Available online at https://journal.xxxxxxx.com/index.php/ijhlp/index

**International Journal of Humanities, Law, and Politics**

**e-ISSN 3025-0536**

Vol. 2, No. 2, pp. 38-44, 2024

# Analysis of the Effect of Nicotine on Brain Activity and Function Using FMRI: Implications for Cigarette Dependence

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**Abstract**

This study examines the effect of nicotine, the main compound in cigarettes, on brain activity and function using functional Magnetic Resonance Imaging (fMRI). Nicotine influences the release of neurotransmitters such as dopamine and serotonin, which affect various aspects of life, including learning, memory, alertness, and emotional balance. Dependence on nicotine can cause withdrawal symptoms, such as anxiety, depression, and sleep disorders. Neurological research shows differences in brain activity in smokers and non-smokers, especially in the ventral (rostral anterior cingulate cortex, insula, opercular, and occipital gyrus) and dorsal (dorsal medial/lateral prefrontal cortex and dorsal anterior cingulate cortex) areas. Brain disorders are also associated with psychological disorders such as anxiety, depression and compulsive behavior. Apart from that, nicotine use can also affect the dopamine and serotonin systems, resulting in sleep disorders and emotional disorders in cigarette addicts.

*Keywords:* Nicotine, cigarettes, brain activity, functional Magnetic Resonance Imaging (fMRI).

## 1. Introduction

Smoking behavior is a global health problem that needs serious attention. Survey data from developed countries in 2005 showed that around 35% of men and 22% of women were smokers. Meanwhile, in developing countries, the figure is higher, with around 50% of men and 9% of women smoking. What is even more worrying is the fact that the age of cigarette consumers tends to get younger from year to year (Stubbs et al., 2017; Jha, 2009). Currently, it is not uncommon to find cases of children in elementary school grades 5 or 6 who have tried smoking and have difficulty quitting.

Ironically, tobacco, the main ingredient in making cigarettes, has been classified as an addictive substance. The negative impact of smoking on health has also been clearly explained through the warning labels on each cigarette pack, including the risk of cancer, heart attack, impotence and various other health problems, including the impact on the fetus (Lestari et al., 2018; Bigwanto et al., 20230. Numerous studies, both in longitudinal, cohort and experimental contexts, have verified this claim. Smoking is known to cause vasoconstriction and atherosclerosis, which in turn can cause subclinical myocardial ischemia, as well as the release of carbon monoxide which increases the risk of hypoxia and hypoxia in the heart.

Apart from the physical impact, the substances in cigarettes, especially nicotine, also affect psychological conditions, the nervous system, and brain activity and function, both in active smokers and people exposed to cigarette smoke (passive smokers). Therefore, research and prevention efforts continue to be needed to reduce the prevalence of smoking and its negative impact on public health. In this context, this article will discuss further the prevalence of smoking, its health impacts, and efforts that can be taken to reduce this smoking problem, especially in developing countries (Palipudi et al., 2015; Fauzi & Pongpanich 2022).

The effects of nicotine are not only limited to physical aspects, but also have a significant impact on the psychological aspects and behavior of individuals who smoke. Nicotine stimulates the release of various chemicals in the brain, including acetylcholine, serotonin, pituitary hormones, and epinephrine. In addition, nicotine also increases the release of dopamine and norepinephrine. The impact of nicotine can be felt in various aspects of life, such as learning ability, memory, level of alertness, and emotional balance.

When someone has become dependent on nicotine, withdrawal can produce a variety of uncomfortable symptoms, including anxiety, feelings of depression, difficulty controlling oneself or irritability, despair, and depression. Smokers who try to quit also have a higher risk of experiencing sleep disorders, decreased ability to remember simple tasks,

and tend to develop compulsive behavior. In some cases, studies have shown a significant correlation between smoking and bipolar emotional disorders, as well as suicidal tendencies.

Emotional and behavioral disorders in cigarette addicts are also closely related to changes in brain activity and function. A number of studies have been conducted to understand the effect of nicotine on brain performance, with subjects from various stages of development, and using various models or research designs. Since the 1980s, research into the impact of nicotine on the brain has used neuroimaging methods, initially starting with Positron Emission Tomography (PET) which involves tracing radioactivity in the blood. PET was later replaced by Magnetic Resonance Imaging (MRI), which allows monitoring of oxygen flow in the blood and has advantages in terms of speed and safety for the subject. Furthermore, about a decade after the use of PET, researchers more often used functional Magnetic Resonance Imaging (fMRI), which has a similar principle of use to MRI, but focuses on brain activity related to cognitive and emotional function.

