
THE ROLE OF PREFRONTAL SYSTEMS IN SEXUAL BEHAVIOR

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Research from a variety of methodologies is demonstrating a role for neuroanatomical structures in different aspects of sexual behavior. This article reviews the particular contribution of prefrontal-subcortical systems to sexual behavior, including regions of prefrontal cortex (i.e., dorsolateral, medial, and orbitofrontal cortex), and associated subcortical structures (i.e., basal ganglia and thalamus). Findings are integrated from functional neuroimaging and clinical studies in humans, as well as animal studies, which convergently illustrate the role of different prefrontal systems. In addition to providing a clearer understanding of normal sexual behavior, appreciation of prefrontal systems in sexual behavior has implications for disorders of sexual behavior. Consistent with their role in other forms of cognition, emotion, and behavior, prefrontal systems serve in an executive capacity to regulate sexual behavior.

Keywords arousal, dorsolateral prefrontal, medial prefrontal, orbitofrontal, sexual

The necessity of sex for reproduction and species survival makes it one of the most fundamental of behaviors on biological, emotional, cognitive, and social levels. Despite its importance, a full understanding of the neuroanatomical basis of human sexual behavior is still being pursued (e.g., Meston & Frohlich, 2000). Such a model would be useful in understanding normal sexual behavior as well as its dysfunction in many psychiatric and neurological disorders. For example, clinical populations with stroke and traumatic brain injury commonly report

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alterations in sexual function and behavior (Aloni & Katz, 1999; Korpelainen et al., 1998). Sexual dysfunction has been associated with a wide array of other neurological and psychiatric illnesses.

Sexual behavior is regarded in terms of emotional, motivational, reward, and homeostatic functions. As such, much research on sexual behavior focuses on structures of the limbic system, including nuclei of the hypothalamus, amygdala, bed nucleus of the stria terminalis (McKenna, 2001; Meston & Frohlich, 2000). Study of the execution of sexual movements and physiological arousal has focused more on brainstem and spinal structures (McKenna, 2000, 2002). However, there has been little synthesis to appreciate the contribution of prefrontal systems to sexual behavior.

FUNCTIONAL ROLES OF PREFRONTAL SYSTEMS

Prefrontal cortex and associated subcortical structures mediate executive functions, which allow for behavior that is more adaptive, goal-oriented, autonomous, and conceptually guided rather than governed by immediate environmental circumstances. Clinical and experimental studies convergently implicate prefrontal systems as critical in mediating various executive functions (Masterman & Cummings, 1997; Tekin & Cummings, 2002; Stuss & Levine, 2002).

Prefrontal systems are formed by interactions between the cortex, striatum, and thalamic nuclei (see Figure 1). Widespread multimodal cortical areas project to the striatum (including caudate, putamen, and nucleus accumbens), which have projections to the globus pallidus. The globus pallidus, in turn, projects to the mediodorsal nucleus, which then projects to prefrontal cortex. Thus, a wide array of influences, including higher-order sensory, emotional, and cognitive, are funneled into prefrontal-subcortical systems. Prefrontal systems are grossly subdivided into three regions: dorsolateral, medial, and orbitofrontal. These systems maintain relatively parallel sets of connections through subcortical structures, each playing distinct roles in cognition, emotion, and behavior.

Prefrontal systems have extensive connections with limbic and brainstem structures that control homeostatic functions (Ongur & Price, 2000). For example, several functional neuroimaging studies demonstrate a role for prefrontal, limbic and striatal structures in hunger and satiety (Del Parigi et al., 2002; Tataranni et al., 1999). Prefrontal systems play an important role in regulating behavior regarding homeostatic functions, and mediating aspects of reward (Rolls, 1996). As such, it is well positioned to regulate sexual behavior.

