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# Impacts of Nicotine on Neurodegenerative Disorders

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## ABSTRACT

Cigarette use is a significant risk factor for cognitive deterioration and dementia. The precise pathobiology of smoking, on the other hand, remains uncertain. Tobacco contains nicotine and many mutagens and carcinogens, wreaking havoc on various body components. Tobacco has a detrimental effect on the development of neurological structures, neurotransmission, and cognitive processes and the development of neurodegenerative disorders, insomnia, and cerebrovascular disease. Nicotine in tobacco smoke has various effects on the human body, including a negative impact on commonly known neurological health. In recent years, considerable effort has been spent on characterizing, revealing, and unearthing new facets of tobacco's negative effect on human life. Therefore, this review aims to explore the relationship between tobacco use and neurodegenerative diseases. To summarize, tremendous effort has been given in recent decades to unveil tobacco harmful to human lives. Nicotine has a wide range of adverse impacts on health, such as a detrimental effect on the brain's generally accepted neurological function.

***Keywords:*** Nicotine; Neurodegenerative Disorders; Parkinson's disease; Tobacco smoking

## INTRODUCTION

WHO has mentioned that the application of tobacco will increase in males by 30% and females by 8% by 2025(1). A considerable number of fields of its association to health remain ambiguous although tobacco has been a topic of research for centuries(2). Environmental tobacco smoke or ETS is still considered to be an unsettling problem and was highlighted in numerous reviews (2,3). Tobacco damages numerous body parts especially the respiratory system and cardiovascular system as it contains over 5000 chemical mixtures of mutagens and carcinogens, of which more than 30 are known as human carcinogens (2,4). As a matter of fact, the development of cancers in many organs are initiated by tobacco as well. Tobacco smoke consists of acetaldehyde, ammonia, hydrogen cyanide, hydrazine and vinyl chloride, formaldehyde, and nitrogen oxides which damage the ciliary epithelium (5-7). These substances are not excluded from electronic cigarettes (ECs), which are another form of nicotine delivery(8). Nevertheless, with EC vapour containing hazardous compounds that are 9-450 times lower than conventional cigarettes, studies have substantiated that the former is safer than the latter (8-10). However, they still have impacts on the health of the smoker as nicotine, a highly addictive substance harming brain development, is still exposed(11). This review desires to explore the connection between tobacco cigarette smoking and neurodegenerative disorder to determine its impacts on Parkinson's disease.

### Parkinson's disease

Parkinson's disease (PD) is the most common neurological movement condition, and it can start decades before symptoms appear (12,13). PD is a multisystemic-synucleinopathy characterized by the presence of Lewy bodies in the midbrain (14,15). Some of the pathogenic risk factors that produce a particular degradation of

dopaminergic neurons in the substantia nigra pars compacta and Lewy body deposits, as well as a wide variety of other CNS and peripheral tissue configurations, include drugs, poisons, pesticides, and brain microtrauma. These actions characterize PD (16,17).

Genomic variation, epigenetic modifications, toxic factors, oxidative stress abnormalities, neuroimmune/ neuroinflammatory reactions, hypoxic-ischemic circumstances, metabolic inadequacies, and ubiquitin-proteasome system malfunction could all play a role in this neuropathological phenotype (18,19). Protein misfolding and aggregation, as well as early neuronal degeneration, are caused by these circumstances (20,21). Current evidence implies that PD is a prion-like disease(17,21). The inability to completely reproduce the ends of linear chromosomes, which produces telomere shortenings, is one of the signs of aging that can lead to PD (22, 23). Parkin 2 (PARK2), microtubule-associated protein tau (MAPT), Synuclein (SNCA), Bone narrow stromal cell antigen 1 (BST1), and PTEN-induced putative kinase 1 (PINK1) mutations may cause recessive and autosomal dominant forms of PD, although various genetic flaws in other loci might represent vulnerability loci associated with sporadic PD while having no family history(24-27). Most inferior loci revealed corresponding to the pathogenic pathways leading to early neurodegeneration in PD are also linked to mutations in main genes dealing with PD-related synucleinopathy(16). Oxidative and endoplasmic reticulum stress, α-Synuclein buildup, autophagic impairment, and mitochondrial dysfunction are all frequently present in the PD pathogenic chain (16,28). Misfolding presynaptic protein generated by the SNCA (synuclein) gene is the main component of the Lewy body, a histological feature of the PD brain (24). By duplication or triplication, the wild-type SNCA gene causes PD(29). An increase in the levels of the common synuclein protein can cause the disorder(26,29). A number of SNPs inside the SNCA gene have been related to a higher risk of sporadic PD(15,22). A GWAS discovered rs356182 within SNCA, a novel SNP that may lower the incidence of Parkinson's disease in Caucasian as well as Chinese populations(30, 31).

