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SEX ADDICTION (S KRAUS, SECTION EDITOR)

Should Sexual Offending Be Considered an Addiction? Implications for Prevention and Treatment Approaches

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Abstract
Purpose of Review Although the neurobiology and neuropharmacology of sexual behavior have not yet been clearly elucidated, several studies characterized the brain areas, neurotransmitters, and circuits involved in sexual disorders. Emphasis has been placed on the importance of brain dopaminergic pathways. The influence of serotonin, testosterone, and luteinizing hormone was also examined.
Recent Findings Many of the addiction's brain networks have been elucidated through identification of neural circuits involving the regulation of reward processes using animal models. In addition, neuroimaging studies have identified the strong links between sexual disorders and specific brain regions.
Summary A deeper understanding of the pathophysiology of sexual addiction should lead to more focused treatment strategies such as naltrexone treatment. Moreover, it should be noted that a variety of neuropsychiatric disorders, such as postencephalitic neuropsychiatric syndromes, temporal lobe epilepsy, tumors in the frontal or temporal regions, and multiple sclerosis, can potentially lead to paraphilic behaviors or be associated with hypersexuality. The challenge for future research is to understand better the most important aspects of these disorders and their complex relationships to highlight new pharmacological targets for the better therapeutic management of deviant sexual disorders as well as hypersexuality.

Keywords Paraphilia · Sex offense · Hypersexuality · Compulsive sexual behavior · Sexual impulsivity · Sexual addiction · Neurobiology · Neuroimaging

This article is part of the Topical Collection on *Sex Addiction*

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Introduction

"Sexual offenders" or "sex offenders" are defined as individuals who have either been officially charged with a sexual crime (e.g., child molestation, rape, exhibitionism, voyeurism), have performed an act that could be officially charged, or committed sexually abusive/aggressive behavior or any sexual act with a person of any age, against the victim's will or, in an aggressive, exploitative, or threatening manner; the term "child molester" refers to those who choose only or primarily a child victim [1–3]. Most of the sexual offenders are males [4•] and this paper will focus on them. There are few reports on female sexual offenders associated with hypersexuality [5]. The terms "sex offenders" or "sexual offenders" and "paraphilic disorders" will be used throughout the paper. In order to clarify the respective use of these words, it is important to remember that not all sexual offenders suffer from a paraphilic disorder but only part of them [6] and that not all patients with a paraphilic disorder are sexual offenders (in some cases, they only suffer from deviant sexual fantasies or urges, or their deviant sexual behavior does not involve a non-consenting person or a child). [7••, 8••]

Paraphilic disorders are sexual stimuli or acts that are deviations from socially accepted sexual behavior. For some individuals, paraphilic fantasies or stimuli are obligatory for erotic arousal and are always included in their sexual activity (exclusive paraphilic disorders). In other cases, the paraphilic preferences occur only episodically whereas, at other times, the person is able to function sexually without deviant stimuli or fantasies [3, 9•]. Paraphilic disorders are distributed from a spectrum of nearly normal behavior to being hurtful or destructive to oneself or others. In the Diagnostic and Statistical Manual Disorder, Fourth Edition, Text Revision (DSM-IV-TR) or in the International Classification of Mental Diseases (ICD-10th), paraphilia were classified in the "Sexual and Gender Identity Disorders" chapter and were characterized by "recurrent, intense, sexually arousing fantasies, sexual urges or behaviors, generally involving (1) non-human objects, (2) the suffering or humiliation of oneself or one's partner, or (3) children or other non-consenting persons that occur over a period of 6 months" (criterion A), which "cause clinically significant distress or impairment in social, occupational, or other important areas of functioning" (criterion B). The most important change in DSM-5 is the distinction between paraphilia and paraphilic disorders: "a paraphilia by itself would not automatically justify or require psychiatric intervention. A paraphilic disorder is a paraphilia that causes distress or impairment to the individual or harm to others." In this conception, having paraphilia would be a necessary but not a sufficient condition to determine a paraphilic disorder. The DSM-5 describes eight specific paraphilic disorders (exhibitionism, fetishism, frotteurism, pedophilia, sexual masochism, sexual sadism, voyeurism, and transvestic fetishism) along with a residual category called "paraphilia not otherwise specified." Patients with paraphilic disorders usually come to medical or legal attention by committing an act against a child or a non-consent adult because most of them, especially adolescents, do not find their sexual fantasies distressing or ego-dystonic enough to voluntarily seek treatment or they may feel ashamed but do not dare to ask for medical advice prior to sexual acting-out. In general, individuals with exhibitionism or pedophilia make up the majority of apprehended sex offenders. The etiology of paraphilias is still unclear despite years of research. Various psychological, developmental, environmental, genetic, and organic factors have been discussed, but none of the theories fully explains paraphilic behaviors. The causes are probably multifactorial, rendering treatment difficult [7••, 8••].

