Influence of Prenatal Methamphetamine Abuse on the Brain

Methamphetamine (MA), a psychostimulant, has become a serious problem in recent years. It is one of the most widely abused psychostimulants in the world.

1. Introduction/Background

1.1. Drug Dependence

Addiction is a set of behavioral, cognitive, and physiological conditions. The main cause for its development is the repeated use of addictive substances; typical symptoms include a strong preference for using the substance repeatedly, altered consciousness after use, and persistent usage despite the damaging effects. Additionally, use of the drug takes priority over other activities and commitments, there is a gradual increase in tolerance, and somatic withdrawal sometimes occurs when use of the substance stops. A frequent motive for substance abuse is curiosity, which can subsequently lead to a state of addiction. Many users first try the drug in order to find out "what's it like" [1]. Other possible motives include stress or problems that the individual is incapable of coping with in any other way, leading to drug use as a means to escape reality. Drug addiction is a global problem. It directly affects a large part of society, and its indirect effects on the families and surroundings of users are even more extensive (**Figure 1**).
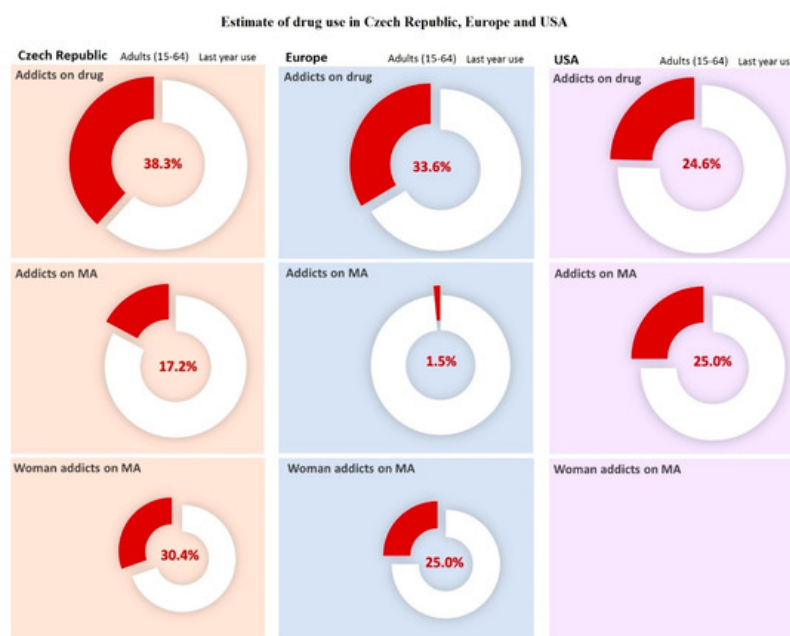

Figure 1. Estimates of drug use in Czech Republic, Europe, and USA. Data was carried out in selected countries over a year in 2017. For American female addicts of methamphetamine (MA), data are not available. For the Czech Republic, the population was estimated at 10,665,677 people for the year 2018 according to United Nations data. Data adopted and modified according to National Monitoring Center for Drugs and Addiction, Annual Report [2]. For Europe, the population was estimated at 513,000,000 people for year 2018 according to Eurostat. Data taken over and modified by The European Monitoring Center for Drugs and Drug Addiction [3]. For USA, the population was estimated at 327,200,000 people for the year 2018, according to United Nations data. Data taken over and adjusted by the National Institute on Drug Abuse [4].

In reducing drug usage, prevention is an important factor. In the prevention of addiction and the use of alcohol and non-alcoholic drugs, the World Health Organization (WHO) distinguishes three targets: (1) primary prevention, i.e., preventing drug use in those who have not had direct contact with the drug; (2) secondary prevention, i.e., preventing addiction in drug users; and (3) tertiary prevention, i.e., preventing the serious and lasting health and social problems created by using drugs, including both resocialization or social rehabilitation and measures aimed at decreasing the transmission of infectious diseases during intravenous drug application (e.g., harm reduction programs) [5].

The initial phase of drug addiction, i.e., when the user is experiencing euphoria and is still discovering the drug's effects, is called the phase of experimental use. During the phase of social use, the user begins to take the drug more regularly, often at higher doses; during this phase, addiction begins to show and the drug slowly becomes a source of various problems. In the course of everyday usage, the drug begins to impact such things as daily routines, moral values, employment, and friendships. Ultimately, the user loses control of their addiction [6]. Chemical dependency (i.e., the need for more of a substance to get the same effects) marks the last stage of addiction, often ending in a fatal overdose or total organ failure.

The treatment of drug addiction is a very complicated and complex process, since addiction affects not only the physiology but also the psychology of the affected individual, often requiring the complete removal of the user from their social environment [6][7][8]. The final goal of treatment is to completely eliminate the addiction. Treatment progresses gradually, since overly quick withdrawal can produce unwanted side-effects, including potentially health-threatening complications [9].

1.2. Stimulant Drugs: Characteristics and the General Mechanism of its Effect

This paper will focus on the effects of methamphetamine (MA), which is considered a stimulant. Stimulant drugs can be further specified as psychostimulants, psychoanaleptics, psychomimetics, and psychomotor stimulants [9]. Caffeine can be undoubtedly be considered the most famous stimulant, whereas amphetamines represent a significant group of illegal stimulants. Other examples include cocaine and its subsequent product, "crack", as well as "party drugs", which are derived from amphetamines [9]. Psychostimulants have strong stimulant effects, affecting not only the central nervous system (CNS), but also the organism. The typical effects of this group of substances include increased wakefulness, shorten sleep cycles, suppressed fatigue, accelerated thinking, improved association and memory, euphoria, and a pleasant feeling of both mental and physical strength [10]. The stimulant effect also leads to increased blood pressure and pulse rate (potentially inducing a hypertensive crisis), changes in blood distribution in favor of muscle tissue, and increased muscle tone. Additionally, there is bronchodilation, which leads to shallow breathing [8][10].