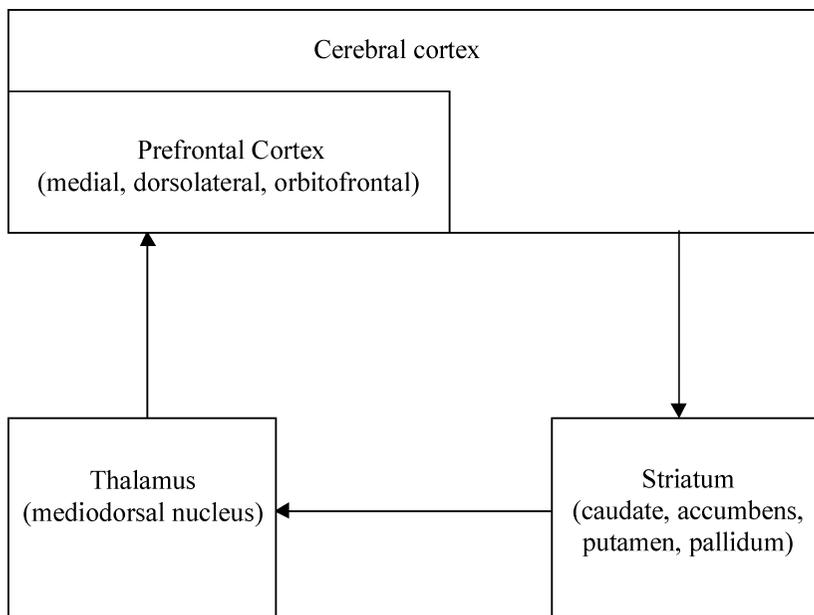


Figure 1. Schematic diagram of prefrontal-subcortical systems mediating executive functions. Contained within this are parallel circuits for medial, dorsolateral, and orbitofrontal regions of prefrontal cortex.

PREFRONTAL SYSTEMS IN SEXUAL BEHAVIOR

Medial Prefrontal Cortex

Medial prefrontal cortex, including the anterior cingulate and subgenual or subcallosal regions, mediates motivational aspects of behavior, such as initiation and persistence (Devinsky et al., 1995; Stuss & Levine, 2002; Swards & Swards, 2003). Individuals with medial prefrontal dysfunction typically exhibit abulia, manifesting a lack of initiative, drive, and spontaneous behaviors. Medial prefrontal cortex also plays a central role in reward and punishment (Tzschentke, 2000). Human neuroimaging studies show that secondary reinforcers, such as money, activate medial prefrontal cortex (Gehring & Willoughby, 2002; Knutson et al., 2000; Elliott et al., 2003). Activation also occurs during aversive gustatory stimulation (Zald et al., 1998). Anterior cingulate neurons also activate in anticipation of reward (Koyama et al., 2001). Medial prefrontal circuits are also activated by novelty (Tulving et al., 1994).

Several lines of evidence implicate the anterior cingulate gyrus in sexual behavior. Lesions of the medial prefrontal cortex in male rats (involving anterior cingulate and adjacent areas) reduces mounting, intromission, and ejaculation (Agmo & Villapando, 1995; Yamanouchi & Arai, 1992). The resultant impairments are partially reversed by administering central dopaminergic stimulants (Agmo & Villapando, 1995). Conversely, anterior cingulate activity increases in estrous, sexually receptive female sheep when exposed to a male, but it is not affected in anestrus females (Ohkura et al., 1997). Consistent with its overall role in behavioral initiation, it has been suggested that the anterior cingulate is responsible for the initiation of sexual behavior, but is less important for its continued execution (Agmo & Villapando, 1995).

Several human studies also implicate the anterior cingulate gyrus in aspects of sexual behavior. Neuroimaging studies in males and females show an increase in blood flow to the region during sexual arousal (Deiber et al., 1999; Stoléru et al., 1999; Rauch et al., 1999; Redoute et al., 2000; Arnow et al., 2002; Karama et al., 2002). People with lesions of the anterior cingulate show a marked reduction in initiation and motivated behaviors, including sex (Nemeth et al., 1988; Devinsky et al., 1995; Mega & Cohenour, 1997).

Orbitofrontal Cortex

Orbitofrontal cortex mediates self-inhibition, social conduct, empathy, and decision making (Malloy et al., 1993; Tekin & Cummings, 2002; Starkstein & Robinson, 1997). Accordingly, individuals with orbitofrontal damage exhibit disinhibition, inappropriate social conduct, and poor judgment. This is related to its role in self-monitoring and correction of performance (Rolls, 1996).

Damage to the ventromedial sector of prefrontal cortex particularly has been shown to impair decision making (Bechara et al., 1999). This was demonstrated with the Iowa Gambling Task, but parallels real-life deficits in judgment. Individuals with ventromedial lesions make poor choices, favoring short-term gains at the expense of long-term losses. Impairment on the Iowa Gambling Task has also been demonstrated in substance abusers (Bechara, 2003) and pathological gamblers, which is not accountable by any other basic cognitive deficits (Cavedini et al., 2002). Thus, ventromedial orbitofrontal cortex would logically play a role in one's assessment and decision making about sexual behaviors such as partner choice and risk taking.

