# The Neurobiology of Sexual Responses and Its Clinical Relevance

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## 7.1 Regulation of Sexual Responses by Hormones and Neurotransmitters

In general, sexual functions—such as desire or sexual response—are modulated by multiple neurotransmitters, neuromodulators, and hormones that interact with central and peripheral neuronal structures. The main neurotransmitters, neuromodulators, and hormones involved in the central regulation of sexual functioning include sex steroids (e.g., testosterone, dihydrotestosterone, or estradiol), cerebral monoamines (e.g., serotonin, dopamine, or noradrenaline), and neuropeptides (e.g., oxytocin or prolactin). In the periphery, the sympathetic and parasympathetic nervous systems with adrenergic and cholinergic components as well as other neurotransmitters and second messengers such as nitric oxide (NO), vasoactive intestinal polypeptide (VIP), and others play an equally important role in an interaction with sex steroid hormones, especially estrogens and androgens. Bancroft and Janssen (2000) proposed the so-called dual control model [1] that describes two separate systems—an excitatory and an inhibitory—which in its original form primarily described psychological factors including three scales: sexual excitation (SES), threat of performance failure (SIS1), and sexual inhibition due to threat of performance consequences (SIS2) (see Fig. 7.1). Although the model was developed to mainly describe psychological aspects of sexual response, it is also useful when it comes to

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M. Lew-Starowicz et al. (eds.), *Psychiatry and Sexual Medicine*,
https://doi.org/10.1007/978-3-030-52298-8_7

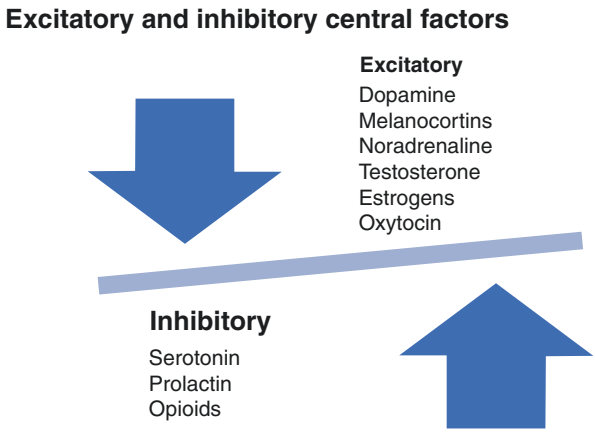


**Fig. 7.1** Summary of inhibitory and excitatory neurotransmitter and hormones that are important for the regulation of sexual drive and function

understanding the complex interaction and influence of neurobiological factors. Altogether, a structured assessment of excitatory and inhibitory aspects provides a solid base for a comprehensive patient history, which in turn provides an understanding of clinical pictures that combine neurological, psychological, and social aspects.

### 7.1.1 The Effects of Sex Steroids on Cerebral Sexual Response

When it comes to excitatory and inhibitory effects on sexual response, sex steroids play a major part. Sex steroids are primarily released in the ovaries, the testicles, and the adrenal cortex. They are involved in the regulation of sexual fantasies, desire, as well as the responsivity to sexual stimuli. The suppression of sex steroids through application of testosterone antagonists (e.g., cyproterone acetate 50–200 mg/day) or LHRH (luteinizing hormone-releasing hormone) LHRH agonists (e.g., triptorelin embonate 11.25 mg every 3 months) leads to marked inhibition of sexual drive, desire, and function, as well as hypogonadism in men, and in women, low levels of androgens also may impair sexual desire. On a neurological basis, sex steroids (testosterone, dihydrotestosterone, and 17ß-estradiol) operate in subcortical as well as cortical areas. Involved subcortical areas comprise the hypothalamus, the amygdala (with nucleus stria terminalis), and the mammillary bodies (for an overview, see [2]). Involved cortical areas include prefrontal and temporal regions. Single case studies show an absent or decreased activation of essential parts of the limbic system and cortical areas during presentation of visual sexual stimuli after application of LHRH agonists. These changes were also present on a subjective level of sexual responsivity [3, 4].

