Deep brain stimulation of the nucleus accumbens core suppresses impulsive choice induced by heroin self-administration

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Abstract

Maladaptive impulsive behaviour is a common phenomenon amongst substance dependent subjects. Treatment interventions aiming at ameliorating impulsive behaviour are suggested to be effective for substance use dependence. Deep brain stimulation (DBS) is currently investigated as a new treatment. The nucleus accumbens (NA) is a candidate brain region due to its involvement in motivational and impulsive behaviour. In the current pilot study the effects of NAcore DBS on heroin induced impulsive choice was investigated in a translational rodent model.

To this end, rats were trained in a delayed reward task (DRT), to study impulsive choice. Upon stable responding, rats were subjected to heroin self-administration and extinction. Throughout heroin self-administration and extinction, rats were trained in the DRT and effects of NAcore DBS on impulsivity as measured in the DRT were investigated.

Impulsive choice was increased during heroin self-administration and decreased towards baseline levels during extinction. NAcore DBS decreased levels of impulsive choice during heroin self-administration, but not during extinction. This suggests that NAcore DBS is able to alter heroin induced impulsive choice.
Introduction

In this pilot study, we aim to integrate the findings of chapter 3, chapter 5, and chapter 6 to investigate whether the beneficial effects of accumbal deep brain stimulation (DBS) on motivational components of heroin taking and seeking are related to accompanying changes in impulsive choice. Maladaptive impulsive behaviour is a common phenomenon amongst substance dependent subjects, including opiate users (de Wit 2009). Chronic heroin intake has been associated with increased impulsive decision making in both preclinical and clinical studies (MacKillop et al. 2011; Perry and Carroll 2008; Schippers et al. 2012; Verdejo-Garcia et al. 2008). For that reason, impulsivity may be a vulnerability factor for poor treatment outcome in substance dependent subjects (Pattij and De Vries 2013; Stevens et al. 2014). Consequently, treatment interventions aiming at ameliorating impulsive behaviour are suggested to be effective for substance use dependence (SUD).

It is hypothesized that drug-induced alterations in the frontostriatal network, including the nucleus accumbens, account for disadvantageous behaviour such as maladaptive impulsivity (Jentsch and Taylor 1999). This integrative role of the NA in reward, motivation and impulsivity suggests that it is a potential target for treatment interventions aiming at reducing impulsive behaviour and preventing relapse. Distinct forms of impulsive behaviour appear to be mediated by distinct neurobiological substrates, including differential involvement of the nucleus accumbens (NA) (Basar et al. 2010; Pattij and Vanderschuren 2008; Winstanley 2011). Particularly, the NAc region is thought to be related to impulsive decision making (Bezzina et al. 2007; Cardinal et al. 2001; Pothuizen et al. 2005).

Recent studies have shown beneficial effects of accumbal DBS measures of substance use disorders and OCD. In animal models, we and others have shown that NAc DBS attenuates drug taking and seeking behaviour for alcohol and opiates (Guo et al. 2013; Henderson et al. 2010; Knapp et al. 2009; Liu et al. 2008; Ma et al. 2013; Nona et al. 2014; Schippers et al. 2017b; Yan et al. 2013). These aforementioned effects are supported by clinical case reports on NA DBS (Kuhn et al. 2014; Valencia-Alfonso et al. 2012; Zhou et al. 2011). Moreover, in preclinical models of impulsive behaviour, NAc DBS can affect impulsivity (Schippers et al. 2017a; Sesia et al. 2010; Sesia et al. 2008). In chapter 6, we reported that the effects of NAc DBS on impulsive behaviour are baseline-dependent, increasing impulsivity in low impulsive animals, while decreasing impulsive behaviour in high impulsive animals (Schippers et al. 2017a).

