Unraveling the Neurochemical Nuances: Comparing Nicotine, Fentanyl, and Marijuana's Impact on Adolescent Insular Emotions

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This review paper explores the dynamic mechanisms by which marijuana, fentanyl, and nicotine modulate the release, uptake, and receptor binding of key neurotransmitters such as dopamine, endorphins, serotonin, and glutamate within an adolescent's insula. The insula plays a pivotal role in the emotional processing of both positive and negative emotions in the brain. The interaction between excitatory and inhibitory neurotransmitters shapes the chemical dynamics of the insula's processing of emotions. The paper offers a multi-faceted approach to investigating the effects of marijuana, fentanyl, and nicotine on neurotransmitters in the insula and their contribution to the emotional experiences of the adolescent brain. This study aims to prove how this investigation of the insula can be enabled through the development and application of medical devices like Neurochemical Monitoring devices, Positron Emission Tomography, Electroencephalography, and Magnetoencephalography, ultimately enhancing researchers ability to comprehend the intricate interactions between substances and emotional states during this critical period of neural development. It underscores the importance of limiting drug usage for adolescents while emphasizing the importance of research into their long-term effects. This paper highlights potential medical devices to further preventive interventions, develop therapeutic strategies, and enable deeper research into the insula to gain a more precise understanding of the intricate relationships between substance use and emotional processing during this critical developmental stage.

Introduction

The adolescent period is a pivotal phase of neural development[1] that is characterized by intricate changes in the brain structure and functions[2]. As an adolescent, the insula, a brain region intricately connected with emotional processing, undergoes notable maturation[2]. Emerging research has shed light on how substances such as nicotine, fentanyl, and marijuana interact with the insula's neurotransmitter systems, influencing the complex interplay of positive and negative emotions in the adolescent brain. Positive emotions being indications of "optimal well-being,"[3] characterized by feelings of joy and contentment. Negative emotions are characterized by feelings such as anxiety or despair, that cause an individual to feel depressed and upset[3]. Understanding the nuanced effects of these substances on insular neurotransmitters is of paramount importance, as it holds implications for the heightened vulnerability of adolescents to substance-induced emotional dysregulation and mental health concerns[3,4]. This research paper embarks on an exploration of the distinct mechanisms through which nicotine, fentanyl, and marijuana modulate insular neurotransmitters, unraveling their contributions to the intricate landscape of adolescent emotional experiences. By delving into this neurochemical tapestry, this study aims to provide a comprehensive understanding of how these substances shape the emotional trajectories of adolescents and contribute to our broader comprehension of substance-related effects on brain development.

This research paper highlights the significance of the insula in processing emotional experiences during adolescence, emphasizing its role as a nexus for substance-induced alterations[4]. Incorporating insights from cutting-edge neuroimaging techniques such as Functional Magnetic Imaging Resonance, Positron Emission Tomography, Electroencephalogram, Magnetoencephalography, as well as neurochemical monitoring, this paper provides a comprehensive overview of the diverse methodologies that can be used to elucidate the effects of these substances on insular neurotransmitters. It looks at possible limitations in its research and addresses them. Limitations such as psychosocial environments and the variability and uniqueness of each individual person are some.

This research paper offers a comprehensive exploration of how nicotine, fentanyl, and marijuana distinctly influence insular neurotransmitters and contribute to the positive and negative emotions experienced by adolescents. By piecing together facts that are already known into a comprehensive overview, this research contributes to a deeper understanding of the intricate relationship between substance use and emotional processing during this critical developmental stage, with potential implications for preventive interventions and therapeutic strategies.

Adults vs. Adolescent Brain Development

In the realm of substance usage, the neurological effects of various substances have garnered substantial attention due to their profound impact on brain function and in turn, on behavior. In order to further this research, it is important to understand the stark differences between an adolescent's brain and an adult's brain. The developmental trajectory of the human brain is a dynamic process, characterized by distinct changes in structure and function from adolescence to adulthood.