In the central nervous system (CNS), testosterone is mainly metabolized to dihydrotestosterone (DHT) and 17ß-estradiol. These substances can either have long-term (between hours and days) or short-term (between seconds and minutes) effects, depending on the underlying mechanism (genomic or non-genomic) [5]. Long-term

effects are due to genomic mechanisms and can lead to synthesis of neurotransmitters relating to the monoamine system. Estradiol however is of high importance for central nervous processing of sexual pleasure and arousal also in men (in penile erection) [6].

The discovery of sex steroids' effects on sexual functioning leads to their clinical and pharmacological application. Clinically, it is well established that supplementing androgens and estradiol/progesterone in cases of hypogonadism or postmenopausal states will increase sexual desire. In contrast, testosterone antagonists or LHRH agonists are used to suppress sexual drive in case of severe sexual paraphilias, sexual offending, and most severe cases of hypersexual disorder. A combination of estradiol and antiandrogens (testosterone blockers) has shown to lead to a decrease in cortical thickness for occipital and prefrontal structures in transgender individuals (man-to-woman). The application of testosterone inversely leads to an increase in cortical thickness for specific brain structures in homosexual transgender patients (woman-to-man) [7]. Although neuroplasticity in adults is far from what we can find in prenatal or prepubertal stages, hormonal treatment seems to be able to lead to significant changes on a neuronal level and in behavior. Although not well examined in these subjects, this may also lead to a profound impact on cognition, emotion, as well as sexual experiences and behavior according to studies in other populations [8].

### 7.1.2 The Effects of Cerebral Monoamines on Sexual Response

Cerebral monoamines, such as serotonin, dopamine, or noradrenaline, have been found to significantly impact sexual functioning. All these monoamines are primarily produced by specific nuclei in the brain stem which maintain projections to various other brain areas and the spinal cord.

#### 7.1.2.1 The Dopaminergic System

The dopaminergic system is important when it comes to motivational and hedonic aspects of sexuality. It is essential for the creation of sexual pleasure and desire and is also involved in further aspects of sexual functioning such as penile erections and lubrication. As shown in Fig. 7.2, the dopaminergic system comprises three parts: a mesolimbic/mesocortical part, a nigrostriatal part, and the hypothalamus.

The mesolimbic areas are part of the reward system. Through projections, they connect the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens (NAcc), the limbic areas (including the amygdala), as well as the prefrontal cortex (PFC) in the forebrain. Together with the nigrostriatal areas, the mesolimbic system regulates motivation toward sexual behavior/stimuli and selective attention toward relevant (sexual) stimuli. Moreover—together with the noradrenergic system—the mesolimbic and nigrostriatal areas steer general psychophysiological arousal in the brain and then the periphery. The nigrostriatal system functionally connects the substantia nigra with the striatum (caudate nucleus and putamen). In general, this dopaminergic pathway modulates movement. The dopaminergic system located in the