The mechanism of these effects is based on direct interactions with neurons and the information transmitted between them. The mechanisms differ among specific substances, yet the basic principle remains the same, i.e., the substances in question increase the mediator concentration in synapses between neurons, with the effect of altered signal transmission. MA, for example, has a destructive influence on dopamine nerves and their endings. Due to adaptive cellular mechanisms, tolerance and addiction develop after repeated usage.

Several mechanisms participate in the development of addiction. Neuroadaptations, which are changes in the organism directed at maintaining homeostasis, is one of them. After the drug effects fade, withdrawal syndrome appears, with typical symptoms including generalized exhaustion, intense fatigue, and widespread body pain. Frequent mood changes and depression are also present. This state usually subsides relatively quickly; however, in some cases, it can persist for several days. Psychostimulants can also lead to anxiety, increased nervousness, and depression. Even a single use can potentially induce a panic attack [11]. Long-term usage can lead to psychosis, with states of paranoia, feelings of persecution, and feeling of being under threat [12]. These problems develop after ingestion of a psychostimulant and cannot be simply explained by the intoxication, yet are not a part of drug cessation states either. Ceasing drug usage is not guaranteed to resolve these problems [13].

2. Methamphetamine

Methamphetamine (also pervitin, methylamphetamine, desoxyephedrine, and methedrine) belongs to the group of wake-promoting amines [14]. The first discovered member of this group, amphetamine, was synthesized in 1887. The group of wake-promoting amines includes hundreds of substances, which were (and still are) often used as a treatment for exhaustion, narcolepsy, increased appetite, and sometimes abused by the military in order to increase the performance of combat units. The base substance for MA synthesis is ephedrine, along with lye and red phosphorus used in its manufacture. A minimum level of knowledge of at least high school grade is generally required, since when done imperfectly this may threaten the health of the user [9]. Pure MA can be obtained in crystalline form; it is, however, more

common to be sold as a microcrystalline white powder with a bitter taste and without a perceptible aroma. Due to the presence of additives originating from home manufacturing, the powder often has a yellow or purple discoloration [15].

MA can be classified as a non-catecholamine sympathomimetic substance, showing a sympathomimetic effect even without possessing the catecholamine structure [14]. MA exhibits stimulatory effects on the CNS [16][17][18] by releasing noradrenaline (NA) from noradrenergic neurons that act on alpha receptors [19]. Amphetamines, on the other hand, have little influence on these receptors. Both serotonin (5-hydroxytryptamine; 5-HT) and dopamine are also released after the administration of MA, leading to increased psychomotor activity. MA initially induces alertness, suppresses fatigue, and increases energy; with higher doses, it produces feelings of euphoria, blissfulness, and increased self-confidence [20][21].

MA accelerates heart activity and increases blood pressure, which leads to hyperthermia, bronchial dilation, and pupil dilation [22]. A strong psychological addiction is created with MA, but without physical addiction [23]. MA is well absorbed by the gastrointestinal tract and mucous membranes. Its lipophilic character enables it to pass through the blood–brain barrier with greater ease compared to amphetamine [24]. Once in the CNS, MA causes an increase in monoamine mediator (dopamine, noradrenaline, serotonin) concentrations in the synapses and in the cytosols of neurons. Simultaneously, neurotransmitter reabsorption is inhibited and the degradation of MA is reduced [25]. In high doses, monoamine oxidase (MAO) is also inhibited. Drug inactivation via MAO is prevented due to the presence of a methyl group on the alpha carbon [24]. Benefiting from this protection, MA is widely distributed throughout the body, and its biological half-life is 12 to 34 h [26].

After the effects subside, there is a lack of neuromodulators, leading to an unpleasant state, which is often called withdrawal syndrome. During long-term use, irreversible changes appear in the mitochondrial metabolism, potentially leading to apoptosis of the damaged neuron [25]. Sexual activity is also affected by long-term use. Other effects include increased nervousness, restlessness, insomnia, bruxism, reduced appetite, and subsequent weight loss [27]. Restlessness and paranoia may potentially lead to paranoid psychosis, which can recur even after discontinuation of drug use [28].

Research has determined that different animal species metabolize MA differently. Rats, for example, use aromatic hydroxylation during its metabolism, whereas rabbits use deamination [24][29]. In humans, a substantial amount of MA is excreted via the urine in an unaltered form (approximately 45% within 24 h). Excretion is highly dependent on pH; while up to 76% can be excreted in acidic urine, only about 2% can be excreted in alkaline urine [30][31]. MA metabolites are also excreted in urine—approximately 15% is metabolized by hydroxylation in the liver to hydroxymethamphetamine. About 7% is metabolized by N-demethylation to amphetamine, which is further processed to hydroxyamphetamine (2–4%) and norephedrine (2%), and subsequently hydroxynorephedrine (0.3%) and phenylacetone (0.9%), which are metabolized to benzoic acid and hippuric acid, respectively [24][29].