The progress of PD is dominantly affected by the oxidative stress. To start with, it impairs nucleic acid stability by oxidizing RNA, enhancing mitochondrial DNA mutation, and triggering translation synthesis(32). Second, it hastens the aggregation of synuclein, disrupting protein homeostasis, parkin aggregation, and proteasome separation(24,33). Ultimately, it activates ATP-sensitive potassium channels, which influence dopamine release and deactivate nicotinic acetylcholine receptors in neurons (nAChRs) Finally, it stimulates the tensin homolog PINK1 as well as the cytoprotective actions of oncogene DJ1(DJ-1) and phosphatase, as well as producing an Akt imbalance that affects cellular self-defenses(34,35). Changes in nitrative or oxidative stress have been associated to toxicity caused by -synuclein(36,37).

**Tobacco Impact on Formation and Differentiation of Neural Basic Structures**

In many parts of the world, tobacco products are a serious public health problem(2). Smoking is an established risk factor for a wide range of disorders, including morphological alterations in the nervous system(38,39).WHO mentioned that there are around 1.1 billion daily smokers worldwide(2). About six million people die each year with 600,000 people dying from second-hand smoke due to second-hand smoke exposure as a result of this(2). Tobacco smoke has about 7000 compounds, including over 4500 carcinogens and around 70 poisons (2). The researchers hypothesize that tobacco toxins which include vinyl chloride, associated with an increased risk of brain cancer, hydrogen cyanide, and arsenic affect brain volume. The smoker absorbs about 15% of cigarette smoke(40). Eighty-five percent of carbon dioxide generated is released into the

environment(2,41). Developing creatures, such as neonates, babies, and foetuses, are particularly vulnerable to cigarette smoke(42,43). Prenatal tobacco smoke exposure increases the incidence of spontaneous abortion, low birth weight, SIDS, and neurodevelopmental, psychiatric, and cardiovascular issues in children (44-46).

Immune systems and developing lungs significantly enhance the change of acquiring future acute and chronic diseases (40). Thus far, research indicates that maternal smoking exposure damages the foetal brain's structural development(47). In postnatal life, morphological abnormalities gained during pregnancy result in cognitive decline, an enhanced dementia risk, difficulty with emotional control, and poorer functioning memory(42,46).

**Neurotransmitters and Tobacco - Receptors, Neurotransmitters, Signalling Pathways**

Nicotinic (nAChR) and muscarinic (mAChR) acetylcholine receptors are located in various cells throughout the body (mAChR) (48,49). Both nicotine and acetylcholine have a strong affinity for the nicotinic receptor; however, the shape of the receptor dictates how strong that affinity is(50, 51). It can range from a high affinity for the both compounds in the 42 subtype, which is present all over the brain and nervous system, to reduced nicotine affinity levels in neuromuscular junction receptors (51-53). Furthermore, nicotine cannot be rapidly taken away from the synaptic cleft, which, as a result of prolonged receptor activation, stimulates and eventually desensitizes postsynaptic neurons, causing signaling problems(2). Furthermore, the presence of menthol, which is commonly utilized, might enhance and extend this desensitization allosterically (2). Nicotine stimulates the nACh receptors of the VTA's dopaminergic neurons, causing extended bursts of dopamine levels into the nucleus accumbens, a component of the reward system thought to help translate desire into action, and thus may play a role in the disproportionally motivational push associated with nicotine and also other drug usage (34,54,55). Smokers have a reduced dopamine transporter but normal D2 dopamine receptor availability, according to a meta-analysis of molecular imaging research on tobacco smoking and brain dopaminergic function (54,56). The researchers are of the opinion that these findings could be attributable to pathophysiological variables, such as genetic predisposition to cigarette addiction or extended nicotine exposure(57,58).

**Impact on Cognition and Memory**

Due to the nACh receptor's association with cognition, tobacco's effect on cognition is classified as acute or chronic(52,59). Nicotine can improve hippocampus-dependent learning and memory, and attention during acute smoking. Second, smoking for an extended period of time inhibits hippocampus-dependent learning and may be a harmful contributor for Alzheimer’s disease(2,60). Additionally, a research of 628 residents of Beijing's Haidian neighbourhood discovered from the RBANS total score that smokers had significantly worse results(2). A repeatable battery for assessing the neuropsychological state consisted of 12 subtests(2). In addition, in a sample of 720 mother-child couples, one study looked at second-hand smoke exposure during pregnancy and later child neurodevelopment at 24 months of age(61,62). To determine the effect of cigarettes, the mental developmental index (MDI) and developmental psychomotor index were calculated and compared to the amount of cotinine in the urine, which is the major metabolite of nicotine(2). The research eliminated mothers who were actively smoking and concentrated on environmental exposition(61). As maternal cotinine levels increased, the study discovered that new born cognitive development slowed dramatically (52,63).