The adolescent brain is characterized by ongoing structural and functional maturation[4]. During this period, the prefrontal cortex, responsible for executive functions such as decision-making and impulse control[4], undergoes considerable development. However, the connections between the prefrontal cortex and other brain regions are still in the process of refinement. This uneven development can lead to a heightened sensitivity to rewards and a relative weakness in inhibitory control, potentially contributing to risky behaviors and impulsivity[5]. Additionally, the limbic system, which plays a role in emotions and motivation, matures earlier, potentially leading to heightened emotional reactivity[6].

The adult brain, in contrast, has undergone a substantial degree of structural maturation and connectivity refinement. The prefrontal cortex has established more robust connections with other brain regions, enhancing cognitive control and decision-making processes[5]. The balance between the prefrontal cortex and limbic system tends to be more stable, resulting in more measured emotional responses and reduced impulsivity[7]. The brain's plasticity, while still present, is generally less pronounced than during adolescence[5], which influences the capacity for learning and adapting to new experiences.

In relation to substance abuse, the heightened sensitivity of the adolescent brain's reward system makes it more susceptible to the reinforcing effects of substances like drugs and alcohol[7]. Understanding these vulnerabilities is crucial for developing effective prevention and intervention strategies to address substance use disorders. As drugs become more accessible, it becomes easier for adolescents and adults to abuse drugs as a way of coping with their mental health[7]. The emotional reactivity associated with adolescent brain development has implications for mental health disorders that often emerge during this period, such as depression and anxiety[6]. Identifying the neural mechanisms underpinning these disorders in the context of adolescent brain dynamics informs targeted interventions.

The Role of the Insula and Neurotransmitters

The insula, a complex region nestled within the cerebral cortex, plays a pivotal role in the processing of both positive and negative emotions[8].

The insula's involvement in the processing of positive emotions is intricately tied to the interplay of neurotransmitters and neuromodulators[8]. Dopamine, a neurotransmitter associated with reward and pleasure[9], is a central player. When an individual encounters a positive stimulus, such as a pleasant taste or a joyful sight, the insula is activated[10]. Dopamine release in response to these stimuli reinforces the neural pathways that underlie these pleasurable experiences[10]. Additionally, endorphins, often referred to as "feel-good" neurotransmitters, contribute to the sensation of positive emotions[11]. These opioid peptides, when released in response to positive stimuli, interact with opioid receptors in the insula, further enhancing the pleasurable sensations associated with positive experiences[11].

The insula's involvement in the processing of negative emotions is just as intricate, driven by an array of neurotransmitters and neuromodulators[2,11,12]. Neuromodulators differ from neurotransmitters due to an unique expression of neurons projected throughout the nervous system[11]. They modulate postsynaptic neurons, altering responses to neurotransmitters that affect positive and negative emotions like GABA and dopamine[11]. When confronted with aversive stimuli, such as pain or distressing images, the insula is activated[9]. This activation prompts the release of neurotransmitters such as glutamate[12], which amplifies neural signaling related to negative emotions[13]. Additionally, the insula's interaction with the amygdala, a brain region critical for emotional processing, further intensifies the experience of negative emotions[14]. Serotonin, a neurotransmitter linked to mood regulation, also plays a role[15]. Reduced serotonin levels have been associated with heightened emotional reactivity[15], potentially exacerbating negative emotional experiences[15,16].

The interplay between excitatory and inhibitory neurotransmitters shapes the chemical dynamics of the insula's processing of emotions. Glutamate, the brain's primary excitatory neurotransmitter, promotes neural activity related to both positive and negative emotions[16]. GABA, the primary inhibitory neurotransmitter, modulates the intensity of this activity by counteracting glutamate's effects[17]. The balance between these neurotransmitters determines the degree of emotional responsiveness within the insula[17]. The chemical processes underlying the insula's processing of positive and negative emotions are not isolated events; they intertwine and overlap, resulting in a complex spectrum of emotional experiences. Dopamine and endorphins contribute to the reinforcement of positive emotions, while glutamate and serotonin intensify the perception of negative emotions.

