

**Hypothalamic cellular and molecular plasticity linked to sexual experience in male rats and mice**

Arnaud JEAN, Sakina MHAOUTY-KODJA & Hélène HARDIN-POUZET \*

Sorbonne Université - Faculté de Sciences et Ingénierie,  
Neuroplasticité des Comportements de la Reproduction  
Neurosciences Paris Seine' UM119 - CNRS UMR 8246 - INSERM UMRS 1130  
7 quai Saint Bernard,  
75 005 Paris,  
France

tel : (33) 1 44 27 36 57

fax : (33) 1 44 27 25 08

[helene.pouzet@sorbonne-universite.fr](mailto:helene.pouzet@sorbonne-universite.fr)

\* Corresponding author

**Highlights:**

- male sexual behavior is subject to learning, which manifests by increasing copulatory performance,
- cellular and molecular modifications underpinning performance improvement increase the reactivity of the mPOA,
- plasticity shares mechanisms similar to those governing memory and learning,
- the molecular and cellular mechanisms of sexual experience in mice differ in part from those in rats,
- the first copulation could be considered as a maturation step allowing the acquisition of fully mature sexual behavior.

**Keywords:**

male sexual behavior; sexual experience; medial preoptic area

**Declaration of interest:**

Authors have no interests to declare

1   **Abstract:**

2   Male sexual behavior is subject to learning, resulting in increased efficiency of experienced males  
3   compared to naive ones. The improvement in behavioral parameters is underpinned by cellular and  
4   molecular changes in the neural circuit controlling sexual behavior, particularly in the hypothalamic  
5   medial preoptic area. This review provides an update on the mechanisms related to the sexual  
6   experience in male rodents, emphasizing the differences between rats and mice.

## 1    **1. Introduction**

2        Reproductive behaviors are essential for the survival of species: to generate a new individual,  
3 gametes must not only be produced, but also transmitted. This review focuses on male sexual  
4 behavior, even female sexual behavior is just as important for successful coupling. Females generally  
5 agree to mate during their period of fecundity, which coincides with ovulation, and a refusal to mate  
6 at other times in the ovarian cycle leads the male to abandon attempts to copulate (Johansen et al.,  
7 2008).

8        The different phases of male sexual behavior are the result of the activation of a dedicated  
9 neural circuit. Sexual experience induces both changes in behavioral parameters and cellular and  
10 molecular modifications in the underlying central circuit. Although this general pattern is found in  
11 many species, this review focuses principally on mice and highlights differences between mice and  
12 rats.

## 14    **2. The reproductive behavior of male rodents improves with experience**

### 16    *2.1. The different phases of male sexual behavior*

17        In laboratory rats and mice, male reproductive behavior is expressed without seasonal  
18 restrictions or hormonal cyclicity, whenever the male comes into the presence of a receptive female,  
19 outside of periods of post-ejaculatory non-interest. The various stages of male sexual behavior  
20 follow a precise sequential order, leading to the release of male gametes into the female genital  
21 tract (Thibault and Levasseur, 2001).

22        The attraction phase results in the simultaneous location of the male and the female at the  
23 same place. It is based almost exclusively on the emission and detection of pheromones and  
24 ultravocalizations, providing spatial information, and information about the identity and  
25 reproductive status of the individuals involved, and about the genetic distance separating them  
26 (Asaba et al., 2014; Ferrero et al., 2013; Pfaff Donald and J neil, 2006). The motivation (or  
27 precopulatory or appetitive) phase precedes copulation and allows its initiation. The male interacts  
28 with the female via diverse investigations, accompanied by further ultravocalizations (Asaba et al.,  
29 2014; Holy and Guo, 2005; Kikusui et al., 2021). The copulatory or consummation phase begins with  
30 the first mounting and intromission of the receptive female by the male. During this process, the  
31 female adopts a lordosis posture, facilitating intromission.

32        In mice, the extravaginal pelvic thrusts are rapid, whereas those performed during intromission are  
33 slower and of a larger amplitude (Collins et al., 2009). A series of mounting events occurs over a  
34 period of about 30 minutes, until ejaculation, which is followed by a torpor lasting about 20 seconds.

1 The male then presents a temporary lack of interest in all receptive females, for a mean of two days  
2 in the C57Bl/6J strain (Mosig and Dewsbury, 1976).

3 Unlike mice, rats are capable of multiple ejaculations. After 7 to 10 intromissions (each lasting 1 or  
4 2 minutes), the male rat ejaculates, grooms himself and rests (for 6 to 10 minutes) and then resumes  
5 mating. A male rat is able to reach successively 7 to 8 ejaculations (Hull and Dominguez, 2007). The  
6 post-ejaculatory interval in rats is defined as the time between the first ejaculation and the next  
7 mounting event. After the final ejaculation, the rat then enters a phase of total sexual satiety, which  
8 lasts for 1 to 3 days (Barfield and Sachs, 1968; Zucker and Wade, 1968).

9 Several models have been developed to explain the mechanisms of passage from one phase to  
10 another (Ball and Balthazart, 2008), including, in particular, the psychohydraulic model of Konrad  
11 Lorenz (Lorenz, 1950) and the rat model of Pfaus (Pfaus, 1996), in which the boundary between the  
12 motivation and copulatory phases is less clear.

## 14 *2.2. Improvement with experience (figure 1)*

15 In adulthood, male sexual behavior is expressed spontaneously, in the presence of adequate  
16 sexual stimuli. Nevertheless, there is an effect of sexual experience, with the parameters of this  
17 behavior improving, and efficacy increasing, following the first coupling.