In contrast, an excessive sexual behavior is characterized by excessive repetitive expression of culturally adapted normophilic (non-deviant) sexual behaviors. According to some authors, this syndrome is referred to as sexual impulsivity [10], sexual addiction [11], or compulsive sexual behavior (CSB) [12]. CSB can be considered to be related to impulse control disorders. Indeed, CSB characterized by craving and impulsivity is associated with a significant level of distress and sexual dysfunction resulting in psychosocial impairments [13]. In 1992, ICD-10 included "excessive sexual drive" as a distinct nosological category, subdividing it into "satyriasis" in men and "nymphomania" in women [14•]. In 2001, the diagnosis of sexual addiction was removed from DSM categories. In fact, some authors view non-drug or behavioral addictive behaviors, such as sexual addiction, as being compulsions (compulsive-impulsive model) that involve a spontaneous desire to act in a particular way, a subjective sense of feeling temporarily out of control, psychological conflict pertaining to the imprudent behavior, settling for less to achieve the same ends, and a disregard for negative consequences. Others use the term compulsion as a simple but intense urge to do something or may define it more precisely as an intense egodystonic urge to engage in a simple, repetitive activity to decrease anxiety. In fact, a narrow definition does not consider the role of higher-order cognitive processes such as planning an action, which is observed in addictions. In the case of compulsion, the act may result in a temporary removal of anxiety but tends not to be experienced as pleasurable which is an essential element in an addictive behavior (for review [15]). In fact, behavioral addictions share with substance-use addictions craving, dependence, tolerance, and abstinence and maybe a shared pathophysiology. A deeper understanding of the pathophysiology of sexual addiction should lead to more focused treatment strategies. Up to now, pharmacological treatment of most of the behavioral addictions is empirical.

Relationships Between Hypersexuality, Early Exposure to Sex, and Sexual Offending

In an online study conducted in a large non-clinical community sample of 8718 German males, self-reported child pornography use was associated with sex drive, sexual fantasies involving children, and antisociality [16]. Participants' mean age was 43.5 years (SD = 13.7); 12.1 % of the individuals were classified into the hypersexual group according to the classical cut-off value of total sexual outlet ≥7 per week; 4.1 % reported sexual fantasies involving prepubescent children, 3.2 % sexual offending against prepubescent children, and 0.1 % a pedophilic sexual preference; in convicted sexual offenders of the sample, antisociality, hypersexuality, and pedophilic interests were also important predictors of sexual reoffending against prepubescent children. Furthermore, hypersexual behavior patterns seem to be more likely in sexual offenders than in community controls [17]. In the same way, Långström and Hanson reported an association between hypersexuality and paraphilic interests in a community sample.

Paraphilias are commonly associated with sexual hyperactivity, often with compulsive and/or impulsive features. In Kafka and Hennen' study [18], paraphilia was associated with sexual hyperactivity in 72–80 % of 120 evaluated men seeking treatment for paraphilias or paraphilias-related disorders.

Hypersexuality was also found among the most important risk factors for sexual offending or reoffending [19, 20]. Similarly, pornography consumption (understood as a behavioral pattern possibly related to hypersexual behavior) was associated with recidivism in a sample of 341 high-risk sexual offenders against children [21]. It should also be mentioned that sex-addictive behavior appears to be more prevalent in anxious or depressed patients [22].

On the other hand, in rare cases, sexual addiction may be associated with indecent exposure or to rapes, but the incidence of sexual offending in sexual addicts is poorly known. The comorbidity of both types of behavior and their relationships remain poorly understood. In both syndromes, SSRIs have been used for treatment [23].

Early childhood sexual stimulation could play a significant role in sexually addictive behavior particularly in childhood sexual abuse, which can lead to sexually dysregulated behavior such as pedophilic fantasies [24, 25].

Some authors have suggested that childhood sexual victimization potentially increases the potential for later sexual acting-out in males [26]. Becker et al. [27] have suggested a probable basis for the development of a deviant sexual arousal pattern in these children. They assume that deviant sexual arousal and behavior are learned in individuals through modeling and conditioning experiences. Concomitant with the experience of pleasure and the absence of aversive consequences (punishment) of sex offenses are cognitive distortions which help the perpetrator deny, minimize, or rationalize his behavior. Early exposure to sex or pornography and sexual violence might also play a role in further sex offending or hypersexuality [28•]. This is consistent with animal studies showing that the impact of damage to neurobiological substrates of the sexual behavioral system on sexual functioning depends on the existence of prior sexual experience [29]. Indeed, lesions before sexual maturity in the anterior hypothalamus for males and the ventromedial hypothalamus for females eliminate sexual behavior in rats whereas the same operation was occurring in animals with sexual maturity and sexual experience has much less of an impact [29].

