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Rats selectively bred for showing divergent behavioral traits in response to stress or novelty or spontaneous yawning with a divergent frequency show similar changes in sexual behavior: the role of dopamine

https://doi.org/10.1515/revneuro-2018-0058
Received June 13, 2018; accepted July 26, 2018; previously published online October 6, 2018

Abstract: Sexual behavior plays a fundamental role for reproduction in mammals and other animal species. It is characterized by an anticipatory and a consummatory phase, and several copulatory parameters have been identified in each phase, mainly in rats. Sexual behavior varies significantly across rats even when they are of the same strain and reared under identical conditions. This review shows that rats of the same strain selectively bred for showing a divergent behavioral trait when exposed to stress or novelty (i.e. Roman high and low avoidance rats, bred for their different avoidance response to the shuttle box, and high and low novelty exploration responders rats, bred for their different exploratory response to a novel environment) or a spontaneous behavior with divergent frequency (i.e. low and high yawning frequency rats, bred for their divergent yawning frequency) show similar differences in sexual behavior, mainly in copulatory pattern, but also in sexual motivation. As shown by behavioral pharmacology and intracerebral microdialysis experiments carried out mainly in Roman rats, these sexual differences may be due to a more robust dopaminergic tone present in the mesocorticolimbic dopaminergic system of one of the two sub-lines (e.g. high avoidance, high novelty exploration, and low yawning rat sub-lines). Thus, differences in genotype and/or in prenatal/postnatal environment lead not only to individual differences in temperament and environmental/emotional reactivity but also in sexual behavior. Because of the highly conserved mechanisms controlling reproduction in mammals, this may occur not only in rats but also in humans.

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Keywords: bNEHR-bNELR rats; dopamine; LY-HY rats; RHA-RLA rats; sexual behavior.

Introduction

It is well known that sexual behavior plays a pivotal role for reproduction in mammals. This form of social interaction is characterized by two main phases, anticipatory and consummatory, and several quantifiable parameters in each of them have been mostly identified in male and female rats because of their availability and the well-characterized sequence of copulatory behavior parameters (for reviews, see Sachs and Barfield, 1976; Meisel and Sachs, 1994; Melis and Argiolas, 1995; Argiolas and Melis, 2013; Sanna et al., 2014a, and references therein, but also Agmo, 1997). Briefly, copulatory behavior of a male rat with a receptive female is characterized by one or more series of sexual activity, which start with a first mount (the male follows the female from the back, put its forepaws in the female flanks, and shows pelvic thrusting), continue with a series of mounts with or without intromissions (which look similar to the mounts but end suddenly with dismounting after penile vaginal insertion), and end with ejaculation (which is characterized by a deep pelvic thrust that lasts several seconds in which the male remains immobile over the female, and is followed by dismounting) within approximately 10–11 min. Ejaculation is followed by a resting period in which the male stays close to the female (the so-called post ejaculatory interval), which ends suddenly within 6–10 min with the beginning of another series of copulatory activity similar to that already described. The number and timing of mounts and intromissions that occur prior to ejaculation are important for pregnancy success, being related to a reflex-mediated production of progesterone, which is fundamental for the implant of fertilized oocytes in the uterine wall. In classic copulation tests, the following measures of copulatory behavior are usually recorded: mount and intromission latency (ML and IL, the time from the moment in which the female was introduced into the experimental cage until the first mount and/or the

first intromission, respectively); mount and intromission frequency (MF and IF, the number of mounts and intromissions in a series of copulatory activity, respectively); ejaculation latency (EL, timed from the first intromission until the first ejaculation); ejaculation frequency (EF, the number of ejaculation in the period of testing), and post-ejaculatory interval (PEI, the time from the first ejaculation until the next intromission). Copulatory efficacy (CE, number of intromission of a given series divided by the sum of the number of mounts and of intromission in the same series) and the inter-intromission interval (III, the ratio between the ejaculation latency of a given series and the number of intromissions in that series) are also often calculated (see Sachs and Barfield, 1976; Meisel and Sachs, 1994; Sanna et al., 2014a). These parameters are usually referred to the first series of copulatory activity, e.g. from the first mount/intromission to the first mount/intromission after the first ejaculation. The latency to the display of the first mount and/or intromission after introducing a receptive female to the test arena is thought to be an index of the motivational aspect of copulation, while the other parameters are considered indexes of sexual performance (see Sachs and Meisel, 1988; Meisel and Sachs, 1994). Also in humans, the sexual response is organized into distinct and sequential phases, which include usually (but not always) sexual desire followed by sexual arousal and orgasm, including ejaculation in males (see Masters and Johnson, 1966; Kaplan, 1979; Leiblum, 1998).

In those conditions that lead to the occurrence of sexual behavior, different (visual, auditory, olfactory, tactile, and, in humans, even imaginative) stimuli reach the central nervous system to activate neural pathways that convey sexual information from the higher brain centers through the spinal cord and the autonomous nervous system to the genital apparatus to induce penile erection in males and vaginal lubrication/clitoris erection in females in order to make sexual intercourse feasible (Masters and Johnson, 1966; Kaplan, 1979; Agmo, 1997; Leiblum, 1998; Argiolas, 2005; Maejima et al., 2015; Holstege, 2016; Poeppl et al., 2016). Spontaneous *ex copula* penile erections can be also elicited in rats in their home cage or neutral arena by volatile substances (i.e. pheromones) released from an estrous female that the male rat can see, hear, and smell, but cannot touch. These non-contact erections are considered a model for psychogenic erections (Sachs, 1997; Melis et al., 2001, 2003, 2004). The above neural pathways contain and are under the control of different neurotransmitters, neuropeptides, and hormones (Argiolas et al., 1988, 1989, 2000; Hull et al., 1995; Melis and Argiolas, 1995, 2003, 2011; Melis et al., 1997a,b; Argiolas, 1999; Argiolas and Melis, 2004, 2013; Hull and Dominguez, 2006, 2007; Paredes, 2014). An altered activity of these substances at the central and peripheral level leads to a dysfunctional sexual behavior, which is a frequent cause of psychological problems in humans and may adversely affect the reproductive potential of animals (Argiolas and Melis, 2005, 2013; Melis and Argiolas 2003, 2011; Hull and Dominguez, 2007; Carvalho and Nobre, 2010, 2011). Among the sexual hormones, testosterone is the main androgen that plays a pivotal role in male reproductive functions (see Hull et al., 2004, Hull and Dominguez, 2007). Indeed, castration (which removes testicles and thus the main source of circulating testosterone) eliminates sexual behavior in animals and humans, revealing the permissive role of this hormone on sexual activity. During sexual behavior, plasma levels of testosterone have been shown to be raised, especially in sexually experienced rats (see Meraz-Medina et al., 2017, and references therein). Of the neuropeptides and neurotransmitter involved in the control of erectile function and copulatory behavior at the central level, the best known neuropeptides are oxytocin, adrenocorticotropin (ACTH), α-melanocyte stimulating hormone (α-MSH), opioid peptides, and corticotropin releasing factor (CRF) (see Bertolini and Gessa, 1981; Dornan and Malsbury, 1989; Argiolas, 1999; Argiolas and Melis, 2004, 2013; Hull et al., 2004; Hull and Dominguez, 2006, 2007; Magariños and Pfaff, 2016), while dopamine, serotonin, noradrenaline, glutamic acid, γ-aminobutyric acid (GABA), anandamide (an endogenous cannabinoid), and nitric oxide have been the most studied neurotransmitters (see Driscoll et al., 1983; Pfaus and Gorzalka, 1987; Pomerantz, 1990, 1991; Pomerantz et al., 1993; Argiolas, 1994; Hull et al., 2002, 2004; Melis and Argiolas, 2002; Melis et al., 2003, 2004, 2005, 2006a, 2012; Hull and Dominguez, 2006, 2007; Sanna et al., 2011, 2012b; Miwa et al., 2011; Sanna et al., 2015a,b, 2016; Magariños and Pfaff, 2016). At the central level, neurotransmitters and neuropeptides control sexual behavior by acting in several brain areas. Among these, the most studied are the medial preoptic area (see Hull et al., 1995, 2004; Hull and Dominguez, 2006, 2007; Gil et al., 2011, 2013), the paraventricular nucleus of the hypothalamus (see Argiolas and Melis, 1995, 2005, 2013; Melis and Argiolas, 1995, 2002, 2003, 2011), the ventral tegmental area, the nucleus accumbens, and the medial prefrontal cortex (PFC), which contain the cell bodies (the first one) and the nerve endings of mesolimbic and mesocortical dopaminergic neurons (the latter two, respectively), which play a key role in the motivational and rewarding properties of natural reinforcing stimuli, such as food, water, and sexual activity (see Fibiger and Phillips, 1988; Wise and Romprè, 1989; Everitt, 1990; Pfaus and Everitt, 1995;

Everitt and Robbins, 2005). As to the role of the paraventricular nucleus of the hypothalamus, this nucleus contributes to the consummatory aspects of sexual behavior, and at the same time also activates mesolimbic/mesocortical dopaminergic neurons, providing a neural substrate for explaining the rewarding properties of sexual activity (Argiolas et al., 1988, 1989; Melis and Argiolas, 1995, 2003, 2011; Argiolas and Melis, 2004, 2005, 2013; Succu et al., 2007). Briefly, dopamine released from these neurons is thought to mediate the transposition of the motivational aspects of natural stimuli into goal-directed behaviors, for instance in the case of sexual activity, the seeking of a sexual partner and of sexual intercourse to reach reward and satisfaction (see Goto and Grace, 2005). The existence of a complex neural circuit, including mesolimbic, mesocortical, incerto-hypothalamic dopamine, and central oxytocin neurons among other neurotransmitters/neuropeptides, and which embraces many other brain areas of the limbic system, from the medial preoptic area to the amygdala, the hippocampus, the bed nucleus of the stria terminalis, and the medial PFC (Hull et al., 2004; Melis et al., 2007, 2009, 2010; Succu et al., 2008, 2011; Paredes, 2014; Will et al., 2014; Maejima et al., 2015; Poeppl et al., 2016; Holstege, 2016; Sanna et al., 2017a,b), may also provide a neural basis for the ability of the above neurotransmitters and neuropeptides to facilitate socio-sexual interactions (Pedersen et al., 1992; Carter and Altemus, 1997; Carter et al., 1997a,b; Melis and Argiolas, 1997, 2003, 2011; Argiolas and Melis, 2004, 2013; Melis et al., 2007; Bodnar 2013; Bisagno and Cadet, 2014; Veening et al., 2015).

Sexual behavior varies significantly across rats, even when they are of the same strain and reared under identical conditions. Such differences should be the result of differences mainly in the genotype, but this is only partially true because these differences are still confounded with the prenatal and postnatal maternal environment in which the rats were grown and with the interactions among siblings. Thus, both genotype and prenatal/postnatal environment may lead to differences in animal and human behavior as well. Accordingly, individual differences in temperament and environmental or emotional reactivity allow predicting a variety of behavioral traits and an increase in the vulnerability to develop certain psychopathologies, which range from anxiety and mood disorders to drug abuse (see Cloninger, 1987; Serretti et al., 2006; Lukasiewicz et al., 2008; Van Laere et al., 2009). This has been supported by studies in rats selectively bred for showing a specific behavioral trait when exposed to a novelty condition or to stress (see Steimer and Driscoll, 2003, 2005, Stead et al., 2006). Among these psychogenetically selected sub-lines of rats, the best known are the Roman high and low avoidance (RHA and RLA) rats, which were originally selected for their different avoidance responses to the shuttle box (see Driscoll and Battig, 1982), the high and low novelty exploration responders (bNEHR and bNELR) rats, which were selectively bred for their different exploratory responses when exposed to a novel environment (see Stead et al., 2006), and the low and high yawning frequency (LY and HY) rats, which were selectively bred for their divergent frequency in showing spontaneous yawning (see Holmgren et al., 1985; Urbá-Holmgren et al., 1990), an innate response whose role is still poorly understood and a matter of discussion (see Argiolas and Melis, 1998; Walusinski, 2010a,b,c; Sanna et al., 2012a; and references therein).