### 18 *- In mice*

19 Most of the studies on sexual experience in mice performed to date involved the C57Bl/6 strain.  
20 However, the experimental protocols used to induce sexual experience may differ between studies,  
21 particularly in terms of the duration and number of exposures to receptive females (Jean et al.,  
22 2017a; Keller et al., 2006a; Naulé et al., 2016; Picot et al., 2014; Swaney et al., 2012).

23 Sexual experience leads to an increase in the efficacy of the appetitive and copulatory phases,  
24 with no impact on the global copulatory pattern. The time lag to the first mounting event and the  
25 duration of olfactory investigations decrease, leading to a shortening of the precopulatory phase.  
26 The number and duration of ultrasound vocalizations during this phase are greater in sexually  
27 experienced than in inexperienced male mice (Arriaga et al., 2012; Ferhat et al., 2016; Mhaouty-  
28 Kodja, 2020). The experience also manifests as a decrease of the number of intromissions and thrust  
29 (Picot et al., 2016) and the intervals between mounting events and intromissions decrease. Overall,  
30 these elements lead to a decrease in the time required for the full completion of sexual behavior,  
31 from introduction to a receptive female to ejaculation and to a decrease of the various intervals and  
32 frequency prior to ejaculation.

33 Sexual experience also facilitates other types of behavior indirectly associated with mating. A  
34 sexually experienced male mouse has an increased olfactory preference for a receptive female

(Hayashi and Kimura, 1974). Also, it is able to discriminate a greater variety of olfactive stimuli provided by the females (Sipos et al., 1992).

*- In rats*

Many more studies have been performed in rats than in mice, and the behavioral parameters improved by sexual experience differ slightly from those in mice, due particularly to the differences in sexual behavior between these two rodents. Sexually experienced rats tend to mount, intromit and ejaculate faster than naive males. The duration of the motivation and copulatory phases is shorter in experienced rats, with a shorter time lag to the first mounting event and a shorter coupling period (Bialy et al., 2000). In addition, the number of ejaculations is greater in rats, with a shorter post-ejaculatory interval (Bialy et al., 2010; Dewsbury, 1969; Glasper and Gould, 2013; Huijgens et al., 2021; Pitchers et al., 2012a).

Sexual behavior has hedonic properties (Tenk et al., 2009), which may be associated with various behavioral reinforcements along the acquisition of sexual experience, such as choosing a preferred site for coupling (Camacho et al., 2004). Experienced rats also display a greater capacity to overcome aversive stimuli to mate (Pfaus et al., 2001).

The behavioral improvement associated with sexual experience is not exclusive to rodents and has been reported in most of the animal models studied, such as hamster, ram or cats (Agmo, 1976; Borg et al., 1992; Bunnell and Kimmel, 1965; Rosenblatt and Aronson, 1958). In all the studied species, it has an impact on the duration of the motivation and copulatory phases. This suggests that cerebral and endocrine modifications occur during learning in the circuits controlling this complex behavior.

### **3. The neural circuit controlling reproductive behavior in male rodents**

This part describes the characteristics and control of the neural circuit underlying male sexual behavior in order to expose, in the next section, the mechanisms that can be at the origin of its improvement.

Several techniques have made it possible to identify the relative roles of the various central areas involved in controlling sexual behavior: microlesions, pharmacological or electrical microstimulations, or mapping established by the detection of immediate-early genes. Several optogenetic studies have confirmed these previous findings (Balthazart, 2020; Kohl et al., 2018; Kunkhyen et al., 2017; Wei et al., 2018).

### 3.1. *The medial preoptic area (mPOA) of the hypothalamus: the integrating center*

The medial preoptic area (mPOA) of the hypothalamus is located in the anterior hypothalamus, between the anterior commissure and the optic chiasma, on either side of the third ventricle. It was first described in rats by Gorski (Gorski et al., 1978). In mice, the precise site of this structure is more difficult to determine than in rats, in which the sexually dimorphic nucleus (SDN) is easy to identify thanks to its particular cytoarchitecture (Tsuneoka, 2019; Tsuneoka et al., 2017).

The mPOA is the principal region of the brain involved in the control of male sexual behavior, as demonstrated in all vertebrate species studied (Pfaff and Joels, 2016). Its electrical stimulation facilitates the execution of sexual behavior (Malsbury, 1971; Merari and Ginton, 1975; Rodríguez-Manzo et al., 2000) and triggers erection in the rat (Giuliano et al., 1996). During the various phases of sexual behavior, a large increase in c-Fos levels is observed in rats, together with increased electrical activity in distinct mPOA group of cells (Shimura et al., 1994). This indicates that there are functional subdivisions in the mPOA contributing to sexual motivation and copulatory performances (Baum and Everitt, 1992; Coolen et al., 1998; Hull et al., 2002; Paredes, 2003; Pfau and Heeb, 1997). After ejaculation, mPOA electrical activity strongly diminishes to almost nothing (Horio et al., 1986; Shimura et al., 1994). Finally, electrolytic lesions of the mPOA abolish the consummatory behavior in rats (Ågmo et al., 1977; Larsson and Heimer, 1964) and ferrets (Cherry and Baum, 1990) and no functional recuperation is observed: no other area of the brain can compensate for the role played by the mPOA in the control of sexual behavior.

### 3.2. *Organization of the control circuit governing male sexual behavior (figure 2)*

Most of the afferents received by the mPOA come from the sensory systems, the olfactory, somatosensory and even auditory systems. Pheromones (Tirindelli et al., 2009) are detected in the vomeronasal organ (VNO) and the main olfactory epithelium (MOE), which project onto the accessory olfactory bulb (AOB) and the main olfactory bulb (MOB), respectively. The AOB innervates the medial amygdala (MeA) directly, or via a relay in the bed nucleus of the stria terminalis (BNST). The MOB also innervates the MeA (Kang et al., 2009). This convergence structure then serves as a relay towards the mPOA. The modes of interaction between the two systems and their functional complementarity in the control of sexual behavior remain to be established (Asaba et al., 2014; Keller et al., 2006b).

