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**Title: Behavioral sensitization to psychostimulants and opioids: what is known in rodents and what still needs to be explored in humans?**

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**Abstract:** Repeated exposure to substances of abuse results in an increase in some behavioral responses. This phenomenon, called behavioral sensitization (BS), is well described in preclinical models. However, its existence in humans is still a matter of debate. After a review of preclinical evidence of BS and its mechanisms in animal models, we reviewed the evidence supporting the existence of BS in humans, despite the limited research available in this regard. We focused our review on opioids and psychostimulants, since they share the ability to promote addictive behaviors. Further, they induce BS despite their distinct sedative and stimulant properties. Moreover, we proposed future research perspectives in this review to address the remaining unsolved questions, especially regarding BS in humans using a harm reduction approach.

**Keywords:** Behavioral sensitization; opioids; psychostimulants

## 1. INTRODUCTION

### 1.1 General consideration on behavioral sensitization

Behavioral sensitization (BS), also known as reverse tolerance, is a phenomenon characterized by an increase in behavioral response, especially locomotor response, induced by repeated administration of the same dose of a psychoactive substance [1–3]. Experimentally, BS was first described in the 1930s [4] and today, it has been demonstrated in several animal models. BS can be divided in two phases: the acquisition and the expression. Classical BS acquisition consists in repeated administration or self-administration of the substance and after a period of abstinence, the administration of the substance (challenge) will increase intensity of motor responses and stereotypies [5,6], which correspond to BS expression. However, some studies have shown that BS could be induced after a single injection [7] and could still be present after a protracted abstinence [8].

BS has been well characterized in rodent models and has recently been described in zebrafish [9]. However, several questions remain unanswered, especially in humans. BS in humans was first described in the 1950s [4] but remains poorly studied, making it very challenging to measure BS in ecological conditions. However, the behavioral disturbances observed in drug-using human subjects seem to be in agreement with the BS mechanisms demonstrated in animal studies [10].

The objective of this review was to describe the existing information regarding BS in preclinical and clinical models. This study focused on psychostimulants and opioids. Indeed, although these drugs have different properties, as stimulants for the first and sedative for the others, they are able to produce BS. Moreover, these are the subjects of the most abundant literature. Thus, we reviewed the current knowledge regarding BS in rodent models as observed with both psychostimulants and opioid molecules, and discussed it in humans. The detailed method of the hypothesis-driven literature review and the tables that describe the methods and results of each article can be found in Tables 1–3 and as supplementary data (Methods; Figure 1: Flow-chart). [We also provided a figure summarizing the main characteristics of BS \(Figure 1\).](#)

### 1.2 Pharmacological mechanisms

BS is thought to involve dopaminergic structures involved in motor functions and reward. Repeated stimulations of brain dopamine receptors induce neuro-adaptive phenomena of the meso-cortico-limbic dopamine pathways [10] and lead to the gradual increase of specific behaviors. Indeed, BS has been experimentally described with pharmacological agents that act directly on the dopaminergic system, such as D1 or D2 receptor agonists, or indirectly, such as cocaine or amphetamines. However, other pharmacological agents, such as cholinergic agonists like nicotine [11], mu opioid receptor agonists like morphine [12], ethanol [13] and delta-9 tetrahydrocannabinol [14] can also induce BS. This suggests the involvement of different neurotransmitters that might induce or express BS through direct or indirect dopamine pathway

modulation (all these drugs will eventually lead to dopamine release in the striatum) [15], especially since a phenomenon of cross-sensitization between drugs has also been described previously. Similarly, variations in mechanisms of action are illustrated by differences in structural changes. An increase in dendritic length and spine density in medium-spined neurons of the nucleus accumbens (NAc) and pyramidal neurons of the prefrontal cortex [16–18] were observed in animals sensitized to stimulants and morphine. On the contrary, no structural changes in the NAc and in medium spined neurons were observed after alcohol sensitization [19].

BS acquisition involves the cellular bodies of dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain. Indeed, repeated injections of psychostimulants [20–22] or mu opioid receptor agonists [23,24] directly in the VTA were demonstrated to be necessary and sufficient to promote BS. In particular, the dopaminergic D1 receptor has been extensively involved in initiating the BS process, since its blockage in the ~~ventral tegmental area~~ VTA and ~~nucleus accumbens~~ (NAc) prevents the acquisition of BS [25,26]. Comparatively, the role of the D2 dopamine receptor is not as well defined; however, it is reportedly mainly involved in BS expression [26]. Concerning other neurotransmitter pathways, GABAB agonists appear to inhibit BS development, which is also inhibited by selective NMDA receptor antagonists [27,28]. Serotonergic transmission is also involved through several receptor subtypes (5-HT1A, 5-HT1B, and 5-HT3) [29].

Once acquired, BS expression rather involved NAc and prefrontal cortex [10]. For instance, whereas repeated intra-NAc injection of amphetamine did not induce BS after ip or intra-NAc challenge, repeated intra-VTA amphetamine injection promoted BS after intra-NAc challenge. ~~Once acquired, BS expression is associated with an increased release of dopamine into the ventral and/or dorsal tegmental areas and/or prefrontal cortex after challenge injection [20]. BS expression is associated with an increased release of dopamine into the ventral and/or dorsal tegmental areas and/or prefrontal cortex after challenge injection.~~ This increase in extracellular dopamine concentration is positively correlated with the increase in behavioral response [4]. BS expression involves both D1-like and D2-like receptor families in the nucleus accumbens, since blocking D1 [30,31] and D2 receptors [26] prevents locomotor activity generated by challenge injection. Among other neurotransmitter pathways, glutamate has been shown to be involved in the expression of BS, since activation of glutamatergic pathways stimulates dopaminergic neuronal activity. Thereby, dopamine release in the nucleus accumbens and results in behavioral hyperactivity [32]. Serotonin is also involved in the expression of BS via its 5-HT2 and 5-HT3 receptors [33,34].

## **2. BEHAVIORAL SENSITIZATION IN RODENTS**

### **2.1. Experimental protocols**

Some parameters such as animal species, sex, experimental environment, injection procedure, or behavioral assessment may vary with different experimental BS protocols; however, they always include three different phases as follows: acquisition, abstinence (or withdrawal), and expression. It should be noted that the term “abstinence” corresponds in this article to the time

between the acquisition and the expression of the BS. It must be differentiated from the cessation of the chronic administration of drugs and the associated physical symptoms.

Most of the studies were conducted in rats (mainly Sprague-Dawley and only a few on Wistar or Long-Evans rats) and male animals. Only four studies were conducted in females [35–38] and seven in mice: four with psychostimulants [39–42] and three with opioids [43–45] (details of animal species are specified in Tables 1, 2, and 3).

The intraperitoneal (ip) route of administration was mostly used in the studies included in this review, and some used the intravenous (iv) or subcutaneous (sc) route or mixed ip and sc.

In animals, BS is generally observed by measuring the locomotor activity, which is recorded with an actimeter to directly measure horizontal activity. However, other parameters may also be used, including stereotypies [46]. It is noteworthy that the recording period greatly differs among studies, ranging from 10 to 240 mins. To ensure comparability between different groups [41,46–48], some studies recorded basal locomotor activity before the acquisition injection. To evaluate BS acquisition, locomotor activity was assessed after each acquisition injection or at the beginning and end of the acquisition phase. For BS expression, locomotor activity was recorded immediately or a few minutes after the challenge.

An important observation was that the animals that remained in the same cage for the entire study duration required a higher dose to acquire BS. A lower dose was needed for those who changed from their home cage to the test cage prior to substance administration. This implies that the environment has an influence on BS, leading to context-dependent sensitization. To decrease the influence of the environment on BS development, a period of habituation to the test cage is usually provided, as in some cases, habituation to the challenge injection procedure. Moreover, some authors increased the drug doses or increased the exposure for several weeks to obtain a clear-cut, context-independent sensitization. More recently, experiments demonstrated that an enriched environment for mice or rats (including 30 days of motor and sensory activities that animals can freely explore, such as tunnels, running wheels, or various landscapes) could reverse or attenuate an acquired BS compared to standard cage housing [49,50].

## **2.2. Studies that identified BS with Psychostimulants**

### *2.2.1. BS acquisition*

Most of the articles were exclusively related to cocaine, followed by different types of amphetamines [46], including methylphenidate [51], methamphetamine [52], MDMA [53] and modafinil [40]. Four studies were conducted in mice [39–42] the others were conducted in rats.

Administration protocols ranged between 3–15 days, with most studies choosing to administer psychostimulants for durations of 5–8 days. The majority of treatments were administered daily.

Some authors experimented twice a day [53,54], while others experienced intermittent injections, alternating with saline injections, most often every 2 days [41,46,55].

Treatment doses for cocaine ranged from 7.5–40 mg/kg/day ip [56] and up to 40 mg/kg/day sc [47,57]. The most common doses were repeated fixed doses of 10–15 mg/kg/day throughout the acquisition phase; however, at times, incremental doses were used from day 2 [46,47,56,58,59]. Treatment doses for amphetamines and amphetamine-like molecules ranged from 1–4 mg/kg.

### *2.2.2. BS Expression*

The withdrawal period varied from 4 hours [40] to 3 months [8] with a majority of the studies reporting it between 7 and 14 days. Most challenges consisted of a single injection of the drug used in the initial treatment (homologous sensitization). To assess cross-sensitization (or heterologous sensitization), a different drug can be administered [40]. Challenges often used the same dose or half of the priming doses. Higher doses could induce new dose dependent stereotypies, which could be a confounding factor with the locomotor activity to be measured [46]. In some cases, several different challenge doses were used to measure the dose-dependent effect [38,60].

Psychostimulants induced BS in all the studies included in this review. After a challenge dose, the sensitized animals showed an overall increase in locomotor activity as compared to the control group, which previously received saline. However, only one study has detailed BS by individuals: in a group of rats that received cocaine, approximately 50% of the rats developed BS on day 7 [59].

Further, BS is observed for up to 3 months after the acquisition phase [8]. Cross-sensitization between amphetamines and cocaine has also been observed [40].

### *2.2.3. Factors influencing BS*

Despite an important degree of variability in study protocols, trends in some parameters that may influence BS acquisition and expression can be inferred. BS appears to be priming injection dose-dependent [39,40], with higher doses inducing the most robust BS. The treatment pattern also seems to be influential. Indeed, repeated treatment with a 48-hour interval between each injection induced a more robust BS than treatment with daily injections [46,61]. This suggests that withdrawal symptoms occurring between injections, although not specifically measured in those studies, could be a crucial factor for BS acquisition. Finally, another study highlighted the major role of the environment in BS acquisition and expression, and revealed it as a possible confounding factor [60].

## **2.3. Studies that identified BS with opioids.**

### *2.3.1. BS acquisition*

In most studies on BS with opioids, morphine was evaluated (a full mu opioid receptor agonist). Few studies have been conducted with other opioids, such as methadone (a full mu opioid

receptor agonist)[62], buprenorphine (a partial mu opioid receptor agonist)[44] and thenorphine (a partial mu opioid receptor agonist)[43]. Three studies were conducted in mice [43–45], and the others were conducted in rats.

Opioid doses during BS acquisition are mostly fixed, but could also be incremental [45]. The dose of morphine administered via sc was 10 mg/kg/d; however, it may vary from 1–30 mg/kg/d, whereas the dose was between 10 and 20 mg/kg/d when injections were given ip. Methadone doses ranged widely from 1–2 mg/kg/d sc [62] and from 2.5–30 mg/kg/d ip [44,45] in increasing doses. Buprenorphine dose ranged from 0.1 mg/kg/d [44] to 1.2 mg/kg/d ip [45] and thenorphine dose from 0.0625 to 1 mg/kg/d ip [43].

The duration of administration varied from 5–16 days, and one injection per day was administered most frequently. Some studies compared the process of acquiring BS induced by buprenorphine, methadone, or morphine to 1–3 injections per day [45,63]. Finally, a few articles detailed protocols experimenting with a single injection of morphine to perform acquisition [7,64–66].

Partial opioid agonists seem to prevent the acquisition of BS to morphine. Indeed, 7 days of buprenorphine after 7 days of morphine treatment, followed by 7 days of abstinence, blocked the effect of a challenge dose of methadone or buprenorphine on day 15 to promote the expression of BS. Buprenorphine also has a lower propensity to promote BS—when mice received buprenorphine for 5 days, they expressed neither heterologous (morphine challenge injection) nor homologous (buprenorphine challenge injection) BS, with the exception of a single experiment [45].