Whether individual differences in temperament and environmental or emotional reactivity can also lead to changes in sexual behavior has not been investigated in detail. Indeed, a Medline search on this theme revealed that sexual behavior has been characterized in some detail only in a few psychogenetically selected rat sub-lines, e.g. the above-mentioned RHA and RLA, the bNEHR and bNELR, and the LY and HY rat sub-lines. A review of the results of these studies reveals that similar changes occur in the sexual behavior (e.g. erectile function, sexual motivation, and copulation) of these rat sub-lines in spite of the fact that their selection was done on the basis of (i) their ability to show a different or opposite behavioral trait when exposed to an aversive condition (RHA and RLA sub-lines) or to a novel environment (bNEHR and bNELR sub-lines), or (ii) the expression of a spontaneous behavior with a divergent frequency (LY and HY sub-lines) (Tables 1 and 2). This review also suggests that the differences in sexual behavior are secondary to differences in the mesolimbic/mesocortical dopaminergic tone between the two rat sub-lines. Accordingly, behavioral pharmacology studies and intracerebral microdialysis experiments, performed so far only in the RHA and RLA rat sub-lines, definitively show that the divergent sexual behavior of these two rat sub-lines is paralleled by the presence of a more robust dopaminergic tone in RHA rats when compared to RLA rats.

RHA and RLA rats

Outbred Roman high-avoidance (RHA/Verh) and Roman low-avoidance (RLA/Verh) are two Wistar-derived lines of rats that for more than 30 years have been phenotipically selected and bred in Switzerland for rapid acquisition

Table 1: Similarities in behavioral, neurochemical, and neuroendocrine traits shown by the RHA/RLA and NEHR/NELR rat sub-lines selectively bred for showing a specific behavioral trait in response to a specific condition.

Psychogenetically selected rat sub-lines					
Trait	**RHA**	**RLA**	**NEHR**	**NELR**	**References**
Impulsivity	High	Low	High	Low	Nagoshi et al. (1991), Moreno et al. (2010), Coppens et al. (2012)
Aggressiveness	Low	Low[a]	High	Low	Moreno et al. (2010), Coppens et al. (2012)
Novelty-seeking	High	Low	High	Low	Nagoshi et al. (1991), Fernandez-Teruel et al. (1997), Kabbaj et al. (2000), Stead et al. (2006), Davis et al. (2008), Manzo et al. (2014)
Propensity to drugs of abuse	High	Low	High	Low	Davies et al. (2008), Fattore et al. (2009) Garcia-Fuster et al. (2010), Tournier et al. (2013), Corda et al. (2014), Mabrouk et al. (2018)
Emotionality	Low	High	Low	High	Driscoll and Battig (1982), Escorihuela et al. (1999), Díaz-Morán et al. (2012), Kabbaj and Akil (2001), Cohen et al. (2017)
Anxiety	Low	High	Low	High	López-Aumatell et al. (2009), Clinton et al. (2011)
Vulnerability to chronic stress	Low	High	Low	High	Gentsch et al. (1982), Castanon et al. (1994), Driscoll et al. (1998) Stedenfeld et al. (2011), Garcia-Fuster et al. (2010)
HPA axis response	Low	High	Very high	Low	Walker et al. (1989), Steimer et al. (1997), Carrasco et al. (2008), Kabbaj et al. (2000), Clinton et al. (2008), Kabbaj and Akil (2001)
Propension to depressive-like symptoms	Low	High	Low	High	Piras et al. (2010), Stedenfeld et al. (2011)
Dopaminergic tone (nucleus accumbens)[b]	High	Low	High	Low	Giorgi et al. (2005), Sanna et al. (2015b), Mabrouk et al. (2018)
Dopaminergic tone (prefrontal cortex)[b]	High	Low	NA	NA	Giorgi et al. (2003a), Tournier et al. (2013), Sanna et al. (2017a)
Noradrenergic tone (nucleus accumbens)[b]	NA	NA	High	Low	Mabrouk et al. (2018)
Noradrenergic tone (prefrontal cortex)[b]	High	Low	NA	NA	Sanna et al. (2017a)

NA, data on this in LY and HY rats are not available.
[a]Aggressiveness was found to be higher in RLA than RHA rats (Coppens et al., 2012).
[b]Inferred by intracerebral microdialysis experiments.

(RHA/Verh) versus extremely poor acquisition (RLA/Verh) of two-way active avoidance in a shuttle box (Driscoll and Battig, 1982), using a stock previously developed by Broadhurst and Bignami (1965).

Subsequent studies with these outbred Swiss Roman sub-lines maintained in Geneva (Switzerland) and from colonies developed in different research centres (i.e. University of Cagliari, Italy; University of Madgeburg, Germany) indicated that emotional rather than learning properties were responsible for their divergent performances in this test (Driscoll and Battig, 1982; Corda et al., 1997; Steimer and Driscoll, 2003). Accordingly, RLA rats are hyperemotional and display a behavioral repertoire characterized by hypomotility and freezing, whereas the less emotional RHA rats display a proactive coping behavior that leads to the rapid acquisition of the avoidance response (Escorihuela et al., 1995) (Table 1). The RLA/Verh rat line presents not only higher emotionality but also higher anxiety and reactivity to a variety of stressful situations (for reviews, see Driscoll and Battig, 1982; Escorihuela et al., 1995; Fernández-Teruel et al., 1997, 2002a,b; Steimer et al., 1997; Driscoll et al., 1998; Steimer and Driscoll, 2003), as shown by (i) their higher responses in the levels of corticosterone, ACTH, prolactin, grooming, defecation, and freezing to stressors or novelty, and (ii) a more intense bradycardia in response to a conditioned emotional stressor, when compared to the RHA/Verh rats (Gentsch et al., 1982; Walker et al., 1989; Escorihuela et al., 1995). RHA/Verh rats are considered a good model for studying novelty (or sensation) seeking (Fernández-Teruel et al., 1997; Siegel, 1997; Driscoll et al., 1998; Escorihuela et al., 1999), as these animals present a high level of impulsivity (Zeier et al., 1978). Neurobiological evidences also show that RHA/Verh rats have stronger mesolimbic dopaminergic responses to drugs of abuse, e.g. cocaine, morphine (Giorgi et al., 1997), and alcohol (Corda et al., 2014) than RLA/Verh rats. Accordingly, several studies have revealed similar associations between exploration, impulsivity, alcohol consumption, and substance abuse in humans (see Nagoshi et al., 1991; Moss et al., 1992). Interestingly,

Table 2: Similarities in the sexual responses and associated dopamine and noradrenaline activity in *ex copula* and *in copula* contexts by the RHA/RLA and NEHR/NELR rat sub-lines selectively bred for showing a specific behavioral trait in response to a specific condition, and in LY/HY rat sub-lines selected for showing a spontaneous behavior (yawning) with a different frequency: comparison with genetically heterogeneous SD rats.

Psychogenetically selected rat sub-lines								
Behavioral traits, levels of	**RHA**	**RLA**	**NEHR**	**NELR**	**LY**	**HY**	**SD**	**References**
Spontaneous penile erection	Low	Low	NA	NA	Low	High	Low	Sanna et al. (2013), Holmgren et al. (1985)
Apomorphine-induced penile erection[a]	High	Very high	NA	NA	High	Very high	High	Sanna et al. (2013), Holmgren et al. (1985)
Apomorphine- induced yawning[a]	High	Very high	NA	NA	High	Very high	High	Giménez-Llort et al. (2005), Sanna et al. (2013), Holmgren et al. (1985)
Noncontact penile erection	High	Low	NA	NA	NA	NA	High	Sanna et al. (2014a,b, 2015a,b, 2017a)
Copulation	Very high	High	Very high	High	Very high	High	High	Sanna et al. (2014a,b), Cummings et al. (2013), Eguibar et al. (2016)
Apomorphine-induced facilitation of copulation[a]	Low	Very high	NA	NA	NA	NA	High	Sanna et al. (2014b)
Haloperidol-induced inhibition of copulation[a]	Low	Very high	NA	NA	NA	NA	High	Sanna et al. (2014b)
Dopamine activity (n. accumbens)[b]	Very high	High	NA	NA	NA	NA	High	Sanna et al. (2015b)
Dopamine activity (prefrontal cortex)[b]	Very high	High	NA	NA	NA	NA	High	Sanna et al. (2017a)
Noradrenaline activity (prefrontal cortex)[b]	Very high	High	NA	NA	NA	NA	NA	Sanna et al., (2017a)

NA, not available.
[a]Low doses of the drug.
[b]Inferred by intracerebral microdialysis experiments.

the outbred Roman lines also differ drastically in several behavioral traits that are strongly influenced by dopamine neurotransmission, such as stereotypic and motor responses induced by direct and indirect dopamine agonists (apomorphine, amphetamine), vulnerability to and acquisition, maintenance, extinction, and reinstatement of drugs of abuse (i.e. cocaine, morphine), and fear-related behaviors (Durcan et al., 1984; Driscoll et al., 1986; Giorgi et al., 1994, 2003a,b, 2005, 2007; Lecca et al., 2004; Fattore et al., 2009). Likewise, the inbred Roman strains exhibit behavioral patterns closely resembling those of the outbred Roman lines, from which they derive, when tested in experimental paradigms that reflect the activity of central dopaminergic systems, e.g. emotionality, impulsivity, novelty/rewarding seeking, fear-related behavior, stereotypic, and motor responses (Escorihuela et al., 1997, 1999; Fernández-Teruel et al., 1997, 2002a,b; Driscoll et al., 1998; Giorgi et al., 2003a,b; Giménez-Llort et al., 2005; Guitart-Masip et al., 2008; López-Aumatell et al., 2009; Moreno et al., 2010).

The inbred Roman strains have been extensively characterized for behavioral and neurobiological phenotypes (Klein et al., 2014; Manzo et al., 2014; Esnal et al., 2016), and based upon various behavioral tests, a molecular genetic mapping program has been performed (Escorihuela et al., 1997; Schwegler et al., 1997; Driscoll et al., 1998). The inbred strains have been maintained in the laboratories at the Autonomous University of Barcelona in Spain (Medical Psychology Unit, Department of Psychiatry and Forensic Medicine) since 1996. The behavioral patterns of the inbred Roman strains were very similar to those previously reported for the RHA/RLA Verh outbred sub-lines although differences in locomotor activity as well as exploratory and self-grooming behavior were actually greater between the inbred strains than between the outbred sub-lines (Escorihuela et al., 1999; Moreno et al., 2010; Estanislau et al., 2013). According to the results of studies showing a higher activation of the hypothalamic–pituitary–adrenal (HPA) axis in outbred RLA vs. RHA rat strains by stress (Gentsch et al., 1982; Walker et al., 1989),

a greater response to a novel environment was also found in inbred RLA as compared to inbred RHA rats, although resting levels of plasma ACTH and corticosterone did not differ between the two inbred strains. An increase of the CRF gene expression in the paraventricular nucleus of the hypothalamus and in other brain areas involved in anxiety and stress-related disorders, likely the central amygdala and the bed nucleus of the stria terminalis, was also found in the inbred lines (Carrasco et al., 2008). Recently, inbred RHA rats have shown to present features that suggest deficits in executive functions, such as attention deficits, worse learning capacity, and deficits in prepulse inhibition of a startle response (see Oliveras et al., 2015; Esnal et al., 2016). As these traits are associated with schizophrenia, and inbred RHA rats present functional alterations in serotoninergic and glutamatergic neurotransmission (i.e. changes in serotoninergic 5HT $_{2A}$ receptors concomitant to changes in glutamic acid mGLU2 receptors in the PFC) believed to have a role in this mental illness, it has been also suggested that inbred RHA rats may be a model for studying these schizophrenia traits (see Fomsgaard et al., 2018, and references therein).

