurodegenerative effects caused by TBI and PD have been correlated with specific proteins in the brain. To understand pathological correlations between PD disease and TBI, the structure and significance of alpha-synuclein must be discussed. A dominant pathological characteristic of PD is the abnormal folding and accumulation of alpha-synuclein in protein deposits known as Lewy bodies. Aggregation and overexpression of alpha-synuclein have been shown to disrupt the cell membrane of dopaminergic neurons, causing neuronal damage [46].

Alpha-synuclein has different structural forms, such as the oligomer and fibrillar forms, which have varying effects on PD pathology. A study conducted by Froula et al. investigated the stable β-amyloid–sheet oligomer form (secondary protein structure) of the alpha synuclein protein in comparison to the fibrillar form to identify their varying abilities to induce characteristics of PD [47]. The various well-defined forms of alpha-synuclein were injected into the striatum of mice, with a monomeric alpha-synuclein injection serving as the control of the experiment. Neuropathological outcomes were monitored by performing immunohistochemistry using an antibody for alpha synuclein, phosphorylated at serine 129. Results showed that in comparison to the monomer-injected mice, fibrils, cellular components that provide stability, produced ~30% loss of dopaminergic neurons in the substantia nigra compacta and loss of dopamine terminals in the striatum. Injection of fibril alpha-synuclein also yielded a higher concentration of alpha-synuclein–positive inclusions. In contrast, injection of the β-sheet oligomer resulted in a smaller loss of dopamine neurons in the substantia nigra compacta but showed no signs of inclusion formation. In addition, the fibrillar form of alpha-synuclein led to notable motor defects, while oligomer-injected mice did not exhibit a decline in motor behavior. It was concluded that the fibrillar form of alpha synuclein had a more significant toxic impact than the β-sheet oligomers due to the fibrillar protein's ability to recruit alpha-synuclein monomers and spread more quickly in vivo. Overall, this research concluded that the fibrillar form of alpha-synuclein plays an important role in the induction of PD-related phenotypes, and interestingly, alpha-synuclein has proven to be a characteristic of TBI.

In an in vivo study by Acosta et al., male rats underwent cortical impact to simulate TBI [46]. Sixty days after TBI surgery, the brain tissues of these

rats were harvested for testing. Characterization of alpha-synuclein in TBI-induced brains was studied through immunofluorescent staining of sections of the substantia nigra. Performing this experiment showed that brain tissue exposed to TBI had an increased accumulation of alpha-synuclein in the ipsilateral substantia nigra pars compacta. TBI resulted in a three-fold upregulation of alpha-synuclein density around the soma and neurites of dopaminergic neurons, which triggered dopaminergic cell death. Researchers concluded that the alpha synuclein overexpression in TBI-exposed brains led to a loss of dopaminergic neurons and served as a connection between TBI and the development of PD pathology [46]. Furthermore, a study from Impellizzeri et al. confirmed this finding. This study analyzed alpha synuclein levels in male mice brains 30 days after the mice were exposed to induced TBI. Through dopamine transporter and alpha-synuclein staining, significant increases in alpha-synuclein expression and significant decreases in dopamine transporters were observed in comparison to controls. Impellizzeri et al. also found a reduction in neurotrophic factors after 30 days, which are biomolecules that support the growth and development of neurons [48]. Overall, findings from these two studies suggest that alpha-synuclein may serve as a notable pathological link between TBI and Parkinson's disease.

Tyrosine Hydroxylase

In addition to alpha-synuclein, tyrosine hydroxylase, an enzyme that plays a key role in the synthesis of dopamine, has been researched as another biological marker in TBI and PD. Shin et al. investigated tyrosine hydroxylase levels in rat brain tissue to determine this enzyme's effect on dopaminergic activity. For this study, a set of rats was first exposed to TBI using a controlled cortical impactor. Thirty days after exposure to TBI, the brain tissues of these rats were harvested for testing. Western blotting techniques were utilized to detect the phosphorylation of tyrosine hydroxylase. Between one and four weeks after exposure to TBI, tyrosine hydroxylase levels decreased significantly at the serine 40 sites. In addition, analysis of the striatal tissue revealed a decrease in potassium-evoked dopamine release. It was concluded that lower tyrosine hydroxylase levels after TBI negatively impacts dopamine concentration in the brain, suggesting a correlation between TBI and the development of PD pathology [49].

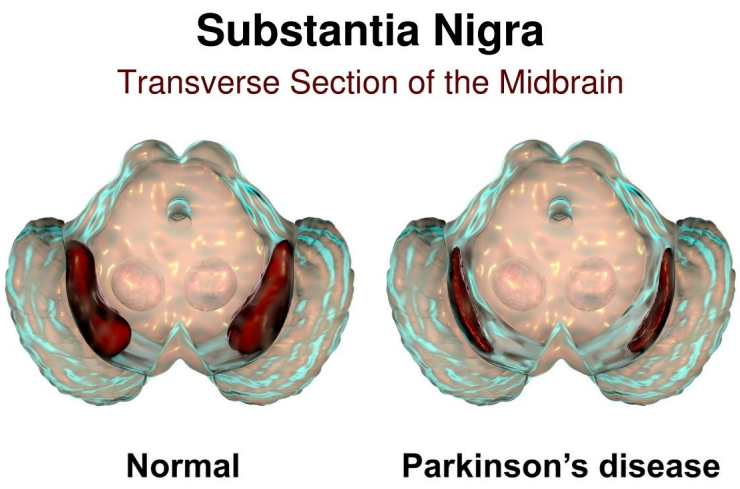


***Figure 3**: Location of the Substantia Nigra--the site of the dopamine-producing neurons. A decrease in these neurons is implicated in the development of Parkinson's Disease.*

Oxidative Stress

Oxidative stress is a phenomenon in which neuronal damage can occur due to the overproduction and accumulation of reactive chemical species that cannot be readily detoxified [50] [51]. Typically, these chemicals are reactive oxygen species (ROS) that take on the form of oxygen containing radicals [50]. This may be because brain cells require and receive large amounts of oxygen. Current literature has discussed oxidative stress in the context of TBI and PD independently, and the similar pathology of both suggests that this is one biological aspect that may link these two afflictions.

Several studies have implicated oxidative stress in TBI pathology through a variety of mechanisms. Hill et al. observed, within hours of injury, an increase in ROS production and the accumulation of reactive aldehydes acrolein and 4-hydroxynonenal, which are indicative of oxidative damage. In addition, Hill et al. observed impairment of Complex I and II activity [50]. These effects were more pronounced in the synaptic mitochondria compared to those that were nonsynaptic.

Another study focused on monitoring the synergistic effects of mechanical strain induced-TBI and paraquat pesticide exposure. Research has been carried out through an in vitro model of undifferentiated SH-SY5Y cells, which are often used to model neuron-like activity in experiments. Cells that underwent a moderate degree of strain experienced greater and longer-lasting mitochondrial membrane depolarization and increased ROS mitochondrial

production, ultimately resulting in the death of dopaminergic neurons. These effects were amplified when combined with exposure to paraquat [52]. Together, these studies suggest that oxidative stress plays a unique role in further propagating neuronal damage from TBI at the cellular level, likely by interfering with the cellular respiration processes in the mitochondria.

