Chapter

Olfaction and Depression: Does the Olfactory Bulbectomized Rat Reflect a Translational Model for Depression?

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Abstract

The olfactory bulbectomized (OBX) rat is extensively used as an animal model to detect putative antidepressant drugs. The model has some unusual characteristics, as it detects antidepressant activity of drugs only after medium to long-term administration, thereby reflecting the human situation, as antidepressants do not work acutely but only after long-term administration. The slow onset of action of antidepressants is a major drawback of current antidepressants and the availability of an animal depression model that potentially reveals rapid onset of antidepressant activity might be a great asset. Although an animal model of depression ideally should reflect correlates of human depression, several 'surrogate' parameters, like 'hyperactivity', reflect astonishingly well the 'antidepressant' profile of antidepressants in human depression. Using a new environment (open field) and a home cage to measure activity, imipramine, a classic tricyclic antidepressant, reduced hyperactivity in OBX rats, both in home cage and open field. Telemetrically measured, OBX-induced hyperactivity was already found after a couple of days and indicated that the OBX model is able to detect early (days) effects of (classic) antidepressants. Although imipramine treatment for 3, 7 and 14 days reduced OBX-induced hyperactivity, daily treatment with imipramine for 14 days, but not for 3 or 7 days, reduced hyperactivity (both in home cage and open field) of OBX rats up to 6 weeks after cessation of treatment, indicating neuroplastic changes in the brain. The attractiveness of the OBX model for detection of antidepressants lies in the resemblance to the human situation (onset of action). Moreover, the model suggests that long-term antidepressant treatment (in rats at least 14 days) leads to long-term behavioral changes that far outlast the presence of the antidepressant in the body. Whether this aspect contributes to efficient antidepressant effects needs further investigation.

Keywords: depression, olfaction, olfactory bulbectomy, animal model, hyperactivity, pharmacology, antidepressants, onset of action, long-lasting effects

1. Introduction

Depression is a prevalent and severe brain disorder that hits many people; it is estimated that it occurs at a 12 months prevalence rate of 7% in Europe [1]. Major depression is mainly characterized by depressed mood, anhedonia, loss of general interest and fatigue. Depression is associated with brain changes in various areas of the prefrontal limbic network [2]. This network involves the orbitofrontal cortex, anterior and posterior cingulate cortex, insula, amygdala, hippocampus and thalamus [3]. Regions associated with olfactory processes have a large overlap with those areas in the prefrontal limbic network and it has been suggested that (reduced) olfaction might be a (cognitive) marker for depression [4]. Croy et al. [5] showed that reduction of olfactory associated functions in the brain of depressed women improved with antidepressant (psycho) therapy to normal control levels, indicating that olfaction may represent a marker for depression. A connection between olfaction and depressive behavior has come strongly forward with the introduction of the olfactory bulbectomized (OBX) rat (see reviews by refs. [6, 7]).

The OBX rat has been strongly advocated as an animal model of depression for various reasons. Rajkumar and Dawe [8] gave an extensive overview and critical discussion on the commonalities between the OBX model and perturbations in the frontal cortex of the human depressed brain. Although it is clear that the brain and behavioral changes in the OBX-brain (of rats) are not directly comparable to the changes in the brain (in particular the frontal cortical areas) of depressed humans, there are considerable similarities that support at least a (partial) role of the OBX rat as modeling (part of) human depressive behaviors [7, 9]. In this paper, the OBX model as used for almost two decades in our laboratory is used. Activity as parameter for detecting 'depression' aspects in rats is widely used and accepted as a sensitive measure of antidepressant effects of various manipulations (antidepressants). Standard use is the measurement of the activity of rats in an Open Field (open arena) during a short test (lasting between 10 and 30 minutes in general). In our research, we also applied telemetric measurements (heart rate, body temperature and activity) in the home cage to measure more refined parameters like day-night rhythms. The present paper is in particular a reflection of our scientific work on the OBX rat model as one of the best (if not the best animal model) model of human depression that can be used to study aspects of the process of depression that cannot be directly studied in humans.

2. Olfactory bulbectomy (OBX) in rats as a depression model

The OBX rat has been extensively used for testing potential antidepressant effects of new and existent drugs [6, 7]. After olfactory bulbectomy in rats, a variety of behavioral changes emerge, including, for example, increased activity, disturbed sexual behavior [10, 11], reduced taste aversion, passive avoidance deficits, impaired spatial learning and impaired food-motivated behavior [12–18]. Following chronic (weeks), but not acute treatment with clinically established antidepressants with various mechanisms of action, normalization of these disturbed behaviors occurs [13–15, 19]. The OBX model therefore is one of the very few (if not only) animal models that share the typical slow onset of action of antidepressants as seen in human depressed patients [20, 21].

One of the most used and validated parameters to study pharmacological effects of putative antidepressants is the hyperactivity induced by olfactory bulbectomy