To our knowledge, the effects of DBS in preclinical impulsivity models have only been studied in drug naive animals. The aim of the experiment described in this chapter is to examine the effects of NAc DBS on impulsive decision making induced by heroin intake. Based on the findings reported in this thesis (chapter 3, 5, and 6 of this thesis;
stages of training, a session was divided into 5 blocks of 12 trials. After initiating the trial been described more elaborately previously (van Gaalen et al. 2006b). Briefly, in the final

through a nose poke into the central nose poke hole, each block started with 2 forced

Delayed reward task

pellet dispenser. A white house light was situated on the same wall as the food tray. 

beam for nose poke detection. On the opposite wall, a food magazine was situated, where

contained an array of five nose poke holes which could be illuminated and had an infrared

(Med Associates Inc., St. Albans, USA) in sound-attenuating ventilated cubicles. One wall

individual data by the equation


Material and Methods

Animals

Male Wistar rats weighing approximately 300 grams at start of experiments were obtained

from Harlan CPB (Horst, The Netherlands) and were housed in pairs until implantation of

DBS electrodes and IV catheter. Animals were kept under a reversed light/dark cycle

(lights on from 7 P.M. until 7 A.M.) at controlled room temperature (21±2°C) and relative

humidity of 60 ± 15%. The experiments were conducted during the dark phase of the

light–dark cycle from Monday – Friday. From the start of delayed reward training until the

end of the behavioural experiments, rats were food-restricted to 90% of their free-feeding

bodyweight. Water was available ad libitum during the entire experiment. All experiments

were approved by the Animal Care Committee of the VU University and VU University

Medical Center of Amsterdam.

Delayed reward task

Apparatus The delayed reward task was conducted in sixteen identical operant chambers

(Med Associates Inc., St. Albans, USA) in sound-attenuating ventilated cubicles. One wall

contained an array of five nose poke holes which could be illuminated and had an infrared

beam for nose poke detection. On the opposite wall, a food magazine was situated, where

the reward (45mg precision pellets, BioServ, Frenchtown, USA) could be delivered via a

pellet dispenser. A white house light was situated on the same wall as the food tray.

Delayed reward task The delayed reward paradigm as employed in our laboratory has

been described more elaborately previously (van Gaalen et al. 2006b). Briefly, in the final

stages of training, a session was divided into 5 blocks of 12 trials. After initiating the trial

through a nose poke into the central nose poke hole, each block started with 2 forced

trials during which either the second (left) or the fourth (right) nose poke hole were

illuminated in a counterbalanced fashion. In the next 10 trials, the animals had a free

choice and both the left and right unit were illuminated. Poking into one position resulted

in the immediate delivery of a small reinforcer (1 food pellet), whereas a nose poke into

the other position resulted in the delivery of a large, but delayed, reinforcer (4 food

pellets). If an animal did not make a response during this choice phase within 10s, an
intertrial interval (ITI) was initiated and the trial was counted as an omission. The position associated with the small and large reinforcer was always the same for each individual, and counterbalanced for the group of rats. Delays for the large reinforcer progressively increased within a session per block of 12 trials as follows: 0, 5, 10, 20, and 40s. Responding into non-illuminated units during the test was recorded, but had no further programmed consequences. The behavioural measure to assess task performance, i.e. the percentage preference for the large reinforcer as a function of delay, was calculated as the number of choices for the large reinforcer choices/(number choices large + small reinforcers) × 100. In addition, the total number of omitted started trials, forced trials and choice trials per block of 10 trials within a session, and the average response latencies to start a trial and to make a response in the nose poke hole associated with the small and large rewards after onset of the stimulus light in the corresponding hole were calculated. Furthermore, hyperbolic curves for the percentage preference were fitted on the individual data by the equation \( V = A/(1 + kD) \); where \( V \) is the preference for the large reward after a delay of \( D \) in seconds, \( A \) is the preference for the large reward at \( D=0s \) and \( k \) describes the steepness of the discounting curve (Mazur 2006). Based on the estimated hyperbolic curve, the indifference point, the delay for which the rats switched their preference over to the immediate, small reward (i.e., the delay on which the preference for large reward <50%) was calculated.

