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The legitimacy of the diagnosis ‘sex addict’

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Summary

Although approximately three to five percent of the adult population struggles with some form of sexual addiction and seek help for it, sex addiction is not recognized as a disorder by the DSM-5TR that is currently used as a diagnostic classification system. It is important to investigate whether sex addiction is a legit disorder so that individuals suffering from it can be diagnosed and treated effectively. Therefore, this report aims to answer the question whether sex addiction is a legit disorder and, consequently, whether it should be included in the DSM or not. The current literature shows that drugs and sex have similar reinforcing properties, mediated by dopamine release in the nucleus accumbens. Furthermore, a form of tolerance, characterized by a decreased response to drugs, can be seen in frequent pornography users as decreased striatal volume and striatal activity to sexual cues. While sensitization to drugs and craving for drugs are typically seen in drug addicts, sensitization to sex and craving for sex is also seen in 'sex addicts', characterized by higher 'wanting' and increased reactivity of certain brain regions after the presentation of sexual cues. Although there are many similarities between drug addiction and sex addiction, the number of studies investigating sex addiction is scarce, especially studies investigating the neurocircuitries underlying sex addiction. Furthermore, very little research has focused on withdrawal in sex addicts. The knowledge on withdrawal in sex addicts comes from self-reports, and studies of the brain of sex addicts during withdrawal are lacking. Thus, more research is needed to provide a solid conclusion on whether sex can become an addiction or not. Therefore, the current exclusion of sex addiction from the DSM is marked by legitimate reasons.

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Introduction

Sexual addiction, also called hypersexuality or compulsive sexual behavior, is a label used by many people in articles, books, and news reports. It is a label commonly given to people compulsively preoccupied with sexual behaviors, regardless of the negative consequences.[1] Moreover, research on sexual behavior in the 1980s suggested that around three to five percent of the adult population struggled with some form of sexual addiction[2]. However, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision (DSM-5TR), doesn't recognize sex addiction as a mental disorder. The word 'addiction' is omitted in the DSM-5TR altogether because of the uncertain definition and negative connotation. Instead, the term (non)substance use disorder is used. The DSM-5TR describes many substance-related disorders, encompassing 10 different classes of drugs, but only one non-substance-related disorder: gambling disorder. Substance-related addictions differ from non-substance-related behavioral addictions in several ways. While substance-related addictions involve the dependence on chemical substances, a non-substance-related behavioral addiction is a dependence on a behavior. Although persistent and recurrent problematic gambling has already been recognized by the DSM-5TR as a disorder, there is also increasing evidence that other behaviors, including exercise, eating, and gaming can be addictive.[3] Behavior science experts believe that any source capable of stimulating an individual could become addictive[4]. Another difference between substance-related addictions and non-substance-related addictions is that some addictive behaviors, such as eating, sex, and using the internet, cannot (easily) be avoided. Similarities are also found. Research has shown that problematic gambling behaviors can result in behavioral symptoms comparable to those produced by substance use disorders.

Interestingly, gambling behaviors activate similar reward systems in the brain as those activated by drugs of abuse.[5] Although gambling disorder is the only non-substance-related disorder included in the DSM-5TR, it is not the only behavioral disorder to show similarities to what can be labeled in the non-medical setting as an addiction. Considerable research has been performed around the compulsive playing of internet games, or internet/gaming addiction. As of yet, there is not enough evidence to include the compulsive playing of internet games in the DSM-5TR[6]. Thus, groups of behavioral addictions, with subgroups like 'sex addiction' and 'shopping addiction', are not (yet) included in the DSM-5TR, due to a lack of peer-reviewed evidence to establish the diagnostic criteria and course descriptions needed to identify these behaviors as mental disorders.[5] Nevertheless, many people seek help for these conditions, and it is, therefore, important to gather information on these issues to improve public health.

The debate about labeling sex addiction as a mental disorder is ongoing as it is accepted by some but rejected by others, including the DSM-5TR. The aim of this report is to answer the question whether sex addiction is a legit disorder and, consequently, whether it should be included in the DSM or not. These questions are answered by comparing the behavior, neurocircuitries, and diagnostic criteria of a substance use disorder as stated in the DSM-5TR with what can be found about sex addiction in literature. For this, a bit of background on the DSM is provided. Then some brain regions important for sexual behavior are mentioned. Finally, the diagnostic criteria, behavior, and brain of drug addicts and sex addicts are compared

to draw a conclusion about whether sex addiction should be included in the DSM or not.

1. The DSM-5TR

The DSM is used as a diagnostic classification system for mental health professionals, guiding them to identify the most prominent symptoms to assess when diagnosing someone with a disorder. The DSM is mostly used in the United States and Australia, but also in the Netherlands, Germany, Belgium, and Luxemburg. The understanding of mental disorders advances over time, as continuous research gives new insights. This has resulted in the revision of the forerunners of the DSM-5TR. The DSM-5TR used nowadays is very new. In 1844, a forerunner to DSM was published by the American Psychiatric Association (APA). It classified hospitalized mental patients and helped to improve the communication about the types of patients in mental hospitals. The first official DSM appeared in 1952 and evolved through several editions to finally become the DSM-5TR that is currently used. The classification of disorders is synchronized with the World Health Organization's International Classification of Diseases (ICD), which is globally used and provides knowledge on the causes, extent, and consequences of human disease and death. The DSM defines a mental disorder as: "A syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities".[7] It has been recognized that many disorders show resemblance and that their boundaries are vague. Although some disorders have very clear boundaries around the symptoms, most disorders are placed on a spectrum with closely related disorders that share symptoms, risk factors, and neuronal changes underlying the behavior. The terms sexual addiction, hypersexuality, or compulsive sexual behavior are used interchangeably, indicating that a sex-addict displays symptoms of obsessive-compulsive disorders, substance-related and addictive disorders, and sexual dysfunctions, which are all included in the DSM-5TR. Before looking at dysfunctional or addictive sexual behavior, it is crucial to understand healthy sexual behavior. Therefore, some information will be given about the brain during sexual behavior of non-addicts next.

2. Sex and the brain

Sexual behavior relies on the processing of sexual stimuli and is driven by sexual desire, consisting of sexual thoughts and fantasies and the motivation to engage in sexual behavior in response to internal and external cues. Sexual desire is influenced by factors such as partner availability, mood, attitude, and health. Many different brain regions must interact for an individual to exhibit sexual behavior, as many parts of the body are involved. Studies have been performed to investigate the brain regions and neurotransmitters involved in sexual behavior. Although there are more brain regions involved in sexual behavior than can be mentioned in this report, the main brain areas involved in sexual behavior in humans are the insula, the cingulate cortex, the prefrontal, and orbitofrontal cortices, the septal region, the amygdala, the hypothalamus, the thalamus, and the reward system (figure 1 and figure 2). Although all regions are important for sexual behavior in many different ways, only a few examples will be further elaborated on.[8]

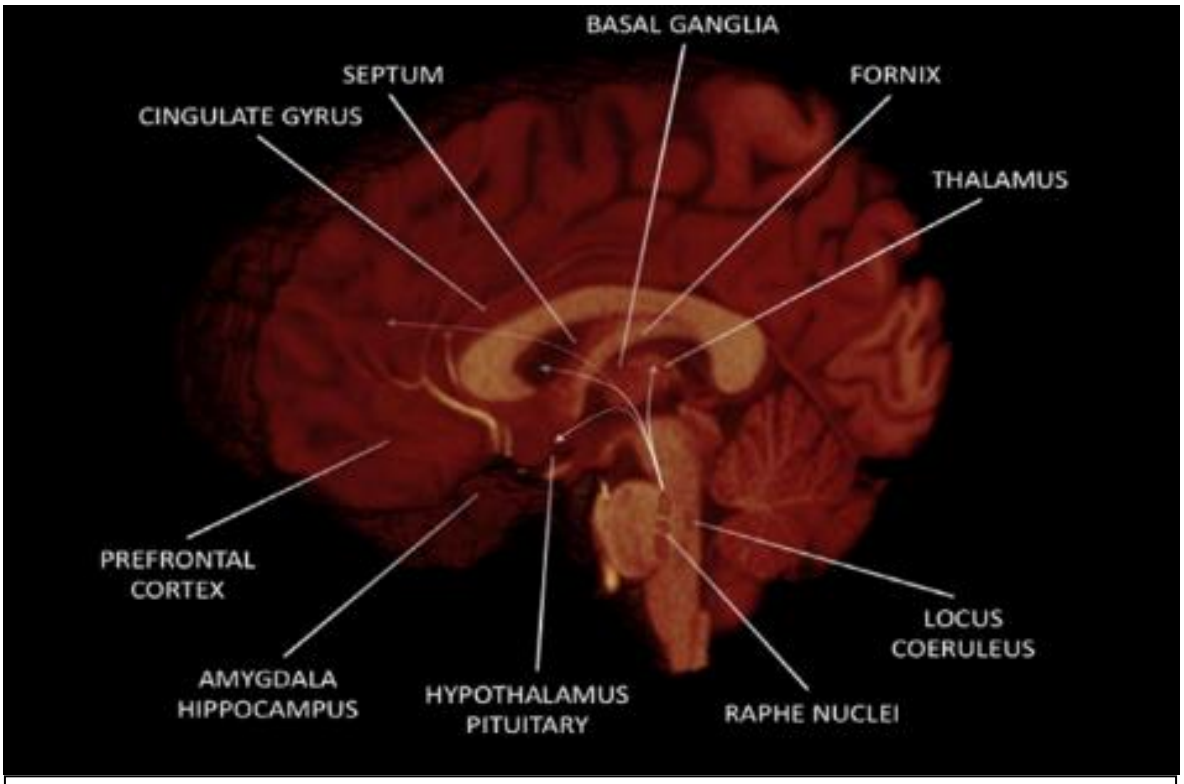

Figure 1. A sagittal section of the human brain. Regions that are important for sexual behavior are indicated with white lines.
Calabrò et al. (2019)[8].