Neurobiology and Neuroimaging of Sexual Offending Associated to Paraphilia and of Sexual Addiction and their Relationships

Neurobiology

Many of the addiction's brain networks have been elucidated through identification of neural circuits involving the regulation of reward processes using animal models [30••]. The reward center, composed of mesolimbic incentive salience circuitry, governs all behaviors in which motivation has a central role, including acquiring food and having sex.

Dopamine (DA) receptors present in cortical and limbic areas are involved in reward and affective behavior, and in the control of impulsivity. Disturbance of nigrostriatal, mesolimbic, and mesocortical dopaminergic transmission may affect affective–impulsive components of behavior. It should be noted that these circuits play a significant role in the positive reinforcing effects of drugs of abuse [31]. Besides, the nucleus accumbens (NAc), containing nerve endings of mesolimbic dopaminergic neurons, appears to mediate the effects of sexual stimulus [32–34]. Furthermore, direct DA receptors stimulation might increase levels of oxytocin and thus may influence sexual activity by improving erectile stimulation. Also, under the effect of oxytocin release, brain regions affecting the activity of mesolimbic dopaminergic neurons mediate reinforcing effects of sexual activity. Moreover, it has been shown that DA release in the shell of the NAc correlates with apomorphine-induced penile erection episodes and is completely abolished by raclopride (a selective D2/D3 receptor antagonist) as well as oxytocin receptor antagonists [34]. This is consistent with Collins'study which showed that the D3 receptor antagonist PG-01037 inhibited the induction of penile erection.

According to some authors, sex addiction may be associated with other disorders characterized by impulsive behavior. In this context, hypersexuality could thus be linked to an initial impulsive behavior involving frontal lobe hyperactivity in connection with dopaminergic transmission [35]. Moreover, it should be noted that hypersexuality has been associated with complications in Parkinson's disease and its treatment with dopaminergic therapy [36, 37]. Indeed, pathological hypersexuality observed in Parkinsonian patients treated with dopamine agonists strongly suggests the involvement of dopaminergic receptors. The administered agonists (pramipexole, ropinirole, pergolide, and bromocriptine) exhibit binding affinity for D2 and D3 receptors [38, 39]. However, the D3 receptor is highly expressed in the brain's limbic area [40, 41]. Thus, the involvement of excessive stimulation of the D2 receptor class and, in particular, the D3 receptor class in mediating this behavior has been suggested. This view is further supported by the observation described among the comments relating a pervasive behavioral syndrome characterized by self-medication and addiction to dopaminergic drugs. Inappropriately increasing doses of dopaminergic medications leads to excessive dopaminergic stimulation and resulted in the development of hypersexuality [42]. Thus, it can be postulated that DA receptor agonists may significantly contribute to the development of hypersexuality [35].

In a neurogenetic study, a variation of expression of a gene encoding for the dopamine receptor D4 can lead to downregulating dopaminergic activity and constitute a factor that may affect youth risk behavior [43]. Besides examining genes for the D1, D2, and D4 dopamine receptors and age at first sexual intercourse (AFSI), it has been shown that the DRD2 allele

was significantly associated with AFSI. Furthermore, this association appears to be higher when the DRD2 allele interacted with a DRD1 allele [44]. It has also been shown that 7-repeat allele was associated with blunted dopamine response, sensation seeking, reward-related ventral striatum reactivity, and impulsivity. In addition, different types of sexual behavior characteristics including sexual arousal have been linked to a variation in the DRD4 gene [45]. It was also suggested that exposure to stressful conditions may modulate DRD4 expression and thereby increase adolescent problem behaviors [46]. The role of the DRD4-allele is not clear since it was suggested that it could amplify favorably or unfavorably the effects of the environment [46].

In addition, it has been shown that both behaviors (sex) and drugs of abuse induce long-term changes in the mesolimbic and nigrostriatal dopamine pathways including sensitization in the nucleus accumbens (NAc) and dorsal striatum [47]. It should also be mentioned that pharmacologically induced (selegine) paraphilic behaviors in Parkinsonian patients [48] may be related to increased dopaminergic stimulation of the nucleus accumbens and mesolimbic/mesocortical circuits [49]. Therefore, an exacerbation of levels of dopaminergic transmission may strengthen aberrant reward sensitivity and could constitute a critical condition leading to these behaviors.

