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Short communication

Focal lesions within the ventral striato-pallidum abolish attraction for male chemosignals in female mice

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HIGHLIGHTS

- We lesion the medioventral striato-pallidum (mvStP) in female mice.
- These lesions abolish female mice innate preference for male chemosignals.
- Lesions of the posterolateral striato-pallidum do not affect this preference.
- The mvStP controls intersexual attraction mediated by chemosignals in female mice.
- The mvStP processes the hedonic properties of biological chemical signals.

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ABSTRACT

In rodents, socio-sexual behaviour is largely mediated by chemosensory cues, some of which are rewarding stimuli. Female mice display an innate attraction towards male chemosignals, dependent on the vomeronasal system. This behaviour likely reflects the hedonic value of sexual chemosignals. The anteromedial aspect of the olfactory tubercle, along with its associated islands of Calleja, receives vomeronasal inputs and sexually-dimorphic vasopressinergic innervation. Thus, we hypothesised that this portion of the ventral striato-pallidum, known to be involved in reward processing, might be important for sexual odorant-guided behaviours. In this study, we demonstrate that lesions of this region, but not of regions in the posterolateral striato-pallidum, abolish the attraction of female mice for male chemosignals, without affecting significantly their preference for a different natural reward (a sucrose solution). These results show that, at least in female mice, the integrity of the anterior aspect of the medioventral striato-pallidum, comprising a portion of the olfactory tubercle and associated islands of Calleja, is necessary for the attraction for male chemosignals. We suggest that this region contributes to the processing of the hedonic properties of biologically significant odorants.

The ventral striatum is a key centre in the processing of rewarding stimuli [1]. The ventral striatum includes the nucleus accumbens (Acb), the olfactory tubercle (Tu) and several associated structures such as the islands of Calleja (ICj) and the striatal cell bridges (CB), whose striatal or pallidal nature is unclear [2]. Given its olfactory nature, related to the direct input from the main olfactory bulb, the Tu is supposed to encode the hedonic properties of olfactory stimuli [3–6]. The ICj are heterogeneous cell clusters whose function remains poorly understood, although they might also play a role in olfactory processing [7,8].

The chemosensory amygdala projects to the medial Tu and associated ICj and CB [6], an area we refer to as the medioventral striato-pallidum (mvStP). A striking feature of the mvStP is that it shows sexually dimorphic vasopressinergic innervation [9], suggesting that it is a node in the neural network for socio-sexual behaviour.

Sexual behaviour is largely mediated by olfactory cues in rodents [10]. Female mice are innately attracted by non-volatile male chemosignals [11,12] detected by the vomeronasal system [13]. The pheromone *darcin*, a major urinary protein, is responsible for female attraction [14]. Male soiled-bedding containing sexual chemosignals [12] or *darcin* alone [15] induce conditioned place preference in female mice. Similarly, vaginal secretions, containing female sexual chemosignals, induce conditioned place preference in male hamsters [16]. Thus, sexual pheromones are rewarding stimuli that promote the first step of sexual behaviour, namely intersexual attraction.

