Cocaine self-administration and social behaviour in extremes of the sensory processing sensitivity trait in rats

Sophie Fennema

Supervisors: Michel Verheij, Judith Homberg

Abstract

Sensory processing sensitivity (SPS) is a trait defined by sensory information processing, emotional reactions, and susceptibility to overstimulation. Individuals scoring high on this trait are differentially susceptible to positive and negative environments. In this study, 22 rats were selected on extremes on the SPS trait. High and low SPS-like rats either underwent cocaine self-administration trials or remained drug naïve. After a training period, where rats had access to self-administration boxes for 1 hour per day, long access exposure trials began, where they were allowed to self-administer cocaine for 6 hours per day. Social interaction and memory was scored before drug exposure, after training, and after long access exposure to the drug. High SPS animals show a greater escalation in cocaine intake compared to low SPS animals, and show more social and less non-social behaviour on the social interaction test. After long access exposure to cocaine, rats show more non-social behaviour compared to naïve rats. This study provides a deeper insight into the nature of addiction in susceptible individuals.

Cocaine self-administration and social behaviour in extremes of the sensory processing sensitivity trait in rats

Substance use is a serious problem, which comes with many health consequences, as well as serious implications on mental health. Cocaine in particular is the second most frequently used illegal drug (Karila *et al.*, 2014), with approximately 14-21 million users per year worldwide (Pomara *et al.*, 2012), and is the drug most often associated with hospital visits in the U.S. (Drug Abuse Warning Network, 2013). Cocaine users have a high psychiatric comorbidity (Falck *et al.*, 2004; González-Saiz *et al.*, 2014; Martínez-Gras *et al.*, 2016), and an increased severity of these disorders (Ford *et al.*, 2009). Users are at a high risk for developing cocaine use disorder, as one in six users will develop dependence (Anthony *et al.*, 1994).

It is difficult to determine why some people develop this dependency, while others do not. Several genetic risk factors have been implied (Hiroi *et al.*, 1997; Crabbe, 2002; Chao & Nestler, 2004), as well as environmental factors, such as low socioeconomic class and poor parental support (Volkow & Li, 2005). Genetic factors contribute to the formation of differentially susceptible individuals, who are more vulnerable to the beneficial and adverse effects of their environment (Belsky, 1997). Susceptibility differences to drug use have been found in rodents as well (Piazza *et al.*, 1989; Crabbe *et al.*, 1994; Piazza *et al.*, 2000).

Sensory processing sensitivity (SPS) is a trait that identifies this vulnerability. It is conceptualized as a reflection of responding to the environment to a greater or lesser extent (Aron & Aron, 1997), where individuals with a higher SPS respond more sensitively to the environment. They are characterized by a greater awareness of environmental subtleties, deeper sensory information processing, stronger emotional reactions, and enhanced susceptibility to overstimulation (Homberg *et al.*, 2016).

Individuals who belong to this vulnerable phenotype benefit more from attachment-based interventions. In a study by Bakermans-Kranenburg *et al.* (2008), parents were videotaped during daily situations at home, after which feedback was provided to stimulate sensitive interaction skills. Children were differentially susceptible to intervention effects, dependent on the presence of the 7-repeat DRD4 allele. Cortisol production lowered in response to the intervention only in children with this polymorphism. Similarly, high SPS predicts a reduction in depression symptoms following a resiliency programme, whereas low SPS individuals did not show a change (Pluess & Boniwell, 2015). Additionally, quality of childcare predicts social functioning for children with high levels of negative emotionality,

but not for non-difficult children (Pluess & Belsky, 2009). Aron and Aron (1997) further investigated highly sensitive people who recalled either troubled or happy childhoods. Those who recalled troubled childhoods were more introverted and emotional than the happy childhood group (Aron & Aron, 1997).

Abusive substances can be self-administered as a way to cope with such stress after adverse environmental circumstances (Wills & Hirky, 1996; Sinha, 2001; Goeders, 2003). Stress exposure in animals has been found to enhance drug self-administration (Zorrilla *et al.*, 2014) and can reinstate drug-seeking behaviour after abstinence (Ahmed & Koob, 1997). It has been hypothesized that stress is not a necessary or sufficient trigger for cocaine use (Matthews *et al.*, 2001; Furnari *et al.*, 2015), but in interaction with a vulnerable phenotype and drug exposure it may lead to the development of addiction (Deroche-Gamonet *et al.*, 2004).

Highly anxious people are more likely to use drugs as a coping mechanism (Lejuez *et al.*, 2008). In fact, a strong relationship between drug use and trait anxiety has been established (Taylor & Del Pilar, 1992; O'Leary *et al.*, 2000; Dixon *et al.*, 2014; Ipser *et al.*, 2015; Lai *et al.*, 2015). However, it is difficult to study behavioural traits as a predictor for addiction in human studies, as traits could have predisposed an individual for use, but they could also be a consequence of the prolonged substance intake. In animal models of addiction, subjects can be controlled for such confounding variables present in human studies. Animal studies are thus vital to study addiction.

In rats, emotional reactions are often assessed with the elevated plus maze. During this test, rats are placed on a maze, consisting of four arms, of which two open and two closed. The duration on the arms is taken as a measure of conflict between exploration and anxiety. An increase in open arm activity reflects the tendency to explore, while an increase in activity on closed arms reflects anxious behaviour (Walf & Frye, 2007). These findings are confirmed by studies on anxiolytic drugs, which increase the percentage of entries and time spent in open arms (Pellow & File, 1986; Hogg, 1996). In contrast, administration of anxiogenic compounds enhance the tendency to stay in the closed arms. Rats that spend relatively much time on closed arms, and thus show high anxiety-like behaviour, show an increased motivation to self-administer cocaine (Homberg *et al.*, 2002; Homberg *et al.*, 2004a) , and more readily escalate cocaine intake (Dilleen *et al.*, 2012).

Further animal research into cocaine addiction conveys a link between substance use and an enhanced susceptibility to the environment (Arenas *et al.*, 2018). This trait can be objectively measured using the prepulse inhibition (PPI) of the startle response, a

phenomenon in which a weaker pre-stimulus inhibits the reaction to a stronger stimulus (Swerdlow *et al.*, 1992). PPI measures the level of sensorimotor gating, the process of filtering out redundant information. If sensorimotor gating is impaired, incoming stimuli are filtered less, and the PPI is decreased, as can be seen in schizophrenia patients (Braff *et al.*, 1978). Mice with a lower PPI initially show a lower preference for cocaine, but once conditioned with a higher dose, display a strong preference (Arenas *et al.*, 2018)

A behaviour that has not yet been studied in connection to substance use, but is related to the vulnerable endophenotype SPS, is sensory information processing, which is reflected in the conditioned freezing response. Conditioned freezing during extinction measures the memory to an aversive cue. After being conditioned to prepare for a shock following a sound, the rat will freeze when hearing the cue. Danger strengthens memory, by increasing activation of the amygdala (Whalen *et al.*, 2004), which is necessary for the formation and consolidation of a danger memory trace (Keifer *et al.*, 2015).

Anxiety and sensorimotor gating exert their influences on social behaviour. Rats with low prepulse inhibition were found to spend less time in social interaction (Goktalay *et al.*, 2014), compared to rats with higher gating. Anxiogenic-like behaviour is reflected by decreased time spent in social behaviour (File & Hyde, 1978; File & Seth, 2003). Using a rat model for animals on high anxious behaviour (HAB) and low anxious behaviour (LAB) (Landgraf & Wigger, 2002), HAB rats were found to spent less time in active social interaction compared to their counterparts (Henniger *et al.*, 2000). Conversely, Ramos *et al.* (1997) did not find a significant correlation between anxiety and social behaviour.

Additionally, rats show differential social behaviour after psychostimulant administration. In a study done by Šlamberová *et al.* (2015), rats were given either amphetamines, cocaine, MDMA or saline. After acute cocaine administration, rats displayed less social interaction compared to the control group (Šlamberová *et al.*, 2015). Social play behaviour is also suppressed by cocaine use (Achterberg *et al.*, 2014).

Furthermore, environment plays a key role in the development of addiction. Environmental enrichment is provided in a spatial or social form, aimed at enhancing sensory, cognitive, and motor functions (Rosenzweig, 1966). A number of studies have demonstrated the effectiveness of environmental enrichment during abstinence in reducing the risks of relapse (Solinas *et al.*, 2008; Thiel *et al.*, 2009; Chauvet *et al.*, 2012; Ewing & Ranaldi, 2018), and as protection against the development of drug addiction (Solinas *et al.*, 2009). Early and adolescent social isolation on the other hand increases the motivation to self-administer cocaine (Baarendse *et al.*, 2014; Fosnocht *et al.*, 2019).

The effects on environment on social behaviour are evident as well. Environmental and social enrichment enhances social memory in rats (Branchi *et al.*, 2006; Toyoshima *et al.*, 2018), whereas social isolation impairs social recognition (Kogan *et al.*, 2000; Kentrop *et al.*, 2018). This study will investigate social behaviour and cocaine addiction in a neutral environment, and will serve as a control for social isolation or an enriched environment in further studies.

Concluding, this research aims to investigate emotional reaction, enhanced susceptibility and sensory information processing as predictors of cocaine self-administration in rats, in order to determine whether sensitive rats are more likely to develop an addiction. Furthermore, this study will aim to answer how low and high SPS rats socially interact with conspecifics and how this behaviour is influenced by cocaine use and withdrawal.

Methods

Animals

55 adult male Wistar rats were acquired from Charles River Laboratories. Rats were weaned at PND 21 and group-housed two per cage in a temperature- and humidity-controlled room, and maintained a reverse 12-12 light-dark cycle with the lights off at 8:00 A.M. Food and water were available ad libitum, except during self-administration. Experiments were performed during dark period, to facilitate behavioural experiments and cocaine self-administration training. A buddy rat was paired with one of the test rats, to prevent solitary housing. During the creation of the social environment (see figure 1), rat pairings were rearranged, so that high and low SPS rats were paired with intermediate SPS rats.

All experimental procedures were performed under a project license from the Central Committee for Animal Experiments of the Radboud University Nijmegen Medical Centre.

SPS selection procedure

Rats were selected on the sensory processing sensitivity-like trait by means of three behavioural tests. Emotional responses were measured by the elevated plus maze, awareness of subtle stimuli was determined by means of prepulse inhibition, and processing of sensory information was evaluated with conditioned freezing.

Elevated plus maze

Anxiety-like behaviour is measured by means of exploration of an elevated plus-shaped maze. Procedure was adapted from Peeters *et al.* (2018). Rats were habituated to the room for at least 1 hour before taking the test. The rats were placed in the center of the maze and were allowed to explore the maze for 5 minutes. The apparatus consists of four elevated arms, of which two are open (100 x 100 cm) and two enclosed by black walls (100 x 100 cm, 40 cm height). Between subjects, the maze was cleaned with 70% ethanol.

The trajectories were recorded and number of entries into open and closed arms, and time spent in each arm was calculated by in-house software. Software recognized the center of gravity (COG) of the rat, and calculated the presence on the open or closed arms based on the COG, or the four paw criterium (COG > 10 cm). More time spent on exploring the open arms versus the closed arms indicated lower anxiety-like behaviour.

Prepulse inhibition

Procedure was adapted from Homberg *et al.* (2011). Animals were habituated to the testing room for at least one hour. Rats were placed into a Plexiglas tube (8.2 cm diameter, 25 cm length), and put in the acoustic startle chamber, with an accelerometer mounted beneath the tube. Each session started with 5 minutes acclimatization in 70 dB background noise, followed by ten blocks of 5 trials of a 120 dB startle stimulus, no stimulus condition, and pre-pulse startle stimuli of 3, 5 or 10 dB above background (70 dB). Between subjects, the tubes were cleaned with 70% ethanol.