Insula

The insula is a cortical structure located between the temporal and frontal lobes. It has been suggested that the insula is involved in arousal, decision-making, emotional processing, and more[9]. A study by Cera et al (2020) collected fMRI, penile tumescence, and eye movement data from men performing a visual sexual stimulation task to investigate the functional connectivity of the insula. They showed that both the anterior and posterior insula was activated following visual sexual stimuli. A stronger effect was found in the posterior, compared to the anterior insula. In the posterior insula, there were three different pathways involved. The first one involved visual attention, the onset of the erection, and sustained erection. The

second one involved only the onset of erection. The third one only involved sustained erection.[10]

Cingulate cortex

The cingulate cortex is part of the limbic system. It is divided into the anterior (ventral and dorsal), middle, and genual subregion[8]. Multiple studies suggest that the anterior cingulate cortex (ACC) plays a role in sexual behavior. A study by Yamanouchi et al. (1992) investigated sexual behavior in male rats with lesions in the anterior part of the cingulate cortex and males with bilateral interruptions of lateral connections of the anterior cingulate cortex. This study showed that rats with these lesions showed a decrease in mount, intromission, and ejaculation activities compared to control rats and compared to rats with posterior cingulate cortex and frontal cortex lesions. Furthermore, in rats with interrupted connections, the sexual activity was much lower compared to control rats. This suggests that the anterior cingulate cortex and its lateral connections are very important in the sexual behavior of male rats.[12]

Prefrontal and orbitofrontal cortices

The prefrontal cortex plays a role in many cognitive processes, such as judgment, attention, working memory, information processing, behavioral organization, coping with new experiences, and more[13]. A study by Ågmo et al. (1995) investigated the role of the medial prefrontal cortex on sexual behavior in male rats by lesions. Their findings suggested that the medial prefrontal cortex is important in the initiation of sexual behavior, and less important for the execution once started.[14] A study by Arnow et al. (2009) investigated brain activation by use of fMRI of women without a history of sexual dysfunction (NHSD) and of women with hypoactive sexual desire disorder (HSDD) following erotic video stimuli. It was shown that HSDD women had more activation in the anterior ventromedial prefrontal cortex, which may indicate that these women devote more attention to evaluating and/or monitoring their responses. Thus, there is a correlation between heightened self-focus and HSDD. Furthermore, greater activation of the orbitofrontal cortex in HSDD women also indicates that more resources are allocated to regions associated with judging subjective responses.[15] This is in line with the finding that while there is the activation of activity in the upper brainstem and cerebellum, as well as insula in men and the somatomotor and somatosensory cortex in women during sexual stimulation, ejaculation, and orgasm, there is a strong inactivation of activity in the left side in the temporal lobe and ventral prefrontal cortex. This implies that a lower level of alertness regarding the environment is very important for normal sexual behavior in humans.[16]

Septal region

Case studies of human patients with septal injury showed significantly different sexual behavior as before the injury. It has therefore been suggested that the septum is involved in mediating sexual behavior[17].

Amygdala

Research on the amygdala, located in the medial temporal lobe, has shown its function in behavioral, vegetative, and endocrine activities and its role in emotional responses. Certain nuclei in the amygdala can alter sex-related activities.[18] For example, in female rats, lesions in the anterior part of the corticomedial amygdala decrease sexual receptivity, while the stimulation of this area increases receptivity[19]. A study by Baird et al. (2004) found a positive relationship between contralateral amygdala volume and sex drive in men and women.[20] Furthermore, in an epileptic

female patient, certain brain areas were investigated with depth electrodes. In this patient, electric stimulation of the right amygdala triggered a feeling very similar to an orgasm, indicating its key role in orgasmic feelings and human sexual behavior.[21]

Hypothalamus

The medial preoptic area/anterior hypothalamus (MPOA/AH) is a brain region that is important in executing behavioral and physiological functions. By lesioning the medial preoptic area/anterior hypothalamus, it had been shown that this area is important in males to control their sexual behavior. It has been hypothesized that this region is involved in the execution, motivation, or regulation of motivation and execution of sexual behavior.[22] Moreover, the paraventricular nucleus, which is an integration center between the peripheral and central nervous systems, plays an important role in the control of sexual activity and erections[23]. Furthermore, an fMRI study on the brain of women during an orgasm showed an increase in activity in the paraventricular nucleus but also in the amygdala, hippocampus, basal ganglia, cerebellum, anterior cingulate, insular, parietal and frontal cortices, lower brainstem, and accumbens-bed nucleus of the stria terminalis-preoptic area[24].

Thalamus

The thalamus is located above the brain stem and it functions as a relay station for motor and sensory signals to the cerebral cortex. It is also involved in sleep and arousal[25]. In a study by Temel et al. (2004) it was shown that the stimulation of the thalamus can increase erection[26]. Furthermore, a study by Park et al. (2001) found that the thalamus, but also the inferior frontal lobe, cingulate gyrus, insula gyrus, corpus callosum, caudate nucleus, globus pallidus, and inferior temporal lobe were significantly activated in women watching erotic movies[27]. Thus, the thalamus does not just serve as a relay station of motor and sensory signals but is also activated during phases of desire, arousal, and orgasm.

Reward system

The dopaminergic reward system in the brain is associated with positive reinforcement for certain behaviors, including sexual behavior. A study by Demos et al. (2012) has shown that increased reward responsivity in the nucleus accumbens to sexual cues is associated with indulgence in sexual activity.[28] Not only in the Nucleus accumbens but also in other parts of the ventral striatum, activity increases when sexual cues are shown to subjects[29]. The mesolimbic reward system, including the nucleus accumbens and the ventral tegmental area, plays a major role in addiction and will be discussed in more detail later in this report. Many brain regions respond to reward and/or have connections with the reward system. These regions include the anterior cingulate cortex, orbitofrontal cortex, ventral pallidum, ventral striatum, prefrontal cortex, hippocampus, amygdala, thalamus, hypothalamus, septal region.[30,31,32] Thus, most of the brain regions just mentioned play a role in sexual behavior and in reward.

Naturally, the involvement of many brain regions in sexual behavior implicates neurotransmitter and modulator involvement. The most important neurotransmitters and modulators involved in human sexual behavior are serotonin, dopamine, norepinephrine, acetylcholine, histamine, opioids, and sex hormones.[8]

