Transient inactivation of the rat nucleus accumbens does not impair guidance of instrumental behaviour by stimuli predicting reward magnitude

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The involvement of the nucleus accumbens (NAc) in the determination of reaction times (RTs) of instrumental responses by the expectancy of future reward was investigated. A simple RT task demanding conditioned lever release was used, in which the upcoming reward magnitude (5 versus 1 pellet) was signalled in advance by discriminative cues. In rats which acquired the task, RTs of instrumental responses were significantly shorter to the discriminative cue predictive of high reward magnitude. Inactivation of the NAc by lidocaine had no effect on RTs and their determination by cue-associated reward magnitudes, and did not affect the rate of correct responses. In keeping with an earlier study, intra-NAc infusion of amphetamine decreased RTs, impaired RT determination by cue-associated reward magnitudes and reduced the rate of correct responses. The unexpected finding that lidocaine inactivation of the NAc had no effect parallels previous data showing that lesions of NAc did not impair RT performance, while manipulation of intra-NAc glutamate or dopamine transmission impaired various aspects of RT performance in comparable tasks. It is suggested that experimental manipulations such as transient and permanent inactivation, which almost completely inhibit NAc neuronal output, allow alternative routes to be used to effectively control behaviour in the task employed here. *Behavioural Pharmacology* 15:55–63

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Introduction

Expected reward value can strongly bias instrumental action (Cohen and Blum, 2002; Gold, 2003). Evidence for this comes from studies showing that the vigour of instrumental responses is determined by expected reward magnitudes. In rats, reaction times (RTs) of conditioned paw or head movements were shorter to those instructive cues predicting higher food reward (Brown and Bowman, 1995; Hauber *et al.*, 2000, 2001). Similarly, in primates, RTs of conditioned reaching or saccadic eye movements decreased with increasing attractiveness of expected rewards predicted by instructive cues (Hollerman *et al.*, 1998; Kawagoe *et al.*, 1998).

The nucleus accumbens (NAc) is a key component of a neural network comprising the amygdala, prefrontal cortex and ventral tegmental area, which subserves the assessment of the reward value of environmental stimuli and the control of goal-directed behaviour (Cardinal *et al.*, 2002). Anatomically, the NAc is interposed between limbic/cortical structures involved in the processing of the incentive significance of cues and motor structures involved in response selection and control (Watanabe, 1986; Everitt *et al.*, 1989; Schoenbaum *et al.*, 1998, 1999; Kelley and Berridge, 2002). The NAc receives glutamatergic input from prefrontal cortex, hippocampus, thalamus and amygdala, and a dopaminergic innervation from the ventral tegmental area (Groenewegen *et al.*, 1996). These afferents converge on dendritic spines of medium-sized spiny neurons in the NAc (Sesack and Pickel, 1990), projecting to the ventral pallidum and the substantia nigra. Therefore, glutamatergic and dopaminergic signals in the NAc might translate motivational signals related to the expected value of reward to motor output. Accordingly, electrophysiological studies demonstrated that striatal neurons show reward expectation-related activation elicited by reward-predicting stimuli (Apicella *et al.*, 1991; Schultz *et al.*, 1992; Kawagoe *et al.*, 1998; Carelli *et al.*, 2000; Lauwereyns, 2002a, b). Furthermore, behavioural studies revealed that the NAc subserves instrumental behaviour elicited by cues associated with natural reward or drugs of abuse (Everitt and Wolf, 2002; Kelly and Berridge, 2002).

In previous studies we investigated effects of reward expectation on the vigour of instrumental action, using a lever-release task in which RTs of instrumental responses were a function of the expected food reward magnitude

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signalled in advance by discriminative stimuli (Hauber *et al.*, 2000, 2001). It has been shown that glutamate and dopamine receptors in the NAc might contribute to processes guiding instrumental behaviour according to predictive information on future reward magnitude: blockade of intra-NAc alpha-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid/kainate (AMPA/KA) or *N*-methyl-D-aspartate (NMDA) receptors increased, while indirect stimulation of intra-NAc dopamine receptors decreased, RTs of instrumental responses guided by reward-predictive cues (Hauber *et al.*, 2000; Giertler *et al.*, 2003). However, in a similar task, a cell-body lesion of the NAc had no effects on guidance of instrumental RT performance by discriminative cues associated with different reward magnitudes (Brown and Bowman, 1995). One possible mechanism to account for this discrepancy is that cell-body lesions could induce post-lesion functional reorganization (e.g. Beal *et al.*, 1991; Alamy *et al.*, 1994), which prevents the demonstration of a role of the NAc. To address this issue in more detail, we investigated, in an RT task as described above, the effects of transient inactivation of the NAc by micro-injection of the local anaesthetic, lidocaine (Delfs *et al.*, 1990; Chen and Reith 1994; Seamans and Phillips, 1994; Graham *et al.*, 1995; Floresco *et al.*, 1996; Coleman-Mesches *et al.*, 1997; Floresco *et al.*, 1999; Howland *et al.*, 2002), in comparison with the well-known robust effects induced by intra-NAc amphetamine (Giertler *et al.*, 2001, 2003).