Gene-regulated expression may also play a role in oxidative stress. Wang et al. examined the role of protein-disulfide isomerase-associated 3 (PDIA3) regulated oxidative stress in augmenting TBI damage [53]. Though this study focuses on the expression of ROS and antioxidant enzymes as a metric for gauging the level of oxidative stress rather than mitochondrial activity, it appears to confirm the findings of Hill et al. While mitochondrial dysfunction and interference with neuronal function appear to be unifying themes connecting TBI and oxidative stress in these studies [50] [52] [53], further research is required to elucidate the exact mechanism to determine a causal relationship. Additional research has sought to characterize the potential role of oxidative stress in the development of PD — more specifically, its impact on the decline of dopaminergic neurons. Paul et al. aimed to evaluate the efficacy of melatonin as an antioxidant capable of providing neuroprotective benefits to mitigate the development of PD. Researchers showed that rats experiencing oxidative stress, as the result of a homocysteine injection in the brain, exhibited a decrease in the number of functioning dopaminergic neurons in the substantia nigra region [54]. The study concluded that melatonin was an effective antioxidant and could prove promising as a treatment. Oxidative stress and the overexpression of alpha synuclein together have been found to possibly cause a synergistic effect in inhibiting the function of cholinergic neurons in the vagus nerve [51]. This study, however, noted that not all cholinergic neurons within the brain were affected by oxidative stress, suggesting that specific regions of the brain and nervous system may be affected differently. A similar pattern has been observed for dopaminergic neurons, with the substantia nigra and striatum being the main regions of focus [54] [55] [56]. A causative relationship has to be made cautiously between oxidative stress and PD due to limited information.

If the aforementioned observations involving oxidative stress have any significant overall impact on dopaminergic neurons, then there may be a causal relationship between TBI and PD. Researchers from Purdue

University used a mild-TBI rat model, immunofluorescence staining, and Western Blot analysis to demonstrate acrolein's role in inducing aggregation and modification of alpha-synuclein, further corroborating the findings from Hill et al. [55]. This study is one of the few that discusses the role of oxidative stress in the potential pathological link between TBI and PD. However, additional research is needed on the effects of oxidative stress and how its association with TBI can influence the development of PD. Specifically, the mechanism of mitochondrial dysfunction and the accumulation of aldehyde byproducts in relation to its interaction with alpha-synuclein requires further research to determine its relation to the development of PD-related symptoms.

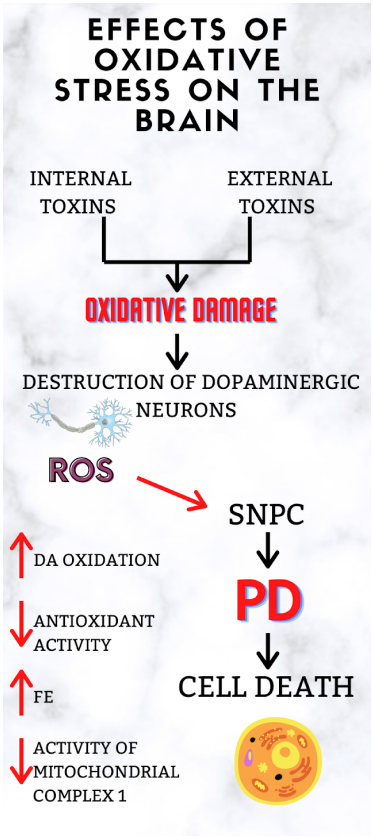


***Figure 4**: General Trends Associated with Oxidative Stress and its Potential Role in PD*

Neuroinflammation

Neuroinflammation has been researched as another biological link between PD and TBI. As dopaminergic neurons are easily susceptible to inflammation, neuroinflammation has been found to be an important characteristic of PD. Impellizzeri et al. conducted a study in 2016 analyzing neuroinflammation processes in the brains of male mice with

induced TBI. Western blot analysis was utilized to analyze midbrain tissue of mice 30 days after exposure to TBI using IκB-α and NF-κB specific antibodies. Performing this analysis showed a significant reduction in IκB-α expression and an increase in NF-κB translocation in mice exposed to TBI. Nuclear κB translocation plays a critical role in the transcriptional stimulation of pro-inflammatory target genes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). iNOS and COX-2 are both neurotoxic markers that can damage dopaminergic neurons. Evaluating iNOS expression revealed that there was a prominent increase in iNOS in the TBI-induced brains in comparison to the control brains. In addition, COX-2 expression increased in the midbrain of mice that suffered TBI [48]. Interestingly, increased COX-2 expression was also detected post-mortem in the substantia nigra of Parkinson's patients [57]. Based on these findings, researchers concluded that neuroinflammatory processes resulting from TBI can lead to the development of PD pathology in the midbrain.

In a 2018 study, Yu et al. examined the role that the expression of the transcriptional factor early growth response-1 (Egr-1) played in inducing neuroinflammation and neurodegeneration in mouse models of PD [58]. Mice were injected with 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP), induced expression and upregulation of Egr-1 in the substantia nigra pars compacta. Upon Egr-1 activation, researchers also noted an increase in interleukin 1-beta (IL-1b) and tumor necrosis factor-alpha (TNF-a), which are cytokines involved in inflammatory responses. Conversely, using Egr-1 knockout mice models, researchers noted that the extent of the inflammatory response and dopaminergic neuronal death was less than in non-knockout models, suggesting that Egr-1 could play a role in linking neuroinflammation to PD pathology. The researchers confirmed these findings by administering mithramycin A, an antibiotic known to displace transcription factors such as Egr-1 from their binding sites. Yu et al. also noted that the protective effects of Egr-1 knockout was largely limited to the substantia nigra, and that this protective effect was not observed in the striatum. Thus, further investigation needed on the specific molecular pathways in the substantia nigra and the striatum.

Other studies have focused on how the presence of pro-inflammatory cytokines affects PD patients. Karpenko et al. quantified the prevalence of different cytokines present in blood samples from PD patient groups at various disease stages using immunosorbent assays. In particular, the

researchers examined samples from the blood serum and cerebrospinal fluid to determine if the presence of TNF-a and interleukin (IL)-typecytokines correlated with the severity and progression of PD [59]. Researchers found that higher levels of IL-1b in the serum and TNF-a in the cerebrospinal fluid were correlated with increased severity and rapid disease progression, but the correlation between other cytokines such as IL-6 and PD was still unclear [59]. Another study in 2018 conducted by Li et al. employed similar methods to evaluate the correlation between cytokines in the blood plasma and PD-related pain found increased levels of IL-1 in the blood serum of PD patients [60]. Because IL-1b is contained within the IL-1 family, these findings appear to corroborate the findings of Karpenko et al., further suggesting that proinflammatory factors may play a role in PD progression, though the exact role remains unclear.

While there is evidence that neuroinflammation, oxidative stress, alpha-synuclein, and tyrosine hydroxylase may provide a link between TBI and PD, these findings are speculative and require further research to prove a causal relationship. Such research could prove useful in the development of new pharmaceutical treatments.

Treatment and Therapeutic Targets

Medical treatment of chronic disease is crucial in ameliorating symptoms, improving disease management, and prolonging life. Current research focuses on prescription drugs and non-invasive treatments for the management of PD, with a particular concentration on relieving motor symptoms such as lack of balance, slowness, or Parkinsonian gait, which is a distinctive change in the walk of a patient with PD [61]. Medications used to treat TBI, regardless of their extremity, have the goal of stabilizing complications that arose from the injury, preventing further symptoms, and minimizing pain to maximize the patient's well-being.

Medication

Pharmaceutical drugs serve as a powerful, successful treatment strategy in combating the detrimental effects of TBI and PD, despite the high prevalence of side effects. Unlike non-invasive treatments such as exercise and behavioral therapy, prescription drugs work biologically to trigger body responses that mitigate and prevent the progression of symptoms.

Rascol et al. discuss medications that have been proven to effectively prevent the worsening of PD symptoms. Some treatments include Levodopa (in combination with Carbidopa), Pergolide, Pramipexole, Ropinirole, and Selegiline [62]. Levodopa is the strongest and most effective treatment used in patients to delay disease progression, lessen persistent and long-term side effects, and improve well-being. Levodopa is also vital in managing acute symptoms of PD relating to body movements such as stiffness, tremors, and slowness of motion. The development of these motor symptoms stems from the lack of dopamine in certain brain areas of patients with PD. Levodopa acts as a dopamine replacement agent to manage motor issues in patients [63]. Conversely, many have speculated that Levodopa can potentially be harmful and directly provoke motor complications. Studies have shown that Levodopa can be noxious to dopaminergic neurons, triggering the advancement of neuron degradation in the substantia nigra [63]. However, there have been few in vivo studies that support these findings in PD patients. Nonetheless, the benefits of Levodopa in mitigating PD symptoms may outweigh the negative controversies that have arisen regarding its efficacy. Much like most existing pharmaceutical drugs on the market, there are numerous side effects of Levodopa, including drowsiness, nausea, and hallucinations. However, Gandhi and Saadabadi discuss that the key in administering Levodopa to Parkinson's patients is to integrate it with a decarboxylase inhibitor like Carbidopa [64]. Carbidopa is commonly prescribed with Levodopa, as it minimizes nausea and blocks Levodopa from being transformed to dopamine prior to moving into the brain, preventing side effects such as vomiting.