3. Influence of Methamphetamine on the CNS and on Selected Parts of the Brain

Every living organism strives for a dynamic balance, called homeostasis. While under the effect of addiction, this balance is threatened by distinct physical and cognitive events, leading to increased stress in the addicted individual [32][33]. Consequently, their behavior is changed; unless the event corresponds to a cognitive depiction based on previous subjective experience, it is accompanied by an increase in excitement, alertness, and cognitive processing [34][35][36][37][38] [39]. The interface between the incoming sensory input and the evaluation process consists of limbic brain structures, including the hippocampus and prefrontal cortex, and the structures directly influencing the limbic system, i.e., the striatum [40].

The control areas in the brain send signals that configure the processing of incoming sensory inputs from moment-to-moment [37][41]. Humans possess unique cognitive flexibility. The brain control system consists of functionally diverse areas that are anatomically separated from the remaining systems of neural response processing [41].The ability to perform countless tasks requires control functions that persist in time and that are capable of not only preventing attention diversion, but of responding quickly to unpredictable demands as well [33].

The selection of samples from rat brains was based on the fact that MA interferes mostly with dopaminergic and serotonergic neural response pathways. MA enters the terminals or neuron via the monoamine transporters (dopamine transporter, serotonin transporter, or norepinephrine transporter), displaces both vesicular and intracellular monoamines, and facilitates the release of monoamines into the extraneuronal space by synaptic transport in the monoamine transporters. Both pathways (dopaminergic and serotoninergic) connect parts of the brain responsible for motor control, fear, pleasure, reward, and addiction mechanisms (**Figure 2**) [22][42].
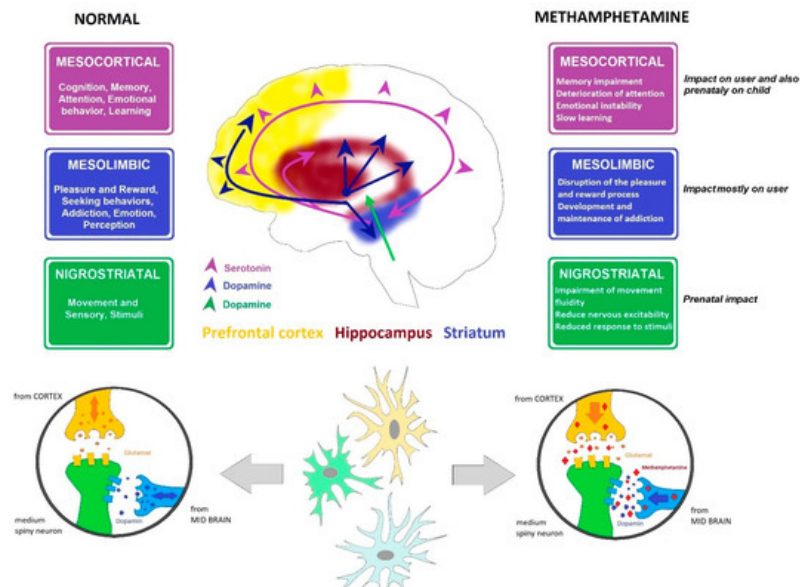
Figure 2. Dopamine and serotonin pathways. Cross-section through the brain showing dopamine and serotonin pathways and their main functions, including affection, mood, memory, sleep, pleasure, reward, and compulsive behavior, and the influence of MA.

3.1. Dopaminergic System

Dopamine is a neurohormone; its release from the hypothalamus inhibits prolactin secretion from adenohypophysis, affects motor system control in the CNS, initiates various behavioral pattern, and modulates the activity of visceral functions. Dopamine is a low molecular weight neurotransmitter and is categorized as a catecholamine. In the bloodstream, dopamine exhibits sympathomimetic effects, such as increasing the systolic blood pressure and the heart rate [43][44]. Dopamine is synthesized from tyrosine or phenylalanine and serves as a precursor for both adrenaline and NA; MAO and catechol-O-methyltransferase (COMT) can degrade it, with homovanillic acid being the final product [45].

Dopaminergic nuclei in the brain are designated as A8, A9, and A10. The most significant are located in the substantia nigra pars compacta (A9) and medially in the ventral tegmental area (A10). Fibers from the substantia nigra are projected into the striatum, and to a lesser extent into the globus pallidus. Fibers from the ventral tegmental area create the mesolimbic dopaminergic system, ending in the ventral striatum, ventral pallidum, septum verum, the amygdala, and the cerebral cortex, mainly the prefrontal cortex and primary motor cortex (**Figure 2**).

Reduced dopamine concentrations in the striatum causes hypokinesis and muscle tremors; lowering the concentration in the prefrontal cortex leads to memory, attention, and motivation disorders. Using MA increases the amount of dopamine accessible to D3 receptors [46], directly stimulating the reward center in the brain. Repeated administration of MA induces long-lasting deficits in the striatal concentrations of dopamine and its metabolites, tyrosine hydroxylase activity, and dopamine transporter binding sites [17][46].

MA causes degeneration of striatal nerve terminals, as shown by long-lasting depletion of dopamine concentration, dopamine transporter, and vesicular monoamine transporter 2 levels. The ability of MA to mobilize dopamine from intraneuronal stores to the extracellular space via dopamine-transporter-mediated outward transport results in elevated extracellular dopamine concentrations. The neurotoxic effects of MA are postulated to occur from subsequent auto-oxidation of dopamine to highly reactive free radicals [17][22][46]. An alternative model suggests that redistribution of dopamine from vesicular storage pools to the cytoplasmic compartment, allowing intraneuronal oxidation, is the primary cause of dopamine terminal injury [46].