Methods

Subjects

Twelve male Sprague–Dawley rats (Charles-River, Sulzfeld, Germany) were housed in groups of up to four animals in transparent plastic cages ($36 \times 52 \times 25$ cm; Ferplast, Nürnberg, Germany). Temperature ($20 \pm 2^{\circ}$C) and humidity ($50 \pm 10\%$) were kept constant in the animal house and a reversed 12:12-hour light/dark cycle was used, with lights on from 19.00 to 07.00 hours. Behavioural testing was performed between 13.00 and 17.00 hours, during the dark phase. Rats were given free access to water. On days without behavioural testing, food was restricted to 12 g standard laboratory maintenance chow (Altromin, Lage, Germany) per animal. On days with behavioural tests, rats received 2–8 g food reward (45 mg pellets, Bioserv, Frenchtown, NJ, USA) in the testing apparatus, depending on their individual performance. On these days, the amount of standard laboratory chow given was adapted to a total of 12 g/animal per day, in order to keep their body weights constant. Rats weighed 200–250 g on arrival and 270–350 g at the time of surgery.

All animal experiments were approved by the proper authorities and carried out according to German Law on the Protection of Animals.

Surgery

For implantation of cannulae, animals were anaesthetized with sodium pentobarbital (50 mg/kg, i.p.) (Sigma–Aldrich Chemie GmbH, Taufkirchen, Germany), following pretreatment with atropine sulphate (0.05 mg/kg, i.p.) (Sigma–Aldrich Chemie GmbH), and secured in a Kopf stereotaxic apparatus (Kopf Instruments, Tujunga, USA). Bilateral 15 mm stainless-steel guide cannulae, with an outer diameter of 0.8 mm, were aimed at the NAc and implanted using standard stereotaxic procedures. The coordinates, with reference to the atlas of Pellegrino *et al.* (1986) (toothbar 5 mm above the interaural line), were: 3.2 mm anterior bregma, 1.7 mm lateral to midline, and 4.0 mm ventral from the dura. The guide cannulae were occluded by stainless-steel stylets. Animals were allowed 3 days for recovery with free access to food before postoperative training was started.

Drug microinfusion

Animals received bilateral intra-NAc infusions of the local anaesthetic drug lidocaine hydrochloride (Sigma–Aldrich Chemie GmbH) (20 µg and 80 µg in 0.5 µl 0.9% sterile saline), the indirect dopamine agonist [+]-α-methyl-phenethylamine (D-amphetamine sulphate; Sigma–Aldrich Chemie GmbH) (20 µg in 0.5 µl 0.9% sterile saline) or vehicle (0.5 µl 0.9% sterile saline).

On injection days, the stainless-steel stylets were removed and injection cannulae (outer diameter, 0.45 mm; length, 18 mm) were lowered at the final site of infusion and attached via polyvinylchloride tubing to microlitre syringes controlled by a syringe pump (Med Associates, St. Albans, VT, USA). The drugs were delivered over a 1-min interval. Injection cannulae were left in position for a further 1 min to allow for diffusion. Each rat remained in its home cage for an additional 5 min before being placed in the test chamber. To adapt animals to infusions, all rats received an intra-NAc infusion of saline (0.5 µl) 11 days post-surgery; the first drug infusion was given 2 days later.

Apparatus

Four operant test chambers ($24 \times 21 \times 30$ cm) (Med Associates) were used. Test chambers were placed in separate sound-attenuating cubicles, with fans providing a constant low level of background noise. Each chamber was supplied with a retractable lever, two stimulus lights, one above the retractable lever, the other above the food receptacle, and a food dispenser with a head entry detector in the receptacle. The experiments were controlled online by a computer system (SmartControl®-Interfaces, MedPC™-Software, Med Associates).