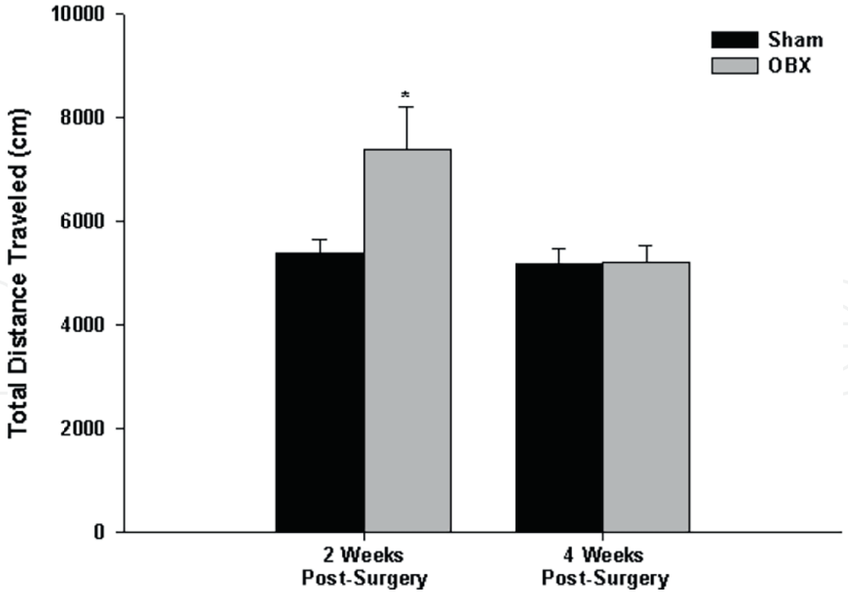


Figure 1.
*Post-surgical hyperactivity in Wistar rats. Total distance traveled (cm ± SEM) in the open field 2 and 4 weeks post-surgery. Bulbectomized Wistar animals are significantly more active than shams 2 weeks after surgery, but this effect is no longer present 4 weeks after surgery. * = p < 0.05 compared to shams. For methods used we refer to refs. [25–29].*

in rats [6, 7], both in an open field test (new environment) and in the home cage [22]. Most OBX studies in rats have been performed in Spague-Dawley (SD) and Wistar (Wi) strains. Because SD rats are considerably more active after olfactory bulbectomy than Wi rats [23] and this hyperactivity after OBX is present for at least 5 months, but possibly lifelong in SD rats [24]. This is not the case in Wi rats, which show hyperactivity 2 weeks after OBX, but not anymore after 4 weeks post-surgery (**Figure 1**), which in our hands makes the SD strain more attractive for OBX studies.

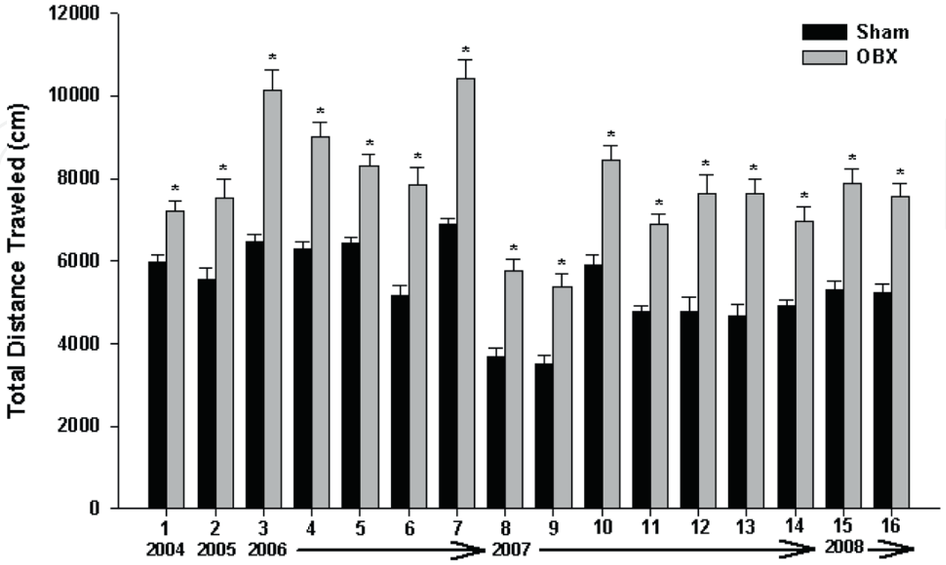


Figure 2.
*Post-surgical open field comparisons over 5 years. Total distance traveled (cm, ± SEM) in the open field 2 weeks post-surgery for 16 different groups of animals. Animals were placed in the open field and allowed to explore for 15 minutes. In total, the N was approximately 750 for both OBX and sham groups. * = p < 0.05 compared to shams. For methods used we refer to refs. [25–29].*

Hyperactivity after OBX is always found in our experiments performed over several years as shown in **Figure 2**, portraying the activity of male Sprague-Dawley rats 2 weeks after sham or OBX surgery over a period of 5 years. Animals were tested in an open field for 15 minutes and the total distance traveled (cm) was measured. Although the level of activity varied over time, OBX always induced hyperactivity.

Although almost all OBX experiments are performed in male rats, whereas depression is more prevalent in the female than in the male human population [30], it is of note that OBX in female rats also leads to enhanced activity [31]. Although the hyperactivity after OBX is generally measured in a new environment (often an Open Field test), this hyperactivity is also present in the home cage and emerges approx. 2–3 days after surgery [22] as shown in **Figure 3**. Although circadian rhythmicity is