Orbitofrontal cortex plays a central role in reward. The pleasurable taste of chocolate activates the caudomedial region of orbitofrontal cortex, whose activity diminishes as the pleasure decreases during continued eating (Small

et al., 2001). Pleasing music also activates orbitofrontal cortex (Blood & Zatorre, 2001), and secondary reinforcers, such as money, activate orbitofrontal cortex (Thut et al., 1997; O'Doherty et al., 2001; Elliott et al., 2003). Lateral orbitofrontal regions represent punishing outcomes, whereas medial regions represent rewarding outcomes (O'Doherty et al., 2000). More directly related to sexual behavior, orbitofrontal activation occurs in response to pleasant touch (Francis et al., 1999). Orbitofrontal cortex also responds to facial attractiveness (O'Doherty et al., 2003). Human neuroimaging studies show activation in orbitofrontal cortex during sexual arousal (Stoléru et al., 1999; Redoute et al., 2000).

Lesions of orbitofrontal cortex do not produce any overt deficits of sexual behavior in rats (de Bruin et al., 1983). However, humans with orbitofrontal lesions show a disinhibition in their behavior that may stem from a fundamental insensitivity to future consequences (Bechara et al., 1994). Not surprisingly, uncharacteristic sexual promiscuity may ensue after a brain injury (Starkstein & Robinson, 1997; Malloy et al., 1993). Miller and colleagues (1986) have described cases of humans with orbitofrontal lesions with resultant changes in sexual behavior, such as inappropriate advances and public masturbation.

Dorsolateral Prefrontal Cortex

Dorsolateral prefrontal cortex mediates conceptual reasoning, mental flexibility, sequencing, planning, and working memory (Masterman & Cummings, 1997; Stuss & Levine, 2002). Accordingly, individuals with dorsolateral lesions tend to be concrete, mentally inflexible, and disorganized. Through its role in working memory, this region also plays a role in mental imagery, demonstrated in both tactile and visual modalities (Yoo et al., 2003; Ghaem et al., 1997). Mental imagery can be an important part of sexual behavior, both autosexual and allosexual (Whipple et al., 1992; Nims, 1975). It is also prominent in the development of paraphilias, and may be useful in their treatment (Kremsdorf et al., 1980; Levine et al., 1990). Thus, prefrontal cortex likely plays a role in the generation of erotic mental imagery. Concordantly, male patients with sexual dysfunction resulting from traumatic brain injury show impairments in sexual imagery evident even after controlling for levels of depression (Crowe & Ponsford, 1999).

Human functional neuroimaging studies often involve erotic imagery and/or retrieval of memories from past sexual experiences, but many have not shown dorsolateral activation. One possible reason for this may be the fact that control conditions often involve an imagery condition as well, although of a

nonsexual nature. Using digital subtraction techniques, both imagery conditions would activate dorsolateral regions and likely be cancelled out. However, one study has shown dorsolateral prefrontal activation in males viewing an erotic video, for no imagery was required (Montorsi et al., 2003).

Laterality of Prefrontal Activation

Evidence suggests a particular role for right prefrontal cortex in sexual arousal and orgasm. Two human neuroimaging studies of normal individuals have convergently found activation of right prefrontal cortex during both visually evoked sexual arousal and orgasm (Tiihonen et al., 1994; Stoléru et al., 1999). The increase in right prefrontal blood flow during orgasm was in contrast to a reduction in blood flow to all other cortical areas (Tiihonen et al., 1994). Orgasmic auras in seizures consistently originate from the right hemisphere (Janszky et al., 2002).

Striatum

The frontal lobes function in close association with the basal ganglia and thalamus (Masterman & Cummings, 1997; Tekin & Cummings, 2002). Similar to prefrontal lesions, those in the basal ganglia can produce mood disturbances, disinhibition, abulia/apathy, and cognitive disturbances (e.g., Trautner, Cummings, Read, & Benson, 1988; Mendez et al., 1989). In conjunction with prefrontal cortex, the striatum plays a role in reward prediction (Schultz et al., 1998; Kawagoe et al., 1998). The ventral striatum (nucleus accumbens) and ventral pallidum are key structures in reward and reinforcement (Koob, 1999; Ikemoto & Panksepp, 1999). The core but not shell region of the nucleus accumbens seems to be the key compartment in reward and behavioral reinforcement (Kelley, 1999). Functional neuroimaging in humans shows that monetary rewards activate the striatum, including the nucleus accumbens (O'Doherty et al., 2001; Elliott et al., 2000; Knutson et al., 2000).