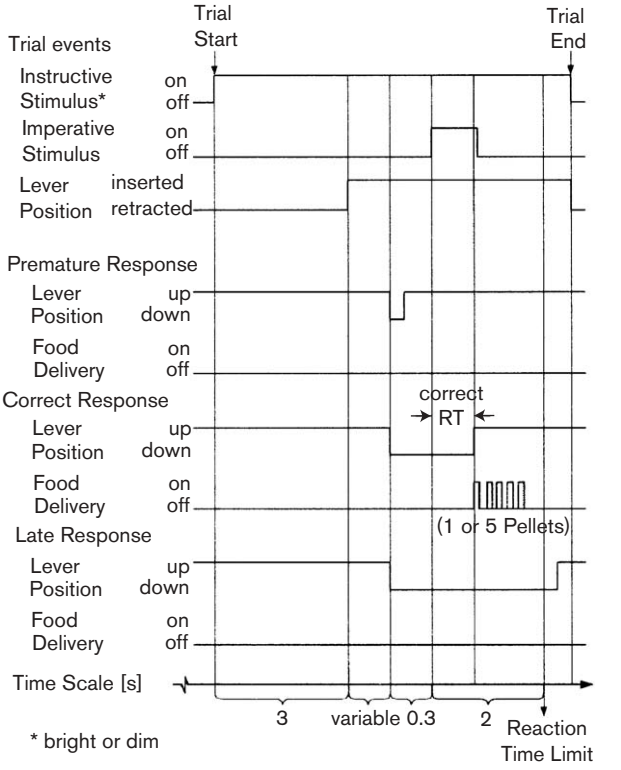
RT task

A simple RT task was used which demands conditioned lever release, with instructive stimuli indicating the reward magnitude to be obtained after a subsequent

imperative stimulus. Rats had to press the lever and to wait for the imperative stimulus, which was provided by the stimulus light above the lever after a foreperiod of 0.3 s. The imperative stimulus signalled to the rats to release the lever quickly and to respond to the food receptacle in which the food pellets were delivered (45 mg pellets, Bioserv, Frenchtown, USA). On each correct trial, the rats received either one or five food pellets. The number of pellets for each trial was pseudo-randomly determined in advance, and was signalled to the rats by two distinct brightness levels of the cue lights which provide the instructive stimuli. After an intertrial interval of 3 s, the instructive stimulus was turned on at the beginning of each trial, 3 s before lever insertion, and remained present until delivery of the food reward. To check for equal perception of instructive stimuli of the two different brightness levels, for 50% of the rats, a bright stimulus was associated with delivery of five pellets and a dim stimulus was associated with delivery of one pellet. For the other 50% of the rats, the opposite pattern was used.

Reaction time (RT), defined as latency from the onset of the imperative stimulus to lever release, and movement time (MT), defined as latency from lever release to photobeam disruption in the food receptacle, were recorded with an accuracy of less than 10 ms. For a correct trial, animals had to release the lever within 2 s. Responses before the onset of the imperative stimulus were defined as 'premature' responses, responses with RT longer than 2 s were defined as 'late' responses. A daily individual session demanded 70 correct trials, i.e. 35 correct trials for each reward magnitude (one and five pellets). A scheme of the order of trial events is given in Fig. 1. This RT task is different from the task used in a previous study (Hauber *et al.*, 2000) in that a fixed foreperiod (0.3 s), instead of a variable foreperiod between lever press and presentation of the imperative stimulus, was used. As a result, RTs became generally shorter, but the differences of RT of responses for high and low reward became larger and thus were more robust. This indicates that, despite the use of a fixed interval, RTs are clearly guided by the expected reward magnitude and not, for instance, by an internal clock.

Fig. 1



Schematic representation of the order of trial events. At the beginning of a trial (after the intertrial interval of 3 s), the instructive stimulus delivered by a cue light above the food receptacle was turned on at one of two brightness levels, which were associated with different reward magnitudes (one or five pellets). After 3 s, the lever was inserted. Thereafter, the rat pressed the lever spontaneously. After the foreperiod of 0.3 s, the imperative stimulus provided by a cue light above the lever signalled the animal to release the lever in order to get the food reward. Responses with RT < 2 s were considered as being correct and were rewarded as indicated by the instructive stimulus. Premature responses initiated before the onset of the imperative stimulus or late responses (RT > 2 s) caused the trial to be repeated with the identical foreperiod and reward magnitude.

Experimental procedure

Training

On the first day, subjects were habituated to the operant chamber. During this period, animals had free access to food pellets that had been placed in the food receptacle. In the following days, a habituation programme commenced whereby the lever was inserted. Once an animal learned to press the lever for reward with a fixed-ratio 1 (FR-1) schedule, it progressed to the final task. After training in the RT task for 2–3 weeks to establish stable performance, animals underwent surgery. After recovery, postoperative training was given for 1 week to attain preoperative accuracy levels.

Testing procedure

All animals were trained in one daily session for 7 days/week during the complete testing period. Every fourth session, all animals received an intra-NAc microinfusion. In the remaining sessions, all animals were subjected to a handling procedure similar to the handling procedure during microinfusion, to minimize stress effects.