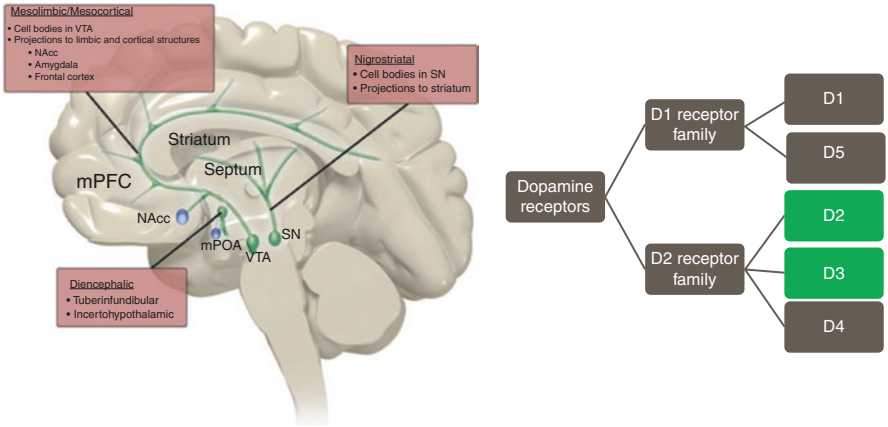


**Fig. 7.2** The dopaminergic system and the dopamine receptor family. Sites of synthesis in the brain stem and diencephalon with projections to striatal, limbic, and cortical brain areas. The green boxes highlight important subreceptors for regulation of sexual drive (modified according to Pfaus, 2009 [12], used with the kind permission of Elsevier and Krüger & Kneer, 2017 [13]). *NAcc* nucleus accumbens, *SN* substantia nigra, *VTA* ventral tegmental area

hypothalamus controls secretion of prolactin from the adenohypophysis through inhibitory effects and also affects further sexual processes such as sexual arousal. All in all, dopamine mainly seems to hold excitatory effects on sexual functioning. In healthy men, dopamine administration has been shown to lead to an increase in sexual appetite and sensation [9]. These effects however seem to be gender specific as the results could not be demonstrated in women [10]. Dopaminergic mechanisms therefore might differ between genders. This assumption is in line with studies investigating the side effects of dopaminergic substances such as dopamine agonists, L-DOPA, or antipsychotics with partially dopamine-agonistic effects (e.g., aripiprazole). Hypersexuality, pathological gambling, or compulsive buying (impulse control disorders) appears more frequently in men than in women, and stimulation of D3-compared to D2-receptors seem to be stronger in terms of increasing respective impulses [11]. And yet, antipsychotics with strong D2-antagonistic effects can lead to severe inhibition of sexual functioning. It remains unclear whether this inhibition is due to an increase in prolactin levels (hyperprolactinemia) or appears as the result of dopamine antagonistic mechanisms. Although some studies are concerned with the effects of dopamine on sexual functioning, little transfer to clinical research has yet occurred.

### 7.1.2.2 The Serotonergic System

The serotonergic system is a complex neurotransmitter system incorporating seven receptor types and various subtypes (Fig. 7.3). Serotonin is synthesized in the raphe nuclei in the brain stem. Various projections reach the spinal cord, the hypothalamus, and limbic (mPOA "medial preoptic area," nucleus accumbens) and cortical areas. Serotonin modulates satisfaction, satiation, and relaxation. Thus, its effect on sexual

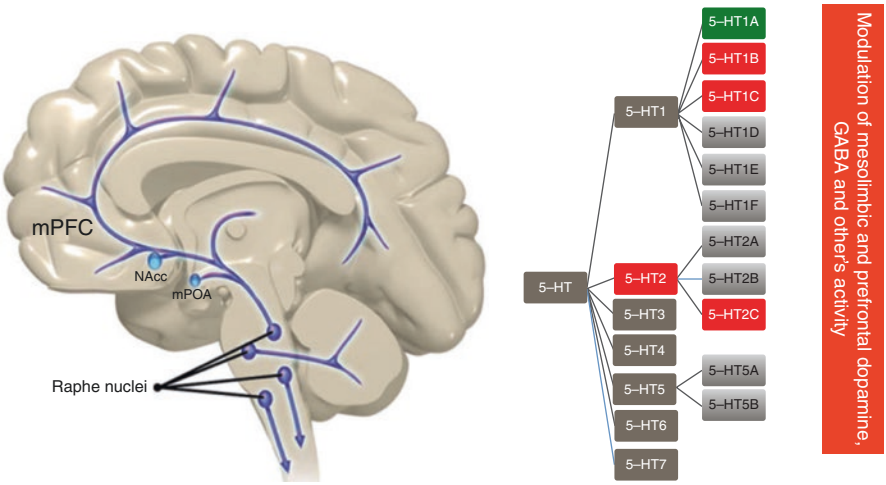


**Fig. 7.3** The serotonergic system with serotonin receptor families. Sexual inhibitory receptors are marked in red, and sexual excitatory subreceptors are marked in green (modified according to Pfaus, 2009, used with the kind permission of Elsevier and Krüger & Kneer, 2017 [13]). *5-HT* 5-hydroxytryptamine, *mPOA* medial preoptic area, *NAcc* nucleus accumbens