### 2.3.2. BS Expression

The challenge was mostly a single injection of the same opioid used in the repeated treatment, but sometimes of another opioid [44,45,62]. Challenge doses were almost always lower than priming doses, often by half or less. Indeed, the definition of BS requires the use of a lower dose than that during the acquisition. However, in one study, Johnson and Napier (2000) injected a challenge dose of 10 mg/kg morphine, which was equal to the daily priming injection [67]. Nevertheless, it was stated that the observed motor phenomenon was the expression of the previously acquired BS.

Morphine can trigger BS expression when acquisition is performed with morphine or methadone. Moreover, BS with other opioids is not always observed. Taracha *et al.* (2009) did not observe BS after a challenge injection of 1 mg/kg methadone following methadone pre-exposure [62]. Other BS were observed with escalating methadone doses, and the challenge dose used morphine or methadone [45]. Two consecutive acquisitions of 7 days of morphine and 7 days of methadone treatment ending with a challenge dose of morphine resulted in the expression of BS [44].

The duration of abstinence before expression varied greatly and ranged from 1–35 days, with the majority of the protocols including 7 days of withdrawal.



## **2.4. Studies that identified cross-sensitization between psychostimulants and opioids**

Some studies have investigated the influence of stimulants and opioids on their respective BS based on their ability to induce the same BS phenomenon separately.

### *2.4.1. BS acquisition*

The different protocols for assessing cross-sensitization were bidirectional, as they used opioids for acquisition (heroin [68] or morphine [7,69]) and psychostimulants for challenge (cocaine [68,69] or amphetamine [7,68]) or reversely, used psychostimulants (amphetamine [7]) for acquisition and opioids for expression (morphine [30]). All studies were conducted in rats.

Two studies investigated the effect of the adding nalbuphine (a mixed  $\mu$ -receptor and kappa-receptor opioid agonist) [70] or buprenorphine [71] with psychostimulants on the acquisition and expression of BS. One study used heroin or cocaine iv self-administration to study both BS development and drug-seeking behavior, using an animal model of craving and addiction [68].

The doses used for acquisition were 50  $\mu$ g/kg iv for heroin [68], 2–30 mg/kg sc or ip for morphine [7,69], 10–30 mg/kg sc or ip for cocaine [70,71], 1 mg/kg sc for amphetamine [30] and 1–2 mg/kg for methamphetamine [72,73]. Those doses were escalating in one study [71] and different doses could be compared to each other [7,51,69].

The duration of the acquisition varied from 1–14 [68] (a single morphine injection [7]), most often from 7–10 days. Injections could be once daily, twice daily [72,73] or every 48 hours [30,69].

Two specific studies investigated the effect of prenatal exposure to opioids on BS [72,73]. Male rat offspring were exposed prenatally to methadone 7 mg/kg sc twice a day [72,73], buprenorphine 3 mg/kg sc daily [72] or morphine 2–4 mg/kg sc twice a day [72] opioid treatment from day 3 to day 20 of gestation (17 days). In these two studies, the offspring were given 1–2 mg/kg of methamphetamine ip for 5 days as a sensitization-inducing treatment. One study used a challenge injection of methamphetamine ip after 4 days of abstinence [73].

### *2.4.2. BS expression in cross-sensitization*

Cross-sensitization between morphine or heroin and psychostimulants is both robust and bidirectional. Repeated administration of heroin or morphine increases the locomotor reaction induced by a subsequent cocaine, methamphetamine, or amphetamine injection [14, 61, 62]. Conversely, repeated administrations of psychostimulants increased the locomotor reaction after a subsequent administration of heroin or morphine [14, 21]. As for opioids only, cross sensitization appears to be less potent and less evident with partial  $\mu$ -opioid agonists than with morphine [71]. We did not find any studies in which the protocol included a partial  $\mu$ -agonist repeated treatment to induce BS with a challenge injection of psychostimulants. Moreover, the administration of buprenorphine (3 mg/kg in sc) during the abstinence phase blocked BS that was induced by cocaine [71]. Similarly, during the cocaine acquisition phase, ip administration of 10 mg/kg nalbuphine (a mixed  $\mu$  and kappa opioid agonist) prevented BS acquisition [70].

The duration of abstinence ranged from 48 hours to 21 days. The challenge doses were 0.25 mg/kg sc for heroin [68], 2–5 mg/kg for morphine sc [7,30], 10–15 mg/kg for cocaine ip [68,69,71], 0.5–1 mg/kg for amphetamine ip or sc [7,30,68] and 1 mg/kg for methamphetamine ip [73].

#### *2.4.3. Factors influencing cross sensitization between psychostimulants and opioids*

[Some substances can potentiate cross-sensitization, such as alcohol \[74\]. Indeed, alcohol sensitized mice show a heightened locomotor response to a single methamphetamine \[75\] or cocaine injection\[76\]. In addition, a single morphine pre-exposure enhanced locomotor activity induced by an alcohol injection \[75,77\].](#)

Prenatal exposure to substances seems to promote BS development in adulthood. Rats born from females exposed during gestation to methadone [72,73], buprenorphine [72], or morphine [72] developed BS induced by methamphetamine (with an increase in locomotor activity). Moreover, prenatal exposure to buprenorphine seemed to potentiate BS more than prenatal exposure to methadone or morphine [72].

One study found that undernutrition favored BS development, both with opioids alone and with cross-sensitization. Chronic undernutrition in rats between day 14 of gestation and day 30 postpartum resulted in the development of BS at lower morphine priming doses (from 5 mg/kg/48 h) compared to normally fed rats (from 7.5 mg/kg/48 h). Similarly, undernourished rats developed behavioral cross-sensitization to a challenge injection of 10 mg/kg of cocaine 48 hours after a priming dose of 7.5 mg/kg of morphine, whereas normally fed rats required a priming dose of 15 mg/kg of morphine to develop it [69].

### **3. BEHAVIORAL SENSITIZATION IN HUMANS**

Very few studies have been conducted to assess BS in humans, as we found only three experimental studies [78–80] and one descriptive study [81]. The three experimental studies were conducted by the same team between 1996 and 2008 [78–80]. These three randomized, placebo-controlled, double-blind studies evaluated BS with 0.25 mg/kg oral doses of D-amphetamine. The study population consisted of healthy male and female volunteers aged 18–45 years, none of whom had a cocaine use disorder. Eleven [78,79] and 58 subjects[80] were included, with an average age of 24 years.

#### **3.1. Study protocols**

Subjects in two studies received D-amphetamine doses every 48 hours for four [78] or six days [79]. The third study [80] consisted of a comparison between three groups as follows: one with three administrations of placebo, another with two administrations of placebo followed by a single dose of D-amphetamine, and the third with three doses of D-amphetamine. Doses were administered every 48 hours. The abstinence period was 48 hours after the last oral dose, before receiving a challenge dose of 0.25 mg/kg of oral D-amphetamine.

The activity was measured immediately after each oral dose of D-amphetamine or placebo. The recording was done every hour for 5 hours. To assess locomotor activity, the first study used a score derived from the Young Mania Rating Scale (YMRS), from which three items could be used to quantify the response to amphetamine i.e., energy, speech, and mood level. Eye blinks were also measured manually [78]. In 1998 and 2001, in addition to the previous criteria, the subject evaluated the substance effect through self-report of perceived sensations after taking the drug (mood, vigor, and appreciation of the substance) [79]. In 2001, these self-questionnaires to assess the subjective effects following substance administration used the "Profile of Mood States" (POMS) and "Addiction Research Center Inventory" (ARCI) scales, which measured vigor/energy, mood level, and substance appreciation. Activity was measured after placebo or amphetamine intake [80].

### **3.2. Main outcomes**

Activity increased significantly between the first and second doses of amphetamine [78–80], and was even greater after the third dose [79,80] mainly in terms of energy level and eye blinking rather than mood and speech levels. At 2–4 hours after the second dose administration, all four activity score items were significantly higher and prolonged as compared to that of placebo or the first dose of D-amphetamine [78]. The results of the third study were less conclusive. Participants who received three doses of D-amphetamine reported a higher subjective measure of amphetamine effect, but the objective measure of blink rate was greater in participants administered with a single dose of D-amphetamine than in those administered all the three doses, which was suggestive of tolerance [80]. All human studies included both women and men. The sample sizes of the first two studies precluded any conclusion based on gender. In the 2001 study, the subjective drug effects after acquisition were reported to be higher in women than in men, but not the eye-blinking response [80].

Our collaborative research team also demonstrated indirect cues of BS in a sample of almost 400 human subjects with multiple substance use disorders recruited from an addiction care setting [81]. In this cross-sectional study, we used self-rated scales assessing both childhood and adult behavior (ASRS [82] and WURS [83] scales), which is intended to screen for adult and childhood hyperactivity and attention deficit disorder. We showed a "gradient effect" between lifetime exposure to cocaine and the score on those scales. Notably, the gradient effect was also observed in patients exempt from significant childhood behavioral disturbances; therefore, we can confidently state that those behavioral disturbances were acquired after the initiation of cocaine use. Because this questionnaire (ASRS) assessed permanent behavioral disturbances (motor impulsivity, planning deficiency, attention deficiency) even in the absence of immediate cocaine use, we concluded that they indirectly reflected a BS to cocaine use [81]. Conversely, according to a gradient of exposure to opioids, participants had lower scores in that sample. As these data are retrospective and recorded during cross-sectional self-rated assessments, the next step would be to record objective measures with actigraphy coupled with real-time drug use assessment.

Considering BS in human participants with cocaine dependence would have direct treatment implications. First, as cross-sensitization is observed between cocaine and amphetamines, the

existence of BS in some subjects could lead to a sensitized motor response to amphetaminic treatments and explain the failure of previous pharmacological trials with amphetamines proposed in a substitution approach [84]. Furthermore, in patients expressing BS, BS itself could constitute a therapeutic target in a harm reduction approach with specific pharmacological probes. As no pharmacological treatment has proven effective in treating cocaine dependence, understanding BS would provide keys to the development of therapeutic strategies.

Translational studies targeting BS in humans with cocaine dependence could be guided by rodent models of BS for use as a screening tool among several pharmacological probes. For example, a recent study showed that long-acting D-amphetamine co-administration suppressed BS induced by intermittent cocaine self-administration [85]. Other studies showed that BS to cocaine and methamphetamine is antagonized by buprenorphine [71].

Notably, human studies attempting to demonstrate the occurrence of BS are scarce, and are limited to studies in healthy volunteers who have a history of amphetamine use but did not meet the dependence criteria at the time of the study. The protocol of psychostimulant administration used in human studies is far from the use pattern in chronically cocaine-dependent patients. Thus, there is an urgent need to identify the presence or absence of BS in this population.

#### 4. CONCLUSION AND PERSPECTIVES

We reviewed the preclinical and clinical literature on BS induced by psychostimulants and opioids. In preclinical studies, all protocols included three different phases of BS (acquisition, abstinence, and expression) with slight variations. These variations could be attributed to the nature and duration of the acquisition phase, interval between injections, duration of abstinence, and nature of the challenge injection.

Despite the relatively ancient discovery of this phenomenon, the last studies use more complex protocols, and attempt to move from descriptive phenomena to pharmacological challenges, such as those described in the cross-sensitization section of this article or environmental modifications to reverse or attenuate BS [50].

Overall, BS is a general phenomenon that seems to be induced by all classes of psychostimulants. However, the results are less robust with different opioid agents. Only morphine induces BS in a consistent and dose-dependent manner. Moreover, all experiments that observed behavioral cross-sensitization between opioids and psychostimulants were performed with morphine. It can be hypothesized that this is due to the pure  $\mu$ -agonist nature of morphine or its short half-life. It is possible that the signaling pathways and neurobiological rearrangements are different with short and intense stimulations as compared to longer stimulations. Furthermore,  $\mu$ -partial agonists could block the acquisition of BS from morphine and have a lower ability to promote BS, which invites research perspectives to address BS in human participants.

As human studies in this regard are scarce and inconclusive, using a translational research agenda to perform useful clinical studies requires several steps. First, confirming the presence

of BS in humans is still needed, especially in patients meeting substance use disorder criteria and those using novel objective measures of locomotion and BS. Furthermore, subjects with severe cocaine and opioid use disorders could present an intermittent use pattern with variable doses, which does not correspond to the preclinical and clinical BS models that we listed in this review. [Furthermore, as alcohol seems to potentiate BS, and patients with cocaine or opioid use disorders often present alcohol use disorders, co-addiction and co-morbidities should be taken into account.](#) Upon meeting these criteria, we would be able to test pharmacological probes suggested by preclinical models to address BS. These pharmacological strategies would allow for the treatment of behavioral disturbances and decrease the burden on the patients.