Three experiments were performed in consecutive order. In the first experiment, the effect of a low dose of intra-NAc lidocaine was investigated. The experiment consisted of two sessions with infusions; the order of microinfusions (vehicle 0.5 µl, 20 µg lidocaine in 0.5 µl vehicle) was randomly assigned to the individual animals

($n = 12$) according to a Latin square design. In the second experiment, the effect of a high dose of intra-NAc lidocaine was examined. The experiment comprised two sessions with infusions; the order of vehicle and lidocaine infusions (vehicle 0.5 µl, 80 µg lidocaine in 0.5 µl) was randomly assigned to individual animals ($n = 11$). In the third experiment, the effect of intra-NAc indirect stimulation of dopamine receptors was investigated. The experiment consisted of two sessions with microinfusions; the order of microinjections (vehicle 0.5 µl, D-amphetamine 20 µg in 0.5 µl) was randomly assigned to the individual animals ($n = 10$). Each animal was tested in all three experiments and received a total of six infusions. However, after experiments 1 and 2, respectively, one animal could not be used for further experiments. For this reason, sample sizes became smaller in later experiments.

Histology

After completion of behavioural testing, animals were euthanized by an overdose of sodium pentobarbital (150 mg/kg, i.p.) (Sigma–Aldrich Chemie GmbH), to control for correct placement of cannulae. Brains were removed rapidly, fixed in 10% formalin for 2.5 h and stored in 30% glucose. Brain sections (30 µm) were cut with a cryostat (Reichert and Jung, Heidelberg, Germany), mounted on coated slides and stained with cresyl violet. Cannulae placements were verified with reference to the atlas of Pellegrino *et al.* (1986).

Data analysis

Results showed that rats discriminated bright and dim stimuli; therefore performance and RT data obtained with both stimulus patterns were pooled. Treatment effects were assessed by within-subjects comparisons of control and drug groups. Due to considerable inter-individual variability of baseline performance, a between-subjects design would be less powerful (Winer, 1971). Two-way ANOVAs were conducted, with treatment and reward magnitude as within-subjects factors, followed by planned contrast analysis.

Each rat had to reach the criterion of 70 correct responses (RT < 2 s) per session. Drug effects on accuracy of task performance were determined by using the rate of correct responses from the total number of trials per session necessary to attain the criterion of 70 correct responses [(correct responses/premature + correct + late responses) × 100%].

The analyses of RT and MT performance were conducted with the RT and MT data from correct responses (RT < 2 s). In order to decrease the influence of outlying data points on arithmetic means, geometric means of RT and MT of responses with expected high and low reward magnitude, respectively, were calculated for each rat for each session. Overall means of RT and MT of responses with expected high and low reward magnitude, respectively, represent the arithmetic average of the geometric means of individual rats. Data were expressed as means ± standard error of the mean (SEM). After postoperative training, rats showed a positive RT and MT difference, i.e. RT and MT of responses with an expected low reward magnitude were significantly longer than those with an expected high reward magnitude. The RT difference was used as an index of RT guidance by reward expectancy (Hauber *et al.*, 2000).

Statistical computations were carried out with the statistic software STATISTICA™ (Version 5.5, StatSoft®, Inc., Tulsa, Oklahoma, USA). The level of statistical significance (α-level) was set at $P < 0.05$.

Results

Histological results

Animals were evaluated only if cannula tip placements deviated less than 0.5 mm from target coordinates in the NAc. No animal was excluded due to cannula misplacement. The locations of cannulae tips for all rats are shown in Fig. 2.

Postoperative performance

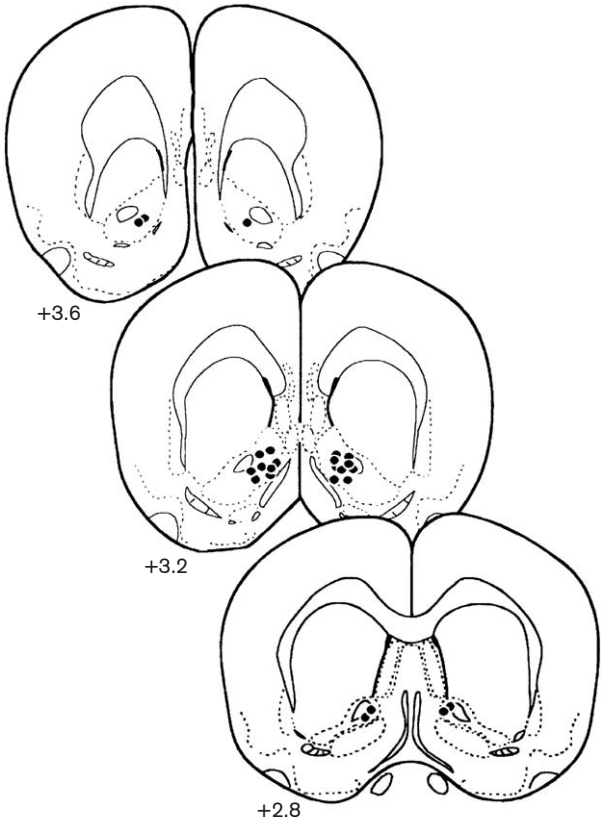
After 6 postoperative days of training, RTs were significantly determined by the number of expected pellets, as signalled by the instructive stimulus. Expectancy of a high reward magnitude produced a significantly positive RT difference of 59 ± 6 ms, i.e. overall RTs were significantly longer with the expectancy of a low reward magnitude (238 ± 9 ms) as compared to a high reward magnitude (180 ± 7 ms) [$F(1,142) = 27.22$; $P < 0.001$; $n = 12$] (not shown).

