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Review

# Electroencephalographic activity during sexual behavior: A novel approach to the analysis of drug effects on arousal and motivation relevant for sexual dysfunctions

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ABSTRACT

The neurobiological bases of human sexual behavior are only partly understood. The etiology of most human sexual dysfunctions is not understood at all. Nevertheless, substantial progress has been made in the treatment of some male sexual disorders. The prime example should be erectile deficiency, where several efficient and safe treatments are available. Pharmacological treatment for premature ejaculation is also available, although it is still in an early stage. Disorders of sexual desire have attracted much attention when women are affected but far less so when men are concerned. Whereas animal models appropriate for testing treatments for problems with erection and premature ejaculation are available, it is questionable whether such models of the desire disorders have predictive validity. There seems to be many factors involved both in reduced and enhanced sexual desire, most of which are unknown. In this review we present some data suggesting that an electroencephalographic analysis of brain activity during exposure to sexually relevant stimuli in male rats and men and during execution of sexual behaviors in male rats may provide useful information. The effects of a commonly used drug, ethanol, on the electroencephalogram recorded during sexual events in rats and men are also described. Although this approach to the analysis of the central nervous activity associated with sexual desire, arousal and behavior is still in its infancy, the data obtained so far show a remarkable similarity between men and rats. This suggests that animal studies of electroencephalographic responses to drugs in sexual contexts may be useful for predicting effects in the human male.



**Contents**



## 1. Introduction

Some male sexual dysfunctions, notably erectile disorders in older men and premature ejaculation in young men, are very common (Hatzimouratidis, 2007). This has inspired search for treatments, and that search has been quite successful. Erectile dysfunction is efficiently treated with phosphodiesterase 5 inhibitors (PDE5I) like sildenafil, tadalafil or vardenafil (Dorsey et al., 2010). Premature ejaculation can be treated with specific serotonin reuptake inhibitors (SSRI, Waldinger, 2007), although none of the classical SSRIs has premature ejaculation as an established indication. However, an SSRI inhibitor effective after acute administration, dapoxetine, is already

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available for clinical use in many countries (see Giuliano and Clement (2012), for a review). There are also newer compounds that have been found active in preclinical tests (Marson et al., 2010; Snoeren et al., 2012), but there will probably pass some time before they are sufficiently tested for entering clinical trials. Nevertheless, there are efficient pharmacological treatments available for the two major male sexual dysfunctions.

The role of animal models of sexual behavior seems to have been essentially nonexistent in the development and preclinical testing of the PDE5Is (see e.g. Jackson et al. (2005), for a summary of the sildenafil history). Whether animal studies stimulated clinical tests of some SSRIs for treatment of premature ejaculation is uncertain, but it has been known for a long time that enhanced serotonergic activity inhibits sexual behavior in male (see Malmnäs (1973), for an example of an early, extensive study) and female rats (Meyerson, 1964). In the first study evaluating the effect of an SSRI (paroxetine) on premature ejaculation (Waldinger et al., 1994), there is no mention of animal studies in the rationale for performing the study. It rather appears to have been founded upon old data showing that the tricyclic antidepressant clomipramine retarded ejaculation in men (Girgis et al., 1982; Goodman, 1980). However, the anticholinergic and/or antiadrenergic properties of this serotonin reuptake inhibitor caused significant adverse effects, among those reduced sexual desire, and clomipramine was not considered a useful treatment option. Since paroxetine has far less anticholinergic and antiadrenergic action than clomipramine, it might, consequently, have been predicted that this drug was a viable option. In subsequent studies of the effects of SSRIs on premature ejaculation (e.g. Waldinger et al., 1997), frequent references are made to animal studies, but the results of these studies appear to be used as support for the clinical findings rather than as an inspiration for them. It seems, then, that animal studies have offered a rather limited contribution to the initial development of treatments both for erectile deficiency and premature ejaculation. To the contrary, ongoing efforts to find superior pharmacological treatments for these disorders appear to rely, at least partially, on data from animal models of sexual behavior (see Chu and Ågmo (2008), Chu et al. (2014), Marson et al. (2010), Snoeren et al. (2012), for examples).

Although not as common as premature ejaculation and erectile deficiency, hypoactive sexual desire disorder affects a substantial number of men. According to epidemiological studies, between 25 and 3% of men complain of a sexual desire lower than they would wish to have (Arnal et al., 1995; Fugl-Meyer and Sjögren-Fugl-Meyer, 1999; Ventegodt, 1998). Despite the rather high incidence of male hypoactive sexual desire disorder, it has been far less studied than the corresponding condition in women. Nevertheless, it appears that men with low sexual desire do not differ from men with normal desire with regard to age, serum testosterone, concomitant illness and medication use (DeRogatis et al., 2012). There is no established, efficient treatment for this condition, even though the human has dreamed of an aphrodisiac for men since times remote (Sandroni, 2001). It must be added that not much serious effort seems to have been made to develop drugs enhancing male sexual desire, though. There is no need to mention the many reasons for this lack of interest. Nevertheless, men diagnosed with hypoactive sexual desire disorder would certainly benefit from treatments restoring their desire to an appropriate level.