The percent decrease in the maximum of the startle response to each prepulse intensity was calculated as $PPI\% = 1 - \frac{starte\ amplitude}{basal\ startle\ amplitude} * 100$. The average of the PPI% for al pre-pulse stimuli and the basal startle amplitude was taken into analysis.

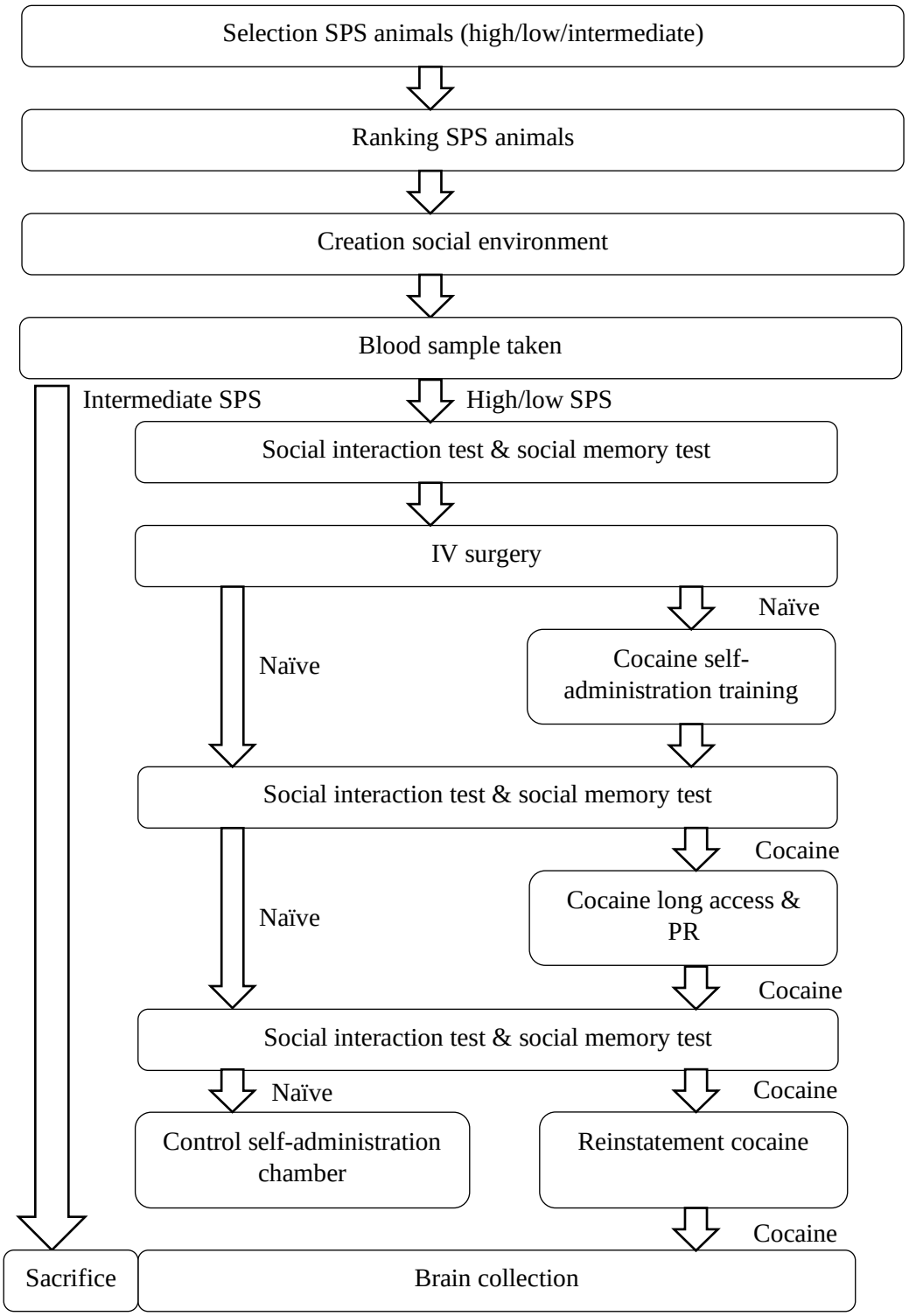

Figure 1: Experimental timeline. After division of animals into high, low, and intermediate SPS, high and low SPS rats were separated into a cocaine or drug naïve group. Both were administered the social interaction and three chamber test at three time points. Only the cocaine group was subjected to the self-administration trials. The drug naïve group was placed in self-administration chambers, but not given cocaine injections before brain collection. Intermediate SPS rats were housed with high or low SPS rats, and used as stranger rats in social interaction and social memory test.

Conditioned freezing response

Procedure to assess the conditioned freezing response was adapted from Schipper *et al.* (2017). Freezing response was tested in three phases on consecutive days. On each day, rats were habituated to the testing room for at least one hour. On the first day, rats were given a habituation trial, in which they were placed inside a Medassociates chamber (30.5 x 24.1 x 21 cm, model VFC-008) for 10 minutes. In the second phase, conditioning trials were applied in the same chamber. After a 2 minute habituation period, a 30 second 85dB 2.8 kHZ stimulus co-termimated with a 1 second 0.6 mA shock, followed by a 1 minute inter-trial interval. In total, 5 tone-shock pairings were administered.

The extinction phase started with a 2 minute habituation period, after which 24 20 second presentations of 85 dB 2.8 kHZ auditory stimuli were presented, with an inter-stimulus interval of 10 seconds. Extinction was analyzed by measuring the time spent freezing per trial, and averaging the amount of freezing for trials 1, 4, 8, 12, 16, 20, and 24. The amount of freezing within 20 seconds was calculated for each trial. Between subjects, the apparatus was cleaned with 70% ethanol.

SPS ranking procedure

Rats were ranked on the variable SPS, based on scores of the elevated plus maze, prepulse inhibition test (PPI% and basal startle amplitude) and conditioned freezing. Ranks of these four parameters were averaged into a final rank. Rats ranking in the top 25% were labelled as high SPS, while the bottom 25% was labelled low SPS.

Less exploration on the open arm of the plus maze indicates a strong emotional response, and thus a higher sensitivity. Rats were ranked on their scores of the COG and the 4 paw criterium (COG > 10 cm). The score for these two parameters were ranked, where the highest percentage distance traveled on open arms / distance traveled on closed arms had the lowest SPS rank. The ranks for the 4 paw criterium and COG were averaged into one rank for emotional reaction.

An increased prepulse inhibition and acoustic startle indicates a greater awareness of subtle stimuli. Ranks for PPI % and basal startle amplitude were calculated. The rat scoring highest for each got the highest SPS rank for each parameter separately. The two ranks were both taken into the analysis.

Lastly, the amount of freezing was measured. During freezing, animals scan the environment for new aversive cues; it is a measure of a deeper processing of sensory information. The amount of freezing within the 24 20 second trials were calculated for trials

1, 4, 8, 12, 16, 20, and 24. The average freezing time was taken over these trials, and ranked, where a higher amount of freezing indicated a higher SPS rank.

Creation social environment

After SPS selection, high and low SPS rats were paired with intermediate SPS rats, and the remaining intermediate SPS rats were paired with each other. Rats continued to be housed in pairs in a Makrolon Eurostandard type III cage, which contained a shelter. Further research will investigate the interacting factor of environment and compare either an enriched environment or social isolation against the control environment, i.e. this study.

Social tests

Both social memory and social interaction test were performed before and after cocaine self-administration training (1 hour / session), and after the long access trials (6 hours / session). Only high and low SPS rats were tested.

Social memory test

The social memory test is used as a measure for sociability and social novelty. The following procedure was adapted from Manfré *et al.* (2018). Behaviour was assessed in three connected Phenotyper 4500 arenas (45 x 45 cm), consisting of one central arena and two lateral ones. The lateral arenas contained a wire mesh cup, in which rats were placed during the social interaction part of the test (see fig 2.)

All animals were habituated to the room an hour before starting the test. The test rat (high or low SPS) was placed into the central arena and was free to explore the arenas alone for 5 minutes in order to habituate. After being taken out for 5 minutes, a stranger rat (intermediate SPS) rat was placed in the wire mesh box in one of two lateral arenas, and the test rat was again placed in the middle arena. The test rat was then taken out for 5 minutes. Then, a novel stranger rat (intermediate SPS) was placed in the other mesh wire box in the other lateral arena, and the test rat (high/low SPS) was placed into the central arena.

Placement of familiar and novel rats was randomized between left and right side. Testing of a test rat with a cagemate as a familiar or novel rat was avoided. Test rat, familiar rat and novel rat pairings were novel for all three social preference tests. The arenas and cages were wiped with 70% ethanol between test subjects.

Time spent in each arena and time spent exploring the wire mesh cages were analyzed with Ethovision XT (Noldus *et al.*, 2001). The parameters measured were time spent in all

chambers, time spent in close proximity to the familiar and novel rats (sniffing), and total distance moved during habituation, first and second interaction. The parameter used for analysis was ratio sniffing novel rat / sniffing familiar rat during the second interaction.

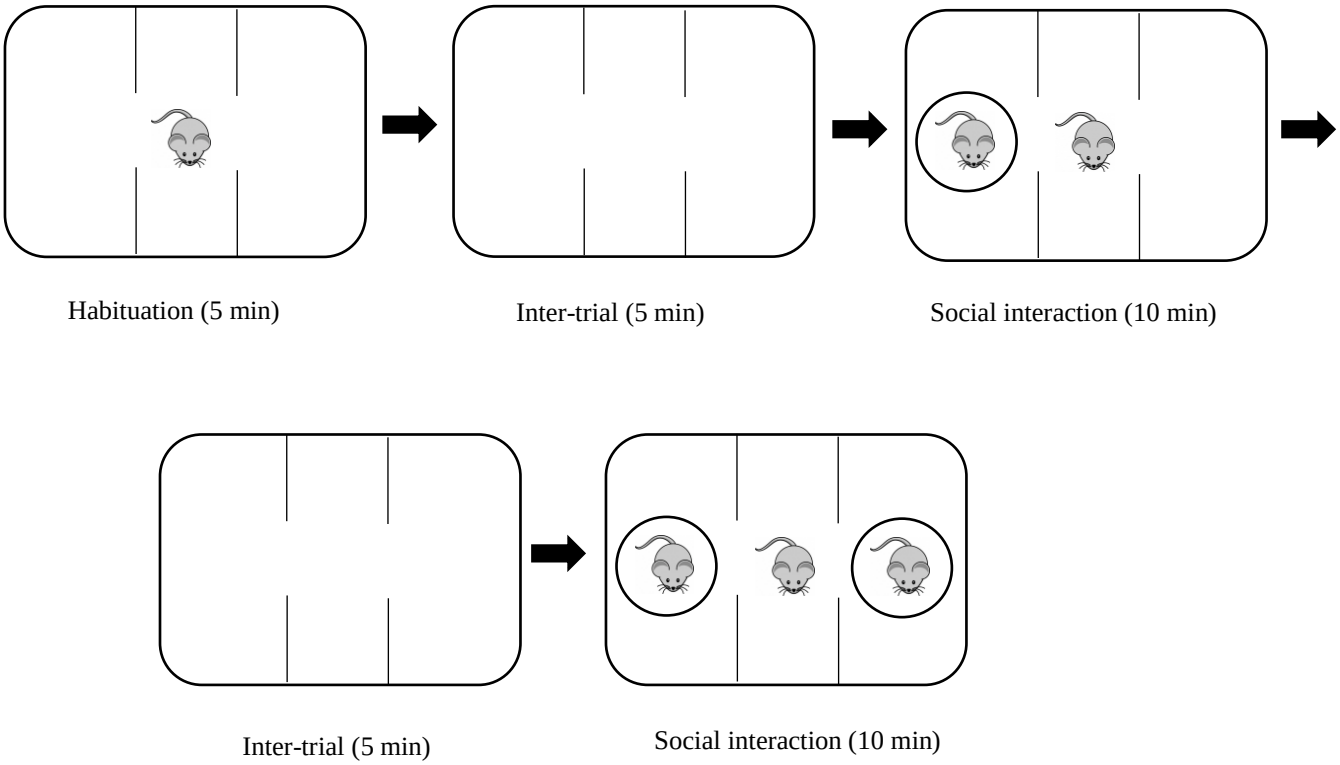

Figure 2: Social memory procedure. The test rat is first habituated to the chambers for 5 minutes. A stranger rat (intermediate SPS) is then placed in a wire mesh cup in one of the lateral chambers, and the test rat (high/low SPS) is again introduced. After the first social interaction, another novel rat (intermediate SPS) is placed into the other cup in the other lateral chamber, for the second social interaction. Between trials, the test rat is placed in its own cage for 5 minutes.