Effects of intra-NAc infusion of lidocaine

Infusion of a low dose of lidocaine (20 µg per side) did not impair the accuracy of task performance [$F(1,11) = 0.04$; $P = 0.85$], as shown in Fig. 3. In addition, RT performance was not affected. The speed of behavioural responses was still determined by the reward magnitudes as predicted by the instructive stimuli, i.e. RTs were shorter after the stimulus predictive of higher reward. A two-way ANOVA on RT data, with treatment and reward magnitude as factors, revealed no significant effect of treatment [$F(1,11) = 0.002$; NS], a significant effect of reward magnitude [$F(1,11) = 14.84$; $P < 0.01$], and no treatment × reward magnitude interaction [$F(1,11) = 0.07$; NS]. Another two-way ANOVA on MT data, with treatment and reward magnitude as factors, revealed no significant effect of treatment [$F(1,11) = 1.26$; NS], a significant effect of reward magnitude [$F(1,11) = 9.62$; $P < 0.01$], and no treatment × reward magnitude interaction [$F(1,11) = 0.02$; NS].

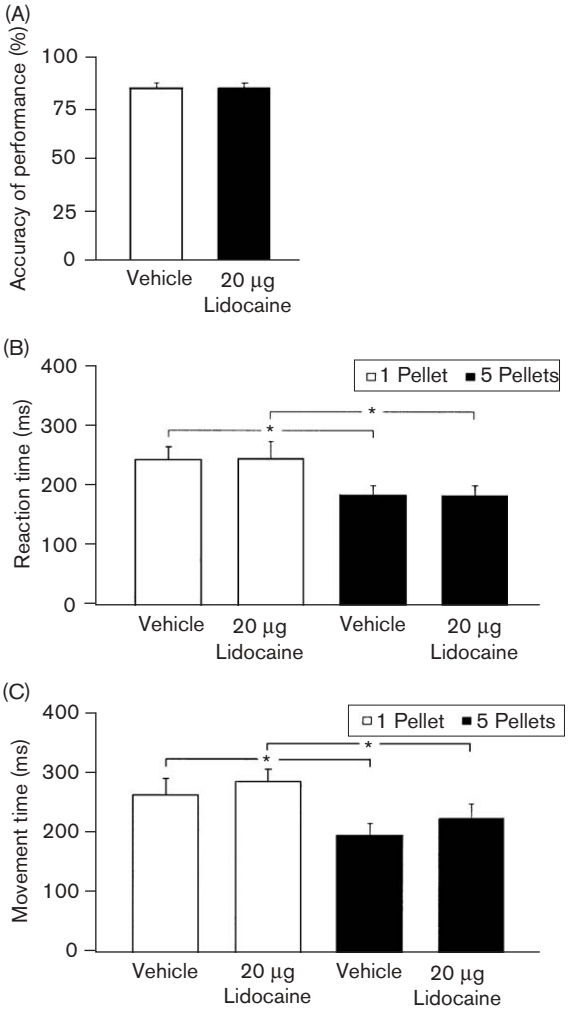
After infusion of a high dose of lidocaine (80 µg/side) into the NAc, the accuracy of task performance was not

Fig. 2



Location of cannula tips in the NAc. The schematics depict the location of cannula tips (●) in the NAc for all rats used for data analysis. Plates are adaptations from the atlas of Pellegrino *et al.* (1986). Numbers beside each plate correspond to millimetres anterior from bregma.