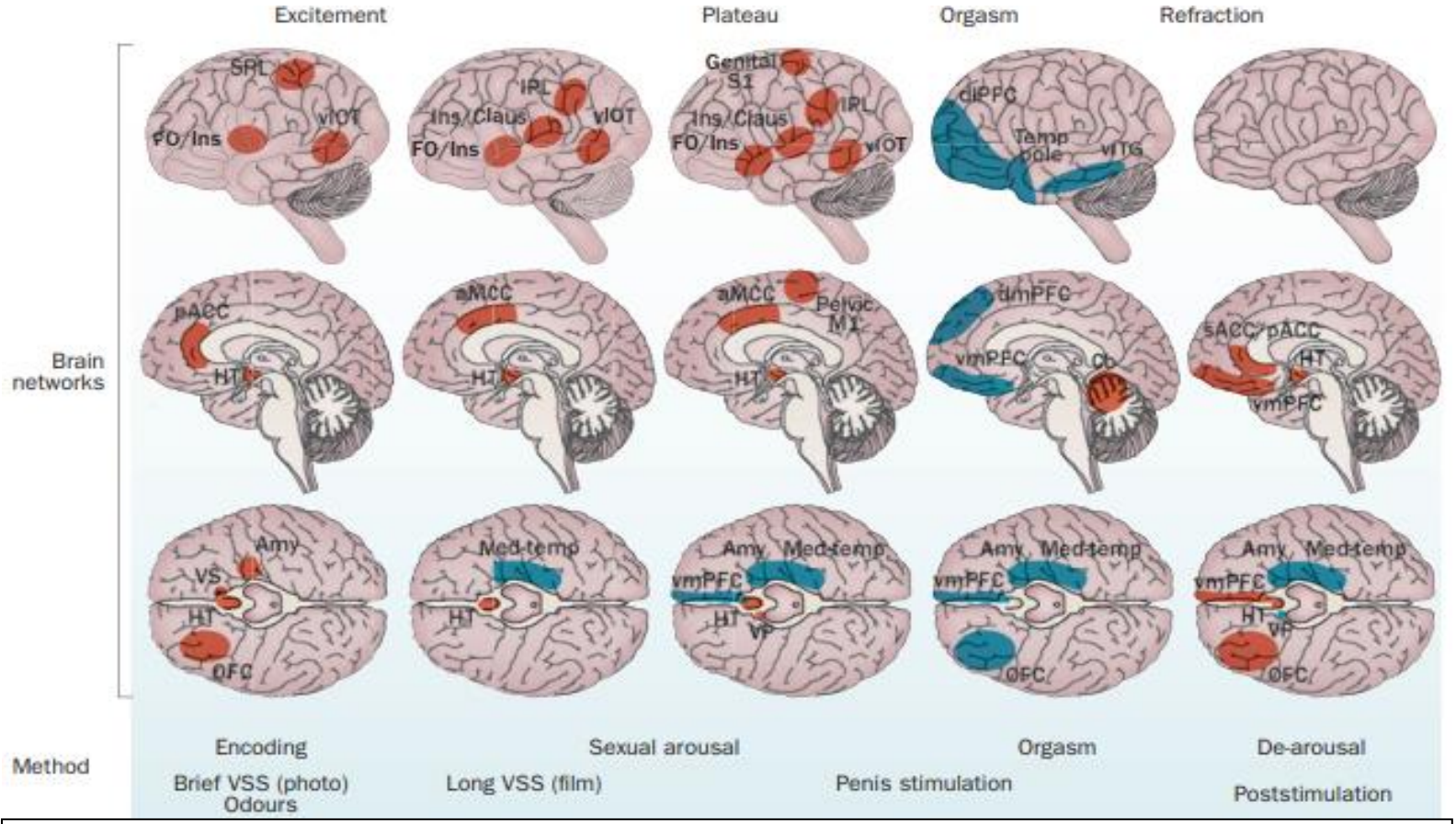

Figure 2. An illustration of brain regions involved in sexual excitement, plateau, orgasm and refraction. The regions involved are the cingulate cortex, amygdala, cerebellum, prefrontal cortex, frontal operculum/anterior insula, somatosensory cortex of external genitalia, hypothalamus, claustrum/posterior insula, intraparietal lobule, medial temporal lobe, orbitofrontal cortex, anterior cingulate cortex, motor cortex, superior parietal lobule, temporal pole, inferior temporal gyrus, occipitotemporal cortex, ventral pallidum, ventral striatum, nucleus accumbens.
Georgiadis et al. (2012)[33].

3. Diagnosis drug addiction

An addiction is a chronic relapsing disorder, identified by persistent, uncontrollable, and compulsive behavior (like drug seeking and use), despite negative consequences[11]. The word ‘addiction’ is derived from the Latin word addicere, which means ‘bound to’ or ‘enslaved by’. Initially, the term was used without indicating the use of substances, but over the years it has become associated with impaired control over the use of substances. However, many recent studies have focused on non-substance-related disorders as addictive behaviors. Impaired control or loss of control over behavior, and the behavior being potentially harmful are central to the definition of an addiction.[34] Diagnostic criteria for a mental disorder identify signs and symptoms including behaviors, effects, personality traits, and cognitive functions, together with the physical signs, symptom combinations, and durations. The DSM-5TR states 11 different diagnostic criteria for a substance use disorder, also called a ‘drug addiction’. The diagnostic criteria of a substance use disorder are based on pathological behavioral patterns, related to the use of the substance. These criteria can be subdivided into four groups: impaired control, social impairment, risky use, and pharmacological criteria. Although substance use disorders differ from non-substance use disorders, also called ‘behavioral addictions’, they show many similarities in behavior and neurology. The behavioral addiction gambling disorder is placed in the DSM-5RT under the same category as ‘Substance-Related and Addictive Disorders’. This suggests that the diagnostic criteria for a behavioral addiction could correspond to the diagnostic criteria for a substance use disorder. The 11 diagnostic criteria are as follows:

1. The substance is taken in larger amounts or over longer periods of time than intended by an individual.

2. There is a desire to cut down or regulate substance use but the individual is unable to do so.

3. The individual spends a lot of time obtaining, using, or recovering from the substance. In some individuals, all activity revolves around the substance.

4. Craving for the substance, most likely when in an environment where the substance was previously used or obtained.

5. Failure to fulfill obligations at work, school, or home.

6. Continuation of substance use despite having social or interpersonal problems caused by the effects of the substance.

7. Important activities may be given up because of substance use.

8. Substance use in situations that are physically dangerous.

9. Continuation of substance use despite the knowledge that it causes physical and mental health problems.

10. Tolerance is characterized by needing an increased dose of the substance to achieve the desired effect.

11. Withdrawal is a syndrome that occurs because of decreasing concentrations of the substance in the blood, usually followed by the consummation of the substance.

Neither tolerance nor withdrawal is a necessary diagnostic criterion for substance use disorder. The severity of the disorder can be estimated by the number of symptoms presented, in which two or three estimates a mild, four or five a moderate, and six or more symptoms a severe disorder. [5]

4. Possible diagnosis sex addiction

The terms sex addiction, hypersexuality, sexual impulsivity, and compulsive sexual behavior are used interchangeably and the criteria corresponding to these different terms are similar. Many different authors have described the behavior of sex addicts, such as Jim Orford, Patrick J. Carnes, and Martin P. Kafka (Figure 3). A sex addiction, similar to drug addiction, is often characterized by uncontrollable, compulsive sexual behaviors, fantasies and urges, and continuation of these activities despite negative consequences.[35,36] The behavior seen in sex addicts can include many different types of sexual behaviors, such as excessive masturbation, telephone sex, cybersex, pornography use, and strip club visitation[37].

Criteria	Hypersexuality: Theory of Dependence (Orford, 1978)	Sex Addiction (Carnes, 1983, 1991)	Sexual Addiction (Goodman, 1998)	Hypersexual Disorder (Stein et al., 2001)	Nonparaphilic Compulsive Sexual Disorder (Coleman, 2003)	Sex Addiction (Carnes, 2005)	Hypersexual Disorder (Kafka, 2010)
Recurrent failure to resist impulses to engage in sexual behavior	X	X	X			X	X
Frequent engaging in those behaviors to a greater extend		X	X			X	X
Persistent desire or unsuccessful efforts to stop, reduce or control sexual behavior	X	X	X	X		X	
Inordinate amount of time spent in obtaining sex, being sexual, or recovering from sexual experiences	X		X			X	X
Preoccupation with the behavior or preparatory activities	X			X	X	X	X
Frequent engaging in the behavior when expected to fulfill occupational, domestic, or social			X	X	X	X	X

obligations							
Continuation of behavior despite negative consequences that are caused or exacerbated by the behavior	X	X	X	X	X	X	X
Need to increase the intensity, frequency, number or risk of behavior to achieve the desired effect or diminished effect with continued behaviors at the same level of intensity		X	X			X	
Giving up or limiting social, occupational or recreational activities because of the behavior		X	X			X	X
Distress, anxiety, restlessness or irritability if unable to engage in the behavior	X		X			X	

Figure 3. An overview of criteria for hypersexuality, sex addiction and compulsive sexual disorder, proposed by different authors.
Carnes[38].

Sex addiction is not included in the DSM and therefore, diagnostic criteria cannot be found either. However, before being rejected from the DSM-5, criteria for hypersexual disorder were proposed. The proposed criteria for Hypersexual Disorder include diagnostic criteria very similar to substance addictions, such as unsuccessful attempts to control or reduce sexual fantasies, urges and behaviors, and continuing the behavior despite physical and emotional negative consequences (figure 4).

Furthermore, the ICD-11 has included compulsive sexual behavior disorder under impulse control disorders. The ICD-11 describes essential features of compulsive sexual behavior disorder as:

A. Over a period of at least 6 months, recurrent and intense sexual fantasies, sexual urges, and sexual behavior in association with four or more of the following five criteria:
   1. Excessive time is consumed by sexual fantasies and urges, and by planning for and engaging in sexual behavior.
   2. Repetitively engaging in these sexual fantasies, urges, and behavior in response to dysphoric mood states (e.g., anxiety, depression, boredom, and irritability).
   3. Repetitively engaging in sexual fantasies, urges, and behavior in response to stressful life events.
   4. Repetitive but unsuccessful efforts to control or significantly reduce these sexual fantasies, urges, and behavior.
   5. Repetitively engaging in sexual behavior while disregarding the risk for physical or emotional harm to self or others.
B. There is clinically significant personal distress or impairment in social, occupational, or other important areas of functioning associated with the frequency and intensity of these sexual fantasies, urges, and behavior.
C. These sexual fantasies, urges, and behavior are not due to direct physiological effects of exogenous substances (e.g., drugs of abuse or medications), a co-occurring general medical condition, or to manic episodes.
D. The person is at least 18 years of age.

Specify if masturbation, pornography, sexual behavior with consenting adults, cybersex, telephone sex, and strip clubs

Figure 4. The proposed diagnostic criteria of hypersexual disorder from the DSM.
Reid et al. (2015)[39].