A study using bilaterally implanted bipolar electrodes, in the lateral hypothalamus and substantia nigra-ventral tegmental area, to generate chronic self-stimulating reward experiences similar to sexual behavior, found that the number of synapses in the CA3 region of the hippocampus and the molecular layer of the motor cortex of rats were significantly increased [50]. Moreover, it is known that chronic brain stimulation induces long-term potentiation (LTP) and thereby increases new synaptic connections or strengthens the existing synapses [51]. However, sustained changes in the ventral tegmental area (VTA) glutamatergic synapses that resemble activity-dependent LTP in other brain regions occur following exposure to a single sensitizing dose of cocaine. This cocaine-induced LTP seems to be mediated via dopamine D5 receptors and activation of N-methyl-D-aspartate (NMDA) receptors [52]. It can be speculated that drugs and sex may have shared neurochemical substrates.

Although ghrelin, a 28-amino acid peptide, is mainly produced and secreted from peripheral tissues, certain parts of the brain might secrete it too. Interestingly, ghrelin has been shown to increase anxiety- and depression-like behavior in rodents [53] and may influence memory formation via hippocampal GHS-R1A [54]. GHS-R1A are expressed in mesocorticolimbic structures including the ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, and prefrontal cortex (PFC) [55]. In addition, reward-related brain areas including VTA and NAc constitute a target for ghrelin [54, 56–58]. The fact that ghrelin is capable of activating the mesolimbic DA system would suggest a significant impact on the incentive value of signals associated with rewards and motivated behaviors. Indeed, intracerebroventricular administration of ghrelin increases accumbal dopamine release, thereby activating the reward systems [58]. Thus, it has been suggested that sexual behaviors may involve ghrelin signaling via the mesolimbic dopamine system [59].

A serotonin influence on sexual behavior has also been demonstrated in animal and clinical studies [60]. Relationships have been found between 5HT dysregulation and specific dimensions of psychopathology: antisocial impulsivity, anxiety, depression, and hypersexuality [61, 62]. Pharmacological treatments modulating serotonin levels seem to have a certain efficiency in both paraphilic and nonparaphilic sexual disorders [63]. Indeed, SSRIs are used to decrease impulsivity. Additionally, SSRIs have proved to be useful in the treatment of hypersexuality due to their inhibitory effects on 5-HT2 receptors [64]. Furthermore, the amygdala is a brain area of serotonergic neurotransmission modulation, and has been implicated in processing the emotional relevance of sensory stimuli [65] and to have an influence on human sexual behavior [66].

Other neurotransmitters modulate the amount of dopamine released in response to a stimulus, with the salience determined by the intensity of the dopamine pulse. Opiates (either endogenous or exogenous) exemplify such modulators. Testosterone, the principal androgen produced by the testes, plays apparently a significant role not only in the development and maintenance of the male sexual characteristics but also in the regulation of sexuality, aggression, cognition, emotion, and personality [67]. In particular, it is a primary determinant of sexual desire, fantasies, and behavior, and it controls the frequency, duration, and magnitude of spontaneous erections. A minimal level of testosterone is necessary for the sexual drive in males; however, the threshold remains questionable. Testosterone levels do not correlate with the intensity of sexual drive. There is no clear evidence that subjects with paraphilias have higher basic testosterone levels, nor data indicating an increased androgen receptor activity. In paraphiliacs, no difference in self-reported measures of sexual behavior was reported with regards to baseline serum testosterone levels (below or above 300 ng/dl) [7••, 8••, 68]. A marked hypersecretion of luteinizing hormone (LH) was reported in response to gonadotrophin-releasing hormone (GnRH) in pedophiles, as compared to controls and other paraphiliacs, whereas baseline LH and testosterone values were within the normal range. These data may indicate a hypothalamic-pituitary-gonadal in pedophiles [69]. The expected benefit of suppressing testosterone to castration level probably derived from decreasing sexual arousal in general.

Neuroimaging

Based on functional magnetic resonance imaging (fMRI) results in healthy men, brain regions have been suggested to be

associated with the neurobehavioral component of sexual arousal [70] (Table 1).