**Table 1.** Behavioral sensitisation cocaine or amphetamine-induced in murine models.

Author Year Journal Reference	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
<b>Peris et al. 1991</b> <i>Brain Research</i> [35]	Female Sprague-Dawley rats Ovariectomy and steroid tt implantation (randomly: Estradiol, Progesterone, EP, Vehicle) Randomization: (Veh, E, P or EP)-(Sal or Coc) N= 12-14 per group	D-2-D0: saline ip inj D1-D8: saline or cocaine 10mg/kg, ip inj 1x/day	Home cage except for D1&D8 in test cage	No	No	Locomotor activity (locomotion) and stereotypy rating by a blind observer, for 50min after inj in D1 and D8  D1: <b>BS+ in Cocaine groups</b> , whatever steroid group (E-Coc, P-Coc, EP-Coc, Veh-Coc) D8: BS+ in Cocaine groups, whatever steroid group. <b>Major BS+ in EC group</b>	Estradiol → increased dopamine release → increased BS+ induced by cocaine
<b>Kalivas et al. 1992</b> <i>Ann NY Acad Sci</i> [58]	Rats	Exp1 & 2: D1: saline or cocaine 15mg/kg ip inj D2-D6: saline or cocaine 30mg/kg ip inj, 1x/day Exp2: D7-D18/D22: drug free D18/D22: challenge dose	BS measure unspecified on D2 (Exp1) and on D18-D22 (Exp2) Extracellular dopamine levels measured in VTA and NAc	Exp1: 1 day Exp2: 11-15 days	Exp1: no Exp2: D18-D22: cocaine 15mg/kg ip inj	BS+ in cocaine groups (data not shown)	Exp1: in cocaine groups, dopamine level increased in VTA after 1 day withdrawal; and in NAc after 11-15 days withdrawal  VTA involved in BS development NAc involved in BS expression
<b>Tzschentke et Schmidt 1998</b> <i>Brain Research</i> [61]	Male Sprague-Dawley rats, 280-320g. Surgery with saline “non-lesion (PBS)” or quinolinic acid “lesion (QuinA)” inj in PL mPFC  Randomization: (PBS or QuinA)-(Sal or Coc) N=10 per group	10 days recovery after surgery  D1-D14: saline or cocaine 10mg/kg ip inj, 1x/day D15= drug-free D16= challenge dose	Habituation in “open space” and “test cage” for 10min/days 2 days before Exp D1, D16: inj followed by 10min in home cage, 10min in open space and 10min in test cage D2-D14: home cage after inj	D14-D16: 48h	D16: cocaine 10mg/kg ip	Locomotor (number of lines crossing) and sniffing activities rating at D1 and D16  Open space: Locomotion: BS+ in PBS-Coc group Rearing: BS+ in PBS-Coc group Grooming: BS+ in QuinA-Coc group  Sniffing-room: Sniffing: BS+ in QuinA-Coc group Up-sniffing: BS+ in PBS-Coc group Down-sniffing: BS+ in Cocaine groups (QuinA and PBS)	Prelimbic area (PL) of mPFC involved in BS development. Glutamatergic afferences from PL to NAc and VTA

Abbreviations: 18MC = 18-methoxycoronaridine, AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, Coc = cocaine, D1/D2 = dopaminergic, E = estradiol, Exp = experience, GSK-3b = glycogen synthase kinase 3b, ILK = integrin-linked, inj = injection, ip = intra peritoneal, iv = intravenous, LiCl = lithium chloride, METH = methamphetamine, MPEP = 6-methyl-2-(phenylethynyl)-pyridine, mPFC = medio prefrontal cortex, NAc = nucleus accumbens, Nic = nicotine, P = progesterone, PI3K= phosphatidylinositol 3 kinase, PL= prelimbic area, pre-ttt = pre-treatment, QuinA = quinolinic acid, Rc = receptor, Rim = Rimonabant, sc = subcutaneous, Sal = saline, ttt = treatment, Veh = vehicle, VTA = ventral tegmental area

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<b>Tzschentke 2000</b> <i>Cereb Cortex</i> [46]	Male Sprague-Dawley rats, 250-300g Surgery with saline "non lesion (PBS)" or quinolinic acid "lesion (QuinA)" inj in various mPFC sub-regions  Randomization: Exp1: (PBS or QuinA)-(Sal or Coc) Exp2: (PBS or QuinA)-(Sal or AMPH) N=10 in each group	11-14 days recovery after surgery  D1: saline or cocaine 10mg/kg or DL-AMPH 1.5mg/kg D2-15: saline or cocaine 20mg/kg ip inj 1x/day or DL-AMPH 4mg/kg, ip inj x1/48h D16: challenge dose D16-D30: drug free D30: challenge dose	D0: 10min habituation in "open space" and "sniffing box" D2,4,6,8,10,12,14= saline, cocaine 20mg/kg or DL-AMPH 4mg/kg inj D1,3,5,7,9,11,13: no inj, monitoring for 10min in "open space" and 10min in "sniffing-box"	24h or 14 days	D16 or D30 Exp1: cocaine 10mg/kg Exp2: DL-AMPH 1.5mg/kg	Locomotor and sniffing activities rating at D1 and D16  Exp1: Similar results as 1998's study BS+ in Cocaine groups (PBS or QuinA) at D1, D16 and D30 for locomotion and up-sniffing BS+ in saline groups (PBS or QuinA) at D16 and D30 for down-sniffing  Exp2: BS+ in AMPH groups (PBS or QuinA), at D1, D16 and D30 for locomotion, rearing, up and down sniffing	PL areas of mPFC involved in BS cocaine-induced initiation (but not in BS AMPH-induced) Infralimbic area neither ACC are involved in BS
<b>Sircar 2000</b> <i>Brain Research</i> [36]	Male Sprague-Dawley rats, 180-225g.  Randomization: (Sal or Coc)-(Mel or Veh)	Exp1: D1-5: saline or cocaine 15mg/kg ip inj x1/d D6-D18: drug free D19: by melatonin (Mel) 30mg/kg or vehicle (Veh) sc inj 15min and right before challenge dose inj  Exp2: D1-5: pre-ttt by Mel or Veh followed by saline or cocaine 15mg/kg ip inj x1/d D6-D18: drug free D19: no challenge dose	Exp1&2: Inj in test cage	D6-D18: 14 days	Exp1: D19: cocaine 15mg/kg ip inj	Stereotypy behaviors rating by blind observer on D1, D2, D5 and D19  Exp1: BS+ in Coc-Mel group  Exp2: BS+ in Coc-Veh group. BS+ alleviated in Coc-Mel group	Melatonin: trends to alleviate the BS cocaine-induced
<b>Szumilinski et al. 2000</b> <i>Brain Research</i> [38]	Female Sprague-Dawley rats, 200-225g  18MC= synthetic ibogaine derived  Exp1: Randomization: (Sal or Coc)-(Veh or 18MC)-(Coc 0, 10, 20 or 40) N=84	Exp1&2: D1-D5: Saline or Cocaine 15mg/kg x1inj/d D6-18: drug free D19: vehicle or 18-MC 40mg/kg  Exp1: D20: challenge dose  Exp2:	Exp1&2: D1-5: habituation in "test cage" for 30min after a saline inj before each inj  Exp1: Locomotor behavior monitoring for 2h after challenge dose at D20  Exp2:	D6-D18: 14 days	Exp1&2: D19: 18-MC 40mg/kg or vehicle inj  Exp1: D20: Cocaine 0, 10, 20 or 40mg/kg IP  Exp2:	Exp1 (locomotor activity) D1-D5: BS+ in Cocaine vs saline chronic ttt group D20: BS+ in cocaine vs saline challenge dose increased when 18-MC (18-MC+C group)  Exp2 (stereotypy): D1-D5: BS+ in Cocaine vs saline group D20: BS+ in Cocaine 40mg/kg group vs Cocaine 20mg/kg, BS++ in Cocaine and Saline+ 1-MC group	18-MC potentialize BS expression with cocaine repeated inj. 18-MC distorts the NAc extracellular dopaminergic answer. There is a dissociation between BS cocaine-induced and dopamine's extracellular level induced by cocaine

	Exp2: Randomization: (Sal or Coc)-(Veh or 18MC)-(Coc 20 or 40) N=48	D20: challenge dose	Stereotypy rating for 30sec at repeated intervals, during 15 to 20min recording sessions		D20: Cocaine 20 or 40mg/kg IP		
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<b>Uz et al. 2002</b> <i>Life Sciences</i> [39]	C5BL/6J (AANAT mutant) and C3H/HeJ male mice, 8 weeks old, 25-30g N=12	D1-D3: saline or cocaine 10 or 20mg/kg or saline, inj at Day and Night	30min habituation in "test cage" + 30min test session before inj, followed by 30min test session	No	No	Locomotor activity monitoring (total beam breaks)  Mutant mice: BS+ day and night, dose-dependent Normal mice: BS+ at day, dose dependent. BS- at night	AANAT mutation = mutation of melatonin synthesis enzyme predominantly expressed in pineal gland → alteration of melatonin, melatonin's metabolites, and others pineal serotonin metabolites → modification of cocaine's action
<b>Izzo et al. 2002</b> <i>Nature Neurosciences</i> [86]	Exp1&2: Male Wistar rats  Exp1&2: (PI3K inhibitor or Veh)-(Sal or Coc) groups  Exp2: rats with cocaine induced BS+ at D5 N= 30  PI3K= enzyme involved in expression of long-term synaptic potentiation	Exp1: D1-D5: pre-ttt by PI3K inhibitor or vehicle ICV 20min before cocaine 15mg/kg or saline ip, 1x/d D6-15: drug free D15: dose challenge  Exp2: D1-D5: cocaine 15mg/kg IP 1x/day, no pre-ttt D6-D15: 10 days withdrawal D15: randomization for pre-ttt by PI3K inhibitor or vehicle ICV 20min before challenge dose D16-D22: drug free D22: challenge dose without pre-ttt	Exp1&2: Test cage for 3h after cocaine/saline inj on D1-D5 & D15	Exp1: D6-D15: 10 days Exp2: D6-D15: 10 days + D16-D22: 7 days	Exp1: D15: cocaine 15mg/kg  Exp2: D15: cocaine 15mg/kg D22: cocaine 15mg/kg	Locomotor activity monitoring (total beam breaks) Exp1: D5 vs D1: BS+ in cocaine/vehicle group BS- in cocaine/PI3K inhibitor group D15: BS+ in cocaine/vehicle and cocaine/PI3K inhibitor groups  Exp2: D15: BS- in cocaine/PI3K inhibitor D22: BS+ in both groups (cocaine/vehicle or cocaine/PI3K/inhibitor at D15)	Signal pathway of PI3 Kinase is involved in cocaine BS+ expression PI3K inhibitor produces a reversible BS expression blockage; but is not involved in development neither long-term maintain of BS cocaine induced



<b>Capper-Loup et al. 2002</b> <i>Journal of Neurosciences</i> [54]	Male Sprague-Dawley rats, 250-350g Exp1: N=56 Exp2: N=49	Exp1: D1-agonist 1 or 3 mg/kg ip combined with D2-agonist 1, 3 or 9mg/kg ip OR D1-agonist 3mg/kg ip OR D2-agonist 3mg/kg ip OR saline, 1x/day  Exp2: D1-D7: cocaine 25mg/kg or saline inj 2x/day for 7 days D8: challenge dose	Exp1: Stereotyped behavior rating at 20 and 50min after ttt Exp2: daily stereotypies rating  Inj in home cage	<b>Exp1:</b> No <b>Exp2:</b> 24h	<b>Exp 1:</b> No <b>Exp 2:</b> D8: D1-agonist 6mg/kg OR D2-agonist 6mg/kg OR D1&D2-agonists combined (3mg/kg each) inj ip	Locomotor activity monitoring by stereotypy rating Exp1: BS- when D1-agonist or D2-agonist ALONE BS+ when D1&D2-agonists combined, whatever their doses  Exp2: BS+ with cocaine repeated inj BS+, not decreased with D1&D2-agonist challenge BS+ decreased with D1 OR D2-agonist alone	Challenge inj of D1&D2-agonist combined leads to a significant increase of stereotypies and prevailing expression of c-Fos striosom's genes in striatum and involving the circuits of basal ganglia
<b>Davidson et al. 2002</b> <i>Eur J of Pharmacology</i> [56]	Male Sprague-Dawley rats, 200g N= 40	D1: cocaine 7.5mg/kg inj ip D2-D7: cocaine 40mg/kg 1inj/d sc D8-D14: drug free D15: challenge dose D16-D21: cocaine 40mg/kg 1inj/d sc D22-D30: drug free D31: challenge dose	Before D1: habituation for 7 days D15&D31: locomotor activity monitoring in "test cage" for 1h	D8-D14: 7 days D22-D30: 9 days	D15: cocaine 7,5mg/kg ip D31: cocaine 7,5mg/kg ip	Locomotor activity monitoring (rating by an observer) D31 BS+ > D15 BS+ « Passive » behaviors: D15 > D31 « Hyperactive / stereotypy »: D31 > D15	No