RHA and RLA rats and sexual behavior

Sanna et al. (2014a) were the first to analyze the copulatory behavior of male outbred RHA and RLA rats with a sexually receptive (ovariectomized and oestrogen + progesterone-primed) female rat in a series of classic copulatory tests, and to compare their behavior with that of Sprague Dawley (SD) rats used as a genetically heterogeneous reference strain. These studies revealed soon a marked difference in coping style when males of the two Roman sub-lines were exposed for the first time to a receptive female, with about 80% of RHA rats becoming engaged in copulatory activity and reaching ejaculation against only 40% of RLA rats. The percentage of RHA rats that became engaged in copulatory activity in the first copulatory test was even higher than that of SD rats (~55%). Although less marked, such differences between RHA and RLA rats (but not between RHA and SD rats) were still present in the second and third copulation tests, but tended to be no longer statistically significant in the fourth and fifth ones. These results show that, once the effect of sexual novelty is overcome by repeated sexual experience, RLA rats are able to engage in sexual activity as well as RHA rats, although even after five copulatory tests the percentage of RLA rats that reached ejaculation in the first series of copulatory activity (~80%) was smaller than that of

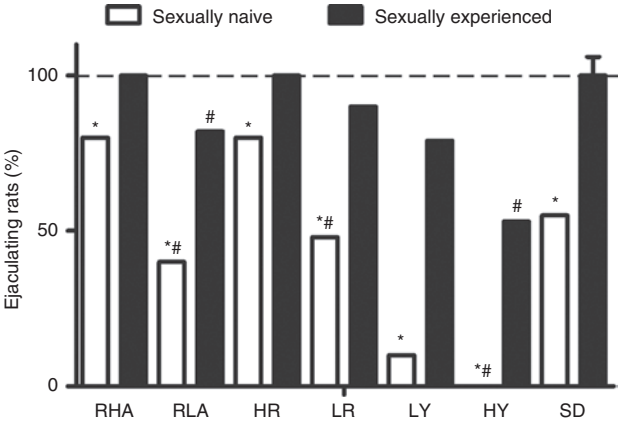

Figure 1: Percent of male rats belonging to the Roman high and low avoidance rat lines (RHA and RLA), the novelty exploration high and low responders rat lines (HR and LR), and the low and high yawning rat lines (LY and HY) that become engaged in copulation and reach ejaculation at the first copulation (sexually naïve condition, empty column) and after 3–5 copulatory tests in RHA and RLA rats and NEHR and NELR rats and 8 copulatory tests in LY and HY rats (sexually experienced condition, black column): comparison with Sprague Dawley (SD) rats.
Data for RHA/RLA rats and SD rats are from Sanna et al. (2014a), for NEHR/NELR rats from Cummings et al. (2013), and for LY/HY rat from Eguibar et al. (2016). The column for sexually naïve HY rats is not present because the value is 0 (e.g. no sexually naïve HY rat copulated to ejaculation in the first copulatory test). [a]Significantly different, naïve vs. experienced, same rat sub-line, for each couple of rat sub-lines. [b]Significantly different, naïve/experienced RLA/LR/HY sub-line vs. naïve/experienced RHA/HR/LY rat sub-line. Error bars are not shown because not present in the source studies cited above.

RHA and SD rats (~100%) (Figure 1). This led to the suggestion that the sexual performance of outbred RLA rats was poorer than that of outbred RHA rats even after the acquisition of a robust sexual experience. Additional differences between the copulatory patterns of outbred RHA and RLA rats were revealed by the analysis of the main copulatory parameters measured in the first series of copulatory activity across the five tests) (Figure 2, Table 3). Thus, in the first series of copulation tests 1–5, RLA rats showed a longer latency to initiate mounting and intromitting, and displayed a smaller number of mounts and intromissions before reaching ejaculation than RHA rats. These findings, together with the smaller number of RLA rats that engaged in copulatory activity, with their longer EL and III, and lower EF (Figures 1 and 2, Table 3), indicate a poorer copulatory performance of RLA rats vs. RHA as well as SD rats (which usually behaved as RHA rats), despite some differences in a few copulatory parameters. Among these, the IF remained stable in RHA rats across the five copulation tests, whereas in SD rats it decreased

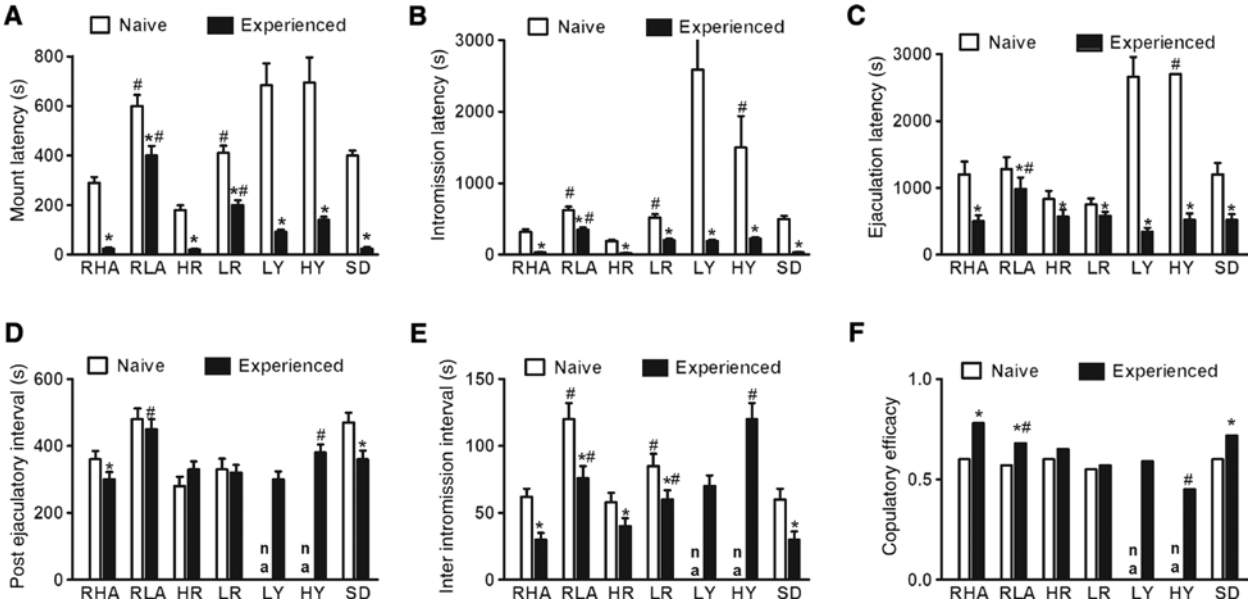

Figure 2: Latencies to mount (A), intromit (B), and ejaculate (C), post-ejaculatory (D) and interintromission (E) intervals and copulatory efficacy (F) calculated in the first series of copulatory activity of male rats belonging to the Roman high and low avoidance rat lines (RHA and RLA), the novelty exploration high and low responders rat lines (HR and LR), and the low and high yawning rat sub-lines (LY and HY) that become engaged in copulation and reach ejaculation at the first copulation (sexually naïve condition, empty column) and after 3–5 copulation tests in RHA and RLA rats and NEHR and NELR rats and 8 copulation tests in LY and HY rats (sexually experienced condition, black column): comparison with Sprague Dawley (SD) rats.

Data for RHA/RLA rats and SD rats are from Sanna et al. (2014a), for NEHR/NELR rats from Cummings et al. (2013), and for LY/HY rat from Eguibar et al. (2016). The very high values (>2700 s) of intromission and ejaculation latencies of sexually naïve HY (but also LY) rats are due to the fact that none of these rats copulated to ejaculation in the first copulatory test. [a]Significantly different, naïve vs. experienced, same rat sub-line, for each couple of rat sub-lines. [b]Significantly different, naïve/experienced RLA/LR/HY sub-line vs. naïve/experienced RHA/HR/LY rat sub-line. NA: values not available.

progressively from a value similar to that of RHA rats in the first copulation test to a value similar to that of RLA rats in the fourth and fifth tests. A general reduction in copulatory activity is also supported by the longer PEI and the lower CE of RLA rats when compared to RHA and SD rats (see Figure 2). The above results also indicate that, besides their poorer sexual performance, RLA rats differ from their RHA counterparts also in a lower level of sexual motivation. Indeed, RLA rats showed longer ML and IL than RHA rats in all five copulation tests, including the last one, in which the copulatory activity appeared to be stabilized as a result of the acquisition of sexual experience (see Figure 2). Accordingly, longer/shorter ML and IL are usually considered as indexes of, respectively, lower/higher levels of sexual motivation (see Sachs and Barfield, 1976; Meisel and Sachs, 1994; Melis and Argiolas, 1995; Pfaus and Everitt, 1995, and references therein). However, as ML and IL are parameters of the copulatory behavior that reflect only the anticipatory phase of sexual behavior as opposed to its consummatory phase, more sophisticated procedures than measuring the ML and IL should be used to confirm that RHA rats have higher levels of sexual motivation than RLA rats. For instance, experiments with the bi-level chambers (Mendelson and Gorzalka, 1987), in which the male rat chases the female from one level to another after each intromission, or with instrumental methods in which the male rat has to learn to press a lever in response to a conditioned stimulus to gain access to a receptive female (Everitt, 1990) should be useful for this purpose.

Why outbred RHA and RLA rats show different behavioral patterns of copulatory activity with a sexually receptive female rat is far from clear, and several hypotheses have been considered. The first is that these differences are determined by the distinct neuroendocrinological profiles of the two Roman lines, and in particular by the higher responsiveness to novelty and/or stressors of the HPA axis of RLA vs. RHA rats. In fact, as recalled in the Introduction, RLA rats respond to environmental stressors with larger increments of circulating ACTH and corticosteroids associated with hypomotility and freezing, whereas RHA rats show milder HPA axis activation together with proactive coping and higher impulsivity (Gentsch et al., 1982; Siegel, 1997; Fernández-Teruel et al., 2002a,b; Steimer and

Table 3: Mean values of mount, intromission, and ejaculation frequencies measured in the first series of copulatory activity of the sexually naïve and sexually experienced RHA/RLA, NEHR/NELR, and HY/LY rat sub-lines: comparison with genetically heterogeneous SD rats.

Copulatory parameters	Psychogenetically selected rat sub-lines													
	RHA		RLA		NEHR		NELR		LY		HY		SD	
	Naive	Experienced	Naive	Experienced	Naive	Experienced	Naive	Experienced	Naive	Experienced	Naive	Experienced	Naive	Experienced
Mount frequency	12	6[a]	7[b]	6	18	11[a]	10[b]	9	NA	17	NA	13	15	6[a]
Intromission frequency	20	20	10	10	15	15	10	9	NA	10	NA	8	21	10[a]
Ejaculation frequency	1.3	3.2[a]	1	1.7[a,b]	NA	NA	NA	NA	NA	NA	NA	NA	1	2.7[a]

The definition of the copulatory parameters is reported in the Introduction section. Data for RHA/RLA rats are from Sanna et al. (2014a), for NEHR/NELR rats from Cummings et al. (2013), for HY/LY rat from Eguibar et al. (2016).
NA: not available.
[a]Significantly different, experienced vs. naive, same rat sub-line, for each couple of rat sub-lines.
[b]Significantly different, naïve/experienced RLA/LR/HY sub-line vs. naïve/experienced RHA/HR/LY rat sub-line.

Driscoll, 2003; Carrasco et al., 2008; Moreno et al., 2010; Díaz-Morán et al., 2012; Tournier et al., 2013). Thus, the exposure to a receptive female, in particular during the first copulatory test, could represent a stressor that preferentially induces behavioral inhibition in RLA rats and may therefore account, at least in part, for their poorer motivation and performance compared to RHA rats. In line with this possibility, the weight of the adrenal glands relative to the body weight was lower in RLA vs. RHA rats used in the study by Sanna et al. (2014a), as found in previous studies in either outbred (Gentsch et al., 1982; Castanon et al., 1994) or inbred (Carrasco et al., 2008) RHA and RLA rats. However, as sexual activity did not influence differentially the weight of the adrenal glands of either RLA and RHA lines (Sanna et al., 2014a) and the weight of testes, epididymides, and seminal vesicles increased to a similar extent in RHA, RLA, and SD rats after five copulation tests when compared to their naïve counterparts (Sanna et al., 2014a), it is unlikely that the different patterns of copulatory behavior that distinguish the two Roman lines could be secondary to or determined by differences in the anatomical and physiological properties of the genital apparatus and/or the HPA axis. Although no data have been provided so far on plasma corticosterone levels in RHA vs. RLA rats during copulatory tests (these data might exclude, perhaps definitively, the differences in the activity of the HPA axis, which may be related to the different pattern of copulatory activity between the two Roman rat lines), since differences in copulatory patterns still persisted even after five copulatory tests, when the effect of novelty on the HPA axis would have been markedly attenuated by repeated sexual activity, it is likely that alternative mechanisms play a more relevant role in these behavioral differences. Accordingly, the more intense HPA axis activation upon exposure to aversive conditions in RLA vs. RHA rats has been found predominantly to be of central origin and include, among others, neural pathways that use CRF as a neuromodulator and brain areas such as the amygdala and the bed nucleus of the stria terminalis (see Carrasco et al., 2008, and references therein).