The principle reason lies in the stimulation of the tyrosine kinase receptor (e.g., insulin-like growth factor 1 receptor (IGF-1R)). It is shown to mediate activation of the phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway, an important mediator of cell survival. PI3K is activated by estrogen, the G-protein-coupled estrogen receptor 1 (GPER1, also known as GPR30). Akt controls expression of the anti-apoptotic molecule Bcl-2 via the cAMP-response element-binding protein (CREB), and can also phosphorylate glycogen synthase kinase 3β (GSK3β) and BAD proteins, thereby inhibiting their pro-apoptotic functions [17][22].

This suggests that the balance among vesicular, cytoplasmic, and extracellular dopamine pools play a key role in the neurotoxic action of MA.

Long-term use leads to a loss of dopaminergic receptors and to reduced dopamine production in general, causing withdrawal states in addicted individuals and triggering the need to increase the dosage of the abused substance [47][48] (**Figure 2**).

3.2. Serotoninergic System

The serotoninergic system in the CNS has a regulatory effect on many functions and modulates the activity of other projection systems. This system is closely linked to the noradrenergic system, which it often supplements. Serotonin is derived from L-tryptophan as 5-HT. Serotonin inactivation is catalyzed through two enzymes, MAO and aldehyde dehydrogenase; the activity of these enzymes leads to the creation of 5–hydroxyindoleacetate (5-hydroxyindoleacetic acid), which is mostly excreted in the urine (as a glucuronic acid conjugate) [49]. Another serotonin metabolic pathway results in the synthesis of melatonin; initially, an acetyl group binds to the amino group of serotonin, resulting in N-acetylserotonin. Subsequently, a methyl group binds the hydroxyl group, creating melatonin.

There are seven known subtypes of serotoninergic receptors (i.e., 5-HT1-7R), both excitatory and inhibitory. The effect of serotonin is strongly dependent on the receptors expressed on the neurons of any given structure. The soma of most neurons in this system are in the raphe nuclei of the reticular formation. Their axons enter both ascending and descending columns, reaching all cortical areas (including the prefrontal cortex) and all limbic system structures (including the hippocampus), with others reaching the striatum, thalamus, hypothalamus, brain stem, cerebellum, and spinal cord. Excessive activity in ascending columns leads to mood changes and behavior disorders. The axons passing through the dorsal horn of the spinal cord are associated with pain transmission (**Figure 2**).

Reductions in forebrain concentrations of serotonin (5-HT) and its metabolites and a decrease of tryptophan hydroxylase activity after MA administration have been described. Lowered serotonin synthesis causes depression and sleep disorders [17][22][50]. MA also causes hyperthermia, which can be lethal. Release of monoamines into the extraneuronal space by synaptic transport in the monoamine transporters suggests that dopamine receptor activation is crucial for methamphetamine-induced hyperthermia. However, when dopamine pools are empty, serotonin starts to play the main role. MA exerts a hyperthermic effect via dopamine transporters, or via serotonin transporters if the dopamine transporters are absent [22].

3.3. The Striatum

The striatum (also called the corpus striatum) is grey matter deep in the telencephalon. It is considered the most significant part of the basal ganglia (evolutionarily one of the oldest structures). The basal ganglia participate in generating and controlling movement, cognitive functions, and the functions of the limbic system.

The basal ganglia are connected to various cerebral pathways; the general signal pathway leads from the cerebral cortex to the basal ganglia. The signal continues from the basal ganglia to the thalamus and finally back to the cerebral cortex. Four types of basal ganglia loops have been described: motor loops, oculomotor loops, limbic circuits, and associative pathways. While describing them, it is important to determine the part of the cerebral cortex from which the stimuli originate; furthermore, it is equally necessary to ascertain the ganglia involved, i.e., functioning as inputs or outputs, and the specific functional area of the cortex that is the intended destination. The information comes predominantly from the motor and somatosensorial areas of the cortex and enters the putamen, taking either direct or indirect pathways. The function of the direct pathway is to support the movement, while the indirect pathway inhibits the thalamus, which increases the excitatory influence on the cortex. Increasing the activity in the direct pathway leads to increased motor activity, while the indirect pathway serves mainly to suppress unwanted movements. The activity in both pathways should be balanced; disturbing this balance leads to hyperkinetic and hypokinetic disorders, respectively [32][51].

The substantia nigra pars compacta, which is rich in dopaminergic neurons, plays a substantial role in the modulation of pathway activity. Dopamine increases the activity of the direct pathway via D1 receptors, while also decreasing indirect pathway activity via D2 receptors ([32][45][52]. The basal ganglia participate in motor function control (and to some extent, cognitive function control as well). Generally, they exert an inhibitory influence on motor activity; motor cortex neurons suppress cortical stimuli both through direct feedback and through the reticular formation. The neurons are activated even before the movement begins, possibly indicating that they take part in its planning as well [52]. It is generally assumed that they also participate in the control mechanisms of intricate movement patterns, such as writing, ball games, and speech [53].

3.4. The Prefrontal Cortex

The prefrontal cortex represents one of the largest cortical areas of the human brain, accounting for roughly 29% of its volume, and is responsible for higher functions. The cortex area of the frontal lobe, which does not belong to motor areas, represents a significant part of the association cortex [54]. There are links to the visual, olfactory, and auditory cortices, providing integration of sensory inputs. The prefrontal cortex, which receives information from various sources, is responsible for planning, decision-making, and creating new ideas. It has connections to the entire brain, especially to the rostral thalamus.