Marijuana

Marijuana, also known as cannabis, is a psychoactive plant that can be consumed for both recreational and medical purposes[18]. Its primary active compound, delta-9-tetrahydrocannabinol (THC), interacts with the endocannabinoid system in the brain[18]. Upon inhalation or ingestion, THC binds to cannabinoid receptors, primarily CB1 receptors, which are located throughout

the central nervous system[18]. This engagement leads to altered synaptic communication and the release of neurotransmitters such as dopamine, which contributes to the characteristic feelings of euphoria and relaxation associated with marijuana use[18]. However, chronic marijuana use can impair cognitive functions and lead to changes in the brain's reward circuitry. Studies suggest that marijuana can lead to heightened positive emotions by increasing the release of dopamine and other neurotransmitters associated with pleasure[19]. The insula's role in processing rewarding stimuli is thus accentuated by THC's effects, contributing to the euphoria often experienced after marijuana use. However, marijuana's impact on negative emotions in the insula is nuanced. While some individuals report reduced anxiety and stress after using marijuana, chronic use can lead to dysregulation of the endocannabinoid system, potentially exacerbating negative emotions over time[20]. The relationship between marijuana and emotional processing in the insula is complex and influenced by factors such as frequency of use and individual susceptibility[21].

Studies have shown the multitude of ways in which recreational usage of marijuana affects adolescents. A study conducted on 198 adolescents ran tests investigating substance-use of marijuana and alcohol[22]. Participants were classified as "primary alcohol or maijuana users" (meaning they had consumed a substance at least more than once[22]. As referred to in table 1[22], the MJ (Marijuana) column only, it is clear how the average adolescent is the youngest compared to adolescents who divulge in both alcohol, marijuana, or neither (the control group). Additionally, it is clear that adolescents use Marijuana more frequently, as MJ use frequency is at a 4.96 while the Control group and Alcohol only groups are below 1.

Additionally, in one of the first studies that evaluated insular thickness in adolescents with heavy marijuana usage to non-users, they found that marijuana users had significantly reduced cortical thickness[23]. This decrease in thickness was found in a variety of places, including the bilateral insula[23]. Further analysis provided negative correlation of insular thickness between adolescents with heavy marijuana usage as they continued into adolescence compared to those who never used[23].

Fentanyl

Fentanyl is a synthetic opioid that is exponentially more potent than morphine and heroin. It is primarily prescribed for severe pain management, but its illicit forms have contributed to a significant opioid crisis[24]. Fentanyl exerts its effects by binding to opioid receptors in the brain, particularly the mu-opioid receptors[24]. This interaction leads to a profound reduction in pain perception and a surge in dopamine release, eliciting feelings of euphoria and relaxation[24]. However, fentanyl's potency also increases the risk of overdose and respiratory depression, which can be fatal[24]. Positive emotions are amplified by fentanyl's interaction with opioid receptors, leading to intense feelings of euphoria and pleasure. The release of dopamine and other neurotransmitters associated with reward contributes to this emotional response[24]. However, fentanyl's impact on negative emotions is a grave concern[25]. The insula's involvement in pain perception and emotional regulation is hijacked by fentanyl, potentially leading to emotional blunting and an inability to process aversive stimuli appropriately[25]. Moreover, fentanyl's depressant effects on the central nervous system can lead to a profound dampening of emotional responsiveness[25], potentially contributing to depressive states.

Analyzing a study regarding fentanyl exposure in Sprauge-Dawley rats, illustrates that adolescent nicotine exposure increases the amount of fentanyl intake[26]. This clearly highlights the effects that drug intake has on adolescents, especially when combining two.