Special attention should be paid to MeA and BNST, regrouped to the name the “extended amygdala”, since they constitute the major projection on mPOA. During the copulatory phase, they display an enhanced Fos-immunoreactivity and they contain a high density of neurons sensitive to androgens. BNST and the posterodorsal subdivision of the MeA are activated by anogenital

1 investigation while a lateral part of the MeA is activated after ejaculation (Snoeren et al., 2014;  
2 Veening and Coolen, 1998).

3       Peripheral projections from the spinal cord also reach the mPOA, carrying somatosensory  
4 information from the genital organs via a relay in the central tegmental field (CTF). The retina,  
5 auditory cortex, raphe nuclei and the nucleus accumbens also project onto the mPOA (Mogenson  
6 et al., 1983; Morin and Studholme, 2014). Finally, the zona incerta (ZI), paraventricular nucleus  
7 (PVN) and the ventromedial nucleus of the hypothalamus (VMH) are also known to synapse to the  
8 mPOA (Simerly and Swanson, 1986).

9       The mPOA is involved in controlling various physiological functions, such as thermogenesis  
10 (Boulant, 2000), sleep (Szymusiak et al., 2001), parental care (Champagne et al., 2003), intermale  
11 aggression (Edwards et al., 1993; Wu et al., 2014, p. 20114), and sexual behavior. In the control  
12 circuit for male sexual behavior, the mPOA projects mostly onto the PVN, and it modulates the  
13 autonomic nervous systems involved in controlling erection and ejaculation in the spinal regions  
14 involved in movement coordination (Raskin et al., 2012; Rizvi et al., 1996). Fine control over motor  
15 acts is also mediated by projections of the mPOA onto the substantia innominata, the ZI and the  
16 pedunculopontine nucleus, which is known for its relationships with the motor cortex and the  
17 nigrostriatal pathway (Simerly and Swanson, 1988). mPOA also innervates the PVN and the VMH ,  
18 which in turn project on mPOA, constituting a feedback loop (Canteras et al., 1994; Geerling et al.,  
19 2010) involved in the regulation of sexual behavior (Argiolas and Melis, 2004; Flanagan-Cato, 2011;  
20 Geerling et al., 2010). Finally, the mPOA is capable of activating the reward circuit via its projections  
21 onto the ventral tegmental area (VTA) (Tobiansky et al., 2016), providing an anatomic basis for the  
22 reinforcing aspects of sexual behavior (Hull and Dominguez, 2019; Pitchers et al., 2010a; Tobiansky  
23 et al., 2013).

### 25 *3.3. Neurotransmitters involved in the control of male sexual behavior*

26       When compared to some other hypothalamic nuclei, such as supraoptic nucleus,  
27 paraventricular nucleus or suprachiasmatic nucleus, a considerable diversity of neuromediators is  
28 found in the mPOA (Argiolas and Melis, 2013; Hashikawa et al., 2016; Simerly et al., 1986). This is  
29 probably linked to the great diversity of neuronal circuits passing through this structure. The next  
30 section focuses on the mediators involved in the control of male sexual behavior. It is of particular  
31 importance to note that almost all the studies have been conducted in rat and that most data were  
32 extended to the mouse by analogy.

Dopamine is the neurotransmitter for which effects on reproductive behavior has been best characterized. Dopamine facilitates copulation and genital responses. Its concentration in the mPOA increases during the different phases of sexual behavior, and its release is specific to sexual behavior (Hull et al., 1995). Three dopaminergic pathways are involved in regulating sexual behavior (Hull et al., 1999). The nigrostriatal pathway regulates the consummation phase of copulation, by favoring the initiation and performance of the copulatory pattern of mounting behavior (Damsma et al., 1992). The mesolimbic pathway is associated with reward and reinforcement aspects and regulates the motivation phase of sexual behavior (Hull et al., 1997). Finally, the dopamine produced by the periventricular region and the ZI is involved in the control of autonomic nervous systems and regulation of the motivational and copulatory components of sexual behavior (Simerly et al., 1986). Although the target cells activated by dopamine are unknown, it has been shown that dopamine in the mPOA enhances sensorimotor integration, removes tonic inhibition on the downstream structures controlling sexual behavior and increases motivation and reinforcement via the mesolimbic system. These processes involve D1-like and D2-like receptors which have distinct but also some synergistic effects, due at least in part to their different thresholds of activation. Low dose of dopamine in the mPOA results in disinhibition of genital reflexes via D2 receptors, moderate level of dopamine activates D1 receptors which stimulate erection centers and finally a high rate of dopamine facilitates ejaculation and inhibits erection, via D2 receptors again. This description of the implication of dopamine D1 and D2 receptors in the control of sexual behavior is the basis of the construction by Dominguez and Hull of an elegant integrative model for rats (Dominguez and Hull, 2005).

Glutamate is the other key neurotransmitter in the activation of sexual behavior (Drago and Busă, 1997). It originates from projections from the lateral septum, the BNST, the MeA, the PVN and the arcuate nucleus (Kocsis et al., 2003), that converge on mPOA, where it acts via AMPA, NMDA (Powell et al., 2003) and mGluR5 and 7 receptors (Li et al., 2013). Glutamate concentration increases during copulation, peaking during ejaculation and then returning to its basal level during post-ejaculatory intervals and the period of satiety (Brudzynski and Pniak, 2002; Dominguez, 2006; Vigdorichik et al., 2012). In the model of Dominguez and Hull, glutamate is the activating signal which generates, after a nitrergic relay, the dopamine increase.