Recently, the brain areas activated in eight adult healthy males during visually evoked sexual arousal were evidenced using positron emission tomography [77]. There were visual association areas (inferior temporal cortex, bilateral) and paralimbic areas related to highly processed sensory information with motivational states and to the control of autonomic and endocrine functions (right insula, right inferior frontal cortex, left anterior cingulate cortex). Activation of some of these areas was positively correlated with plasma testosterone levels. However, the link between neuronal activity and deviant sexual behavior or hypersexuality remains unclear [78]

Voon and col have recently published that CSB subjects had a greater desire but similar liking scores in response to sexually explicit videos. Exposure to sexually explicit cues in CSB compared to non-CSB subjects was associated with activation of the dorsal anterior cingulate, ventral striatum, and amygdala. Functional connectivity of the dorsal anterior cingulate-ventral striatum-amygdala network was associated with subjective sexual desire (but not liking) to a greater degree in CSB relative to non-CSB subjects. The dissociation between desire or wanting and liking is consistent with theories of incentive motivation underlying CSB as in drug addictions. Neural differences in the processing of sexual-cue reactivity were identified in CSB subjects in regions previously implicated in drug-cue reactivity studies [79•].

As modern neuroimaging techniques become available, several studies suggested that impulsivity and aggression might be related to the altered inferior frontal white matter. For instance, in an imaging study, axial diffusion tensor images (DTI) acquired using a pulsed gradient, double spin echo, echo planar imaging method found that certain aspects of impulsivity were associated with decreased white matter organization in the inferior frontal cortex [80], altered frontal white matter microstructure in inferior frontal areas, which modulates executive function and inhibitory control [81] and alterations in orbitofrontal and limbic regions [82]. Furthermore, it has been shown that patients showing greater proclivities to violence or antisocial behavior have inferior frontal lesions [83, 84]. However, according to Miner's work, the DTI measures, fractional anisotropy (FA) (a scalar metric which provide a quantitative analysis of white matter tract coherence) [85, 86], and mean diffusivity (MD) (which is a measure of the average molecular motion independent of any tissue directionality and is affected by cellular size and integrity) [85, 87] do not show any difference between CSB patients and controls in the inferior frontal region, but rather a significant negative association between the CSB and superior frontal MD [80]. Furthermore, a positive association with FA and negative MD has been described as being associated with the severity of anxiety symptoms [88]. This is in line with increased FA and decreased MD found in patients with panic disorder and posttraumatic stress disorder [88, 89]. Additionally, in brain regions similar to the superior frontal region, DTI studies have shown an increased FA in obsessive-compulsive disorder (OCD) patients [88, 90, 91]. This highlights that CSB is not only characterized by impulsivity but also associated with other components involving emotional reactivity and anxiety.

Combining emotional, sexual, motivational, and vegetative aspects, paraphilia, specifically pedophilia, reflects the complexity of this disorder. Functional magnetic resonance imaging in combination with emotional and/ or sexual stimuli allows highlighting impairment in brain activity. Thus, abnormal neural activities in subcortical (i.e., hypothalamus) and cortical (i.e., left dorsolateral prefrontal cortex, dorsomedial prefrontal cortex) regions have been shown in pedophilia during sexual arousal [92]. Given the fact that, in healthy subjects, the hypothalamus and the dorsal midbrain are known to be involved in the vegetative-autonomic component of sexual arousal [71, 77, 93], it was suggested, in pedophilic patients, possible neural correlates of lack of sexual interest toward adults in pedophilic patients [92]. Thus, deficits in pedophilic patients may be interpreted regarding modified interaction between sexual and emotional functions [94]. Several studies have also supported the hypothesis that cognitive, neurological dysfunction of the frontal brain areas could be associated with pedophilia in male patients [95]. The cognitive component of sexual-cognitive processing seems to be associated with the orbitofrontal cortex and is often reported as

Table 1 Association between brain regions and neurobehavioral following sexual arousal in healthy men

Brain regions	Neurobehavioral	References
Superior parietal cortex	Cognitive component	[71]
Orbitofrontal cortex	Cognitive component	[71]
Cortex and the insular cortex	Emotional component	[72]
Amygdala	General processing of emotions	[65, 71, 73]
Dorsomedial prefrontal cortex	Processing of emotional and sexual stimuli	[74–76]
Cingulate gyrus caudal part of the left anterior	Appetitive or motivational component	[71, 72]
Insula and rostral part of the anterior cingulate cortex, hypothalamus	Autonomic component	[71, 72, 77]

dysfunctional in pedophilia [96–98]. Indeed, functional or structural abnormality of this region may lead to disinhibition of sexual behavior and can affect emotional processes [95]. Based on a fMRI research in pedophilia, abnormal activation patterns in the amygdala and orbitofrontal were highlighted [99], suggesting that anomalies related to these areas could be involved in the etiology of pedophilia [95, 97]. Additionally, Cantor et al. [100] have reported in the left and right temporal and parietal brain regions a decreased white matter volume in 44 male pedophiles as compared with 53 subjects convicted of nonsexual crimes. Schiltz et al., [101] have also observed a reduced right amygdala volume in 13 male pedophiles (heterosexual in 6 cases, homosexual in 3 cases, and bisexual in 4 cases) as compared with 15 controls (without any pedophilia). This abnormality could appear early in life in relationship with environmental or hormonal factors and could later be associated with changes in sexual interest. The amygdala could be involved in sexual behavior in relationship with past sexual experiences. In the same way, paraphilias or, at least, conditions that look very much like paraphilias, have also been reported as the result of brain trauma especially during childhood [102–104], temporal or frontal lobe damage [105, 106], or epilepsy [107, 108], especially in men.