Nicotine

Nicotine, a potent alkaloid found in tobacco, is responsible for the addictive properties of tobacco products. Upon inhalation, nicotine quickly reaches the brain by crossing the blood-brain barrier[27]. It stimulates the release of neurotransmitters such as dopamine and norepinephrine, creating a pleasurable sensation. These neurotransmitter releases reinforce the reward pathway in the brain, leading to addiction[27]. Long-term nicotine exposure can lead to alterations in synaptic plasticity and the development of nicotine dependence[26]. Prolonged nicotine exposure can lead to desensitization of these receptors, potentially blunting the initial euphoric response and fostering dependence[26,27]. Building an addiction to nicotine has been reported to have a dampening effect on negative emotions[27]. The insula's involvement in processing aversive stimuli is mitigated by nicotine's influence on neurotransmitter systems, reducing the perception of negative emotions such as anxiety and stress[28]. This dual impact on both positive and negative emotions underscores nicotine's intricate modulation of insular activity. The interaction between nicotine and the brain's acetylcholine receptors also contributes to cognitive enhancement, which partly explains the appeal of nicotine-containing products[26–28].

The study below that was conducted in rats further explains the dependence adolescents have on other drugs once exposed to nicotine[29]. Due to the effect of neurotransmitters in the adolescent insula and brain, adolescent rats exhibit greater behavioral sensitivity to other drugs[29]. In contrast, adult rats faced no response to nicotine exposure[29].

Various Drugs and Effects of Substance Abuse

While marijuana, nicotine, and fentanyl differ in their origins and legal statuses, they all impact the brain's neurotransmitter

Table 1 Identifying usage of primary marijuana in adolescent users compared to primary alcohol users, both, and none[22].

	Control	MJ only	Alc only	MJ + Alc
N	37	39	23	90
Proportion male	.54[d]	.72[d]	.61[d]	.88[a,b,c]
Age	16.05 (1.18)	15.97 (1.06)	16.35 (1.11)	16.31 (1.09)
Adjusted Pumps	5.56 (.60)	5.49 (.60)	5.39 (.53)	5.68 (.60)
Proportion Explosions	.20 (.10)	.18 (.11)	.18 (.08)	.20 (.10)
Total drinking days (out of 30; from TLFB)	.11 (.31)[c,d]	.23 (.43)[c,d]	3.22 (3.63)[a,b]	4.98 (5.17)[a,b]
Average drinks per drinking day (TLFB)	0.62 (2.85)[c,d]	1.08 (2.39)[c,d]	4.66 (4.03)[a,b]	6.99 (5.06)[a,b]
Total MJ days (out of 30; from TLFB)	0.05 (.23)[b,d]	14.64 (12.49)[a,c]	.09 (.29)[b,d]	16.74 (11.95)[a,c]
Alcohol use frequency (Never = 0 to Every day = 8)	.32 (.48) [c,d]	.49 (.51) [c,d]	3.39 (1.85) [a,b]	3.92 (2.35) [a,b]
MJ use frequency (Never = 0 to Every day = 8)	.21 (.42)[b,d]	4.69 (3.46)[a,c]	.13 (.34)[b,d]	5.76 (3.00)[a,c]
Hard drug use (last 3 months); possible range 0 to 8	.24 (.76)[d]	.56 (.99)[d]	.52 (.95)[d]	1.27 (1.47)[a,b,c]
Hard drug use (ever); possible range 0 to 9	1.16 (1.85)[d]	1.74 (1.71)[d]	2.22 (2.11)	2.83 (2.02)[a,b]
Proportion smoked cigarette in last month	.41[d]	.62	.57	.69[a]
IMPSS	9.46 (3.53)[d]	9.92 (4.30)[d]	11.09 (4.21)	11.87 (3.47)[a,b]
CASS-S	22.59 (12.04)[d]	26.18 (16.03)[d]	27.91 (9.56)	32.66 (14.97)[a,b]
CBCL	15.00 (9.79)[b,d]	23.46 (16.35)[a]	19.70 (12.04)	24.54 (11.99)[a]
CDI	2.59 (3.29)	3.59 (3.75)	3.17 (3.41)	2.83 (2.76)
RCMAS	48.38 (12.95)	49.26 (13.23)	49.04 (10.50)	49.26 (12.18)