The third neurotransmitter with a determinant role in the control of rat sexual behavior is thus nitric oxide (NO) (Lagoda et al., 2004; Sato et al., 1998). Several studies have investigated the interactions between dopamine, glutamate and NO in the mPOA, and the links with copulatory behavior (Dominguez et al., 2004; Hull and Dominguez, 2006; Lorrain et al., 1996; Sato and Hull, 2006), culminating in the model proposed by Hull and Dominguez for the rat. The release of



glutamate in the mPOA during mating activates the phosphorylation of NMDA receptors, triggering an influx of calcium into the target neurons. This calcium influx activates calmodulin, and then nNOS. This enzyme is located in the close vicinity of glutamatergic synapses and NMDA receptors, through its interaction with PSD-95 (post-synaptic density-95 protein). The NO produced as a result diffuses to the dopaminergic terminals present in the mPOA, where it increases dopamine release and inhibits the dopamine transporter (DAT) (Dominguez and Hull, 2005; Paredes and Ågmo, 2004; Sanna et al., 2020). The extracellular concentration of dopamine therefore increases, leading to an activation of sexual behavior, via the sequential recruitment of the cells expressing D2, then D1 and finally D2 receptors. However, the precise identity of the cells expressing the various components of the model and their precise location in the mPOA are not known. It should be also noted that the steroid sex hormones and their receptors are not considered in this model.

Other neuromediators play a role in the control of sexual behavior, but with a less determinant effect. These molecules include serotonin (Fernández-Guasti et al., 1992; Hull et al., 2004; McIntosh and Barfield, 1984; Verma et al., 1989), GABA (Fernandez-Guasti et al., 1986; Qureshi and Södersten, 1986; Rodríguez-Manzo et al., 2000) and norepinephrine (Mallick et al., 1996; McIntosh and Barfield, 1984; Pfaff and Joels, 2016). The sexual behavior is under constant inhibitory control to assure that the behavior occurs only under the proper circumstances. Serotonin and GABA are involved in the inhibition and disinhibition process to induce sexual behavior (Snoeren et al., 2014). Serotonin also regulates the behavioral quiescence following ejaculation via the reduction of glutamate signaling to the mPOA (Will et al., 2014). On the opposite, norepinephrine has globally an activational effect on sexual behavior (Pfaff Donald and J neil, 2006). Oxytocin increases the release of dopamine in the mPOA and activates the genital reflexes, via projections from the PVN onto spinal and genital structures. Its release into the bloodstream at the time of ejaculation also plays a role in sexual satiety (Argiolas and Melis, 2004; Gil et al., 2011; Melis et al., 2007; Thackare et al., 2006; Witt and Insel, 1994).

### *3.4. Effect of the steroid sex hormones on male sexual behavior*

Sexual behavior is an integrated form of behavior, requiring the existence of systems of communication between the peripheral organs involved in the maturation and expulsion of gametes and the nervous system involved in the control of sexual behavior. This communication is mediated by the various sex hormones. During the perinatal and pubertal periods, these hormones have organizational effects, permitting the subsequent expression of reproductive behavior during adulthood (Phoenix et al., 1959; Schulz et al., 2004). In particular, for male rats and hamsters, a threshold amount of circulating testosterone is required for the initial, peri-pubertal, expression of

1 mating behavior (Goldfoot and Baum, 1972; Meek et al., 1997). In this context, it is interesting to  
2 mention that the age of initiation of copulation can be advanced in the rat male by early  
3 administrations of sex hormones or electrical stimulation in the pre-pubertal period or electrical  
4 stimulation of the flank in the presence of a receptive female (Baum, 1972; Goldfoot and Baum,  
5 1972).

6 Testosterone is considered to be the principal hormone necessary for the control of male sexual  
7 behavior. Its concentration in the plasma ranges between 1 and 5 ng/ml for the C57Bl/6 strain and  
8 does not vary between the different phases of sexual behavior (Amstislavskaya and Popova, 2004;  
9 Batty, 1978a). However, the exposure of a male to an inaccessible receptive female, the urine of a  
10 receptive female, pheromones, or ultravocalizations from a receptive female induces an increase in  
11 this concentration (Amstislavskaya and Khrapova, 2002; Batty, 1978b; Maruniak and Bronson, 1976;  
12 Nyby, 2008; Singer et al., 1988; Wysocki et al., 1983). Unlike mice, for rats, studies have reported an  
13 increase in the plasma concentration of testosterone during copulation (Bonilla-Jaime et al., 2006;  
14 Kamel et al., 1975), but this increase was not found in other studies (Balin and Schwartz, 1976;  
15 Shulman and Spritzer, 2014). Anyway, the reported increases in testosterone concentration during  
16 sexual behavior, of the order of 1 to 10 ng/ml, are much smaller than the increase by a factor of 40  
17 observed during nycthemeral variations, suggesting that this increase may not be so determinant  
18 for the execution of sexual behavior (see below the Nyby model).

19 In adult animals, castration leads to a change in sexual behavior according to a well-defined  
20 loss sequence, with first a loss of ejaculation, then of mounting behavior with intromission, and,  
21 finally, of the motivation phase. Castration thus induces an almost total abolition of sexual behavior  
22 and a change in the erectile reflexes in most animals (Clemens et al., 1988; Hull et al., 2002).  
23 Testosterone supplementation restores each of the components of sexual behavior, in the opposite  
24 order to their disappearance (Clemens et al., 1988; Hull et al., 2002). In the rat, a low threshold  
25 amount of circulating testosterone is required to maintain mating following castration (Damassa et  
26 al., 1977). In ferret, a seasonal species, a dose-dependent effect of testosterone was observed on  
27 the duration of intromission (Lambert and Baum, 1991). In mice, castrated male on testosterone  
28 supplementation display no major differences with respect to intact animals, despite the lack of  
29 restoration of the pulsatile nature of testosterone secretion (Raskin et al., 2009). Thus, the presence  
30 of testosterone appears to be essential for sexual behavior, through an effect facilitating, rather  
31 than triggering, copulation.