Social interaction test

The social interaction test is used to observe the interaction between two animals. Two unfamiliar rats of the same group were placed in a Phenotyper 4500 cage (dimensions 45 cm x 45 cm), and were allowed to move freely for 10 minutes. Behaviour was recorded and scored on social contact (animal establishes contact with part of its body to the other anima's body part), social interest (animal approaches or follows other animal), non-social behaviour (animal moves away from other animal or performs individual actions) and passive behaviour

(animal receives social contact from other animal, without participating in social contact intself). Behaviours were adapted from (Rodríguez-Arias *et al.*, 1998; Šlamberová *et al.*, 2015; Manfré *et al.*, 2018) and scored using BORIS software (Friard & Gamba, 2016). The chamber was wiped with 70% ethanol between subjects.

Surgery

13 high and 12 low SPS rats were implanted with a catheter in the right jugular vein. Before surgery, rats received locally applied subcutaneous injections of lidocaine (4 mg/kg) and bupivacaine (1mg/kg). General anaesthesia was induced with 5% isoflurane, and maintained with 2% isoflurane. A catheter was connected to a mesh, which was implanted subcutaneously underneath the shoulder blades. To prevent blockage, catheters were flushed daily with 0.2ml 50 USP heparinized saline, as well as 35mg Cefazolin. When not in use, a plastic seal and aluminium cap was placed on the cannula.

After surgery, carprofen (5mg/kg) was administered subcutaneously. Rats were given at least seven days to recover from surgery, in which they were monitored for weight and behaviour. Catheters were flushed daily with 50 USP heparin in 0.2ml saline until endpoint. Three rats did not recover from surgery.

Humane endpoint was reached when cannula was obstructed or when body weight dropped below 85% of the pre-surgery weight for three consecutive days during recovery. No animals reached the requirements for this humane endpoint.

Drugs

Cocaine was provided by National Institute on Drug Abuse (NIDA), Rockville, MD, and was dissolved in 0.9% saline.

Cocaine self-administration

Of the 22 rats with implanted catheters, 10 rats were cocaine naïve, of which 5 high and 5 low SPS. 12 rats were in the cocaine self-administration group, of which 7 high and 5 low SPS.

Self-administration chambers

Cocaine self-administration was performed in standard operant chambers (28x26x20 cm), equipped with a swivel system, allowing rats to move freely during self-administration sessions. Drugs were delivered by a 15 rpm syringe pump (Razel Scientific Instruments).

Each operant chamber contained an active and an inactive response lever, which were presented at the start of a session. A press of the active lever delivered cocaine (0.5 mg/kg/infusion), followed by a light above the lever for 20 seconds, indicating a time-out period. A press on the inactive lever had no consequence. The chambers were cleaned with 70% ethanol between sessions.

Training

After at least 7 days of recovery from surgery, rats were allowed access to cocaine via a fixed ratio 1 lever press response for 1 hour a day. Training was performed for 13 days. Non-contingent (experimenter delivered) cocaine administration and/or shaping was applied when rats had a response rate lower than five in the first hour.

Long access

After training, social interaction and three chamber preference test was performed again, after which the long access self-administration phase started. Procedure was adapted from Verheij *et al.* (2018) and Ahmed and Koob (1998). Rats were allowed access to cocaine for 6 hours per day, for 21 days. Manual infusions occurred when rats received less than 5 infusions within the first hour, and when less than 10 infusions were administered within 2 hours.

Progressive ratio

Directly after the long access trials, rats were subjected to a progressive ratio schedule for two days, to determine the breaking point, e.g. the maximum effort a rat will exert to receive a cocaine infusion (Richardson & Roberts, 1996).

Reinstatement

Social interaction and three chamber test were taken again after the PR self-administration schedule. Because biomarkers in brain and blood would be analyzed, compulsive drug use had to be reinstated. Rats in the cocaine group were allowed access to the self-administration chambers for 6 hours per day, on a FR1 schedule, for 7 additional days.

Control

After division of low and high SPS rats in the cocaine and drug naïve group, both groups underwent a catheter placement surgery.

To control for transport, rats in the drug naïve group were taken into the self-administration rooms, together with the cocaine group. During the reinstatement period, rats in the drug naïve group were placed in the operant chambers for 30 minutes. The light cue was presented was at 5, 10, and 20 minutes

Biomarkers

Blood was collected via a tail cut one day after creation of social environment. 24 hours after the latest cocaine infusion, all rats were decapitated and their brains and trunk blood collected. Blood and several stress-related brain regions will be analyzed for mRNA and protein levels of biomarkers known to be involved in SPS (Licht *et al.*, 2011), molecules of the dopamine and noradrenaline system (Chen *et al.*, 2011; Todd *et al.*, 2015), and mRNA and protein levels of the GABA and glutamate system (Craige *et al.*, 2015; Filip *et al.*, 2015; Froger-Colléaux & Castagné, 2016). These results will be discussed in further research.

Statistics

Drug self-administration was analyzed using a repeated measures ANOVA with the factors SPS-levels (low/high) and self-administration sessions. An ANOVA for each time point (before drug exposure, after cocaine training, and after long access exposure to cocaine) was performed for social memory with the factors SPS-level and drug exposure (cocaine or naïve) on sniffing behaviour. A repeated measures ANOVA of SPS-level, drug exposure and time points (before drug exposure, after cocaine training, and after long access exposure to cocaine) was then performed to analyse the effect over time. This repeated measures ANOVA was also done for the social interaction effect, for each behaviour (social, interest, non-social and passive behaviour). An ANOVA for each time point and each behaviour of social interaction was performed for social interaction, with the factors SPS-level and drug. Correlations were analyzed using the point-biserial correlation option of the Pearson test in SPSS. Statistical analyses were conducted with IBM SPSS Statistics version 23.

Results

SPS level predicts increase of cocaine self-administration

Long access cocaine self-administration increases over time (within-subjects session effect: $F(20,180) = 2.370$, $p = 0.001$), and this increase is dependent on SPS level (within-subjects SPS x session effect: $F(20,180) = 1.728$, $p = 0.032$; between-subjects SPS effect: $F(1,9) = 2.57$, $p = 0.143$; see figure 3). A post-hoc analysis per session reveals higher cocaine administration for high SPS compared to low SPS for session 15 ($F(1,9) = 8.042$, $p = 0.02$), 16 ($F(1,9) = 7.787$, $p = 0.021$), 17 ($F(1,9) = 6.948$, $p = 0.027$). In session 18, a p-value of 0.057 was found between high and low SPS ($F(1,9) = 4.776$).

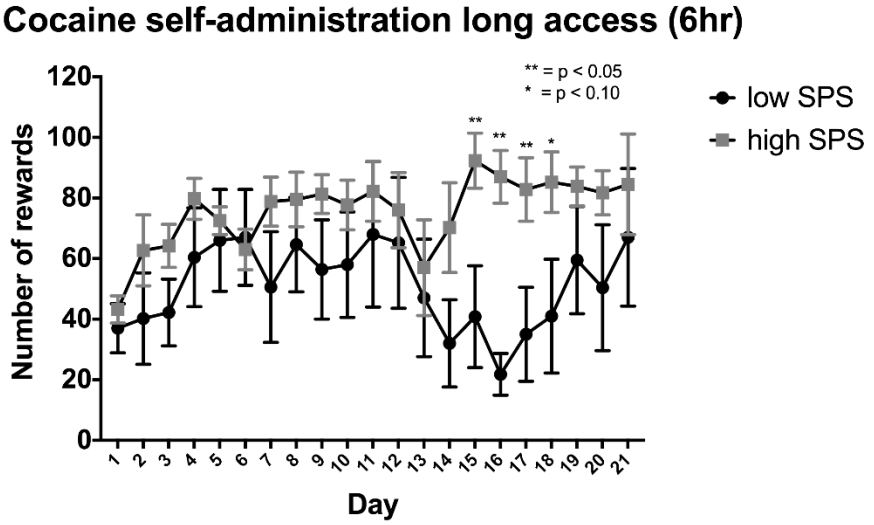

Figure 3. Cocaine self-administration intake during long access exposure. High SPS rats show a greater escalation of cocaine intake compared to low SPS rats ($p = 0.032$). Between session 15 and 17 high SPS rats show a significantly higher cocaine intake compared to low SPS rats ($p < 0.05$). In session 18, a p-value of 0.057 is found between the two groups.

Effect of cocaine addiction on social memory

A p-value of 0.06 was found after cocaine training (SPS x cocaine exposure interaction effect: $F(1, 17) = 4.048$), using the sniffing of novel rat / sniffing familiar rat ratio during the second social interaction as a measure for social memory (see figure 5). No interaction effect was found before cocaine training ($F(1,17) = 0.381$, $p = 0.545$) and after long access to cocaine (Lga) ($F(1,17) = 1.436$, $p = 0.247$). No main effects for drug exposure (before cocaine: $F(1,17) = 0.29$, $p = 0.597$; after cocaine training: $F(1,17) = 2.287$, $p = 0.149$; after Lga: $F(1,17) = 0.061$, $p = 0.807$) and SPS (before cocaine: $F(1,17) = 1.340$, $p = 0.263$;

after cocaine training: F(1,17) = 2.084, p = 0.167; after Lga: F(1,17) = 0.042, p = 0.840) were found for all time points.

A repeated measures ANOVA revealed no significant session effect within-subjects effect for social memory scores (session effect: F(2,34) = 1.7, p = 0.198).