A. "A persistent pattern of failure to control intense, repetitive sexual impulses or urges resulting in repetitive sexual behaviour, manifested in one or more of the following:
   1. Engaging in repetitive sexual behaviour has become a central focus of the individual's life to the point of neglecting health and personal care or other interests, activities and responsibilities.
   2. The individual has made numerous unsuccessful efforts to control or significantly reduce repetitive sexual behaviour.
   3. The individual continues to engage in repetitive sexual behaviour despite adverse consequences (e.g., marital conflict due to sexual behaviour, financial or legal consequences, negative impact on health).
   4. The person continues to engage in repetitive sexual behaviour even when the individual derives little or no satisfaction from it.
B. The pattern of failure to control intense, repetitive sexual impulses or urges and resulting repetitive sexual behaviour is manifested over an extended period of time (e.g., 6 months or more).
C. The pattern of failure to control intense, repetitive sexual impulses or urges and resulting repetitive sexual behaviour is not better accounted for by another mental disorder (e.g., Manic Episode) or other medical condition and is not due to the effects of a substance or medication.
D. The pattern of repetitive sexual behaviour results in marked distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. Distress that is entirely related to moral judgments and disapproval about sexual impulses, urges, or behaviours is not sufficient to meet this requirement."[40]

Additional clinical features are described as well:

E. “Compulsive Sexual Behaviour Disorder may be expressed in a variety of behaviours, including sexual behaviour with others, masturbation, use of pornography, cybersex (internet sex), telephone sex, and other forms of repetitive sexual behaviour.
F. Individuals with Compulsive Sexual Behaviour Disorder often engage in sexual behaviour in response to feelings of depression, anxiety, boredom, loneliness, or other negative affective states. Although not diagnostically determinative, consideration of the relationship between emotional and behavioural cues and sexual behaviour may be an important aspect of treatment planning.

Individuals who make religious or moral judgments about their own sexual behaviour or view it with disapproval, or who are concerned about the judgments and disapproval of others or about other potential consequences of their sexual behaviour, may describe themselves as ‘sex addicts’ or describe their sexual behaviour as ‘compulsive’ or using similar terms. In such cases, it is important to examine carefully whether such perceptions are only a result of internal or external judgments or potential consequences or whether there is evidence that impaired control over sexual impulses, urges, or behaviours and the other diagnostic requirements of Compulsive Sexual Behaviour Disorder are actually present.”[40]

5. The brain of an addict

Many brain areas, pathways, and neurotransmitters have been found to play a role in developing and sustaining an addiction. A drug addiction results in changes in the brain, and underlying behavioral abnormalities as seen in addicted individuals. These changes can persist for a long time, even after an individual stops taking drugs[41]. For example, chronic drug abuse leads to an increase in dendritic spines in branches projecting to the nucleus accumbens[42]. The mesolimbic reward pathway and its role in addiction have received the most attention, and will therefore be the main focus of this report. A cycle of addiction can be divided into three stages: binge/intoxication, preoccupation/anticipation and withdrawal/negative effects[43]. A drug addiction often starts with an individual taking the substance because it feels good or because it relieves stress and negative emotions. After binging a drug, an individual needs more of the drug to achieve the same effect, something that is called tolerance. Taking more of a drug and developing a tolerance for it often leads to dependence on that drug. Although tolerance is developed after sustained drug abuse, an addict that abstains from drug use experiences sensitization, a phase in which the effects of drugs are increased, leading to intense cravings. Not taking the drug of abuse can lead to withdrawal, which is accompanied by negative physical and mental effects.[42] Studies have shown that an opportunity for electrical stimulation to brain pleasure areas resulted in self-stimulation of these areas, both in rodents and in humans[44,45]. The dopaminergic mesolimbic pathway is especially important for mediating reward. This pathway originates mostly from the Ventral Tegmental Area (VTA), which is a dopamine-producing nucleus, located in the mid-brain. A minor component of dopamine fibers originates from parts of the substantia nigra and the retrorubral cell field. The mesolimbic dopaminergic axons are primarily projecting to the Nucleus Accumbens (NAcc) in the ventral striatum, the amygdala, bed nucleus of stria terminals, olfactory tubercle, lateral septal area, and lateral hypothalamus, but project to various thalamic, habenular, and hypothalamic loci, and to the diagonal band of Broca as well.[31] The VTA also has dopaminergic projections to the prefrontal cortex, hippocampus, and ventral pallidum, as can be seen in figure 5.[32]

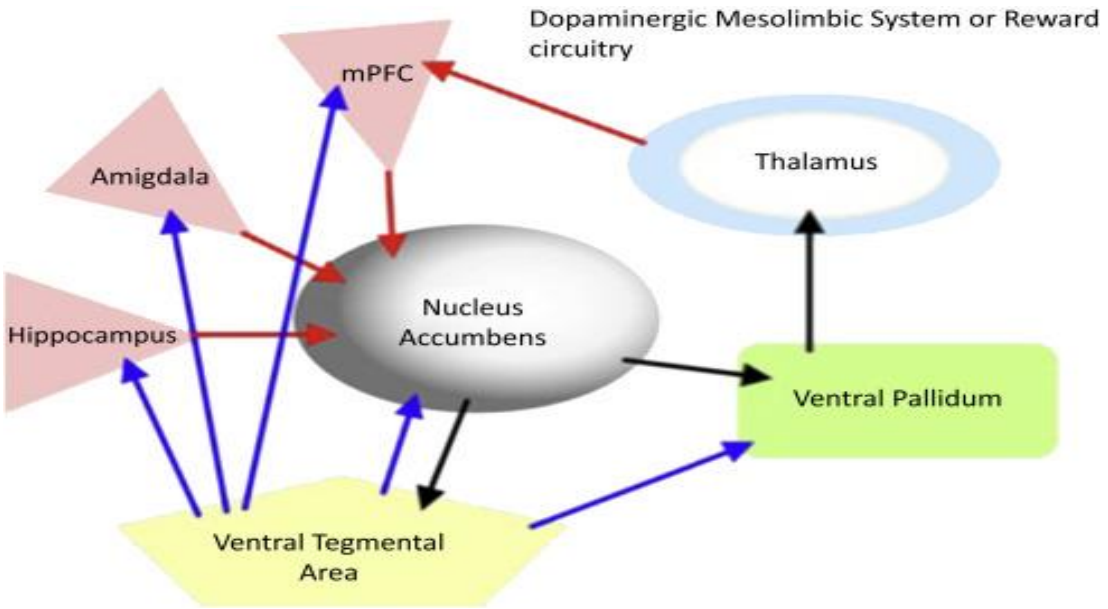

Figure 5. Important projections of the dopaminergic mesolimbic system, in which the nucleus accumbens and VTA play central roles. This pathway is important for motivated behavior and reward.
Cannizzaro & Diana (2016)[32].

5.1. Drug binge/intoxication: *reinforcement, tolerance, dependence*

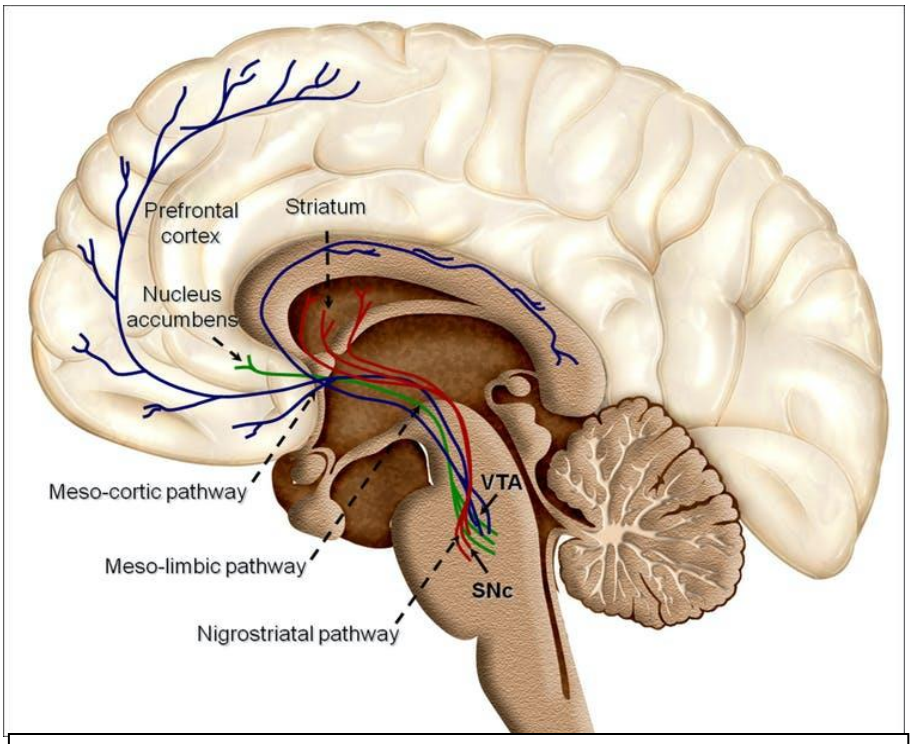

Figure 6. An illustration of three important dopaminergic pathways: mesocortical (blue), mesolimbic (green) and nigrostriatal (red). The transition from drug use to drug abuse is associated with the switch from the mesolimbic to the nigrostriatal pathway.
Arias-Carrión et al. (2010)[46].