32 The effects described above are due to the combined action of testosterone and of its two  
33 principal active metabolites, estradiol (E2) and dihydrotestosterone (DHT) (Roselli et al., 2003).  
34 Supplementation with both these metabolites is required for a complete restoration of sexual

behavior after castration (Attila et al., 2010; Baum and Vreeburg, 1973; Cooke et al., 2003). Testosterone and DHT bind to the androgen receptor (AR), whereas E2 binds to the estrogen receptors, ER $\alpha$  and ER $\beta$ . In the brain, all the zones involved in the regulation of sexual behavior express these receptors (Cunningham et al., 2012). These signaling pathways have been shown to have different effects on the control of the different phases of copulatory behavior (Clancy et al., 1995). In the rat, inhibition of the AR greatly decreases all parameters of sexual behavior (McGinnis et al., 1996; Russell et al., 2012), whereas ER $\alpha$  inhibition only alters certain types of behavior occurring during the motivation phase (Gladue and Clemens, 1980; Vagell and McGinnis, 1998), and ER $\beta$  inhibition has no apparent effect, indicating a lack of involvement of this receptor in the control of sexual behavior (Sano et al., 2013). In mice, transgenic models, like ubiquitous KO, spontaneous mutant or KO restricted to the nervous system, made it possible to specify the importance of brain aromatase (Brooks et al., 2020), and the respective roles of the different receptors for the sex hormones, AR, ER $\alpha$  and ER $\beta$  (for review see (Mhaouty-Kodja, 2018).

Castrated rats have lower levels of dopamine in the mPOA (Du et al., 1998; Hull et al., 1997), due to lower levels of NO synthesis (Du and Hull, 1999; Sato et al., 2005) and probably linked to the upregulation of nNOS expression by sex steroids (Panzica et al., 2006). According to the model proposed by Nyby (Nyby, 2008), testosterone plays a dual role in the control of sexual behavior. Basal levels of testosterone secretion are responsible for ensuring that the brain remains in a state of sensitivity compatible with the activation of sexual behavior, through the maintenance of nNOS expression in the mPOA in particular. When the male encounters a receptive female, the sensory stimuli are processed in the brain, leading to a triggering of male sexual behavior, but also to the release of GnRH and LH, which cause a transient increase in plasma testosterone levels. This increase also affects the reward system, positively modulating anxiety, analgesia, the genital reflexes and the learning process (Aikey et al., 2002; Arnedo et al., 2002, 2000; Edinger et al., 2004; Edinger and Frye, 2004; Pednekar and Mulgaonker, 1995; Wood, 2002; Wood et al., 2004).

Another steroid hormone rarely cited in this context, progesterone, may also play a role in regulating reproductive functions in males (Heller et al., 1958). It is synthesized by the Leydig cells and the adrenal glands, and its plasma concentration is similar in men and women during the follicular phase (Oettel and Mukhopadhyay, 2004). As progesterone is the metabolic precursor of testosterone, it is difficult to say whether it acts directly on the circuit controlling sexual behavior. This questioning is reinforced by the demonstration in certain contexts, in particular pathological contexts, of crosstalks between the receptors for the different sex steroid hormones, whether at the level of their expression or their signaling pathways. For example, increasing circulating levels of progesterone can lead to an upregulation of estrogen receptor (Cenciarini and Proietti, 2019;

Saha et al., 2021; Singhal et al., 2016). However, it is interesting to note in this regard that mPOA is rich in progesterone receptors (Andersen and Tufik, 2006; Lauber et al., 1991), that male mice with an ubiquitous progesterone receptor deletion displayed enhanced mating performance and that this effect was duplicated in wild type males by administering a progesterone receptor antagonist drug (Schneider et al., 2005). Studies of male mice with a neural knockout of the progesterone receptor will certainly help to clarify progesterone implication in the control of male sexual behavior.

#### **4. Plasticity linked to sexual experience: cellular and molecular modifications of the mPOA (figure 3)**

As explained above, sexual behavior is subject to improvements in motivational and copulatory parameters with sexual experience. This is associated with neural and gonadal modifications to various previously described systems implicated in the control and execution of sexual behavior. This section focuses on the modifications to the mPOA induced by sexual experience. These modifications differ slightly between rats and mice, according to the subtle differences in copulatory behavior between these two species.

##### **4.1. In rats**

Many more studies have been published on the modifications occurring in rats than of those occurring on mice, thanks largely to the contributions of Elaine Hull and Juan Dominguez, the authors of most of the studies presented below. The levels of several proteins and peptides in the mPOA are durably modified by sexual experience, with increases in the levels of nNOS and the number of cells immunoreactive for this enzyme (Dominguez et al., 2006), in the levels of oxytocin receptors and their mRNAs (Gil et al., 2013, 2011) and in the number of D2-positive cells. Sexually experienced rats killed after ejaculation have been shown to have a greater number of c-Fos-immunoreactive cells (Baum and Everitt, 1992; Lumley and Hull, 1999; Nutsch et al., 2016). Levels of the phosphorylated form of DARP32 (p-DARP32), a protein involved in the intracellular dopamine pathway, and of phosphorylated NMDA receptors are higher in these rats (McHenry et al., 2012). They also have higher levels of cytochrome oxidase activity (Sakata et al., 2002) and of heme oxygenase 1 and 2 activity (Robison et al., 2017). Taken together, these data indicate that the mPOA acquires greater reactivity with sexual experience.