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<b>Li et al. 2004</b> <i>Eur J of Neuroscience</i> [60]	Male Sprague-Dawley rats, 200-225g Exp1 groups: Novel-Coc, Novel-Sal, Home-Coc, Home-Sal N=40 Exp2: N=23	<b>Exp1:</b> D1-D8: saline or cocaine 15mg/kg, ip inj, 1x/day  <b>Exp2:</b> D1: saline or cocaine escalating doses 7.5, 15 and 30mg/kg, 1h between two inj. D2-D8: saline or cocaine 30mg/kg, 1x/day D9: saline or cocaine escalating doses 7.5, 15 and 30mg/kg, 1h between two inj.	Exp1: habituation for 7 days previous randomization in "Home" or "Novel" groups. "Home" = test cage for 7 days, "Novel" = test cage for Exp1. Inj after 60min of habituation in test cage and monitoring for 90min after inj  Exp2: habituation for 7 days before inj in home cage	<b>Exp1:</b> No <b>Exp2:</b> 24h	<b>Exp1:</b> No  <b>Exp2:</b> escalating doses at D9 (7.5, 15 and 30mg/kg)	Locomotor activity monitoring (cage crossovers): <b>Exp1:</b> BS+ between D8 and D1 for Novel-Cocaine group but not in Home-Cocaine group  <b>Exp2:</b> BS+ at D1 for 30mg/kg cocaine dose BS+ at D9 from 15mg/kg cocaine dose	BS induction associated with structural neuroplasticity in mPFC and NAc core (major neuronal density) and not in NAc shell
<b>Ramos et al. 2005</b> <i>Behavioral Brain Research</i>	Males Wistar rats, 260-300g N=?	D1: saline inj D2: saline or MDMA 5mg/kg ip (morning) + saline or MDMA 10mg/kg ip (evening)	Inj at 7 and 10p.m. Monitoring between 9a.m. and 2p.m.	12 days (D7-D17)	D18: MDMA 5mg/kg ip	Locomotor activity monitoring (total distance) at D2, D3, D6 and D18 for 105min after inj.	Dorsal mPFC involved in MDMA BS development

[53]	Ibotenic acid lesion in dorsal mPFC or “sham” lesion at D-5 or D11	D3-D6: saline or MDMA 15mg/kg ip x2/d D7-D17: drug free D18: challenge dose	D1: 2h habituation in test cage after saline inj			BS+ for sham-MDMA group between D3 and D6, and between D2 and D18 BS- for lesioned rats	
<b>Zhang et al. 2007</b> <i>Neuropsychopharmacology</i> [47]	Male Sprague-Dawley rats, 150-200g Cocaine: N=12-15 per group, 3 groups ranked according to their behavioral response to cocaine 1 <sup>st</sup> inj Saline: N=18-22 per group, randomized in 3 groups  Pergolide = D1/D2 receptor agonist Ondansetron = 5-HT3 receptor antagonist DMSO = vehicle	<b>Cocaine groups (C-):</b> D1: cocaine 7.5mg/kg sc, D2-D5: cocaine 40mg/kg sc <b>Saline groups (S-):</b> D1-D5: saline inj  <b>C &amp; S- groups:</b> D6-D14: drug free D15-D19: pergolide/saline (P/S) OR pergolide/ondansetron (P/O) OR DMSO/saline (D/S), x2/day D20-28: drug free D29: challenge dose	Habituation for 7 days in vivarium before D1 D29: habituation for 30min before challenge dose inj in test cage. Monitoring for 60min	D6-D28= 24 days (D15-D28 with P/S, P/O or D/S)	D29: cocaine 7.5mg/kg IP	Locomotor activity monitoring by behavioral ratings and photobeam-breaks (ambulation), 60min after D29 challenge inj  BS+ (ambulation & stereotypy) for C-D/S and C-P/S groups Major BS+ for C-D/S group	BS+ associated with increasing of NR2B unit of NMDA-R expression in NAc-shell. Expression of NRB2 is modified by the association of Pergolide and Ondansetron
<b>Scheggi et al. 2007</b> <i>J of Neurochemistry</i> [8]	Males Sprague-Dawley rats, 125-150g ExpA-1: N=5-32 per group  MPEP = mGluR5 receptor antagonist	D1-D8: cocaine 10mg/kg or saline inj ip, 1x/day D9-D18: drug free <b>ExpA-1:</b> D19: challenge dose (cocaine group + 10 controls) D29: challenge dose (5 cocaine and 5 controls) <b>ExpA-2:</b> D29: challenge dose <b>ExpA-3:</b> D29: MPEP 5mg/kg or saline ip + challenge dose  <b>ExpB:</b> D19: challenge dose (cocaine group + 5 controls) 3 months drug free M3: challenge dose	Habituation for 7 days in vivarium before D1. After each inj, “test cage” session for 35min	<b>ExpA:</b> 10 or 20 days <b>ExpB:</b> 10 days and 3 months	<b>ExpA-1:</b> D19: cocaine 10mg/kg ip D29: cocaine? mg/kg <b>ExpA-2:</b> D29: cocaine 10 or 20mg/kg <b>ExpA-3:</b> D29: cocaine 10mg/kg  <b>ExpB:</b> D19: cocaine 10mg/kg M3: cocaine 10mg/kg	Locomotor activity and stereotypy monitoring for 30min at D19 ExpA-1: BS+ in cocaine group for stereotypy, rearing and locomotor activity ExpA-2: BS+ in cocaine group for stereotypy ExpA-3: BS-  ExpB: D29: BS+ in cocaine group for stereotypy, rearing and locomotor activity M3: BS+ in cocaine group for stereotypy	BS expression can least after a long-term withdrawal but diminished. Modification of dopamine receptor D1/DARPP-32/PKA pathway in mCPF, is major after 10 days withdrawal compared to after 3 months withdrawal

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<b>Wooters et al. 2008</b> <i>J of Neuropsychopharmacology</i> [51]	Males Sprague-Dawley rats, 250-275g Randomization: Nic0.2, Nic0.4, Nic0.8 or Sal N=16 per group	D1-D10: nicotine 0.2, 0.4 or 0.8mg/kg or saline inj sc, 1x/day D11-D24: drug free D25-D27: challenge dose	D0: habituation in test cage for 60min D1-D10: locomotor activity monitoring for 60min after each inj	D11-D24: 14 days	D25-D27: methylphenidate 2.5mg/kg	Locomotor activity monitoring= total distance travel for 60min after each inj (D25-D27) BS+ when nicotine for D1-D10, but not at D25-27 when saline challenge doses (BS+ dose dependent) BS+ at D25-27 when methylphenidate challenge (BS+ nicotine priming dose dependent)	No Conclusion: nicotine helps the BS development
<b>Chen et al. 2008</b> <i>J of Neurochemistry</i> [57]	Males Sprague-Dawley rats, 125-120g N=70 Randomization in 2 groups: microinjection in NAc core by viral vector iLK inhibitor (siLK) or blank viral vector (GFP) ILK = kinase up-regulated in NAc core and mPFC in cocaine-sensitized rats	D1-D7: siLK groups: cocaine 40mg/kg or saline inj sc D8-D15: drug free D16-D29: Doxycycline ttt (in drinking water), 2ml/L/day D30: challenge dose	Habituation for 7 days in vivarium after surgery. Test cage for 15min before and 60min after each inj	22 days: 8 days withdrawal + 14 days with doxycycline in drinking water	D30: cocaine 15mg/kg ip	Locomotor activity monitoring (ambulation) and behavioral rating Ambulation: BS+ for C-GFP group; BS- for C-siLK group Stereotypy: BS+ for C-GFP and C-siLK groups	Involvement of Integrin Linked Kinase (ILK) in NAc core in induction of BS. Involvement of ILK in neuronal plasticity by increasing of dendritic density in NAc
<b>Lee et al. 2009</b> <i>Neuroscience Letters</i> [87]	Male Sprague-Dawley rats, 260-270g Randomization in 11 groups N=6 per group	D1-D10: saline or cocaine 15mg/kg ip D11-D13: drug free D14: challenge dose	Habituation for 7 days in home cage Habituation for 1h in test cage before each inj Locomotor activity monitoring for 1h after each inj	D11-D13: 3 days	D14: cocaine 15mg/kg ip	Locomotor activity monitoring (total distance travel) BS++ in Coc-Coc group BS – in HT7 acupuncture dot group	BS cocaine-induced is associated with an increase of Tyrosine kinase expression in VTA  HT7 acupuncture dot prevents BS cocaine-induced expression and prevents Tyrosine kinase expression in VTA
<b>Boudreau et al. 2009</b> <i>J of Neurochemistry</i> [59]	Males Sprague-Dawley rats, 250-275g	D1: cocaine 15mg/kg or saline ip D2-D6: cocaine 30mg/kg or saline ip D7: cocaine 15mg/kg or saline ip	Habituation for 10 days in vivarium D0: habituation for 20min in test cage D1: habituation for 20min before inj, locomotor activity monitoring for 2h D2-D6: inj in home cage	Locomotor activity monitoring= No Biochemical analysis after 1day, 7days or 2days of withdrawal	No	Locomotor activity monitoring (total distance travel) for 2h after inj on D7  Between D1 and D7, BS+ in nearly 50% of cocaine pretreated rats	Increasing of AMPA-R surface expression in NAc in rats with cocaine BS+. Involvement of ERK2, CAMKII and PKA pathways in NAc