It is the only area of the cortex with projections directly into the hypothalamus and septal areas, with a significant role in the regulation of the limbic system. There is a direct bidirectional link between them, with the prefrontal cortex taking part in learning and memory processes [54][55]. Damage to the prefrontal cortex manifests in severe psychological disorders, including apathy, memory loss, aggression, obsession, loss of social restraint, and emotional instability [54][56][57][58][59].

2.5. Hippocampus

The hippocampus is a paired structure in the telencephalon, occupying the middle part of the temporal lobe in both hemispheres. Information from the cerebral cortex and limbic system is processed in the hippocampus and subsequently sent to the frontal thalamus, then ultimately back to the cerebral cortex. This rhythmic, repetitive activity of the hippocampus creates a basis for complex integration processes, such as storing of information as long-term memory [60]. It is part of the limbic system, mediating both short-term and long-term memory and orientation in space [61][62][63]. The ability to orientate in space and time allows the individual to perceive their position in relation to their environment, as well as in relation to changes in velocity and positioning in time [61][64]. Any damage can manifest as learning disorders (long-term memory), disruptions to short-term memory, and even complete amnesia [65].

There is a large number of cells encoding the perception of space in the brain; they are located both in the hippocampus and in other structures, such as the cerebellum and cerebral cortex [66]. The structure of the hippocampus is essentially identical in most mammals [41][67][68][69]. If the subject is placed in a confined and defined space, the pyramidal cells in this area of the brain (along with the granule cells in the cerebellum) begin to produce strong excitatory signals [70][71][72][73]. An analysis of the involved cells can be performed using the open arena experiment with free movement or using either the radial or Morris water mazes [74][75]. The cells are less sensitive to the vertical dimension in land-based mammals (e.g., rats), while in bats all three basic dimensions produce strong signals [61][76]. The cells associated with head orientation, found in several brain structures linked to the hippocampus, were discovered by Taube et al. [77]. These cells produce signals when the animal looks in a certain direction; unlike the visual angle, the position in space is not relevant for the function of these cells.

Additionally, cells sensitive to both the head direction and general orientation of the animal in space were also found in the hippocampus [61][76][78]. Any disruption of this structure can lead to the emotional instability of the animal, manifesting as anxiety states, depression, or obsession [56][79][80][81][82].

References

1. Segal, B.; Morral, A.R.; Stevens, S.J. Adolescent Substance Abuse Treatment in the United States: Exemplary Models from a National Evaluation Study; Routledge: Abingdon, UK, 2014.

2. Office of the Government of the Czech Republic. Annual Report on the State of the Drugs Problem for the European Monitoring Center for Drugs and Drug Addiction: Czech Republic; Office of the Government of the Czech Republic: Prague, Czech Republic, 2018; ISBN 978-80-7440-219-7.

3. Staeheli, S.N.; Veloso, V.P.; Bovens, M.; Bissig, C.; Kraemer, T.; Poetzsch, M. LC-MS/MS Screening Method Using Information-Dependent Acquisition of Enhanced Product Ion Mass Spectra for Synthetic Cannabinoids Including Metabolites in Urine. Drug Test. Anal. 2019.

4. NIDA. Methamphetamine. Retrieved. Available online: https://www.drugabuse.gov/drugs-abuse/methamphetamine (accessed on 5 November 2019).

5. Walsh, N. Harm Reduction: Focal Point for Viral Hepatitis; World Health Organization: København, Denmark, 2019; Available online: https://www.who.int/hepatitis/news-events/03_prevention-preventing-infection.pdf?ua=1 (accessed on 9 May 2019).

6. Vindenes, V.; Yttredal, B.; Øiestad, E.L.; Waal, H.; Bernard, J.P.; Mørland, J.G.; Christophersen, A.S. Oral fluid is a viable alternative for monitoring drug abuse: Detection of drugs in oral fluid by liquid chromatography-tandem mass spectrometry and comparison to the results from urine samples from patients treated with methadone or buprenorphine. J. Anal. Toxicol. 2011, 35, 32–39.

7. Lindsay, M.K.; Burnett, E. The use of narcotics and street drugs during pregnancy. Clin. Obstet. Gynekol. 2013, 56, 133–141.

8. Sobell, L.C.; Sobell, M.B.; Ward, E. Evaluating Alcohol and Drug Abuse Treatment Effectiveness: Recent Advances; Pergamon Press: New York, NY, USA, 1980.

9. Švestka, J.; Češková, E.; Náhunek, K. Psychofarmaka V Klinické Praxi; Grada Publishing: Prague, Czech Republic, 1995.

10. Weiss, R.D.; Potter, J.S.; Griffin, M.L.; Provost, S.E.; Fitzmaurice, G.M.; McDermott, K.A.; Carroll, K.M. Long-Term outcomes from the national drug abuse treatment clinical trials network prescription opioid addiction treatment study. Drug Alcohol Depend. 2015, 150, 112–119.

11. McKetin, R.; Dawe, S.; Burns, R.A.; Hides, L.; Kavanagh, D.J.; Teesson, M.; Saunders, J.B. The profile of psychiatric symptoms exacerbated by methamphetamine use. Drug Alcohol Depend. 2016, 161, 104–109.

12. Birbaumer, N.; Veit, R.; Lotze, M.; Erb, M.; Hermann, C.; Grodd, W.; Flor, H. Deficient fear conditioning in psychopathy: A functional magnetic resonance imaging study. Arch. Gen. Psychiatry 2005, 62, 799–805.