These modifications induced during the sexual experience can be placed in the model of Dominguez and Hull. Stimulation of the glutamatergic pathways during the first mating leads to an increase in the level of phosphorylated NMDA receptors in the mPOA (Vigdorchik et al., 2012) which is therefore more reactive when it is stimulated during the second mating. The increased activity of

nNOS (Lagoda et al., 2004) leads to a faster production of NO, then to a faster and more massive release of dopamine which more rapidly initiates the D2 / D1 / D2 receptor cascade (McHenry et al., 2012) and the execution of sexual behavior. This kind of long-term memory process at the level of the glutamatergic afferents of mPOA thus makes it possible to explain the reduction in the duration of the various phases of sexual behavior in an experienced rat (Vigdorchik et al., 2012).

#### 4.2. *In mice*

Compared to the rat, fewer studies are available on characterizing modifications induced by sexual experience in mice. The first such study (Swaney et al., 2012) showed that sexually experienced male mice had larger numbers of AR-expressing cells specifically in the mPOA, the number of cells expressing ER $\alpha$  remaining unchanged. These results differ from our observations demonstrating that AR and ER $\alpha$  level in the mPOA are not affected by sexual experience (Jean et al., 2017a). This can probably be explained by the more complex paradigm that was used by Swaney et al., leaving the male 3 weeks interacting with receptive females and then one week with non-receptive females. In these conditions, experienced animals present a faster increase in c-Fos expression than naive animals, in the zones of the brain implicated in the control of sexual behavior, including the mPOA in particular (Swaney et al., 2007). Our study of the phosphorylation of ERK1/2 in the mPOA showed that this modification is triggered by events in the motivation phase and that the level of phosphorylation increases in experienced animals (Jean et al., 2017b). These findings are consistent with those of Taziaux et al. (Taziaux et al., 2011). Taken together these data confirm that, as for rats, the acquisition of sexual experience in mice leads to a higher reactivity of the mPOA in the presence of a receptive female.

Our work has extended the characterization of modifications to the mPOA during the acquisition of sexual experience. We first showed that the modification of the mPOA network is a progressive process that is complete about 14 days after the first coupling (Jean et al., 2017a). This characteristic of a progressive modification suggests a maturation process leading to a new state of differentiation of the neural network. This hypothesis is reinforced by the work of Swaney et al. demonstrating that the imprinted gene *Peg3* plays an essential role in encoding the neural effects of mating experience (Swaney et al., 2007). Our results also indicates that the shortening of the various phases of behavior under sexual experience is accompanied by epigenetic modifications, as demonstrated by the increase in the levels of H3 histones displaying trimethylation of the lysine 27 residue (H3K27me3) in sexually experienced males (Jean et al., 2017a).

1 We then explored if the levels of sex steroid hormones are affected by sexual experience.  
2 Ejaculation in mice is associated with changes in steroid hormone levels, with a large decrease in  
3 plasma testosterone concentration and a parallel increase in the concentrations of corticosterone  
4 and progesterone. Hypothalamic concentrations seem to follow the same pattern. However, neither  
5 these changes nor the levels of expression of the AR and ER $\alpha$  receptors in the mPOA (Jean et al.,  
6 2017a) are affected by sexual experience, providing support for the notion that presence of sexual  
7 steroids is permissive for sexual behavior, but does not trigger it.

8 Regarding the morpho-functional characteristics of mPOA, we have shown that sexually  
9 experienced males have a higher density of dendritic spines of the “mushroom” type, but a normal  
10 overall density of spines. This phenomenon is associated with an increase in the levels of PSD-95,  
11 suggesting that sexual experience induces the differentiation of spines already present in the mPOA  
12 towards a mature phenotype, rather than the formation of new immature spines (Jean et al., 2017a).  
13 Sexual experience is also accompanied by an increase in the levels of GluN1 (but not those of GluN2),  
14 indicating an increase in glutamate sensitivity in the mPOA, together with an increase in the levels  
15 of calbindin (Jean et al., 2017a), one of the intracellular buffers of calcium (Lüscher and Malenka,  
16 2012). An increase in calcium levels in response to the activation of NMDA receptors could,  
17 therefore, trigger the establishment of plasticity mechanisms. In a perspective to apply the  
18 Dominguez and Hull model to the mouse, these elements are interesting because they complement  
19 data showing that the release of dopamine in mPOA is necessary for the execution of sexual  
20 behavior (Szczyepka et al., 1998; Wersinger et al., 1997). However, to our knowledge, no data is  
21 available on dopamine levels in an experienced male mouse compared to a naive one.

22 The most striking finding of our work is that, by contrast to what has been reported for the rat,  
23 there is no increase in the number of cells expressing nNOS or in NOS enzymatic activity in  
24 experienced male mice (Jean et al., 2017a), even if there are nNOS expressing cells in the mPOA  
25 (Scordalakes et al., 2002). There is, therefore, a need to develop a model specific to the mouse  
26 involving new actors, different from those included in the Dominguez and Hull rat model. For this  
27 reason, we investigated the roles of other types of cells. Astrocytes are probably not involved,  
28 because there is no change in their morphology, in the number of cells expressing GFAP, nor in GFAP  
29 expression in the mPOA. By contrast, experienced male mice display an increased expression of Iba-  
30 1, a specific marker of microglia (Jean et al., 2017a). More detailed studies should now be performed  
31 to determine the possible role of microglia. The work of Lenz and McCarthy (Lenz and McCarthy,  
32 2015a) on the role of prostaglandins in male development may provide interesting leads (see  
33 Conclusion below).