There are rodent procedures available for quantifying male sexual desire (reviewed in Ågmo et al., 2004), but their predictive value is not well known. However, sexual approach behavior in male rats, an indicator of the intensity of sexual motivation (Ågmo, 2003; Spiteri and Ågmo, 2006), is reduced by fluoxetine (Matuszczyk et al., 1998). Administration of this SSRI as treatment for depression is known to have several deleterious effects on sexual functions in some men (Clayton et al., 2002), but a controlled study in healthy subjects failed to detect any reduction of sexual desire (Madeo et al., 2008), although ejaculation was retarded. Despite the contradictory data concerning the effects of fluoxetine in men, it could be maintained that because of the potential similarity between rats and humans with regard to drugs inhibiting sexual behavior, there should also be a potential similarity with regard to drugs enhancing desire. However, clinical evaluation of one of the few drugs known to reliably enhance sexual motivation in male rats, yohimbine (Clark et al., 1984; Viitamaa et al., 2006), has failed to reveal any effect on sexual desire in men (Rowland et al., 1997), making it impossible to ascertain whether rodent models really have any predictive value or not.

There are also men finding their sexual desire overly intense, and sometimes out of control. According to the ICD-10 (World Health Organization, 2010), these men could receive the diagnosis of satyriasis, the male label for excessive sexual drive. The DSM-IV-TR (American Psychiatric Association, 2000) does not include a similar diagnosis, but it was argued that it should be added to the DSM-5 (Marshall and Briken, 2010; Reid et al., 2012; Vroege et al., 1998). The arguments were evidently not convincing enough since the DSM-5 does not include any notion of hyperactive sexual desire disorder (American Psychiatric Association, 2013).

Since some of the paraphilias have been found to be associated with an unusually high sexual desire and sexual activity (Kafka, 1997, 2003), an efficient treatment of the former could be drugs or other interventions reducing sexual desire. In fact, several procedures have been employed to that end. They include androgen antagonists (Bradford and Pawlak, 1993; Czerny et al., 2002) or drugs reducing gonadotrophin release (Briken et al., 2000) or a combination of both (Hill et al., 2003). Drugs enhancing serotonergic activity like the SSRIs, also reduce sexual desire (Greenberg and Bradford, 1997; Greenberg et al., 1996; Kraus et al., 2007). Thus, there are several treatments with reasonably well established efficacy for reducing sexual desire in the human male (see Garcia and Thibaut (2011), for a review). All these treatments have been known to reduce sexual activity in males of many mammalian species for a long time (reviewed in Ågmo, 2007), but just as was the case for the treatment of premature ejaculation with SSRIs, it is uncertain whether the animal data actually inspired the clinical use. Independently of this issue, it can be concluded that several pharmacological treatments exist for reducing an overly intense sexual desire. This is in sharp contrast to the absence of drugs enhancing that desire.

Despite the effectiveness of the treatments for reducing sexual desire mentioned above, there are several side effects reducing compliance (Guay, 2009). Consequently, there is need for the development of more specific drugs with less side effects and improved long-term tolerability. As was the case for drugs enhancing sexual desire, it is possible that the employment of animal models could be helpful in this effort.

A serious problem hampering the search for drugs enhancing or reducing sexual desire is our lack of knowledge of the etiology of the desire disorders. Even though a lot is known about the endogenous determinants of sexual desire, i.e. the gonadal hormones and several transmitters, none of the known determinants seems to be altered in men suffering from low desire, as mentioned. Likewise, the cause of the large interindividual differences in sexual activity found in rodents, humans and other mammals remains elusive. The most obvious explanation for the interindividual variation, differences in the concentration of circulating gonadal hormones, was eliminated many years ago (Ågmo, 1976; Beach and Fowler, 1959; Damassa et al., 1977). No other convincing explanation has been found so far. Even in the case of an extreme example of the variation in the intensity of sexual activity, the non-copulating male rat, it has been difficult to detect an underlying difference from sexually active males. The non-copulating males consistently fail to display copulatory behavior in standard mating tests, and they do not approach a sexually receptive female more than they approach another male. Exposure to bedding soiled by females does not activate Fos in the olfactory pathway, at difference to copulating males (Portillo and Paredes, 2004). The non-copulating

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