Furthermore, Pergolide, Pramipexole, Ropinirole, and Selegiline are dopamine agonists that function by emulating the actions of dopamine. Studies have shown that dopamine agonists are efficacious as both monotherapies and adjunct therapies in treating motor abnormalities and dyskinesia, known as involuntary muscle disorder [62]. However, there is still insufficient research on the performance of these dopamine agonists in Levodopa-naive patients and a lack of verification that these promote neuroprotective mechanisms. Rascol et al. discuss that for many patients, dopamine agonists other than Levodopa have proven to be more effective. However, as with Carbidopa, co-prescribing dopamine agonists has proved to significantly mitigate symptoms compared to monotherapies like Levodopa alone [65]. In their study, Rascol et al. examined the efficacy of both Levodopa and Ropinirole in alleviating PD

symptoms. A patient's risk of developing dyskinesia was found to be almost three times lower while taking Ropinirole alone, as opposed to Levodopa alone. Ropinirole and Levodopa taken together more effectively reduced the likelihood of worsening PD symptoms [65].

Numerous pharmaceutical medications serve to ease the pain of patients who have experienced TBI. Unlike PD, which is characterized by a specific set of side effects common to each patient, TBI symptoms are diagnosed on a case-by-case basis [37]. Therefore, diagnostic procedures differ with each patient and prescription dosages directly correlate to the severity of the TBI [66]. For milder forms of TBI such as brain damage that are blast-related (caused by air pressure changes),focal (caused by contact),diffused (caused by force),or from concussions, the process of diagnosis involves examining solely the history of the incident and direct cause of injury [66]. However, for acute brain injuries such as skull fractures, bruising of brain tissue known as cerebral contusions, or hematomas, prognosis is determined via analysis of imaging tests and a patient's clinical presentation. In most mild cases, recommended medications include over-the-counter pain relief drugs such as Naproxen and Acetaminophen [67].

Other prescription medications directly targeted to reduce both physical pain and emotional trauma experienced by TBI patients include anticonvulsants, antidepressants, antipsychotics, and medications relieving motor complications. Anticonvulsant medication is utilized in patients who experience epileptic episodes due to their TBI and works to prevent the occurrence of seizures [68]. Antiepileptic drugs, such as Gabapentin and Topiramate, inhibit excessive neuronal excitability and thus prevent the escalation of existing seizures. Used to treat many forms of neurological and mental illnesses, antidepressants and antipsychotics are common treatments for patients who suffer from both PD and TBI. As both PD and TBI directly influence the levels of neurotransmitter signaling in the brain, antidepressants and antipsychotics serve to combat any psychiatric disorders that may arise, such as depression and hallucinations [69].

Amantadine, an antiviral medication that was first prescribed to combat the Influenza A virus, has increasingly been proven to significantly reduce prevalent symptoms of PD such as stiffness, tremor, and slowness of movement known as bradykinesia [70]. Amantadine has also been shown to stimulate the functional recovery of those who suffer from motor dysfunction related to TBI. Furthermore, Chang and Ramphul point out

that the primary advantage of Amantadine is its low side effect profile, which allows it to properly function without excessive harm. Though Amantadine has been prescribed to patients suffering from PD and to patients suffering from TBI, few studies have examined the effect of Amantadine in treating PD and TBI simultaneously [70]. Thus, further research is needed to determine the drug's efficacy in patients with both disorders. Acosta et al. demonstrate the possibility for a molecular mechanism that could be harnessed to create new medication for PD [55]. Newer and more advanced medications can target acrolein in the body to impede and moderate oxidative stress. With the existing research on the effectiveness of prescription medications, many classes of drugs can be utilized to target symptoms of PD and TBI both individually and simultaneously.

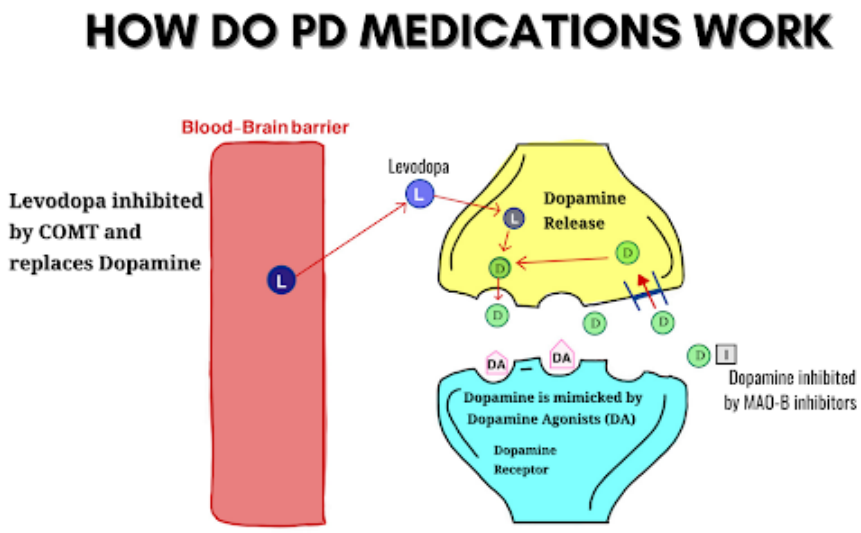


Figure 5: *Mechanism behind Levodopa, a PD dopamine agonists*

Non-invasive treatment (CognitiveTherapies/Exercising)

Non-invasive treatments for PD and TBI have demonstrated efficacy in many studies. Such treatments center on physical and cognitive rehabilitation to ameliorate many of the common symptoms found in both PD and TBI, including motor weakness and stability. A common appearance of motor weakness in PD and TBI patients is an abnormal gait [71]. An abnormal gait is characterized by an asymmetric rhythm that affects the ability of the patient to walk effectively and can manifest as shuffling steps, gait initiation failure, or freezing of gait [72]. Another appearance of motor weakness is a lack of balance, which can be characterized by an unusually increased number of falls [73]. Many studies

have been successful in their focus on exercise as a possible method of improving gait, balance, mobility, and overall motor symptoms of patients with Parkinson's disease [74]. Furthermore, basic treadmill exercises have markedly improved most motor symptoms in comparison to other forms of movement, such as dance and yoga [75]. To maximize therapeutic benefit, other studies have coupled exercise with other forms of stimulation.

A new study found that combining rhythmic auditory stimulation (RAS) and treadmill training greatly improved the overall gait performance of the participants. RAS was implemented in this study through the use of music to capture their innate internal timing process and improve their gait parameters. All participants in the trial reported no side effects during the entirety of the rehabilitation process. Overall, it was concluded that the addition of Rhythmic Auditory Stimulation to treadmill exercise offers complementary advantages to PD patients' balance, stride count, and overall gait performance [76]. Due to the loss of rhythmic movements that characterize gaits in PD patients, rhythmic auditory stimulation provides compensation for this loss.

