

The New Classes of Synthetic Illicit Drugs Can Significantly Harm the Brain: A Neuro Imaging Perspective with Full Review of MRI Findings

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Review Article

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Abstract

Synthetic drugs contain substances that are pharmacologically similar to those found in traditional illicit drugs. Some of the most commonly abused synthetic drugs include synthetic marijuana, bath salts, ecstasy, N-bomb, methamphetamine and anabolic steroids. Many of them share the same chemical properties and physiologic responses with the drugs they mimic and may exaggerate the pathologic response in the brain leading to addiction. These drugs have detrimental (and often irreversible) effects on the brain and primarily affect the central nervous system by two mechanisms: 1) Neural hyper stimulation via increasing activation of certain neurotransmitters (norepinephrine, dopamine, and serotonin), 2) Cause significant reduction in CNS neural connectivity affecting various brain regions such as the basal ganglia, hippocampus, cerebellum, parietal lobe, and globus pallidus. Furthermore these drugs sometimes have severe, life-threatening adverse effects on the human body. A few structural MRI studies have been conducted in synthetic drug abusers to reveal the effects of these drugs on the brain parenchyma. This review article will describe the potential brain imaging findings in synthetic drug abusers as demonstrated by several case reports and the primary literature.

Keywords: MRI; Pharmacologically; Pathophysiologic; Cannabinoids; Cathinone; N-methylamphetamine

Abbreviations: MRI: Magnetic Resonance Imaging; THC: Tetra Hydro Cannabinol; OFC: Orbito Frontal Cortex; FLAIR: Fluid Attenuation Inversion Recovery; MDPV:

Methylene Dioxy Pyro Valerone; ADC: Apparent Diffusion Coefficient; BOLD: Blood Oxygen Level Dependent; MDMA: Methylene Dioxy-Methamphetamine; AAS: Anabolic-Androgenic Steroids.

Introduction

Synthetic drugs contain substances that are pharmacologically similar to those found in traditional illicit drugs, such as cocaine, methamphetamine, and marijuana. Some of these synthetic counterparts are available in various forms as over the counter medications and thereby easily accessible to the general population. These particular over the counter medications are sold under various names including Jazz, Scooby Snax, Spice and Bath Salts, among others. Synthetic drug abuse is a growing epidemic worldwide. Many of these drugs are addictive stimulants, and their repeated use causes long term or irreversible damage to dopaminergic, adrenergic and serotonergic pathways in the brain. Some of the most commonly abused synthetic drugs include synthetic marijuana, bath salts, ecstasy, N bomb, methamphetamine and anabolic steroids. Many of them share the same chemical properties and physiologic responses with the drugs they mimic and may exaggerate the pathologic response in the brain leading to addiction. Furthermore these drugs sometimes have severe, life-threatening adverse effects on the human body, including triggering seizures, cardiac arrhythmias, acute infarction, and even sudden death. However, most of these drugs' pathophysiologic and toxic effects have not been well studied in the human population, hence resulting in unknown and unpredictable outcomes. In the meantime, recent advances in medical imaging have made it easy to study the brain parenchyma with great detail. A few structural MRI studies have been conducted in synthetic drug abusers to reveal the effects of these drugs on the brain parenchyma. This review article will describe the potential brain imaging findings in synthetic drug abusers as demonstrated by several case reports and the primary literature.

Objective

Evaluate the effect of commonly abused new synthetic drugs on the brain based on abnormal findings detected by Magnetic Resonance Imaging (MRI).

Discussion

Synthetic Cannabinoids (Synthetic /Marijuana/ Spice K2)

On average the US market introduces five synthetic drugs every month, which means 60 different names in a year. Synthetic marijuana has grown into the second most commonly abused drug among young males. In fact, in

2012, 11% of American high school seniors disclosed using synthetic marijuana within the last year [1].

Synthetic cannabinoids are a combination of herbs and spices with similar effects as marijuana; however, they can be four times as potent. This drug is usually spread on herbal material before being smoked, usually in joints or pipes. This chemical regulates and binds more strongly to the same brain receptors as delta-9-tetra hydro cannabinol (THC), the psychoactive component in marijuana, which may account for its stronger and more unpredictable effects. Its psychological effects are analogous to those of marijuana including altered perception, paranoia, excessive anxiety, violent behavior and suicidal thoughts [2]. Previous studies have found that chronic marijuana users present with a decreased brain volume in the orbito frontal cortex (OFC), a brain region that is related to addiction, but otherwise demonstrate increased brain connectivity [3]. Yet, limited research has been performed on the effect of synthetic cannabinoids on the brain. Especially, there are few records revealing MRI findings in patients under the influence of synthetic cannabinoids in the acute setting. Few studies available to date have demonstrated abnormal restricted diffusion involving large portions of vascular territories or, alternatively, presenting in an embolic pattern.