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<p><b>Valjent et al., 2010</b> <i>Neuropsychopharmacology</i> [28]</p>	<p>Male 8-week-old C57BL/6J mice</p>	<p>Exp 1 : D0: saline or cocaine 20 mg/kg, ip</p> <p>Exp 2: Pre-ttt by saline, SCH23390 (D1/D5 receptor antagonist) 0.1 mg/kg, ip, haloperidol 0.5 mg/kg or raclopride 0.3 mg/kg. D0: cocaine 20 mg/kg, ip</p> <p>Exp 3: cocaine 20 mg/kg ip or GBR12783 (Dopamine transporter blocker) 15 mg/kg ip</p> <p>Exp 4: Pre-ttt by saline or MK801 (NMDA antagonist) 0.15 mg/kg, ip. D0: cocaine 20 mg/kg, ip</p>	<p>Habituation to the test apparatus, handling, and injection procedure for 3 consecutive days before. Challenge injection in the same environment than acquisition injections</p>	<p>Exp 1: 2 to 84 days</p> <p>Exp 2, 3, 4: 7 days</p>	<p>Exp1 D2 to D84: cocaine 20 mg/kg, ip</p> <p>Exp 2: D7 cocaine 20 mg/kg, ip</p> <p>Exp 3: D7: cocaine 20 mg/kg ip or GBR12783 15 mg/kg ip</p> <p>Exp 4: D7 cocaine 20 mg/kg, ip +/- MK801 0.15 mg/kg, ip before D7</p>	<p>Exp 1: Locomotor activity increased at all time points in cocaine/cocaine group. Sensitization ration increase between D2 D7 and decreased to remain stable at D56 and D84</p> <p>Exp 2: no BS with SCH23390. No effect of haloperidol or raclopride pre-ttt</p> <p>Exp 3: BS- in GBR12783/GBR12783 mice BS+ in GBR12783/cocaine and in cocaine/GBR12783 mice</p> <p>Exp 4: BS- when MK801 pre-ttt. BS+ when MK801 before challenge dose</p>	<p>Exp 1: a single cocaine exposure induces a behavioral sensitization that is long-lasting and increases during the first week</p> <p>Exp 2: Strong evidence that the induction of locomotor sensitization by a single cocaine exposure requires dopamine D1 receptors.</p> <p>Exp 3: dopamine is sufficient to induce context-dependent locomotor sensitization, but that other monoamines may be involved in its full expression</p> <p>Exp 4: NMDA receptors are essential for the induction of sensitization, not for its expression.</p>
<p><b>Xu et al. 2011</b> <i>J of Neurochemistry</i> [52]</p>	<p>Male Sprague-Dawley rats, 220-240g N= 220</p> <p>Randomization in 2 groups IP inj Exp2,3,4: microinj in NAc core or NAc shell. 5-7 days recovery before Exp</p> <p>GSK3b = enzyme involved in dopamine-mediated behavior SB216763 = GSK3b inhibitor</p>	<p>Exp1: D-2-D0: saline D1-D14: saline or METH 1mg/kg D15-D19: drug free D20: saline or LiCL 100mg/kg before challenge dose</p> <p>Exp2,3,4: D1-D14: vehicle or LiCL 100mg/kg or SB216763 30min after saline or METH</p>	<p>Test cage for 2h after each inj</p>	<p>D15-D19: 5 days</p>	<p>D20: METH 1mg/kg ip</p>	<p>Locomotor activity monitoring (total distance travel) for 2h after each inj</p> <p>D1-D14: BS+ in Sal+METH group BS- in LiCl(NAc core)+METH group BS+ alleviated in SB(NAc core)+METH group BS+ not alleviated in SB(NAc shell)+METH group</p> <p>D20: BS+ alleviated in LiCL(NAc core)+METH group compared to Sal+METH group</p>	<p>BS METH-induced is related with an increasing of GSK3b activity in NAc core.</p> <p>The SB216763 and LiCl antagonists alleviate or inhibit the BS when injected in NAc core (but not in NAc shell)</p>
<p><b>Kupferschmidt et al. 2012</b> <i>British J of Pharmacology</i> [48]</p>	<p>Males Wistar rats, 275-300g N=55</p> <p>Inj in right lateral ventricle of AM251 agonist CB1 and/or CRF 7days recovery period</p> <p>Groups according to average level of activity at D0</p>	<p>D2: cocaine 15mg/kg or saline ip inj D3-D7: cocaine 30mg/kg or saline ip inj 1x/day D8: cocaine 15mg/kg or saline ip inj D9-D20: drug free D21: AM251 0, 10 or 100µg, icv and challenge dose</p>	<p>D0: habituation in test cage for 60min before and 120min after a saline ip inj D2&amp;D8: habituation for 60min before inj D21, D24, D27: habituation for 60min before 120min monitoring</p>	<p>D9-D20: 12 days</p>	<p>D21, D23, D25: pre-ttt by AM251 0, 10 or 100 µg icv + 30min after a challenge dose of CRF 0.5 mg icv, cocaine 15mg/kg ip or saline icv</p>	<p>Locomotor activity monitoring (total distance travel), during 60min before and 120min after inj</p> <p>BS+ if saline before CRF and cocaine challenge BS- is AM251 10 or 100 µg before CRF and cocaine challenge</p>	<p>Involvement of cannabinoid CB1-R and corticotropic axis (CRF) in BS expression. AM251 antagonist of CB1-R prevent BS expression after a challenge dose of cocaine or CRF in cocaine pre-exposed rats</p>

<b>Khroyan et al. 2015</b> <i>Biochem Pharmacol</i> [55]	Male ICR Charles Richers rats, 6weeks old, 25-30g N=8-10 per group	<b>Exp1-4:</b> “drug sessions” 1day/2 and “vehicle sessions” 1day/2 <b>Exp1:</b> “drug sessions” with AT-1001 0.3-10mg/kg or AT-1012 1-10mg/kg sc inj <b>Exp2:</b> “drug sessions” with cocaine 1, 5, 10 20, or 30mg/kg sc inj <b>Exp3:</b> “drug sessions” with AT-1001 0.3, 1, 3 or 10mg/kg or AT-1012 1, 3, or 10mg/kg sc inj before cocaine 5mg/kg inj <b>Exp4:</b> “drug sessions” with AT-1001 0.3, 1, 3 or 10mg/kg sc inj before cocaine 30mg/kg inj	Habituation for 3-4 days before Exp1 Habituation in test cage for 1h before inj	No	No	Locomotor activity monitoring by behavioral ratings, for 30min avec inj  <b>Exp1:</b> BS- for AT-1001 3 OR 10mg/kg and for AT-1012 10mg/kg groups <b>Exp2:</b> BS+ for cocaine 20 OR 30mg/kg groups <b>Exp3:</b> BS+ for groups with pre-ttt by AT-1001 0-3mg/kg OR AT-1012 0-3mg/kg. BS- after pre-ttt by AT-1001 10mg/kg OR AT-1012 10mg/kg <b>Exp4:</b> BS+ for groups with pre-ttt by AT-1001 0-3mg/kg. BS- after pre-ttt by AT-1001 10mg/kg	Involvement of $\alpha 3\beta 4$ nAChR (Acetylcholine nicorinic receptor) in BS AT-1001 and AT-1012 antagonist ligands prevent cocaine BS
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Abbreviations: 18MC = 18-methoxycoronaridine, AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, Coc = cocaine, D1/D2 = dopaminergic, E = estradiol, Exp = experience, GSK-3b = glycogen synthase kinase 3b, ILK = integrin-linked, inj = injection, ip = intra peritoneal, iv = intravenous, LiCl = lithium chloride, METH = methamphetamine, MPEP = 6-methyl-2-(phenylethynyl)-pyridine, mPFC = medio prefrontal cortex, NAc = nucleus accumbens, Nic = nicotine, P = progesterone, PI3K= phosphatidylinositol 3 kinase, PL= prelimbic area, pre-ttt = pre-treatment, QuinA = quinolinic acid, Rc = receptor, Rim = rimonabant, sc = subcutaneous, Sal = saline, ttt = treatment, Veh = vehicle, VTA = ventral tegmental area

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
<b>Liu et al. 2016</b> <i>Pharmacology, Biochemistry and Behavior</i> [88]	Male Sprague-Dawley rats, 280-350g N=24 per group  D-serine = NMDA-R agonist	D1-D6: saline or cocaine 15mg/kg ip D6-D20: drug free D20: D-serine or D-serine antagonist ip inj followed 1h after by challenge dose	Habituation for 7 days in home cage D1-D6, D20: test cage just after each inj	D6-D20: 14 days	D20: cocaine 15mg/kg, 1h after D-serine or D-serine antagonist ip inj	Locomotor activity monitoring (total distance travel) for 60min after each inj D1-D6: BS+ in cocaine vs saline group D20: BS- in D-serine 30 and 100mg/kg ip inj 1h before cocaine dose challenge groups Same results if D-serine micro-inj directly in NAc	BS cocaine-induced is associated with dose-dependent decreasing of D-serine expression Deterioration of D-serine synthesis enzymes Involvement of ERK-CREB-Fos transduction pathway in the effect of D-serine on BS
<b>Wuo-Silva et al. 2016</b> <i>Frontiers in Pharmacology</i> [40]	3-month-old Swiss EPM-M2 mice, 40-45g Repartition in groups according to their basal locomotor activity N=12 per group (Total N=84 for Exp1, 5, 6)	Exp1&5&6: D1-D3: habituation  <b>Exp1:</b> D4: by modafinil 64mg/kg or vehicle ip inj + challenge dose  <b>Exp5:</b> D4: by modafinil 64mg/kg or vehicle ip inj + challenge dose  <b>Exp6:</b> D4: by cocaine 20mg/kg or saline ip inj + challenge dose	Exp1&5&6: D1-D3: habituation for 10min in “open field” and to inj session D4: Priming + challenge dose after 4h + locomotor activity monitoring after 30min (Exp1&6) or 5min (Exp5)	Exp1&5&6: D4: 4h between priming and challenge dose	<b>Exp1:</b> D4: Modafinil 16, 32 or 64mg/kg IP, 4h after Modafinil or vehicle priming  <b>Exp5:</b> D4: Cocaine 5, 10 or 20mg/kg ip, 4h after Modafinil or vehicle priming	Locomotor activity monitoring (total number of entrances in any floor units) for 10min, 30min (Exp1&6) or 5min (Exp5) after D4 challenge dose inj  <b>Exp1:</b> BS+ as soon as 4h after Modafinil inj. BS+ is dose-dependent and increased when Modafinil acquisition  <b>Exp5:</b> BS+ from cocaine 5mg/kg. BS+++ increased with Modafinil 64mg/kg acquisition and cocaine 20mg/kg challenge dose  <b>Exp6:</b> BS+ for all cocaine pre-ttt groups and BS+ for Sal-Mod64 group	BS rapid-onset development when induced by Modafinil Crossed and bidirectional BS with rapid onset when association of Modafinil+Cocaine

					<b>Exp6:</b> D4: Modafinil 16, 32 or 64mg/kg ip, 4h after Cocaine or saline priming	BS+++ increased with cocaine 20mg/kg acquisition and Modafinil 64mg/kg challenge dose	
<b>Marinho et al. 2017</b> <i>Pharmacology, Biochemistry and Behavior</i> [41]	3-month-old Swiss male mice, 35-40g  Rimonabant= antagonist of CB1-R	<b>D1-D2:</b> habituation  <b>D3-D17:</b> "sensitization phase": no inj or cocaine 5mg/kg or saline ip inj D18: drug free D19-D26: "post-sensitization", saline or vehicle or Rimonabant 1 or 10mg/kg ip inj D27-D29: drug free D30: saline ip inj D32: challenge dose	D1-D2: habituation in open field for 10min after saline ip inj. Basal locomotor activity monitored at D2. D3-D17: min open filed session at 5min after each inj D19-D26: 10min sessions of open field at 30min after inj D30-D32: 10min open filed session at 5min after inj	D18-D32: 15days withdrawal	<b>D32:</b> cocaine 10mg/kg or saline ip inj	Locomotor activity monitoring (total number of entrances in any squares) BS+ for cocaine acquisition groups At D26, BS- for Coc-Rim 10mg/kg group compared to control groups At D32, BS- for Coc-Rim 10mg/kg group compared to Coc-Vehicle and Coc-Rim 1mg/kg groups	Rimonabant= antagonist of CB1-R, prevents BS cocaine-induced  Rimonabant 10mg/kg decreases C-Fos expression in caudate-putamen and basolateral amygdala

Abbreviations: 18MC = 18-methoxycoronaridine, AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, Coc = cocaine, D1/D2 = dopaminergic, E = estradiol, Exp = experience, GSK-3b = glycogen synthase kinase 3b, ILK = integrin-linked, inj = injection, ip = intra peritoneal, iv = intravenous, LiCl = lithium chloride, METH = methamphetamine, MPEP = 6-methyl-2-(phenylethynyl)-pyridine, mPFC = medio prefrontal cortex, NAc = nucleus accumbens, Nic = nicotine, P = progesterone, PI3K= phosphatidylinositol 3 kinase, PL= prelimbic area, pre-ttt = pre-treatment, QuinA = quinolinic acid, Rc = receptor, Rim = rimonabant, sc = subcutaneous, Sal = saline, ttt = treatment, Veh = vehicle, VTA = ventral tegmental area