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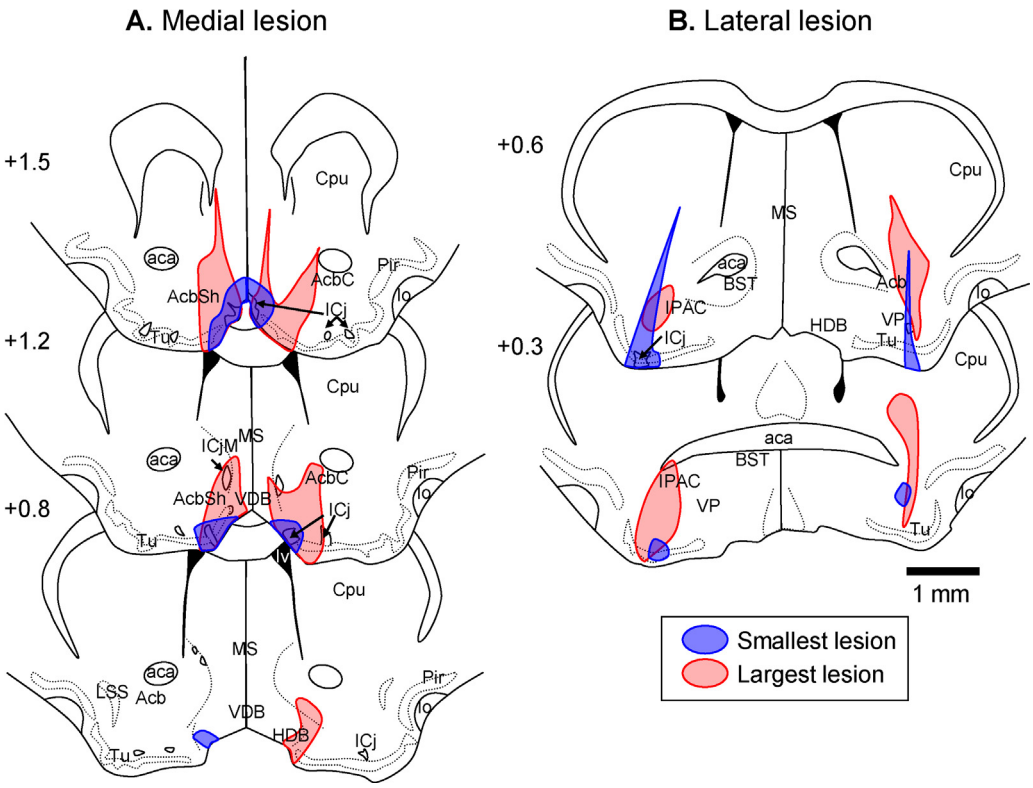

Fig. 1. Camera lucida drawings of 50 μm-thick coronal, Nissl-stained sections, showing the smallest and largest lesions of A. MEDIAL group and B. LATERAL group. Numbers represent mm from Bregma in the antero-posterior plane, based in [22]. Abbreviations: aca: anterior comissure; AcbC: nucleus accumbens core; AcbSh: nucleus accumbens shell; BST: bed nucleus of the stria terminalis; Cpu: caudatus-putamen; HDB: horizontal limb of the diagonal band; ICj: islands of Calleja; ICjM: major island of Calleja; IPAC: interstitial nucleus of the posterior limb of the anterior comissure; lo: lateral olfactory tract; LSS: lateral stripe of the striatum; MS: medial septum; Pir: piriform cortex; Tu: olfactory tubercle; VDB: ventral diagonal band; VP: ventral pallidum.

Reward includes at least three components, namely "liking" (hedonia), "wanting" (motivation) and learning [17]. Instrumental paradigms make it possible to study the two last components, but measuring "liking" in non-human animals is not straightforward. One possibility is to investigate the unconditioned responses elicited by rewarding stimuli [18]. Thus, the innate attraction displayed by mice towards sexual chemosignals can be used as a measure of liking [19,20].

In this study, we tested whether the mvStP, including a portion of the medial Tu and anteromedial ICj, might be involved in the innate attraction (or liking) for sexual chemosignals in female mice. To do so, we measured the unconditioned preference for male chemosignals of females bearing electrolytic lesions of medial regions of the ventral striato-pallidum, and compared their effects with control lesions of posterolateral striato-pallidum (plStP), which receives scarce inputs from vomeronasal amygdala [6].

We used 51 adult female mice (CD1 strain). To ensure that their preference for male pheromones were innate to reflect liking, we used "chemically-naïve" females [11]. Briefly, pregnant females acquired from Harlan (Barcelona, Spain) were housed in the absence of adult males or male-derived chemicals. Nineteen days after delivery, pups were sexed, males were removed and their female siblings were housed in groups of 4–8 animals, with food and water *ad libitum*. These females were used from week 9 of age. The innate attraction response is not dependent on hormonal status in "chemically-naïve" females [21], and thus we did not control for this variable.

The animals were treated throughout according to the European Communities Council Directive of November 24th, 1986 (86/609/EEC) and procedures were approved by the Committee of Ethics on Animal Experimentation of the University of València.