**Heroin self-administration**

**Apparatus**  Self-administration of heroin was conducted in sixteen identical operant chambers (Med Associates Inc., St. Albans, USA) in sound-attenuating ventilated cubicles. On one wall, 2 levers were situated, of which one was a retractable, active lever, which was presented during a session. A cue light was situated above the active lever. All boxes were equipped with an auditory clicker.

**Acquisition**  Rats were trained to self-administer heroin (diacetylmorphine-HCl, dissolved in 0.9% sterile saline, Slotervaart Hospital, The Netherlands) by pressing the active lever on a fixed-ratio-1 (FR1) schedule of reinforcement, whereby every lever press was reinforced with one infusion of 40μl heroin (100μg/kg/infusion) with a duration of 2s. Training consisted of 2.5h daily sessions (Monday-Friday). Heroin infusions were accompanied by a 5s presentation of the cue light and 5 short auditory clicks of 0.8s each. A house light was turned on during the entire session. Responses on the inactive lever were registered, but had no programmed consequences. After each drug infusion, a timeout period of 15s was introduced, during which a lever press had no consequences. Responses on the active and inactive lever were registered, during availability of the drug and during the time-out period. After nine days, rats had acquired a stable responding on
FR1 and the FR schedule of reinforcement was increased to FR2 (2 days) and FR4 (9 days), in which every second or respectively fourth active lever press was reinforced. 

Extinction  Subsequently, responding for heroin was extinguished. For 10 daily sessions of 60min, animals were placed in the operant chamber, but lever pressing did not result in the delivery of heroin or presentation of the heroin-associated cues.

Surgery

When all rats showed stable baseline performance in the DRT, they were surgically equipped with DBS electrodes and an intravenous catheter. Prior to surgery, rats received 5mg/kg Ketofen 1% s.c. and 8,33mg/kg Baytril 2.5% s.c.. Rats were implanted with a silicone catheter in the right jugular vein, under isoflurane gas anesthesia (±2%). Following catheter implantation, DBS electrodes (Plastics One, Roanoke, VA, USA) were bilaterally implanted using the following coordinates relative to bregma (Paxinos and Watson 1998): NAcore 2.3mm anteroposterior, 7.4mm dorsoventral, 2.7mm mediolateral under an angle of 8° relative to the midline sagittal plane of the skull (Pattij et al. 2007). Catheter pedestal and DBS electrodes were anchored to the skull with six stainless steel screws and dental acrylic cement. Until start of the self-administration experiments, catheters were locked with taurolidine-citrate catheter lock solution to prevent clot formation and bacterial growth. During self-administration, IV catheters were daily flushed with 0.05 ml sterile saline solution containing 0.25mg/ml heparin and 0.08mg/ml gentamicin.

Deep brain stimulation

Deep brain stimulation was performed with a digital stimulator (DS8000, World Precision Instruments, Sarasota, FL, USA) and stimulus isolator (DLS100, World Precision Instruments, Sarasota, FL, USA). During stimulation sessions, the electrode implants were attached to stimulation cables, which were attached to a stimulus isolator through a four-channel commutator (Plastics One, Roanoke, VA, USA). For stimulation, biphasic square pulses with 60μs pulse width, 200μs zero time, and 130Hz frequency were used. Stimulation intensity was set at 75μA, which is estimated to activate passing nerve fibres within 0.5 to 1mm radius (McIntyre and Grill 2001; Ranck 1975). These stimulation parameters are comparable to previously reported work on DBS in rats (Baunez et al. 2007; Darbaky et al. 2003; Sesia et al. 2010; Sesia et al. 2008; Tan et al. 2010; van der Plasse et al. 2012). Sham stimulation was applied by attaching the rats to DBS cables without stimulation. Stimulation was initiated 5min before the start of a session. Stimulation days were separated by at least two days. On other weekdays, baseline sessions were performed during which rats were attached to DBS cables to maintain habituation to the procedure and avoid procedural differences between test and baseline sessions.
Experimental design