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
<b>McDougall et al. 2017</b> <i>Behav Brain Research</i> [37]	Preweaning male (N=426) and female (N=426) Sprague-Dawley rats Exp1: N=24 (N=4 per group) Exp2: N=48 (N=4 per group) Exp4: N=128 Exp5: N=48 (N=4 per group)  SCH23390= selective D1-R antagonist Raclopride= selective D2-R antagonist EEDQ= irreversible D1&D2R antagonist	<b>Exp1 (ip inj):</b> D0: Saline-saline or SCH23390 0.5mg/kg + Raclopride 0.5mg/kg followed by cocaine 30mg/kg inj after 15min D1: challenge dose  <b>Exp2 (ip inj):</b> D0: EEDQ 0, 7.5 or 15mg/kg D1: saline or cocaine 30mg/kg D3: challenge dose  <b>Exp4 (ip inj):</b> D0: saline or cocaine 30mg/kg D1: Raclopride 0, 0.1 or 0.5 mg/kg OR SCH23390 0, 0.1 or	Locomotor activity monitoring (total distance travel) in test cage -Monitoring for 30min on acquisition day (D0 for Exp1&4, D1 for Exp2&5) -Monitoring for 120min on test day (D1 for Exp1&4, D3 for Exp2&5)	<b>Exp1:</b> 24h <b>Exp2:</b> 48h <b>Exp4:</b> 24h <b>Exp5:</b> 48h	<b>Exp1:</b> D1 cocaine 20mg/kg <b>Exp2:</b> D3 cocaine 20mg/kg <b>Exp4:</b> D1 cocaine 20mg/kg <b>Exp5:</b> D3 cocaine 20mg/kg	Locomotor activity monitoring (total distance travel) <b>Exp1:</b> on acquisition day (D0), locomotor activity induced by cocaine is lower in the SCH23390+Raclopride group than in the group without. On test day (D1): equal BS+ in both groups  <b>Exp2:</b> on acquisition pre-ttt day (D0): no differences of locomotor activity induced by cocaine in EEDQ groups. On test day (D3): BS- in EEDQ 7.5 and 15mg/kg groups  <b>Exp4:</b> on test day (D1), BS- in Raclopride 0.5mg/kg, and in SCH23390 group, and major BS- in Raclopride 0.5mg/kg+SCH23390 group	No involvement of ontogenesis induction. Induction of BS in Stimulation of D1 and D2-R is not BS induction in weaned rats does not require the D1 and D2-R stimulation  On the contrary, BS expression in preweaned rats is inhibited by D1-R antagonist (SCH23390), as in adult rat

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		0.5mg/kg OR SCH23390+Raclopride 0.1 or 0.5mg/g each, followed by challenge dose  <b>Exp5:</b> D0: saline or cocaine 30mg/kg D1: EEDQ 0, 7.5 or 15mg/kg D3: challenge dose				<b>Exp5:</b> on test day (D3), BS- in EEDQ groups	
<b>Kang et al. 2017</b> <i>Eur J Neurosci</i> [42]	D2-Cre(+) transgenic and Dr-Cre(-) WT control mice, 10-13 weeks old  Inj in NAc of AAV viral vectors 3 weeks recovery	Habituation of ip inj with saline inj over 3 days D1-D5: saline or cocaine 15mg/kg D6-D19: drug free D20: challenge dose	Habituation in individual cages when AAV acquisition inj Habituation for 60min in test cage before D1 first inj	D6-D19: 14 days	D20: cocaine 10mg/kg ip	Locomotor activity monitoring by ambulation (photobeam breaks) for 30min after each inj with concomitant photoinhibition  Locomotor activity increases in all groups when successive cocaine inj ⇔ BS+ BS+ in both D2-Cre(+) and (-) when cocaine acquisition No significant difference with photo-inhibition	Optogenetic inhibition of D2-R in NAc medium spiny neurons (MSN) does not affect the cocaine-induced BS induction or development. Photo-inhibition of MSN D2-R during withdrawal does not affect the cocaine-induced BS expression
<b>Barbosa-Méndez et Salazar-Juarez 2018</b> <i>J of Psychiatric Research</i> [89]	Male Wistar rats, 250-280g N=224 (total) N=32 (Exp1, Exp2, N=8 per group) N=56 (Exp3, Exp4, N=8 per group) N=48 (Exp5, N=8 per group)  IP inj Randomization Exp1: Sal, NIC, COC and NIC+COC groups Exp2: Sal, NIC, COC, NIC+COC groups Exp3,4: with mecamylamine inj (non-selective antagonist of nACh-R)	Exp1: D0-D15(induction): saline or nicotine 0.4mg/kg and/or cocaine 10mg/kg D15-D35(extinction): saline inj D35-D60(expression): challenge dose  Exp2: D-10-D0 (acquisition): saline or nicotine 0.4mg/kg and/or cocaine 10mg/kg D1(testing): challenge dose	Home cage 30min/day sessions of habituation in test cage for 3 days  Exp1: locomotor activity monitoring for 60min after each inj Exp2: D1: locomotor activity monitoring 30min and 240min after inj	Exp1: D15-D35: 20 days  Exp2: 24h	Exp1: D35 à J60: saline or nicotine (0.4mg/kg) and/or cocaine (10mg/kg)  Exp2: D1: saline or nicotine (0.4mg/kg) and/or cocaine (10mg/kg)	Locomotor activity monitoring (photo-beam interruption)  Exp1: D35-D65: BS in COC+NIC, COC and NIC groups. BS++++ increased and extended in COC+NIC group  Exp2 : D11: BS in COC+NIC, COC and NIC groups. BS+ increased and extended in COC+NIC group	Co-ttt NIC+COC potentiate and extend the BS induced by cocaine and nicotine.  Involvement of nACh-R in BS development. Alleviating of BS COC+NIC induced by nACh-R antagonist
Abbreviations: 18MC = 18-methoxycoronaridine, AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, Coc = cocaine, D1/D2 = dopaminergic, E = estradiol, Exp = experience, GSK-3b = glycogen synthase kinase 3b, ILK = integrin-linked, inj = injection, ip = intra peritoneal, iv = intravenous, LiCl = lithium chloride, METH = methamphetamine, MPEP = 6-methyl-2-(phenylethynyl)-pyridine, mPFC = medio prefrontal cortex, NAc = nucleus accumbens, Nic = nicotine, P = progesterone, PI3K= phosphatidylinositol 3 kinase, PL= prelimbic area, pre-ttt = pre-treatment, QuinA = quinolinic acid, Rc = receptor, Rim = rimonabant, sc = subcutaneous, Sal = saline, ttt = treatment, Veh = vehicle, VTA = ventral tegmental area							

**Table 2.** Behavioral sensitization opioids-induced in murine model.

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
Vanderschuren et al. 2001 <i>Eur J of Neuroscience</i> [7]	Male Wistar rats, 180-200g N=32 (saline challenge dose, n=7-16 per group) N=30 (Mor 2mg/kg challenge dose, n=8-16 per group) N=31 (Mor 5mg/kg challenge dose, N=7-16 per group) N=30 (AMPH challenge dose, N=7-15 per group)	D-3weeks: saline or morphine 2, 10 or 30mg/kg sc inj D1: saline ip or sc inj, followed 1h after by challenge dose	Habituation for 7 days in home cage D-3weeks: acquisitioninj in home cage D1: habituation for 2h in test cage before inj	21 days	D1: saline ip or sc followed 1h after by Morphine 2mg/kg sc or Morphine 5mg/kg sc or AMPH 1mg/kg ip	Locomotor activity monitoring (mean distance travel in 10min blocks) for 2h before inj, 1h after first inj (Mor) and 1h (AMPH), 2h (Mor 2mg/kg) or 3h (Mor 5mg/kg) inj D1: BS+ in acquisition Morphine 10 or 30mg/kg groups. BS- in acquisition Morphine 2 mg/kg group Increased BS+ after AMPH inj in all groups (Morphine 2, 5 and 10mg/kg)	Dopamine and Cholinergic released in NAc, dose-dependent increase with morphine acquisition Dopamine and Cholinergic released in caudate putamen are only slightly increased after morphine acquisition
Johnson et Napier 2000 <i>Synapse</i> [67]	Male Sprague-Dawley rats, 280-310g N=36  Micro-inj in Ventral Pallidum  CTOP= $\mu$ antagonist, VP inj SCH23390= D1-R antagonist, VP-inj Morphine 10mg/kg, ip inj  Randomization in 6 groups: Sal-Sal, Sal-Mor, CTOP-Sal, SCH-Mor, CTOP-Mor and dorCTOP-Mor (in dorsal VP)	D1-D5: basal locomotor activity monitoring D6-10: VP inj (Sal or CTOP or SCH) followed by ip inj (Sal or Mor) 15min after D11-D12: saline ip inj D13: challenge dose	Habituation for 7 days before surgery and 1 week recovery D1-D5: basal locomotor activity monitoring D6-D13: habituation in test cage 15min before each inj, and monitoring for 90min after inj	D10-D13: 72h	D13: morphine 10mg/kg ip	Locomotor activity monitoring by ambulation (photobeam breaks) for 90min  D6-D10: BS+ in Sal-Mor and SCH-Mor groups  D13: BS+ in Sal-Mor, dorCTOP-Mor and SCH-Mor groups	Involvement of CTOP $\mu$ opioid-R and D1-R of Ventral Pallidum in locomotion's increasing during a morphine repeated inj ttt  Involvement of CTOP $\mu$ opioid-R in BS expression after a withdrawal
Scheggi et al. 2002 <i>Neuroscience</i> [8]	Male Sprague-Dawley rats, 125-150g N=40 per Exp  Dizocilpine= NMDA-R antagonist	Exp1: D1-D7: morphine 10mg/kg sc inj D8-D14: drug free D14: challenge dose Exp1bis: D1-D14: saline or cocaine 40mg/kg ip inj D15-D25: drug free Exp2: D1-D7: saline or morphine 10mg/kg or sal+dizocilpine	Habituation for 1 week before Exp1/2 D1-D7: inj in "inj cage" D8-D14: home cage D15: 15min habituation in test cage before challenge dose inj Exp1bis/2bis: D1-D14: inj in test cage D15-D25: home cage D25: test cage	Exp1/2: D8-D14: 7 days Exp1bis/2bis: D15-D25: 10 days	Exp1: D15: mor 5mg/kg sc  Exp1&2: D15: morphine 5mg/kg sc. Exp1bis & 2bis: D25 cocaine 10mg/kg ip	Locomotor activity monitoring (number of photo-beam interruption) and stereotypy ranking for 95min (Exp1) or 45min (Exp1bis) Exp1&1bis: BS+ in Mor and Coc groups Exp2: Locomotion: BS+ Mor > Mor+Diz >> Sal > Diz Stereotypy: BS+ Mor > Mor+Diz >> Diz, Sal Exp2bis:	NMDA-R are not involved in BS morphine induction Dizocilpine inhibits NMDA-R and BS cocaine induction Increased expression of GluR1, NR1, NR2B receptors in NAc core



		0.1mg/kg or mor+dizocilpine 0.1mg/kg sc inj D8-14: drug free D15: challenge dose Exp2bis: D1-D14: saline or cocaine 40mg/kg or sal+dizocilpine 0.1mg/kg or coc+dizocilpine 0.1mg/kg sc and ip inj D15-D25: drug free D25: challenge dose					Locomotion: BS+ Coc > Coc+Diz >> Diz, Sal Stereotypy: BS+ Coc > Coc+Diz > Diz > Sal	
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Abbreviations: AMPH = amphetamine, AMS = amilsupride, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, BNX= benoxathian, BUP = buprenorphine, Coc = cocaine, D1/D2 = dopaminergic, Diz = dizocilpine, Exp = experience, HDAC= histone deacetylase, inj = injection, ip = intra peritoneal, iv = intravenous, Mor = morphine, mPFC = medio prefrontal cortex, MTD = methadone, NAc = nucleus accumbens, pre-ttt = pre-treatment, R = receptor, Rim = rimonabant, Sal = saline, sc = subcutaneous, SCH = SCH23390, The= thenorphine, TSA= Trichostatin A, TTD = three times a day, ttt = treatment, Veh = vehicle, VLO= ventrolateral orbital cortex, VTA = ventral tegmental area