Females were randomly assigned to three groups: SHAM-operated ($n = 14$), MEDIAL lesion ($n = 27$) and LATERAL lesion ($n = 10$). For stereotaxic surgery, animals were deeply anaesthetized with sodium pentobarbital (60 mg/kg, i.p.), and administered atropine (0.4 mg/kg, i.p.) to prevent cardio-respiratory depression and buprenorphine (Buprex, Schering-Plough; 0.02 mg/kg, s.c.) for analgesia. Mice were placed on a stereotaxic frame (David Kopf Instruments 963-A, Tujunga CA, EE.UU). Coordinates were adjusted from [22]. The experimenter drilled a hole in the skull to insert a stainless steel electrode (250 μm of diameter, Ugo Basile, Varese, Italy). Lesions were performed by passing a constant (negative) current of 0.8 mA for 15 s. In SHAM surgery the electrode was inserted but no current was applied. An observer unaware of the treatment of the samples performed the post-mortem evaluation of the span of the lesions (Fig. 1, Table 1).Since we were interested in testing the role of the projection from the vomeronasal amygdala to the mvStP, which is especially substantial to the medial ICj [6], we used the volume of these structure as aprioristic criterion for the inclusion of mice in the analysis of the MEDIAL lesion group. The sections of the ICj between levels Bregma +1.9 and +0.8, were drawn using a camera lucida, drawings scanned and digital images calibrated and binarized with ImageJ software (NIH). Total volume of the anteromedial ICj plus the major ICj was estimated for each hemisphere using the Cavallieri method. Animals bearing lesions of at least a 40% of the volume of the mentioned ICj in each hemisphere and of more than a 50% of their total volume in both hemispheres, were included in the analysis. Mice showing unilateral ($n = 5$), small or no lesion ($n = 6$), or enlarged ventricles due to a misplacement of the electrode ($n = 3$) were discarded (not

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Table 1
Total volume (right plus left hemisphere) of the lesion in MEDIAL and LATERAL lesion group, and main regions affected by the lesions in each mouse brain. Abbreviations: aca: anterior comissure; AcbC: nucleus accumbens core; AcbSh: nucleus accumbens shell; plAcb: posterolateralaccumbens; vCpu: ventral caudatus-putamen; amICj: anteromedial island of Calleja; ICjM: major island of Calleja; Pir: piriform cortex; mTu: medial olfactory tubercle; lTu: lateral olfactory tubercle; VDB: ventral diagonal band; VP: ventral pallidum; *affected unilaterally.

Medial lesion Specimen	Volume (mm^3)	Affected nuclei
M1	3,1	amICj, ICjM, mTu, AcbSh*
M2	2,8	amICj, ICjM, mTu
M3	1,7	amICj, ICjM, mTu
M4	2,9	amICj, ICjM, mTu, AcbSh
M5	3,9	amICj, ICjM, mTu, AcbC*, AcbSh, aca
M6	3,3	amICj, ICjM, mTu, VDB
M7	1,7	amICj, mTu, VDB
M8	4,2	ICjM, mTu, AcbSh, VDB
M9	1,5	amICj, ICjM, mTu
Average volume	2,8	
S.E.M	0,3	
Lateral lesión Specimen	Volume (mm^3)	Affected nuclei
L1	1,2	plAcb, lTu, VP
L2	3,9	plAcb, lTu, VP, vCpu
L3	2,2	plAcb, lTu, VP
L4	3,8	plAcb, lTu, VP, vCpu
L5	3,2	plAcb, lTu, VP
L6	3,1	plTu, vCpu, VP
L7	3,9	plAcb, lTu, VP, vCpu
L8	3,3	plAcb, lTu, VP, vCpu, Pir*
Average volume	3,1	
S.E.M	0,3	

shown). For the LATERAL lesion group, selected as a control, we included animals showing bilateral lesions of posterolateral striato-pallidal areas ($n = 8$). Total volume of the lesions was determined using Computer Assisted Stereology Toolbox software (Olympus Danmark, A/S) (Table 1). Student's *t*-tests revealed neither significant differences in the span of the lesions between hemispheres (left *vs.* right, MEDIAL lesion group, $p = 0.34$, LATERAL lesion group, $p = 0.64$), nor in the total lesioned area between groups (MEDIAL *vs.* LATERAL, $p = 0.54$) (Table 1).

Fourteen days after surgery, we tested the preference of the females for male chemosignals in two-choice tests [19]. As a source of chemosignals, we employed bedding soiled by adult males and females. Female-soiled bedding was collected from large home cages (22 × 47 × 15 cm) containing 6 adult females (different from the experimental ones) after four days of use. Male-soiled bedding was collected from 6–8 dominant males housed individually in small home cages (22 × 22 × 15 cm) over the same period. Bedding soiled by the different males was thoroughly mixed to ensure a homogeneous source of male chemosignals throughout the experiments. Immediately after being collected, male- and female-soiled bedding was frozen (−20 °C) until use.