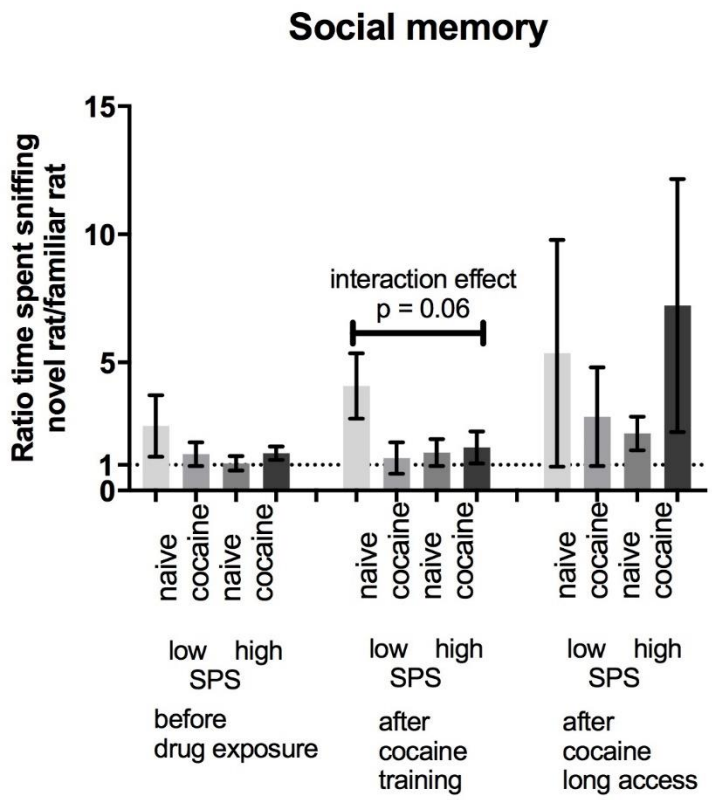

Figure 4. Ratio of time spent sniffing the novel rat versus the familiar rat during the second social interaction of the social memory test is displayed. An interaction effect (SPS-level and drug) on social memory with a p-value of 0.06 is found only after training.

Effect of cocaine addiction on social interaction

The social interaction test was at three time points: before drug exposure, after cocaine training, and after long access to cocaine. Behaviours that were tested for effects were social, interest, non-social, and passive behaviour.

Social behaviour

No SPS x treatment interaction effect was found after training (SPS x interaction effect: F(1,17) = 0.364, p = 0.554) and after long access exposure (SPS x interaction effect:

F(1,17) = 0.498, p = 0.490). However, this was the case before drug exposure, when no treatment difference was present yet (SPS x interaction effect: F(1,17) = 6.271, p = 0.023).

High SPS animals showed more social behaviour (SPS effect: F(1,17) = 16.45, p = 0.001) compared to their low SPS counterparts before drug exposure (see figure 5A). No main SPS effect after cocaine training (SPS effect: F(1,17) = 0.341, p = 0.567) and after long access exposure (SPS effect: F(1,17) = 3.231, p = 0.09) was found.

Drug naïve rats showed no difference on the social behaviour compared to rats who underwent cocaine self-administration before drug exposure, (drug exposure effect: F(1,17) = 0.033, p = 0.859), after cocaine training (drug exposure effect: F(1,17) = 0.000, p = 0.998), and after Lga (drug exposure effect: F(1,17) = 1.594, p = 0.224).

After performing a repeated measured ANOVA (social interaction test x SPS x drug exposure), a session effect was present for each behaviour (session effect: F(2,34) = 37.922, p = 0.000; see figure 6A).

Interest behaviour

No SPS x drug exposure interaction effect was found after training (F(1,17) = 0.371, p = 0.550) and after Lga (F(1,17) = 2.433, p = 0.137). However, this was the case before drug exposure, when no drug exposure difference was present yet (F(1,17) = 7.963, p = 0.012.

No difference was found between high and low SPS-like animals before drug exposure (SPS effect: F(1,17) = 0.255, p = 0.620) and after cocaine training (SPS effect: F(1,17) = 2.399, p = 0.14). After long access exposure, high SPS animals showed less interest behaviour compared to low SPS animals (SPS effect: F(1,17) = 6.051, p = 0.025).

No drug exposure effect in interest behaviour was found for before drug exposure, (drug exposure effect: F(1,17) = 0.064, p = 0.803), after cocaine training (drug exposure effect: F(1,17) = 0.202, p = 0.659) and after Lga (drug exposure effect: F(1,17) = 2.218, p = 0.155) .

After performing a repeated measured ANOVA (social interaction test x SPS x drug exposure), a session effect was present for each behaviour (session effect: F(2,34) = 5.874, p = 0.006; see figure 6B).

Non-social behaviour

No SPS x drug exposure interaction effect was found before cocaine exposure (F(1,17) = 1.887, p = 0.187), after training (F(1,17) = 1.408, p = 0.252) and after long access exposure (F(1,17) = 0.580, p = 0.457; see figure 5D).

High SPS animals showed less non-social behaviour (SPS effect: $F(1, 17) = 23.823$, $p = 0.000$), compared to their low SPS counterparts before drug exposure (see figure 5B). No main SPS effect after cocaine training (SPS effect: $F(1,17) = 0.528$, $p = 0.477$) and after long access exposure (SPS effect: $F(1,17) = 0.308$, $p = 0.586$) was found.

No drug exposure effect was found for before drug exposure (drug exposure effect: $F(1,17) = 1.954$, $p = 0.180$). After cocaine training, naïve rats showed no difference in non-social behaviour compared to rats who underwent cocaine self-administration (drug exposure effect: $F(1,17) = 0.202$, $p = 0.659$). Rats after being exposed to cocaine (Lga) showed more non-social behaviour compared to naïve rats (drug exposure effect: $F(1,17) = 5.606$, $p = 0.03$; see figure 5C).

After performing a repeated measured ANOVA (social interaction test x SPS x drug exposure), a session effect was present (session effect: $F(2,34) = 36.714$, $p = 0.000$; see figure 6C).

Passive behaviour

No SPS x drug exposure interaction effect was found before drug exposure ($F(1,17) = 3.168$, $p = 0.093$), after training ($F(1,17) = 0.056$, $p = 0.815$) and after Lga ($F(1,17) = 0.042$, $p = 0.830$).

No difference was found between high and low SPS-like animals before drug exposure (SPS effect: $F(1,17) = 3.463$, $p = 0.08$), after cocaine training (SPS effect: $F(1,17) = 0.361$, $p = 0.581$), and after long access cocaine exposure (SPS effect: $F(1,17) = 1.725$, $p = 0.206$).

No main effect of drug exposure was found before drug exposure ($F(1,17) = 0.545$, $p = 0.470$), drug training ($F(1,17) = 0.99$, $p = 0.757$), and after long access drug exposure ($F(1,17) = 2.801$, $p = 0.112$).

After performing a repeated measured ANOVA (social interaction test x SPS x drug exposure), a session effect was present (session effect: $F(2,34) = 0.000$; see figure 6D).

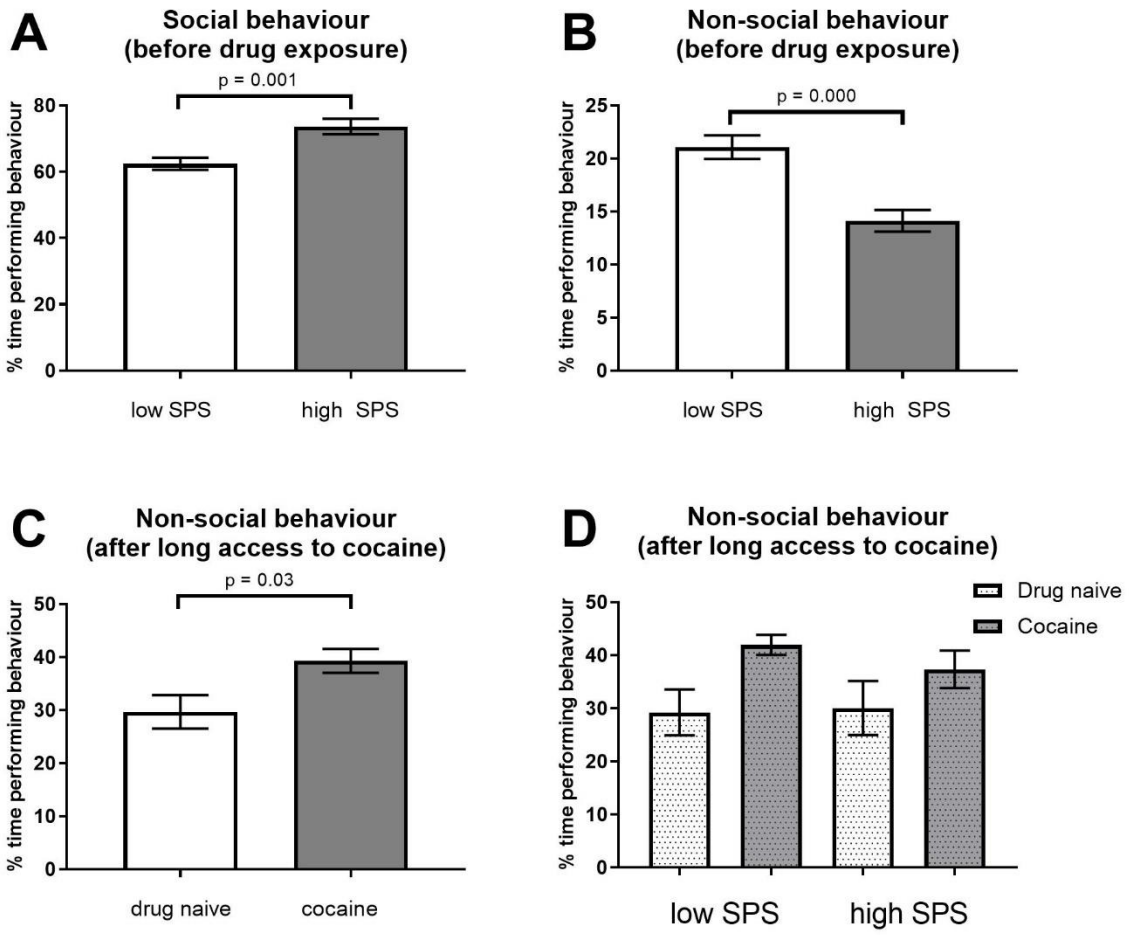

Figure 5. Percentage of time spent performing a behaviour on the social interaction test. (A) High SPS-like rats perform more social behaviour than low SPS-like rats before drug exposure ($F(1,17) = 16.45$, $p = 0.001$). (B) High SPS animals show less non-social behaviour than low SPS animals ($F(1,17) = 28.823$, $p = 0.000$). (C) After being exposed to cocaine, rats show an increase in non-social behaviour ($F(1,17) = 5.606$, $p = 0.03$). (D) No interaction effect on non-social behaviour was present for SPS x drug exposure ($F(,17) = 0.580$, $p = 0.457$).