Sixteen rats were trained in the delayed reward task as described above. Following DRT training, rats received bilateral DBS electrodes aimed at the NAcore and an IV catheter (Figure 7.1). After one week of recovery, rats were trained in the DRT to re-establish baseline performance during four weeks. Upon stable baseline behaviour, rats were habituated to attachment of the DBS cables during the DRT sessions for one week. Subsequently, 11 rats were trained to self-administer heroin and 5 rats were trained to self-administer saline (0.9% sterile saline instead of heroin) in addition to three DRT sessions a week. DRT training and testing was conducted in the morning, prior to heroin self-administration or extinction, to avoid direct influence of heroin consumption on decision-making. NAcore DBS was applied during DRT sessions on the 7th and 9th day of FR4 schedule of heroin self-administration, in a randomized within-subject fashion. Likewise, NAcore DBS was applied during DRT sessions on the 10th and 13th day of extinction training.

Figure 7.1 Schematic overview showing the experimental design of the present study. Delayed reward task training was conducted in the morning, prior to heroin self-administration or extinction. DBS was applied during the delayed reward task on day 7 and 9 of FR4 heroin/saline self-administration and day 10 and 13 of extinction. FR fixed ratio, DBS deep brain stimulation, SA self-administration, EXT extinction.

Electrode placement verification

After completion of the behavioural tests, animals were sacrificed and brains were removed and rapidly frozen using -80°C isopentane. Coronal sections of 40μm were cut on a cryostat and stained with cresyl violet for determination of the electrode placements. Only animals with correct electrode placements were included in the analyses.

Statistical analyses

All data are presented as means ± standard errors of the mean and were analysed using IBM SPSS Statistics 20.0 (IBM, New York, USA). Behavioural data from the DRT and self-administration were analysed using one way ANOVA or repeated measures ANOVA, with self-administration group (heroin or saline) as between-subjects factor and session or DBS treatment as within-subjects factor. In all repeated measures of ANOVA, degrees of freedom were corrected with Huyn-Feldt corrections, in case Mauchly’s test was significant and sphericity assumptions were violated. In case of statistical significant main
effects, further post hoc t-tests were performed, corrected for multiple comparisons. Statistical significance was set at $p<0.05$ for all analyses.

Results

**Histology and exclusion of rats**

The location of the DBS electrode placements in the NAcore is depicted in Figure 7.2. Most of the placements were dorsomedial within the NAcore at the level of 2.20mm and 1.70mm rostral to bregma. In the heroin group, one rat had misplaced DBS electrodes and one rat had a clogged catheter. In addition, one rat displayed a high number of start omissions in the DRT during the DBS test days (24±13.8, one test day all trials were omitted). In the saline group, one rat did not achieve stable baseline performance on the DRT after surgery (<50% preference for the large reward on all delays). This resulted in eight rats for heroin and four rats for saline self-administration group that were included in the analyses.

![Figure 7.2](image-url)  
**Figure 7.2** Verification of DBS electrodes placement in the NAcore at the level of 2.70, 2.20, 1.70, and 0.70mm rostral to bregma. Rats with placements of DBS electrodes at 2.70mm rostral to bregma were excluded from analysis. Grey circle depicts estimated maximal stimulation area around an electrode tip (McIntyre and Grill 2001; Ranck 1975). Drawings are adapted from Paxinos and Watson (1998).