For instance, a prior case report about two women (ages 22 and 26) with stroke like symptoms hours after having consumed synthetic marijuana demonstrated an extensive area of acute infarction within the middle cerebral artery vascular territory. Similarly, another study presenting 19 and 26 year old siblings that had used synthetic cannabis revealed multi-embolic acute infarcts within the middle cerebral artery vascular territory. Yet, a case of a 50 year old male that was found unconscious after synthetic cannabis use the night prior to presentation demonstrated a bilateral symmetric pattern of abnormal diffusion restriction on MR diffusion imaging involving many regions of the brain, not limited to a single vascular territory. Fluid attenuation inversion recovery (FLAIR) images also showed abnormal hyper intense signal within the hippocampi, basal ganglia, posterior limbs of the internal capsules, bifrontal cortex, cerebral peduncles, posteroinferior cerebellar hemispheres, and the cerebellar vermis (Figures 1 and 2). The fact that this patient did not have other clinical manifestations or causes of embolic stroke to support these MRI findings may sustain the hypothesis that synthetic marijuana can result in direct neurotoxicity, presumably by affecting mitochondrial function similar to tetrahydrocannabinol

(THC) [4]. This pattern is that of a global hypoxic ischemic injury.

Other MRI findings reported in a 24 year old male with a first time seizure after Spice use included diffuse sulcal FLAIR hyper intensity as well as leptomeningeal enhancement on post contrast imaging (Figure 3). Such

findings denote how important it is for medical physicians to consider synthetic marijuana intoxication in the differential diagnosis of a first time seizure. Identification of the aforementioned imaging findings can also be valuable for early diagnosis of synthetic marijuana toxicity, which has become an increasing issue in the emergency setting [5].

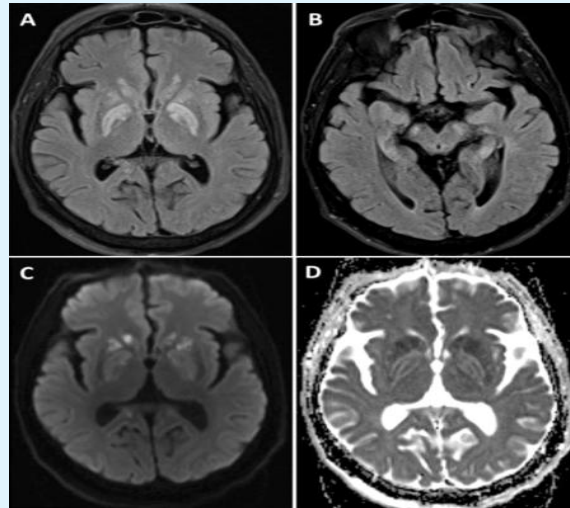


Figure 1: MR images of the brain of a 50 y/o patient following synthetic cannabis use. (A) The basal ganglia and (B) the hippocampi and cerebral peduncles exhibit FLAIR hyper intensities bilaterally. Panels C & D show symmetric restricted diffusion in the basal ganglia bilaterally demonstrating: (C) “hyper intensity on diffusion weighted imaging (DWI) and (D) hypo intensity on the apparent diffusion coefficient (ADC) map” “Courtesy of Sherwani et al., 2015”[4].

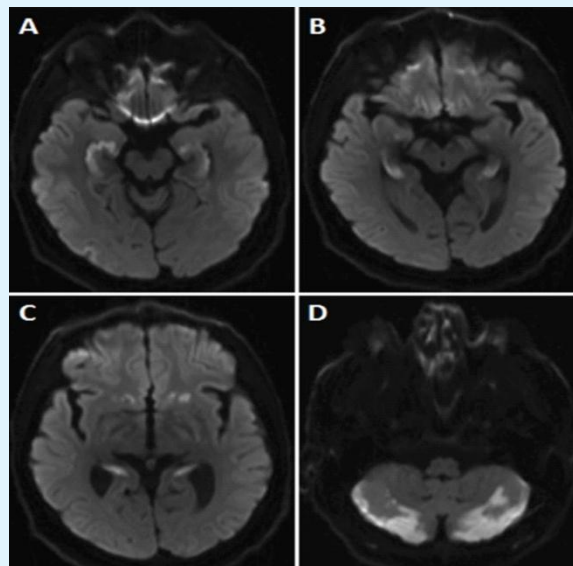


Figure 2: DWI images of the brain demonstrate “symmetric pattern of restricted diffusion” that correlated with areas of hyper intensities on FLAIR images (not presented) “Courtesy of Sherwani et al., 2015” [4].