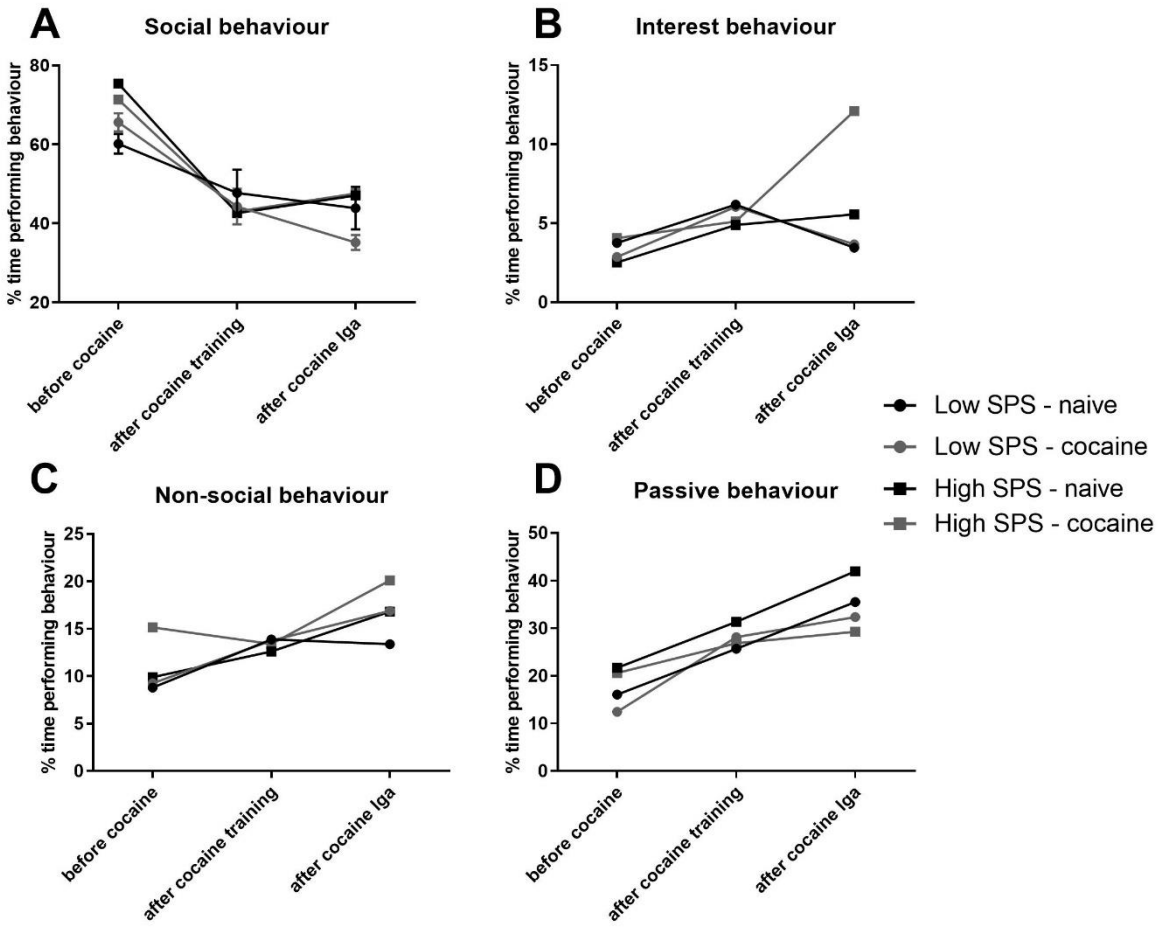

Figure 6. Percentage of time spent performing a behaviour on the social interaction test, over time points. (A) Percentage of time spent performing social behaviour decreases significantly over time points (p = 0.000). (B) Interest behaviour increases after sessions (p = 0.006). (C) Non-social behaviour increases over time (p = 0.000). (D) Passive behaviour behaviour increases over time (p = 0.000).

Validation SPS selection criteria

A Pearson analysis revealed that of the SPS selection criteria, exploration on elevated plus maze (4 paw and center of gravity criterium), basal startle amplitude correlated significantly with SPS rank. Prepulse inhibition and conditioned freezing showed a correlation of 0.36 (p = 0.08) and 0.30 (p = 0.14) respectively with SPS rank, but did not correlate with exploration and startle reflex (see table 1).

Only the social memory and interaction scores before drug exposure, but not after, were correlated with any SPS criteria. Social memory scores correlated only with prepulse inhibition scores, not with any other selection criteria or SPS rank.

Of the social interaction scores, social, passive, and non-social behaviour significantly correlated with exploration on the elevated plus maze, whereas interest behaviour showed a p-value of 0.08 for the correlation with exploration. Social and non-social behaviour further correlated with basal startle amplitude and SPS rank. Prepulse inhibition correlated with none of the social interaction scores. Conditioned freezing behaviour showed a correlation of 0.37 ($p = 0.08$) and -0.38 ($p = 0.07$) with interest and non-social behaviour respectively.

No significant correlations between total self-administration over long access exposure and SPS criteria and scores on social interaction and memory were found. SPS rank correlated with cocaine intake. Of the selection criteria for SPS, exploration on elevated plus maze (4 paw criterium) and basal startle reflex showed a correlation of -0.53 ($p = 0.09$) and 0.57 ($p = 0.06$) with cocaine intake respectively.

	EPM (4 PAW)		**EPM (COG)**		**BASAL STARTLE**		**PPI**		**FREEZING**		**SPS RANK**	
	r	p	r	p	r	p	r	p	r	p	r	p
EPM (4 PAW)			**0,98**	**0,00**	**-0,49**	**0,01**	0,05	0,82	-0,12	0,56	**-0,64**	**0,00**
EPM (COG)					**-0,49**	**0,01**	0,03	0,89	-0,13	0,53	**-0,67**	**0,00**
BASAL STARTLE							0,13	0,54	0,19	0,36	**0,66**	**0,00**
PPI									-0,22	0,29	0,36	0,08
FREEZING											0,30	0,14
SOCIAL MEMORY (BEFORE COC)	0,04	0,86	0,03	0,88	-0,13	0,55	**-0,66**	**0,00**	0,26	0,26	-0,22	0,29
SOCIAL INTERACTION (BEFORE COC)												
SOCIAL	**-0,59**	**0,00**	**-0,62**	**0,00**	**0,41**	**0,05**	0,16	0,45	0,00	0,99	**0,61**	**0,00**
INTEREST	0,36	0,08	0,36	0,08	-0,20	0,35	-0,12	0,59	0,37	0,08	-0,07	0,74
NON-SOCIAL	**0,49**	**0,02**	**0,49**	**0,02**	-0,40	0,06	-0,21	0,32	-0,38	0,07	**-0,70**	**0,00**
PASSIVE	**0,44**	**0,03**	**0,49**	**0,02**	-0,28	0,19	-0,04	0,84	0,26	0,22	-0,36	0,84

Table 1. Correlations of SPS selection criteria exploration on elevated plus maze (EPM) 4 paw and center of gravity (COG) criterium, basal startle amplitude, prepulse inhibition (PPI) and freezing with each other and social memory and interaction test.

	SELF-ADMINISTRATION TOTAL (OVER LONG ACCESS)	
	Correlation (r)	p-value (p)
EPM (4 PAW)	-0,53	0,09
EPM (COG)	-0,49	0,12
BASAL STARTLE	0,57	0,06
PPI	-0,03	0,92
FREEZING	-0,05	0,88
SPS RANK	**0,60**	**0,05**
SOCIAL MEMORY		
BEFORE COCAINE	-0,29	0,39
AFTER COCAINE TRAINING	-0,14	0,69
AFTER LONG ACCESS	0,06	0,87
SOCIAL INTERACTION		
BEFORE COCAINE		
SOCIAL	-0,20	0,56
INTEREST	0,36	0,28
NON-SOCIAL	-0,10	0,77
PASSIVE	0,44	0,18
AFTER COCAINE TRAINING		
SOCIAL	0,11	0,76
INTEREST	0,53	0,10
NON-SOCIAL	0,04	0,90
PASSIVE	0,46	0,16
AFTER LONG ACCESS		
SOCIAL	0,17	0,62
INTEREST	-0,28	0,40
NON-SOCIAL	0,04	0,92
PASSIVE	-0,37	0,26

Table 2. Correlations with p-values of total rewards obtained during self-administrations sessions during long access with SPS selection criteria exploration on elevated plus maze (EPM) 4 paw and center of gravity (COG) criterium, basal startle amplitude, prepulse inhibition (PPI) and freezing. No significant correlations between scores on the social interaction or memory test and cocaine intake were found.

Discussion

The main objective of the present study was to assess the predictive value of behavioural measures sensory information processing, emotional reaction and enhanced susceptibility to overstimulation, to identify the vulnerable phenotype sensory processing sensitivity on cocaine self-administration, and determine how social behaviour changes over time as a function of SPS and cocaine intake. This research shows that high SPS-like animals show a greater escalation in cocaine self-administration compared to low SPS-like animals (see figure 3). High SPS animals show more social behaviour compared to their low SPS counterparts (see figure 5A), and this difference remains stable after cocaine exposure. The drug increases non-social behaviour (see figure 5C). Cocaine has a decreasing effect on social memory in low SPS animals, but not in high SPS animals (see figure 4).

Sensory processing sensitivity and cocaine self-administration

High SPS animals show a greater escalation in cocaine intake over long access self-administration compared to low SPS animals. Post-hoc analysis reveals differences between the groups between sessions 15-18, where high SPS animals show a higher motivation for cocaine. Figure 3 shows an escalation of cocaine intake when animals were exposed to self-administration for 6 hours per day. This change in hedonic set point reflects a transition of drug use to drug addiction (Ahmed & Koob, 1998). High SPS animals show a higher sensory information processing, more emotional reactions, and an enhanced susceptibility to overstimulation, compared to low SPS animals. Animals who show more emotional reactions and an enhanced susceptibility to overstimulation show an increased intake in cocaine (Henniger *et al.*, 2000; File & Seth, 2003; Goktalay *et al.*, 2014). In humans, SPS correlates with a wide range of psychological problems, such as depression, anxiety (Liss *et al.*, 2008) and poor social skills (Neal *et al.*, 2002; Liss *et al.*, 2008), which are known risk factors for

substance abuse (Guo *et al.*, 2001; Swendsen *et al.*, 2010). Based on these studies, a higher cocaine intake for high SPS animals was expected.

While the overall SPS rank significantly correlates with cocaine intake (see table 2), of the single SPS measures, only basal startle amplitude and exploration on the elevated plus maze show moderate correlations with self-administration. Rats that show more emotional reactions on the elevated plus maze have been found to show an increased motivation to self-administer cocaine (Homberg *et al.*, 2002; Homberg *et al.*, 2004b) and express higher rewarding effects of cocaine (Pelloux *et al.*, 2009). High-anxiety rats display high startle amplitudes (Uvnäs-Moberg *et al.*, 1999), an association which is found in this study as well (see table 2). Conversely, Wheeler *et al.* (2017) show opposite results, with low startle rats showing increased cocaine intake. While Wheeler *et al.* (2017) used self-administration as a model for addiction, the drug access of the rats is limited to 2 hours per day, and tested a new concentration when the number of responses was stabilized. Ahmed and Koob (1998) demonstrated that in short access (1 hour) self-administration, cocaine intake remains stable over time, whereas addiction is characterized by an escalation in intake. The study by Wheeler *et al.* (2017) might thus reveal the acute effects of cocaine in the system, instead of chronic cocaine addiction.

Enhanced susceptibility to overstimulation, measured by the PPI, was expected to have a predicting value on cocaine intake, as mice with a lower PPI show a lower sensitivity to the conditioned rewarding effects of cocaine (Arenas *et al.*, 2018). Low PPI animals are less sensitive to conditioned place preference (CPP) effects at low cocaine doses, but more sensitive compared to their high PPI counterparts at higher doses. High PPI animals on the other hand have a lower, but stable sensitivity (Arenas *et al.*, 2018). No correlation was found between PPI and cocaine intake during long access, corroborating these findings. Animals with a lower sensorimotor gating show a differential susceptibility, whereas the more inhibiting group does not, leading to a zero correlation between PPI and cocaine intake. Startle reflex and PPI are not associated (see table 2), and measure different features (Swerdlow *et al.*, 2001).

The amount of conditioned freezing was not found to be a predicting value for cocaine addiction (see table 2). This may be an indication that this behavioural measure cannot be fully conceptualized as sensory information processing. Moreover, conditioned arousal and sensory information processing are both regulated by the amygdala, but are two distinct processes (Kapp *et al.*, 1992). Freezing may thus reflect arousal above sensory information

processing. Alternatively, the non-significant weak relationship may be due to limited power. An increased number of subjects will have to provide more evidence.