**Impulsive choice during heroin self-administration**

All animals showed a stable preference for the large reward during baseline DRT training, before start of the self-administration procedures (delay $F(4, 44)=31.96$, $\varepsilon=0.67$, $p<0.001$;
session × delay $F(8,88)=0.76$, $\epsilon=0.93$, N.S.). Furthermore, rats in the heroin group readily acquired heroin self-administration during nine daily sessions on an FR1 reinforcement schedule and distinguished between active and inactive lever (session $F(8,56)=2.35$, $p=0.03$; lever $F(1,7)=0.50$, N.S.; lever × session $F(8,56)=6.12$, $p<0.001$). Subsequently, they revealed stable responding on an FR2 (session $F(1,7)=0.53$, N.S.; lever $F(1,7)=15.06$, $p=0.006$; lever × session $F(1,7)=2.64$, N.S.) and FR4 self-administration schedule (session $F(5,35)=2.06$, N.S.; lever $F(1,7)=21.03$, $p=0.003$; lever × session $F(5,35)=2.92$, $p=0.03$; Figure 7.3 A). During ten subsequent sessions, responding was extinguished and all rats rapidly attenuated responding on the previously active lever (session $F(9,63)=4.21$, $p<0.001$; lever $F(1,7)=5.90$, $p=0.045$; lever × session $F(9,63)=6.32$, $p<0.001$; Figure 7.3 B).

Saline self-administration revealed stable responding during all fixed-ratio schedules, without differentiating the preference for the active or inactive lever (FR1: session $F(8,24)=1.34$, N.S.; lever $F(1,3)=2.67$, N.S.; lever × session $F(8,24)=2.95$, $p=0.019$; FR2: session $F(1,3)=1.03$, N.S.; lever $F(1,3)=1.31$, N.S.; lever × session $F(1,3)=1.21$, N.S.; FR4: session $F(5,15)=0.61$, N.S.; lever $F(1,3)=0.38$, N.S.; lever × session $F(5,15)=1.22$, N.S.; Figure 7.3 A). The absence of stimuli during ten extinction sessions did not influence responding on either lever in the saline group (session $F(9,27)=1.38$, N.S.; lever $F(1,3)=0.42$, N.S.; lever × session $F(9,27)=0.74$, N.S.; Figure 7.3 B).

During the period of heroin or saline self-administration and extinction, the rats were trained three times a week on the DRT. Heroin but not saline exposure altered the preference for the large reward (session × group $F(4,40)=2.78$, $p=0.040$; session × delay × group $F(16,160)=1.70$, $p=0.052$). Analyses of the indifference points revealed no significant difference (session $F(4,40)=0.72$, $\epsilon=0.74$, N.S.; session × group $F(4,40)=0.45$, $\epsilon=0.74$, N.S.; group $F(1,10)=0.16$, N.S.; Figure 7.4 A). However, additional analyses of the percentage change in indifference point compared to baseline levels showed that the indifference point decreased in the heroin group over time (session $F(4,40)=1.65$, $\epsilon=0.69$, N.S.; session × group $F(4,40)=2.09$, $\epsilon=0.69$, N.S.; group $F(1,10)=4.34$, $p=0.064$; Saline group: session $F(4,12)=0.54$, N.S.; Heroin group: session $F(4,28)=292$, $p=0.008$). Post-hoc comparisons showed that the indifference point of the heroin group was significantly decreased during FR2 compared to baseline, indicating increased impulsive choice ($p=0.013$; Figure 7.4 B). Analyses of parameters of motivation revealed a significant interaction between session and group for ITI responses ($F(4,40)=5.17$, $\epsilon=0.40$, $p=0.024$) and forced trials omissions ($F(4,40)=6.32$, $p<0.001$). Post-hoc analyses revealed no significant differences for ITI responses. Forced trial omissions differed between groups during the FR1 phase of self-administration. Notably, the difference was very small (saline 2.3±0.5 vs heroin 3.1±0.6). Start omissions ($F(4,40)=2.41$, N.S.), choice omissions ($F(4,40)=1.23$, $\epsilon=0.62$, N.S.), response latencies to start ($F(4,40)=1.52$, N.S.) and for a small ($F(4,40)=1.42$, $\epsilon=0.68$, N.S.) and large reward ($F(4,40)=0.90$, $\epsilon=0.39$, N.S.) were not altered.
Effects of NACore DBS on heroin-induced impulsive choice