Fig. 3



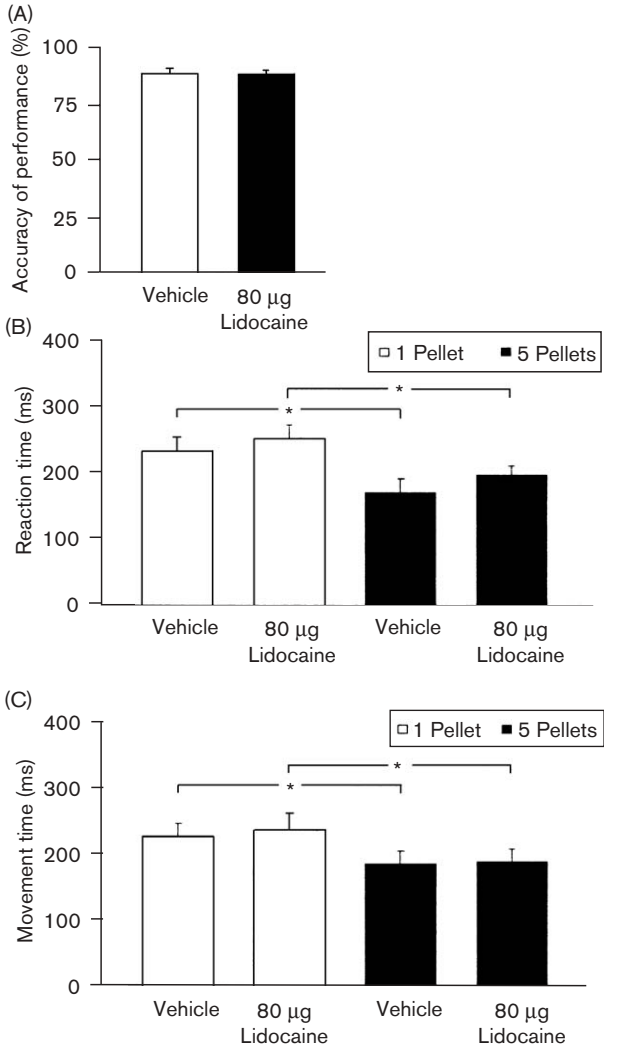
Effects of a bilateral intra-NAc infusion of lidocaine (20 µg in 0.5 µl vehicle) or vehicle (0.5 µl) on accuracy of task performance (A), reaction times (B), and movement times (C). Data are expressed as means + SEM. Symbols indicate significant differences (*$P < 0.01$: 1 versus 5 pellets), determined by a two-way ANOVA followed by *post-hoc* analysis with planned contrasts.

altered [$F(1,10) = 0.001$; NS: Fig. 4]. Furthermore, RT performance was not affected. The speed of behavioural responses was a function of reward magnitude as predicted by the instructive stimuli, i.e. RTs were shorter after the stimulus predictive of higher reward. A two-way ANOVA on RT data, with treatment and reward magnitude as factors, revealed no significant effect of treatment [$F(1,10) = 4.77$; $P = 0.054$], a significant effect of reward magnitude [$F(1,10) = 17.17$; $P < 0.01$], and no treatment × reward magnitude interaction ($F(1,10) = 0.10$; $P =$ NS). Two-way ANOVA on MT data, with treatment and reward magnitude as factors, also revealed no significant effect of treatment [$F(1,10) = 0.24$; NS], a significant effect of reward magnitude [$F(1,11) = 17.70$; $P < 0.02$], and no treatment × reward magnitude interaction ($F(1,11) = 1.10$; NS) (Fig. 5).