Sexual activity in the rat increases activation of the nucleus accumbens, but not the striatum (Robertson et al., 1991). Interactions between the amygdala and accumbens mediate stimulus-reward associations involving sexual reinforcement (Everitt et al., 1999). Male rats with dopamine depletions (6-OH-DA lesions) of the accumbens show fewer erections, longer latency to display non-contact erections, and longer latency to ejaculate during copulation (Liu et al., 1998). Lesions of the nucleus accumbens in female rats increase the rejection of male rats (Rivas & Mir, 1990, 1991).

The effects of nucleus accumbens lesions on human sexual behavior are still tentative. One recent case report of a male patient with a relatively selective lesion of the nucleus accumbens reported a loss of interest in pleasure and sex (Goldenberg et al., 2002). Concordantly, human neuroimaging studies have reported activation in the head of the caudate and ventral pallidum (Rauch et al., 1999; Redoute et al., 2000).

Thalamus

In addition to its role in sensory and arousal processes, nuclei of the thalamus participate in prefrontal-subcortical systems. Anatomical and physiological studies of the mediodorsal thalamus suggest a role for it in processes of reward and punishment (Tzschentke, 2000; Meunier et al., 1997). Animal studies have shown a role for the mediodorsal thalamus in learning and reversal of reward contingencies, consistent with participation in orbitofrontal-amygdala circuits (Chudasama et al., 2001). Human neuroimaging studies indicate activation of the thalamus, along with other structures in the orbitofrontal circuit, during sexual arousal (Karama et al., 2002).

Lesions of the thalamus have been noted to produce alterations in sexual behavior, often characterized by disinhibition. Ortega and colleagues (1993) reported the case of a female who manifested exhibitionism, incest, scopophilia, and zoophilia. She was arrested multiple times and died in jail, after which autopsy revealed severe demyelination in the thalamus, mesencephalon, and frontal lobes. Acute mania, chorea, and hypersexuality developed in a male after right thalamic infarction (Inzelberg et al., 2001). Insidious neurological illness has led to criminal convictions for sex offenses. Spinella (2004) reported the case of a left thalamic stroke proximal to the lateral ventricles, accompanied by disinhibition and cognitive symptoms of a mediodorsal thalamic lesion.

PREFRONTAL SYSTEMS AND DISORDERS OF SEXUAL FUNCTION

Sexual Hypoarousal and Dysfunction

Given the role of prefrontal systems in sexual arousal, they are a logical target for studying and therapeutic treatment of sexual arousal disorders. A study of males with psychogenic erectile dysfunction showed differential patterns of activation in prefrontal and subcortical structures while viewing an erotic video (Montorsi et al., 2003). Apomorphine, a central dopamine agonist, enhanced the activation of prefrontal and subcortical structures during arousal. More work

in this area involving females with sexual dysfunction or other treatments, such as androgens, could be fruitful in devising strategies for treatment of sexual dysfunction.

Sex Offenders

There is evidence from both sex offenders and clinical studies suggesting a dysfunction of prefrontal systems in sex offenses. Miller and colleagues (1986) have reported cases of people with orbitofrontal lesions manifesting inappropriate sexual advances and public masturbation. Hypersexuality has been reported in several cases of frontotemporal dementia, one of which noted the onset of homosexual pedophilia (Dell & Halford, 2002; Mendez et al., 2000). A functional neuroimaging (fMRI) study of a homosexual pedophile showed activation in right orbitofrontal cortex when exposed to pictures of young males (Dressing et al., 2001). Discrete lesions of the subcortical components of prefrontal circuits can produce similar behaviors. Inappropriate hypersexuality was reported in an adult with bilateral pallidal lesions due to carbon monoxide poisoning (Starkstein et al., 1989). Hypersexuality was also reported in an elderly male patient with a lacunar infarct of the subthalamic nucleus, creating hypometabolism in the basal forebrain, temporal lobes, medial prefrontal cortex, and striatum (Absher et al., 2000). Acute mania, chorea, and hypersexuality developed in a male after right thalamic infarction (Inzelberg et al., 2001).