Mice were habituated for two days to the experimenter and the test cage (25 × 50 × 30 cm), which contained two glass dishes filled with clean bedding in opposite corners. On the third day, the females were introduced again in a test cage with female bedding in both dishes (control), and their exploratory behaviour was video recorded for five minutes. To minimize variability and ensure balanced investigation of the test cage, animals that spent twice as much time investigating one of the dishes than the other in the control situation were discarded (SHAM $n = 3$; MEDIAL, $n = 2$; LATERAL, $n = 2$). After this test, animals rested for five minutes, and were introduced in another test cage in which the left dish contained female and the right dish contained male-soiled bedding (male preference test) and their behaviour was recorded for five minutes. The videos were analyzed by using the video-track software package SMART 2.5 (Panlab, Cornellà, Spain). Data were analyzed with the SPSS 15.0 software package.

We calculated a preference score as "Time spent in right dish/Total time spent in both dishes". A repeated measures ANOVA with GROUP (SHAM-operated, MEDIAL lesion, LATERAL lesion) as between-subjects factor and TEST (control, male preference test) as within-subjects factor of this score revealed a significant effect of the second order interaction TEST x GROUP ($F_{2,25} = 3.66$, $p = 0.04$), a significant TEST effect ($F_{2,25} = 23.34$, $p < 0.001$) but non-significant effect of the factor GROUP ($F_{2,25} = 1.88$, $p = 0.17$). Post-hoc pair wise comparisons revealed significant differences between the control and male preference tests both in the SHAM ($p = 0.001$) and in the LATERAL ($p < 0.001$) groups. In contrast, the preference score of the animals of the MEDIAL group did not differ between tests ($p = 0.57$) (Fig. 2A). A Student's *t*-tests comparing the preference score in the male preference test with the chance value (0.5) revealed that both SHAM and LATERAL mice, but not MEDIAL, displayed preference for male chemosignals, ($p < 0.001$, $p = 0.018$, and $p = 0.78$ respectively) (Fig. 2A). Thus, at least in female mice, the integrity of the mvStP is necessary for the attraction towards male chemosignals.

A one-way ANOVA between groups revealed that groups differed significantly in locomotion ($F_{2,25} = 4.805$, $p = 0.017$). A SNK post-hoc analysis revealed that the difference was due to significantly higher locomotion in MEDIAL group animals (Fig. 2B). Hyperlocomotion has been shown in rodents upon deletion or downregulation of dopamine D3 receptors, which are highly expressed in the area affected by the medial lesion [23–25]. Interestingly, it was previously suggested that this hyperlocomotion was due to a dysfunctional exploration due an impaired processing of chemosensory cues by Tu and ICj [24].

We find unlikely that lack of attraction for male pheromones observed in MEDIAL-lesioned females derives from increased motor activity. An ANOVA revealed no differences between groups in basal investigatory behaviour in the control test ($F_{2,25} = 2.070$; $p = 0.147$) (Fig. 2C). Therefore, lesions of the mvStP slightly enhanced locomotion but had no significant effects on exploratory behaviour of female bedding.

To check whether lesions had specific or general effects on consummatory responses driven by rewarding stimuli, we tested another reward-mediated response, namely sucrose-sweetened *vs.* water preferential intake. One week after the pheromone preference tests, mice were deprived of water (20:00 p.m.–8:00 a.m.) and habituated for 2 days for 15 min (8:00 a.m.–13:00 a.m) to the test cage (25 × 25 × 30 cm) with two bottles containing water. On the third day, animals were placed again in the test cage with one bottle containing tap water and the other a 5% sucrose solution, and the licks on each bottle were automatically registered with a lickometer for 15 min (Packwin software, Panlab, Spain).