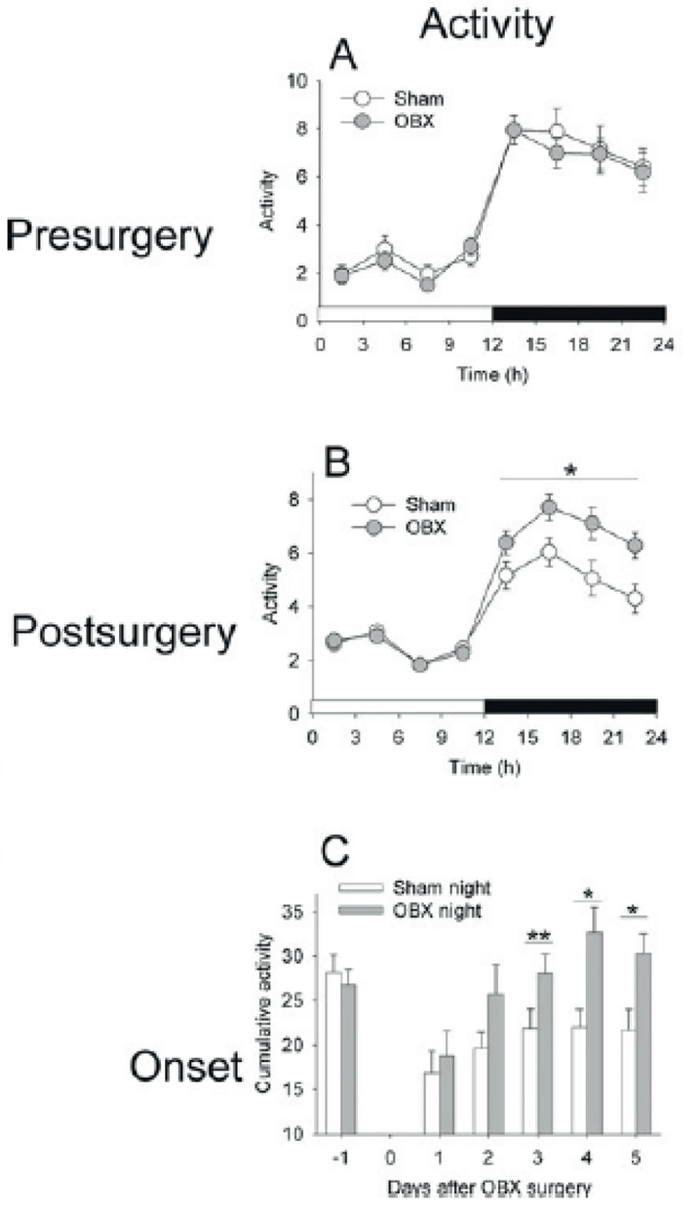


Figure 3.
Circadian rhythmicity of locomotor activity (A, B) before (A) and after olfactory bulbectomy (B). Postsurgical data reflect the average over 14 days starting immediately after surgery. (C) represents the onset of the changes in locomotor activity induced by OBX (day 0) over the first 5 days during the nocturnal phase. For methods used we refer to ref. [22].

not affected, OBX rats display several changes in basal circadian amplitudes in the home cage, besides increased nocturnal activity, enhanced nocturnal body temperature and decreased heart rate, confirming earlier findings [19, 32].

Although olfaction is clearly abolished after complete OBX, several aspects of OBX-induced changes cannot be simply explained by loss of olfaction persé. Anosmia in rats, induced by rinsing the olfactory epithelium with zinc sulphate ($ZnSO_4$), does not lead to hyperactivity in an open field [33, 34]. This lends support to the notion that dysfunctional systems in the brain and particularly the limbic system that involves a variety of neurochemical and pharmacological changes in various neurotransmitter systems are involved, including, for example, the serotonergic and noradrenergic systems [7].

Remarkably, many of the behavioral and biochemical changes induced by OBX can be reversed by chronic administration of almost all antidepressants [6, 35]. Moreover, several more recently developed or applied techniques or models to treat depression in humans, also appear to work in the OBX model in rats, like deep brain stimulation of the infralimbic prefrontal cortex [36], a multi-targeted food intervention [16] and environmental enrichment [37].

The OBX model in male rats has received its 'fame' as depression model, because of the activity of antidepressants in it [35]. Antidepressants with various mechanisms of action (SSRIs, SNRIs, NRIs, TCAs and others) exert inhibition of OBX-induced hyperactivity [38]. Characteristically, this inhibition does not occur after acute, but after (sub) chronic administration of antidepressants. This pattern of activity follows the human situation, where antidepressants only work after chronic administration (weeks-months [39]). The OBX model in rats accordingly is very efficient and reliable in predicting putative antidepressant activity of new psychoactive drugs or substances, although the model is also generating false positive and false negative results [35].

3. Does the OBX model in rats detect fast-onset antidepressants?

The question is whether the OBX model in rats can be used for detection of fast-onset antidepressants, that is, compounds that exert antidepressant activity acutely or after a short interval (hours or days; not weeks). Clinical studies have indicated that low doses of intravenous ketamine and one of its enantiomers (esketamine) exert antidepressant effects, especially in treatment-resistant depression [40, 41]. However, studies on (es)ketamine in the OBX model are scarce. In one study [42] a single intraperitoneal injection of ketamine 24 h before testing did not affect hyperactivity in an Open Field in mice, although some other anhedonic-like behaviors were reversed. Similarly, ketamine did not inhibit hyperactivity in OBX rats 24 h after 10-mg/kg IP injections [43].

Although several other potential strategies for fast-onset antidepressants are in development [44] no emerging data are available yet in the olfactory bulbectomized rat model. Still, theoretically, the OBX model in rats should be able to detect fast(er) onset of antidepressant activity, but more fundamental research should be performed into the early changes in the brain after such a drastic phenomenon as ablation of the complete olfactory machinery.

4. Imipramine: onset of action and long-term effects in the OBX rat model

Although the OBX model seems to generate an 'ideal' model to accurately predict the antidepressant onset, this is in particular based on the effects of classical antidepressants

(see [35]). However, in using the tricyclic antidepressant imipramine as standard antidepressant in our OBX rat research [25–29], we did interesting observations. Most OBX/antidepressant studies measure effects 14 days after starting treatment in behaviourally stable (hyperactive in an Open Field) animals. However, imipramine (20 mg/kg, IP) already reduced activity to sham-control levels after 7 days of IMI treatment [25]. Although not tested after 7 days, the SSRI escitalopram (5 and 10 mg/kg, PO) like imipramine (20 mg/kg, PO) reduced hyperactivity to sham-operated rat levels, showing the 'classical' effects of SSRI- and TCA-antidepressants [25].