Both the nucleus accumbens and the VTA project to the ventral pallidum. The ventral pallidum plays a key role in processing the rewarding signals from drugs. A study by Hubner et al. (1990) demonstrated that lesioning the ventral pallidum resulted in a significant decrease in cocaine and heroin self-administration. These results suggest an important role of the ventral pallidum in the reinforcing effects of drugs and lesioning attenuates the reinforcing effects. Furthermore, the projections from the nucleus accumbens to the ventral pallidum might be a common pathway for mediating the expression of opiate and stimulant reinforcement.[47] Another important brain region mediating addiction is the dorsal striatum. A study by Belin et al. (2008) found that lesioning the connections between the nucleus accumbens core and the dorsal striatum greatly decreased cocaine-seeking behavior in rats. These results demonstrate the underlying neural mechanisms of persistent drug-seeking behavior, as seen in addicts.[48] There is also evidence that the dorsal striatum is involved in the switch from controlled to compulsive drug-seeking behavior (figure 6).[49,50] A study by Zhou et al. (2019) also found that the ventral striatum promotes drug use in humans, whereas adaptations in the dorsal striatum promote the transition to addictive use by habit formation[51]. The experience of reward after activities such as eating, sex, or drug use, is accompanied by an increase in extracellular mesolimbic dopamine. This increase in dopamine stimulates an individual to repeat the rewarding behavior.[52] The idea that mesolimbic dopamine is important in the reinforcement of drug use is supported by a study by Pettit et al. (1991) who showed that there is a positive correlation between the amount of self-administrated cocaine by rodents, and the amount of extracellular dopamine in the Nacc. They also found a correlation between the dose and the level of self-administration. It was hypothesized that a higher dose of cocaine may increase cocaine intake because the reinforcing effects produced by the dose are higher. Indeed, dopamine levels in the nucleus accumbens increased as the self-administration dose of cocaine was increased.[53] Furthermore, in a study by Corrigall et al. (1992) rats that were trained to self-administrate nicotine received lesions in their mesolimbic dopamine system. Following these lesions, the self-administration of nicotine was reduced.[54] These results indicate the importance that the mesolimbic

projections play in the reinforcement of substance use. In a study by Volkow et al. (2002) it has been shown in humans that the intensity of euphoric feelings induced by methylphenidate significantly correlates with the levels of dopamine released in the striatum. The study demonstrated that the rewarding effects of substances are associated with increased levels of striatal dopamine and dopamine D2 receptor occupancy by dopamine.[55]

Drugs of abuse directly or indirectly increase the amount of extracellular dopamine in the nucleus accumbens, which is important for its reinforcing effects. However, since drugs have this effect both in addicts and in non-addicts, increased levels of dopamine alone do not explain addiction. The reward pathway in humans is integrated with many other brain regions and is, therefore, able to color experiences with certain emotions and direct an individual's behavior towards rewarding stimuli. One of the brain regions projecting to the nucleus accumbens is the amygdala. The amygdala is involved in the feeling of emotions and plays a role in deciding whether an experience is pleasurable or aversive. Based on that, an individual can decide whether the experience should be repeated or avoided. Furthermore, the amygdala has an important role in memory formation, and in associating experiences and cues. Another brain region integrated with the mesolimbic pathway is the hippocampus, which is important for learning and memory. These memories include when or where and with whom something happened, which are then processed by the prefrontal cortex. The prefrontal cortex is the brain region that ultimately determines the behavior of an individual.[42] Dopamine in the prefrontal cortex influences impulse control, memory, attention, and cognitive flexibility[56]. Following drug intake, human brain scans reveal immediate activity changes in the nucleus accumbens, amygdala, sublenticular extended amygdala, VTA, and prefrontal cortex. Furthermore, these regions are important in the cocaine-induced feeling of rush.[42] Studies have shown that dysfunction in the prefrontal cortex is common to addicts, and is associated with more drug use, and a greater likelihood of relapse. Furthermore, dysfunction in the prefrontal cortex attributes to impaired response inhibition and salience attribution, craving, decreased self-

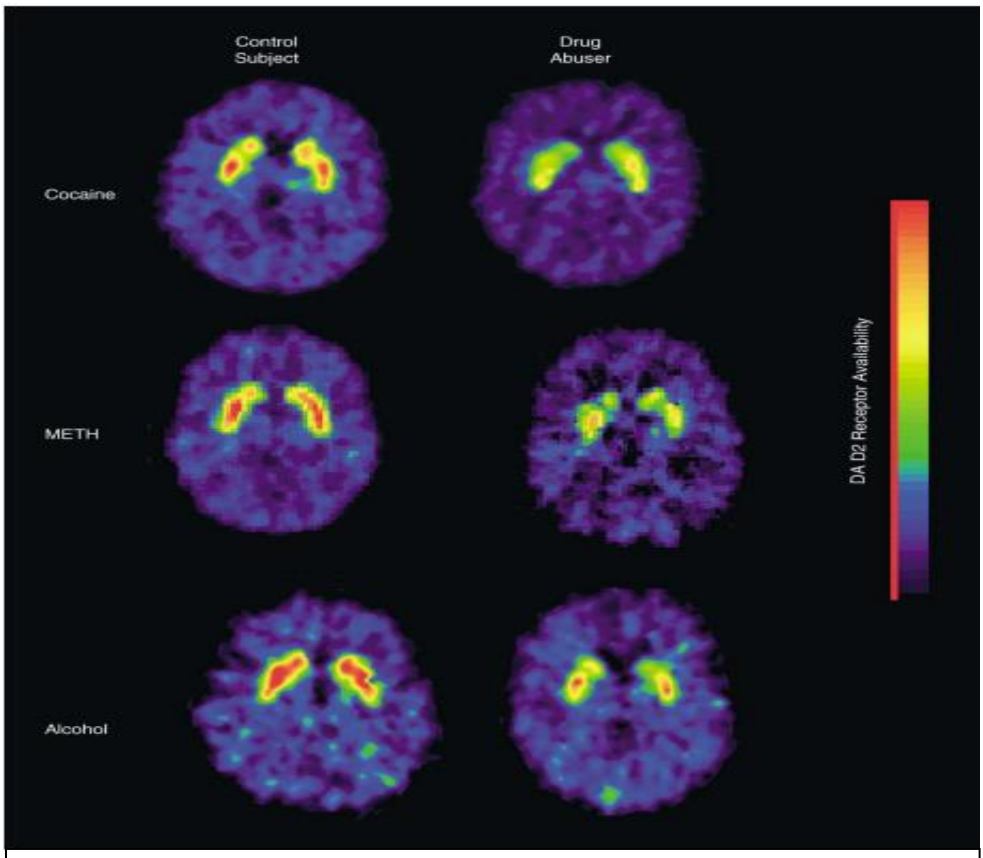

Figure 7. PET scan of the human brain of drug addicts and control subjects. A reduction in dopamine D2 receptors is clearly visible in addicts in the basal ganglia.
Volkow et al. (2002)[55].

awareness, and compulsive use.[57]

Drugs initially increase the concentrations of dopamine in the nucleus accumbens, which induces dopamine-responsive cells to increase the production of cyclic AMP. Cyclic AMP activates CREB, which enhances the expression of genes that code for proteins that decrease the reward circuity. This leads to tolerance and dependence, in which the same dose of a drug doesn't lead to the same feeling of reward, and the individual becomes depressed in the absence of the drug.[42] drug-associated cues evoke compensatory mechanisms that decrease the effect of the drug. This indicates that tolerance is greater in the presence of drug-associated cues[58]. Furthermore, studies have shown that the increase in striatal dopamine and feelings of euphoria following drug use is lower in addicts compared to controls[59]. Moreover, it has been shown that alcohol, cocaine, methamphetamine, and heroin abusers have reduced levels of dopamine D2 receptors in the brain (figure 7)[60,61,62,63]. A loss of dopamine transporters is accompanied by a slower motor function and a poorer memory. It has been hypothesized that individuals with low levels of dopamine receptors, either genetic or by experience, are more at risk of developing a drug addiction. Thus, low levels of dopamine D2 receptors can both be a cause and consequence of addiction. Individuals with low D2 receptor levels and a mesolimbic dopaminergic activation likely experience less dopamine-mediated pleasure from daily activities and are therefore more susceptible to wanting the extreme pleasure that comes with the increased dopamine in the brain after drug use.[55]