We calculated the total amount of licks made by the animals during the test from both bottles and the preference score (Licks to the 5% sucrose solution/Total number of licks). An ANOVA comparing these measures revealed that neither the total number of licks ($F_{2,19} = 1.09$; $p = 0.36$; Fig. 2D) nor the preference score ($F_{2,19} = 0.23$; $p = 0.79$; Fig. 2E) were different between groups. A Student's *t*-tests comparing the pooled preference score with the chance value revealed that, overall, this measure was significantly different from 0.5 ($p < 0.01$). Thus, in contrast to preference for male chemosignals, the lesions of mvStP did not significantly affect the preference for a sweet solution.

Amygdalo-striatal circuits are crucial for reward processing [26]. The cortical division of the amygdala, including both olfactory and vomeronasal nuclei, sends important projections to the Tu and ICj [4–6]. Also, scarce input from the medial amygdala reaches the medial region of the Tu [27]. We have hypothesised that this amygdalo-striatal pathway might underlie the rewarding properties of pheromones [4,6]. The present results show that the integrity

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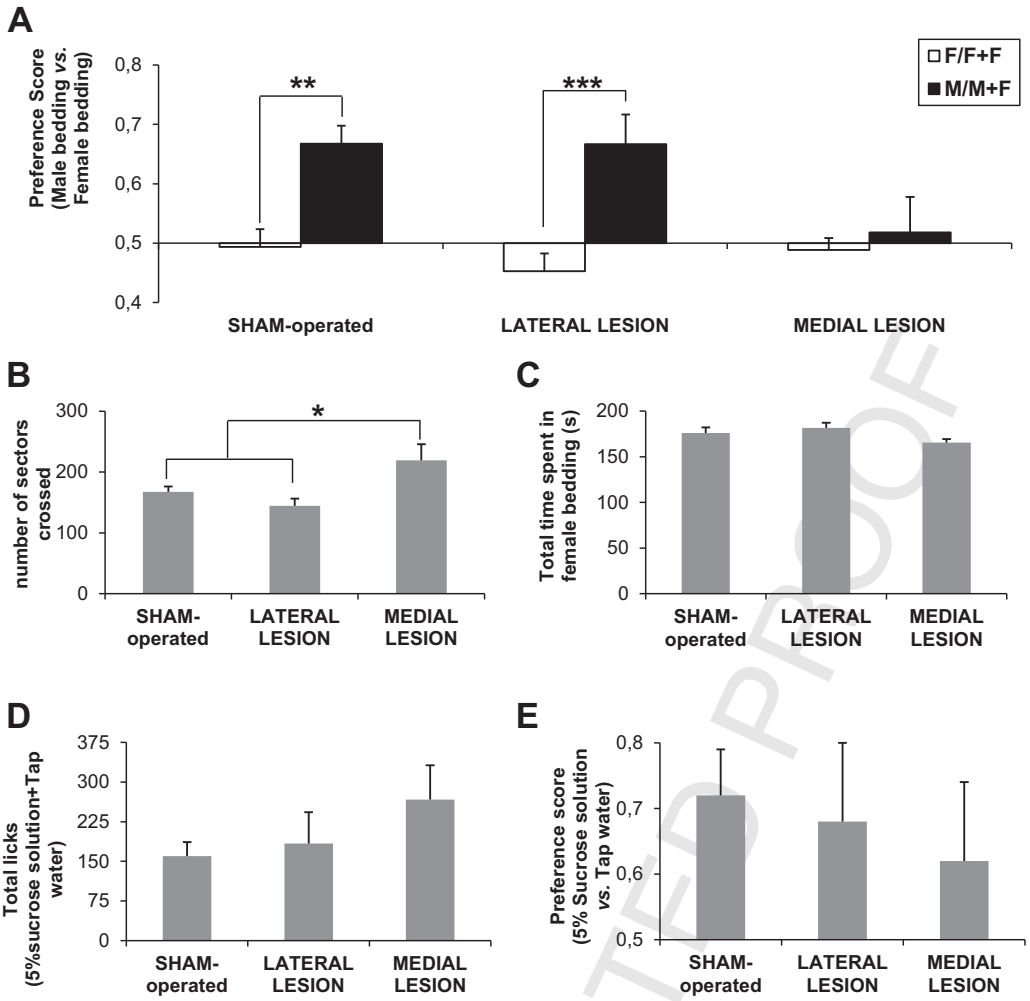

Fig. 2. Bar charts (mean ± S.E.M.) showing preference for male chemosignals, locomotion, bedding investigation, total intake of liquid and preference for a sweet solution in SHAM-operated, LATERAL and MEDIAL groups. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$>

A. Preferential investigation of male-soiled bedding. Control, F/F + F, white bars; Male preference test, M/F + M black bars; see main text. SHAM-operated and LATERAL groups significantly preferred male-soiled bedding in the male preference test, but female mice bearing a MEDIAL lesion did not.