It is important to recognize that the use of neuroimaging technologies such as fMRI in research regarding nicotine and cigarette dependence does have enormous value in understanding the impact of smoking on the brain. However, problems with limited human resources, equipment and high costs limit access to this technology in various countries, including Indonesia. Therefore, it is important to look for more affordable alternatives to understand the impact of nicotine dependence on brain activity and function.

In this paper, we will discuss various empirical studies from the latest international journals, especially those published between 2010 and 2011, which discuss the effect of nicotine dependence on the brain using neuroimaging techniques, especially fMRI. Although this technology may not always be available in all research laboratories, research utilizing fMRI can provide important insights into the neurobiological mechanisms behind nicotine dependence.

Through exposure to this empirical research, we can better understand the changes that occur in the brains of individuals who chronically smoke, as well as how nicotine dependence affects various aspects of brain activity and function. This may provide an important foundation for more effective prevention and intervention efforts related to nicotine dependence. With the knowledge gained from this research, we can develop better strategies to address the problems of smoking and nicotine dependence, even in the context of limited resources.

## 2. Structure and Function of Brain Parts

The human brain is an organ that has a very complex structure and each has its own special function. In general, the human brain can be divided into two hemispheres, namely the left and right hemispheres. When viewed from the side, the human brain can be divided into four large parts, namely the temporal, frontal, parietal and occipital lobes. The outer part of the brain, adjacent to the skull, is called the cortex.

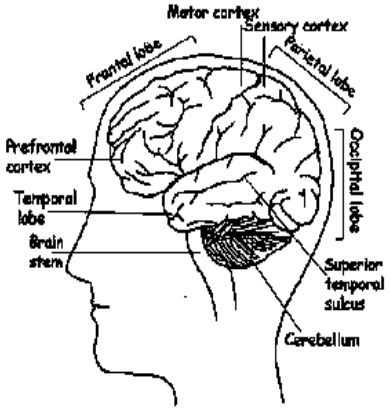


**Figure 1:** Brain Structure

One of the main differences in function between the two left and right hemispheres of the brain is that language acquisition is located in the left hemisphere, while recognition and facial recognition are related to the right hemisphere. In Figure 2, you can see the brain areas involved in language function. This area begins to become active in babies aged two to three months when they are introduced to several words. Figure 3 shows the parietal cortex which can be divided into superior (upper part) and inferior (lower part) areas related to spatial processing, as well as number comprehension and arithmetic (Soeroso et al., 2018).

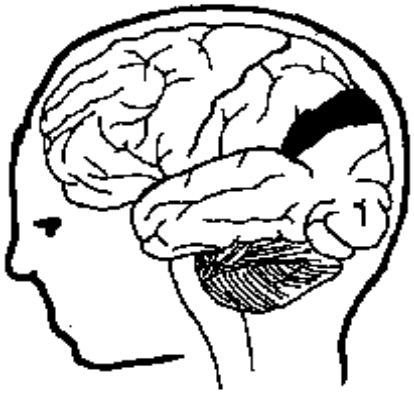

**Figure 2:** Left angular gyrus (language area)

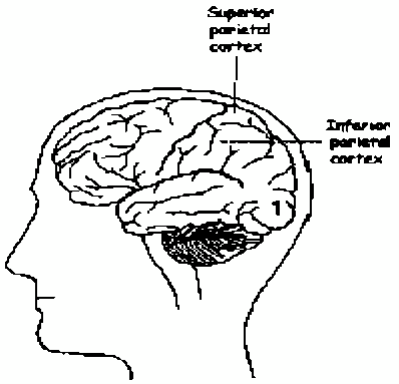


**Figure 3:** Text co r _ Parie et al

In addition to various functional areas in the brain, we also have two important types of tissue, namely gray matter (GM) and white matter (WM). GM is the outermost layer in the brain which generally connects the cerebral cortex and neocortex. The GM network consists of six layers of nerve cells which have an important role in information processing such as sensation, conscious control of muscle movements, thought processes, and reasoning (Satyana et al., 20200. The presence of GM within the insula, which is a hidden area between the frontal, parietal, and temporal lobes (often referred to as the insula opercula), correlates with an individual's ability to recognize the feelings they are experiencing, including in the context of smoking.

GM experienced development from the early to mid-teens, then experienced a volume decline of around 5% per decade. GM volume in the front of the brain decreases more slowly than in the back of the brain. Meanwhile, WM is located under the cerebral cortex and/or neocortex. WM has an important role as an indicator of nervous system maturity because it contains structures that influence the efficiency and speed of information transmission in the brain.