5.2. Sex binge/intoxication: *reinforcement, tolerance, dependence*

It has been shown that the mesolimbic reward pathway plays a big role in substance addiction. However, this pathway is very important in sexual behavior as well. Behaviors that are beneficial for the survival of a species, such as reproduction, feeding, and drinking are rewarding so that the behavior is repeated. A study by Kippin et al. (1998) investigated the role of classical conditioning in the copulatory preferences of male rats. The male rats that had been trained to associate a certain neutral odor with sexual activity, preferred to ejaculate with females bearing the odor. The research suggests that olfactory conditioning results in an ejaculatory preference.[64] When the conditioned odor alone was presented to the males, a significant increase in activity was found in the lateral hypothalamic nucleus and the nucleus accumbens core.[65] This indicates that these brain regions are important in sexual behaviors. A study by Pfaus et al. (1990) investigated the brains of rats during sexual activities using microdialysis. When male rats were placed in a mating chamber and a receptive female was presented, dopamine release significantly increased in the nucleus accumbens. Furthermore, the dopamine transmission increased quickly during copulation and decreased after removal of the female. However, striatal dopamine transmission increased only significantly during copulation.[66] These results indicate the importance of dopamine in the reward areas of the brain during sexual behavior, possibly contributing to sex addiction. Another study by Pfaus et al. (1989) found that the administration of dopamine receptor antagonists in the brain of male rats altered copulatory behavior, depending on the site of activation in the brain. Blockade of mesolimbic dopamine receptors may delay the initiation of sex, while mesostriatal blockade (a combination of the nigrostriatal and mesolimbic pathway) may decrease the ejaculation threshold, in which a low threshold means early ejaculation[67]. The dopamine receptors involved in male sexual

behavior are of the D2 subtype, but D1-D2 receptor interaction is well established and D1 and D2 receptors might have opposite roles in the preoptic area.[68] The amygdala has also been shown to be an important structure in substance addiction, by associating the pleasurable emotional responses to certain experiences, such as drug-taking with the feeling of euphoria. This amygdala and ventral striatum interaction has also been shown to be important in associating sexual cues. A study by Everitt et al. (1989) showed that bilateral lesions of the basolateral region of the amygdala in male rats resulted in a decreased response to a neutral stimulus that had been associated with an oestrous female. Furthermore, rats with these lesions were less sensitive to the omission of this conditioned reinforcer than controls. Unconditioned sexual behavior was not altered in the lesioned rats[69].

A study by Holstege et al. (2003) compared the male brain during ejaculation with the brain during sexual stimulation. Intense activation was found in the mesodiencephalic transition zone, which includes structures such as the thalamic nuclei, and the VTA (figure 8). Furthermore, there was increased regional cerebral blood flow in the cerebellum. Although many other brain regions were activated during ejaculation, what is striking about the activation of the VTA and the cerebellum during ejaculation, is that it corresponds to the activation of these areas during the experience of a cocaine and heroin rush. These results implicate that the strongly reinforcing effects of sex and substances are mediated by the same underlying neurological processes.[70]

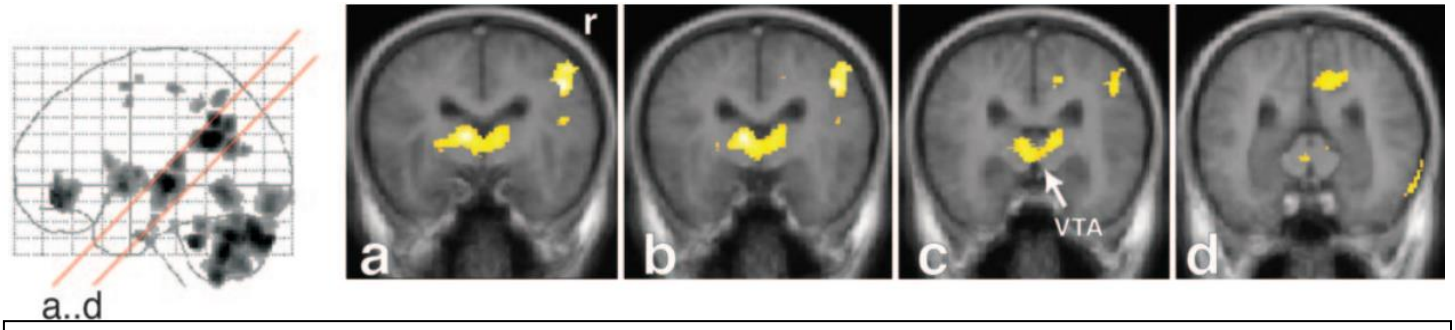

Figure 8. Illustration of brain activation during ejaculation. The activity in the VTA is clearly increased. Holstege et al. (2003)[70].

Frohmader et al (2010) confirmed that drugs and sex activate the same cells involved in the regulation of reward and reinforcement. It was specifically shown that neurons in the nucleus accumbens core and shell, basolateral amygdala, and anterior cingulate area of the medial prefrontal cortex are both activated by sex and drugs[71].

A study by Kühn and Gallinat (2014) investigated how the structural and functional neural changes correlated to the frequency of pornography use. The average amount of pornographic use of participants in this study was 4.09 hours per week. Kühn and Gallinat found a negative correlation between grey matter volume of the right caudate and frequency of pornography use. Thus, grey matter volume of the right caudate of the striatum was smaller when more pornography was used. The part of the caudate in which reduced grey matter was found was within the range of structures that are associated with reward. The left putamen is involved in processing sexual stimuli. Task-related functional activation of the left putamen of the striatum in individuals that

use more pornography was lower when sexual cues were presented than in individuals that used less pornography. Furthermore, connectivity from the caudate to the dorsolateral prefrontal cortex was lower in individuals who used more pornography, which has been associated with loss of behavioral control in general, making individuals vulnerable to addiction or sustaining addiction[72]. More frequent usage of pornography might lead to downregulation and decreased functioning of the brain reward system, which in return leads to the need for more stimulation to receive the same rewarding feeling. However, decreased striatal volume can also be the cause of frequent pornography use. Individuals with a decreased experience in pleasure might need more external stimuli to experience pleasure and might use pornography to feel good.[72] This is very similar to the findings of tolerance and the decreased dopamine receptor levels in drug addicts.

Evidence suggests that alterations in the frontal lobe, hippocampus, hypothalamus, septum, amygdala, and reward pathway are seen in hypersexual patients. Lesioning the frontal lobe may result in disinhibition of sexual behavior, while lesioning the temporal lobe, which includes the hippocampus and amygdala, may result in higher sexual drive.[73] The case study of patients with septal damage that was mentioned before suggests that a dysfunctional or lesioned septal area can result in hypersexuality[74]. Moreover, hypersexuality has been shown to result from diencephalic hypothalamic injury in a study by Miller et al (1986)[75]. Hypersexuality is often seen in Parkinson’s disease patients receiving dopamine replacement therapies. As shown in other studies as well, hypersexuality in Parkinson's patients is associated with increased sexual desire and hedonic responses following sexual cues. These behavioral differences are accompanied by significant blood oxygen level-dependent signal changes in the limbic, paralimbic, somatosensory, prefrontal, and occipital cortices corresponding to emotional, autonomic, visual, motivational, and cognitive processes. fMRI showed that increased sexual desire correlated with enhanced activation of the orbitofrontal cortex, cingulate cortex, and ventral striatum. Patients off their dopamine drugs showed decreases in activation during the presentation of sexual cues, indicating that dopaminergic drugs can release inhibition of neuronal circuits in the cortex, resulting in compulsive sexual behavior.[76]

6.1. Drug preoccupation/anticipation (craving): *sensitization, craving, and cues*

After drug-taking, the CREB activity is high, and eventually, tolerance is developed. However, if an addict doesn't take drugs, the CREB activity declines, and the tolerance makes way for sensitization, the enhancement of the effects of drugs[77]. Sensitization initiates craving, an intense urge to take the drug again, which is a key element to the relapse in drug addicts. The incentive-sensitization theory of addiction consists of the following ideas: addictive drugs increase dopamine transmission. This neural system attributes 'incentive salience' to events and cues associated with the activation of this system. In this way, certain stimuli become attractive, which is associated with 'wanting'. Drugs can stimulate neuroadaptations in this neural system, making it hypersensitive (sensitized) to drugs and drug-associated cues. The sensitization of incentive salience transforms the 'wanting' into craving. This sensitization of neural systems responsible for incentive salience may occur independently of the neural system responsible for 'liking' and the system for withdrawal[78].

Another important molecule for addiction is FosB. Studies have shown that prolonged induction of the molecule FosB, which is produced in the nucleus accumbens, causes mice to become hypersensitive to drugs. These mice were prone to relapsing, which implies that FosB increases long-term sensitivity in the reward pathway. However, FosB is also produced in mice during repetitious non-drug rewards, such as excessively running the wheel, indicating that FosB has a general role in the development of compulsive behavior. Studies have shown that the orbitofrontal cortex becomes hyperactive during drug cravings.[55] Furthermore, the amygdala and the nucleus accumbens influence the craving for more drugs, which becomes stronger when the pleasurable feelings wear off.[42] A study by Meil et al. (1997) showed another important function of the basolateral amygdala. They found that the basolateral amygdala is important for the conditioned incentive properties of drugs, but not for reinforcement. Basolateral lesions abolish the ability of drug-related cues to reinstate responding.[79] Drug addicts are extra sensitive to drug-related cues compared to non-addicts. When drug-related cues, such as a video of someone using cocaine, are shown to cocaine addicts, the nucleus accumbens, amygdala, and cortical regions increase in activity. An increase in activity in these regions is also shown in gambling addicts who are shown a picture of a slot machine.[42] Furthermore, a study by Li et al. (2015) compared the brains of healthy subjects, relapsers, and non-relapsers after exposure to heroin-related cues and found a significant increase in brain response in the heroin-dependent group compared to healthy subjects in the mesolimbic pathway, prefrontal regions and visuospatial-attention regions. Relapsers however show significantly greater cue-induced craving and brain response in the bilateral nucleus accumbens/subcallosal cortex and cerebellum compared to non-relapsers. These results indicate that increased activation in the nucleus accumbens and cerebellum can predict relapse in heroin addicts.[80]

6.2. Sex preoccupation/anticipation (craving): *sensitization, craving, and cues*

Adaptation of the VTA and nucleus accumbens neurons are the underlying cause of behavioral sensitization. Sensitization in a drug addict is a phase in which the individual is hypersensitive to drug cues, and the pleasurable effects are increased[81].