A few studies have also researched the loss of rhythm in the movements of patients with PD and its correlation with the appearance of abnormal gait. A study conducted in 1997 focused on the effect of rhythmic auditory stimulation on the gait velocity and cadence of PD patients. The study found that a faster RAS resulted in a significant improvement in gait velocity and cadence, indicating that rhythmic auditory facilitation could be a successful technique in gait rehabilitation [77]. Another study incorporated rhythmic auditory cues of a metronome beat to analyze the overall effect PD patients' performance on single and dual-motor tasks. No significant change in gait performance was observed when the metronome beat was implemented as a standalone; however, significant improvement was observed in patients who experienced a combination of a rhythmic auditory cue and an attentional cue (e.g., requiring patients to focus on taking big steps) [78]. This study corroborates the claim that some type of incorporation of rhythmic auditory stimulation can have a significant positive change in gait performance of Parkinson's disease. Nevertheless, the topic of RAS and treadmill training as a therapeutic strategy to improve gait appearance lacks recent research and requires further investigation.

Other forms of exercise, such as aquatic exercise, may also provide therapeutic benefit to PD patients. A randomized controlled trial studied

the effects of aquatic exercise therapy on the improvement of Parkinsonian gait. The experimental group performed various exercises in a community pool setting for two 45-minute sessions per week for a total of six weeks, whereas the control group received their normal treatment, which only consisted of medication. Both the experimental and control groups demonstrated an improvement in gait, yielding inconclusive evidence for the benefits of aquatic exercise as a potential therapeutic technique [79]. Another study sought to compare the effectiveness of both on-land gait training and aquatic gait training to mitigate peripheral neuropathies, a common occurrence for PD patients. The study concluded that the improvements from the inclusion of aquatic-based gait training in conjunction with traditional on-land gait training were similar to the improvements of the control group that did not undergo any aquatic-based gait training [80]. Despite original postulates that aquatic-based therapies would provide benefit to PD patients, current research does not provide durable support for this claim.

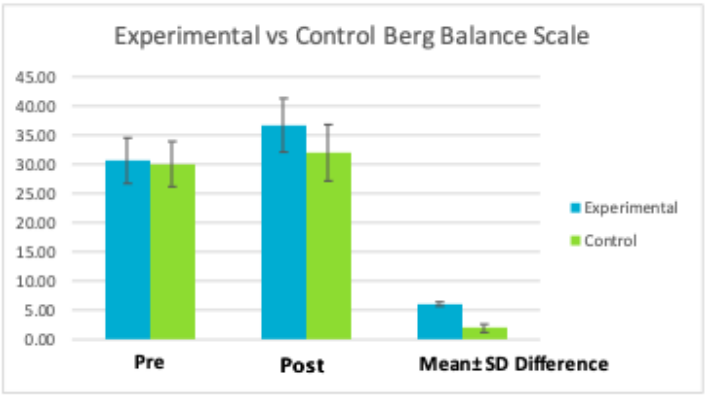
As with PD, cognitive and physical therapy have received attention as a potential therapeutic avenue. Alberto Esquenazi et al. focused on specific methods of locomotor therapy that targeted the gait velocity and spatiotemporal symmetry of TBI patients. Researchers tested the effects of an end effector robot, a robotic exoskeleton, and treadmill training with manual assisted partial-body weight-support (Lokomat). The Lokomat training method included a harness and a robotic orthosis, which were used on a treadmill. The partial-body weight-supported treadmill training method used a LiteGait body weight support system in tandem with a treadmill. Esquenazi et al. found significant improvement in the participants' self-selected velocity with all three methods of intervention, as well as a significant improvement in maximal velocity with the exclusion of the group that used an end effector robot [81]. Overall, improvements in gait speed, gait symmetry, and walking endurance were observed. Similarly, Peters et al. researched the impact of intensive mobility training on balance and gait speed of chronic TBI patients. Though various subjects reported fatigue and pain throughout the experiment, the researchers noted significant improvement within the three months of the trial. Thus, Peters et al. concluded that the high consistency with these pain and fatigue reports prove the possibility of using intensive mobility training to continue to be a possible therapeutic technique for the TBI patients [82]. While the aforementioned studies analyzed a variety of different techniques, both found a significant

improvement in gait performance, pointing to their possible effectiveness as a therapeutic intervention for patients with TBI.

Berg Balance Scale

Experimental vs Control

A Comparison of Locomotor Therapy Interventions: Partial-Body Weight-Supported Treadmill, Lokomat, and G-EO Training in People with Traumatic Brain Injury



Experimental Group (N=14)

		Error
Pre	30.64	3.91
Post	37	4.6
Mean ± SD difference	6.07	0.35

Control Group (N=14)

		Error
Pre	30.07	3.87
Post	32.00	4.82
Mean ± SD difference	1.93	0.7

Figure 6: *Berg Balance Scale comparing the following Locomotor Therapy Interventions: Partial- Body Weight-Supported Treadmill, Lokomat, and gait velocity and spatiotemporal symmetry using an end effector robot (G-EO) Training in patients with TBI.*

With the intersection between technology and medicine, additional studies have focused on the use of different forms of virtual reality simulations to improve the balance and overall motor symptoms of patients with Parkinson's disease. When comparing virtual reality rehabilitation to conventional physical therapy, Hao Feng et. al. concluded that the use of virtual reality by patients with PD resulted in a greater improvement in their balance and gait. The study consisted of a 12-week rehabilitation program in which the experimental group received balance and gait training using virtual reality (VR) technology. While the experiment demonstrated that balance and gait significantly increased with VR therapy, the study did

not control for variables such as age, time of onset, and level of interest with the VR therapeutic modality [83]. Despite this, the study demonstrated that the inclusion of exercises that use VR technology is a possible therapy to improve Parkinson's balance and mobility. Another study researched VR-based balance rehabilitation in TBI patients. Through a randomized controlled trial, virtual reality therapy was compared to the traditional home-based exercise programs currently utilized to help improve the balance in TBI patients. There were 6-week, 12-week, and 24-week follow-ups, where both the experimental group and the control group saw significant improvements in balance [84]. Despite the improvement in the balance of TBI patients who participated in VR-based rehabilitation, this improvement did not exceed that of the home-based exercise programs. The conclusion of both studies suggests that virtual reality may be a plausible therapeutic technique that improves balance for both PD patients and TBI patients.

Although many of the studies mentioned above solely focused on either PD or TBI, these non-invasive treatments and therapies include a combined improvement of symptoms of both PD and TBI. Additionally, other treatments and therapies that may not be specifically marketed towards PD or TBI, but include an improvement in their symptoms as well. As previously mentioned, many prescription medications that are used to combat symptoms of PD and TBI include mental health drugs, such as antipsychotics and antidepressants. Targeted to alleviate internal psychological disorders, these classes of medication aid in minimizing the mental pain and suffering that occurs as an accompaniment to neurological disorders such as TBI and PD.

Symptoms of both often include psychosis, depression, anxiety, and personality disorders [85]. Furthermore, a recent study found a correlation between depression and other psychiatric symptoms and increased motor severity [86]. Research done by Conrad et al. illustrates that the appearance of depression, anxiety, and various personality-related disorders have been statistically proven to be more prevalent in those who have PD and TBI. Many types of treatment, both non-invasive and in the form of prescription medication, such as psychotherapy, antidepressant drugs, and neuromodulation, are utilized to minimize the effects of depression and anxiety that appear in both PD patients and TBI patients. Makio Takahashi and colleagues conducted a multicenter randomized study in which they analyzed the effectiveness of pairing duloxetine, a serotonin and

norepinephrine reuptake inhibitor (SNRI), with paroxetine and escitalopram, which are selective serotonin reuptake inhibitors (SSRIs), to improve depressive symptoms, apathy, and gait freezing in PD patients. The study concluded that the combination of SNRIs with SSRIs improved both the freezing of the gait and the depressive symptoms in PD patients. However, the study did not indicate any significant change in feelings of apathy in the participants [87]. Nevertheless, treatments that provide a combined improvement for both PD patients and TBI patients must continue to develop and improve.