13. Hebb, D.O. Textbook of Psychology, 3rd ed.; W.B. Saunders Company: Philadelphia, PA, USA, 1972.

14. McCusker, J.; Bigelow, C.; Vickers-Lahi, M.; Spotts, D.; Garfield, F.; Frost, R. Planned duration of residential drug abuse treatment: Efficasy versus effectiveness. Addiction 1997, 92, 1467–1478.

15. Štefunková, M. Metamfetamin (Pervitin): Situace v eu a Její Globální Kontext; Centrum adiktologie, Psychiatrická klinika 1. LF UK a VFN v Praze: Praha, Czech Republic, 2010.

16. Zhang, Y.; Mayer-Blackwell, B.; Schlussman, S.D.; Randesi, M.; Butelman, E.R.; Ho, A.; Kreek, M.J. Extended access oxycodone self-administration and neurotransmitter receptor gene expression in the dorsal striatum of adult C57BL/6 J mice. Psychopharmacology 2014, 231, 1277–1287.

17. Fumagalli, F.; Gainetdinov, R.R.; Valenzano, K.J.; Caron, M.G. Role of dopamine transporter in methamphetamine-induced neurotoxicity: Evidence from mice lacking the transporter. J. Neurosci. 1998, 18, 4861–4869.

18. Plessinger, M.A. Prenatal exposure to amphetamines. Risks and adverse outcomes in pregnancy. Obstet. Gynecol. Clin. N. Am. 1998, 25, 119–138.

19. Dubertret, C.; Gorwood, P.; Ades, J.; Feingold, J.; Schwartz, J.C.; Sokoloff, P. Meta-Analysis of DRD3 gene and schizophrenia: Ethnic heterogeneity and significant association in caucasians. Am. J. Med. Genet. Part A. 1998, 81, 318–322.

20. da Silva Santos, A.M.; Kelly, J.P.; Doyle, K.M. Dose-Dependent effects of binge-like methamphetamine dosing on dopamine and neurotrophin levels in rat brain. Neuropsychobiology 2017, 75, 63–71.

21. Camp, D.M.; Browman, K.E.; Robinson, T.E. The effects of methamphetamine and cocaine on motor behavior and extracellular dopamine in the ventral striatum of Lewis versus Fischer 344 rats. Brain Res. 1994, 668, 180–193.

22. Numachi, N.; Ohara, A.; Yamashita, M.; Fukushima, S.; Kobayashi, K.; Hata, H.; Watanabe, H.; Hall, F.S.; Lesch, K.P.; Murphy, D.L.; et al. Methamphetamine-Induced hyperthermia and lethal toxicity: Role of the dopamine and serotonin transporters. Eur. J. Pharmacol. 2007, 572, 120–128.

23. Šlamberová, R. Drug in pregnancy: The Effects on mother and her progeny. Physiol. Res. 2012, 61, 123–135.

24. Cho, B.I. Methamphetamine abuse: Epidemiologic issues and implications. NIDA Res. Monogr. 1991, 115, 99–106.

25. Thrash, B.; Thiruchelvan, K.; Ahuja, M.; Suppiramaniam, V.; Dhanasekaran, M. Methamphetamine-Induced neurotoxicity: The road to Parkinson's disease. Pharmacol. Rep. 2009, 61, 966–977.

26. Lampert, S.M.; Kaye, A.D.; Urman, R.D.; Manchikanti, L. Drug testing and adherence monitoring in substance abuse patients. In Substance Abuse; Springer: New York, NY, USA, 2015; pp. 621–631.

27. Yui, K.; Ikemoto, S.; Goto, K.; Nishijima, K.; Yoshino, T.; Ishiguro, T. Spontaneous Recurrence of Methamphetamine-Lnduced Paranoid-Hallucinatory States in Female Subjects: Susceptibility to Psychotic States and Implications for Relapse of Schizophrenia. Pharmacopsychiatry 2002, 35, 62–71.

28. Vavříková, B.; Binder, T.; Živný, J. Characteristics of a population of drug dependent pregnant women in Czech Republic. Čes. Gynekol. 2001, 66, 285–291.

29. Sipes, T.E.; Geyer, M.A. DOI disruption of prepulse inhibition of startle in the rat is mediated by 5-HT2A and not by 5-HT2C receptors. Behav. Pharnmacol. 1995, 6, 839–842.

30. Vavříková, B.; Binder, T.; Živný, J.; Vítková, I. Placental and umbilical cord changes in drug-addicted women. Čes. Gynekol. 2001, 66, 345–349.

31. Bauer, C.R.; Shankaran, S.; Bada, H.S.; Lester, B.; Wright, L.L.; Krause-Steinrauf, H.; Smeriglio, V.L.; Finnegan, L.P.; Maza, P.L.; Verter, J. The Maternal Lifestyle Study: Drug exposure during pregnancy and short-term maternal outcomes. Am. J. Obstet. Gynecol. 2002, 186, 487–495.

32. Chang, L.; Alicata, D.; Ernst, T.; Volkow, N. Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. Addict. Soc. Study Addict. 2007, 102, 16–32.

33. Anckarsater, H. Central nervous changes in social dysfunction: Autism, aggression, and psychopathy. Brain Res. Bull. 2006, 69, 259–265.

34. Ma, F.; Xie, H.; Dong, Z.Q.; Wang, Y.Q.; Wu, G.C. Expression of ORL 1 mRNA in some brain nuclei in neuropathic pain rats. Brain Res. 2005, 1043, 214–217.