Upon stable responding on an FR4 schedule of self-administration, the effects of NACore DBS on heroin-induced impulsive choice were assessed in the DRT. A significant interaction between DBS treatment, self-administration group and delay indicated that DBS had differential effects in the heroin and saline group (DBS × group \(F(1,10)=1.17\), N.S.; DBS × delay × group \(F(4,40)=3.09, p=0.026\)). Further analyses revealed a specific effect of
NAcore DBS on impulsive choice of the heroin group (DBS $F(1,7)=1.31$, N.S.; delay $F(4,28)=19.42$, $p<0.001$; DBS $\times$ delay $F(4,28)=3.47$, $p=0.020$; Figure 7.5 A), the saline group remained unaffected (DBS $F(1,3)=3.78$, $p=0.147$; delay $F(4,12)=16.54$, $p<0.001$; DBS $\times$ delay $F(4,12)=2.14$, N.S.; Figure 7.5 B). Post-hoc analyses of the heroin group showed that on the 5sec delay, NAcore DBS increased the preference for the large reward significantly compared to sham stimulation ($t(7)=2.58$, $p=0.036$). These findings were not supported by the analyses of the indifference points, presumably because the indifference points are around a delay of 25s for the heroin group (DBS $F(1,10)=4.70$, $p=0.055$; DBS $\times$ group $F(1,10)=1.75$, N.S.; group $F(1,10)=0.49$, N.S.). Other parameters of motivation were not significantly altered by NAcore DBS (ITI responses $F(1,10)=0.21$, N.S.; omissions start $F(1,10)=0.58$, N.S.; omissions choice $F(1,10)=0.28$, N.S.; omissions forced $F(1,10)=2.40$, N.S.; latency small reward $F(1,10)=1.35$, N.S.; latency large reward $F(1,10)=0.01$, N.S.; latency start trial $F(1,10)=1.24$, N.S.; Table 7.1).

When heroin self-administration was extinguished after ten sessions, effects of NAcore DBS on impulsive choice were re-assessed. Analyses showed that NAcore DBS did not alter the preference for the large reward at this stage in both groups (DBS $F(1,10)=0.10$, N.S.; group $F(1,10)=0.09$, N.S.; DBS $\times$ group $F(1,10)=0.40$, N.S.; DBS $\times$ delay $\times$ group $F(4, 40)=1.74$, N.S.; Figure 7.5 C and D). This was supported by the absence of significant effects on the indifference point (DBS $F(1,10)=0.06$, N.S.; group $F(1, 10)=0.27$, N.S.; DBS $\times$ group $F(1,10)=0.78$, N.S.). In addition, parameters of motivation were not significantly altered (ITI responses $F(1,10)=0.07$, N.S.; omissions start $F(1,10)=1.85$, N.S.; omissions choice $F(1,10)=0.88$, N.S.; latency small reward $F(1,10)<0.001$, N.S.; latency large reward $F(1,10)<0.001$, N.S.; latency start trial $F(1,10)=0.58$, N.S.), except omissions of forced trails revealed a significant interaction between group and DBS treatment ($F(1,10)=5.40$, $p=0.043$). Post-hoc analyses revealed a significant, yet small, difference between groups during NAcore DBS (saline $1.0\pm 0.4$ vs heroin $2.6\pm 0.4$; Table 7.2).

On DBS test days, self-administration was assessed in the afternoon, in the absence of acute DBS. During the FR4 schedule of reinforcement, rats that had received NAcore DBS in the morning during DRT displayed significantly less responses (active and inactive) in the self-administration paradigm ($F(1,10)=5.25$, $p=0.045$), independent of self-administration group (group $F(1,10)=0.54$, N.S.; session $\times$ group $F(1,10)=1.12$, N.S.). DBS on the final extinction days did not exhibit effects on responding in the extinction context ($F(1,10)=0.14$, N.S.).
Figure 7.5 Percentage choice for large reward in the DRT during sham stimulation and NAcore DBS during A heroin self-administration on FR4 schedule, B saline self-administration on FR4 schedule, C extinction of heroin self-administration and D extinction of saline self-administration.
Table 7.1 Effects of 75µA NAcore DBS on auxiliary measures in the DRT during the period of heroin or saline self-administration on a FR4 schedule