The corpus callosum (CC) is the largest WM structure in the human brain. The CC plays a role in connecting the two cerebral hemispheres and plays an important role in various aspects of brain function, including coordination between the two cerebral hemispheres and some aspects of language. By understanding the structure and function of various brain components such as GM and WM, we can better understand how smokers and individuals affected by nicotine dependence experience changes in their brain activity and function as a result of nicotine exposure and its effects.

**Table 1:** Brain Areas and Functions

| Regions | Function |
|---|---|
| Cerebellum | - Interval timing, adjustment of voluntary motor movements, attention and memory processing, association with the vestibular system. |
| Basal ganglia | - Balance, fine adjustment of motor movements, inhibitory motor control, integration of emotions, execution of movements. |
| | - Caudate nucleus: Control of voluntary movements, higher level motor control (cognition and memory), learning of new motor movements, execution of complex automotive movements, motivational drive. |
| | - Putamen: Mainly motor function. |
| | - Globus pallidus: Sends information between the basal ganglia and the cortex. |
| | - Substantia nigra: Main in dopamine synthesis. |
| | - Subthalamic nucleus: Control of voluntary movements, higher level motor control (cognition and memory), learning of new motor movements, execution of complex automotive movements, motivational drive. |
| Temporal lobe | - Memory and emotions. |
| | - Amygdala: Response to emotional and emotionally charged stimuli, associative learning, formation of new memories, modulation of memory storage. |
| | - Hippocampus: Memory, navigation. |
| | - Superior temporal gyrus: Complex auditory and language processing. |
| Thalamus | - Filtering, partitioning, processing, sending information between subcortical and cortical areas, motivation. |
| Hypothalamus | - Appetite, sexual response, visceral control, pleasure, aggression. |
| Anterior cingulate | - Emotional processing and attention, adaptation to new situations, attention shifts, movement planning. |

| | |
|---|---|
| Prefrontal cortex | - Attention processing, executive function, impulse control, emotion modulation. |
| | - Dorsolateral: Connection with basal ganglia and posterior cavity, selection of behavior and short-term memory, generation of new movements, task practice, monitoring performance of new movements. |
| | - Orbitofrontal: Social errors, visual face discrimination, connections with temporal and limbic structures. |
| | - Medial: Closely connected to the anterior portion of the cingulate. |
| Parietal cortex | - Motor selection, selection of auditory and visual cues, processing of spatial surroundings, monitoring the sequence and timing of movements. |

### 2.1. Nicotine, Cigarette (nicotine) Addiction Behavior, and Substance Withdrawal Symptoms

The terms 'addiction' and 'dependence' are often used interchangeably. In the Guidelines for Classification and Diagnosis of Mental Disorders in Indonesia III (PPDGJ-III), it is explained that:

"Dependence syndrome is a collection of physiological, behavioral and cognitive phenomena that arise as a result of the use of a particular substance or group of substances that has a higher priority for the individual compared to behavior that has been favored in the past. The main characteristic of a dependence syndrome is desire (often very strong and even too strong) use of psychoactive drugs (whether prescribed or not), alcohol, or tobacco. There may be evidence that those who re-use substances after a period of abstinence will relapse more quickly than individuals who are not addicted at all. Awareness Subjective urges to use substances usually occur when trying to stop or overcome substance use."

Meanwhile, the state of withdrawal is described as:

"A group of symptoms of various forms and degrees of severity that appear after absolute or relative cessation of administration of the substance following continuous and long-term and/or high-dose use of the substance. The onset and course of the withdrawal state are usually time-limited and related to the type and the dose of previously used substances. Withdrawal states may be accompanied by complications of seizures."

To diagnose a withdrawal state, several guidelines that can be used are as follows:

- Withdrawal may be an indicator of a dependency syndrome, and a diagnosis of a substance dependency syndrome should also be considered.
- Withdrawal should be recorded as the primary diagnosis if it is the reason for referral and is serious enough to require special medical attention.
- Physical symptoms may vary depending on the type of substance used. Psychological disorders such as anxiety, depression, and sleep disorders are common in withdrawal states. One characteristic is that patients report that withdrawal symptoms will subside if they continue using the substance.