1 In conclusion, in mice, the modifications in the mPOA induced by sexual experience are  
2 different from those observed in rats. However, the observed modifications ultimately lead to an  
3 increase in mPOA excitability mediated by complex cellular interactions involving neuronal and non-  
4 neuronal cells.

## 6 **5. Other central structures modified by sexual experience**

7 Other central structures, such as the hippocampus, the prefrontal cortex, the extended  
8 amygdala and the nucleus accumbens, display changes in functional activity with sexual experience.  
9 All these diverse regions express receptors for steroid hormones.

10 Two studies on the hippocampus and one on prefrontal cortex have shown enhanced  
11 neurogenesis and modifications in the dendritic arborization in sexually experienced male rats  
12 (Glasper et al., 2015; Glasper and Gould, 2013; Leuner et al., 2010) suggesting that sexual experience  
13 induces changes to these networks, leading to an increase in their reactivity.

14 Regarding MeA and BNST, essential for the activation of mPOA during copulation, few data are  
15 available. BNST does not appear to be affected by sexual experience, as the number of cells  
16 expressing c-Fos remains unchanged (Parfitt and Newmann, 1998). In hamsters MeA, different  
17 subpopulations are activated between naive and sexually experienced animals (Biggs and Meredith,  
18 2020). For the rat, a conversion of MeA dendritic spines (in the posterodorsal part) toward a  
19 mushroom phenotype was described with sexual experience (Zancan et al., 2018) and oxytocin  
20 participates in this spine remodeling (Becker et al., 2017). However, expression of the immediate  
21 early gene *Arc*, a marker of plasticity, does not appear to be affected by experience (Turner et al.,  
22 2019).

23 In the first part of this article, we noted that sexual behavior is a natural activator of the reward  
24 circuit by triggering the release of dopamine into the mesolimbic system (Balfour et al., 2004; Fiorino  
25 et al., 1997; Fiorino and Phillips, 1999; Pfaus et al., 1990). Several modifications to this circuit are  
26 induced by sexual experience, particularly in the nucleus accumbens, in which the  
27 electrophysiological properties of the spiny neurons are modified (Goto et al., 2015; Pitchers et al.,  
28 2012b), together with their dendritic arborization (Pitchers et al., 2010a), these changes being  
29 associated with an increase in the levels of NMDA NR1 and AMPA GLUR2 expression. The increased  
30 reactivity within the reward circuit was confirmed by the increase in the number of cells displaying  
31 immunoreactivity to  $\Delta c$ -Fos, the truncated form of c-Fos, which is known to be involved in behavioral  
32 reinforcement processes (Pitchers et al., 2010b). The potentiation of this circuit could also at least  
33 partly account for the increase in sexual motivation and behavioral efficacy induced by sexual  
34 experience.

## 6. Conclusion

Given the importance of reproduction for the survival of species, improvements in copulatory performance could be seen as a way of increasing the chances of meeting a potential partner (Dewsbury, 1982). The increase in the efficacy of sexual behavior achieved by decreasing the duration of the motivation and copulatory phases makes it possible to limit the time and energy spent on performing a behavioral task during which the male and female become easy prey for their predators (Pfaff and Joels, 2016; Pfaus et al., 2001).

Studies performed in rats and mice have demonstrated the participation of multiple molecules in the increase in mPOA reactivity. In rats, Hull's model explains how interactions between the glutamatergic, dopaminergic and nitrergic systems can exert facilitating effects on sexual behavior at the level of the mPOA. Nevertheless, this model does not take into account the potential influence of sex steroids on the modulation of these different systems of neurotransmission.

In mice, the number of studies performed remains small, but the results obtained to date confirm that sexual experience induces an increase in the global activity of the mPOA. Our work has shed new light on the mode of mPOA activation, as we have shown that the NO system is not impacted, and our findings suggest a role for microglial cells in this process. Nonetheless, further studies are required to better understand the sequence of cellular and molecular events in this species, which is increasingly used in transgenic models.

Interestingly, the modifications driven by sexual experience are reminiscent of certain known mechanisms involved in perinatal regulation of the establishment of sexual dimorphism in the mPOA, a prerequisite for the expression of adult male behavior (Lenz and McCarthy, 2015b) : the chain of events linking testosterone and the prostaglandins produced by the microglia results in a local increase in glutamate concentration and an increase in the density of dendritic spines required for the expression of adult male sexual behavior (Lenz and McCarthy, 2015b; Lenz and Nelson, 2018; VanRyzin et al., 2020). It is, therefore, possible that some of these actors are involved in improving male sexual behavior during adulthood in mice, through mechanisms similar to those operating during the perinatal period, since the first copulation leads to an increase in the density of mature dendritic spines, probably through a microglial intervention, and this is accompanied by an increase in glutamatergic transmission.

We can thus form the hypothesis that sexually naive males are not "fully adults". The first sexual behavior would thus represent the last stage of maturation of the circuit of control of the reproductive behavior and allow the acquisition of an effective and mature sexual behavior.



1

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7

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**Figure Legends:**

**Figure 1. Illustration of the effects of the sexual experience.**

A: experimental paradigm. Naive males are in contact for the first time with a receptive female for 10 hours. They then return to their home cage and 14 days later they are placed in the presence of a new receptive female for 10 hours. The behavior parameters are measured on video recordings.  
B: Compilation of data from (Jean et al., 2017a, 2017b).