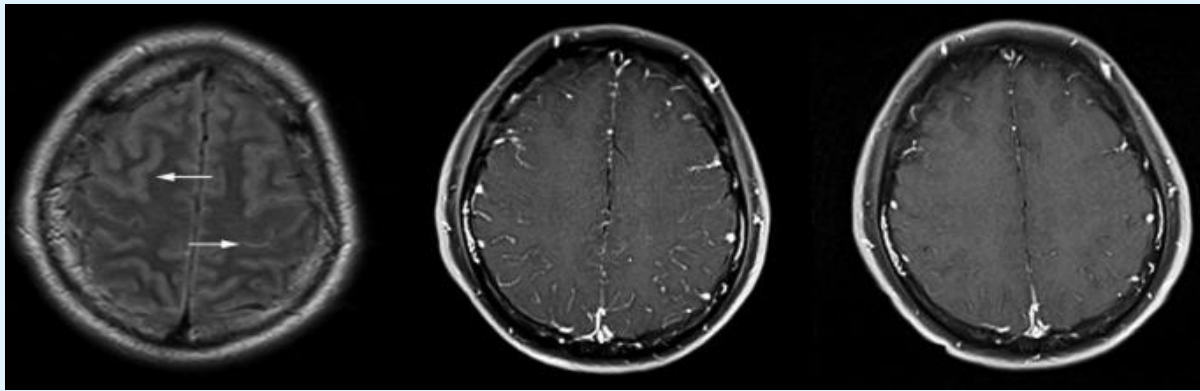


Figure 3: Initial T2-weighted MR FLAIR image of the brain demonstrates bilateral sulcal hyper intensity (white arrows) on the far left in this 24 y/o following Spice use. Initial T1-weighted post-contrast image shows diffuse leptomeningeal enhancement (middle image). Follow-up T1-weighted post-contrast image taken 2 weeks later, demonstrates resolution of leptomeningeal enhancement (far right) "Courtesy of de Havenon et al., 2011" [5].

Synthetic Cathinone ("Bath Salts"/Bliss/Ivory Wave)

More recently, new designer drugs have emerged with vigorous addictive potential such as synthetic cathinones ("Bath Salts"), also labeled as Bliss, Vanilla Sky, and Ivory Wave. These synthetic drugs stimulate the central nervous system by inhibiting the reuptake of norepinephrine and dopamine leading to severe CNS adverse effects or even death. These stimulants are usually snorted / sniffed, but can be smoked, taken orally or injected. Their symptoms include insomnia, depression, suicidal ideation, seizures and panic attacks as well as tachycardia that could lead to myocardial infarction (heart attack) and stroke. Bath salts have similar effects to other CNS stimulants such as cocaine, which is known to induce acute intraparenchymal and subarachnoid hemorrhage as well as ischemic infarction [2].

Kramer et al. identified abnormal diffusion restriction in the splenium of the corpus callosum and subcortical white matter in a case of a 36 year old man with bath salt intoxication, accompanied by dysautonomia and encephalopathy [6]. Kramer, et al. also demonstrated subcortical white matter signal abnormalities on brain MRI in a 14 year old girl with onset of hyponatremia after synthetic cathinone use [7].

In a previous animal research study, functional magnetic resonance imaging (fMRI) of male rat brains showed significant reduction of neural connectivity, especially between the frontal cortex and striatum, including connectivity between the prelimbic prefrontal

cortex and other frontal cortical regions and the insular cortex with the dorsal, ventral and hypothalamic striatal regions, after administration of one dose of MDPV (Methylenedioxypropylvalerone), one of the most potent bath salts. A similar disruption of brain functional connectivity has been observed in patients with psychosis and associated with cognitive dysfunction, visual and auditory hallucinations. These findings suggest that disruption of such neural connectivity could contribute to the harmful effects of MDPV. Sequential direct imaging of these brain alterations may represent a potential marker for future development of treatment for bath salts intoxication and understanding of their detrimental effect in humans [8].

MDMA (Ecstasy/Molly)

3, 4-Methylenedioxy-methamphetamine (MDMA) is a synthetic drug of the phenethylamine class and shares similar chemical properties with stimulants and hallucinogens. It affects the brain by increasing the activity of dopamine, norepinephrine and serotonin. However, compared to methamphetamine, MDMA causes a greater release of serotonin, but a lesser release of dopamine. This relative excess in serotonin release may account for the mood elevating effects seen in MDMA users. Subsequent depletion in brain serotonin reserve may be involved in the long-lasting depression, confusion, and selective injury in working memory and attention activities seen in chronic MDMA users. Imaging findings in ecstasy users include alterations in brain activity in areas that have a role in emotion, cognition and motor function, which corresponds to their euphoria, distorted perception

of time and increased motor activity. Ecstasy is primarily administered orally [9].

A prior study by Watkins et al. demonstrated higher brain activity in fMRI of both the right and left hemisphere during semantic processing in ecstasy poly drug abusers when compared to control subjects while preserving behavior. Particularly, the right superior parietal lobule and left precuneus exhibited the highest activation including regions within Brodmann Areas 7, 39 and 40. Lifetime abuse of ecstasy correlated with rising intensity of BOLD (blood-oxygen level dependent) signal in the right parietal region, with a statistical significance ($p=0.042$). Such significant findings were not found within the left hemisphere. This may indicate the right hemisphere could be more vulnerable to the prolonged neurophysiological effects observed after ecstasy use. This study supports prior records associating lifetime use of ecstasy with disrupted functional neural connectivity. Congruent findings have been demonstrated in Alzheimer patients during semantic object naming activity. Additionally, the behavior of ecstasy polydrug users was not affected in the face of increased brain activity, which supports the hypothesis that ecstasy polydrug users have decreased cortical efficacy in the process of semantic encoding, probably due to neurotoxicity of 5-HT by ecstasy.