RHA and RLA rats, erectile function, and sexual behavior: role of dopamine

Among the central mechanisms involved in the behavioral differences existing between RHA and RLA rats, those that may play a main role are the differences in the activity of neurotransmitters at the central level. In this respect, dopamine is the neurotransmitter most studied. Indeed, numerous studies have revealed that differences

in the activity of mesolimbic and mesocortical dopaminergic systems occur in RHA and RLA rats (see above) and that such differences play also a role in the differences in sexual behavior seen in these two rat strains (Sanna et al., 2014b, 2015a,b, 2017a).

RHA and RLA rats, erectile function, and dopamine

It is well known that dopamine plays a facilitatory role in erectile function. Accordingly, low doses of apomorphine, a mixed D1/D2 receptor agonist that activates all dopamine receptor subtypes, induces penile erection (and yawning) in laboratory animals and humans, and both these responses are mediated mainly by the stimulation of dopamine receptors of the D2 rather than D1 family (Melis and Argiolas, 1995; Argiolas and Melis, 1995, 1998, and references therein). Recently, the characterization of at least three D2-like receptor subtypes, namely D_2 (with the D_2 short and D_2 long splice variants), D_3, and D_4 (Seeman and Van Tol, 1994; Sokoloff and Schwartz, 1995; Missale et al., 1998), allowed the synthesis of selective agonists and antagonists of these receptor subtypes, which have also been used to identify the dopamine D2 receptor subtypes involved in penile erection (and yawning) in male rats. The most recent studies on this subject confirmed a main role of D_2 but not D_3 receptor subtype in penile erection and yawning, and also a pro-erectile but not a pro-yawning effect of D_4 receptor activation (Sanna et al., 2011, 2012b) although with some controversy (see Collins et al., 2007, 2009; Depoortère et al., 2009). A picture similar to that described above is also found in outbred RHA and RLA rats, but with important differences between the two rat lines in the pro-erectile (and pro-yawning) response to dopamine receptor agonists, a finding highly suggestive of, and in line with the different dopaminergic activity of RHA and RLA rats, which is involved in their different behavioral responses (see above). Accordingly, although under basal conditions (i.e. upon vehicle injection), the frequencies of penile erection (and yawning) episodes of the two rat lines/strains were statistically indistinguishable from those of genetically heterogeneous SD rats, used as an external reference line/strain, low doses of subcutaneous (S.C.) apomorphine (0.02–0.08 mg/kg) induced in these rat lines penile erection (and yawning) episodes with the typical inverted-U shape with the following rank order of responsiveness: RLA > RHA > SD (Sanna et al., 2013). Conversely, a more robust stereotyped behavior was observed at the dose of apomorphine of 0.1 mg/kg S.C. in RHA rats vs. RLA and SD rats, thereby blunting the frequency of penile erection (and yawning) episodes in RHA rats. These results are in line with those of another study that showed a more robust decrease in locomotor activity and yawning in inbred RLA rats when compared to inbred RHA rats after low doses of apomorphine similar to those used in the above study, whereas RHA rats were much more responsive to the stereotyped behavior induced by the high doses of apomorphine (Giménez-Llort et al., 2005).

As found in SD rats, the pro-erectile (and pro-yawning) effect of apomorphine in the outbred Roman lines were mainly mediated via stimulation of dopamine D2-like receptors, with a predominant contribution of the D_2 subtype (Sanna et al., 2013). Accordingly, both penile erection (and yawning) induced by apomorphine was markedly reduced in all rat lines/strains by pretreatment with L 741,626, a selective D_2 receptor antagonist with an affinity for the D_2 receptors 40- and 85-fold higher than that for D_3 and D_4 receptors, respectively (Kulagowski et al., 1996), but not by pretreatment with SB277011A, a D3 receptor antagonist with a D_3/D_2 receptor affinity ratio of ≅100 (Reavill et al., 2000; Stemp et al., 2000). Moreover, not only D_2 but also D_4 receptors are involved in the pro-erectile effect of apomorphine in outbred RHA and RLA rats, as found in heterogeneous SD rats (Melis et al., 2005, 2006b; Sanna et al., 2011, 2012b). Accordingly, (i) pretreatment with the selective D_4 receptor antagonists L-745,870 (Patel et al., 1997) and FAUC 213 (Löber et al., 2001) reduced the frequency of apomorphine-induced penile erections (but not of yawns) by about 40% in both RHA and RLA rats; and (ii) the D_4 receptor agonist, PD 168,077, induced penile erection episodes (but not yawning) in both RHA and RLA rats, although with a frequency lower than that of apomorphine, as previously shown in SD rats (Sanna et al., 2011, 2012b). Moreover, L-745,870 and FAUC 213 almost completely abolished the pro-erectile effect of systemic PD 168,077, not only in SD rats (Sanna et al., 2011, 2012b) but also in outbred RLA and RHA rats (Sanna et al., 2013). This confirms that also in the two Roman rat lines penile erection is also under the control of D_4 other than D_2 receptors and that the stimulation of D_4 receptors per se is able to induce penile erection (see Brioni et al., 2004; Melis et al., 2005, 2006b; Sanna et al., 2011, 2012b; Sanna et al., 2013). Finally, the inability of PD 168,077 to induce yawning in either RLA or RHA rats, as also previously observed in SD rats, is also in line with the view that D_4 receptors are not involved in the yawning response induced by the mixed dopamine D1/D2 receptor agonist apomorphine and the D_2/D_3 agonist pramipexole (Collins et al., 2007, 2009; Depoortère et al., 2009; Sanna et al., 2011, 2012b).

The reason why outbred RLA rats show more penile erection (and yawning) episodes after apomorphine and PD 168,077 (Sanna et al., 2013), when compared with their respective RHA counterparts, is poorly understood. One possibility is that the density and/or affinity of dopamine receptors mediating this behavioral response is higher in RLA rats than in RHA rats (Sanna et al., 2013). As recalled above, the pro-erectile (and pro-yawning) effects of dopamine receptor agonists (i.e. apomorphine and pramipexole) are mediated by the activation of D2-like receptors, mainly of the D_2 subtype. One of the brain sites where these receptors are located is the paraventricular nucleus of the hypothalamus. Accordingly, (i) the injection of mixed D1/D2 dopamine receptor agonists such as apomorphine and pramipexole into the paraventricular nucleus induces penile erection and yawning, while the injection of the selective D4 receptor agonist PD 168,077 induces penile erection only (see Melis et al., 1987, Melis et al., 2005, 2006b; Argiolas and Melis, 2005; Succu et al., 2007; Sanna et al., 2011, 2012b; Löber et al., 2012, and references therein), and (ii) recent double staining immunohistochemistry studies have shown that dopamine receptors of the D_2 and D_4 subtypes are co-localized in the cell bodies of parvocellular oxytocinergic neurons projecting to extra-hypothalamic brain areas and to the spinal cord (Baskerville and Douglas, 2008; Baskerville et al., 2009; see also Melis and Argiolas, 2011). The activation of these D2-like receptors by dopamine receptor agonists or by endogenous dopamine released by incerto-hypothalamic dopaminergic neurons originating in the A13 and A14 cell groups of Dahlström and Fuxe (1964), which impinge on paraventricular oxytocinergic cell bodies (Buijs et al., 1984; Lindvall et al., 1984), stimulates in turn oxytocinergic neurotransmission in several extra-hypothalamic brain areas (i.e. the ventral tegmental area, the hippocampus, the amygdala, the medulla oblongata, and the spinal cord). Oxytocin released in these brain areas leads in turn to penile erection (and yawning) (Argiolas and Melis, 1995, 1998, 2005; Melis and Argiolas, 1999, 2003, 2011; Baskerville and Douglas, 2008; Baskerville et al., 2009; Sanna et al., 2012a). Unfortunately, no data are available on the density and/or the affinity of these D2-like receptors in the paraventricular nucleus of the outbred RHA and RLA rats. However, binding studies in brain homogenates from outbred Roman rats (Giorgi et al., 1994) as well as autoradiography studies in the inbred Roman strains (Guitart-Masip et al., 2006) using radiolabeled selective D1-like and D2-like receptor antagonists showed a higher density of D_1 and D_3 binding sites in the nucleus accumbens and the medial PFC of RHA rats and a larger number of D_3 binding sites in the islands of Calleja of the ventral striatum of RLA rats. These findings led to the proposal that the higher number of D_1 and D_3 receptors in limbic structures of RHA rats was responsible for the more intense hyperactivity induced by high doses of apomorphine and other dopamine mimetic drugs in RHA rats when compared to RLA rats (Giorgi et al., 1994; Guitart-Masip et al., 2006). A lower availability of dopamine D2 autoreceptors (measured by dopamine receptor binding and mRNA assays) was recently found in the substantia nigra, ventral tegmental area, caudate putamen, and nucleus accumbens, together with a higher amphetamine-induced dopamine release in inbred RHA rats, when compared to their RLA counterparts (Tournier et al., 2013). Together, the above findings are in line with the view that RHA rats have a nigrostriatal and mesolimbic dopaminergic tone higher (more robust) than that of RLA rats due to the low presence of inhibitory presynaptic D2 autoreceptors in the cell bodies of dopaminergic neurons in the substantia nigra and in the ventral tegmental area and/or to a higher number of and/or to higher affinity dopamine receptors in the nucleus accumbens, striatum, and PFC. Further studies are necessary to ascertain whether similar changes in dopamine receptors occur also in incerto-hypothalamic dopaminergic neurons and in the cell bodies of oxytocinergic neurons bearing dopamine receptors of the two Roman rat sub-lines (see above).

Outbred RHA and RLA rats show also different numbers of noncontact erections, e.g. RHA rats show more noncontact erections than RLA rats when placed in the presence of an inaccessible, sexually receptive female (Sanna et al., 2015b, 2017a). These are pheromone-mediated penile erections, indistinguishable from those occurring spontaneously or induced by drugs and/or neuropeptides, which are observed in sexually potent male rats exposed to an inaccessible, receptive (ovariectomized oestrogen + progesterone primed) female that the male can see, hear, and smell but not touch, and are considered an index of sexual arousal (Sachs et al., 1994; Sachs, 1997; Melis et al., 2003; Argiolas and Melis, 2013). As noncontact erections occur concomitantly to an increase in extracellular dopamine in the paraventricular nucleus (Melis et al., 2003), which is released from incerto-hypothalamic neurons impinging on, and which activates D_2 and D_4 receptor subtypes localized in the cell bodies of oxytocinergic neurons mediating penile erection (Melis et al., 2003; Sanna et al., 2011, 2012a) (see also above), this suggests that also when penile erection occurs in a physiological context, a higher dopaminergic activity occurs not only in the dopaminergic mesolimbic system but also in the incerto-hypothalamic system of RHA rats when compared to RLA rats. However, whether the increased activity of

incerto-hypothalamic dopaminergic neurons in the paraventricular nucleus of RHA rats is secondary to changes in dopamine receptor availability and/or affinity, as found in the substantia nigra, ventral tegmental area, caudate putamen, and nucleus accumbens (Giorgi et al., 2003a; Guitart-Masip et al., 2006; Tournier et al., 2013) (see also above), remains to be ascertained.

RHA and RLA rats, copulatory behavior, and dopamine

The higher (more robust) dopaminergic tone of RHA rats vs. RLA rats (see above) may also play a role in the different patterns of copulatory behavior reviewed earlier (see Section on RHA and RLA rats and sexual behavior) between RHA and RLA rats (Sanna et al., 2014a), although a role of other neurotransmitters such as serotonin and GABA cannot be completely ruled out (Giorgi et al., 1994, 2003a; Corda et al., 1997; Hull et al., 2004). In fact, a large body of experimental evidence shows that dopamine facilitates both the anticipatory and the consummatory phases of sexual behavior. These facilitatory effects are mediated by (i) the mesolimbic brain areas, which include the ventral tegmental area and the nucleus accumbens, where dopamine transmission stimulates the appetitive aspects of sexual activity (e.g. sexual arousal and motivation) in laboratory animals and in humans (Everitt, 1990; Pfaus et al., 1990; Pfaus and Everitt, 1995; Pfaus, 2010; Melis and Argiolas, 2011), and (ii) the medial preoptic area and paraventricular nucleus of the hypothalamus, where dopamine drives the consummatory aspects of sexual behavior such as penile erection, copulation, and ejaculation (sexual performance) (Hull et al., 1991, 1995, 1999; Pfaus and Phillips, 1991; Argiolas and Melis, 1995, 2005; Melis and Argiolas, 1995, 1997, 2011; Moses et al., 1995; McKenna, 2000; Melis et al., 2003; Dominguez et al., 2004, 2006; Succu et al., 2007).