The finding that imipramine has already inhibitory effects on OBX-induced hyperactivity after 7 days of treatment, indicates that the OBX hyperactivity model is very sensitive to antidepressant effects. Probably, disturbed systems in the brain after olfactory bulbectomy, which lead to almost immediate behavioral and physiological effects [22] are influenced in such a way by certain drugs (e.g. antidepressants) that hyperactivity is quite rapidly depressed to normal levels. It is completely unknown what underlies these processes and future research is needed to unravel possible mechanisms.

The classical OBX model uses a 14 days treatment period to find putative antidepressiant drug effects. The question arose whether drug treatment for a long period (e.g. 14 days) led to sustained effects on activity if drug treatment is stopped. In other words, is hyperactivity returning rapidly or delayed after discontinuation of the antidepressant [25]. In the latter study, the activity of sham and OBX rats was measured 1, 2, 6 and 10 weeks after cessation of the tricyclic antidepressant imipramine (20 mg/kg, PO) or escitalopram (5 and 10 mg/kg, PO) treatment. After these periods of drug cessation, no drug levels are present anymore in the experimental rats. One, 2 and 3 weeks after stopping 14 days of treatment with vehicle, escitalopram (5 and 10 mg/kg) and imipramine (20 mg/kg), the three antidepressant-treated groups still showed comparable activity levels as the sham-operated groups; 6 weeks after stopping treatment the escitalopram-treated animals returned to their initial hyperactivity-level as observed 14 days after OBX. In contrast, the imipramine group still did not differ from the sham group. Only 10 weeks after cessation of treatment the imipramine group (and both escitalopram groups also) showed hyperactivity like before.

In a separate study, we examined the onset of action of imipramine (10 mg/kg, IP) and vehicle measuring activity in an Open Field test. First, 120 Wistar male rats were run in an open field and were assigned, based on their basal activity into equal activity groups. Half of the animals were olfactory bulbectomized, and half obtained sham surgery. After surgery, animals recovered for 2 weeks. Animals were then assigned to four groups with regard to their post-surgical open field activity so that there were equal numbers of more or less active animals in each treatment group (N = 15–20 animals per group).

All animals received one intraperitoneal injection per day for 3, 7 or 14 days. On days 1, 3, 7 and 14, animals were tested in the open field, 30 minutes after injection, to observe the onset of action of imipramine. All animals were also tested 1, 2 and 6 weeks after cessation of treatment to observe any long-lasting effects of imipramine treatment. No acute effects of imipramine were found on day 1 after the very first injection in all three groups (**Table 1**). Bulbectomized rats in all groups remained significantly more active compared to sham-operated groups.

After 3 days of treatment, imipramine significantly reduced the hyperactivity of the OBX group, towards the sham level (**Figure 4** top). This effect of imipramine was short-lived: 1, 2 and 6 weeks after cessation of treatment olfactory bulbectomized animals returned to their enhanced OBX level. Bulbectomy-induced hyperactivity

	Group 1 (3 days treatment)	Group 2 (7 days treatment)	Group 3 (14 days treatment)
Sham vehicle	4411 ± 317.3	4999 ± 430.2	3992 ± 355.7
OBX vehicle	6703 ± 523.4*	6915 ± 387.8*	6202 ± 596.9*
Sham imipramine	3530 ± 213.3	3531 ± 219.9	3633 ± 352.5
OBX imipramine	4818 ± 262.9*	5535 ± 855.4*	5194 ± 592.5*

*Data are expressed as mean distance traveled (cm) ± SEM. Group 1 = animals receiving imipramine or vehicle for 3 days; group 2 = animals receiving imipramine or vehicle for 7 days; and group 3 = animals receiving imipramine or vehicle for 14 days. Methods as described in refs. [25–29]. * = $p < 0.05$ compared to the corresponding sham group.*

Table 1.
Acute effects (on day 1 of all three groups) of imipramine on vehicle treatment or sham-bulbectomized activity and olfactory bulbectomy-induced hyperactivity in an open field (15 minutes in a 70 × 70 × 45 cm chamber under fluorescent lighting using Noldus Etho Vision^R during the light period (9–13 h)).

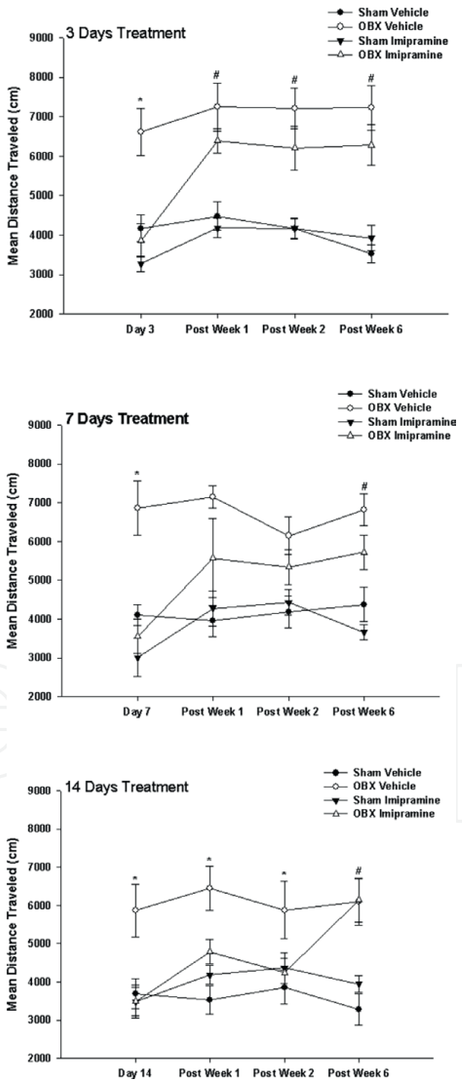


Figure 4.
*Effects of 3 (top), 7 (middle) and 14 (bottom) days of imipramine (IP) or vehicle treatment (IP) on sham-operated or olfactory bulbectomized rats in the open field after three, seven or 14 days of treatment as well as 1, 2, 6 weeks after cessation of treatment. Data are expressed as mean distance traveled (cm) ± SEM. * = $p < 0.05$ compared to all animals, OBX and sham, in all groups. # = $p < 0.05$ for both imipramine and vehicle OBX animals, compared to corresponding shams. Methods as described in ref. [22].*

was clearly present up to 6 weeks after cessation of 3 days of imipramine treatment. No effect of habituation to the open field was seen. After 7 days of treatment, imipramine significantly reduced the hyperactivity of the OBX group, towards the sham level (**Figure 4** middle). Like after 3 days of treatment, no effects of imipramine were found 1, 2 or 6 weeks after cessation of the 7-day treatment.