A possible drawback of the aforementioned study was the difference in polydrug exposure between subjects and controls. Additionally, unrecognized factors, such as socioeconomic, genetic or environmental, other than ecstasy could have played a role on the observed MRI findings. Further studies on brain activity are encouraged to support these findings and identify whether this augmented cortical excitability after ecstasy use has significant clinical implications, such as cognitive decline, seizures or lower excitability threshold, and whether similar alterations in brain activity are observed after incident MDMA use [10].

Other studies that have evaluated the effect of ecstasy on the human brain by means of diffusion and perfusion MRI, have found significantly higher apparent diffusion coefficients (ADC) ($p<0.025$) and ratios of relative cerebral volume in the globus pallidus of ecstasy users as compared with controls (Figure 4). Moreover, the increased cerebral volume in the globus pallidus was directly correlated with the time frame of ecstasy use ($p<0.04$). These findings agree with those of previous studies proposing that the globus pallidus is especially susceptible to the effects of ecstasy [11].

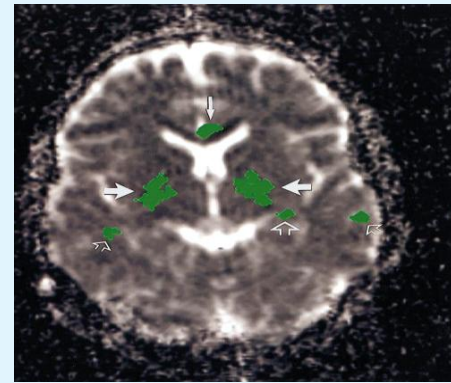


Figure 4: ADC map acquired after voxel evaluation to contrast “mean ADC values between ecstasy nonusers and ecstasy users.” The green areas denote considerably greater ADC values in ecstasy users versus ecstasy nonusers. These areas are localized in “the bilateral globi pallidi (thick solid arrows), the cingulate gyrus (thin solid arrow), the bilateral temporal cortex (small open arrows), and the left parahippocampal gyrus (large open arrow)” “Courtesy of Reneman et al., 2001” [11].

N-Bomb (Smiles, 25i)

N-bomb is another phenethylamine with potent central nervous system stimulant and hallucinogenic properties mimicking LSD or mescaline (a hallucinogen derived from a cactus plant) that acts as a full agonist of the serotonin receptor, 5-HT_{2A}. Some of its adverse effects include confusion, agitation, seizure, hyperpyrexia, clonus, visual and auditory hallucinations, rhabdomyolysis and even death. It is more commonly administered via the oral or sublingual route [12]. LSD users have shown decreased connectivity within brain networks and increased connectivity between brain networks that do not usually interact on brain fMRI. Particularly, the visual cortex has exhibited more communication with other brain regions, accounting for the vivid hallucinations experienced by LSD users [13]. Yet, N-bomb may have a permanent deleterious effect on the central nervous systems as suggested by a previous case study of a 16-year-old boy presenting with seizure like activity and hallucinations, severe ataxia, left sided weakness, difficulty with activities of daily living and higher executive dysfunction after ingesting N-bomb about 18 months prior to his admission. MRI demonstrated scattered foci of FLAIR hyper intensity throughout the cerebral white matter (Figure 5) correlating with toxic leukoencephalopathy. Even though there are few treatment options, prompt recognition of

cerebral structural alterations by this drug as demonstrated by MRI could hasten rehabilitation depending on the extent of damage [14].

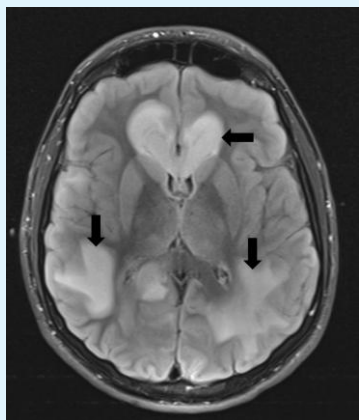


Figure 5: MRI of the brain of 16 y/o boy presenting with seizure 18 months prior to ingestion of N-bomb. There is increased T2-weighted signal intensity (black arrows) showing toxic leukoencephalopathy “Courtesy of Humston et al., 2017” [14].