However, a study by Fiorino et al. (1999) revealed that sensitization resulting from drug administration can “cross-sensitize” to sex and that increased release of dopamine in the nucleus accumbens may contribute to the facilitation of consummatory and appetitive aspects of sexual behavior. In their study, male rats were either given saline or a D-amphetamine injection. Three weeks after the last injection, sexual behavior was tested in these male rats, who were sexually naïve. The efflux of dopamine in the nucleus accumbens of D-amphetamine sensitized rats was increased compared to non-sensitized saline rats when a receptive female was presented behind a screen. Furthermore, the sensitized rats exhibited facilitated sexual behavior indicated by significant shorter latencies to mount and intromit. The increase in dopamine efflux in the nucleus accumbens of sensitized rats during copulation was higher compared to non-sensitized saline rats. These results support the hypothesis that mesolimbic dopamine has a role in motivating behavior. Furthermore, the results indicate that changes in this pathway contribute to sensitized behavior in response to drug administration, but also in response to natural stimuli.[82] The transcription factor delta FosB, causing sensitization in drug addicts, has been shown to increase in the nucleus accumbens in response to sexual behavior. Expression of delta FosB in the nucleus accumbens is associated with sexual reward and overexpression with increased aspects of sexual behavior such as copulatory efficiency, which is shown in hamsters[83]. Thus, it can be concluded that delta FosB also plays a key role in mediating sexual behavior and possibly sex addiction as well. Chronic exposure to delta FosB inducing stimuli can also increase the consumption of other natural rewards.[84] This is very similar to the finding that drug addicts are more vulnerable to developing addictions to other substances than non-addicts are. A study by Gola et al. (2017) investigated the brain reactivity to erotic stimuli and monetary gains, comparing the brains of problematic pornography users (PPU) and controls. Results showed that PPU had increased activation in the ventral striatum for cues predicting erotic pictures, but not for cues predicting monetary gains. The sensitivity for sexual cues was significantly related to the severity of the problematic pornography use, the frequency of sexual activity, and the increased behavioral motivation to watch sexual images, indicative of a higher ‘wanting’. Liking was not different between PPU and control subjects, indicating dissociation of ‘wanting’ and ‘liking’.[85] This is in line with the incentive salience theory of addiction, as seen in drug addicts. Moreover, a study by Voon et al. (2014) compared the brain reactivity to sexual cues in compulsive sexual behavior (CSB) subjects and control subjects. The study shows a greater sensitivity to sex-related cues in CSB subjects compared to control subjects. Following sexually explicit cues, greater activation of the dorsal anterior cingulate, ventral striatum, and amygdala was found in CSB compared to control subjects, which was associated with greater sexual desire, but not greater liking, in CSB subjects. Stronger activation in these regions and greater wanting, but not liking, is also found in drug addicts[86]. There is overlap in the neural response to sexual cues in CSB subjects, and the response to drug cues in drug addicts. This implicates overlap in the neural networks underlying drug addiction and sex addiction. A study by Klucken et al. (2016) showed that subjects with compulsive sexual behavior disorder had a different brain response to cues that were conditioned with sexual stimuli compared to healthy control subjects. Increased activity in the amygdala and a decreased ventral striatal prefrontal cortex coupling were found. Subjects with compulsive sexual behavior established associations between neutral cues and sexual stimuli easier. This could both be a cause or consequence of sexual behavior. Furthermore, the decreased ventral striatal prefrontal coupling causes

impaired regulation processes, such as an altered control of impulsivity and impairment of inhibition, that support the maintenance of problematic behavior.[87] This finding is in accord with studies on the drug-addicted brain.[88] Individuals with problematic hypersexual behavior have a lower threshold for sexual desire and experience heightened levels of sexual desire after seeing sexual stimuli. Furthermore, altered activity in the prefrontal cortex and subcortical areas, including the caudate nucleus, submarginal gyrus, anterior cingulate cortex, and right thalamus can be seen. Altered activation in these regions implies that excessive attention is paid to sexual stimuli and that there is an automatic response to sexual stimuli because responses cannot be mediated properly. In individuals with problematic hypersexual behavior, the prefrontal cortex has been shown to overreact following sexual cues compared to controls, and underreact following neutral cues, something is also seen in drug addiction.[89]

7.1. Drug withdrawal/negative effects

Kornetsky et al. (1979) suggested that the abuse liability of drugs such as cocaine and morphine may be related to their ability to decrease brain stimulation reward thresholds and therefore increase reward[90]. However, chronic drug use increases reward thresholds and thereby decreases reward during withdrawal. When low levels of substances are detected in an addict, the body starts going through withdrawal. Withdrawal is a combination of negative physical and mental effects resulting from low body substance levels and psychological dependence. The decrease in dopamine and dopamine D2 receptors in the brain as seen in drug addicts, may contribute to the feelings of anhedonia and depression that addicted individuals experience during withdrawal. Furthermore, a decrease in dopamine in the brain might decrease sensitivity to reinforcing stimuli that are not drug-related, and addicts may take the drug again to compensate for the decreased activation of the dopaminergic mesolimbic pathway. Interestingly, the dopamine receptor reduction is also associated with a decrease in activity in the orbitofrontal cortex, which might be one of the mechanisms underlying the compulsive drug administration in an addict[55]. Chronic opiate exposure leads to overall changes and impairment of the VTA neurons, which contributes to the aversive state during withdrawal. The initial use of substances such as alcohol, cocaine, amphetamine, and nicotine may enhance the functioning of the hippocampus, resulting in an increased formation of drug-context associations. This contributes to the formation of an addiction. however, withdrawal from substances leads to hippocampus-dependent learning and memory deficits, which can lead to relapse to substance use in an attempt to lessen these deficits.[91]

Besides changes in the dopaminergic pathways, increases in norepinephrine and corticotrophin-releasing hormones are implicated in withdrawal (figure 9). These molecules can produce aversive or anxiety-like states during the withdrawal of substances of abuse.[43] The locus coeruleus is located in a noradrenergic nucleus located in the brain stem and projects to the spinal cord and many brain regions. It regulates arousal and response to stressful situations. The symptoms of opioid withdrawal are caused by increased neuronal activity in among others the locus coeruleus[92]. A mechanism by which the locus coeruleus is activated during withdrawal is by the cAMP pathway, which is upregulated during drug abuse and after abstinence[93]. This is possibly due to an increase in CREB levels. Evidence for this is found in individuals who chronically administrate morphine[94]. The behavioral and physical symptoms of withdrawal such as shakes and diarrhea are mediated by the hypothalamus and locus coeruleus, whereas the motivational aspects of withdrawal mostly involve the nucleus accumbens[95]. A study by Maldonado and Koob (1993) supports the idea that the locus coeruleus is involved in the physical symptoms of withdrawal. Rats with lesions of the locus coeruleus showed less severe withdrawal symptoms; mastication, rearing, ptosis, eye twitch, hyperactivity, and piloerection were significantly lower.[96] Furthermore, the injection of noradrenergic receptor antagonists in the bed nucleus of the stria terminalis in rats lowers the opiate withdrawal-induced conditioned place aversion. Noradrenergic neurons projecting to the BNST from the caudal medulla are also activated during withdrawal and lesions of these projections also decrease the withdrawal-induced place aversion[97].

7.2. Sex withdrawal/negative effects

An important stage of addiction is withdrawal. A study by Potenza (2006), 98 percent of sex addicted patients reported withdrawal symptoms following a reduction in

sexual behavior, 94 percent failed to reduce or control addictive sexual behavior, 92 percent spent increased amounts of time on sexual activities, 94 percent spent significant time preparing for or recovering from sexual activities and 85 percent continued sexual behavior despite negative consequences.[34] Sex addicted patients describe an intense feeling of dysphoria and depression when attempting to reduce sexual behavior.[98] In a study by Andreassen et al. (2018), sex addicted patients reported feeling restless and troubled while abstaining from sexual activities.[99] However, the knowledge on withdrawal in sex addicts comes from self-report studies. The brain of sex addicts during withdrawal and the underlying neurocircuitries of withdrawal have yet to be investigated.