After 14 days of treatment, imipramine significantly reduced the hyperactivity of the OBX group, towards the sham level (**Figure 4** bottom). However, this effect was still present 1–2 weeks after cessation of the treatment. Six weeks after cessation the level of (hyper) activity of the imipramine pretreated group had returned to the OBX sham level.

The results of this experiment show that the olfactory bulbectomy model is suitable to detect the onset of action of antidepressants, and also for examining the lasting behavioral effects after cessation of sub-chronic treatment, an effect that has hardly been examined. Interestingly, our results indicate that while treatment for 3 or 7 days may be behaviourally effective, these effects are less stable and treatment should continue for 14 days or more to allow for long-term antidepressant effects (which may be dependent on changes in brain plasticity) to take place. This makes the bulbectomy model attractive for observing not only the onset of action of antidepressants but also the optimal dose duration for long-term therapeutic effects after cessation of treatment.

For quite some time, it was suggested that the addition of 5-HT_{1A} receptor antagonists to settled antidepressants might facilitate a shorter onset of action than the antidepressants alone [20]. Cryan et al. [45] found that the addition of pindolol, a β-adrenoceptor antagonist and partial 5-HT_{1A} receptor (ant) agonist, did not affect the onset time when given for 3, 7 and 14 days in combination with the SSRI paroxetine, indicating that the olfactory bulbectomy model may not be suitable for the detection of onset of action. However, since paroxetine was given at a dose of 2.5 mg/kg, this dose may have been too low to elicit any behavioral effects before day 14 of treatment. Moreover, the quality of pindolol as 5-HT_{1A} receptor antagonist is also questionable. In a subsequent study examining the highly selective 5-HT_{1A} receptor antagonist WAY100635, Cryan et al. [46] found that the addition of WAY100635 to paroxetine treatment did not alter onset of action (after 3 and 7 days of treatment), nor did the drug, when given alone, affect the onset time. Like earlier found in human depression, the addition of a 5-HT_{1A} receptor antagonist, at least in the bulbectomy model, does not facilitate a shorter onset of action compared to animals treated with an antidepressant alone.

Several studies have examined the effects of antidepressants with combined mechanisms of action (like SNRIs or NDRIs) or combination of different antidepressants on olfactory bulbectomy-induced behaviors. For example, it has been proposed that triple reuptake inhibitors (TUIs), inhibiting serotonin, noradrenaline and dopamine transporters would have a faster onset [47]. Quite to the contrary however, Breuer et al. [27] found that TUIs have a slower onset of action compared to imipramine, which was already active after 3 days of administration (see **Figure 4**). Similarly, in a study examining the effects of dual treatment with sertraline (an SSRI) and reboxetine (a selective noradrenaline reuptake inhibitor), Harkin et al. [9] found that treatment had no added effect on bulbectomy-induced hyperactivity in the open field; the drugs, either alone or in combination, did not have any behavioral effect until day 14 of treatment. The current experiment has shown that bulbectomized animals do respond to 10 mg/kg imipramine treatment after 3, 7 and 14 days and that these effects, after cessation of treatment, are dependent upon treatment duration. Interestingly, we have shown previously that treatment with imipramine at 20 mg/kg significantly altered bulbectomy-induced hyperactivity for up to 10 weeks after

cessation of treatment [25]. Also, when observing the lasting effects of pramipexole, a dopamine D_2/D_3 receptor agonist, on bulbectomy-induced hyperactivity, we found that while treatment with 1.0 mg/kg did not elicit any behavioral changes during the treatment period of 14 days (perhaps because this dose may have increased activity in the bulbectomy animals), this dose did have a behavioral effect after cessation of treatment [29]. Thus, normalization of hyperactivity may not only be dependent upon the duration of treatment but also upon the dosage used.

It has been previously shown that chronic treatment, whether with SSRIs or TCAs, leads to a sustainable effect in the open-field paradigm [25]. This suggests that antidepressant treatment may perhaps result in semi-permanent changes in brain plasticity. There is evidence that chronic antidepressant treatment may have a significant effect on NMDA receptors, an effect that has been shown to be sustainable for several days after cessation of treatment [47]. Bulbectomy leads to significant elevations in NMDA receptor levels in the rat prefrontal cortex, an effect that was sustainable until at least 5 weeks following bulbectomy [48]. In addition, Keilhoff et al. [49] also found that chronic imipramine treatment increased neurogenesis in the hippocampal subventricular zone and amygdala of bulbectomized animals, indicating that chronic antidepressant treatment may also have significant effects on neurogenesis in the adult brain and that therapeutic effects of antidepressants may be neurogenesis-dependent [50].