Ketamine (Cat Valium, Jet, Special K)

Ketamine is a dissociative anesthetic with some hallucinogenic properties that cause dissociation, sedation, hallucinations and amnesia. It is available in powder or liquid form and is usually injected, mixed into

drinks, snorted or smoked by young adults [1]. Chronic ketamine use causes damage to many organs such as the brain. Yet there is only one study documenting brain changes via MRI in 21 chronic ketamine addicts of 0.5 to 12 years, some of which were apparent 2 to 4 years after ketamine addiction. Such changes included cortical atrophy in the frontal, parietal or occipital cortices. The initial lesions on T2-weighted imaging appeared as patchy hyper intense foci throughout the subcortical white matter after only one year of ketamine addiction (Figure 6). By 3 years of addiction, these lesions extended into the internal capsule. After 4 years of addiction, similar hyper intense foci appeared to spread to the more inferior cerebral hemispheres, cerebellum, and the brainstem. During this period, areas of abnormal diffusion restriction correlated with FLAIR hyper intensities in the insula and parahippocampal gyrus. Yet, after 5 years of addiction, signal abnormality involving the parahippocampal gyrus was also evident. By 6 years, the striatum exhibited hyper intense lesions. After 7 years of addiction, cortical atrophy had extended to the frontal, parietal and occipital regions. One of the patients of this study was taking ecstasy and amphetamine in addition to ketamine and showed early cortical atrophy involving the rectus gyri after only 0.5 years of taking this combination of drugs. Similar findings were observed in another patient that had consumed a high dose of ketamine (3 g per during 3 years). In the rest of the patients, lesions in the midbrain appeared after 7 years of addiction. The aforementioned lesions persisted after 10 to 12 years (Table 1).

| Years of abuse | 0.5 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 10 | 12 |
|--|--------|----|----|---------|--------|----|---|---------|----|----|
| Cerebellum | -- | • | • | • | • | • | • | • | • | • |
| Patchy signal abnormality in cerebral white matter | • | • | • | • | • | • | • | • | • | • |
| Cortex | • + | -- | • | • ++ | • | • | • | • | • | • |
| Limbic System | -- | -- | -- | -- | -- | • | • | • | • | • |
| Internal Capsule | -- | • | • | • | • | • | • | • | • | • |
| Striatum | -- | -- | -- | -- | -- | -- | • | • | • | • |
| Diencephalon | -- | -- | -- | -- | • | • | • | • | • | • |
| Brainstem | -- | -- | -- | -- | • * | • | • | • ** | • | • |
| Cortical atrophy (frontal/parietal/occipital) | • | -- | • | • | • | • | • | • | • | • |

Table 1: Affected regions and atrophy in the brains of ketamine addicts in correlation with years of addiction

- = positive lesions ;
- = negative lesions

Severity of brain damage: Light (up to 2 regions), moderate (3-4 regions), severe (5 or more regions)

+ This is a patient on 3 types of abusive drugs including ketamine with previous early lesions

++This is a patient with 3g of ketamine per day

* First lesions emerged in the pons after 4 years of addiction

** The lesions in the midbrain emerged after 7 years of addiction

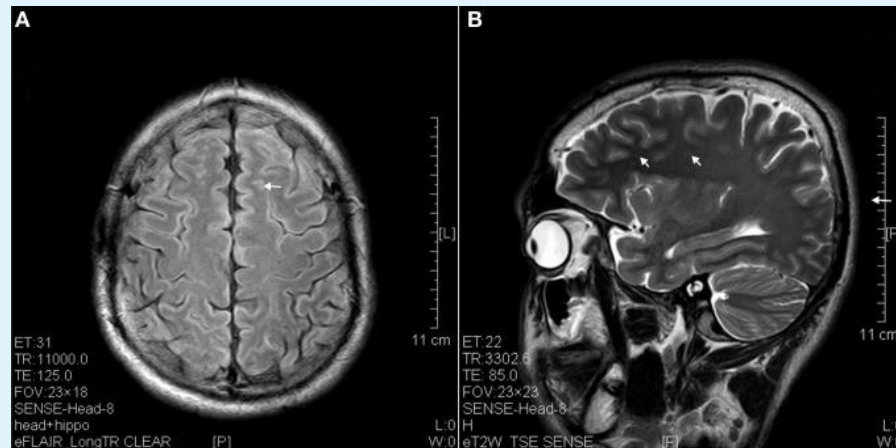


Figure 6: Examples of T2/FLAIR hyper intense foci (arrow) involving the subcortical white matter of ketamine addicts. “(A) FLAIR sequence of a 1-year ketamine addict. (B) T2-weighted sequence of a 3-year ketamine addict”“Courtesy of Wang et al., 2013” [15].

In this study MRI proved to be a valuable tool to detect the widespread brain damage that even a single drug such as ketamine leads to after just a few years of addiction. It also illustrated how increasing dosage or combining ketamine with other drugs of abuse could accelerate the damages [15].