function is mainly inhibitory (for receptor subtypes 5-HT (5-hydroxytryptamine)$_{2C}$, 5-HT$_{1B}$, 5-HT$_{1C}$), although stimulation of receptor subtype 5-HT$_{1A}$, a receptor responsible for decreased serotonin and increased dopamine transmission, can lead to excitatory effects [14, 15]. As shown in animal studies, in parts of the hypothalamus (anterolateral areas), serotonin release is increased during ejaculation, while dopamine release is decreased in the nucleus accumbens. These processes—with potential involvement of endogenous opioids and endocannabinoids—might be able to explain sexual satiation and the refractory period [12]. Serotonin also seems to be able to inhibit (esp. in mesolimbic and hypothalamic areas) or facilitate release of dopamine, depending on receptor subtypes. Through connections to the spinal cord, serotonin inhibits sexual reflexes, i.e., automatically executed sexual functions such as erection, lubrication, and orgasm (ejaculation).

It is of great importance to be aware of the different receptor subtypes and the effects that serotonin can have on human sexual function when it comes to choosing and prescribing medication. Moreover, patients need to be informed about the potential side effects of serotonergic medication, which is widely used for the treatment of depression. Studies have shown that even different compounds with a shared mechanism of action (e.g., selective serotonin reuptake inhibitors (SSRI)) might widely differ in their effects on sexual function. Sertraline medication, for example, most frequently causes sexual dysfunction, while escitalopram medication may less often affect sexual function [16]. Imaging studies investigating the side effects of antidepressant medication on sexual function demonstrate a decreased activity of different parts of the cingulate cortex during processing of visual sexual stimuli [17].

#### 7.1.2.3 The Noradrenergic System

The noradrenergic system is important in order to generate adequate psychophysical activation necessary for sexual responses. A low noradrenergic tone could lead to fatigue and inappetence, while a (too) high noradrenergic tone could lead to stress and overexcitement. In case of premature ejaculation and/or fear of failure, stress, or anxiety, elevated brain noradrenergic levels can be expected. Noradrenaline, generated in the locus coeruleus, projects to the hypothalamus, the spinal cord, the cerebellum, the limbic system, and various cortical areas [12]. Moreover, the noradrenergic system is connected to sex steroids. Estradiol, for instance, can increase the synthesis of noradrenaline, as demonstrated in animal models. Also, pharmacological compounds (e.g., trazodone) with peripheral effects on α1-receptors may lead to priapism, a painful state of enduring erection. Substances affecting β-receptors by contrast may lead to inappetence and depression [18].

### 7.1.3 Clinical Implications of Monoaminergic Factors

Cerebral monoamines are widely used as pharmacological treatment by neurologists and psychiatrists. Serotonin, dopamine, and noradrenaline play key roles in the central nervous system. They are synthesized in major areas of the brain stem and show extensive projections to the limbic system, the cortex, and—for serotonin and noradrenaline—the spinal cord. That way they impact multiple areas of human condition and behavior. While most SSRIs and SNRIs potentially lead to sexual dysfunction, other compounds show less effects on sexual function: bupropion is a selective dopamine and noradrenaline reuptake inhibitor, and like agomelatine, a melatonin agonist, it rarely affects sexual function while used to treat mood disorders.