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
<b>Zhao et al. 2004</b> <i>Acta Pharmacol Sin</i> [43]	Kumming mice, 18-22g N=40 (N=10 per group, 5 male and 5 female)  Thenorphine: sc inj Morphine: ip inj  Thenorphine= partial agonist of $\mu$ -opioid receptor	Exp1: D1-D7: veh or Thenorphine 0.0625, 0.25 or 1.0mg/kg D8-D14: withdrawal D15: veh, The 0.0625, 0.25 or 1.0mg/kg Exp3: D1-D7: Veh+veh, Veh+Mor 20mg/kg, The (0.0625, 0.25 or 1.0mg/kg)+Mor 20mg/kg. 30min interval between 2 inj D8-D14: withdrawal, or Veh or The 0.0625, 0.25 or 1.0mg/kg in control group (Veh+Veh+The and Veh+Mor+The) D15: morphine 10mg/kg +/-The 0.0625, 0.25 or 1.0mg/kg	Habituation for 3 days Exp1: D1, D7, D15: test cage for 10min after inj Exp3: D15: test cage for 30min after inj	Exp1&3: D8-D14: 7 days	Exp1: D15: veh, The 0.0625, 0.25 or 1.0mg/kg Exp3: D15: morphine 10mg/kg +/- The 0.0625, 0.25 or 1.0mg/kg	Locomotor activity monitoring (ambulometer) for 30min, 10min (Exp1) or 30min (Exp3) after inj Exp1 (Thenorphine acquisition and challenge): D1, D7, D15: BS-, no BS induction Exp3 (Morphine acquisition and challenge): D15: BS- with alleviation degree Thenorphine acquisition dose dependent. Extinction of BS with The 0.25 or 1.0mg/kg in groups: (Veh+Veh), (Veh+Mor), (Veh+Mor+The), (The+Mor)  The inhibition starts 10min after mor challenge dose inj and lasts 50min	Thenorphine= dose dependent inhibition of development, transfer and induction of morphine induced BS  When administrated alone (Exp1), Thenorphine do not produce BS+ but a tolerance phenomenon
<b>Cordonnier et al. 2007</b> <i>British J of Pharmacology</i> [44]	Male OF1 mice, 20-22g N=10-12 per group  Ip inj, 2x/day (AMS, RB101), or 1x/day (BUP or MTD)  Amilsupride= D2-R antagonist RB101 = inhibitor of enkephalins' enzymatic degradation	D1-D7: saline or morphine 20mg/kg Exp1: D8-D14: AMS 20mg/kg or MTD 2.5mg/kg or BUP 0.1mg/kg or RB101 80mg/kg or Veh or AMS+MTD/BUP/RB101/Veh D15: morphine 10mg/kg  Exp2: D8-D14: saline inj	Habituation not indicated D1, D7, D15: test cage after inj	Exp1: 24h but D8-D14 (8 days) without morphine  Exp2: D8-D14= 8days	Exp1: D15: morphine 10mg/kg  Exp2: D15: RB101 80mg/kg or BUP 0.1mg/kg or MTD 2.5mg/kg or AMS 20mg/kg+MTD/BUP/RB101	Locomotor activity monitoring (photo-beam interruption) for 60min after challenge dose inj  Exp1: D15: BS+ when (D8-D14) Veh/RB101/MTD/BUP/AMS alone groups. BS- in (D8-D14) AMS+RB101 group. BS+ alleviated in (D8-D14) AMS+BUP group	AMS+RB101 inhibits BS morphine-induced expression AMS+BUP partially inhibits BS morphine-induced expression MTD alone potentiates BS morphine-induced expression

		D15: RB101 80mg/kg or BUP 0.1mg/kg or MTD 2.5mg/kg or AMS 20mg/kg+MTD/BUP/RB101				BS+ unchanged in (D8-D14) AMS+MTD group. BS+ potentiated in (D8-D14) Veh+MTD  Exp2: BS+ potentiated in (D15) BUP/MTD/RB101 alone groups BS+ alleviated in (D15) AMS+BUP/MTD/RB101	
<b>Taracha et al. 2009</b> <i>Progress in Neuro-Psychopharmacology &amp; Biological Psychiatry</i> [62]	Male Sprague-Dawley rats, 289-211g  SC inj  Randomization N=10-12 per group	D1-D16 (with D7 and D14 inj free): saline or Morphine 10mg/kg or MTD 1mg/kg or MTD 2mg/kg D16-D30: withdrawal D31: MTD 1mg/kg	Habituation for 7 days before Exp Test cage for 30min before inj  D1, D16, D31: test cage for 30min before and after inj D2-D15: test cage for 30min before inj and post-inj cage for 2h after inj	D16-D30: 15 days	D31: MTD 1mg/kg	Locomotor activity monitoring D1, D16 and D31 for 30min (total distance travel)  D16: BS+ in Mor and MTD2 groups, BS- In MTD1 group (but increased compared to saline group)  D31: BS+ potentiated in Mor pre-treated rats. BS+ alleviated in MTD2 group. BS- in MTD1 group	C-Fos expression in caudate putamen increased during MTD challenge dose in Mor pre-treated rats, compared to MTD pre-treated rats.

Abbreviations: AMPH = amphetamine, AMS = amisupride, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, BNX= benoxathian, BUP = buprenorphine, Coc = cocaine, D1/D2 = dopaminergic, Diz = dizocilpine, Exp = experience, HDAC= histone deacetylase, inj = injection, ip = intra peritoneal, iv = intravenous, Mor = morphine, mPFC = medio prefrontal cortex, MTD = methadone, NAc = nucleus accumbens, pre-tt = pre-treatment, R = receptor, Rim = rimonabant, Sal = saline, sc = subcutaneous, SCH = SCH23390, The= thenorphine, TSA= Trichostatin A, TTD = three times a day, tt = treatment, Veh = vehicle, VLO= ventrolateral orbital cortex, VTA = ventral tegmental area

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
<b>Liu et al. 2012</b> <i>Brain Research</i> [66]	Male Sprague-Dawley rats, 180-200g  Exp2: N=86 (27-32 per group) 3 groups: "no surgery", "sham surgery" or "septal lesion". 7 days recovery	Exp1&2: D1: saline or morphine 1, 3, 10 or 30 mg/kg, sc inj D2-D7: withdrawal D8: morphine 3mg/kg sc inj	Exp2: 7 days recovery. Habituation for 5 days before Exp. No habituation in cage test. Exp1&2: D1: test cage for 4h D2-D7: home cage D8: test cage for 4h	Exp1&2: D2-D8: 7 days	Exp1&2: D8: morphine 3mg/kg	Locomotor activity monitoring (total distance travel) for 240min (Exp1)  Exp1: D8: locomotor activity increases up to 30-100% according to dose dependent Mor acquisition inj. Major increasing in Mor 3-30mg/kg groups, during the first 120min.  Exp2: D8: BS+ increased in "no surgery" and "sham lesion" groups. BS- in "septal lesion" group	Involvement of septal nucleus in BS induction, and not in rewarding and antinociceptive effects Lesion in septal nucleus blocks BS morphine-induced induction

<p><b>Allouche et al 2013</b> <i>Progress in Neuro-Psychopharmacology &amp; Biological Psychiatry</i> [45]</p>	<p>Male OF1 mice, 23-25g 64 groups, N= 10-20 per group Ip inj</p>	<p>“Binge” exp: inj x1/day D1: MTD 3.75 or BUP 0.15 mg/kg D2: MTD 7.5 or BUP 0.3 mg/kg D3: MTD 15 or BUP 0.6 mg/kg D4: MTD 22.5 or BUP 0.9 mg/kg D5: MTD 30 or BUP 1.2 mg/kg</p> <p>“TTD” exp (inj x3/day): D1: MTD 1.25 or BUP 0.05 mg/kg D2: MTD 2.5 or BUP 0.1 mg/kg D3: MTD 5 or BUP 0.2 mg/kg D4: MTD 7.5 or BUP 0.3 mg/kg D5: MTD 10 or BUP 0.4 mg/kg</p> <p>Control Binge and TTD groups: D1-D5: saline inj</p>	<p>Home cage until challenge dose. Test cage for 60min after challenge dose inj</p>	<p>24h or 7 days or 14 days or 35 days</p>	<p>Mor 10mg/kg (heterologous sensitization) or MTD 2.5mg/kg or BUP 0.1mg/kg (homologous sensitization)</p>	<p>Locomotor activity monitoring (numbers of photo-beams interruption) for 60min after challenge dose inj</p> <p>MTD Binge or TTD groups: Homologous and heterologous BS+</p> <p>BUP Binge groups: Heterologous BS+ only after 14 days withdrawal. Before 14 days withdrawal: heterologous and homologous BS-</p> <p>BUP TTD groups: Homologous and heterologous BS-</p>	<p>No</p>
<p><b>Wei et al. 2016</b> <i>Neuroscience Letters</i> [64]</p>	<p>Male Sprague-Dawley rats, 250-300g Surgery for canula intra VLO. 7 days recovery. Randomisation in 4 groups: Sal/Sal, BNX/Sal, Sal/Mor, BNX/Mor N=16 per group BNX= alpha 1 adrenoceptor antagonist</p>	<p>D1: saline or BNX 2µg/0.5µL intra-VLO inj, followed 30min after by saline or Mor 10mg/kg ip inj 30min D1-D7: withdrawal D8: locomotor activity monitoring</p>	<p>No specified</p>	<p>D1-D7: 7 days</p>	<p>J8: 1 inj de 5mg/kg de morphine IP</p>	<p>Locomotor activity monitoring (total distance travel) for 4h on D8</p> <p>BS+ significantly increased in Sal/Mor group vs Sal/Sal group BS- significantly alleviated in BNX/Mor group compared to Sal/Mor group</p>	<p>BNX in VLO inhibits BS induced expression but not development. Involvement of ERK pathways</p>
<p><b>Wei et al. 2016</b> <i>Brain Research</i> [65]</p>	<p>Male Sprague-Dawley rats, 250-300g Surgery for canula intra-inj of TSA (HDAC inhibitor) in VLO (major subdivision of PFC). 7 days recovery. N=64 Randomisation in 4 groups: Sham-Sal, Sham-Mor, VLLOL-Sal and VLLOL-Mor</p>	<p>D-2-D-1: saline inj D1: saline or morphine 10mg/kg ip inj D2-7: withdrawal D8: morphine 5mg/kg ip inj</p>	<p>Unspecified Cage test for locomotor activity monitoring after inj on D1 and D8</p>	<p>D1-D8: 7 days</p>	<p>D8: morphine 5mg/kg ip inj</p>	<p>Locomotor activity monitoring (total distance travel) for 240min on D1 and D8:</p> <p>D1 (BS development): locomotor activity increased in Sham-Mor and VLLOL-Mor groups D8 (BS expression): BS+ in Sham-Mor group. BS- in VLLOL-Mor group.</p>	<p>Involvement of HDAC locating in VLO in BS expression. VLO-lesion blocks the BS morphine-induced expression but not its development. During BS expression phase: increasing of p-ERK, aCh3K0 and BDNF (but not ERK) levels in VLO</p>

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Abbreviations: AMPH = amphetamine, AMS = amilsupride, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, BNX= benoxathian, BUP = buprenorphine, Coc = cocaine, D1/D2 = dopaminergic, Diz = dizocilpine, Exp = experience, HDAC= histone deacetylase, inj = injection, ip = intra peritoneal, iv = intravenous, Mor = morphine, mPFC = medio prefrontal cortex, MTD = methadone, NAc = nucleus accumbens, pre-ttt = pre-treatment, R = receptor, Rim = rimonabant, Sal = saline, sc = subcutaneous, SCH = SCH23390, The= thenorphine, TSA= Trichostatin A, TTD = three times a day, ttt = treatment, Veh = vehicle, VLO= ventrolateral orbital cortex, VTA = ventral tegmental area