Social interaction

The social interaction test was scored on four behavioural measures: social contact, interest behaviour, non-social behaviour, and passive behaviour. These measures were adapted from *Manfré et al. (2018)*, in which social interaction was scored by the following behaviours: nape attacking, pinning, social contact, allogrooming, approaching, following, moving away and solitary. The number of behavioural measures was reduced, to eliminate behaviours of low occurrence, and integrate behaviours which could not be distinguished from each other from the used camera angle (e.g. social nose contact vs allogrooming and approaching vs following). A second scoring was applied for one time point, to see whether dividing the behaviours into multiple behaviours would give a clearer insight, but this was found to give similar results. For the goal of this study, the four measures provided enough insight. Passive behaviour is a behavioural measure not yet quantified in other studies, but taken into account, because of the high occurrence. Since this behaviour produced no effects, and the fact that the behaviour reflects the behaviour of the conspecific, it is recommended to not score this in further studies.

High SPS animals show less exploration and high anxiety-like behaviour (see table 1). These rats show more emotional reactions and have an enhanced susceptibility to overstimulation, which are predictive of less time spent in social interaction (File & Hyde, 1978; File & Seth, 2003; Goktalay *et al.*, 2014). It was therefore hypothesized that these animals show less social behaviour on the social interaction test. Contrary to this hypothesis, high SPS animals show more social behaviour and less non-social behaviours compared to low SPS animals before cocaine exposure (see figure 5A). Likewise, research in humans suggests that highly sensitive people view social situations as rewarding and positive, instead of emotional (Acevedo *et al.*, 2014). In response to positive social stimuli, greater SPS scores were associated with stronger activations in VTA, implicated in reward processing (Acevedo *et al.*, 2014). In these people, not limbic emotional processes, but higher executive functioning processes are engaged during social stimuli. This provides support for the finding that SPS is related to heightened responsivity to positive environments.

Animals exposed to long access drug self-administration showed more non-social behaviour than naïve rats (see figure 5C). This finding is consistent with other research, where rats displayed less social interaction (Šlamberová *et al.*, 2015) and less social play behaviour (Achterberg *et al.*, 2014) after cocaine administration. Simultaneous increases of dopamine, serotonin and noradrenaline underlie this inhibitory effect (Achterberg *et al.*, 2014). One possible explanation is that a high dose of cocaine may have an anxiogenic effect, depending on the anxiety-like behaviour of the rat, as proposed by Rogerio and Takahashi (1992). This appears to be the case for acute and chronic cocaine administration and withdrawal (Yang *et al.*, 1992; Sarnyai *et al.*, 1995; Basso *et al.*, 1999). Contrasting these findings, a study by Stoker and Markou (2011) found no anxiety-like behaviour during withdrawal from chronic cocaine. The effect is unlikely to be fully explained by the anxiogenic properties of cocaine, as the anxiolytic drug diazepam increases social exploration, but reduces social play. A second possibility is that the rewarding value of social play *(Vanderschuren et al., 2016)* is overshadowed by the value of cocaine. However, cocaine and social pairings produce equal CPP, and an even greater CPP if cocaine interacts with a social context *(Thiel et al., 2008)*, indicating that there is no direct competition. Furthermore, when rats are presented with mutually exclusive choices between social interaction and the drug to which the rat was addicted, the operant social reward eliminated drug self-administration *(Lemos et al., 2020)*.

Because the social interaction test is taken two weeks after the last cocaine infusion, rats are in withdrawal, and may suffer from post-cocaine anhedonia (Markou & Koob, 1991). Anhedonia reflects a reward deficit, lowering the rewarding value of social interaction. Post-cocaine anhedonia could therefore underlie the absence of social interest during cocaine withdrawal. Another possible contributor is cocaine-induced locomotion. An association between high locomotion and low social interaction (Tikal & Benesová, 1975) could modulate the non-social effect of cocaine. Locomotion is increased in days following cocaine use *(Perrine et al., 2015)*, and may thus contribute to the non-social behaviour displayed on rats following chronic self-administration.

No difference in SPS level in social interaction was found after cocaine training (see figure 6), where animals only had drug access for 1 hour per day. When rats have had access to cocaine self-administration for 1 hour per day, abstinence has no effect on further cocaine intake, while long access rats make a complete recovery to previous cocaine intake (Ahmed & Koob, 1998). The long access rats show a transition from drug intake to drug addiction. An addiction is not formed in rats with short access, as can be seen in the rats in this study after

receiving cocaine training. Because the social interaction test was performed two weeks after the last infusion, no acute effects of cocaine were present.

Social memory

For the social memory test, no differences were found on SPS and drug exposure level. A p-value of 0.06 for the SPS x drug exposure interaction effect was found was found after training, where cocaine-treated animals showed a lower social memory than drug naïve animals, but only in the low SPS group (see figure 4). Low SPS animals seem to be more susceptible for the acute negative memory effects of cocaine, whereas high SPS animals are not affected. This is consistent with findings that SERT KO rats, a rat model related to high SPS phenotype *(Homberg et al., 2016)*, show no decrease in cognitive flexibility following chronic cocaine self-administration for 1-hour sessions *(Nonkes et al., 2013)*.

Immediate cocaine withdrawal (3 days) is paired with increased LTP in the prefrontal cortex *(Huang et al., 2006)* and CA1 region of the hippocampus *(Thompson et al., 2004)*, which possesses social memory engram. Long-term cocaine withdrawal however, is associated with memory and learning impairments (Thompson *et al.*, 2004; Ladrón de Guevara-Miranda *et al.*, 2017). Notably, cocaine withdrawal from long access exposure had no influence on social memory of low and high SPS rats. If there are any memory impairments, the effects are not strong enough to impact social memory.

Outcomes on the social memory test did not change over sessions, indicating that a habituation effect of the three chamber test was not present.

Limitations and future research

Animal research allows control over environmental factors and is a way to manipulate variables. Several known genetic markers underlying the SPS phenotype are known. A number of genes within the dopamine system were found to contribute significantly to variability in the SPS trait *(Chen et al., 2011)*. Furthermore, an association between SPS and the serotonin transporter-linked polymorphic region (5-HTTLPR) is established, where high SPS in human subjects was related to the s/s allele *(Licht et al., 2011)*. The 5-HTTLPR polymorphism is absent in the rat serotonin transporter gene, but SERT KO rats show similarities to the human s-allele carrier *(Houwing et al., 2017)*. SERT KO rats show

avoidance on open arm on the elevated plus maze *(Kalueff et al., 2007)*, that high SPS rats in this research also display. However, it is unclear whether a SPS rat model can be conceptualized based on three behavioural measures, representing the three factors of SPS. Freezing in particular does not correlate with other measures of SPS. The startle reflex does contribute to SPS level, but may already be represented by the anxiety-like behaviour on the elevated plus maze.

The primary limitation regards the number of subjects in this study. Of the 12 rats who received cocaine infusions, five were low SPS and seven were high SPS. For further studies, it is recommended to select a higher sample size, for increased power. A secondary limitation involves the effect over session of the social interaction test. A decrease in social behaviour (see figure 5A) and increase in non-social behaviour (see figure 5C) can be explained by the acute and chronic effects of cocaine. Alternatively, this effect can be explained by habituation. It may be possible that social novelty decreases as rats perform the test for a second and third time. Because the social interaction test was taken directly after the social memory test, rats may have habituated to social interaction and not view it as rewarding as before. This habituation effect over time is not present for social memory, where cocaine was not found to effect social memory scores.

The present results provide support for the hypothesis that SPS influences cocaine intake, but further research with larger groups is needed to provide conclusive evidence. High SPS animals show more social behaviour compared to their low SPS counterparts, and this difference remains stable after cocaine exposure, while non-social behaviour increases after cocaine exposure. Cocaine has a decreasing effect on social memory in low SPS animals, but not in high SPS animals. Future research will focus on the protective versus harmful role of social isolation versus social enrichment in cocaine addiction in SPS rats, and its role on social behaviour.

References

Acevedo, B.P., Aron, E.N., Aron, A., Sangster, M.-D., Collins, N. & Brown, L.L. (2014) The highly sensitive brain: an fMRI study of sensory processing sensitivity and response to others' emotions. *Brain and Behavior*, **4**, 580-594.

Achterberg, E.J.M., Trezza, V., Siviy, S.M., Schrama, L., Schoffelmeer, A.N.M. & Vanderschuren, L.J.M.J. (2014) Amphetamine and cocaine suppress social play behavior in rats through distinct mechanisms. *Psychopharmacology*, **231**, 1503-1515.

Ahmed, S.H. & Koob, G.F. (1997) Cocaine- but not food-seeking behavior is reinstated by stress after extinction. *Psychopharmacology*, **132**, 289-295.

Ahmed, S.H. & Koob, G.F. (1998) Transition from Moderate to Excessive Drug Intake: Change in Hedonic Set Point. *Science*, **282**, 298.

Anthony, J.C., Warner, L.A. & Kessler, R.C. (1994) Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology*, **2**, 244-268.

Arenas, M.C., Navarro-Francés, C.I., Montagud-Romero, S., Miñarro, J. & Manzanedo, C. (2018) Baseline prepulse inhibition of the startle reflex predicts the sensitivity to the conditioned rewarding effects of cocaine in male and female mice. *Psychopharmacology*, **235**, 2651-2663.

Aron, E.N. & Aron, A. (1997) Sensory-processing sensitivity and its relation to introversion and emotionality. *Journal of Personality and Social Psychology*, **73**, 345-368.

Baarendse, P.J.J., Limpens, J.H.W. & Vanderschuren, L.J.M.J. (2014) Disrupted social development enhances the motivation for cocaine in rats. *Psychopharmacology*, **231**, 1695-1704.

Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., Mesman, J., Alink, L.R.A. & Juffer, F. (2008) Effects of an attachment-based intervention on daily cortisol moderated by dopamine receptor D4: A randomized control trial on 1- to 3-year-olds screened for externalizing behavior. *Development and Psychopathology*, **20**, 805-820.

Basso, A.M., Spina, M., Rivier, J., Vale, W. & Koob, G.F. (1999) Corticotropin-releasing factor antagonist attenuates the "anxiogenic-like" effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats. *Psychopharmacology*, **145**, 21-30.

Belsky, J. (1997) Variation in susceptibility to environmental influence: An evolutionary argument. *Psychological Inquiry*, **8**, 182-186.

Braff, D., Stone, C., Callaway, E., Geyer, M., Glick, I. & Bali, L. (1978) Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology*, **15**, 339-343.

Branchi, I., D'Andrea, I., Fiore, M., Di Fausto, V., Aloe, L. & Alleva, E. (2006) Early Social Enrichment Shapes Social Behavior and Nerve Growth Factor and Brain-Derived Neurotrophic Factor Levels in the Adult Mouse Brain. *Biological Psychiatry*, **60**, 690-696.

Chao, J. & Nestler, E.J. (2004) Molecular neurobiology of drug addiction. *Annual review of medicine*, **55**, 113-132.

Chauvet, C., Goldberg, S.R., Jaber, M. & Solinas, M. (2012) Effects of environmental enrichment on the incubation of cocaine craving. *Neuropharmacology*, **63**, 635-641.

Chen, C., Chen, C., Moyzis, R., Stern, H., He, Q., Li, H., Li, J., Zhu, B. & Dong, Q. (2011) Contributions of dopamine-related genes and environmental factors to highly sensitive personality: a multi-step neuronal system-level approach. *PloS one*, **6**, e21636-e21636.