Additional research in this sector is aimed at determining the effect of smoke on brain functions. Cohort research was undertaken on 1739 mother-newborn couples to assess the impact of prenatal alcohol and cigarette exposure on child brain function(2). As a result, infants whose parents were constantly exposed to higher tobacco doses during pregnancy showed considerably lower right–central and right–parietal beta, also low gamma and gamma EEG power, as contrasted to those exposed to more reduced cigarette doses (2,64). The researchers assert that these findings may indicate an aberrant development of cortical networks (2,64). In general, the results indicated that all degree of prenatal tobacco exposure affects the brain activity of newborns(2,44,64).

In a study of 239 children aged 8, researchers discovered a link between cotinine, a nicotine metabolite, levels during pregnancy and executive function, as assessed by the Behaviour Rating Inventory of Executive Function(2). Tobacco was shown to be associated to three parts of the evaluation: initiative (the ability to initiate things on one's own), cognitive skills (the ability to remember important details needed to perform a project), and organization (the flexibility to move work or warehousing locations around)(8, 65, 66).In addition, the discovery of this research backed up the idea that even low-dose second-hand smoke exposure during pregnancy can have an impact on a child's development(54). Nevertheless, it should be noted that one study discovered that smoking had no statistically significant effect on cognition(67). One study looked at a variety of studies on nicotine's impact on tobacco, and one of its subcategories explored the cognitive differences between previously non-smokers and abstinent smokers following nicotine injection(68). According to the research, nicotine has different impacts on comprehension based on smoking habits and symptoms of withdrawal (55). Evoked potential investigations in smokers reveal cortical and subcortical bioelectric impairment(2). A motor-evoked potential (MEP) examination utilizing transcranial magnetic stimulation revealed that tobacco users had inferior motor cortex activity (lower MEP amplitude) than the control group(69). The N200 component of event-related potentials (EPRs) has been reported to have a lower amplitude in smokers than in non-smokers in studies(2). The N200 wave appears to be a starting component of ERP and is thus "prepared" to complete a cognitive activity(2). Its diminished amplitude indicates a preclinical disturbance of cognitive control, resulting in cognitive impairment(2,38).

**Neurodegenerative Diseases**

As more data emerges linking smoking to cognitive decrease, such as Alzheimer's disease, the processes underlying this association remain unknown (51,53). Cigarettes use was connected to a faster reduction in functional abilities and a more rapid decrease in the amount of the entorhinal cortex in adults with mild cognitive impairment compared to those who did not use tobacco(60). Other research have connected tobacco use to memory loss, hippocampus atrophy, and reduced glucose metabolism in the brain(23). However, neither of these investigations found a connection between smoking history and CSF AD pathology (A42, t-tau, or p-tau)(70,71). Several behavioural problems have been associated to rapid atrophy in certain brain regions, according to some beliefs(42). Furthermore, smokers have a younger relative brain age than non-smokers due to tobacco's impact on the degeneration of white and grey matter (65,69,72). Fast shrinking in particular brain regions has been related to a variety of behavioural disorders, according to some theories(73). Alzheimer's disease in its beginning phases, smokers have less grey matter, a lower density of gray matter volume, and a quicker rate of atrophy in areas with morphological irregularities (compared to non-smokers)(2,74). In terms of how

smoking and alcohol intake alter brain structure ageing, more research is needed, especially when all brain regions are examined (38,65,75).

According to meta-analyses, smoking also decreases white substance structural stability, which is a potential risk for the disease(54). Tobacco use has been linked to Alzheimer's disease and many sclerosis, and has been found to shorten the period between diagnosis and secondary progressive MS development(20).

**In Parkinson's Disease, Nicotine's Dopaminergic System Protective Effect**

PD is the most rapidly progressing neurological condition(25). The global patient population has grown from 2.5 million in 1990 to 6.1 million in 2016(2). One of the main causes of this significant increase is population aging, however other factors, like as a decline in the prevalence of smoking habit, may also be playing a role(51). Despite the multiple harmful repercussions of smoking, numerous researches demonstrate that the tobacco usage and PD progression and death are inversely related(51). Despite the enormous statistical evidence, nothing is known about the underlying roots of the link(51). Dorn was the first to suggest that smoking could protect against PD development 60 years ago(2). The studies looked at a variety of populations and time periods, but they all came to the same conclusion: various types of smoking, such as cigarettes, pipes, and cigars, reduce the risk of PD and death, with present smokers having a lower chance than former smokers(2).Current smokers had a 30% and 40% decreased likelihood of PD at baseline and during follow-up, respectively, when compared to non-smokers(51). In general, current tobacco use, tobacco consumption, and time since quitting were all linked to an elevated risk of PD in this research(76).

## CONCLUSIONS

Tobacco is particularly harmful in the development of neurodegenerative diseases, impacts cognition, and has a relationship with the amount of grey matter in the brain. In the future, it turns out to be particularly important to control tobacco's effects better and to treat smoking as a significant public health problem. New data about tobacco's harmful effects have been uncovered and described in recent years. Tobacco smoke nicotine has many adverse effects on the human body, including a detrimental effect on the brain's generally accepted neurological health.

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