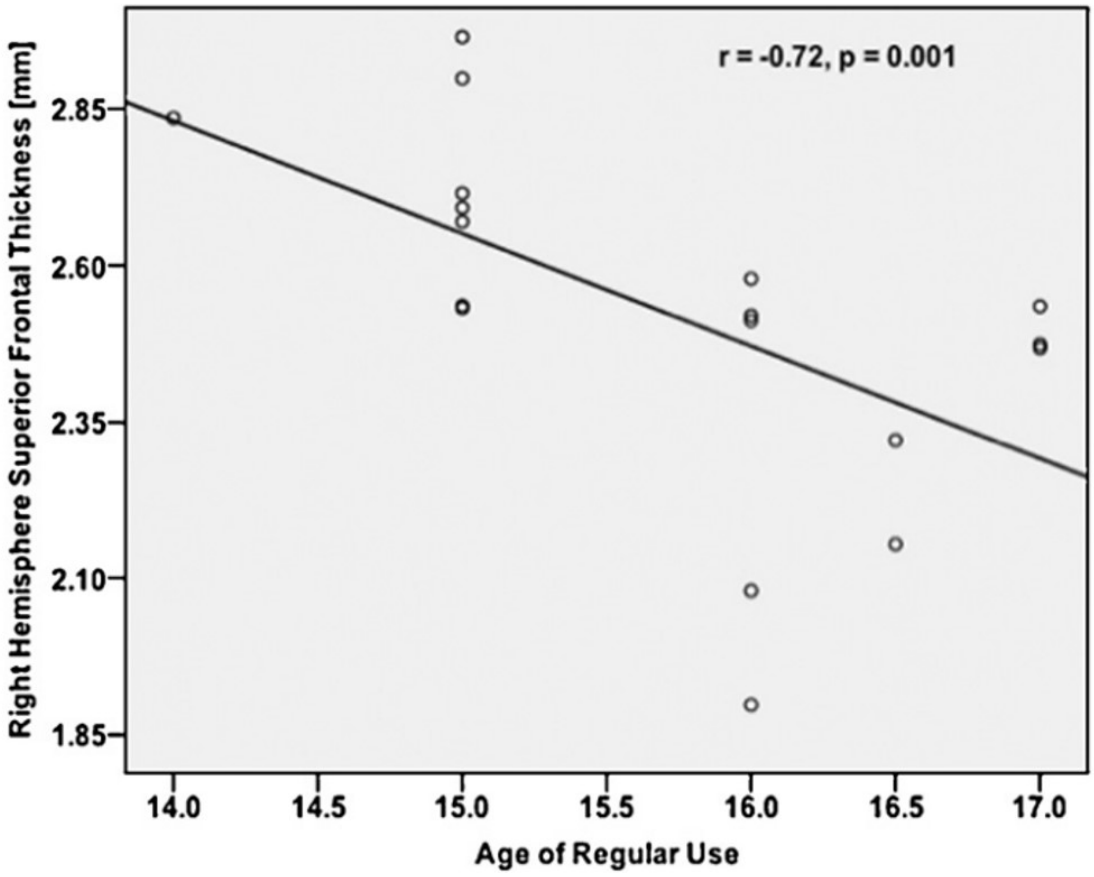

Fig. 1 Negative correlation of the Right Hemisphere Superior Frontal Thickness as age of regular use increases[23].