Using positron emission tomography (PET), the right inferior temporal cortex and superior frontal gyrus showed a decreased regional cerebral metabolic rate for glucose reflecting brain dysfunction resulting in a reduction in glucose metabolism in the temporal and frontal cortices involved in cortical regulation of sexual arousal [109].

Moreover, pedophilic urges and behaviors could be related to a disturbance in striato-thalamo-cortical networks. This is in line with decreased gray matter portions within the striatum and the orbitofrontal cortex in pedophiles [110] and cognitive deficits associated with prefrontal and motor processing loops [109, 111].

Furthermore, in a study conducted by Walter et al. with 13 male pedophilic patients [92], an abnormal neural activity in several brain regions, including subcortical and cortical brain regions, especially the hypothalamus and the dorsal midbrain has been shown. It is the same with cortical areas like the dorsolateral prefrontal cortex (DLPFC). However, in healthy subjects (Table 1), subcortical regions (hypothalamus and the dorsal midbrain) have been proposed to be involved in the vegetative-autonomic component of sexual arousal [71, 77, 93]. Thus, lack of sexual interest toward adults in pedophilic patients may be linked to the fact that they have less of ability to recruit vegetative-autonomic regions during the sexual stimulus. In addition, a significant number of these patients exhibit personality disorders [112] including obsessive-compulsive personality [113] and emotional immaturity [106, 111, 114, 115]. No significant correlation was found between pedophilia and any single personality disorder; however, interpersonal deficits including empathic deficits may contribute to the motivation of pedophilic acts [115, 116]. Further, using PET, Mendez et al. reported fronto-temporal dementia and bilateral hippocampal sclerosis in pedophilic patients [106]. In addition, one case of a tumor in the right orbitofrontal cortex has been reported by Burns and Swerdlow in pedophilic patients [96]. These cases thus highlight the potential role of these brain regions in the etiology of pedophilia.

Some authors posited that determining factors could occur during the prenatal period leading to the development of atypical age sexual interests. Thus, early developmental factors, present before birth, could potentially affect physical development [117]. Furthermore, studies carried out by Cantor, using magnetic resonance imaging (MRI), reinforced this neurodevelopmental hypothesis. For example, he showed, in pedophilic patients, white matter deficiencies localized to both the temporal and parietal lobes of the brain. To support this hypothesis, Cantor et al. suggested a possible disconnection in the brain network that responded to sexual signals after having recognized them [100]. In addition, an association between pedophilia and lower cognitive capacity has been interpreted as being the result of impaired neurodevelopment or head trauma before the age of 13 [118, 119].

Implications for Prevention and Treatment Approaches

The beginnings of treatment of the paraphilias can be traced back to the late nineteenth century at a similar time though not directly connected to the new concept of sexual deviance as a medical condition. Interestingly, the initial treatment approach of paraphilias was that of surgical castration, used first for therapeutic purposes in 1892 regarding a patient with imbecility and neuralgic pain of the testis and hypersexuality [120]. In general, pharmacological treatment of sex offenders should follow the principles of the Risk-Needs Responsivity Model, meaning that the higher the risk, the more intensive the proposed effects of medication should be. The criminogenic needs addressed by medications are sexual deviance/paraphilia and hypersexuality/sexual preoccupation [121].

Although hypersexuality or sexual addiction is relatively common, controlled trials on pharmacological treatments are still lacking. The available literature on this topic consists primarily of open-label trials and case-report series in non-deviant hypersexual subjects. In general, pharmacological interventions should be part of a more comprehensive treatment plan including psychotherapy and, in most cases, behavior therapy (for review of the available pharmacological treatments: [122]; for review of the available psychotherapeutic treatments [123].

The literature on treatment of hypersexuality associated to paraphilia is scarce; in many cases of paraphilias,

hypersexuality is not reported or not specifically addressed. For treatment of deviant sexual behavior, please refer to "The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Paraphilias" [8••] and to the "WFSBP Guidelines for the treatment of adolescent sexual offenders with paraphilic disorders" [7••].