N- Methylamphetamine (Meth, Ice, Glass)

N-methylamphetamine is another common synthetic drug with strong CNS stimulant properties that cause long-lasting harm to the dopaminergic and serotonergic brain pathways. The induced release of dopamine into brain regions involved in feelings of pleasure can result in the rush of intense sensation experienced by meth abusers [2]. Chronic meth abuse is also associated with violent behavior, confusion, insomnia, and psychotic features. The drug can be swallowed, smoked, snorted or injected. Meth shares similar effects with other stimulants such as amphetamines, which have been found to decrease cortical gray matter volume and increase striatal volume on MRI [16]. However, there have been limited imaging studies performed in meth users. Yet, a recent innovative study involving 22 subjects with a history of crystal meth use utilized MRI to create comprehensive spatial cortical maps to assess irregularities in their cortex, white matter, hippocampus and ventricles. These maps showed a significant level of gray matter scarcity in the paralimbic, limbic and cingulate cortices ($p < .05$).

Crystal meth abusers had a 7.8% decrease in the volume of the hippocampus as compared with controls, with an associated decrease in memory performance ($p < 0.01$) as well as substantial white matter hypertrophy ($p < 0.01$). The cingulate gyrus was the region affected the most, showing 11.3% volume loss when compared to the average of controls ($p < 0.05$). According to these MRI findings, prolonged methamphetamine abuse triggers selective cerebral damage that negatively affects memory function. It could also influence the cingulate-limbic pathways and medial temporal lobe leading to neuroadaptation or even cell death. Further studies are encouraged to correlate these structural alterations to already established metabolic changes and exhaustion of dopamine and serotonin receptors. In this effort, MRI may provide key features to estimate the integrity of the cortex and hippocampus and determine the clinical implications of these findings [17]. A previous case study of a 38 year old man intoxicated with crystal meth and with significant neurological manifestations showed prominent white matter FLAIR hyper intensities involving all the lobes of the cerebral hemispheres (Figure 7). They corresponded to hypo intense foci on the T1-weighted sequence and abnormal diffusion restriction. Therefore, white matter signal changes can be contributed to crystal meth intake in patients suspected of drug abuse or overdose, and MRI can be a beneficial tool to demonstrate these brain abnormalities [18].

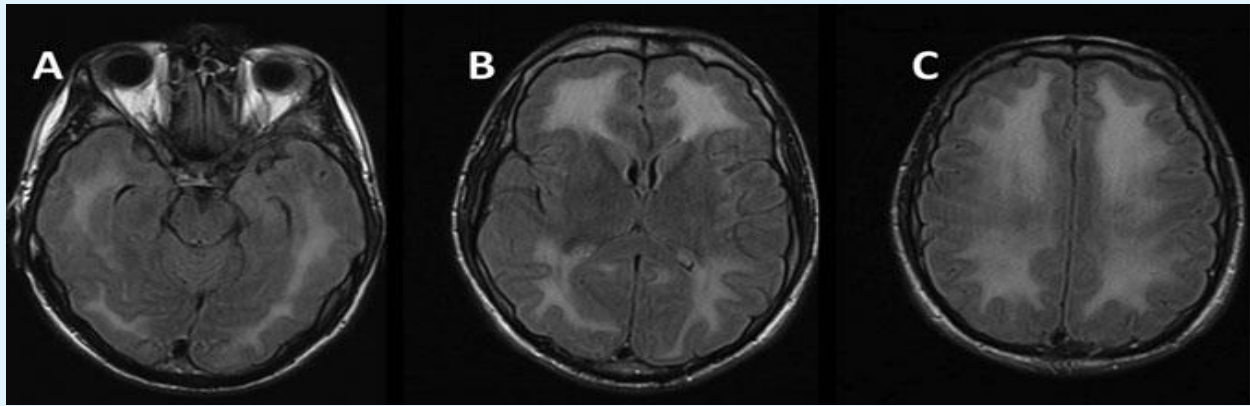


Figure 7: 38 y/o following metamphetamine use with FLAIR imaging showing confluent signal hyper intensity of the supratentorial white matter “Courtesy of Mobius et al., 2014” [18].

Methadone (Saliva, Waver, Amidone)

Methadone is a synthetic narcotic that stimulates receptors and has similar effects yet different chemical properties as morphine or heroin. It can be used to manage pain and opioid addiction and can cause drowsiness, constipation, weakness, sweating, and mood swings among others. It is usually swallowed or injected [2]. Previous studies have associated intoxication with other synthetic opioids, such as oxycodone, with significant toxic leukoencephalopathy of the basal ganglia, especially the globi pallidi externa [19]. In contrast, a couple of cases of methadone intoxication in children have resulted in bilateral cerebellar edema (Figure 8), as reported in a case of delayed encephalopathy in a 30-month-old girl presenting with coma after methadone intoxication. A couple of days following the intoxication, she manifested psychomotor agitation, ataxia, slurred speech, and abnormal movements. An MRI 19 days after the intoxication revealed signal abnormalities in the hippocampi, basal ganglia, substantia nigra, trapezoid bodies, and central tegmental tracts [20]. MRI findings on a similar case of a 3 year old girl presenting with cerebellitis after methadone ingestion showed diffuse cerebellar edema, effacement of the fourth ventricle with resulting obstructive hydrocephalus, and watershed zone acute infarcts [21]. One plausible theory that may explain the selective involvement of the cerebellum is that synthetic opioids have a high affinity for the mu opioid receptors, which are more concentrated in the cerebellum and limbic system, according to human postmortem studies [19].