Conclusion

While the incidence of Traumatic Brain Injury has demonstrated a positive correlation with the onset of Parkinson's disease, further research is required to determine the biological and cognitive mechanisms of this association. The incidence of TBI, and thus PD, was found to disproportionately affect certain age and gender groups, being more prevalent in men than women, with women experiencing slower disease progression and older age at symptom onset.

Studies regarding the influence of gender and prevalence of TBI showed contradictory results, pointing to the importance of further research. When studying patients with both PD and TBI, researchers found the risk of developing PD and/or head injury to increase greatly with age [5].

Research has correlated PD with genetic and environmental risk factors (paraquat exposure, malignant melanoma, skin carcinoma, and increased dairy consumption) [10] [11] [13]. Further research is required to understand the impact of TBI on the onset of PD in greater depth. Furthermore, PD patients are more likely to experience TBI during the prodromal period of their disease. These results could indicate that with a decline in motor function due to aging, individuals are more likely to experience TBI from falling, which could increase their chances of developing PD. While the incidence of TBI can lead to an increased chance of developing PD, the prodromal period of PD can increase an individual's chances of experiencing a TBI from incidents such as falls. Therefore, the direction of the correlation is unclear, and further research is required.

When understanding the biological correlation between TBI and the onset of PD, it can be concluded that TBI leads to overaccumulation of alpha-synuclein in the substantia nigra; these accumulations are also a prominent characteristic of Parkinson's disease. Decreased levels of tyrosine hydroxylase serve as another pathological link between TBI and PD. The presence of alpha-synuclein has been observed in patients with TBI as well as patients with PD, and thus serves as a potential link between both conditions. Significant decreases in tyrosine hydroxylase in TBI can result in a decrease in dopamine and potentially initiate the onset of Parkinson's disease, which is also associated with a loss of dopaminergic neurons in the brain. While tyrosine hydroxylase and alpha-synuclein are good biological markers for understanding the link between TBI and the onset of PD, further experimental research is needed to validate their clinical value. Further research is also needed to supply the currently insufficient research on the role of oxidative stress and neuroinflammation as a biological correlate between TBI and the onset of PD.

Research on the cognitive effects of TBI and PD demonstrate that PD patients who suffered from TBI had greater cognitive decline compared to patients who did not suffer from TBI. Furthermore, hippocampal damage, a region correlated with subsequent cognitive decline, was present in patients who experienced either TBI or PD. However, it is unclear whether TBI could aggravate the symptoms of prodromal PD or directly lead to PD.

The discussion on therapeutic targets and prescriptions determined effective medications that treat the symptoms of PD and TBI independently. These include antidepressants, muscle relaxants, and even over the counter treatments. However, more research is needed to understand medications and therapeutic targets that can alleviate symptoms of TBI-induced PD.

In addition to therapeutic targets, non-invasive treatments have been identified to potentially target symptoms from both PD and TBI. Both PD patients and TBI patients present similar motor symptoms; therefore, non-invasive treatments such as the incorporation of treadmill activity and virtual reality therapy can potentially target these symptoms for improvement. The combination of invasive and non-invasive treatments could possibly treat patients who experience TBI-induced PD. Therefore, while TBI can be understood as a potential non-genetic risk factor for the

development of PD, more research is required to understand the extent of this correlation and the implications of current research. Understanding the causal link between Traumatic Brain Injury and the incidence of Parkinson's Disease would allow for more precise treatment plans that could potentially prevent the onset of PD.

References

1. Beitz, Janice M. (2014). Parkinson's Disease: A Review. *Frontiers in Bioscience,* 6(1), 65–74. https://doi.org/10.2741/S415.

2. Rugbjerg, K., Ritz, B., Korbo, L., Martinussen, N., & Olsen, J. H. (2008). Risk of Parkinson's disease after hospital contact for head injury: Population based case-control study. BMJ, 337(dec15 2), a2494–a2494. https://doi.org/10.1136/bmj.a2494

3. Hayes, R. L., Jenkins, L. W., & Lyeth, B. G. (1992). Neurotransmitter-mediated mechanisms of traumatic brain injury: acetylcholine and excitatory amino acids. Journal of neurotrauma, 9 Suppl 1, S173–S187.

4. Parkinson, J. (1817). Essay on the Shaking Palsy. *London: Whittingham and Rowland, for Sherwood, Neely and Jones*.

5. Majdan, M., Plancikova, D., Brazinova, A., Rusnak, M., Nieboer, D., Feigin, V., & Maas, A. (2016). Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. The Lancet. Public health, 1(2), e76–e83. https://doi.org/10.1016/S2468-2667(16)30017-2

6. Vitaz, T. W., Jenks, J., Raque, G. H., & Shields, C. B. (2003). Outcome following moderate traumatic brain injury. Surgical neurology, 60(4), 285–291. https://doi.org/10.1016/s0090- 3019(03)00378-1

7. Ascherio, A., & Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: risk factors and prevention. The Lancet. Neurology, 15(12), 1257–1272. https://doi.org/10.1016/S1474-4422(16)30230-7

8. Peeters, W., van den Brande, R., Polinder, S., Brazinova, A., Steyerberg, E. W., Lingsma, H. F., & Maas, A. I. (2015). Epidemiology of traumatic brain injury in Europe. *Acta neurochirurgica*, *157*(10), 1683–1696. https://doi.org/10.1007/s00701-015-2512-7

9. Quadri, M., Mandemakers, W., Grochowska, M. M., Masius, R., Geut, H., Fabrizio, E., Breedveld, G. J., Kuipers, D., Minneboo, M., Vergouw, L. J. M., Carreras Mascaro, A., Yonova- Doing, E., Simons, E., Zhao, T., Di Fonzo, A. B., Chang, H.-C., Parchi, P., Melis, M., Correia Guedes, L., ... International Parkinsonism Genetics Network. (2018). LRP10 genetic variants in familial Parkinson's disease and dementia with Lewy bodies: A genome-wide linkage and sequencing study. *The Lancet. Neurology*, *17*(7), 597–608. https://doi.org/10.1016/S1474-4422(18)30179-0

10. Chen, H., O'Reilly, E., McCullough, M. L., Rodriguez, C., Schwarzschild, M. A., Calle, E. E., Thun, M. J., & Ascherio, A. (2007). Consumption of dairy products and risk of Parkinson's disease. American journal of epidemiology, 165(9), 998–1006. https://doi.org/10.1093/aje/kwk089

11. Olsen, J. H., Friis, S., & Frederiksen, K. (2006). Malignant melanoma and other types of cancer preceding Parkinson disease. Epidemiology (Cambridge, Mass.), 17(5), 582–587. https://doi.org/10.1097/01.ede.0000229445.90471.5e

12. Dick, F. D., De Palma, G., Ahmadi, A., Scott, N. W., Prescott, G. J., Bennett, J., Semple, S., Dick, S., Counsell, C., Mozzoni, P., Haites, N., Wettinger, S. B., Mutti, A., Otelea, M., Seaton, A., Söderkvist, P., Felice, A., & Geoparkinson study group (2007). Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. Occupational and environmental medicine, 64(10), 666–672. https://doi.org/10.1136/oem.2006.027003

13. Lee, P. C., Bordelon, Y., Bronstein, J., & Ritz, B.

(2012). Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease. Neurology, 79(20), 2061–2066. https://doi.org/10.1212/WNL.0b013e3182749f28

14. Hutson, C. B., Lazo, C. R., Mortazavi, F., Giza, C. C., Hovda, D., & Chesselet, M. F. (2011). Traumatic brain injury in adult rats causes progressive nigrostriatal dopaminergic cell loss and enhanced vulnerability to the pesticide paraquat. Journal of neurotrauma, 28(9), 1783–1801. https://doi.org/10.1089/neu.2010.1723

15. Camacho-Soto, A., Warden, M. N., Searles Nielsen, S., Salter, A., Brody, D. L., Prather, H., & Racette, B. A. (2017). Traumatic brain injury in the prodromal period of Parkinson's disease: A large epidemiological study using medicare data. Annals of neurology, 82(5), 744–754. https://doi.org/10.1002/ana.25074