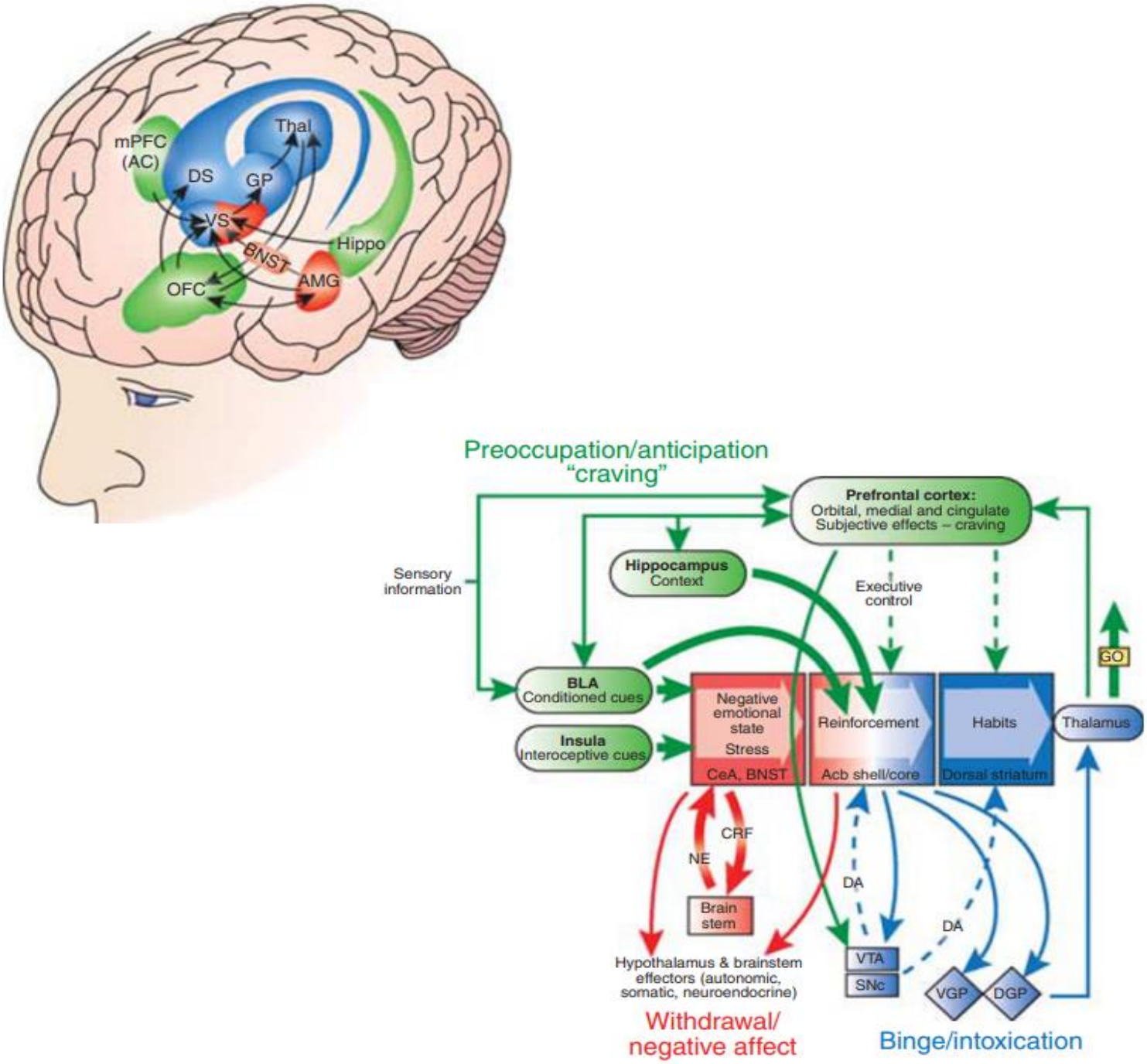

Figure 9. A schematic illustration of the brain areas and molecules involved in addiction, divided into three stages: binge/intoxication, preoccupation/anticipation and withdrawal/negative effects. Acb, nucleus accumbens; BLA, basolateral amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; VGP, ventral globus pallidus; DGP, dorsal globus pallidus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; NE, norepinephrine; CRF, corticotropin-releasing factor; DA, dopamine; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; VS, ventral striatum; DS, dorsal striatum; Hippo, hippocampus; Thal, thalamus.
Koob et al. (2010)[43].

Discussion/conclusion

Although a large number of people report having symptoms of sex addiction and receive therapy for it, very little research is done on the brain adaptations in individuals with such symptoms, resulting in the exclusion of ‘sex addiction’ from the DSM-5TR. Therefore, the aim of this report was to investigate the legitimacy of the diagnosis of ‘sex addiction’ and whether the disorder should be taken up in the DSM or not. By means of literature research, current insights into the characteristics of a substance use disorder/drug addiction and a sex addiction were summarized.

Sexual behavior is complex and involves the activation and deactivation of many parts of the brain, such as the insula, cingulate cortex, thalamus, amygdala, orbitofrontal and prefrontal cortices, hypothalamus and septal region. Most of these brain regions are integrated with the reward pathway, which has been shown to play a crucial role in forming and sustaining an addiction. Furthermore, Frohmader et al. (2010) found that neurons in the nucleus accumbens core and shell, basolateral amygdala, and anterior cingulate area of the medial prefrontal cortex, are activated in a similar way by drugs and sex. It was long known that sex is a rewarding behavior, encouraged by the brain because it helps the survival of a species. Studies such as the one by Pfaus et al. (1990) demonstrate the importance of dopamine in the nucleus accumbens in the rewarding aspect of sexual behaviors. Although the release of dopamine and activation of the nucleus accumbens, amygdala, and prefrontal cortex are important for the formation of an addiction, this can be seen both in addicts and in non-addicts, thus in itself does not explain addiction. Tolerance, sensitization, craving, and withdrawal are important aspects of addiction. Tolerance in drug addicts is associated with reduced mesolimbic functioning and decreased levels of dopamine and dopamine D2 receptors in the striatum. A study by Kühn and Gallinat (2014) showed that increased hours of pornography use, a sexual activity also seen in addicts, is associated with decreased striatal volume and striatal activity to sexual cues. However, these subjects were not diagnosed with addiction. Sensitization in addicts is characterized by an increase in sensitivity to drugs and drug cues. A study by Voon et al. (2014) showed that subjects with compulsive sexual behaviors show greater sensitivity to sex-related cues than healthy subjects. Furthermore craving, and higher ‘wanting’ but not ‘liking’ per se as seen in drug addicts, is also seen in problematic pornography users. Withdrawal in drug addicts is characterized by negative physical and mental effects and changes in dopamine, norepinephrine and corticotrophin-releasing hormones. Withdrawal in sex addicts has been self-reported as negative physical and mental effects, but the brain of sex addicts during withdrawal has yet to be investigated. Table 1 shows an overview of important characteristics of the brain of a drug addict compared to characteristics of the brain of a sex addict.

Although the current studies provide some evidence supporting the idea that sex can be addictive, more research, especially research on the brain, is needed to state this with certainty. Most research on sexual behavior focuses on healthy individuals or individuals that frequently use pornography. Moreover, the studies that do investigate ‘sex addicts’, often study the behavior of such addicts and not the underlying brain patterns. The knowledge of mental disorders continues to be advanced with more research and more cases, implicating that the current exclusion of sex addiction from the DSM-5TR does not necessarily mean that sex addiction is not a real disorder. Rather, not enough is known to give an accurate statement on this topic, and the

current exclusion of sex addiction from the DSM is therefore marked by legitimate reasons.

DRUG ADDICTION	SEX ADDICTION
Increased dopamine release in the nucleus accumbens following drug use.	Increased dopamine release in the nucleus accumbens following sexual activities.
Decreased self-administration of drugs following mesolimbic lesions in rats.	Delayed initiation of copulation following mesolimbic dopamine receptor antagonists in rats.
A shift from the ventral to the dorsal striatum, associated with the shift from use to addiction.	?
Important role of the amygdala, hippocampus, nucleus accumbens, VTA and PFC.	Important role of the in amygdala, hippocampus, nucleus accumbens, VTA and PFC.
Prefrontal cortex dysfunction found in drug addicts is associated with compulsive use and craving.	Decreased ventral striatal prefrontal coupling found in sex addicts is associated with altered control of impulsivity and inhibition.
Drug craving involving increased activation of multiple brain areas.	Sexual craving involving increased activation of the same brain areas.
Downregulation of reward in addicts, lower dopamine and D2 receptor levels as cause or consequence.	Decreased striatal volume and downregulation of reward system as cause or consequence.
Sensitization and craving for drug and drug cues.	Sensitization for sexual activities and sexual cues.
Increased delta FosB in sensitization.	Increased delta FosB in response to sexual behavior.
'Wanting' and 'liking' involves different neural processes and 'wanting' is increased in addicts.	'Wanting' and 'liking' involve different neural processes and just 'wanting' is higher in addicts.
Withdrawal.	Self-reported withdrawal symptoms.

Table 1. A summary of what is seen in the brain of a drug addict compared to the brain of a sex addict.

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