When treating sexual disorders, such as hypersexuality, premature ejaculation (PE), or paraphilias, SSRI side effects however might be useful. In some countries, dapoxetine is an approved SSRI for treatment of PE. Basically, all compounds with a serotonergic mechanism of action may be effective in treating PE (esp. paroxetine (ninefold extension of ejaculation latency; [19]) or clomipramine up to 50 mg). In the USA, flibanserin, a compound once developed to treat depression, is an approved drug for treatment of hypoactive sexual desire disorder (HSDD) in women [20]. The effects, however small, once more demonstrate the potential that lies within pharmacological treatment of sexual dysfunction and the importance of neurotransmitters for sexual function.

### 7.1.4 The Effects of Neuropeptides on Sexual Response

Neuropeptides, such as prolactin, oxytocin, or vasopressin, modulate behavior. The latter two are also known as “social neuropeptides” as they primarily affect social behavior [21]. Prolactin, however, although affecting more than 300 human processes, is mostly known for its effect on lactation in breastfeeding women [22]. The

effects of prolactin on sexual response are mostly inhibitory. After reaching orgasm, prolactin levels are increased by 50% in men and by 100% in women [23]. Prolactin—among endogenic opioids such as ß-endorphin—could play a role in sexual satiation. While studies in animals show that endogenic opioids act in the central nervous system and affect the reward system [12], an increase in prolactin might lead to sexual satiation through inhibition of specific dopamine-related neurons. Thereby, sexual drive could decrease [24–26]. Further inhibitory effects of prolactin can be observed in the clinical use of antipsychotics. After intake of antipsychotic medication with strong D2-antagonistic effects (such as haloperidol, risperidone, or amisulpride), chronic hyperprolactinemia has been observed. Despite these findings, the relevance that prolactin holds for male physiology remains widely unknown.

Despite thousands of publications on oxytocin during the last 20 years, there is no approval for this peptide in any psychiatric or sexual disorder. Although there is evidence that oxytocin facilitates species propagation in general [27], studies on the effects of oxytocin on sexual drive and function were predominantly negative (Burri et al., Behnoush et al.), while there might be some effect on partner interaction and perception of postorgasmic state. Case reports indicate some effect in delayed orgasm; however, a clear recommendation is not possible.

## 7.2 Peripheral Mechanisms Regulating the Arousal Response

In the periphery, sex steroids and neurotransmitters have substantial effects in both men and women in the cavernosal tissues.

In men, erection can be triggered through two mechanisms: reflexogenic and psychogenic erections. Psychogenic erections are due to sexual cues (visual, olfactory, fantasies, auditory) and are generated and processed in the brain as described above. Reflexogenic erections are due to genital (primarily penile) stimulation. They have in common an activation of sacral neurons (S2–S4) and from there via the cavernous nerve, a triggering of the erectile mechanism by the parasympathetic fibers. The cavernous nerve initiates the process signaling relaxation of the arterial and corpus cavernosal smooth muscle cells, increasing the penile blood flow and thereby inducing an erection.

The arousal response is a balance between neurotransmitters promoting sexual arousal (relaxation of smooth muscle cells) via the parasympathetic pathways and inhibiting (contracting smooth muscle cells) via the sympathetic pathways. The sympathetic nerve terminals release noradrenaline (NE) which contract smooth muscle cells and play a major role in flaccidity and detumescence. NO and acetylcholine are the major parasympathetic components. NO is produced in the nerve endings (nNO) and in the endothelium of blood vessels and corpus cavernosum (eNO). It diffuses into the smooth muscle cell and induces relaxation by increasing the intracellular level of cyclic nucleotide guanosine monophosphate (cGMP). Acetylcholine has an indirect effect as it stimulates NO and eNO and inhibits NE

release [28]. Androgens also have a peripheral effect in men, where they maintain the structural and functional integrity of the penile tissue, maintain the function and plasticity of the penile nerve and ganglia, and stimulate the activity of NO synthase [29].