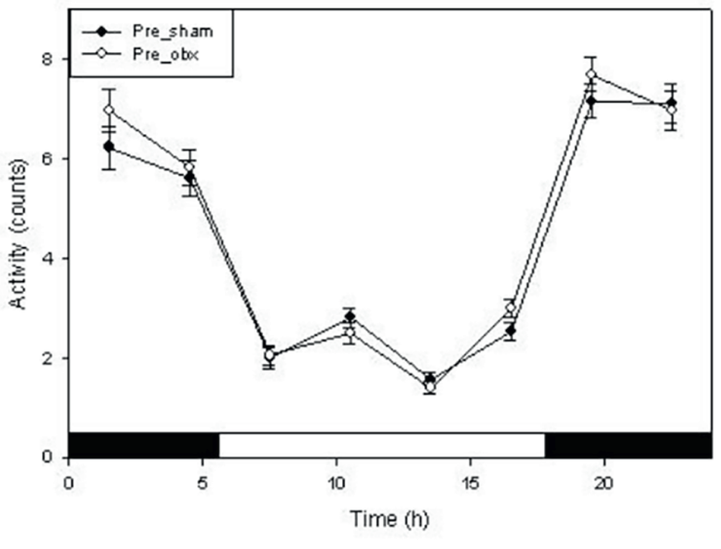
The fact that imipramine was active in the OBX model after only 3 days of once-daily administration is comparable to effects found with the 5-HT_4 receptor agonist RS 67333, in which the bulbectomized animals showed normalized activity in the open field after 3 days of treatment [51]. However, while bulbectomized animals in the current experiment showed normalized activity in the open field on day 3 or day 7 of treatment, the effect disappeared 1 week after cessation of treatment, suggesting that a longer treatment duration is needed for sustainable behavioral effects. That imipramine was behaviourally active after 3 days of treatment further supports the findings of Cryan et al. [45] which show that bulbectomized animals show attenuation of 8-OH-DPAT-induced hypothermia after only 3 days of combined treatment with pindolol and paroxetine, suggesting that these animals do show changes in 5-HT_{1A} receptor sensitivity. In an experiment examining the effects of WAY-163909 (3 mg/kg), a 5-HT_{2C} receptor agonist, Rosenzweig-Lipson et al. [52] found that this drug had a faster onset of action in the olfactory bulbectomy model, compared to traditional SSRIs, in that bulbectomy-induced hyperactivity was reduced after 5 days of treatment. Similarly, in a study examining the effects of pramipexole (a dopamine D_2/D_3 agonist) on bulbectomy-induced hyperactivity, pramipexole, at doses of 0.3 and 0.1 mg/kg, was also active in the olfactory bulbectomy model after 7 days of treatment, comparable to imipramine and 7 OH-DPAT [29]. The results of these studies therefore indicate that the onset of action may not be strictly and only regulated by 5-HT_{1A} receptors.

While we cannot completely rule out that treatment with 5-HT_{1A} receptor antagonists may help to facilitate a faster onset of action, more studies must be done to pinpoint the mechanism behind the onset phenomenon before better and perhaps faster, treatments can be found. It has previously been shown that antidepressant treatment may work relatively quickly for some patients, who report improvements in mood after only 1 week of treatment [53, 54], though there is much debate as to whether or not this early onset of action in patients is due to a placebo effect. However, what if the therapeutic effects of antidepressant treatment are entirely reliant upon neurogenesis? Alterations in neurogenesis in the human adult brain may only occur after chronic, but not acute, antidepressant treatment [55]. If the therapeutic action of antidepressants is indeed entirely dependent upon neurogenesis, it may be difficult to

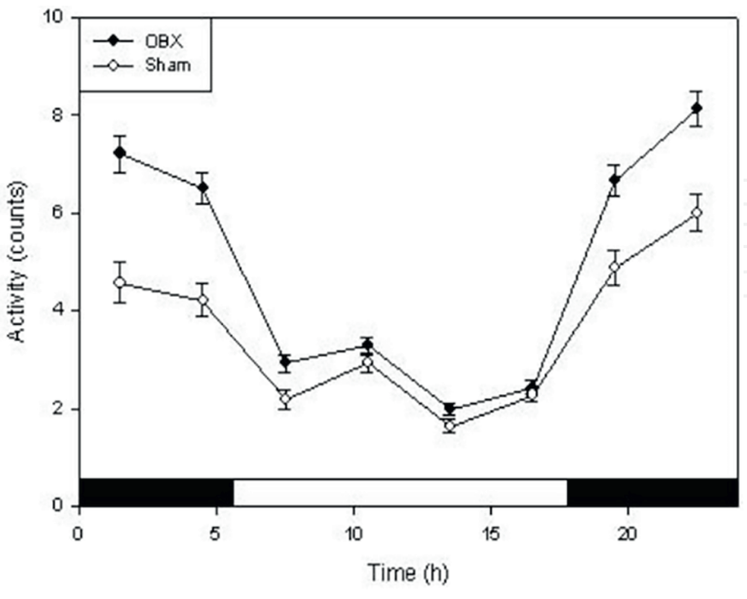
find new treatments with faster onset. However, this remains a subject for scrutiny, as the working mechanisms behind antidepressant efficacy are not yet fully understood and therefore must be further examined.

5. Effects of OBX and imipramine on activity in the home cage

Although olfactory bulbectomy leads to hyperactivity in a new environment (mostly an Open Field situation is used to measure activity), we have previously shown, using telemetric methods, that OBX-ed rats also display hyperactivity in their home cage that emerges already significantly 2–3 days after surgery (see **Figure 4** and [22]). A cohort



(A)



(B)

Figure 5.
(A) Presurgery 24 h baseline: Circadian rhythm of locomotor activity before OBX/sham surgery (3 h blocks). No differences exist between the group that will undergo OBX surgery (n = 21) and the group that will undergo sham surgery (n = 21). Black/white bar represents night/day cycle respectively. (B) 24 h curves of 19 days of post OBX/sham surgery, 3 h blocks. Methods as described in ref. [22].

of 48 male SD rats were implanted with radio-telemetric transmitters and after 2 weeks of recovery randomized into two groups that either were olfactory bulbectomized or sham-operated. During recovery from transmitter implantation for 4 days baseline telemetric measures were continuously measured (activity, heart rate and temperature) but only activity is shown here. After OBX- and sham-surgery telemetric measures were continuously measured for 19 days. Six months after OBX/sham surgery, a 14-day treatment period with either imipramine (10 mg/kg, IP) or vehicle (saline, IP) was given to either half of the OBX- and half of the sham-operated rats (**Figure 5**).