There are also several case reports of various medications that have been tried to control the dopamine treatment-related compulsions [122, 124, 125], especially in Parkinsonian patients. The atypical antipsychotics, serotoninergic antidepressants, histaminergic (H2 receptors) antagonists, or antiandrogens (cyproterone acetate, medroxyprogesterone acetate, or GnRH agonists may rarely be used in cases of aggressive sexual behavior) have been found to be of some benefit. Antiepileptics, such as topiramate or zonisamide, were associated with the resolution of impulse control disorders such as hypersexuality in several cases. Family involvement and psychotherapy may also be beneficial.

SSRIs

In the past decade, numerous case reports have described the efficacy of SSRIs or clomipramine in the treatment of paraphilias, as well as non-paraphiliac hypersexuality [126–128]. Indeed, one proposed mechanism of action relates the anti-obsessional effects of SSRIs to the hypothesis that hypersexuality and some paraphilias may be related to OCDs, or even impulsive control disorders [129]. But, despite the increasing clinical use of SSRIs for paraphilias and hypersexuality, double-blind controlled trials with these agents are lacking [7••, 8••].

The only double-blind study conducted by Wainberg et al. [64] compared 20–60 mg citalopram versus placebo in 28 homosexual men with CSB in a 12-week trial. Significant treatment effects were observed on sexual desire/drive, the frequency of masturbation, and pornography use. Fluoxetine has also been shown to be effective in improving mood and reducing inappropriate sexual behavior in subjects with sexual addiction. A daily dose of 20–40 mg has demonstrated efficacy in open studies [130]. The dosage must be increased to the dosages used in obsessive-compulsive disorders in case of insufficiency or lack of efficacy. The SSRIs are also often used to treat the frequently associated depressive symptoms. Indeed, nonparaphilic sexual addictions are often associated with depression, compulsion, and impulsivity [62].

A critical analysis of all studies that involved the use of SSRIs in the treatment of paraphilias concluded that the results of psychotropic drug interventions are not favorable [126]. Rösler and Witzum [131] suggested that they might be effective only in men with a definite OCD component to their sexual behavior. SSRIs have already been included in clinical practice for the treatment of sexual offenders, with specific indications, although more research demonstrating efficacy is much needed (for critical review, see Garcia and Thibaut [132]).

Opioid Antagonists

As neural differences in the processing of sexual-cue reactivity were identified in CSB subjects in regions previously implicated in drug-cue reactivity studies, treatments already used in drug- or alcohol-addicts have been tried in hypersexual patients [92] and paraphiliac patients. Naltrexone is a long-acting opioid antagonist used clinically in the treatment of alcohol dependence or drug abuse. By blocking the capacity of endogenous opioids to trigger dopamine release in the nucleus accumbens in response to reward, naltrexone helps extinguish this reward's addictive power. Opiate receptors are also located on GABAergic interneurons that inhibit ventral tegmental area dopaminergic neurons. Ryback (2004) [133], in an open prospective study, has reported the efficacy of naltrexone, in association with cognitive behavior therapy (mean duration 26 weeks), in 21 hypersexual males who were juvenile pedophiles and legally adjudicated sexual offenders (in-patients) and who met any of the following self-reported criteria: (1) excessive masturbation (>3 times per day), (2) feeling unable to control arousal, (3) spending more than 30 % of awake time in sexual fantasies, or (4) having sexual fantasies or behavior that regularly intruded into and interfered with their functioning in the treatment program. Comorbidities were frequent (mostly ADHD, intermittent explosive disorder, or substance abuse). After having been treated for more than 2 months, 13 patients had their naltrexone administratively stopped, thus providing a before, during, after, and resumption-of-treatment design. Outcome measures were self-report daily sexual fantasies and masturbation numbers. Sexual offense recidivism was not reported. A positive result was recorded if there was more than a 30 % decrease in any self-reported criterion and if this benefit lasted, at least, 4 months. Concomitant medications were SSRIs, antipsychotics, mood stabilizers, or stimulant medications. In 15 cases, naltrexone efficacy was considered as sufficient, and patients continued to respond for at least 4 months to an average dose of 160 mg per day with decreased sexual fantasies and masturbation. Dosages above 200 mg per day were not more helpful. The mean duration of naltrexone treatment was 1.2 year. Administrative discontinuation of naltrexone in a subset of 13 patients resulted in reoccurrence of symptoms that began when the tapered dose reached 50 mg per day. Leuprolide (a GnRH agonist, 3.75 or 7.5 mg/month) was added in six cases of lack of naltrexone efficacy after 3 months (the most severe pedophiles). Five of six patients who did not

benefit from naltrexone (the most serious cases) responded favorably to leuprolide.