To the best of our knowledge, three studies are available that provide support for a role of the different dopaminergic tone between RHA and RLA rats in the different patterns of copulatory behavior of the two Roman rat lines.

The first study investigated the effect of apomorphine and haloperidol (a classic dopamine D2-like receptor antagonist), given systemically alone or in combination, on the copulatory behavior of sexually experienced outbred RHA and RLA rats, in comparison to the effect of these drugs on the copulatory behavior of genetically heterogeneous, sexually experienced SD rats. Other than confirming that after five copulation tests RHA rats still show a better sexual performance and higher sexual motivation than RLA rats (these rats usually show significantly longer latencies to initiate mounting and intromitting as well as to ejaculate in the first series of copulatory activity, perform fewer mounts and intromissions, and display longer lasting inter-intromission and post-ejaculatory intervals and a lower copulatory efficacy than RHA rats) (Sanna et al., 2014a), this study shows that the copulatory pattern of both RHA and RLA rats is differentially facilitated by apomorphine and impaired by haloperidol (Sanna et al., 2014b), in keeping with the well-established facilitatory role of central dopamine neurotransmission in sexual behavior (Pfaus et al., 1990; Hull et al., 1995, 1999; Melis and Argiolas, 1995, 2011; Melis et al., 2003; Pfaus, 2010). Interestingly, this study also shows that both apomorphine and haloperidol were more effective in sexually experienced RLA than RHA rats, as if RLA rats were more sensitive to both the stimulation and the blockade of dopamine receptors than RHA rats (Sanna et al., 2014b). Accordingly, in RHA (and SD) rats apomorphine induced changes in only a few copulatory parameters and usually at the highest dose tested (0.08 mg/kg) (e.g. apomorphine in these two rat lines/strains decreased EL, MF, and IF only, without modifying ML, IL, EF, PEI, III, and CE when given at the dose of 0.08 mg/kg), whereas in RLA rats the dopamine agonist decreased ML, IL, EL, and III and increased EF and CE already at the dose of 0.02 mg/kg and decreased MF and IF at the dose of 0.08 mg/kg. Likewise, in RHA rats haloperidol induced only minor changes in most copulatory parameters at the dose of 0.1 and 0.2 mg/kg (e.g. in these rats the drug decreased only IF and CE). On the other hand, in SD rats haloperidol increased ML, IL, PEI, and III and decreased IF and CE without modifying EL, MF, and EF, whereas in RLA rats it increased ML, IL, EL, PEI, and III, and decreased EF and IF, without modifying MF and CE when given at the dose of 0.2 mg/kg, but not 0.1 mg/kg, which was ineffective. However, with the dose of 0.1 mg/kg of haloperidol, a trend toward copulatory changes similar to those induced by the dose of 0.2 mg/kg was observed in RLA rats.

The higher sensitivity to haloperidol of RLA rats when compared with RHA and SD rats was further demonstrated by the ability of the dose of 0.1 mg/kg of haloperidol to antagonize/abolish the majority of changes in the copulatory parameters induced by 0.08 mg/kg of apomorphine in RLA rats. In addition, at the dose of 0.2 mg/kg, haloperidol further impaired copulation in RLA rats so that their copulatory parameters became indistinguishable from those observed after the administration of the same dose of haloperidol alone. In other words, low doses of apomorphine enhance the copulatory performance and sexual motivation of RLA rats, making their sexual behavior very similar to that of RHA rats or at least to that of SD

rats. In contrast, low doses of haloperidol, which induce modest changes in the sexual performance of RHA rats, further impair the copulatory performance and sexual motivation of RLA rats when compared to those of RHA rats as well as SD rats.

The second study investigated the activity of the mesolimbic dopaminergic system of RHA and RLA rats by measuring extracellular dopamine and its main metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) directly in dialysates obtained from the shell of the nucleus accumbens of sexually naïve (i.e. never exposed to a receptive female) and sexually experienced (i.e. submitted to five preliminary copulation tests and showing the differences described above in the copulatory pattern) RHA and RLA rats during the anticipatory (e.g. in the presence of an inaccessible receptive female, when male rats show noncontact penile erections) and consummatory (classic copulation tests with a receptive female) phases of sexual behavior by intracerebral microdialysis (Sanna et al., 2015b). As recalled in the Introduction section, sexual activity is a natural rewarding stimulus, which increases mesolimbic dopamine activity as well as other natural rewarding stimuli (i.e. food). This causes a well-documented increase of the concentration of extracellular dopamine in the dialysate obtained from the shell of the nucleus accumbens by intracerebral microdialysis (see Pfaus and Phillips, 1989; Pfaus et al., 1990; Pfaus and Everitt, 1995; Pfaus, 2010; Melis and Argiolas, 2011, and references therein). This study shows that, when exposed to a sexually receptive, inaccessible female, RHA rats show more noncontact erections (see above) than their RLA counterparts and confirms that, when sexual interaction is allowed, more sexually naïve RHA rats engage in copulation and reach ejaculation than sexually naïve RLA rats. The differences in copulatory behavior and its parameters are more pronounced in the first test, and persist, although reduced, even when sexual novelty is overcome by repeated sexual experience as already described (see above) (Sanna et al., 2014a,b). As expected, sexual (anticipatory and consummatory) activity occurs concomitantly to an increase in extracellular dopamine and its main metabolite DOPAC in the dialysate obtained from the shell of the nucleus accumbens in both sexually naïve and sexually experienced RHA and RLA rats, but with important differences between the two Roman rat lines in the naïve and experienced condition (Sanna et al., 2015b). Briefly, in sexually naïve rats, extracellular dopamine and DOPAC increase much more in the dialysate obtained from RHA than RLA rats (RHA rats, dopamine +200% and DOPAC +100% above baseline; RLA rats, dopamine +100% and DOPAC +50% above baseline). In sexually naive RHA, but not RLA rats, dopamine (but not DOPAC) increase is already observed during the anticipatory phase (e.g. inaccessible female) of sexual activity. In sexually experienced rats, extracellular dopamine and DOPAC increase much more than in sexually naïve rats in both RHA (dopamine +300% and DOPAC +150% above baseline) and RLA (dopamine +150% and DOPAC +100% above baseline) rats. However, also in the sexually experienced condition, dopamine increase in the anticipatory phase is observed in RHA but not RLA rats. Surprisingly, and at variance from the sexually naïve condition, DOPAC increased to the same extent in both RHA and RLA rats. All the above differences occur in spite of the fact that both sexually naïve and experienced RHA and RLA rats have similar baseline levels of extracellular dopamine and DOPAC during the habituation period, that is, before the receptive female is placed in the mating apparatus, in line with previous studies (Giorgi et al., 2003b, 2005, 2007; Corda et al., 2014). A detailed analysis of the results of this study leads to the suggestion that sexual experience accelerates, rather than potentiates, the activity of mesolimbic dopaminergic neurons in RHA rats, thereby leading to an anticipation of the increment in dopamine release in the nucleus accumbens to the initial period of sexual activity. Conversely, in RLA rats the overall amount of dopamine released during copulation in the nucleus accumbens of the sexually experienced group was uniformly distributed throughout the copulation period and significantly larger than that of sexually naïve rats. In other words, in RLA rats sexual experience induces a general increase in the activity of mesolimbic dopaminergic neurons during copulation, so that their functional tone becomes similar to that of the mesolimbic projection of sexually experienced RHA rats. As discussed above, the larger increases in extracellular dopamine that occur in the nucleus accumbens of sexually naïve and experienced RHA rats during sexual activity (comprising both the presence of the inaccessible receptive female and copulation) compared with their RLA counterparts found in this study further support the hypothesis of a more robust functional tone of the mesolimbic dopaminergic pathway in RHA than RLA rats.

The third and last study that provides evidence for a role of a different dopaminergic tone between RHA and RLA rats in the different copulatory patterns of the two Roman rat lines analyzes the changes that occur in the concentrations of extracellular dopamine and DOPAC during sexual behavior of sexually naïve and sexually experienced RHA and RLA rats in the medial PFC (Sanna et al., 2017a), another area that contains dopamine and may play a role in sexual behavior. In fact, the medial PFC contains the nerve endings of the mesocortical

dopamine neurons, which have their cell bodies localized in the ventral tegmental area as the mesolimbic dopamine neurons; however, as for the nucleus accumbens, the exact role of this brain area in sexual behavior is far from clear. Indeed, lesions of the medial PFC are usually found unable to alter the sexual behavior of male rats with a sexually receptive female (Fernandez-Guasti et al., 1994; Agmo et al., 1995; Hernandez-Gonzales et al., 1998, 2007; Kakeyama et al., 2003; Balfour et al., 2006; Afonso et al., 2007), nor the expression of conditioned place preference for sexual reward (Davis et al., 2010). However, medial PFC lesions, which did not alter the appearance of conditioned place preference for sexual reward, abolished in the same animals the ability to form conditioned aversion toward sexual activity when paired with aversive stimuli (Davis et al., 2010), and selective cell firing during approaching behaviors of a male rat toward an inaccessible sexually receptive female has been measured in the medial PFC of male rats (Febo, 2011). These findings support the hypothesis that the medial PFC activation during sexual behavior plays a role in the integration of external and internal information for the execution and control of goal-directed behaviors rather than in the expression of innate responses to natural reinforcers (see Goto and Grace, 2005). Irrespective of the exact role of the medial PFC in sexual behavior, this third study shows that the concentrations of extracellular dopamine and DOPAC also increase in the dialysate from the medial PFC of male RHA and RLA rats placed in the presence of an inaccessible female rat and even more markedly during direct sexual interaction (copulation) (Sanna et al., 2017a). Such increases in dopamine and DOPAC are found in both sexually naïve and experienced animals, but they are higher in RHA than in RLA rats and in sexually experienced RHA and RLA rats when compared to their naïve counterparts, as found in the nucleus accumbens. However, it has to be noted that, while the changes in the release of extracellular dopamine in the medial PFC of sexually naïve and sexually experienced rats during sexual activity occur in the presence of similar basal levels of dopamine in the dialysate collected from the medial PFC before the introduction of the sexually receptive female, the changes in the release of extracellular DOPAC occur in the presence of basal levels of DOPAC in RHA rats at least twofold higher than those of RLA rats, as if dopamine activity in the medial PFC of RHA rats were higher than that of RLA rats. Nonetheless, also in this study, the increase in extracellular dopamine and DOPAC in the medial PFC occurs concomitantly with the differences in sexual activity during both the anticipatory (e.g. different numbers of noncontact penile erection) and consummatory (e.g. differences in copulatory patterns revealed by the changes in several copulatory parameters) phases of sexual activity, with RHA rats displaying higher levels of sexual motivation and copulatory performance than RLA rats in both the sexually naïve and experienced conditions.

The latter study also investigates how the concentration of extracellular noradrenaline changes in the dialysate obtained from the medial PFC of sexually naïve and sexually experienced RHA and RLA rats during sexual activity (Sanna et al., 2017a). As found for extracellular dopamine, extracellular noradrenaline increases in the dialysate from the medial PFC of male RHA and RLA rats placed in the presence of an inaccessible female rat and more markedly during copulation. Such increase is found in both sexually naïve and experienced animals, but is higher in RHA than in RLA rats, and in sexually experienced RHA and RLA rats when compared to their naïve counterparts. Conversely, as found with DOPAC but in contrast to dopamine, the changes in the release of extracellular noradrenaline in the medial PFC occur in the presence of basal level of this neurotransmitter in RHA rats at least twofold higher those of RLA rats, as if noradrenaline activity in the medial PFC of RHA rats were higher than that of RLA rats. Thus, as found with dopamine, a more robust noradrenergic tone seems to occur in sexually naïve and experienced RHA rats vs. RLA rats during sexual activity. The higher (more robust) noradrenergic tone may also have a role (participate) in the higher sexual motivation and better sexual performance, which still persist after the acquisition of a stable baseline of sexual activity, found in RHA rats compared to RLA rats, as suggested above for dopamine. Furthermore, as the activity of dopamine released in the medial PFC may be influenced by noradrenaline, which is present in the medial PFC at higher levels than dopamine, and in particular by the noradrenaline transporter (NET) (see Carboni et al., 1990, 2006; Gresch et al., 1995; Westernik et al., 1998), and dopamine and noradrenaline often cooperate in many medial PFC functions, from working memory and attentional set formation and shifting to reversal learning, response inhibition, and response to stress (see Robbins and Arnsten, 2009), this raises the possibility that in the medial PFC not only dopamine but also noradrenaline, alone or together, plays a role not only in the sexual differences between RHA and RLA rats but also in the other behavioral differences found between the two Roman rat lines (see above).