In women, the arousal response, genital vasocongestion, vaginal lubrication, and clitoral engorgement are also a result of increased genital blood flow. Several studies have shown the presence of adrenergic, cholinergic and non-adrenergic, and non-cholinergic (NANC) neurotransmitters in the clitoral and vaginal tissue, regulating the smooth muscle tone and thereby the sexual arousal response in an interaction with the effect of sex steroids. The most important neurotransmitters in women are NE that contracts smooth muscle cells and thereby decreases genital blood flow. In contrast, vasoactive intestinal polypeptide and NO relax smooth muscle cells and thereby increase genital blood flow inducing lubrication and engorgement of the clitoris and labia. Sex steroids (estrogens and androgens) are crucial for the maintenance, structure, and function of the genital tissue. In women, estrogens have a direct role on the peripheral sexual response in women, where they are important for blood flow to the vagina and clitoris and lubrication, which is illustrated by the reduced lubrication that many women experience associated with estrogen deficiency during menopause. Estrogens and androgens facilitate the maintenance of the genital tissue, and the NANC nerve stimulated genital blood flow, as well as modulated neural and endothelial NO synthase and thereby the smooth muscle relaxation [30].

## 7.3 Brain-Body Functional Connection: Findings from (Functional) Imaging

Nowadays, imaging studies are able to identify activation of specific brain areas during sexual arousal or processing of (mostly visual) sexual stimuli. Cortical and subcortical activation has been demonstrated in the occipitotemporal cortex, in the precentral gyri and cinguli gyri, and in the superior and inferior parietal lobules during visually induced sexual arousal. Moreover, activation has been detected in parts of the frontal lobe and several thalamic regions, the ventral striatum (VS), and the amygdala. Studies in men (homosexual and heterosexual) show that visual presentation of preferred sexual stimuli leads to activation in the hypothalamus, the amygdala, the claustrum, the VS, the central lobe, the anterior cingulate gyrus, and the orbitofrontal cortex (OFC) [21]. It seems that activation of the hypothalamus (alongside the VA) reflects the intensity of sexual stimuli best: the stronger the activation of the hypothalamus, the higher subjectively reported sexual arousal [31, 32]. Reaction patterns to specific stimuli allow for a classification of participants concerning their sexual orientation [33] and preference (in this case, pedophilia [34]). All in all, results correspond to a behavioral neurobiological model proposed by Redouté and coworkers (2000) [35]. This model describes cognitive, motivational, emotional, and autonomous components of sexual stimulus central processing [35].

Functional imaging has been able to demonstrate deviant central processing of sexually relevant stimuli in men and women who suffer from sexual dysfunction [36–39]. Participants with hypoactive sexual desire disorder (HSDD), for instance, show less activation of brain areas connected to the processing of sexually relevant stimuli while presenting more activation of cortical brain areas connected to social and visual cognition, such as self-observation. Moreover, they show strong activation of prefrontal brain areas, which altogether leads to the hypothesis of increased observation and evaluation of individual sexual reaction in people with HSDD. This increased attention toward oneself in turn might lead to dysfunctional emotional reactions such as the experience of insufficiency, shame, or fear of failure. Meta-analyses of sexual stimuli central processing reviewed existing models and developed new ones. One model proposes a similarity of involved brain regions between sexual behavior and other reinforcement such as intake of water and food or social contact. Georgiadis and Kringelbach (2012) describe the so-called pleasure cycles that consist of expectation, consummation, and satiety [40] (Fig. 7.4).

Another study conducted by Poeppl and coworkers (2014) [41] identified two sets of neuronal structures: one set primarily associated with psychosexual arousal (i.e., a mental representation of arousal) and a different set primarily connected to somatosexual arousal (i.e., lubrication or penile erection). Psychosexual arousal seems to be connected to neuronal structures concerned with cognitive and affective evaluation of sexually relevant stimuli, the creation of sexual appetite, top-down modulation of attention and stimulus processing, and the initiation of autonomous processes (i.e., multiple cortical areas, the amygdala, the hypothalamus, and the basal ganglia). Somatosexual arousal however seems to be connected to neuronal structures concerned with processing of somatosensory stimuli, emotion, and autonomous functions (several areas in the region of the cingulate gyrus, the insula, and the basal ganglia). Moreover, both neuronal sets seem to be subcortically interconnected via the claustrum and putamen, so that information exchange between these areas is enabled.