Effects of intra-NAc infusion of D-amphetamine

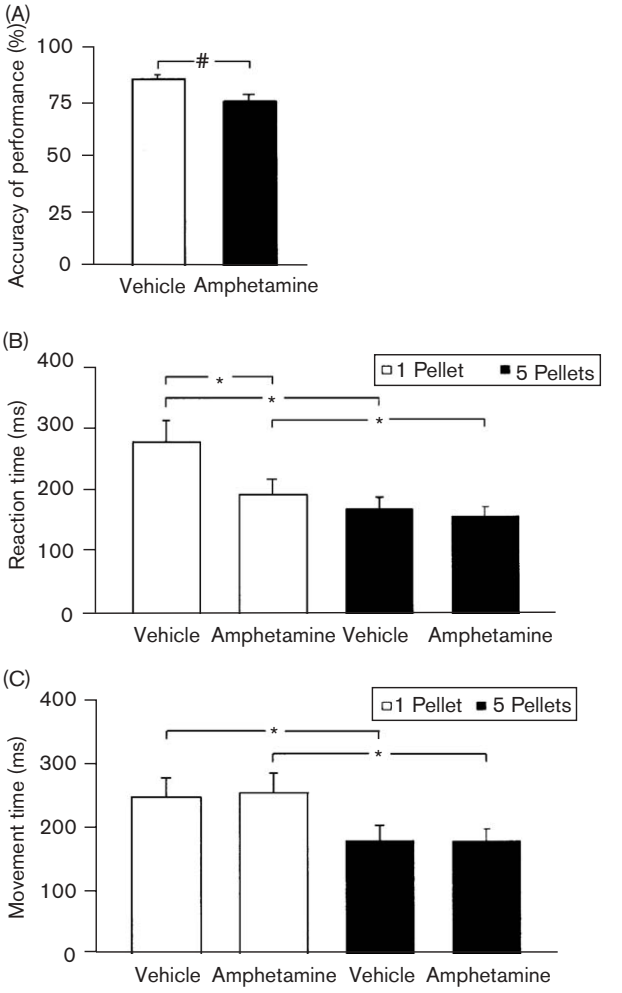
After intra-NAc infusion of D-amphetamine, the accuracy of task performance was significantly impaired [main effect of treatment: $F(1,9) = 10.12$; $P = 0.01$]. Also, RT of responses to the stimulus predictive of low reward magnitude were significantly shorter [$F(1,9) = 17.27$; $P < 0.01$]. A two-way ANOVA on RT data, with treatment and reward magnitude as factors, revealed a significant effect of treatment [$F(1,9) = 12.72$; $P < 0.01$], a significant effect of reward magnitude [$F(1,9) = 11.31$; $P < 0.01$] and a significant treatment × reward magnitude interaction [$F(1,9) = 11.86$; $P < 0.01$]. In contrast, intra-NAc infusion of D-amphetamine had no significant effect on MT [$F(1,9) = 0.02$; NS], a significant effect of reward magnitude [$F(1,9) = 13.27$; $P < 0.01$] and no treatment × reward magnitude interaction [$F(1,9) = 0.41$; NS].

Fig. 4



Effects of a bilateral intra-NAc infusion of lidocaine (80 µg in 0.5 µl vehicle) or vehicle (0.5 µl) on accuracy of task performance (A), on reaction times (B), and on movement times (C). Symbols indicate significant differences (*$P<0.01$ for 1 versus 5 pellets), determined by a two-way analysis of variance followed by *post-hoc* analysis with planned contrasts.

Fig. 5



Effect of intra-NAc stimulation of catecholamine release by microinfusion of amphetamine (20 µg in 0.5 µl vehicle) or vehicle (0.5 µl) on the accuracy of task performance (A), on reaction times (B) and on movement times (C). Symbols indicate significant differences (*$P<0.01$ for 1 pellet versus 5 pellets; #$P<0.05$ for vehicle versus amphetamine group), determined by a two-way analysis of variance followed by *post-hoc* analysis with planned contrasts.

Discussion

The present results are consistent with previous findings in intact rats (Brown and Bowman, 1995; Hauber *et al.*, 2000, 2001) and primates (Bowman *et al.*, 1996; Shidara *et al.*, 1998) that RTs of instrumental responses were shorter to cues predicting higher reward magnitude. Furthermore, the present study confirms an earlier result that intra-NAc amphetamine both decreased RT and affected RT determination by cue-associated reward magnitudes (Giertler *et al.*, 2003). Paradoxically, transient inactivation of the NAc by lidocaine had no effect on RTs or their determination by cue-associated reward magnitudes. This latter finding corroborates previous data that excitotoxic lesions of the NAc did not affect the speeding of RT as a function of reward-size expectation (Brown and Bowman, 1995).

Intra-NAc infusion of amphetamine compromised the accuracy of performance, shortened RT and affected guidance of RT by cue-related reward magnitudes. This pattern of impairments is in accord with the effects of intra-NAc amphetamine determined in a recent study from our laboratory using the same RT task (Giertler *et al.*, 2003). The lowered accuracy of performance is due to the reduced proportion of correct responses, i.e. responses initiated within 2 s after presentation of the imperative stimulus. This, in turn, is predominantly

brought about by an amphetamine-induced increase of premature responses, which has been consistently demonstrated to occur in various RT tasks after systemic and intra-NAc administration of amphetamine (e.g. Cole and Robbins, 1987; Baunez *et al.*, 1995; Harrison *et al.*, 1997). Likewise, RTs were found to be shortened after intra-NAc amphetamine, as also observed after systemic administration (e.g. Baunez *et al.*, 1995; Brown *et al.*, 1996). However, in the present task, amphetamine selectively shortened the RT of responses with an expected low, not high, magnitude, and left MT unaffected. As MTs were not significantly altered by intra-NAc amphetamine, a non-specific motor activation is unlikely to account for the effects measured on RT. Rather, non-motor effects might decrease the RT of responses directed to expected low reward. The lack of effect of amphetamine on the RT of responses directed to the higher reward is most probably the result of a ceiling effect, because respective RTs in our vehicle-treated animals were already below 200 ms and close to the estimated maximal reactive capacity of rats (Spirduso and Abraham, 1981).