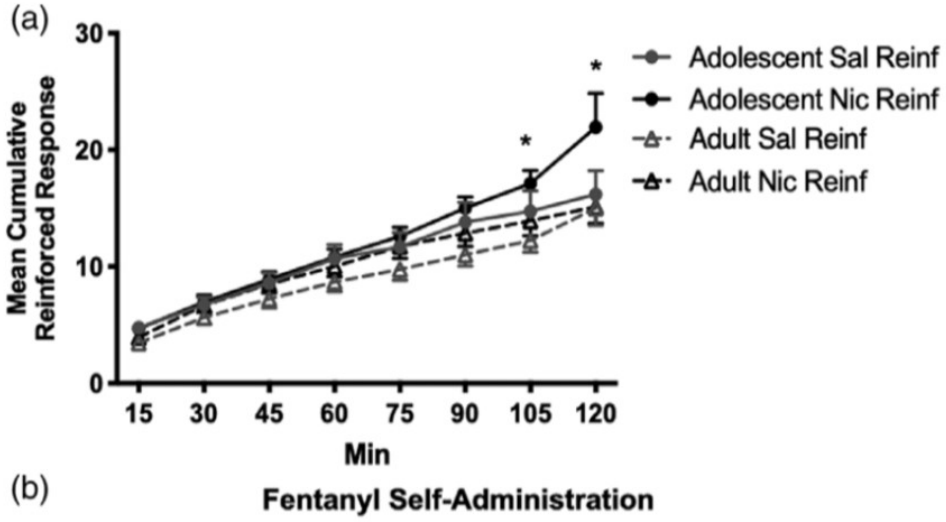

Fig. 2 Adolescent and adult response data over time for the enhancement of fentanyl self-administration in Sprague–Dawley rats[26].

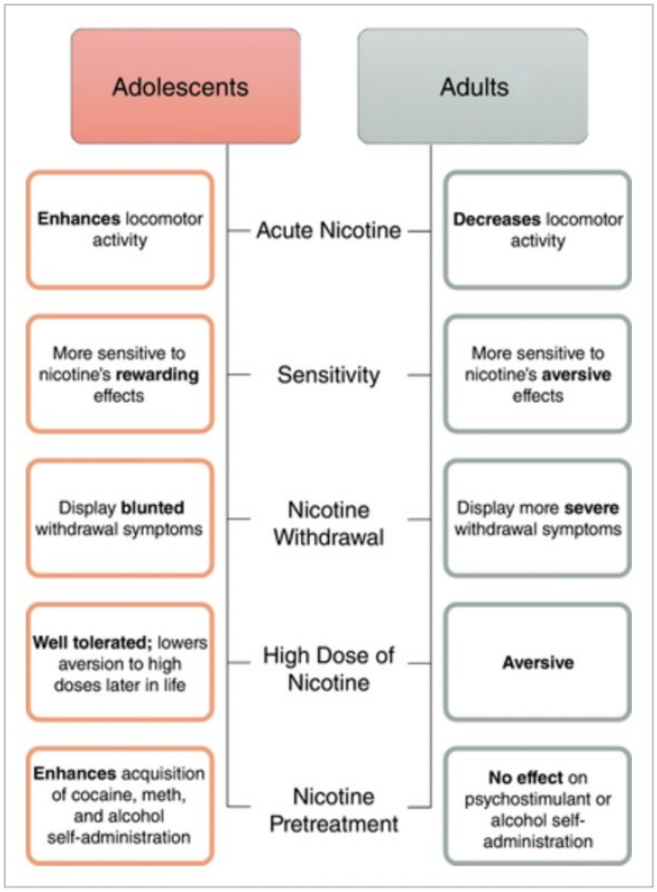

Fig. 3 Preclinical studies using rodent models indicate that nicotine produces age-specific behavioral responses[29].

systems to induce varying degrees of euphoria and reward. Each substance's effects on the brain's reward circuitry contribute to their addictive potential, although the underlying neurological mechanisms differ. The insula's intricate involvement in processing both positive and negative emotions is significantly influenced by the mechanisms of nicotine, marijuana, and fentanyl. While nicotine and marijuana often accentuate positive emotions and mitigate negative emotions, fentanyl's effects are characterized by intense positive emotions and potential emotional blunting. Despite this, there is still much to learn about the insula and its processes.