## 7.4 Sex, Bonding, and Age: (Why) Does Our Sexual Appetite Deteriorate?

"In our 20s, we have sex; in our 30s, we have dinner." The older we and our relationships get, it seems the less interested we are in sex. In fact, there is evidence that interest in pleasure and exploration wanes with old age [40]. Studies using SPECT (single-photon emission computed tomography) show a 6–8% loss of dopamine transporters per decade [42, 43]. Keeping in mind that dopamine holds excitatory effects for sexual response and modulates lust and sexual motivation, its loss with age could explain a decrease in sexual interest. Evolutionarily speaking, a loss of dopamine and thereby sexual appetite seems reasonable as reproduction usually has been completed at a certain stage in life.

Moreover, the formation of partner bonds seems to lead to a decrease in sexual appetite. In rodents, mating leads to an activation of the VTA, thus resulting in

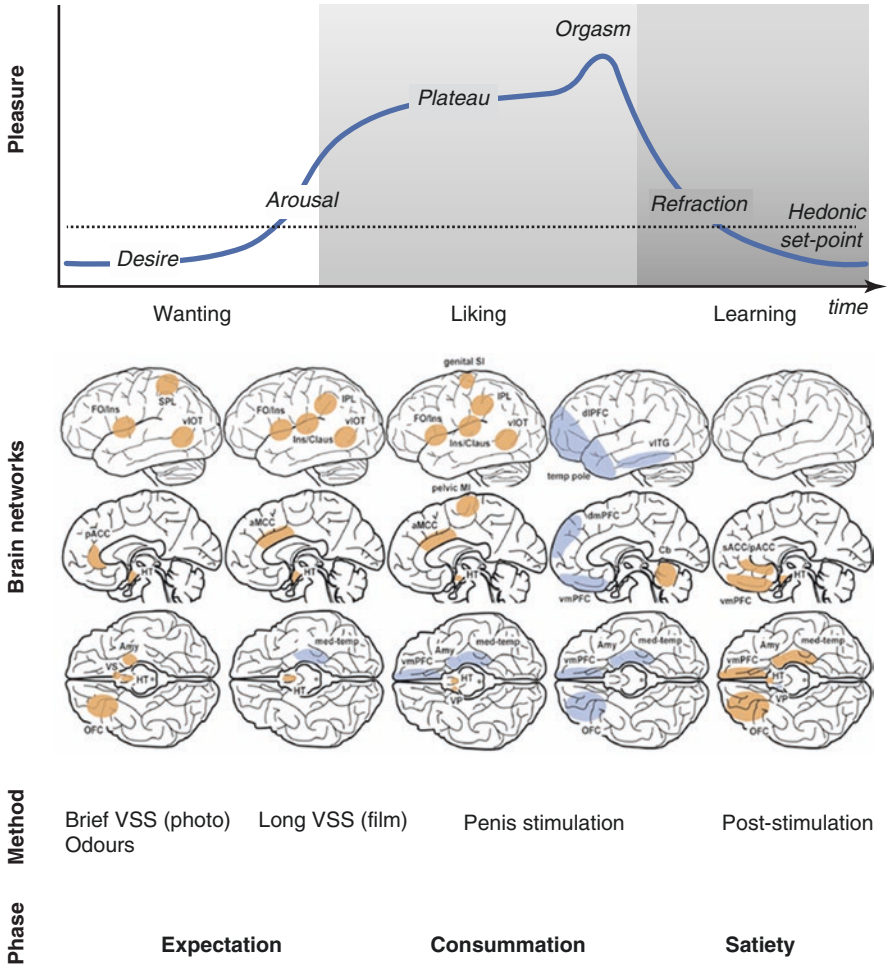


**Fig. 7.4** The functional neuroanatomy of the sexual response cycle in humans and its overlap with models in drug addiction. Note the fine balancing between activated (orange) and inhibited brain areas (blue). With kind permission from Georgiadis and Kringelbach (2012) [40]