16. Dahodwala, N., Shah, K., He, Y., Wu, S. S., Schmidt, P., Cubillos, F., & Willis, A. W. (2018). Sex disparities in access to caregiving in Parkinson disease. Neurology, 90(1), e48–e54. https://doi.org/10.1212/WNL.0000000000004764

17. Mollayeva, T., Mollayeva, S., & Colantonio, A. (2018). Traumatic brain injury: sex, gender and intersecting vulnerabilities. Nature reviews. Neurology, 14(12), 711–722. https://doi.org/10.1038/s41582-018-0091-y

18. Van Den Eeden, S. K., Tanner, C. M., Bernstein, A. L., Fross, R. D., Leimpeter, A., Bloch, D. A., & Nelson, L. M. (2003). Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. American journal of epidemiology, 157(11), 1015–1022. https://doi.org/10.1093/aje/kwg068

19. Cerri, S., Mus, L., & Blandini, F. (2019). Parkinson's Disease in Women and Men: What's the Difference?. Journal of Parkinson's disease, 9(3), 501–515. https://doi.org/10.3233/JPD-191683

20. Haaxma, C. A., Bloem, B. R., Borm, G. F., Oyen, W. J., Leenders, K. L., Eshuis, S., Booij, J., Dluzen, D. E., & Horstink, M. W. (2007). Gender differences in Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry, 78(8), 819–824. https://doi.org/10.1136/jnnp.2006.103788

21. Picillo, M., Nicoletti, A., Fetoni, V., Garavaglia, B., Barone, P., & Pellecchia, M. T. (2017). The relevance of gender in Parkinson's disease: a review. Journal of neurology, 264(8), 1583–1607. https://doi.org/10.1007/s00415-016-8384-9

22. Albrecht, J. S., Hirshon, J. M., McCunn, M., Bechtold, K. T., Rao, V., Simoni-Wastila, L., & Smith, G. S. (2016). Increased Rates of Mild Traumatic Brain Injury Among Older Adults in US Emergency Departments, 2009-2010. The Journal of head trauma rehabilitation, 31(5), E1–E7. https://doi.org/10.1097/HTR.0000000000000190

23. McGuire, C., Kristman, V. L., Martin, L., & Bédard, M. (2017). Characteristics and Incidence of Traumatic Brain Injury in Older Adults Using Home Care in Ontario from 2003-2013. Canadian geriatrics journal : CGJ, 20(1), 2–9. https://doi.org/10.5770/cgj.20.228

24. Gardner, R. C., Burke, J. F., Nettiksimmons, J., Goldman, S., Tanner, C. M., & Yaffe, K. (2015). Traumatic brain injury in later life increases risk for Parkinson disease. Annals of neurology, 77(6), 987–995. https://doi.org/10.1002/ana.24396

25. Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA. Head trauma preceding PD: a case-control study. Neurology. 2003 May 27;60(10):1610-5. doi: 10.1212/01.wnl.0000068008.78394.2c. PMID: 12771250.

26. Taylor, C. A., Bell, J. M., Breiding, M. J., & Xu, L. (2017). Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002), 66(9), 1–16. https://doi.org/10.15585/mmwr.ss6609a1

27. Savica, R., Grossardt, B. R., Bower, J. H., Ahlskog, J. E., & Rocca, W. A. (2016). Time Trends in the Incidence of Parkinson Disease. JAMA neurology, 73(8), 981–989. https://doi.org/10.1001/jamaneurol.2016.0947

28. Spangenberg, S., Hannerz, H., Tüchsen, F., & Mikkelsen, K. L. (2009). A nationwide population study of severe head injury and Parkinson's disease. Parkinsonism & related disorders, 15(1), 12–14. https://doi.org/10.1016/j.parkreldis.2008.02.004

29. Raj, R., Kaprio, J., Korja, M., Mikkonen, E. D., Jousilahti, P., & Siironen, J. (2017). Risk of hospitalization with neurodegenerative disease after moderate-to-severe traumatic brain injury in the working-age population: A retrospective cohort study using the Finnish national health registries. PLoS medicine, 14(7), e1002316. https://doi.org/10.1371/journal.pmed.1002316

30. Goldman, S. M., Tanner, C. M., Oakes, D., Bhudhikanok, G. S., Gupta, A., & Langston, J. W. (2006). Head injury and Parkinson's disease risk in twins. Annals of neurology, 60(1), 65–72. https://doi.org/10.1002/ana.20882

31. Bower, J. H., Maraganore, D. M., Peterson, B. J., McDonnell, S. K., Ahlskog, J. E., & Rocca, W. A. (2003). Head trauma preceding PD: a case-control study. Neurology, 60(10), 1610–1615. https://doi.org/10.1212/01.wnl.0000068008.78394.2c

32. White, D. L., Kunik, M. E., Yu, H., Lin, H. L., Richardson, P. A., Moore, S., Sarwar, A. I., Marsh, L., & Jorge, R. E. (2020). Post-Traumatic Stress Disorder is Associated with further Increased Parkinson's Disease Risk in Veterans with Traumatic Brain Injury. Annals of neurology, 88(1), 33–41. https://doi.org/10.1002/ana.25726

33. Rugbjerg, K., Ritz, B., Korbo, L., Martinussen, N., & Olsen, J. H. (2008). Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. BMJ (Clinical research ed.), 337, a2494. https://doi.org/10.1136/bmj.a2494

34. Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology, 65(8), 1239–1245. https://doi.org/10.1212/01.wnl.0000180516.69442.95

35. Benito-León, J., Louis, E. D., Posada, I. J., Sánchez-Ferro, Á., Trincado, R., Villarejo, A., Mitchell, A. J., & Bermejo-Pareja, F. (2011). Population-based case–control study of cognitive function in early Parkinson's disease (NEDICES). *Journal of the Neurological Sciences*, *310*(1– 2), 176–182. https://doi.org/10.1016/j.jns.2011.06.054

36. Broeders, M., Velseboer, D. C., de Bie, R., Speelman, J. D., Muslimovic, D., Post, B., de Haan, R., & Schmand, B. (2013). Cognitive change in newly-diagnosed patients with Parkinson's disease: a 5-year follow-up study. Journal of the International Neuropsychological Society : JINS, 19(6), 695–708. https://doi.org/10.1017/S1355617713000295

37. Weintraub D, Doshi J, Koka D, et al. Neurodegeneration Across Stages of Cognitive Decline in Parkinson Disease. Arch Neurol.

2011;68(12):1562–1568. doi:10.1001/archneurol.2011.725

38. Draper, K., & Ponsford, J. (2008). Cognitive functioning ten years following traumatic brain injury and rehabilitation. Neuropsychology, 22(5), 618–625. https://doi.org/10.1037/0894-4105.22.5.618

39. LoBue, C., Denney, D., Hynan, L. S., Rossetti, H. C., Lacritz, L. H., Hart, J., Womack, K. B., Woon, F. L., & Cullum, C. M. (2016). Self-Reported Traumatic Brain Injury and Mild Cognitive Impairment: Increased Risk and Earlier Age of Diagnosis. Journal of Alzheimer's disease : JAD, 51(3), 727–736. https://doi.org/10.3233/JAD-150895

40. Brown, E., Goldman, S., Meng, C., & Tanner, C. (2020). Head Injury and Parkinson's Disease (PD) Phenotype. Retrieved October 06, 2020, from https://index.mirasmart.com/AAN2020/PDFfiles/AAN2020-001261.html

41. Schiehser, D. M., Filoteo, J. V., Litvan, I., Pirogovsky-Turk, E., Lessig, S. L., & Song, D. S. (2016). Cognitive functioning in individuals with Parkinson's disease and traumatic brain injury: A longitudinal study. *Parkinsonism & Related Disorders*, *30*, 58–61. https://doi.org/10.1016/j.parkreldis.2016.05.024