**Table 3.** Cross-behavioral sensitization opioids and cocaine-induced in murine model

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
De Vries et al. 1998 <i>Eur J of Neuroscience</i> [68]	Male Wistar rats, 270-320g Intravenous catheter implanted 5-7 days before exp. N=5 per group Randomisation: cocaine/heroin acquisition + cocaine/heroin/AMPH reinstatement test	Self-administration sessions of cocaine 500µg/kg, 2h/day for 10-11 days OR heroin 50µg/kg 3h/day sessions for 14-15 days. Extinction sessions with saline inj, 2h sessions for 3 weeks. Reinstatement with challenge dose after 3 weeks of extinction sessions.	Home cage habituation for 14 days. Self-administration / extinction sessions: test cage 10min after each inj Before challenge dose: habituation in a novel environment for 3 days + test cage habituation for 2h After challenge dose: locomotor activity monitoring	Extinction phase: 18 sessions of 2h saline inj for 3 weeks	Saline inj before and between each drug session. cocaine 10mg/kg ip, AMPH 1.0mg/kg ip, heroin 0.25mg/kg sc	Locomotor activity monitoring (total distance travel) for 90-120min after challenge dose. BS+ potentiated in cocaine acquisition group with AMPH test BS- potentiated in cocaine acquisition group with heroin test BS+ potentiate in heroin acquisition with AMPH or cocaine test	No
Vanderschuren et Kalivas 2000 <i>Psychopharmacology</i> [32]	Male Wistar rats, 180-200g N=14-15 per group No randomization 3 groups:	D1: saline or morphine 2, 10 or 30mg/kg, sc inj D2-D21: drug free D22: challenge dose	Home cage habituation for 7 days D1: inj in home cage D2: test cage habituation for 2h before locomotor activity monitoring D22: locomotor activity monitoring for 1h after saline inj and for 1-3h after challenge dose	D2-D21: 21 days	D22: saline ip or sc inj + morphine 2 or 5mg/kg sc or AMPH 1mg/kg ip inj after 1h	Locomotor activity monitoring (total distance travel) BS+ in morphine 10 and 30mg/kg groups BS- in morphine 2mg/kg group BS+ potentiated by AMPH challenge dose in all morphine groups (2, 10 and 30mg/kg)	With morphine acquisition: dose-dependent increases of dopamine and ACh released in NAc. Alleviated increases in caudate putamen.
Bijjou et al. 2002 <i>Neuroscience</i> [30]	Male Wistar rats, 200-220g Intra-VTA canula implantation and multi-region mCPF lesions surgery or placebo lesions (Sham group) 12 days of recovery  24 groups according to the 1 <sup>st</sup> motor response. N= 6-9 per group	Saline or AMPH 1mg/kg/48h sc or intra-VTA Saline inj the other days.	Home cage and test cage habituation during recovery Before inj: habituation in test cage for 1h After inj: test cage for 2h	4, 7 or 15 days	D4 post-ttt: AMPH 0.5mg/kg sc OR D7 post-ttt: morphine 2mg/kg sc or 1µg/0.5ul/side intra-VTA OR D15 post-ttt: AMPH 0.5mg/kg sc	Locomotor activity monitoring (difference of total distance between before and after challenge dose): BS+ in Sham + (D4)AMPH group BS- in mCPF 6-OHDA lesion group BS+ potentiate in Sham + (D7)morphine group BS+ in Sham + (D15)AMPH group	6-OHDA bilateral lesion of dopaminergic neuronal ending in mCPF and amygdala → inhibition of BS AMPH-induced development and of BS potentiated by morphine inj Involvement of VTA
Abbreviations: Ach = acetylcholine, AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, BUP = buprenorphine, Coc = cocaine, D1/D2/D3 = dopaminergic, Exp = experience, inj = injection, ip = intra peritoneal, iv = intravenous, METH = methamphetamine, mPFC = medio prefrontal cortex, MTD = methadone, NAc = nucleus accumbens, Nal = nalbuphine, pre-ttt = pre-treatment, R = receptor, sc = subcutaneous, Sal = saline, ttt = treatment, Veh = vehicle, VTA = ventral tegmental area							

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
<b>Placenza et al. 2008</b> <i>Psychopharmacology</i> [71]	Male Long-Evans rats, 350-370g N=24  D13-D15: intra-NAc canula implantation 3-4 days of recovery No randomization D18: mini pump sc implantation for BUP or placebo (Sham) inj 4 groups: (cocaine or saline) + (Sham or BUP)	D1: saline or cocaine 15mg/kg ip inj D2-D6: saline or cocaine 30mg/kg ip inj D7: saline or cocaine 15mg/kg ip inj D8-D17: drug free D18-D22: Sham or BUP 3mg/kg sc inj D23: challenge dose	D0: test cage habituation for 1h D1&D7: inj and locomotor activity monitoring in test cage D2-D6: inj in home cage D23: locomotor activity monitoring in test cage	D8-D17 : 10 days	D23: cocaine 15mg/kg ip	Locomotor activity monitoring (number of photo-beam interruptions) for 1h (D1&D7), or for 120min (D23) Similar basal locomotor activities in 4 groups. D23: BS+ in coc-Sham group vs coc-BUP and sal-BUP/Sham groups BS- in coc-BUP group	Buprenorphine → *Increases the basal Glutamate level in NAc in cocaine or saline acquisition groups. *Increases the extracellular dopamine level in NAc after cocaine challenge dose in cocaine pre-treated rats *Inhibits BS cocaine-induced expression → No BS potentiation between cocaine and BUP inj
<b>Velazquez et al. 2010</b> <i>Neuroscience</i> [69]	Male Wistar rats from different litters, 267-326g D-rats: provoked deprivation period at D14 of pregnancy and at D30 of weaning, 267-275g, 10 groups C-rats: controls, 320-326g, 10 groups	D1-D10: saline or morphine 5, 7.5, 10 or 15mg/kg ip inj, 1x/48h (5 inj) D11-D12: drug free D12: challenge dose	D1-D10: before each inj: saline inj + basal locomotor activity monitoring	D11-D12: 48h	D12: saline inj followed by cocaine 10mg/kg ip inj	Locomotor activity monitoring (total distance) for 1h before and 2h after inj (D1-D10), and for 1h before and after challenge dose inj (D12)  BS+ in all morphine groups BS+ potentiated in D-rats with at least morphine 7.5mg/kg priming (7.5 or 10mg/kg) BS- potentiated in C-rats with morphine 5, 7.5 or 10mg/kg priming BS+ potentiated in C-rats with morphine 15mg/kg priming	Deprivation facilitates BS development and its potentiation  Extracellular dopamine release increases in NAc core
<b>Smith et al. 2013</b> <i>Pharmacol Biochem Behav</i> [70]	Male Long-Evans rats, 230-250g Randomisation: Coc, Sal, Coc+Nal groups Intravenous catheter implantation at D17  Nalbuphine = mixed mu/kappa agonist	D1-D10: saline or cocaine 10mg/kg or cocaine 10mg/kg+nalbuphine 10mg/kg ip inj	Home cage habituation for 7 days and test cage habituation for 5min/day for 2 days  Saline and cocaine inj 15min before testing Nalbuphine inj 20min before testing	No	No	Locomotor activity monitoring (total distance) for 5min, 15 min after saline/cocaine inj BS+ in Coc group with a significant increase of locomotor activity between D5-D10 BS- in Sal and Coc+Nal groups	No Nalbuphine inhibits the BS cocaine-induced development
Abbreviations: Ach = acetylcholine, AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, BUP = buprenorphine, Coc = cocaine, D1/D2/D3 = dopaminergic, Exp = experience, inj = injection, ip = intra peritoneal, iv = intravenous, METH = methamphetamine, mPFC = medio prefrontal cortex, MTD = methadone, NAc = nucleus accumbens, Nal = nalbuphine, pre-ttt = pre-treatment, R = receptor, sc = subcutaneous, Sal = saline, ttt = treatment, Veh = vehicle, VTA = ventral tegmental area							
Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results

<b>Chiang et al. 2014</b> <i>Addiction Biology</i> [72]	Pregnant Sprague-Dawley rats, 200-250g Randomisation: prenatal ttt from E3 to E20 = Veh sc inj x2/day, Mor 2-4mg/kg sc inj x2/day, MTD 7mg/kg sc inj x2/day, BUP 3mg/kg sc inj x1/day  Male offspring, 8-12 weeks old, 250-350g N= 7-12 per group No randomization	D1-D5: saline or METH 2mg/kg ip inj, 1x/day	Weaning at 28 days old Test cage for 30min before and 2h after METH inj	No	No	Locomotor activity monitoring (total distance traveled) for 2h D1: similar basal and post-1st inj locomotor activity in all groups D5: BS+ in all METH groups: BUP+METH >> MTD+METH / Mor+METH / Veh+METH	Involvement of NAc's D1-R in increasing of BS MTD-induced in offspring exposed to buprenorphine in prenatal period. Significant diminishing of D1-R mRNA expression in NAc and of adenylyl cyclase level compared to other groups.  No modification of D2, D3, NOP, mu, or kappa receptors
<b>Wong et al. 2014</b> <i>Behavioral Brain Research</i> [73]	Pregnant Sprague-Dawley rats  Prenatal ttt: E3-E20: saline or MTD 7mg/kg sc inj 2x/day  Offspring, 5 weeks old No randomization N= 8 per group	D1-D5: saline or METH 1mg/kg ip inj, x1/day D6-D9: drug free D9: challenge dose	Weaning at 21 days old Home cage habituation D1-D5: test cage habituation for 60min before each inj,	D6-D9: 4 days	D9: saline or METH 1mg/kg ip inj	Locomotor activity monitoring (total distance travelled) for 10min before and 120min after inj  BS+ in sal+METH group BS+ potentiated in MTD+METH group during METH acquisition and during METH challenge dose	No Methadone potentiate BS METH-induced during METH acquisition (induction) and during METH challenge (expression) in young rats
Abbreviations: Ach = acetylcholine, AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization, BUP = buprenorphine, Coc = cocaine, D1/D2/D3 = dopaminergic, Exp = experience, inj = injection, ip = intra peritoneal, iv = intravenous, METH = methamphetamine, mPFC = medio prefrontal cortex, MTD = methadone, NAc = nucleus accumbens, Nal = nalbuphine, pre-ttt = pre-treatment, R = receptor, sc = subcutaneous, Sal = saline, ttt = treatment, Veh = vehicle, VTA = ventral tegmental area							

**Table 4.** Behavioral sensitization drug-induced in humans

Author Year Journal	Subjects (number, sex, stem, conditions)	Acquisition	Experimental environment	Withdrawal	Challenge dose	Behavioral sensitization	Physio pathologic results
<b>Strakowski et al. 1996</b> <i>Biol Psychiatry</i> [78]	Healthy volunteers, 18-45 years old, males and females (betaHCG -) Mean age: 24 years old N=11 Randomized and double-blinded protocol	Group1: D1, D3: AMPH 0.25mg/kg per os D2, D4: placebo  Group2: D1, D3: placebo D2, D4: AMPH 0.25mg/kg per os	Measure of locomotor activity and vital signs every hour for 5 hours following each AMPH/placebo administration	No	No	Locomotor activity monitoring by 3 blinded raters, 2 hours after AMPH/placebo administration: mood, level of activity/energy, rate and amount of speech, eye-blink rate  BS+ with significant increase of level of energy/activity, mood, speech and eye-blink after the 2 <sup>nd</sup> dose of AMPH in both groups	No
<b>Strakowski et Sax 1998</b> <i>Biol Psychiatry</i> [79]	Healthy volunteers, 18-45 years old, males and females (betaHCG -) Mean age: 24 years old N=11 Randomized and double-blinded protocol	Group1: D1, D3, D5: AMPH 0.25mg/kg per os D2, D4, D6: placebo  Group2: D1, D3, D5: placebo D2, D4, D6: AMPH 0.25mg/kg per os	Measure of locomotor activity and vital signs every hour for 5 hours following each AMPH/placebo administration	No	No	Locomotor activity monitoring by 3 blinded raters: mood, level of activity/energy, rate and amount of speech, eye-blink rate; and subjective evaluation of substance's effects  BS+ with significant increase of level of energy/activity and eye-blink after the 3 <sup>rd</sup> dose of AMPH in both groups Progressive increase of BS+ between 1 <sup>st</sup> , 2 <sup>nd</sup> and 3 <sup>rd</sup> dose of AMPH	No
<b>Strakowski et al. 2001</b> <i>Neuropsychopharmacology</i> [80]	Healthy volunteers, 18-45 years old, males and females (betaHCG -) Mean age: 24 years old N=58 (28 women, 30 men) Randomized and double-blinded protocol.	Group1 (PPP) D1, D3, D5: placebo  Group2 (PPA) D1, D3: placebo D5: AMPH 0.25mg/kg per os  Group3 (AAA) D1, D3, D5: AMPH 0.25mg/kg per os	Measure of locomotor activity and vital signs 90min before and every hour for 5 hours after each AMPH/placebo administration  Urine tests every day (to eliminate other psychoactive substance dose)	No	No	Locomotor activity monitoring by eye-blink rate (video-recorded) and subjective evaluation of substance's effects  BS+ for energy level significantly increased in AAA group, vs PPA and PPP groups BS+ for mood level in AAA group vs PPA group (but not significant) BS+ for energy and mood levels significantly increased in women vs men BS- for eye-blink rate	No
Abbreviations: AMPH = amphetamine, BS+ = positive/appearance of behavioral sensitization, BS- = negative/absence/easing of behavioral sensitization							

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Definition	Increase of behaviour after substance exposure (at least one, but more often repeated)	
Drug of abuse concerned	All	
Main brain structures involved	Ventral tegmental area (VTA)(for initiation )	Nucleus accumbens (NAc) (for expression)
Main neurotransmission system involved	Dopamine, glutamate,	
Influencing factors	Pattern of administration during acquisition, duration of withdrawal period, dose, drug's efficacy	
Species concerned	Mainly rodents, still in debate for humans	
Behavior concerned	Locomotor activity, stereotypies	

Figure 1: Specification sheet of behavioral sensitization



**Declarations of interest:** Unrelated to the present work, FV has served in Advisory Boards for ACCORD Healthcare, Camurus AB, and has congress fees paid by ACCORD Healthcare, Camurus AB, Recordati.