Antiandrogen Treatments

Some case reports of antiandrogen treatment success in patients with hypersexuality associated with neurological disorders or to paraphilias will be described.

Medroxyprogesterone Acetate

Some case reports support the use of medroxyprogesterone acetate (MPA) for the treatment of hypersexuality or paraphilic behaviors in older patients with dementia. The beneficial effect of MPA (300 mg/week for 1 year) on acting out (compulsive masturbation, exhibitionism, and rape attempts) was reported in four patients (75 to 84 years old) with dementia [134]. Exhibitionism and rape attempts were successfully treated with MPA (150–200 mg/2 weeks) in two men with dementia (71 and 84 years old, respectively) [7••, 8••, 135]. A hypersexual pedophiliac sex offender was treated with the antiandrogen medroxyprogesterone acetate for 500 days [136]. MPA therapy resulted in decreased libido, few side effects, and no recurrence of sex offenses, without any change in the patient's sexual orientation. Cross et al. [137] have reported the efficacy of MPA (at least 300 mg daily) in 10 male patients with dementia and inappropriate hypersexual behaviors. All patients have received other psychotropic medications before MPA treatment.

Cyproterone Acetate

Davies [138] reported the efficacy of cyproterone acetate in nine juvenile patients with mental retardation who masturbated in public. He also described the effectiveness of cyproterone in three adolescent males with severely mental retardation, who were physically aggressive to other patients and staff, and who showed no response to conventional treatment. In addition, four cases of sexual hyperactivity associated with chromosomal disorders in adolescent males were treated effectively with cyproterone.

GnRHa

Dickey [139, 140] reported the case of a male patient (28 years old) with multiple paraphilia and hypersexuality successfully treated for 6 months (1992) and 10 years (2002) with long-acting leuprorelin (7.5 then 3.75 mg/month) as compared with previous MPA (max 550 mg/week for 32 months) or cyproterone acetate (CPA) treatment (200–500 mg/week for 14 months), and observed that suppression of androgen of testis origin alone was sufficient for treatment. Bone demineralization was observed after 3 years and treated with calcium and vitamin D. Gynecomastia was also reported.

Single case reports of successful leuprorelin treatment (7.5 mg/month) of a patient with exhibitionism and Huntington's disease [141], or of a 43-year-old male patient with exhibitionism, hypersexuality, fronto-temporal dementia, and Klüver-Bucy Syndrome [142] were also published. Efficacy was reported at the third month. Weight gain, asthenia, and muscular pain were also reported.

Conclusion

Although the neurobiology and neuropharmacology of sexual behavior remain unclear, there has been significant research that aims to highlight the neuronal circuits and neurotransmitters involved in sexual disorders. Given the diagnostic characteristics of paraphilias and compulsive sexual behaviors as outlined in DSM-IV and the fact that treatment modulating the central nervous system 5-HT is efficient in both disorders, some authors speculate that these disorders could be considered as obsessive-compulsive spectrum disorders or as compulsive-impulsive disorders [63, 143]. In contrast, other authors consider that they belong to addictive disorders. In fact, hypersexuality shares with substance-use addictions craving, dependence, tolerance, and abstinence and maybe a common pathophysiology (Voon et al., [79•]). A deeper understanding of the pathophysiology of sexual addiction should lead to more focused treatment strategies such as naltrexone treatment. Moreover, it should be noted that a variety of neuropsychiatric disorders, such as postencephalitic neuropsychiatric syndromes, temporal lobe epilepsy, tumors in frontal or temporal regions, and multiple sclerosis, can potentially lead to paraphilic behaviors or be associated to hypersexuality [144]. The challenge for future research is to understand better the most important aspects of these disorders and their complex relationships to highlight new pharmacological targets for the better therapeutic management of deviant sexual disorders as well as hypersexuality.

In clinical practice (and particularly in forensic populations), an assessment of criminal history and pedophilic interests in hypersexual individuals and vice versa should be systematic. In general, the criminogenic needs addressed by medications are sexual deviance/paraphilia and hypersexuality/sexual preoccupation. The literature on treatment of hypersexuality associated to paraphilia is scarce. In many cases of paraphilias, hypersexuality is not reported or not specifically addressed. The WFSBP recommendations have highlighted preferred combination of psychotherapy and antiandrogens in the case of adult paraphilic patients at high risk of sexual

acting-out such as pedophiles or serial rapists, especially when hypersexuality is observed.

Compliance with Ethical Standards

Conflict of Interest Dr. A. Chagraoui and Dr. F. Thibaut declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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