Changes in dopaminergic neurotransmission similar to those described above, which occur in the mesolimbic and mesocortical dopaminergic neurons, may also occur in incerto-hypothalamic and tubero-infundibular dopaminergic neurons innervating the medial preoptic area

and the paraventricular nucleus of the hypothalamus of RHA and RLA rats (see above). These neurons also play a key role in the control of both the appetitive (i.e. sexual motivation) and consummatory phases of sexual behavior (i.e. penile erection, ejaculation, and sexual performance) by interacting with many other neuronal systems such as those containing excitatory and inhibitory aminoacids, nitric oxide, oxytocin, and opioid peptides (Argiolas and Melis, 1995, 2005, 2013; Hull et al., 1995, 1999; Melis and Argiolas, 1995; Dominguez et al., 2004, 2006; Melis and Argiolas, 2011). Alterations in the density and/or affinity of dopamine receptors, mainly D2-like receptors of the D_2 and D_4 subtype (Sanna et al., 2011, 2012a), and also in the extracellular concentrations of dopamine in these brain areas may also play a role in the differences in non-contact erections, in copulatory parameters, and in the differential sexual responses to apomorphine and haloperidol observed between RHA and RLA rats (Sanna et al., 2014a,b, 2015a,b). Thus, studies aimed at characterizing the role of dopamine neurotransmission in the medial preoptic area and in the paraventricular nucleus of the two Roman rat lines are necessary to clarify this point.

bNEHR and bNELR rats

Selectively bred novelty exploration high responder (bNEHR) and low responder (bNELR) rats are other two rat sub-lines that originate from SD rats psychogenetically selected for their extremely different response in novelty exploration, e.g. locomotion, at the University of Michigan, Ann Arbor (MI, USA) in the inhouse breeding colony of the laboratory of Prof. H. Akil (see Stead et al., 2006), with bNEHR rats vigorously exploring a novel environment and bNELR rats showing limited novelty-induced activity. As seen in RHA and RLA rats, these two rat sub-lines also exhibit numerous different behavioral traits: bNEHR rats exhibit exaggerated aggression (Kerman et al., 2011), impulsivity (Flagel et al., 2011), and proclivity to addictive behaviors (Davis et al., 2008; Garcia-Fuster et al., 2010; Cummings et al., 2011; Flagel et al., 2011) when compared with bNELR rats, which are characterized by exaggerated anxiety and immobility (Kabbaj et al., 2000; White et al., 2007; Perez et al., 2009; Flagel et al., 2010; Clinton et al., 2011, 2008), depressive-like behavior, and stress vulnerability (Clinton et al., 2011; Stedenfeld et al., 2011; Garcia-Fuster et al., 2012) (Table 1). An huge amount of experimental work suggests that, among neurobiological differences that may contribute to the high vs. low novelty-seeking trait in these two rat sub-lines, and also in commercially available (nonselectively bred) NEHR and NELR rats, differences in the dopaminergic system are those that may play a main role (e.g. Hooks et al., 1991, 1994; Piazza et al., 1991; Hooks and Kalivas, 1994; Rouge-Pont et al., 1998; Lemaire et al., 1999; Rosario and Abercrombie, 1999; Kabbaj et al., 2000; Kabbaj and Akil, 2001; Perez et al., 2009; Clinton et al., 2011). Accordingly, numerous studies have shown that nonselectively and selectively bred NEHR rats show increased dopaminergic activity in the nucleus accumbens under basal conditions and increased responsiveness to dopaminergic drugs (e.g. psychostimulants) but lower D_2 mRNA and D_2 receptor binding compared to NELR rats (Hooks et al., 1991, 1994; Flagel et al., 2010; Garcia-Fuster et al., 2010), and that bNEHR rats are more prone to self-administer cocaine (Davis et al., 2008; Cummings et al., 2011), while bNELR rats appear as a useful new rodent model for studying comorbid depression-like behaviors and anxiety. Finally, fast-scan cyclic voltammetry experiments revealed that bNEHRs also exhibit a larger number of spontaneous dopamine release events in the nucleus accumbens and a higher reward-induced dopamine release compared to bNELR rats (Flagel et al., 2011). However, a role for other neurotransmitters in the numerous behavioral differences found between bNHRH and bNELR rats cannot be ruled out. Among these are serotonin and noradrenaline. A possible involvement of serotonin is suggested by findings showing an altered activation of serotoninergic cell groups in bNELR rats vs. bNEHR rats and an altered expression of tryptophan hydroxylase and of the serotonin transporter, which play a key role in serotonin neurotransmission (Kerman et al., 2011). As to the possible involvement of noradrenaline, it is important to note that a very recent work (appeared when this review was almost completed) confirmed not only the existence of a different dopaminergic tone between the two rat sub-lines at the level of the nucleus accumbens by means of sophisticated microdialysis coupled to mass spectrometry and a stable isotope labeling technique but also provided evidence for a role of noradrenaline in the different locomotory responses of the two rat lines to a novel environment, which was used for their selective breeding, at the level of this forebrain nucleus. Accordingly, a higher noradrenergic tone was found in the nucleus accumbens of bNEHR vs. bNELR rats, as found for dopamine (although to a lesser extent), and noradrenaline in this nucleus seemed to be responsible for the higher locomotory response of bNEHR rats vs. bNELR rats (e.g. blockade of noradrenergic receptors in the nucleus accumbens was found to be able to abolish the hyperlocomotion of bNEHR rats) (Mabrouk et al., 2018).

bHNER and bLNER rats and sexual behavior

To the best of our knowledge, only one study has examined whether differences exist in the sexual behavior in selectively bred bNEHR and bNELR rats (Cummings et al., 2013). This study revealed that bNEHR and bNELR rats, which showed the well-known difference in locomotion when exposed to a novel environment, demonstrate distinct patterns of sexual behavior when put together with a sexually receptive female rat, with differences in copulation parameters very similar to those seen in RHA and RLAs (Sanna et al., 2014a). Accordingly, bNEHR rats initiated and become engaged in sexual behavior and reached ejaculation when put together for the first time with a sexually receptive female in a number much higher (≈80%) than that of bNELR rats (≈50%) (Figure 1). These differences were still found present in the second copulation test but with a tendency to disappear in the third, fourth, and fifth one (Figure 1). In particular, in the first copulation test, bNEHR rats show shorter latencies to mount and intromit, more intromissions and mounts, and shorter inter-intromission intervals than bNELR rats (Figure 2, Table 3). These differences in copulatory parameters between bNEHR and bNELR rats occurred with minor changes in the PEI or CE between the two rat lines (Figure 2). Together, these findings suggest that bNEHR rats have higher motivation for sexual activity and show better sexual performance than bNELR rats: that is, the high/low novelty exploration phenotype affects both sexual motivation and behavior, with bNELR male rats demonstrating reduced motivation for sexual activity compared to bNEHR males, as observed in the two Romans rat lines (Sanna et al., 2014a). This work also revealed only minor differences in the body weight, seminal vesicles, and epididymides between sexually naïve and sexually experienced bNEHR and bNELR rats, except for the adrenal glands, whose weight was found smaller in bNELR than bNERH rats irrespective of the level of sexual experience, and a tendency of sexual activity/experience to increase the weight of the seminal vesicles of bNELR rats (Cummings et al., 2013). Even these findings are similar to those found in RHA and RLA rats (Sanna et al., 2014a) (see above) and contribute to rule out apparently a main role of the neuroendocrine hypothalamic–adrenal and hypothalamic–gonadal axes in the different patterns of sexual behavior of bNEHR and bNELR rats.

bNEHR and bNELR rats, sexual behaviour, and dopamine

In view of the fact that bNEHR and bNELR rats share with the RHA and RLA rats several behavioral and coping styles when exposed to a novel environment or aversive stressful conditions as well as neurochemical similarities (e.g. differences in central dopaminergic function, such as increased dopaminergic activity in the nucleus accumbens under basal conditions, increased responsiveness to dopaminergic drugs of bNEHR vs. bNELR rats, lower D_2 mRNA and D2 receptor binding in bNEHR vs. bNELR rats (Hooks et al., 1991, 1994; Flagel et al., 2010; Garcia-Fuster et al., 2010; Mabrouk et al., 2018), as well as more proclivity of bNEHR vs. bNELR rats to self-administer cocaine (Davis et al., 2008; Cummings et al., 2011) (see Tables 1 and 2), it is likely that the different sexual patterns of bNEHR and bNELR rats are also secondary to the differences in central dopaminergic function between the two rat lines, as already shown for RHA and RLA rats (see above and Sanna et al., 2015a,b, 2017a). Accordingly, the higher/lower motivation for sexual activity and the better/worse sexual performance of bNEHR rats vs. bNELR rats may well be due to the higher/lower dopamine activity and/or the lower/higher D_2 mRNA and D_2 receptor binding present in the nucleus accumbens of bNEHR rats and bNELR rats, respectively, under basal conditions (see Hooks et al., 1991, 1994; Flagel et al., 2011; Mabrouk et al., 2018), which leads to an increased/decreased probability, respectively, that sexually relevant stimuli will elicit/not elicit appropriate sexual responses, i.e. a faster/slower initiation of copulatory activity, as observed in the two Romans rat lines. Unfortunately, to the best of our knowledge, no study is available so far that was aimed at verifying whether differential changes in dopamine activity usually seen in brain areas involved in the control of sexual behavior (such as the nucleus accumbens, the ventral tegmental area, the medial PFC, the medial preoptic area, and the paraventricular nucleus of the hypothalamus) occur concomitantly to the different patterns of sexual behavior in bNEHR and bNELR rats. Nonetheless, in view of the above-recalled differences in baseline and novelty-evoked levels of extracelluar dopamine (and noradrenaline) found in the nucleus accumbens of bNEHR and bNELR rats, it is likely that changes in dopamine output occur also in the nucleus accumbens of male rats belonging to these two sub-lines during sexual activity. These neurochemical changes might be related in some way to their differences in copulatory activity in the sexually naive and experienced condition, e.g. they may be influenced by sexual experience, as found for dopamine output in the nucleus accumbens of RHA and RLA rats (see above). Always by analogy with RHA and RLA rats, similar changes in dopamine (and noradrenaline) activity may also occur in other brain areas in which dopamine plays a role in sexual behavior, such as the medial

PFC, the medial preoptic area, and the paraventricular nucleus of the hypothalamus (see above). It is important to note that, as recalled above (see Section RHA and RLA rats, sexual behavior, and dopamine), both dopamine and noradrenaline outputs are found increased during sexual activity in the medial PFC of both RHA and RLA rats in a rat-line (RHA rats have values of both neurotransmitters higher than RLA rats) and sexual experience-level manner (sexually experienced RHA rats have output values of both neurotransmitters higher than those of sexually experienced RLA rats) and with noradrenaline (but not dopamine) basal values in RHA rats about twofold higher than those of RLA rats (Sanna et al., 2017a). This finding resembles the higher values of basal noradrenaline found in the nucleus accumbens of bNEHR rats compared to bNELR rats (Mabrouk et al., 2018) and raises the possibility that basal noradrenaline output may also be higher in the nucleus accumbens of RHA rats than RLA rats, revealing another similarity between the Roman and NE rat lines. Unfortunately, noradrenaline output was not measured during sexual activity in the nucleus accumbens of sexually naïve and experienced RHA and RLA rats (Sanna et al., 2015b); thus, further studies are necessary to verify this possibility as well as whether similar changes in dopamine activity occur also in the medial preoptic area and in the paraventricular nucleus of the hypothalamus of both RHA and RLA and bNEHR and bNELR rat sub-lines.