Understanding these effects is crucial for developing targeted interventions and treatments for substance-related emotional dysregulation, ultimately enhancing our ability to mitigate the adverse emotional consequences of substance use. Further research into the neural mechanisms underlying these emotional alterations will undoubtedly contribute to a more comprehensive understanding of addiction and emotional processing in adolescents.

Neuroimaging Techniques

Medical advancements have spurred the development of innovative tools and technologies that enable researchers to delve deeper into the intricate interplay of neurotransmitters in the insula and their role in shaping emotional states. These medical devices offer unique insights that contribute to our understanding of how these substances affect the adolescent brain. However, a current limitation of them is running these tests can be extremely expensive [30–33] and not a viable option for most users.

Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging is a non-invasive imaging technique that has revolutionized our understanding of brain activity. By measuring changes in blood flow, fMRI allows researchers to observe neural activity in real-time [30]. When investigating the effects of nicotine, fentanyl, and marijuana on the insula, fMRI can identify regions of heightened activation or deactivation [30], shedding light on the specific areas influenced by these substances during emotional processing [34]. This technology can help map out how neurotransmitters are modulated by these substances in response to positive and negative stimuli.

Positron Emission Tomography (PET)

PET is another imaging technique that provides insights into brain function at the molecular level [31]. By tracking the distribution of radioactive tracers that bind to specific neurotransmitter receptors, PET allows researchers to quantify receptor availability and activation [31]. This is particularly relevant when investigating the impact of substances like nicotine, fentanyl, and marijuana on the insula's neurotransmitter systems. PET scans can reveal how these substances influence the release and binding of neurotransmitters [31], offering a deeper understanding of their effects on emotional states.

Electroencephalography (EEG) and Magnetoencephalography (MEG)

EEG and MEG are techniques that measure electrical and magnetic activity [32], respectively, in the brain. These methods provide high temporal resolution [32], allowing researchers to capture the rapid changes in neural activity associated with emotional processing. When studying the effects of substances on the insula's neurotransmitters, EEG and MEG can uncover how different substances alter the timing and patterns of neural responses to emotional stimuli [32].

These technologies offer insights into the immediate effects of nicotine, fentanyl, and marijuana on emotional processing in the adolescent brain [32].

Neurochemical Monitoring Techniques

Advances in neurochemical monitoring techniques, such as microdialysis and in-vivo voltammetry, provide a direct window into neurotransmitter release and levels in specific brain regions [33]. When investigating substances' effects on insular neurotransmitters, these techniques can reveal how substances modulate the release of dopamine, serotonin, and other neurotransmitters in response to emotional cues [33]. By obtaining real-time information on neurotransmitter dynamics [33], researchers can better understand the chemical changes that contribute to altered emotional states.

Methodology

Search Strategy

This review paper was focused heavily on research keywords such as insula, insular, marijuana, nicotine, fentanyl, opioids, neurotransmitters, GABA, endorphins, serotonin, Functional Magnetic Imaging Resonance, Positron Emission Tomography, Electroencephalogram, Magnetoencephalography, neurochemical monitoring, adolescents, legalization, drug-use, and FDA.

Inclusion Criteria and Data Extraction

This research paper included reviews from other case studies previously done regarding adolescent drug-use. It relied heavily on known information and compiled various sources together to prove one argument, while accounting for possible limitations. Data from case studies were selected based on size of population and relation to current drug-use statistics. By referring to

studies done on rats that have shown to have a similar developmental path and questionnaires to humans, this paper was able to consider multiple perspectives.

Discussion

Restatement of Key Findings and Implications/Significance

The development and application of these medical devices offer a multi-faceted approach to investigating the effects of nicotine, fentanyl, and marijuana on neurotransmitters in the insula and their contribution to the emotional experiences of the adolescent brain. These technologies provide a bridge between neurochemical processes and behavioral outcomes, ultimately enhancing our ability to comprehend the intricate interactions between substances and emotional states during this critical period of neural development.