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<tr>
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<th>Heroin</th>
<th>Saline</th>
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<tbody>
<tr>
<td></td>
<td>0µA</td>
<td>75µA</td>
</tr>
<tr>
<td>ITI pokes (#)</td>
<td>210.0 ± 45.6</td>
<td>171.9 ± 47.9</td>
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<tr>
<td>Omission start (#)</td>
<td>5.6 ± 1.1</td>
<td>5.3 ± 1.1</td>
</tr>
<tr>
<td>Omission choice (#)</td>
<td>4.9 ± 0.8</td>
<td>4.6 ± 1.0</td>
</tr>
<tr>
<td>Omission forced trials (#)</td>
<td>3.0 ± 0.7</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Latency small reward (s)</td>
<td>0.74 ± 0.07</td>
<td>0.71 ± 0.04</td>
</tr>
<tr>
<td>Latency large reward (s)</td>
<td>0.79 ± 0.10</td>
<td>0.85 ± 0.12</td>
</tr>
<tr>
<td>Latency start trial (s)</td>
<td>2.22 ± 0.22</td>
<td>2.36 ± 0.22</td>
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Table 7.2 Effects of 75µA NAcore DBS on auxiliary measures in the DRT during the extinction period after heroin or saline self-administration

<table>
<thead>
<tr>
<th></th>
<th>Heroin</th>
<th>Saline</th>
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<tbody>
<tr>
<td></td>
<td>0µA</td>
<td>75µA</td>
</tr>
<tr>
<td>ITI pokes (#)</td>
<td>288.8 ± 66.2</td>
<td>331.6 ± 99.8</td>
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<tr>
<td>Omission start (#)</td>
<td>5.3 ± 1.6</td>
<td>4.0 ± 0.7</td>
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<tr>
<td>Omission choice (#)</td>
<td>4.9 ± 1.3</td>
<td>4.3 ± 0.8</td>
</tr>
<tr>
<td>Omission forced trials (#)</td>
<td>1.8 ± 0.4</td>
<td>2.6 ± 0.4</td>
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<tr>
<td>Latency small reward (s)</td>
<td>0.73 ± 0.05</td>
<td>0.91 ± 0.24</td>
</tr>
<tr>
<td>Latency large reward (s)</td>
<td>0.72 ± 0.05</td>
<td>0.73 ± 0.06</td>
</tr>
<tr>
<td>Latency start trial (s)</td>
<td>2.32 ± 0.30</td>
<td>2.03 ± 0.17</td>
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Discussion

In this pilot study, we addressed the hypothesis that DBS would reduce heroin-induced impulsive decision making. The data presented here are preliminary data with weak statistical effects and derived from small groups, especially with respect to the saline-trained group. Therefore, the results obtained here should be interpreted with caution. Nevertheless, the findings of this pilot study point toward a reduction of heroin-induced impulsive choice by NAcore DBS.

Rats that were subjected to heroin self-administration showed an increase in impulsive decision making as a consequence of accumulative heroin intake, consistent with our previous study (Schippers et al. 2012). NAcore DBS applied in the DRT during the heroin self-administration phase increased the preference for the large reward on the 5s delay, indicating a decreased impulsive choice in the heroin self-administration group. Similar NAcore DBS stimulation parameters did not alter impulsive choice after heroin taking was extinguished and impulsive choice had returned to control levels. The observed
effects were specific for rats with a history of heroin during self-administration, since impulsive choice in the saline self-administration group was not altered by NAcDBS.

Our results are in line with previous findings that DBS decreases impulsive behaviour in rats (Schippers et al. 2017a; Sesia et al. 2008). These studies have focused on the effects of DBS on baseline behaviour in drug-naive animals. To our knowledge, this is the first study that investigated the effects of NAcDBS on impulsive behaviour in animals concurrently self-administering heroin. This study shows that maladaptive impulsive decision making as a consequence of heroin intake can be influenced by DBS, potentially contributing to beneficial treatment effects of DBS on substance dependence.