increased dopamine activity in the prefrontal cortex (PFC) and nucleus accumbens (NAcc). The oxytocin systems in the medial nucleus of the amygdala (MeA), the PFC, and the NAcc are also activated during mating. The concurrent activation of both systems potentially results in the development of a pair-bond formation [44–46]. In monogamous prairie voles, higher densities of oxytocin receptors (OTR) in the NAcc, the caudate putamen (CP), and the PFC [45, 47] are found compared to montane voles with a polygamous bonding style. The importance of oxytocin and vasopressin for bonding has further been demonstrated in animal studies. After administration of oxytocin in female voles and administration of vasopressin in male voles, an acceleration of pair-bonding has been observed [48].

Dopamine, on the other hand, decreases over time during sexual relations in a pair-bond. Animal studies have shown that the presentation of a novel sexual stimulus (e.g., a novel mate) leads to reinitiation of sexual activity in a state of sexual satiation and goes in hand with increased levels of dopamine in the NAcc [49]. This phenomenon, known as "the Coolidge effect," tries to give an explanation for sexual boredom in long-term relationships. Its name goes back to Calvin Coolidge, 30th President of the United States (1923–1929). Story has it that the President and his wife were taken off on separate tours when visiting a government farm. Mrs. Coolidge asked the man in charge of the chicken pens if the rooster copulated more than once a day. The man replied: "dozens of times" and Mrs. Coolidge asked him to "tell that to the President." The president, however, when presented with the rooster situation, asked: "Same hen every time?". When informed that the rooster had "a different one each time," he asked to "tell that to Mrs. Coolidge." Studies in ram and sheep demonstrate the effect: when repeatedly exposed to the same mate, time to ejaculation in rams increases over time. When exposed to novel mates, however, time to ejaculation in rams stays short and does not change significantly [50].

When counseling couples with sexual dissatisfaction, it is important to keep in mind that novel sexual stimuli—or in more therapeutic language "common new experiences"—can renew sexual interest and stimulate the release of dopamine. Moreover, imaging studies have shown that activation patterns (e.g., dopaminergic areas such as VTA or dorsal striatum) can be similar for long-term and short-term romantic love couples that describe vivid romantic feelings for their partner even after many years. Long-term romantic love in these people further shows activation of serotonergic and opioidergic areas connected to affiliation (e.g., globus pallidus, substantia nigra, n. raphe, insula, cingulate gyrus) [51]. It seems that long-term romantic love is associated with more calmness and serenity, yet it does not exclude the experience of desire and lust. Furthermore, it is important to distinguish between intimacy and romance. While romance can develop quickly and unexpectedly, it takes time to build up intimacy. The higher the level of intimacy a couple has reached over time, the more challenging it becomes to experience desire, passion, and excitement. Fluctuations in the level of intimacy seem to hold a key, especially for women, while men do not necessarily need such changes of intimacy in order to experience desire [52]. Another important factor, when it comes to "renewing the flame," is shared and novel experiences, as curiosity and novelty hold a chance for increased dopamine levels. In contrast, perception of pain or erectile dysfunction may inhibit these mechanisms as a function of negative feedback to the brain.

## 7.5 Key Messages

- Hormones and neurotransmitters of the peripheral and central nervous system play a pivotal role in regulating sexual functions.
- An understanding of excitatory (e.g., dopamine, noradrenaline, testosterone) and inhibitory factors (e.g., serotonin, prolactin, opioids) is not only helpful for a

basic understanding of sexual functions but also for appropriately considering pharmacological interactions and side effects on sexuality.
- There is neuroplasticity also in the "sexual brain," and this may be significantly influenced by a number of factors such as personal history, trauma, drug intake, age, length of relationship, and many others, and these need to be carefully assessed in every sexual history taking.

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