LY and HY rats

Low yawning (LY) and high yawning (HY) rats are two SP-derived rat sub-lines selectively bred for their different low vs. high yawning frequency, with HY rats showing a mean of 20 spontaneous yawns per hour and the LY rats 1–2 yawns per hour (Holmgren et al., 1985; Urbá-Holmgren et al., 1990). HY rats show also a higher frequency of spontaneous penile erection episodes than LY, with a linear correlation between these two behavioral patterns. This correlation persists also when the frequency of both penile erection and yawning is increased by treatment with mixed dopamine D1/D2 receptor agonists, such as apomorphine and bromocriptine (Holmgren et al., 1985) and the selective dopamine D2-like receptor agonist quinpirole (Eguibar et al., 2003) and oxytocin (Eguibar et al., 2015), and when dopamine agonist-induced responses are antagonized with metoclopramide (Holmgren et al., 1985). When exposed to a novel condition, HY rats also show higher levels of self-grooming behavior than LY rats, as if they had more propensity to develop higher levels of anxiety than LY rats (Eguibar and Moyaho, 1997). These findings resemble to some extent those found in inbred and outbred RLA rats, which are more sensitive to low doses of apomorphine and other selective D_2 receptor agonists: e.g. apomorphine and other selective dopamine D2-like receptor agonists induce in RLA rats a higher number of yawnings (Giménez-Llort et al., 2005; Sanna et al., 2013) and penile erection episodes, as well as higher levels of self-grooming when exposed to novel conditions (Escorihuela et al., 1999; Estanislau et al., 2013) with respect to RHA rats (Sanna et al., 2013).

LY and HY rats and sexual behavior

Other similarities between LY and HY rats and RHA and RLA rats, and also bHNER and bLNER rats, are evident when analyzing in detail the organization of the copulatory pattern of the LY and HY rat sub-lines (Eguibar et al., 2016). The first one is that a significant number of HY rats fail to copulate to ejaculation not only when exposed to sexually receptive females for the first time but also after repeated exposure to sexually receptive females (Figure 1) (Portillo et al., 2010; Eguibar et al., 2016). Accordingly, no sexually naïve HY rat (e.g. 0% of them) copulated to ejaculation in the first two copulation tests, a value that increased to 20% and 50% after four and eight copulatory tests, respectively, after acquisition of sexual experience. In contrast, ≈10% of sexually naïve LY rats reached ejaculation in the first two copulatory tests, a value that increased to 40% and 80% after four and eight copulatory tests, respectively (Eguibar et al., 2016). This leads to the percentage of sexually inexperienced (naïve) HY rats that become engaged in copulatory behavior with a receptive female to be significantly lower than that of LY rats, as found in both RHA and RLA and bHNER and bLNER rat sub-lines (see above) (Figure 1). However, at variance from RHA and RLA rats and bHNER and bLNER rats, which acquire a stable level of sexual activity after three to five copulatory tests, LY and HY rats reach a stable level of sexual activity only after seven to eight copulatory tests, as if they acquired sexual competence at a lower rate than that of both RHA and RLA and bHNER and bLNER rat sub-lines (Eguibar et al., 2016). Attempts to identify the reason why a high proportion of HY rats failed to copulate to ejaculation even after repeated exposure to a sexually receptive female led to the conclusion that the behavioral deficit in non-copulator HY male rats could not be explained by an alteration in partner preference, food-related odor recognition, motor coordination, general reward system, or differences in plasmatic levels of testosterone. However, as

non-copulator HY male rats present clear deficits in recognizing sexually relevant odors, this could explain, at least in part, the deficient execution of the copulatory pattern in these rats (Portillo et al., 2010). In fact, this kind of deficiency may lead to a lower sexual motivation in these animals with respect to those with a normal perception of sexually relevant odors, as reported for other non-copulator rats (Portillo and Paredes, 2003, 2004) or mice (Portillo et al., 2013). Irrespective of the reason why many HY rats failed to copulate to ejaculation, several differences in copulatory parameters are evident between the LY and HY sub-lines that become engaged in copulation. Among these, the most evident was the EL of sexually naïve HY rats, which is shorter than that of LY rats; moreover, even after four to seven copulation tests, e.g. when LY and HY rats have become sexually experienced, the proportion of HY rats that reached ejaculation was still lower than that of LY rats (Figure 1), with HY rats showing longer PEI and higher number of copulatory bouts that delay ejaculation and lower CE than LY rats (Figure 2, Table 3). Together, these differences lead to a different temporal organization of the copulatory session, with HY rats reaching ejaculation in a mean time of 14 min against the 9 min of LY rats (Eguibar et al., 2016).

LY and HY rats, sexual behavior, and dopamine

The lower sexual motivation and worse sexual performance of HY rats vs. LY rats and the different responsiveness to dopamine agonists of HY rats vs. LY rats (HY rats are more responsive than LY rats to mixed dopamine agonists such as apomorphine and bromocriptine, see above) resemble the lower sexual motivation and worse sexual performance of RLA rats when compared to RHA rats (Sanna et al., 2014a) and the higher responsiveness of RLA rats vs. RHA rats to the facilitatory effects of apomorphine and inhibitory effects of haloperidol on yawning, erectile function, and sexual behavior (Giménez-Llort et al., 2005; Sanna et al., 2013, 2014a,b). As these differences between RHA and RLA rats are thought to be secondary to a different dopaminergic tone existing in the two Roman rat lines (e.g. RHA rats have a more robust mesolimbic and mesocortical dopaminergic tone than RLA rats, see Section on RHA and RLA rats, sexual behavior, and dopamine), it is tempting to speculate that a different central dopaminergic tone also exists between the LY and HY rat sub-lines and that this difference is also responsible for the differences in the copulatory patterns of LY and HY rats. In line with this possibility, an enhanced binding of dopamine D1-like receptor agonists was found in the subregions of the caudate-putamen of HY rats when compared to LY rats (Diaz-Romero et al., 2005). In contrast, no support for a possible difference in the central dopaminergic tone between HY and LY rats was provided by the results of studies that have investigated the effect of dopamine agonists (SKF 38393 and quinpirole) on the grooming behavior in HY and LY rats, as these drugs induced similar effects on both the number and duration of grooming episodes (e.g. SKF 38393 increased and quinpirole decreased these responses to the same extent in both rat sub-lines) (Eguibar et al., 2003). As it is unknown whether these results indicate the absence of any relationship between grooming and sexual behavior or whether some relationship exists between self-grooming and sexual behavior in male rodents, further experiments are warranted to test this possibility not only with the LY and HY rat sub-lines but also with RHA and RLA rat sub-lines.

Concluding remarks

In this review, we have considered the available studies that analyze sexual behavior in male rats obtained by strong inbreeding processes that show an opposite behavioral phenotype, e.g. usually opposite or contrasting behavioral responses when exposed or put into the presence of an aversive situation (i.e. foot shock, RHA and RLA rats) or to a novel environment (i.e. NEHR and NELR rats) or for the manifestation of a specific innate response (i.e. yawning, LY and HY rats). The review of these studies reveals that these psychogenetically selected rat sub-lines also show different patterns of sexual behavior with a sexually receptive female rat. As the individual behavioral responses of experimental animals are the result of complex interactions between genetic factors and environment (Cools et al., 1990; Overstreet et al., 1992; Fernandez-Teruel et al., 1997), it is likely that both genotype and prenatal/postnatal environment contribute to the differences found in the sexual behavior of the above psychogentically selected rat sub-lines. Accordingly, these differences have certainly a genetic basis, as they are due in part to the strong inbreeding process utilized for their selection, which exalts the role of their genotype. However, other factors, mainly environmental, e.g. the prenatal and postnatal maternal environment in which rats were grown together with the interactions among siblings, are certainly involved as well (see Moyaho et al., 2009; Ugarte et al., 2011). Moreover, it is also likely that similar differences occur not only in the rat sub-lines analyzed here but also in other animals of

the same strain psychogenetically selected for other specific divergent or contrasting behavioral traits.

It is really noteworthy that the differences in the patterns of sexual behavior of male rats with a sexually receptive female rat found between RHA and RLA rats are very similar to those found in NEHR and NELR rats, in spite of the different behavioral response chosen for their psychogenetic selection and inbreeding process (RHA and RLA rats were selected for their divergent response in the active avoidance test, while NEHR and NELR rats were selected for their different responses to a novel environment) (Table 1). Accordingly, the differences between RHA and RLA rats and NEHR and NELR rats are particularly evident in the sexually naïve condition (e.g. when male rats are put together with a receptive female for the first time), and tend to decrease but not disappear in the subsequent copulation tests, that is, with the acquisition of sexual experience (Figures 1 and 2, Table 3). The two Roman and the two novelty exploration rat sub-lines show many other similarities: RHA and NEHR rats show proactive coping behavior, are highly impulsive, novelty seekers, hypoemotional, and prone to assume drugs of abuse, and become drug addicts, while RLA and NELR rats are hyperemotional, show passive coping styles (hypomotility and freezing), high levels of anxiety, higher activation of the HPA axis when exposed to stressors than their RHA and NRHR counterparts, and are prone to present depressive-like symptoms (see RHA and RLA rats and NEHR and NELR rats sections) (Table 1). Even more interestingly, and as already explained above (see RHA and RLA rats and NEHR and NELR rats sections), many of the above differences are thought to be secondary to a more robust dopaminergic tone present in one of the two rat sub-lines, namely the RHA in the Roman sub-lines (Durcan et al., 1984; Driscoll et al., 1986, 1998; Giorgi et al., 1994, 2003a,b, 2005, 2007; Escorihuela et al., 1997, 1999; Fernández-Teruel et al., 1997, 2002a,b; Lecca et al., 2004; Giménez-Llort et al., 2005; Guitart-Masip et al., 2008; Fattore et al., 2009; López-Aumatell et al., 2009; Moreno et al., 2010; Piras et al., 2010) and the NEHR in the novelty exploration sub-lines (Hooks et al., 1991; Piazza et al., 1991; Hooks et al., 1994; Hooks and Kalivas, 1994; Rouge-Pont et al., 1998; Lemaire et al., 1999; Rosario and Abercrombie, 1999; Kabbaj et al., 2000; Kabbaj and Akil, 2001; Perez et al., 2009; Clinton et al., 2011). It is likely that this is true also for the differences in sexual behavior, although evidence for the existence of a more robust dopaminergic tone that could be involved in the different patterns of copulatory behavior has been shown so far only in RHA and RLA rat sub-lines. In fact, a higher dopaminergic tone in the nucleus accumbens and medial PFC of RHA rats vs. RLA rats has been ascertained (i) by the more marked effects of low doses dopamine agonists (i.e. apomorphine) and antagonists (i.e. haloperidol) to facilitate and inhibit not only *ex copula* penile erections (and yawning) but also sexual behavior, respectively (Sanna et al., 2013, 2014b), and (ii) by intracerebral microdialysis experiments, which clearly demonstrated the existence of an increased mesolimbic and mesocortical dopaminergic activity in RHA vs. RLA rats in sexually naïve and sexually experienced RHA and RLA rats either when exposed to an inaccessible sexually receptive female (when they show noncontact penile erections) or during sexual interaction (copulation) (Sanna et al., 2015a,b, 2017a). Similar studies in bNEHR and bNELR rats are warranted for providing definitive evidence for this hypothesis.

Important similarities also exist in the differences between the patterns of copulatory behavior of LY and HY rats and those of RHA and RLA rats and bNEHR and bNELR rats (Figures 1 and 2, Table 3), although the selection and inbreeding of the LY and HY rat sub-lines is based on the frequency of the occurrence of a behavior that occurs spontaneously (e.g. yawning), rather than when animals are exposed to a specific experimental condition (stress or novelty) as was done for the Roman and NE rat sub-lines. Accordingly, significant differences in copulatory parameters occurred between LY and HY rats, which persisted even after repeated copulatory tests, as found in both RHA rats vs. RLA rats and bNELR rats vs. bNEHR rats (Figures 1 and 2, Table 3). However, at variance from RHA and RLA rats and bNEHR and bNELR rats, the main difference between LY and HY rats is the duration of the copulatory session, which lasts 8–10 min and 6–8 min in sexually naïve and experienced LY rats, respectively, and 16–18 min and 8–10 min in sexually naïve and experienced HY rats, respectively, which leads to a different temporal organization of the copulatory session (e.g. a marked slowdown of sexual activity in HY rats when compared to LY rats) (Eguibar et al., 2016). Whether this difference is secondary to a different dopaminergic tone between LY and HY rats, as discussed above for Roman and NE rat sub-lines, is unknown. Nonetheless, this possibility exists, as HY rats treated with mixed dopamine D1 and D2-like receptor agonists (apomorphine, bromocriptine, and quinpirole) showed more penile erections and yawning episodes than their LY counterparts (Holmgren et al., 1985, Urbá-Holmgren et al., 1990), as was found in RLA rats vs. RHA rats (Table 2)(see above).