Miller and colleagues (1986) have described cases of humans with orbitofrontal lesions with resultant changes in sexual behavior such as inappropriate advances and public masturbation. In one sample of traumatic brain injury patients, a proportion (6.5%) of individuals with no such prior history committed sexual offenses such as exhibitionism, frotteurism, toucherism, voyeurism, or overt sexual aggression (Simpson et al., 1999). Hypersexuality also occurs in frontotemporal dementia (Dell & Halford, 2002). One case described by Mendez and colleagues (2000), noted the manifestation of homosexual pedophilia.

Insidious neurological illness has led to criminal convictions for sex offenses. A few cases of multiple sclerosis have been associated with frontal lobe dysfunction and hypersexuality (e.g., Gondim Fde & Thomas, 2001). The case mentioned earlier by Ortega and colleagues (1993) involved a female sex offender with multiple paraphilias (exhibitionism, incest, scopophilia, and zoophilia). She was arrested multiple times and died while incarcerated, after which autopsy revealed severe demyelination in the thalamus, mesencephalon,

and frontal lobes. Another case of multiple sclerosis was reported in a young man, also involving frontal and periventricular structures. He manifested hypersexuality and fetishism, leading eventually to imprisonment (Huws et al., 1991). A recent case has been reported of an individual with inappropriate sexual behaviors following the onset of multiple sclerosis affecting the frontal lobes via diaschisis (Frohman et al., 2002). He had no premorbid history of sexual offenses, but was incarcerated for sexually propositioning one minor and sexually assaulted another, as well as an adult female.

Orbitofrontal cortex plays an important role in empathy (Eslinger, 1998; Spinella, 2002), and sex offenders are noted to be deficient in empathy (Marshall et al., 2001). A sample of sex offenders found smaller left frontal lobe volume relative to normal controls (Wright et al., 1990). Spinella et al. (in press) have shown impaired sex offenders to have impaired performance on tasks sensitive to orbitofrontal dysfunction (i.e., go/no-go, antisaccades, and delayed alternation).

Sexual Addiction

Given the role of prefrontal systems in reward and reinforcement, it is not surprising that various forms of addiction have been associated with prefrontal dysfunction. Mood-altering drugs such as nicotine and cocaine have been shown to activate anterior cingulate, subcallosal gyrus, and ventral striatum in functional neuroimaging studies (Kilts et al., 2001; Breiter et al., 1999; Stein et al., 1998). Cravings in opioid addicts correlate with changes in regional blood flow (PET) in inferior frontal and orbitofrontal cortex (Sell et al., 2000). Similarly, positive relationships were found between craving intensity and metabolism in the orbitofrontal cortex, dorsolateral prefrontal cortex (Brody et al., 2002). Goldstein and Volkow (2002) have proposed a model of drug addiction that encompasses intoxication, bingeing, withdrawal, and craving in terms of prefrontal activity. Addictions associated with prefrontal system dysfunction are not limited to psychoactive drugs, but also include pathological gambling (Cavedini et al., 2002; Bazanis et al., 2002).

Sexual addiction have yet to be investigated in terms of prefrontal-system dysfunction. However, given the consistent findings of prefrontal involvement in addiction and the commonalities between many forms of addiction, research in this area is indicated. Spinella and White (in review) have shown that scores on the Sexual Compulsives Anonymous Questionnaire (SCAQ) correlate positively with symptoms of prefrontal dysfunction as measured by the Frontal

Systems Behavior Scale (FrSBe). Thus, symptoms of sexual addiction show a graded relationship with symptoms of prefrontal dysfunction.

CONCLUSIONS

Collectively, these studies provide convergent evidence that prefrontal systems are involved in various aspects of sexual behavior including arousal, reward and punishment, imagery, judgment, initiation, and inhibition. The findings have been generally consistent across humans and nonhuman species. There is also consistency between findings in healthy individuals and those in clinical or forensic populations. Prefrontal systems appear to play a regulatory role in sexual behavior, which is also consistent with their role in other forms of cognition, emotion, and behavior. Prefrontal systems have reciprocal connections with numerous other forebrain and brainstem structures, hierarchically positioning it to serve in an executive capacity.

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