Figure 6 shows the circadian rhythms of locomotor activity in the home cage before OBX/sham surgery (5A) portrayed in 3 h blocks. No differences exist between the groups that will undergo OBX surgery (N = 21) and the sham surgery group (N = 21). **Figure 6B** shows the average circadian activity over 19 days of post-OBX (N = 19)/ sham surgery (N = 17); OBX rats showed an overall increased activity (surgery main effect ($F(1,37) = 20.5$; $p < 0.001$), but mainly during the night (day: surgery main effect $F(1,37) = 4.412$, $p < 0.05$; night: surgery main effect $F(1,37) = 24.748$, $p < 0.001$).

After 14 days of vehicle, OBX rats receiving vehicle were still overall more active than shams receiving vehicle (main surgery effect, $F(1,19) = 5.391$, $p < 0.05$), which appeared a stronger nocturnal hyperactivity (vehicle night blocks: main operation effect $F(1,19) = 5.329$, $p < 0.05$; vehicle day blocks: effect $F(1,19) = 4.038$, $p = 0.059$,

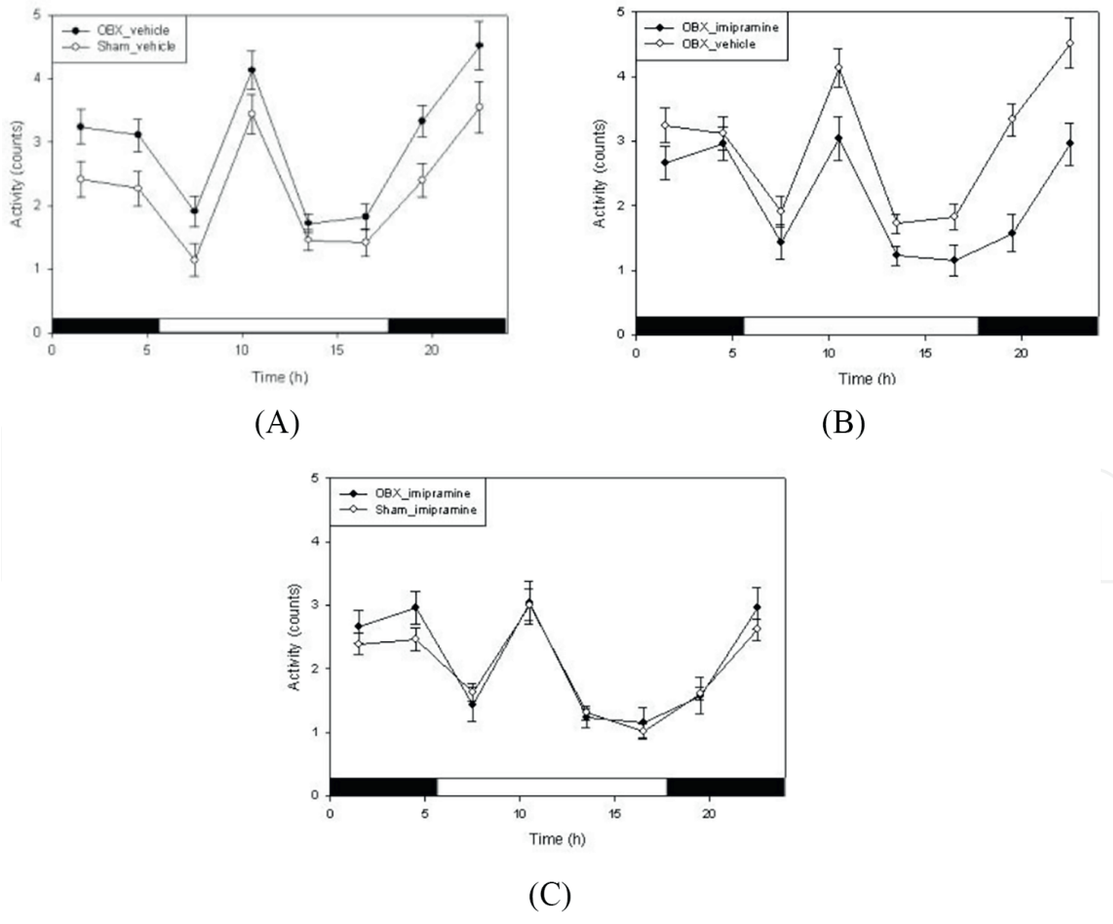


Figure 6.
*24 h activity pattern of 14 days imipramine administration, 3 h blocks (A) OBX vehicle vs. sham vehicle; (B) OBX imipramine vs. sham imipramine; (C) OBX vehicle vs. OBX imipramine. Black/white bar represents night/ day cycle respectively. The peak in activity seen around 10 h is due to the daily injection stress (compare the peak in **Figure 5** vs. **Figure 6**). Methods as described in ref. [22].*

NS) (see **Figure 6A**). OBX animals that were treated with imipramine were however no longer different from sham animals treated with imipramine (surgery effect $F(1,17) = 0.588$, $p = 0.454$, NS) (see **Figure 6C**). As a result, OBX animals receiving imipramine were no longer identical to OBX animals getting vehicle (main treatment effect $F(1,18) = 8.832$, $p < 0.01$), the diminished activity in imipramine OBX rats being present during day as well as night (see **Figure 6B**).