B. Locomotion (as measured by dividing the cage in four parallel sectors and counting the number of crossings between them using the automated system) during the control plus male preference test. Mice bearing a medial lesion displayed enhanced locomotor activity.

C. Total time in seconds investigating both dishes in the control (F + F). The surgery did not affect basal chemoinvestigatory behaviour displayed by female mice.

D. Total licks performed during the sucrose preference test. No significant differences were found between groups.

E. Preference for 5% sucrose solution. (Number of licks performed on the 5% sucrose solution bottle/Total licks). No differences were found between groups.

Abbreviations: F: female-soiled bedding, M: male-soiled bedding.

of the region targeted by vomeronasal inputs, which we refer to as mvStP, is necessary for the behavioural expression of sexual chemosignals liking in female mice, providing the first functional piece of evidence supporting this hypothesis.

Previous studies showed medio-lateral heterogeneity within the ventral striatum. Rats readily learn to self-administer low concentrations of cocaine in the medial Tu, whereas higher concentrations are needed to achieve self-administration in adjoining structures (medial shell of the Acb and posterolateral Tu [1]). In contrast, dorsolateral regions play an important role in habit formation with increasing experience of the animals with the reward.

Our results parallel these findings, but the distinction found here is likely due to the nature of the attractive chemical signals. Innately attractive chemosignals are detected by the vomeronasal system [13], which targets preferentially the medial regions. With experience, volatile male odorants acquire attractive properties by association with the non-volatile chemosignals [11]. Thus, it is possible that lateral parts of the ventral striato-pallidum play a role in processing volatile odorants in experienced animals, but this suggestion remains to be tested.

The neural network of socio-sexual behaviour [28] includes sexually dimorphic nuclei, such as preoptic area and ventromedial hypothalamus. These nuclei are involved in the control of paracopulatory and copulatory components of sexual behaviour [29,30]. We recently showed that an area of the mvStP is targeted by sexually dimorphic vasopressinergic innervations [9]. Based on this, we proposed that this region should be included in the socio-sexual behaviour network. Here, we show that the lesions of the mvStP abolish innate attraction towards sexual chemosignals, which can be regarded as paracopulatory behaviour [21], adding functional evidence to support this proposal.

We acknowledge that the electrolytic lesions do not allow targeting selectively the different components of the ventral striato-pallidal complex. Thus, although medial lesions consistently affected to the ICj and Tu, other structures such as the Acb and VDB were affected in some of the animals (see Table 1). Future studies using more selective methods should investigate the

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contribution of these different nuclei to the observed behaviour. In particular, it would be interesting to explore the role of the ICj. Although roles in processing sex-related odours and/or modulation of reproductive events have been previously suggested [2,8], scarce evidence is available supporting these statements. Interestingly, adult-born neurons incorporate into the ICJ [31], whose number and structure vary with aging [32]. Since adult neurogenesis is essential for olfactory-guided social behaviours [33] and olfactory dysfunction is a feature of aging and neurodegeneration [34], we expect that future studies will shed light about the contribution of this unexplored archipelago to those phenomena.

In conclusion, our data suggest that the mvStP plays a key role in the processing of the hedonic properties of biologically significant chemical signals in the context of socio-sexual and reward-directed behaviour, and defines this region as an important node in mediating sexual attraction of females through male chemosignals. Future work is needed to investigate the contribution of the mvStP to the same behaviour in males, in the response of animals in front of different chemosignals from the ones used here, and the roles of other pathways important for chemical communication.

Finally, it would be interesting to investigate the possibility of a role of this region of the mvStP, and the portions of the amygdala that project to it, in sexual attraction mediated by other sensory modalities [35]. Indeed, human neuroimaging studies reveal significant activation of the amygdala and ventral striatum in view of sexually arousing images [36,37]. It would be also interesting to investigate whether sexual orientation (what gender is sexually arousing) might be influenced by the function of this circuitry [37].

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