Crabbe, J.C. (2002) Genetic Contributions to Addiction. *Annual Review of Psychology*, **53**, 435-462.

Crabbe, J.C., Belknap, J.K. & Buck, K.J. (1994) Genetic animal models of alcohol and drug abuse. *Science (New York, N.Y.)*, **264**, 1715-1723.

Craige, C.P., Lewandowski, S., Kirby, L.G. & Unterwald, E.M. (2015) Dorsal raphe 5-HT(2C) receptor and GABA networks regulate anxiety produced by cocaine withdrawal. *Neuropharmacology*, **93**, 41-51.

Deroche-Gamonet, V., Belin, D. & Piazza, P.V. (2004) Evidence for Addiction-like Behavior in the Rat. *Science*, **305**, 1014.

Dilleen, R., Pelloux, Y., Mar, A.C., Molander, A., Robbins, T.W., Everitt, B.J., Dalley, J.W. & Belin, D. (2012) High anxiety is a predisposing endophenotype for loss of control over cocaine, but not heroin, self-administration in rats. *Psychopharmacology*, **222**, 89-97.

Dixon, L.J., Stevens, E.N. & Viana, A.G. (2014) Anxiety sensitivity as a moderator of the relationship between trait anxiety and illicit substance use. *Psychology of Addictive Behaviors*, **28**, 1284-1289.

Drug Abuse Warning Network (2013) The DAWN Report: Update on Drug-Related Emergency Department Visits Attributed to Intentional Poisoning: 2011, Rockville, MD.

Ewing, S. & Ranaldi, R. (2018) Environmental enrichment facilitates cocaine abstinence in an animal conflict model. *Pharmacology Biochemistry and Behavior*, **166**, 35-41.

Falck, R.S., Wang, J., Siegal, H.A. & Carlson, R.G. (2004) The prevalence of psychiatric disorder among a community sample of crack cocaine users: An exploratory study with practical implications. *Journal of Nervous and Mental Disease*, **192**, 503-507.

File, S.E. & Hyde, J.R. (1978) Can social interaction be used to measure anxiety? *British journal of pharmacology*, **62**, 19-24.

File, S.E. & Seth, P. (2003) A review of 25 years of the social interaction test. *European journal of pharmacology*, **463**, 35-53.

Filip, M., Frankowska, M., Sadakierska-Chudy, A., Suder, A., Szumiec, L., Mierzejewski, P., Bienkowski, P., Przegaliński, E. & Cryan, J.F. (2015) GABAB receptors as a therapeutic strategy in substance use disorders: focus on positive allosteric modulators. *Neuropharmacology*, **88**, 36-47.

Ford, J.D., Gelernter, J., DeVoe, J.S., Zhang, W., Weiss, R.D., Brady, K., Farrer, L. & Kranzler, H.R. (2009) Association of psychiatric and substance use disorder comorbidity with cocaine dependence severity and treatment utilization in cocaine-dependent individuals. *Drug and alcohol dependence*, **99**, 193-203.

Fosnocht, A.Q., Lucerne, K.E., Ellis, A.S., Olimpo, N.A. & Briand, L.A. (2019) Adolescent social isolation increases cocaine seeking in male and female mice. *Behav Brain Res*, **359**, 589-596.

Friard, O. & Gamba, M. (2016) BORIS: A free, versatile open-source event-logging software for video/audio coding and live observations. *Methods in Ecology and Evolution*, **7**.

Froger-Colléaux, C. & Castagné, V. (2016) Effects of baclofen and raclopride on reinstatement of cocaine self-administration in the rat. *European journal of pharmacology*, **777**, 147-155.

Furnari, M., Epstein, D.H., Phillips, K.A., Jobes, M.L., Kowalczyk, W.J., Vahabzadeh, M., Lin, J.-L. & Preston, K.L. (2015) Some of the people, some of the time: field evidence for associations and dissociations between stress and drug use. *Psychopharmacology*, **232**, 3529-3537.

Goeders, N.E. (2003) The impact of stress on addiction. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*, **13**, 435-441.

Goktalay, G., Kayir, H., Ulusoy, G.K. & Uzbay, T. (2014) Social interaction of rats is related with baseline prepulse inhibition level. *Neuroscience letters*, **582**, 125-129.

González-Saiz, F., Vergara-Moragues, E., Verdejo-García, A., Fernández-Calderón, F. & Lozano, O.M. (2014) Impact of psychiatric comorbidity on the in-treatment outcomes of cocaine-dependent patients in therapeutic communities. *Substance abuse*, **35**, 133-140.

Guo, J., Hawkins, J.D., Hill, K.G. & Abbott, R.D. (2001) Childhood and adolescent predictors of alcohol abuse and dependence in young adulthood. *Journal of studies on alcohol*, **62**, 754-762.

Henniger, M.S.H., Ohl, F., Hölter, S.M., Weißenbacher, P., Toschi, N., Lörscher, P., Wigger, A., Spanagel, R. & Landgraf, R. (2000) Unconditioned anxiety and social behaviour in two rat lines selectively bred for high and low anxiety-related behaviour. *Behavioural Brain Research*, **111**, 153-163.

Hiroi, N., Brown, J.R., Haile, C.N., Ye, H., Greenberg, M.E. & Nestler, E.J. (1997) FosB mutant mice: loss of chronic cocaine induction of Fos-related proteins and heightened

sensitivity to cocaine's psychomotor and rewarding effects. *Proceedings of the National Academy of Sciences of the United States of America*, **94**, 10397-10402.

Hogg, S. (1996) A review of the validity and variability of the Elevated Plus-Maze as an animal model of anxiety. *Pharmacology Biochemistry and Behavior*, **54**, 21-30.

Homberg, J.R., Arends, B., Wardeh, G., Raasø, H.S., Schoffelmeer, A.N.M. & de Vries, T.J. (2004a) Individual differences in the effects of serotonergic anxiolytic drugs on the motivation to self-administer cocaine. *Neuroscience*, **128**, 121-130.

Homberg, J.R., Olivier, J.D.A., Blom, T., Arentsen, T., van Brunschot, C., Schipper, P., Korte-Bouws, G., van Luijtelaar, G. & Reneman, L. (2011) Fluoxetine exerts age-dependent effects on behavior and amygdala neuroplasticity in the rat. *PloS one*, **6**, e16646-e16646.

Homberg, J.R., Raasø, H.S., Schoffelmeer, A.N.M. & de Vries, T.J. (2004b) Individual differences in sensitivity to factors provoking reinstatement of cocaine-seeking behavior. *Behavioural brain research*, **152**, 157-161.

Homberg, J.R., Schubert, D., Asan, E. & Aron, E.N. (2016) Sensory processing sensitivity and serotonin gene variance: Insights into mechanisms shaping environmental sensitivity. *Neuroscience and biobehavioral reviews*, **71**, 472-483.

Homberg, J.R., van den Akker, M., Raasø, H.S., Wardeh, G., Binnekade, R., Schoffelmeer, A.N.M. & de Vries, T.J. (2002) Enhanced motivation to self-administer cocaine is predicted by self-grooming behaviour and relates to dopamine release in the rat medial prefrontal cortex and amygdala. *The European journal of neuroscience*, **15**, 1542-1550.

Houwing, D.J., Buwalda, B., van der Zee, E.A., de Boer, S.F. & Olivier, J.D.A. (2017) The Serotonin Transporter and Early Life Stress: Translational Perspectives. *Frontiers in cellular neuroscience*, **11**, 117-117.

Huang, C.-C., Lin, H.-J. & Hsu, K.-S. (2006) Repeated Cocaine Administration Promotes Long-Term Potentiation Induction in Rat Medial Prefrontal Cortex. *Cerebral Cortex*, **17**, 1877-1888.

Ipser, J.C., Wilson, D., Akindipe, T.O., Sager, C. & Stein, D.J. (2015) Pharmacotherapy for anxiety and comorbid alcohol use disorders. *The Cochrane database of systematic reviews*, **1**, CD007505-CD007505.

Kalueff, A.V., Fox, M.A., Gallagher, P.S. & Murphy, D.L. (2007) Hypolocomotion, anxiety and serotonin syndrome-like behavior contribute to the complex phenotype of serotonin transporter knockout mice. *Genes, brain, and behavior*, **6**, 389-400.

Kapp, B.S., Whalen, P.J., Supple, W.F. & Pascoe, J.P. (1992) Amygdaloid contributions to conditioned arousal and sensory information processing *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction.* Wiley-Liss, New York, NY, US, pp. 229-254.

Karila, L., Zarmdini, R., Petit, A., Lafaye, G., Lowenstein, W. & Reynaud, M. (2014) Addiction à la cocaïne : données actuelles pour le clinicien. *La Presse Médicale*, **43**, 9-17.

Keifer, O.P., Jr., Hurt, R.C., Ressler, K.J. & Marvar, P.J. (2015) The Physiology of Fear: Reconceptualizing the Role of the Central Amygdala in Fear Learning. *Physiology (Bethesda, Md.)*, **30**, 389-401.

Kentrop, J., Smid, C.R., Achterberg, E.J.M., van Ijzendoorn, M.H., Bakermans-Kranenburg, M.J., Joëls, M. & van der Veen, R. (2018) Effects of Maternal Deprivation and

Complex Housing on Rat Social Behavior in Adolescence and Adulthood. *Frontiers in behavioral neuroscience*, **12**, 193-193.

Kogan, J.H., Frankland, P.W. & Silva, A.J. (2000) Long-term memory underlying hippocampus-dependent social recognition in mice. *Hippocampus*, **10**, 47-56.

Ladrón de Guevara-Miranda, D., Millón, C., Rosell-Valle, C., Pérez-Fernández, M., Missiroli, M., Serrano, A., Pavón, F.J., Rodríguez de Fonseca, F., Martínez-Losa, M., Álvarez-Dolado, M., Santín, L.J. & Castilla-Ortega, E. (2017) Long-lasting memory deficits in mice withdrawn from cocaine are concomitant with neuroadaptations in hippocampal basal activity, GABAergic interneurons and adult neurogenesis. *Disease Models & Mechanisms*, **10**, 323.

Lai, H.M.X., Cleary, M., Sitharthan, T. & Hunt, G.E. (2015) Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: A systematic review and meta-analysis. *Drug Alcohol Depend*, **154**, 1-13.

Landgraf, R. & Wigger, A. (2002) High vs low anxiety-related behavior rats: an animal model of extremes in trait anxiety. *Behavior genetics*, **32**, 301-314.

Lejuez, C.W., Zvolensky, M.J., Daughters, S.B., Bornovalova, M.A., Paulson, A., Tull, M.T., Ettinger, K. & Otto, M.W. (2008) Anxiety sensitivity: a unique predictor of dropout among inner-city heroin and crack/cocaine users in residential substance use treatment. *Behav Res Ther*, **46**, 811-818.

Lemos, C., Salti, A., Amaral, I.M., Fontebasso, V., Singewald, N., Dechant, G., Hofer, A. & El Rawas, R. (2020) Social interaction reward in rats has anti-stress effects. *Addiction Biology*, **n/a**, e12878.

Licht, C., Mortensen, E. & Knudsen, G. (2011) *Association between Sensory Processing Sensitivity and the 5-HTTLPR Short/Short Genotype*.

Liss, M., Mailloux, J. & Erchull, M.J. (2008) The relationships between sensory processing sensitivity, alexithymia, autism, depression, and anxiety. *Personality and Individual Differences*, **45**, 255-259.