42. Joyce, J. M., Monchi, O., Ismail, Z., Kibreab, M., Cheetham, J., Kathol, I., Sarna, J., Martino, D., & Debert, C. T. (2020). The impact of traumatic brain injury on cognitive and neuropsychiatric symptoms of Parkinson's disease. *International review of psychiatry (Abingdon, England)*, *32*(1), 46–60. https://doi.org/10.1080/09540261.2019.1656177

43. Hanganu, A., Bedetti, C., Degroot, C., Mejia-Constain, B., Lafontaine, A. L., Soland, V., Chouinard, S., Bruneau, M. A., Mellah, S., Belleville, S., & Monchi, O. (2014). Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally. *Brain: a journal of neurology*, *137*(Pt 4), 1120–1129. https://doi.org/10.1093/brain/awu036

44. Sun L., Zhao M., Zhang J., Liu A., Ji W., Li Y., Yang X., Wu Z. MiR-144 promotes β-amyloid accumulation-induced cognitive impairments by targeting ADAM10 following traumatic brain injury. Oncotarget. 2017; 8: 59181-59203. Retrieved from https://www.oncotarget.com/article/19469/text/

45. Silva, P. H. R., Speedo, C. T., Baldassarini, C. R., Benini, C. D., Ferreira, D. A., Barreira, A. A., & Leoni, R. F. (2019). Brain functional and effective connectivity underlying the information processing speed assessed by the Symbol Digit Modalities Test. NeuroImage, 184, 761–770. https://doi.org/10.1016/j.neuroimage.2018.09.080

46. Acosta, S. A., Tajiri, N., Pena, I. D., Bastawrous, M., Sanberg, P. R., Kaneko, Y., & Borlongan, C. V. (2015). Alpha-Synuclein as a Pathological Link Between Chronic Traumatic Brain Injury and Parkinson's Disease. *Journal of Cellular Physiology, 230*(5), 1024-1032. doi:10.1002/jcp.24830

47. Froula, J. M., Castellana-Cruz, M., Anabtawi, N. M., Camino, J. D., Chen, S. W., Thrasher, D. R., Freire, J., Yazdi, A. A., Fleming, S., Dobson, C. M., Kumita, J. R., Cremades, N., & Volpicelli-Daley, L. A. (2019). Defining α-synuclein species responsible for Parkinson's disease phenotypes in mice. *Journal of Biological Chemistry*, *294*(27), 10392–10406. https://doi.org/10.1074/jbc.RA119.007743

48. Impellizzeri, D., Campolo, M., Bruschetta, G., Crupi, R., Cordaro, M., Paterniti, I., . . . Esposito, E. (2016). Traumatic Brain Injury Leads to

Development of Parkinson's Disease Related Pathology in Mice. *Frontiers in Neuroscience,10*. doi:10.3389/fnins.2016.00458

49. Shin, S. S., Bray, E. R., Zhang, C. Q., & Dixon, C. E. (2011). Traumatic brain injury reduces striatal tyrosine hydroxylase activity and potassium-evoked dopamine release in rats. *Brain Research*, *1369*, 208–215. https://doi.org/10.1016/j.brainres.2010.10.096

50. Hill, R. L., Kulbe, J. R., Singh, I. N., Wang, J. A., & Hall, E. D. (2018). Synaptic Mitochondria are More Susceptible to Traumatic Brain Injury-induced Oxidative Damage and Respiratory Dysfunction than Non-synaptic Mitochondria. Neuroscience, 386, 265–283. https://doi.org/10.1016/j.neuroscience.2018.06.028

51. Musgrove, R. E., Helwig, M., Bae, E.-J., Aboutalebi, H., Lee, S.-J., Ulusoy, A., & Di Monte, D. A. (2019). Oxidative stress in vagal neurons promotes parkinsonian pathology and intercellular α-synuclein transfer. Journal of Clinical Investigation, 129(9), 3738–3753. https://doi.org/10.1172/JCI127330

52. Wang, F., Franco, R., Skotak, M., Hu, G., & Chandra, N. (2014). Mechanical stretch exacerbates the cell death in SH-SY5Y cells exposed to paraquat: Mitochondrial dysfunction and oxidative stress. NeuroToxicology, 41, 54–63. https://doi.org/10.1016/j.neuro.2014.01.002

53. Wang, W.-T., Sun, L., & Sun, C.-H. (2019). PDIA3-regulated inflammation and oxidative stress contribute to the traumatic brain injury (TBI) in mice. Biochemical and Biophysical Research Communications, 518(4), 657–663. https://doi.org/10.1016/j.bbrc.2019.08.100

54. Paul, R., Phukan, B. C., Justin Thenmozhi, A., Manivasagam, T., Bhattacharya, P., & Borah, A. (2018). Melatonin protects against behavioral deficits, dopamine loss and oxidative stress in the homocysteine model of Parkinson's disease. Life Sciences, 192, 238–245. https://doi.org/10.1016/j.lfs.2017.11.016

55. Acosta, G., Race, N., Herr, S., Fernandez, J., Tang, J., Rogers, E., & Shi, R. (2019). Acrolein-mediated alpha-synuclein pathology involvement in the early post-injury pathogenesis of mild blast-induced Parkinsonian neurodegeneration. Molecular and Cellular Neuroscience, 98, 140– 154. https://doi.org/10.1016/j.mcn.2019.06.004

56. Ren, X., Hinchie, A., Swomley, A., Powell, D. K., & Butterfield, D. A. (2019). Profiles of brain oxidative damage, ventricular alterations, and neurochemical metabolites in the striatum of PINK1 knockout rats as functions of age and gender: Relevance to Parkinson disease. Free Radical Biology and Medicine, 143, 146–152. https://doi.org/10.1016/j.freeradbiomed.2019.08.008

57. Przedborski, S. (2007). Neuroinflammation and Parkinson's disease. In *Handbook of Clinical Neurology* (Vol. 83, pp. 535–551). Elsevier. https://doi.org/10.1016/S0072-9752(07)83026-0

58. Yu, Q., Huang, Q., Du, X., Xu, S., Li, M., & Ma, S. (2018). Early activation of Egr-1 promotes neuroinflammation and dopaminergic neurodegeneration in an experimental model of Parkinson's disease. Experimental Neurology, 302, 145–154. https://doi.org/10.1016/j.expneurol.2018.01.009

59. Karpenko, M. N., Vasilishina, A. A., Gromova, E. A., Muruzheva, Z. M., & Bernadotte, A. (2018). Interleukin-1β, interleukin-1 receptor antagonist, interleukin-6, interleukin-10, and tumor necrosis

factor-α levels in CSF and serum in relation to the clinical diversity of Parkinson's disease. *Cellular Immunology*, *327*, 77–82. https://doi.org/10.1016/j.cellimm.2018.02.011

60. Li, D., Song, X., Huang, H., Huang, H., & Ye, Z. (2018). Association of Parkinson's disease- related pain with plasma interleukin-1, interleukin-6, interleukin-10, and tumour necrosis factor- α. *Neuroscience Letters*, *683*, 181–184. https://doi.org/10.1016/j.neulet.2018.07.027

61. Moustafa, A. A., Chakravarthy, S., Phillips, J. R., Gupta, A., Keri, S., Polner, B., Frank, M. J., & Jahanshahi, M. (2016). Motor symptoms in Parkinson's disease: A uni ed framework. Neuroscience and biobehavioral reviews, 68, 727–740. https://doi.org/10.1016/j.neubiorev.2016.07.010

62. Rascol, Olivier, et al. "Treatment Interventions for Parkinson's Disease: An Evidence Based Assessment." The Lancet, vol. 359, no. 9317, May 2002, pp. 1589–98. ScienceDirect, doi:10.1016/S0140-6736(02)08520-3.