Over the 2 weeks after imipramine treatment stopped, OBX rats that had received imipramine increased their nocturnal activity, almost being different again from sham animals that had received imipramine (imipramine group: surgery effect $F(1,17) = 3.482$, $p = 0.079$, NS, see **Figure 7**). OBX animals that were in the vehicle group still displayed overall (but mainly nocturnal) hyperactivity (sham group: surgery effect $F(1,19) = 5.687$, $p < 0.05$). Whereas during treatment, imipramine OBX rats were less active than vehicle OBX rats, 2 weeks after cessation they were no longer different (OBX group: treatment effect $F(1,18) = 1.182$, $p = 0.291$, NS, see **Figure 7C**).

Unfortunately, we have not tested all these parameters in the various groups at later stages (weeks 6 and 10). We assume that the home cage activities in the various treatment groups show a comparable pattern as observed in the Open Field (as described earlier). The telemetric data (we also gathered body temperature and heart rate-not used here) on activity in the home cage strongly reflect similar findings when OBX- and sham-operated animals are tested in the Open Field, although the effects

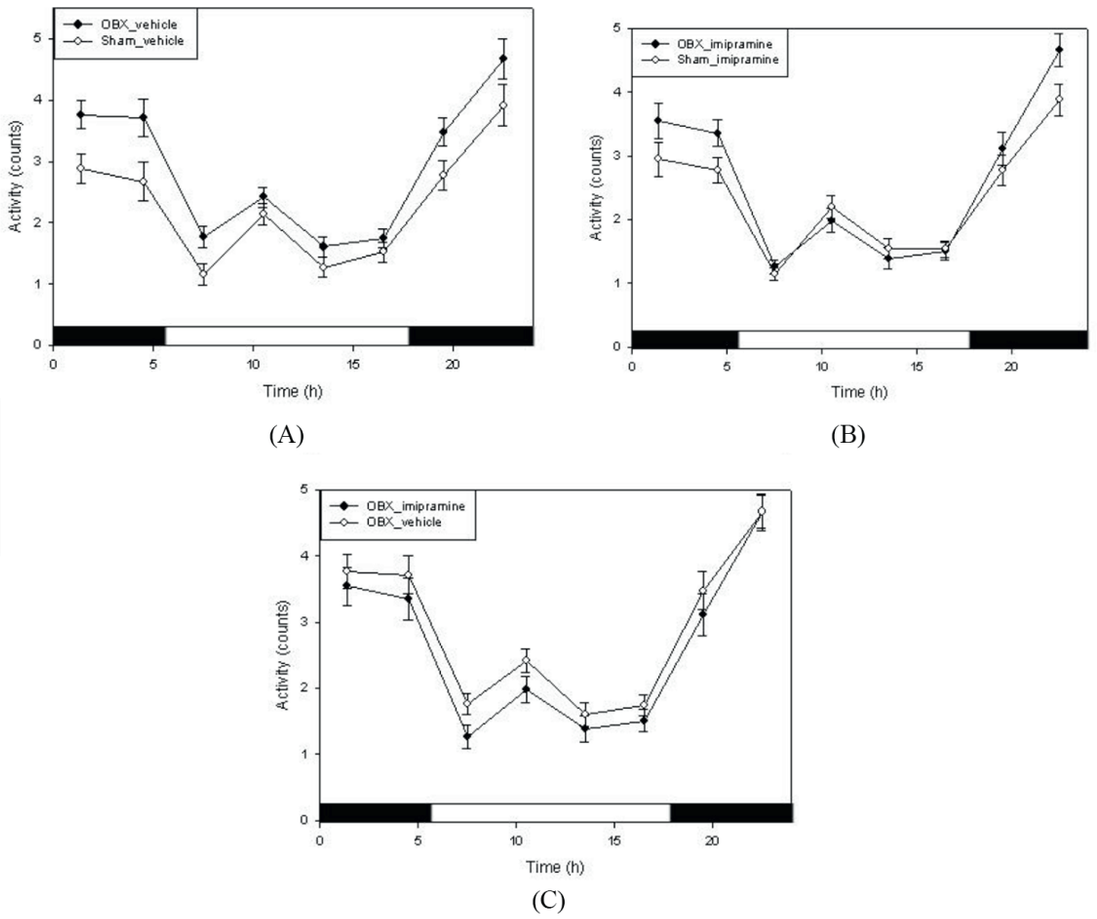


Figure 7.
Average 24 h activity circadian rhythm of the 2-week period after stopping imipramine treatment, 3 h blocks (A) OBX vehicle vs. sham vehicle; (B) Sham-imipramine vs. OBX imipramine. (C) OBX imipramine vs. OBX vehicle. Black/white bar represents night/day cycle respectively. Methods as described in ref. [22].

are more pronounced. This possibly reflects that a new environment induces additional stress that enhances activity, both in sham and OBX rats, which was already found earlier [22].

6. The olfactory bulbectomy model in rats: a model of what?

Although the OBX model in rats (and to a lesser extent mice) is primarily known for its detection of antidepressant activity in a molecule, the model has several other interesting features, in particular, to study degenerative processes in the brain after removing the olfactory bulbs. OBX leads to widespread trans-neuronal degeneration, cognitive decline, reduced volumes of several brain structures (hippocampus, nucleus caudatus and amygdala), disruption of the blood-brain barrier and several other serious changes [7, 15]. All these aspects make the OBX model in rats attractive, as has also been illustrated in the present chapter with regard to onset of behavioral changes after OBX, but also neuroplastic changes after long-term administration of antidepressants. Whether these changes reflect effects on neurodegenerative processes is not clear yet. Much research using the model is needed to show its further contribution to neuroscience.

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