Together, the results of the studies reviewed here lead to the identification of differences in sexual behavior in rat sub-lines psychogenetically selected for their ability to show specific (often opposite and contrasting)

characteristics (traits) and in rat sub-lines selectively bred on the basis of the frequency of the occurrence of a behavior that occurs spontaneously, like yawning. As these differences between rat sub-lines are secondary to genetic and environmental factors, which may contribute to alterations in sexual behavior mediated by changes in the activity of central neurotransmitters (i.e. dopamine, noradrenaline, but also others may be involved, i.e. serotonin, see below), it is likely that, depending on the behavioral criteria used for the psychogenetic selection or the frequency of the specific behavior spontaneously shown, phenotypes may be generated that are strongly related to each other in terms of behavioral traits and that may also share other central and/or peripheral neural and neuroendocrine substrates of their distinct behavioral patterns. This makes psychogenetically selected animal sub-lines or animals bred selectively for their frequency in showing a spontaneous behavior useful animal models for investigating associations between function of neurotransmitters and behavior, including sexual behavior, either under physiological conditions or in other conditions, as in the presence of specific alterations of the central nervous system (neurological lesions and/or mental pathologies) or following the administration of psychoactive drugs (Figure 3) (see also Steimer and Driscoll, 2005). In this regard, it is noteworthy that among neurotransmitters that play a main role in sexual behavior, and whose activity (tone) is altered in the rat sub-lines reviewed here, dopamine appears as one of the most involved. This is in line not only with the studies that show that dopamine plays a key role in sexual behavior but also with studies showing that animals in which dopamine synthesis and dopamine receptors are eliminated by knocking out the genes responsible for the synthesis of tyrosine hydroxylase and dopamine receptors (of the D1 and the D2 families) show a hypoactive phenotype, while those knocked out for the gene that synthesizes the dopamine transporter (DAT) show a hyperactive phenotype (see Viggiano et al., 2003a; Leo et al., 2018). A higher mesolimbic dopaminergic tone has been found to occur also in Neaples high-excitability rats, considered as an animal model of the attention deficit and hyperactive disorder (ADHD), when compared to the Neaples low-excitability rats (Viggiano et al., 2003b). The latter rat sub-lines have been selectively bred for their different behavior (nonselective attention) in spatial novelty tasks in a Làt-maze (Gonzalez-Lima and Sadile, 2000; Viggiano et al., 2003b).

In spite of these considerations, there are some limitations to this study. First, this review is focused mainly on the role of dopamine as the neurotransmitter that plays a main role in the differences in sexual behavior of the rat sub-lines analyzed in this study. This is because the available studies have focused their attention on the different tones of this and not on other neurotransmitters present in these animals. However, as recalled in the sections dedicated to the different rat sub-lines, differences in the tone of other neurotransmitters have been found to occur in RHA and RLA rats and bNELR and bNELR rats, and these differences may also play a role in the differences in sexual behavior found between these rat sub-lines. Among these, serotonin is certainly one of those that deserves

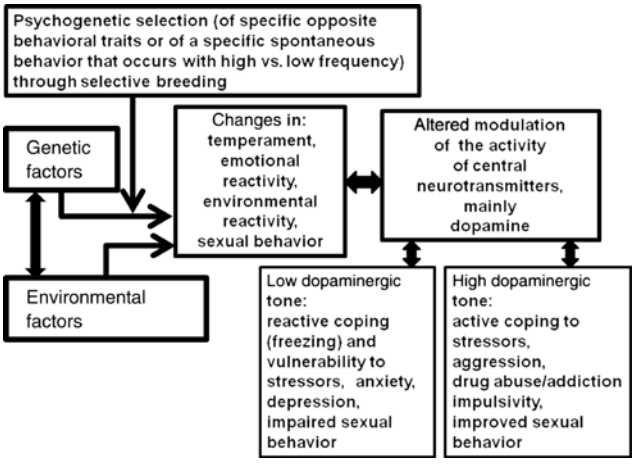

Figure 3: A hypothetical schematic representation of how psychogenetic selection influences sexual behavior by altering central dopamine activity.
Selective breeding of laboratory rats that show opposite specific behavioral traits when exposed to an adversive condition or to a novel environment or that show a spontaneous behavioral response with low vs. high frequency facilitates the passage of the genetic background of these opposite behavioral traits to the next generations, leading to changes in neurotransmitter activity at the central level. Among neurotransmitters that are known to be more and differentially influenced by this kind of selective breeding is dopamine, which plays a key role in motivational, arousing, and rewarding processes by acting at the level of the mesocorticolimbic brain areas (i.e. nucleus accumbens and medial prefrontal cortex). Accordingly, psychogenetic breeding leads to two rat sub-lines that show different mesocorticolimbic dopaminergic tones. The rat sub-lines with the more robust dopaminergic tone are more prone not only to showing active coping against adversive conditions or to a novel environment and more impulsivity but also to assuming drugs of abuse and becoming easily engaged in sexual activity with a sexually receptive female, while the rat sub-lines with the lower dopaminergic tone show reactive coping with freezing, vulnerability to stressors, anxiety, and depression and are less prone to becoming engaged in sexual activity with a receptive female. Due to the highly conserved mechanisms involved in reproduction, psychogenetic selection may influence sexual behavior and increase the occurrence of abnormal sexual behavior and sexual dysfunctions not only in rats but also in humans.

consideration. Accordingly, experimental evidences are available, which suggest a higher central tone of serotonin in RHA rats vs. RLA rats and in bNEHR rats vs. bNELR rats. The higher serotoninergic tone of RHA rats compared to RLA rats has been inferred first by intracerebral microdialysis studies showing that typical antidepressants that increase serotonin neurotransmission by blocking serotonin reuptake (i.e. cloramipramine and fluoxetine) given systemically or by reverse dialysis increases extracellular serotonin levels in dialysate obtained from the PFC of RHA rats more than RLA rats (Giorgi et al., 2003a,b) and, more recently, by studies showing that RHA rats show increased $5HT_{2A}$ but not $5HT_{1A}$ receptors in the PFC but not in the striatum (Fomsgaard et al., 2018). The increase in $5HT_{2A}$ receptors in the PFC was not found concomitant with an increase in $5HT_{2A}$ receptor gene expression in the PFC, but rather with a decrease in the striatum (Fomsgaard et al., 2018). Increased baseline levels of the tryptophan-hydroxylase and serotonin transporter genes, which play a key role in serotoninergic neurotransmission, were also found in selected brainstem nuclei of bNEHR rats compared to bNELR rats (Kerman et al., 2011). These differences have been related to the higher levels of aggression and higher levels of testosterone and corticosterone in bNEHR rats compared to bNELR rats during aggression, in line with a facilitatory role of serotonin in aggressive behavior (see Kerman et al., 2011, and references therein). However, it is unlikely that the differences in serotoninergic tone identified in the above studies may play a role in the differences in sexual behavior between RHA and RLA rats and bNEHR and bNELR rats. In fact, to the best of our knowledge, no evidence that may support this hypothesis is available in any of the above rat sub-lines and, perhaps more importantly, serotonin is considered as a neurotransmitter that plays an inhibitory role in sexual behavior, thus opposite to that facilitatory of dopamine (see Melis and Argiolas, 1995, and references therein). This should rule out a role of serotonin in RHA rats and bNEHR rats, as these rat sub-lines show higher sexual motivation and better copulatory performance not only than those of their RLA and bNELR counterparts but also of genetically heterogeneous rat lines. It is likely that this applies also to RLA rats and bNELR rats, although further experiments are necessary to clarify this point.

Second, it is unknown whether associations between neurotransmitter function and changes in sexual behavior similar to those found in these animal models occur also in humans. This is due to the difficulties in translating rodents's sexual behavior parameters measured during copulatory tests to human sexual behavior. However, this is highly likely and would be even not very surprising. Accordingly, (i) irrespective of the fact that many neurotransmitters and/or neuropeptides may be involved in determining behavioral traits and impulsivity, high levels of sexual arousal and hypersexuality (i.e. dopamine, excitatory amino acids, oxytocin, and others), hypersexuality and paraphilias (which are characterized by recurrent, intense, sexually arousing fantasies, urges, or behaviors, often involving nonhuman objects, suffering or humiliation of oneself or one's partner, or children, or other nonconsenting persons) can be observed in patients with Parkinson's disease treated with dopaminomimetic drugs (from L-DOPA to direct dopamine receptor agonists) and that the intensity of these symptoms decrease by reducing the dose of the dopaminomimetic drugs used or when the drugs are discontinued (see Solla et al., 2015, and references therein); and (ii) potent psychostimulants such as cocaine, which increases dopamine activity by blocking dopamine transporters, and amphetamines (e.g. methamphetamine), which increases dopamine activity by blocking dopamine transporter and increasing vesicular dopamine release, have been commonly associated not only with heightened sexual desire and arousal and enhanced sexual pleasure but also with risk-taking behaviors, including risky sexual behavior in men and women (for a review see Frohmader et al., 2010, and references therein).

Third, a relationship between hypersexual behavior (e.g. excessive sexual behavior associated with a person's decreased ability to control his/her sexual behavior) and personality traits has been long debated in research and clinical practice (see Rettemberger et al., 2016, and references therein), leading to characterize these persons with labels such as satyriasis, nymphomania, or DonJuanism (Levine 2010), and relations between trait impulsivity (i.e. sensation-seeking), behavioral impulsivity (i.e. behavioral risk-taking), and high levels of sexual arousal and risky sexual behavior (that causes negative long-term consequences, such as unplanned pregnancy, human immunodeficiency virus (HIV) transmission, and other sexually transmitted diseases) have been also described among young men and women (see Derefinko et al., 2014; Skakoon-Sparling et al., 2016, and enclosed references).

Finally, the couples of selectively bred rat sub-lines analyzed for differences in sexual behavior are only three, RHA vs. RLA rats (high vs. low avoidance in the shuttle box), bNEHR vs. bNELR rats (high vs. low responding to a novel environment), and HY vs. LY rats (high vs. low yawning frequency). This reduces the generalization of these changes in sexual behavior to other rat sub-lines selectively bred for other behavioral traits. More rat sub-lines selectively bred for showing differences in other

behavioral traits are required to reduce or eliminate such limitation.

In spite of the above limitations, this review shows that animals selectively bred for showing opposite changes in a few behavioral traits or for showing a specific behavior with a different frequency show also parallel changes in sexual behavior. This may help to predict similar changes in sexual behavior not only in other rat sub-lines selectively bred for showing yet untested opposite behavioral traits but may also be translated, although with the necessary attention, to the expression of divergent behavioral traits and associated changes in sexual behavior in humans. In other words, studying sexual behavior of psychogentically selected rat sub-lines can help explain or understand aspects of human sexual behavior as well as elucidate the genetic and environmental interaction behind normal/abnormal sexual behavior in humans. For instance, although the involvement of dopamine in sexual behavior is well established, it is still unknown to what extent genetic components in humans may be a risk for deviant sexual behavior. Accordingly, rats are a predictive model of human sexual function, and many of today's available treatments for the human sexual dysfunctions have been discovered in rats. Among these are the well-known phosphodiesterase type V inhibitors, which had enormous success around the world, and dopaminergic agonists, which had poor success not because they do not facilitate erectile function in humans but because of their collateral effects (see Argiolas, 2005, and references therein).

Acknowledgments: This work was partially supported by grants from the University of Cagliari (CAR 2014, PRID 2015 and FIR 2016) to AA, MRM, and FS, and by a MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca Scientifica) grant (Scientific Independence of Young Researchers, SIR 2014, Project Code no. RBSI-14IUX7) to FS.

Conflict of interest statement: The authors declare no conflicts of interest in this work.

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