63. Olanow, C. Warren, et al. "Levodopa in the Treatment of Parkinson's Disease: Current Controversies." Movement Disorders: Official Journal of the Movement Disorder Society, vol. 19, no. 9, Sept. 2004, pp. 997–1005. PubMed, doi:10.1002/mds.20243

64. Gandhi, Kavita R., and Abdolreza Saadabadi. "Levodopa (L-Dopa)." StatPearls, StatPearls Publishing, 2020. PubMed, http://www.ncbi.nlm.nih.gov/books/NBK482140/.

65. Rascol, Olivier, et al. "A Five-Year Study of the Incidence of Dyskinesia in Patients with Early Parkinson's Disease Who Were Treated with Ropinirole or Levodopa." New England Journal of Medicine, vol. 342, no. 20, May 2000, pp. 1484–91. Taylor and Francis+NEJM, doi:10.1056/NEJM200005183422004

66. Chung, P., Khan, F. (2013). Traumatic brain injury (TBI): overview of diagnosis and treatment. *Journal of Neurology and Neurophysiology*. 5(1). doi:10.4172/2155-9562.1000182

67. DiTommaso, C., et al. (2014). Medication Usage Patterns for Headache Treatment after Mild Traumatic Brain Injury. *Headache*, 54(3), 511–519. PubMed, doi:10.1111/head.12254.

68. Kirmani, B. F., et al. (2016). Role of Anticonvulsants in the Management of Posttraumatic Epilepsy. *Frontiers in Neurology*, 7. PubMed Central, doi:10.3389/fneur.2016.00032

69. Conroy, S. K., et al. (2020)Depression Comorbid With Stroke, Traumatic Brain Injury, Parkinson's Disease, and Multiple Sclerosis: Diagnosis and Treatment. *FOCUS*, 18(2), 150–161. *focus.psychiatryonline.org (Atypon)*, doi:10.1176/appi.focus.20200004.

70. Chang, C., and Kamleshun, R. (2020). Amantadine. StatPearls, StatPearls Publishing, PubMed, http://www.ncbi.nlm.nih.gov/books/NBK499953/.

71. Basford, J. R., Chou, L. S., Kaufman, K. R., Brey, R. H., Walker, A., Malec, J. F., Moessner, A. M., & Brown, A. W. (2003). An assessment of gait and balance deficits after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, 84(3), 343–349. https://doi-org.libproxy.berkeley.edu/10.1053/apmr.2003.50034

72. Jankovic, J. (2015). Gait Disorders. *Neurologic*

Clinics, *33*(1), 249–268. https://doi.org/10.1016/j.ncl.2014.09.007

73. Fasano, A., Canning, C. G., Hausdorff, J. M., Lord, S., & Rochester, L. (2017). Falls in Parkinson's disease: A complex and evolving picture: Falls and PD. *Movement Disorders*, *32*(11), 1524–1536. https://doi.org/10.1002/mds.27195

74. Combs-Miller, S. A., Dugan, E. L., Beachy, A., Derby, B. B., Hosinski, A. L., & Robbins, K. (2019). Physiological complexity of gait between regular and non-exercisers with Parkinson's disease. *Clinical biomechanics* (Bristol, Avon), 68, 23–28. https://doi.org/10.1016/j.clinbiomech.2019.05.032

75. Rawson, K. S., McNeely, M. E., Duncan, R. P., Pickett, K. A., Perlmutter, J. S., & Earhart, G. M. (2019). Exercise and Parkinson Disease: Comparing Tango, Treadmill, and Stretching. Journal of neurologic physical therapy : JNPT, 43(1), 26–32. https://doi.org/10.1097/NPT.0000000000000245

76. Calabrò, R. S., Naro, A., Filoni, S., Pullia, M., Billeri, L., Tomasello, P., Portaro, S., Di Lorenzo, G.,Tomaino, C., & Bramanti, P. (2019). Walking to your right music: a randomized controlled trial on the novel use of treadmill plus music in Parkinson's disease. *Journal of Neuroengineering and Rehabilitation*, 16(1), 68. https://doi.org/10.1186/s12984-019-0533-9

77. McIntosh, G. C., Brown, S. H., Rice, R. R., & Thaut, M. H. (1997). Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 62(1), 22–26. https://doi.org/10.1136/jnnp.62.1.22

78. Ghai, S., Ghai, I., Schmitz, G., & Effenberg, A. O. (2018). Effect of rhythmic auditory cueing on parkinsonian gait: A systematic review and meta-analysis. *Scientific Reports*, 8(1), 506. https://doi.org/10.1038/s41598-017-16232-5

79.Carroll, L. M., Volpe, D., Morris, M. E., Saunders, J., & Clifford, A. M. (2017). Aquatic Exercise Therapy for People With Parkinson Disease: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*, 98(4), 631–638. https://doi.org/10.1016/j.apmr.2016.12.006

80. Ilaria, C., Roberto, M., Francesca, B., Paola, O., Daniele, V., Davide, F., Giuseppe, F. (2019). Land Plus Aquatic Therapy Versus Land-Based Rehabilitation Alone for the Treatment of Freezing of Gait in Parkinson Disease: A Randomized Controlled Trial, *Physical Therapy*, 99(5), 591–600, https://doi.org/10.1093/ptj/pzz003

81. Esquenazi, A., Lee, S., Wikoff, A., Packel, A., Toczylowski, T. and Feeley, J. (2017), A Comparison of Locomotor Therapy Interventions: Partial- Body Weight–Supported Treadmill, Lokomat, and G-EO Training in People With Traumatic Brain Injury. PM&R, 9: 839-846. doi:10.1016/j.pmrj.2016.12.010

82. Peters, D. M., Jain, S., Liuzzo, D. M., Middleton, A., Greene, J., Blanck, E., Sun, S., Raman, R., & Fritz, S. L. (2014). Individuals With Chronic Traumatic Brain Injury Improve Walking Speed and Mobility With Intensive Mobility Training. *Archives of Physical Medicine and Rehabilitation*, *95*(8), 1454–1460. https://doi.org/10.1016/j.apmr.2014.04.006

83. Feng, H., Li, C., Liu, J., Wang, L., Ma, J., Li, G., Gan, L., Shang, X., & Wu, Z. (2019). Virtual Reality Rehabilitation Versus Conventional Physical Therapy for Improving Balance and Gait in Parkinson's Disease Patients: A Randomized Controlled Trial. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, 25,

4186–4192. https://doi.org/10.12659/MSM.916455

84. Tefertiller, C., Hays, K., Natale, A., O'Dell, D., Ketchum, J., Sevigny, M., Eagye, C. B., Philippus, A., & Harrison-Felix, C. (2019). Results From a Randomized Controlled Trial to Address Balance Deficits After Traumatic Brain Injury. *Archives of physical medicine and rehabilitation*, 100(8), 1409–1416. https://doi.org/10.1016/j.apmr.2019.03.015

85. Reijnders, J. S. A. M., Ehrt, U., Weber, W. E. J., Aarsland, D., & Leentjens, A. F. G. (2008). A systematic review of prevalence studies of depression in Parkinson's disease: The Prevalence of Depression in PD. *Movement Disorders*, *23*(2), 183–189. https://doi.org/10.1002/mds.21803

86. Nagayama, H., Maeda, T., Uchiyama, T., Hashimoto, M., Nomoto, N., Kano, O., Takahashi, T., Terashi, H., Hamada, S., Hasegawa, T., Hatano, T., Takahashi, T., Baba, Y., Sengoku, R., Watanabe, H., Inoue, M., Kadowaki, T., Kaneko, S., Shimura, H., & Kubo, S. (2017). Anhedonia and its Correlation with Clinical Aspects in Parkinson's Disease. *Journal of the Neurological Sciences*, *372*, 403–407. https://doi.org/10.1016/j.jns.2016.10.051

87. Takahashi, M., Tabu, H., Ozaki, A., Hamano, T., Takeshima, T., & for the REBORN study group. (2019). Antidepressants for Depression, Apathy, and Gait Instability in Parkinson's Disease: A Multicenter Randomized Study. *Internal Medicine*, *58*(3), 361–368. https://doi.org/10.2169/internalmedicine.1359-18