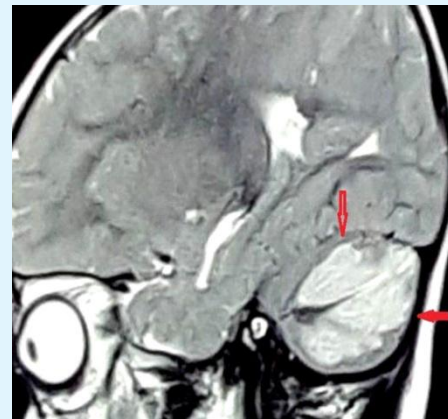


Figure 8: 3 y/o following ingestion of methadone demonstrating diffuse cerebellar edema manifested by diffuse FLAIR hyper intensity involving the bilateral cerebellar hemispheres in a patient under the influence of synthetic opioids “Courtesy of Hosseini et al., 2017 [22].

Fentanyl (King Ivory, Jackpot, Apache)

Fentanyl is a synthetic opioid with an analgesic effect 100 times stronger than morphine. It can be injected, smoked, sniffed or taken orally. A fentanyl patch is abused by releasing its gel content and then ingesting, injecting, or placing it under the tongue in small pieces for lingual absorption. Analogously to other opioids, fentanyl is a selective receptor agonist with quick duration of action that leads to euphoria, relaxation, sedation, respiratory depression, pupillary constriction and pain relief. The

transdermal fentanyl patch has been employed to manage acute and chronic pain in patients not responsive to less strong analgesics [2]. However, it can have deleterious CNS effects when used on a long term basis. In a case report by Sub Yoo, et al. an 85 year old man developed mental decline, hypoxia, pupillary miosis, semi-coma, subsequent gait impairment, akinetic mutism, memory loss and reduced activity of daily living among other neurological deficits after attaching a fentanyl patch. More than a month after the hypoxic episode, Brain MR findings showed confluent symmetric bilateral cerebral periventricular white matter FLAIR hyper intensities (Figure 9), suggestive of delayed hypoxic leuko-encephalopathy [23]. This case is another great example for the benefits of MRI as a tool for early detection of acute neurological decline in an otherwise healthy elderly patient.

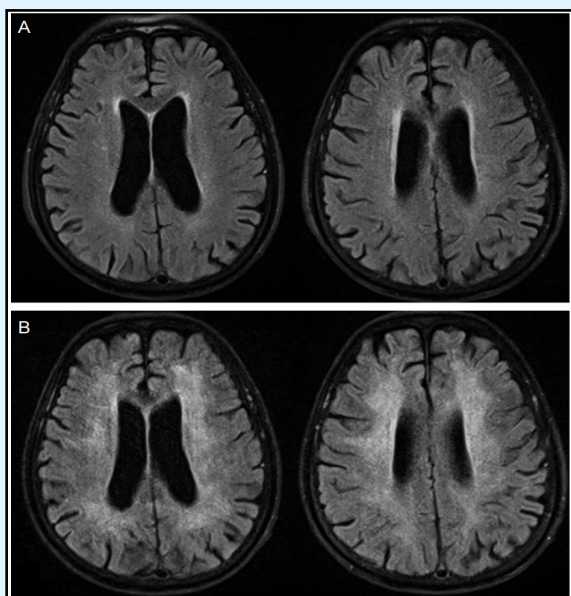


Figure 9: FLAIR images of the patient A) on initial admission and B) 40 days following contact with fentanyl patch reveals symmetrical areas of signal hyperintensity in the deep and periventricular white matter, bilaterally, excluding the gray matter "Courtesy of Sub Yoo, et al., 2015" [23].

Anabolic Androgenic Steroids (Pumpers, Gear, Juice)

The use of anabolic-androgenic steroids (AAS), which are synthetic variation of testosterone, has been linked to psychiatric symptoms such as increased aggression and cognitive impairment. However the long term adverse

effect of AAS on the human brain has not been well studied. A recent study comparing matched controls to the MRI and fMRI findings of 10 male weight lifters with long-term use of AAS found they had right amygdala enlargement ($P=0.002$) and decreased resting state functional connectivity between the right amygdala and brain regions associated with spatial memory and cognitive function, such as the hippocampus, amygdala, striatum, and frontal cortex. These findings could account, in part, for the psychiatric and cognitive dysfunctions seen in AAS users. They had decreased dorsal anterior cingulate cortex scyllo-inositol levels ($P=0.004$) and increased glutamine/glutamate ratios ($p=0.028$). AAS users also had an inferior performance on visuospatial cognitive tasks when compared with controls ($P=0.053$). The MRI irregularities found on this study could suggest increased glutamate turnover and enhanced susceptibility to neurodegenerative or neurotoxic events, which could be linked to the cognitive impairment related to AAS use [24].