Manfré, G., Novati, A., Faccini, I., Rossetti, A.C., Bosch, K., Molteni, R., Riva, M.A., Van der Harst, J.E., Nguyen, H.P. & Homberg, J.R. (2018) BACHD rats expressing full-length mutant huntingtin exhibit differences in social behavior compared to wild-type littermates. *PLOS ONE*, **13**, e0192289.

Markou, A. & Koob, G.F. (1991) Postcocaine anhedonia. An animal model of cocaine withdrawal. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, **4**, 17-26.

Martínez-Gras, I., Ferre Navarrete, F., Pascual Arriazu, J., Peñas Pascual, J., de Iceta Ruiz de Gauna, M., Fraguas Herráez, D., Rubio Valladolid, G. & Addiction Psychiatry Investigation, G. (2016) Psychiatric comorbidity in a sample of cocaine-dependent outpatients seen in the Community of Madrid drug addiction care network. *Adicciones*, **28**, 6-18.

Matthews, K., Dalley, J.W., Matthews, C., Tsai, T.H. & Robbins, T.W. (2001) Periodic maternal separation of neonatal rats produces region- and gender-specific effects on biogenic amine content in postmortem adult brain. *Synapse*, **40**, 1-10.

Neal, J.A., Edelmann, R.J. & Glachan, M. (2002) Behavioural inhibition and symptoms of anxiety and depression: Is there a specific relationship with social phobia? *British Journal of Clinical Psychology*, **41**, 361-374.

Noldus, L.P., Spink, A.J. & Tegelenbosch, R.A. (2001) EthoVision: a versatile video tracking system for automation of behavioral experiments. *Behavior research methods, instruments, & computers : a journal of the Psychonomic Society, Inc*, **33**, 398-414.

Nonkes, L.J.P., Maes, J.H.R. & Homberg, J.R. (2013) Improved cognitive flexibility in serotonin transporter knockout rats is unchanged following chronic cocaine self-administration. *Addiction biology*, **18**, 434-440.

O'Leary, T.A., Rohsenow, D.J., Martin, R., Colby, S.M., Eaton, C.A. & Monti, P.M. (2000) The relationship between anxiety levels and outcome of cocaine abuse treatment. *The American Journal of Drug and Alcohol Abuse*, **26**, 179-194.

Peeters, D., Rietdijk, J., Gerrits, D., Rijpkema, M., de Boer, S.F., Verkes, R.-J. & Homberg, J.R. (2018) Searching for neural and behavioral parameters that predict anti-aggressive effects of chronic SSRI treatment in rats. *Neuropharmacology*, **143**, 339-348.

Pelloux, Y., Costentin, J. & Duterte-Boucher, D. (2009) Anxiety increases the place conditioning induced by cocaine in rats. *Behavioural Brain Research*, **197**, 311-316.

Pellow, S. & File, S.E. (1986) Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: A novel test of anxiety in the rat. *Pharmacology Biochemistry and Behavior*, **24**, 525-529.

Perrine, S.A., Ghoddoussi, F., Desai, K., Kohler, R.J., Eapen, A.T., Lisieski, M.J., Angoa-Perez, M., Kuhn, D.M., Bosse, K.E., Conti, A.C., Bissig, D. & Berkowitz, B.A. (2015) Cocaine-induced locomotor sensitization in rats correlates with nucleus accumbens activity on manganese-enhanced MRI. *NMR in Biomedicine*, **28**, 1480-1488.

Piazza, P.V., Deminiere, J.M., Le Moal, M. & Simon, H. (1989) Factors that predict individual vulnerability to amphetamine self-administration. *Science*, **245**, 1511.

Piazza, P.V., Deroche-Gamonent, V., Rouge-Pont, F. & Le Moal, M. (2000) Vertical shifts in self-administration dose-response functions predict a drug-vulnerable phenotype

predisposed to addiction. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, **20**, 4226-4232.

Pluess, M. & Belsky, J. (2009) Differential susceptibility to rearing experience: the case of childcare. *Journal of child psychology and psychiatry, and allied disciplines*, **50**, 396-404.

Pluess, M. & Boniwell, I. (2015) Sensory-Processing Sensitivity predicts treatment response to a school-based depression prevention program: Evidence of Vantage Sensitivity. *Personality and Individual Differences*, **82**, 40-45.

Pomara, C., Cassano, T., D'Errico, S., Bello, S., Romano, A.D., Riezzo, I. & Serviddio, G. (2012) Data available on the extent of cocaine use and dependence: biochemistry, pharmacologic effects and global burden of disease of cocaine abusers. *Current medicinal chemistry*, **19**, 5647-5657.

Ramos, A., Berton, O., Mormède, P. & Chaouloff, F. (1997) A multiple-test study of anxiety-related behaviours in six inbred rat strains. *Behavioural brain research*, **85**, 57-69.

Richardson, N.R. & Roberts, D.C. (1996) Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. *Journal of neuroscience methods*, **66**, 1-11.

Rodríguez-Arias, M., Miñarro, J., Aguilar, M.A., Pinazo, J. & Simón, V.M. (1998) Effects of risperidone and SCH 23390 on isolation-induced aggression in male mice. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*, **8**, 95-103.

Rogerio, R. & Takahashi, R.N. (1992) Anxiogenic properties of cocaine in the rat evaluated with the elevated plus-maze. *Pharmacology Biochemistry and Behavior*, **43**, 631-633.

Rosenzweig, M.R. (1966) Environmental complexity, cerebral change, and behavior. *American Psychologist*, **21**, 321-332.

Sarnyai, Z., Bíró, É., Gardi, J., Vecsernyés, M., Julesz, J. & Telegdy, G. (1995) Brain corticotropin-releasing factor mediates 'anxiety-like' behavior induced by cocaine withdrawal in rats. *Brain Research*, **675**, 89-97.

Schipper, P., Henckens, M.J.A.G., Borghans, B., Hiemstra, M., Kozicz, T. & Homberg, J.R. (2017) Prior fear conditioning does not impede enhanced active avoidance in serotonin transporter knockout rats. *Behavioural Brain Research*, **326**, 77-86.

Sinha, R. (2001) How does stress increase risk of drug abuse and relapse? *Psychopharmacology*, **158**, 343-359.

Šlamberová, R., Mikulecká, A., Macúchová, E., Hrebíčková, I., Ševčíková, M., Nohejlová, K. & Pometlová, M. (2015) Effects of psychostimulants on social interaction in adult male rats. *Behavioural pharmacology*, **26**, 776-785.

Solinas, M., Chauvet, C., Thiriet, N., El Rawas, R. & Jaber, M. (2008) Reversal of cocaine addiction by environmental enrichment. *Proceedings of the National Academy of Sciences*, **105**, 17145.

Solinas, M., Thiriet, N., Rawas, R.E., Lardeux, V. & Jaber, M. (2009) Environmental Enrichment During Early Stages of Life Reduces the Behavioral, Neurochemical, and Molecular Effects of Cocaine. *Neuropsychopharmacology*, **34**, 1102-1111.

Stoker, A.K. & Markou, A. (2011) Withdrawal from chronic cocaine administration induces deficits in brain reward function in C57BL/6J mice. *Behavioural brain research*, **223**, 176-181.

Swendsen, J., Conway, K.P., Degenhardt, L., Glantz, M., Jin, R., Merikangas, K.R., Sampson, N. & Kessler, R.C. (2010) Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey. *Addiction (Abingdon, England)*, **105**, 1117-1128.

Swerdlow, N., Geyer, M. & Braff, D. (2001) Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology*, **156**, 194-215.

Swerdlow, N.R., Caine, S.B., Braff, D.L. & Geyer, M.A. (1992) The neural substrates of sensorimotor gating of the startle reflex: a review of recent findings and their implications. *Journal of psychopharmacology (Oxford, England)*, **6**, 176-190.

Taylor, D.N. & Del Pilar, J. (1992) Self-esteem, anxiety, and drug use. *Psychological reports*, **71**, 896-898.

Thiel, K.J., Okun, A.C. & Neisewander, J.L. (2008) Social reward-conditioned place preference: A model revealing an interaction between cocaine and social context rewards in rats. *Drug and Alcohol Dependence*, **96**, 202-212.

Thiel, K.J., Sanabria, F., Pentkowski, N.S. & Neisewander, J.L. (2009) Anti-craving effects of environmental enrichment. *International Journal of Neuropsychopharmacology*, **12**, 1151-1156.

Thompson, A.M., Swant, J., Gosnell, B.A. & Wagner, J.J. (2004) Modulation of long-term potentiation in the rat hippocampus following cocaine self-administration. *Neuroscience*, **127**, 177-185.

Tikal, K. & Benesová, O. (1975) Social contact behavior in rats selected for high and low activity and defecation rates. *Activitas nervosa superior*, **17**, 61-62.

Todd, R.M., Ehlers, M.R., Müller, D.J., Robertson, A., Palombo, D.J., Freeman, N., Levine, B. & Anderson, A.K. (2015) Neurogenetic variations in norepinephrine availability enhance perceptual vividness. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, **35**, 6506-6516.

Toyoshima, M., Yamada, K., Sugita, M. & Ichitani, Y. (2018) Social enrichment improves social recognition memory in male rats. *Animal cognition*, **21**, 345-351.

Uvnäs-Moberg, K., Björkstrand, E., Hillegaart, V. & Ahlenius, S. (1999) Oxytocin as a possible mediator of SSRI-induced antidepressant effects. *Psychopharmacology*, **142**, 95-101.

Vanderschuren, L.J.M.J., Achterberg, E.J.M. & Trezza, V. (2016) The neurobiology of social play and its rewarding value in rats. *Neuroscience and biobehavioral reviews*, **70**, 86-105.

Verheij, M.M.M., Contet, C., Karel, P., Latour, J., van der Doelen, R.H.A., Geenen, B., van Hulten, J.A., Meyer, F., Kozicz, T., George, O., Koob, G.F. & Homberg, J.R. (2018) Median and Dorsal Raphe Serotonergic Neurons Control Moderate Versus Compulsive Cocaine Intake. *Biological psychiatry*, **83**, 1024-1035.

Volkow, N. & Li, T.-K. (2005) The neuroscience of addiction. *Nature Neuroscience*, **8**, 1429-1430.

Walf, A.A. & Frye, C.A. (2007) The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nature protocols*, **2**, 322-328.

Whalen, P.J., Kagan, J., Cook, R.G., Davis, F.C., Kim, H., Polis, S., McLaren, D.G., Somerville, L.H., McLean, A.A., Maxwell, J.S. & Johnstone, T. (2004) Human amygdala responsivity to masked fearful eye whites. *Science (New York, N.Y.)*, **306**, 2061-2061.

Wheeler, M.G., Duncan, E. & Davis, M. (2017) Low startle magnitude may be a behavioral marker of vulnerability to cocaine addiction. *Synapse (New York, N.Y.)*, **71**, 46-50.

Wills, T.A. & Hirky, A.E. (1996) Coping and substance abuse: A theoretical model and review of the evidence *Handbook of coping: Theory, research, applications.* John Wiley & Sons, Oxford, England, pp. 279-302.

Yang, X.M., Gorman, A.L., Dunn, A.J. & Goeders, N.E. (1992) Anxiogenic effects of acute and chronic cocaine administration: neurochemical and behavioral studies. *Pharmacology, biochemistry, and behavior*, **41**, 643-650.

Zorrilla, E.P., Logrip, M.L. & Koob, G.F. (2014) Corticotropin releasing factor: a key role in the neurobiology of addiction. *Frontiers in neuroendocrinology*, **35**, 234-244.