Concerns and limitations

Understanding the functions of the insula in relation to drug usage, specifically in adolescence, comes with several limitations. Generalized findings about insula involvement in drug use may not necessarily hold true for every individual, as its impact can vary from person to person, presenting challenges in making broad generalizations.

Insular Unreliability

The insula is a highly complex brain region involved in various functions, including sensory processing, emotions, and decision-making. Pinpointing its specific role in drug use can be challenging due to this complexity. The insula does not work in isolation; it interacts with other brain regions. Understanding its functions in drug use requires considering these interactions and being able to isolate one function from the other. Brain structure and function can vary greatly among individuals. What may be true for one person regarding insula involvement in drug use may not apply to another, making it difficult to generalize findings. Causation between insula activity and drug use is challenging to distinguish. Brain changes associated with drug use might be a consequence of addiction rather than a cause, and vice versa. It is still unclear whether or not changes in the insula contribute to drug addiction or if drug addiction can lead to changes in the insula.

Conducting experiments that directly manipulate the insula, especially in adolescence, in relation to drug use in humans is ethically and practically challenging. With the brain still developing, it is important to conduct a study with as little variability as possible, including the maturation of the insula. This limits the ability to establish causal links definitively. While animal studies can provide valuable insights, there are differences in brain structure and function between species. Translating findings from animal research to humans can be problematic.

Psychosocial Factors

Drug usage and addiction is also influenced by psychosocial factors such as stress, social environment, and peer pressure [35]. Conducting a study to limit these factors or create similar psychosocial settings is difficult to replicate.

Different drugs can have varying effects on the insula. Some may enhance its activity, while others may suppress it, making generalizations difficult [2,3]. While there is a growing body of research on the insula and drug use, our understanding is still incomplete. Many studies are correlational or rely on animal models due to the difficulty of conducting certain types of research in humans.

Ethical Concerns

Due to this paper calling for assessments to be conducted on adolescents, it is vital to keep in mind ethical concerns. Due to adolescents being minors, a variety of opinions need to be considered including the child, their parents, and the professional. It is key to keep in mind "parental consent, children's rights, confidentiality, separation of parent and child during assessment, and the use of multiple sources of information and appropriate measures," [36] when conducting assessments on minors. This study recommends non-invasive ways to conduct these assessments, with the hope of preventing fear of them and the potential harm of running tests on a minor's brain.

General Conclusions on Limitations

Despite these limitations, ongoing research continues to advance our understanding of the insula's role in drug use. Combining neuroimaging techniques, behavioral studies, and animal models can provide valuable insights into the complex interplay between the insula and drug addiction.

Recommendations and Closing Thoughts

With marijuana being the most used drug for adolescents [37] and its legalization in various states all over the United States [38], the ability for adolescents to find ways to come into contact with it is skyrocketing [38]. Similarly, access to nicotine is increasing and adolescents are finding ways to access it [39], despite FDA limiting selling to 21 and older [40]. While these changes are happening at a legislative level, limiting legal drug-use for adolescents while research on their effects is ongoing is crucial. This requires more preventative measures over policy changes. Adolescents still find ways to gain access to drugs despite what the policy at the

time states[39], therefore it is important that preventative measures start taking place in order to limit its availability overall.

Adolescence is a period of rapid brain development[1], and the impact of drugs during this critical phase can have long-lasting consequences on cognitive, emotional, and behavioral functioning[2]. The incomplete understanding of the nuanced interactions between drug use and developing brains underscores the need for caution. Protecting adolescents from potential harm is paramount, as their well-being and future prospects are at stake. By implementing restrictions on legal drug use for this vulnerable population, policymakers and healthcare providers can prioritize safety and evidence-based decision-making, ensuring that any potential risks are thoroughly assessed before exposing adolescents to substances that may have far-reaching implications for their health and future outcomes.

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