Methcathinone (Ephedrone, Cat, Jeff)

Methcathinone (Ephedrone, Cat, Jeff) is an addictive psychoactive stimulant that shares chemical properties and clinical effect with both cathinone and methamphetamine. Similarly to these drugs, ephedrone regulates the level of serotonin, dopamine and norepinephrine. It also heightens the flight or fights reflex and increases feelings of euphoria, blood pressure, body temperature and heart rate. Additionally, Ephedrone creates feelings of irritability and moodiness by decreasing the levels of serotonin. Its prolonged use is also associated with depression, insomnia and psychosis. Although the drug is mostly inhaled, it can also be smoked, injected or ingested [25]. Few studies have explored the neurotoxic impact of ephedrone abuse on the brain. In a study by Okujava, et al. MR imaging of 38 patients with ephedrine induced encephalopathy revealed T1 hyper intense signal in the globus pallidus in 31 patients. Twenty six of these patients had additional T1 hyper intensities in the substantia nigra, 17 in the dentate nucleus of cerebellum, 11 on the anterior pituitary gland, and 3 in the bilateral cerebral white matter (Figure 10). Most of these patients presented with ataxia, postural disturbances, dysarthria, facial and lower extremity dysphonia, as well as bradykinesia. Ephedrone abuse for longer than 6 months was correlated with significant disability that did not regress nor improve despite drug cessation. Even though the abnormalities on MR were more prominent in patients with recent frequent methcathinone use, this had no impact on the severity of their clinical presentation [26]. These clinical findings

correlate with the proposed methcathinone-induced Parkinsonism seen in different patients after intravenous administration of ephedrone due to manganese intoxication, which is a highly neurotoxic component of this drug. Such patients have also shown increased signal

intensity in the globi pallidi, midbrain, pituitary gland, and cerebellar hemispheres. MRI of the brain is a useful tool in the comprehensive evaluation of ephedrone encephalopathy, which may aid in early detection and diagnosis of this condition [27].

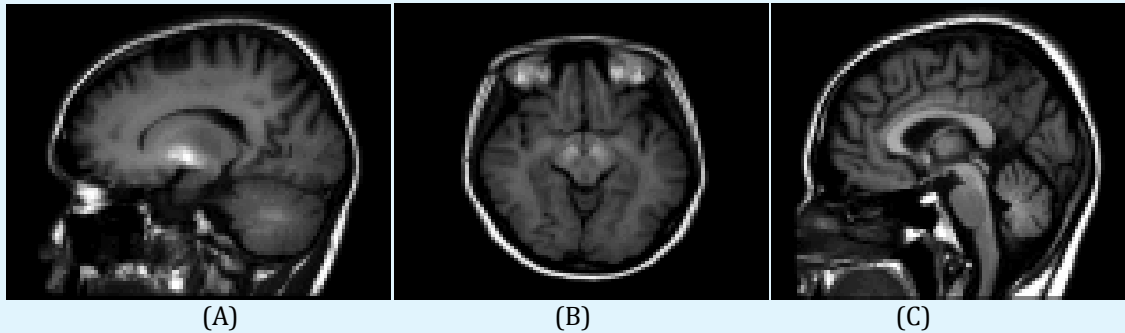


Figure 10: “Brain MRI T1-weighted sequence of a patient with ephedrone encephalopathy”: A) T1 hyper intense signal in the cerebellar white matter and globi pallidi, B) cerebral peduncles, and C) anterior pituitary gland “Courtesy of Okujava et al, 2017”[26].

Conclusions

The incidence of abuse of new designer synthetic illicit drugs has substantially increased in the past decade. These drugs have detrimental (and often irreversible) effects on the brain and primarily affect the central nervous system by two mechanisms: 1) Neural hyper stimulation via increasing activation of certain neurotransmitters (norepinephrine, dopamine, and serotonin), 2) Cause significant reduction in CNS neural connectivity affecting various brain regions such as the basal ganglia, hippocampus, cerebellum, parietal lobe, and globus pallidus. These CNS alterations are otherwise typically manifested in the clinical settings of psychosis, depression, suicidal thoughts as well as motor, memory and executive dysfunction.

Understanding these subtle and overt findings in the setting of brain alteration due to synthetic drug abuse can help with early detection, diagnosis, confirmation, and subsequently offer prognosis of brain tissue damage in the clinical setting. In addition, neuroimaging can aid with prompt recognition of the exact location and extent of pathology, therefore distinguishing which specific drugs may have been used and therefore guide treatment options. For instance, imaging correlation can significantly hasten initiation of rehabilitation or other

supportive care by identifying the level and location of damage.

Indeed, from a research standpoint, neuroimaging offers strong value in deciphering how certain brain structures are affected by each synthetic drug, thereby directing future research and facilitating development of more selective treatment options. Further investigations are necessary and encouraged for better correlation of imaging findings to each class of these new designer synthetic drugs.

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