35. Mena, J.C.; Cuellar, H.; Vargas, D.; Riascos, R. PET and SPECT in drug and substance abuse. Top. Magn. Reson. Imaging 2005, 16, 253–256.

36. Raine, A.; Yang, Y. The neuroanatomical bases of psychopathy: A review of brain imaging findings. In Handbook of Psychopathy; Patrick, C.J., Ed.; Guilford: New York, NY, USA, 2004.

37. Bechara, A. The role of emotion in decision making: Evidence from neurological patients with orbitofrontal damage. Brain Cognit. 2004, 55, 30–40.

38. Amen, D.G.; Stubblefield, M.; Carmicheal, B.; Thisted, R. Brain SPECT findings and aggressiveness. Ann. Clin. Psychiatry 1996, 8, 129–137.

39. Bayer, S.A.; Altman, J.; Russo, R.J.; Zhang, X. Timetables of neurogenesis in the human brain based on experimentally determined patterns in the rat. Neurotoxicology 1993, 14, 83.

40. Rolls, E.T.; Treves, A. Neural Networks and Brain Function; Oxford University Press: Oxford, UK, 1998.

41. Bullmore, E.; Sporns, O. Complex brain networks: Graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 2009, 10, 186.

42. Maren, S.; Phan, K.L.; Liberzon, I. The contextual brain: Implications for fear conditioning, extinction and psychopathology. Nat. Rev. Neurosci. 2013, 14, 417–428.

43. Li, H.; Scholl, J.L.; Tu, W.; Hassell, J.E.; Watt, M.J.; Forster, G.L.; Renner, K.J. Serotonergic responses to stress are enhanced in the central amygdala and inhibited in the ventral hippocampus during amphetamine withdrawal. Eur. J. Neurosci. 2014, 40, 3684–3692.

44. Krugel, L.K.; Biele, G.; Mohr, P.N.C.; Li, S.C.; Heekeren, H.R. Genetic variation in dopaminergic neuromodulation influences the ability to rapidly and flexibly adapt decisions. Proc. Natl. Acad. Sci. USA 2009, 106, 17951–17956.

45. Mansour, A.; Meador-Woodruff, J.H.; Bunzow, J.R.; Civelli, O.; Akil, H.; Watson, S.J. Localization of dopamine D2 receptor mRNA and D1 and D2 receptor binding in the rat brain and pituitary: An in situ hybridization-receptor autoradiographic analysis. J. Neurosci. 1990, 10, 2587–2600.

46. Bourque, M.; Liu, B.; Dluzen, D.E.; Di Paolo, T. Sex differences in methamphetamine toxicity in mice: Effect on brain dopamine signalling pathways. Psychoneuroendocrinology 2011, 36, 955–969.

47. Drago, J.; Padungchaichot, P.; Accili, D.; Fuchs, S. Dopamine receptors and dopamine transporter in brain function and addictive behaviors: Insights from targeted mouse mutants. Dev. Neurosci. 1998, 20, 188–203.

48. Hollerman, J.R.; Schultz, W. Dopamine neurons report an error in the temporal prediction of reward during learning. Nat. Neurosci. 1998, 1, 304–309.

49. Holick, K.A.; Lee, D.C.; Hen, R.; Dulawa, S.C. Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. Neuropsychopharmacology 2008, 33, 406–417.

50. Frankle, W.G.; Lombardo, I.; New, A.S.; Goodman, M.; Talbot, P.S.; Huang, Y.; Hwang, D.; Slifstein, M.; Curry, S.; Abi-Dargham, A.; et al. Brain serotonin transporter distribution in subjects with impulsive aggressivity: A positron emission study with McN 5652. Am. J. Psychiatry 2005, 162, 915–923.

51. Won, L.; Bubula, N.; McCoy, H.; Heller, A. Methamphetamine concentrations in fetal and maternal brain following prenatal exposure. Neurotoxicol. Teratol. 2001, 23, 349–354.

52. Barrett, K.E.; Barman, S.M.; Boitano, S.; Brooks, H.L. Ganong's Review of Medical Physiology, 23rd ed.; McGraw-Hill Medical: New York, NY, USA, 2009.

53. Guyton, A.C.; Hall, J.E. Textbook of Medical Physiology, 11th ed.; Elsevier: Amsterdam, The Netherlands, 2006.

54. Campbell, T.G. The best of a bas bunch: The ventromedial prefrontal cortex and dorsal anterior cingulate cortex in decision-making. J. Neurosci. 2007, 27, 447–448.

55. Waberžinek, G.; Krajíčková, D. Základy Speciální Neurologie; Karolinum: Praha, Czech Republic, 2006.

56. Apergis-Schoute, A.M.; Gillan, C.M.; Fineberg, N.A.; Fernandez-Egea, E.; Sahakian, B.J.; Robbins, T.W. Neural basis of impaired safety signaling in obsessive compulsive disorder. Proc. Natl. Acad. Sci. USA 2017, 114, 3216–3221.

57. Gillan, C.M.; Apergis-Schoute, A.M.; Morein-Zamir, S.; Urcelay, C.P.; Sule, A.; Fineberg Sahakian, B.J.; Robbins, T.W. Functional neuroimaging of avoidance habits in obsessive-compulsive disorder. Am. J. Psychiatry 2015, 172, 284–293.

58. Blair, R.J. Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. J. Neurol. Neurosurg. Psychiatry 2001, 71, 727–731.