People who try cigarettes and then become dependent or addicted do so because of the chemicals contained in cigarettes. Apart from causing dependence, these substances also have a negative impact on the body's organs. Some of the chemicals contained in cigarettes and their smoke when burned include carbon monoxide, tar and nicotine. When a cigarette is burned, nicotine enters the body through cells in the mouth, nose and respiratory tract. The lungs quickly absorb nicotine and distribute it throughout the body through the bloodstream. Nicotine in the blood also reaches the brain, where it triggers the release of several substances, such as dopamine, and activates the central and sympathetic nervous systems. The real impact of this process is increased alertness, heart rate and blood pressure in smokers. The absorbed nicotine accumulates in the blood and the effects will slowly wear off after about two and a half hours.

Considering the bad impact of nicotine on health, the government has regulated the distribution of tobacco, which is the main ingredient in making cigarettes, in Law of the Republic of Indonesia Number 36 of 2009, Article 113. However, in reality the circulation of cigarettes is still very widespread, and more and more people are becoming consumers. cigarette. Why do people find it difficult to stop smoking? The nicotine regulation model explains that cigarette addicts attempt to maintain nicotine levels in their blood and avoid withdrawal symptoms. The two-way interaction between nicotine's influence on the brain, which then produces psychological effects such as a decreased ability to recognize emotions and a tendency to depression, makes cigarette addicts continue to smoke to stay enthusiastic and calmer (Kristina et al., 2015; Astuti et al., 2020). Social environmental factors, such as family and peer groups, also influence smoking addiction behavior.

Research on the effect of nicotine on the brain using the fMRI (functional Magnetic Resonance Imaging) method is still limited due to constraints in terms of equipment, expertise and costs. Therefore, summaries of the latest scientific research from international journals can be a learning alternative to bridge the gap in this research. The results of this research reveal several important findings:

a). Smoking addiction behavior is correlated with brain activity in the left precuneus area, right angular gyrus, left superior parietal/motor cortex, and middle occipital gyrus.

b). Smokers' brains have different activity from non-smokers' brains in various brain areas, including the ventral, dorsal and mesolimbic tissue areas.

c). Disorders of the brain are also associated with psychological disorders such as anxiety, depression, anger, restlessness, difficulty concentrating, and compulsive behavior.
d). Changes in gray matter (GM) in the insula are associated with the experience of emotions and bodily sensations as well as a decrease in the ability to verbalize emotions. Decreased white matter (fractional anisotropy [FA]) in the left prefrontal cortex correlates with brain damage.
e). Nicotine also increases intrasynaptic dopamine concentrations in the ventral striatum/nucleus accumbens (VST/NAc) and serotonin as a sleepiness-inhibiting neurotransmitter, which causes sleep disorders.
f). Cigarette addicts have a risk of decreased "prospective memory," which is thought to be related to the prefrontal cortex, hippocampus and thalamus areas.

## 3. Discussion

Apart from that, the effect of nicotine is also seen in the dorsal or upper part of the brain, including the dorsal medial/lateral prefrontal cortex and the dorsal anterior cingulate cortex. This area is involved in decision making, impulse control, and emotional regulation. Mesolimbic networks such as the anterior cingulate, hippocampus, and medial orbital also experience different activity in smokers.

Cigarette addiction behavior is also related to psychological disorders such as anxiety, depression, anger, restlessness, difficulty concentrating, and compulsive behavior. This shows that cigarette addiction has a complex impact on an individual's psychological well-being. Increased gray matter in the insula, which occurs due to the effects of nicotine, can affect an individual's ability to recognize and verbalize emotions. However, a decrease in white matter in the left prefrontal cortex can indicate pathology in the brain.

Nicotine also affects neurotransmitters such as dopamine and serotonin, which play a role in mood regulation, concentration, and sleep. This can cause sleep disorders in smokers. Apart from that, cigarette addicts also have a risk of decreasing "prospective memory" which is related to the prefrontal cortex, hippocampus and thalamus areas. Prospective memory is the ability to remember and carry out tasks that have been planned in the future.

Overall, the effects of nicotine on the brain have broad and complex impacts. This explains why people find it difficult to quit smoking, because dependence on nicotine involves complex interactions between different areas of the brain and neurotransmitters. Social environmental factors also influence smoking addiction behavior. However, it is important to remember that stopping smoking has major long-term health benefits. Although difficult, various programs and approaches have been developed to assist individuals in the process of quitting smoking.

The effect of nicotine on the brain is a very complex phenomenon, encompassing multiple aspects of mental and physical functioning. Nicotine affects different areas of the brain, which can lead to varying effects in smokers. Some of the main impacts include changes in brain activity, psychological disorders, sleep disturbances, and cognitive impairment.