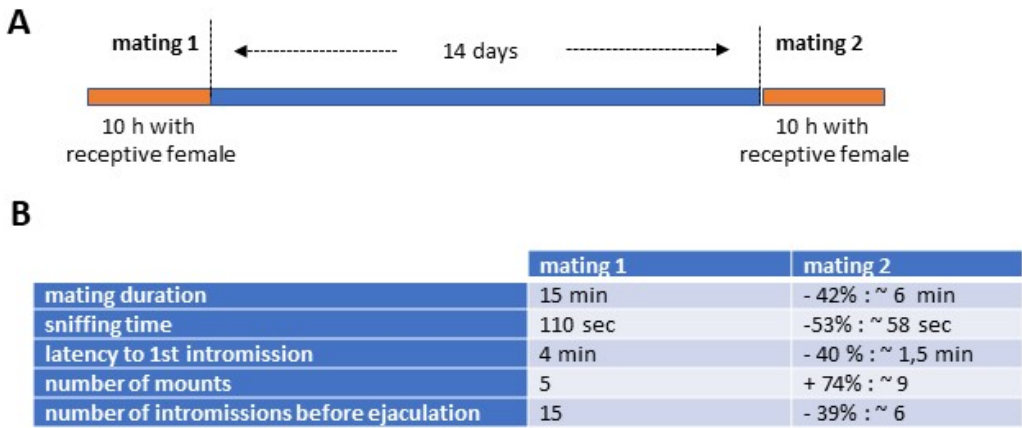
**Figure 2. Synthetic diagram of the afferences and efferences of the mPOA, leading to the realization of male sexual behavior.**

VNO: vomeronasal organ; MOE: main olfactory epithelium; AOB: accessory olfactory bulb; MOB: main olfactory bulb; BNST: bed nucleus of the stria terminalis; MeA: medial amygdala; CTF: central tegmental field; ZI: zona incerta; PVN: paraventricular nucleus of the hypothalamus; USV: ultrasonic vocalization.

**Figure 3. Comparison of the effects of sexual experience on mPOA between rats and mice.**

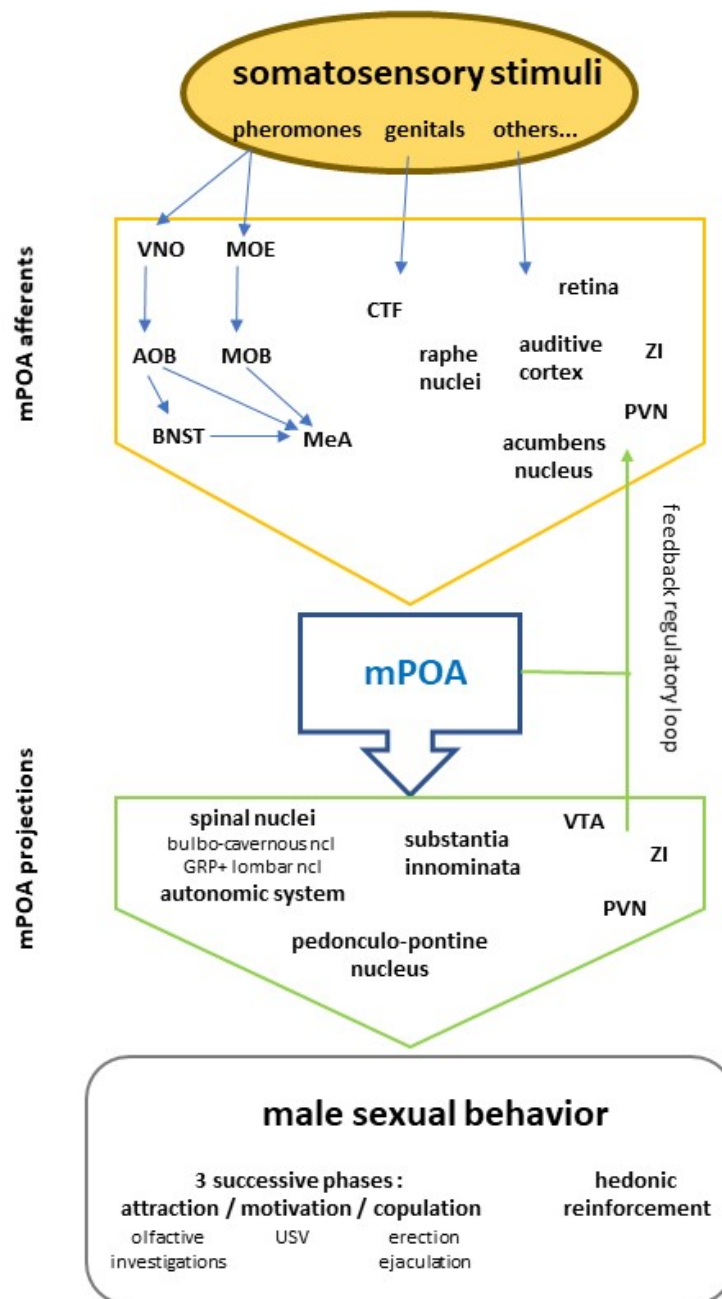
Three phenomena can be identified: 1) an increase in the stimulation of mPOA, 2) an increase in the cellular and molecular pathway within the mPOA, resulting in 3) an increased excitability of the mPOA which leads faster and more efficient sexual behavior. Data in rats produced the Dominguez and Hull model (Hull and Dominguez, 2006). The data in mice are more fragmented (Jean et al., 2017a, 2017b; Swaney et al., 2012; Taziaux et al., 2011). However, they demonstrate that the molecular and cellular mechanisms are different from those of the rat, even if the consequences are similar in terms of improved sexual behavior.

1 **Figure 1. Illustration of the effects of the sexual experience.**



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**Figure 2.** Synthetic diagram of the afferences and efferences of the mPOA, leading to the realization of male sexual behavior.



**Figure 3.** Comparison of the effects of sexual experience on mPOA between rats and mice.