59. Brower, M.C.; Price, B.H. Neuropsychiatry of frontal lobe dysfunction in violent and criminal behavior: A critical review. J. Neurol. Neurosurg. Psychiatry 2001, 71, 720–726.

60. Burgess, N.; Maguire, E.A.; O'Keefe, J. The human hippocampus and spatial and episodic memory. Neuron 2002, 35, 625–641.

61. Stuchlik, A. Dynamic learning and memory, synaptic plasticity and neurogenesis: An update. Front. Behav. Neurosci. 2014, 8, 106.

62. Nakazawa, K.; Quirk, M.C.; Chitwood, R.A.; Watanabe, M.; Yeckel, M.F.; Sun, L.D.; Tonegawa, S. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science 2002, 297, 211–218.

63. Kesner, R.P.; Gilbert, P.E.; Barua, L.A. The role of the hippocampus in memory for the temporal order of a sequence of odors. Behav. Neurosci. 2002, 116, 286–290.

64. Bannerman, D.M.; Sprengel, R.; Sanderson, D.J.; McHugh, S.B.; Rawlins, J.N.P.; Monyer, H.; Seeburg, P.H. Hippocampal synaptic plasticity, spatial memory and anxiety. Nat. Rev. Neurosci. 2014, 15, 181.

65. Simões, P.F.; Silva, A.P.; Pereira, F.C.; Grade, S.; Milhazes, N.; Borges, F.; Ribeiro, C.F.; Macedo, T.R. Methamphetamine induces alternations on hippocampal NMDA and AMPA receptor subunit levels and impairs spatial working memory. Neuroscience 2007, 150, 433–434.

66. Honey, R.C.; Good, M. Associative modulation of the orienting response: Distinct effects revealed by hippocampal lesions. J. Exp. Psychol. Anim. Behav. Process. 2000, 26, 3–14.

67. Bannerman, D.M.; Rawlins, J.N.P.; Good, M.A. The drugs don't work—or do they? Pharmacological and transgenic studies of the contribution of NMDA and GluR-A-containing AMPA receptors to hippocampal-dependent memory. Psychopharmacology 2006, 188, 552–566.

68. McCutcheon, J.E.; Marinelli, M. Age matters. Eur. J. Neurosci. 2009, 29, 997–1014.

69. Squire, L.R. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. Psychol. Rev. 1992, 99, 195.

70. Caputi, A.; Fuchs, E.C.; Allen, K.; Le Magueresse, C.; Monyer, H. Selective reduction of AMPA currents onto hippocampal interneurons impairs network oscillatory activity. PLoS ONE 2012, 7, e37318.

71. O'Keefe, J.; Nadel, L. The Hippocampus as a Cognitive Map; Oxford University Press: Oxford, UK, 1978.

72. Rawlins, J.N.; Olton, D.S. The septo-hippocampal system and cognitive mapping. Behav. Brain Res. 1982, 5, 331–358.

73. O'Keefe, J.; Dostrovsky, J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. 1971, 34, 171–175.

74. Mariano, T.Y.; Bannerman, D.M.; McHugh, S.B.; Preston, T.J.; Rudebeck, P.H.; Rudebeck, S.R.; Campbell, T.G. Impulsive choice in hippocampal but not orbitofrontal cortex-lesioned rats on a nonspatial decision-making maze task. Eur. J. Neurosci. 2009, 30, 472–484.

75. Pothuizen, H.H.; Zhang, W.N.; Jongen-Relo, A.L.; Feldon, J.; Yee, B.K. Dissociation of function between the dorsal and the ventral hippocampus in spatial learning abilities of the rat: A within-subject, within-task comparison of reference and working spatial memory. Eur. J. Neurosci. 2004, 19, 705–712.

76. Stuchlik, A.; Rehakova, L.; Rambousek, L.; Svoboda, J.; Vales, K. Manipulation of D2 receptors with quinpirole and sulpiride affects locomotor activity before spatial behavior of rats in an active place avoidance task. Neurosci. Res. 2007, 58, 133–139.

77. Taube, J.S.; Muller, R.U.; Ranck, J.B. Head-Direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. J. Neurosci. 1990, 10, 420–435.

78. Stuchlik, A.; Rezacova, L.; Vales, K.; Bubenikova, V.; Kubik, S. Application of a novel Active Allothetic Place Avoidance task (AAPA) in testing a pharmacological model of psychosis in rats: Comparison with the Morris Water Maze. Neurosci. Lett. 2004, 366, 162–166.

79. Barkus, C.; McHugh, S.B.; Sprengel, R.; Seeburg, P.H.; Rawlins, J.N.P.; Bannerman, D.M. Hippocampal NMDA receptors and anxiety: At the interface between cognition and emotion. Eur. J. Pharmacol. 2010, 626, 49–56.

80. Pentkowski, N.S.; Blanchard, D.C.; Lever, C.; Litvin, Y.; Blanchard, R.J. Effects of lesions to the dorsal and ventral hippocampus on defensive behaviors in rats. Eur. J. Neurosci. 2006, 23, 2185–2196.

81. Deacon, R.M.; Bannerman, D.M.; Rawlins, J.N. Anxiolytic effects of cytotoxic hippocampal lesions in rats. Behav. Neurosci. 2002, 116, 494–497.

82. Nicolini, H.; Cruz, C.; Camarena, B.; Orozco, B.; Kennedy, J.L.; King, N.; Sidenberg, D. DRD2, DRD3 and 5HT2A receptor genes polymorphisms in obsessive-compulsive disorder. Mol. Psychiatry 1996, 1, 461–465.