We observed large individual differences in baseline impulsivity in both the heroin and the saline treated animals. Previous work has shown that effects of NAcDBS on impulsive behaviour are dependent on baseline measures: high trait impulsivity can be reduced by NAcDBS, whereas low impulsivity is suggested to be elevated by NAcDBS (Schippers et al. 2017a). As such, studying larger cohorts will create opportunities to explore individual effects in more depth.

To date, one clinical case report has specifically investigated the effects of NA DBS on gambling behaviour in a patient treated for severe alcohol dependence and this report showed a tendency towards less risky choice behaviour when DBS was applied (Heldmann et al. 2012). Despite differences in the employed paradigm and drug of abuse (heroin versus alcohol), these findings are in line with the current data, suggesting that NA DBS improves behavioural control in substance dependent subjects.

The current hypotheses on the mechanism of DBS postulate that DBS restores abnormal pathological network activity (Florence et al. 2016). In light of this, it is conceivable that NAcDBS changes the neuronal network that has been altered by chronic heroin intake. Chronic heroin abuse leads to adaptations in the frontostriatal network, which are considered to be involved in the development and maintenance of heroin addiction (Dacher and Nugent 2011; Goldstein and Volkow 2011; Kauer and Malenka 2007; Van den Oever et al. 2008). In addition, the frontostrital network has shown to play a crucial role in maladaptive forms of impulsive behaviour (Cardinal 2006; Clark et al. 2004; Dalley et al. 2008; Diekhof and Gruber 2010; Winstanley et al. 2004). Therefore, it is postulated that alterations in the frontostrital network induced by drug use may account for the disadvantageous behaviour such as impulsivity (Diekhof and Gruber 2010; Jentsch and Taylor 1999). The present findings show that NAcDBS improves impulsive decision making, which was altered as a result of heroin intake, suggesting that DBS restored the altered frontostrital network activity.

The current data, together with previous studies (Dalley et al. 2005; McNamara et al. 2010; Schippers et al. 2012), show that after a period of extinction, the effect of heroin on impulsive decision making disappears. In addition, no effects of DBS on impulsive
choice were observed after the animals had extinguished heroin self-administration. This suggests that the abovementioned effects of heroin on neuronal networks are transient, and disappear when heroin is not available anymore. However, many studies have found cellular alterations in PFC and PFC to NA projections in heroin-trained animals after a period of extinction or abstinence (Shen and Kalivas 2013; Van den Oever et al. 2008; Van den Oever et al. 2010a). In addition, clinical studies report decision making difficulties in former opiate dependents (Biernacki et al. 2016; Clark et al. 2006; Li et al. 2013) and high relapse rates after long periods of abstinence (Hser et al. 2015). Despite this, in the present study, no long lasting effects of heroin intake were observed on impulsive decision making. Perhaps prolonged heroin consumption in humans has more severe effects on cognition than was modelled in the present study.

In this study, we focused on heroin-induced changes in DRT performance. It would, however, be interesting to investigate whether attenuated cue-induced reinstatement by accumbal DBS (as reported in chapter 5) is related to decreased impulsive choice in the same subjects. Such direct relationship is not self-evident, though. For instance, previous work from our laboratory showed acute pharmacological challenges with methylphenidate decreased impulsive choice but increased reinstatement of cocaine seeking (Broos et al. 2012a), indicating that not all beneficial manipulations of impulsivity may have attenuating effects on reinstatement behaviour.

In conclusion, the current preliminary data show that NAcore DBS applied in the DRT during the heroin self-administration decreased impulsive choice, whereas similar stimulation parameters did not alter impulsive choice after heroin taking was extinguished. The observed effects suggest that NAcore DBS reduces heroin-induced impulsive decision making, which might be, at least in part, an explanation for the beneficial treatment effects of DBS in substance dependent patients.