Different brain activity was seen in the ventral and dorsal areas. In ventral areas, such as the occipital gyrus and insula, there is different brain activity due to nicotine exposure. This can affect emotions, bodily sensations, and the ability to verbalize emotions. On the other hand, in dorsal areas, such as the dorsal medial/lateral prefrontal cortex (dm/dlPFC) and dorsal anterior cingulate cortex (dACC), there is a decrease in white matter (fractional anisotropy [FA]) which correlates with brain pathology. Disturbances in the dlPFC can hinder balance, control of body movements, emotional integration, and various cognitive aspects.

Apart from that, the influence of nicotine is also related to cognitive impairment, especially in the aspect of prospective memory. Disorders of the hippocampus and thalamus can cause a decrease in the ability to remember tasks and plan daily activities. Mesolimbic networks are also affected by nicotine, including medial orbital activity related to social regulation, visual processing of faces, emotions, and attention. Cigarette addicts often experience psychological disorders such as anxiety, depression, difficulty concentrating, and compulsive behavior.

In addition, nicotine affects the hormones dopamine and serotonin, which makes it difficult for cigarette addicts to sleep. Even though it seems that nicotine can prevent drowsiness, the side effects are sleep disorders such as insomnia, restless sleep, and easy waking. This sleep disorder can affect emotional stability, ability to concentrate and memory. In order to maintain long-term health, quitting smoking is a very important step. Although quitting smoking can be challenging, there are many programs and supports available to assist individuals in overcoming nicotine addiction and starting their journey to better health.

### 3.1. Intervention P addict Cigarette

Intervention for cigarette addicts is an important step in helping individuals overcome nicotine dependence. An effective approach involves collaboration between pharmaceutical sciences and psychology. One psychopharmaceutical method that has proven successful is administering Bupropion HCl Sustained Release (SR) at a dose of 150 mg once a day orally, which can then be increased to twice a day starting on day 4, for a minimum duration of four weeks. Apart from that, it is also important for cigarette addicts to take part in Practical Group Counseling (PGC).

PGC is carried out twice a week with a minimum duration of 60 minutes per session for eight weeks. The material discussed in PGC includes education about cigarette addiction, strategies for overcoming substance withdrawal, and

efforts to prevent relapse. Apart from that, participants are also taught how to identify situations that can trigger the desire to smoke, develop the ability to overcome negative emotions, reduce stress, and how to overcome thoughts of trying cigarettes again. The PGC also includes discussion of the importance of developing a healthier lifestyle and obtaining social support.

During the intervention process, the use of vanilla or cardamom apple flavored gum can also help cigarette addicts suppress anxiety and tension. It is important to remember that this intervention must be carried out continuously and structured to provide optimal results. Apart from curative efforts, prevention of cigarette consumption is also very important, especially if done since adolescence and for those who have not tried smoking. Some prevention strategies include limiting smoking areas, increasing cigarette taxes and prices, displaying prominent warnings about the dangers of smoking and images of the negative effects of smoking on cigarette packaging, as well as producing and broadcasting anti-smoking advertisements through various media. This prevention effort aims to reduce incentives for individuals, especially teenagers, to start smoking.

## 4. Conclusion

Based on the information that has been described, we can conclude that the use of nicotine in cigarettes has a significant impact on the brain and behavior of individuals. Nicotine influences the release of a number of neurotransmitters, including dopamine and serotonin, which play a role in emotional regulation, motivation and mental balance. The impact of nicotine use on the brain includes changes in activity in various parts of the brain, such as the frontal cortex, limbic system, and mesolimbic network.

Individuals who are dependent on nicotine may experience withdrawal symptoms, such as anxiety, depression, and sleep disorders when trying to quit smoking. Cigarette addicts also have a higher risk of experiencing emotional disorders, such as bipolar disorder and suicidal tendencies. Changes in brain activity and function associated with nicotine use have been identified through neuroimaging methods, primarily fMRI.

In an effort to overcome nicotine dependence, there is an intervention involving the administration of Bupropion HCl SR and practical group counseling sessions. This is a holistic approach that focuses on the pharmacological and psychological aspects of cigarette addiction. Apart from that, preventing cigarette consumption is also an important part of overcoming the smoking problem, especially in the younger generation.

In conclusion, the influence of nicotine on the brain and behavior is an important topic in scientific research, and a better understanding of this process can help in developing more effective intervention strategies and stronger prevention efforts against cigarette addiction. In addition, interdisciplinary collaboration between pharmaceutical sciences and psychology is an objective step in helping individuals overcome nicotine addiction and reduce the negative impacts associated with smoking.

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