Intra-NAc stimulation of dopamine transmission is known to invigorate instrumental responding for food-related cues (e.g. Taylor and Robbins, 1984; Kelley and Throne, 1992; Burns *et al.*, 1993). Thus, one possible mechanism underlying the reduced RT to the cue predicting low-reward magnitude might be an amplification of the reinforcing signal provided (Giertler *et al.*, 2003).

Intra-NAc infusion of a low (20 μg) and a high dose (80 μg) of lidocaine did not have significant effects either on RTs and their guidance by expected reward magnitudes or on accuracy of task performance. However, in the case of the high dose of lidocaine, there was a trend towards a significant effect ($P = 0.054$). Thus, it cannot be excluded that, for example, a higher dose of lidocaine might affect RT guidance. The lack of effect was unexpected in view of previous findings that intra-NAc infusion of the preferential dopamine receptor antagonist haloperidol, the NMDA receptor antagonist AP5 and the AMPA/kainate receptor antagonist CNQX, impaired various aspects of RT performance in the same (Giertler *et al.*, 2003) or a comparable task (Hauber *et al.*, 2000).

It is unlikely that these negative results are simply due to the use of inappropriate drug concentrations or volumes. Intracranial lidocaine infusions are widely used for reversible inactivation of circumscribed neuronal populations (Mogenson and Yang, 1991; Chen and Reith, 1994; Coleman-Mesches *et al.*, 1997; Evans and Cory-Slechta, 2000; Vazdarjanova *et al.*, 2001; Howland *et al.*, 2002), in particular in the NAc (Delfs *et al.*, 1990; Seamans and Phillips, 1994; Floresco *et al.*, 1996, 1999), and the volume and concentration used here were comparable with these studies.

Behavioural studies indicate that recovery after subcortical lidocaine inactivation occurs within 15–45 min (Demer and Robinson, 1982; Cooper *et al.*, 1989). According to Floresco *et al.* (1996), behavioural effects after intra-NAc infusion of lidocaine can be observed up to 10–12 min. In our task, depending on the individual performance, a session was completed 10–15 min after intra-NAc infusion of lidocaine, i.e. within the period of its presumed maximum efficacy. Taken together, these data suggest that the concentration and the timing of lidocaine infusions were appropriate to inactivate major parts of the NAc during the behavioural experiment performed here. Thus, the present data suggest that a presumed transient inactivation of the NAc did not affect RT performance and its guidance of cue-related reward magnitudes.

A similar result has been reported after a permanent lesion of the NAc using the neuroexcitoxin ibotenic acid (Brown and Bowman, 1995). The lack of effect of an acute inactivation renders unlikely the possibility that the initiation of post-lesion functional compensatory processes account for the negative results following a permanent lesion. By contrast, pharmacological manipulation of intra-NAc neurotransmission by amphetamine, as shown here and in a previous study using the same task (Giertler *et al.*, 2003), as well as by AP5, CNQX or haloperidol using a comparable task (Hauber *et al.*, 2000), affected different aspects of performance. This apparent paradox is difficult to explain. Simple reasoning suggests that transient lidocaine activation of the NAc, and blockade of ionotropic glutamate receptors in the NAc, should have at least some behavioural effects in common.

The fact that alternative techniques used to block different aspects of neuronal functions in the NAc can have different behavioural outcomes deserves further consideration. Regarding locomotor activity, it is well known that cell-body lesions of the NAc produce hyperactivity (Annett *et al.*, 1989; Everitt *et al.*, 1991; Reading and Dunnett, 1995), which is seen particularly following lesions of the NAc core compartment (Parkinson *et al.*, 1999). Likewise, there is evidence that AMPA/KA receptor antagonism in the entire NAc enhanced locomotor activity (Roozendaal *et al.*, 1990; Boldry, 1992; Burns *et al.*, 1994). However, AMPA/KA receptor blockade in the NAc shell versus core can elicit different motor effects (Burns *et al.*, 1994; Maldonaldo and Kelley, 1994). Regarding intra-NAc NMDA receptors, it has been demonstrated that their blockade decreased (Maldonado and Kelley, 1994) or increased spontaneous locomotor activity (Burns *et al.*, 1994; Cornish and Kalivas, 2000). On the other hand, intra-NAc infusion of $GABA_A$ agonists inhibited locomotion (e.g. Scheel-Kruger *et al.*, 1977; Wong *et al.*, 1991). Although drug concentrations, stereotaxic coordinates for microinfusions and other methodological issues differ across these studies, it is evident that,

with regard to locomotor activity, different pharmacological techniques to inhibit aspects of NAc neuronal activity produce variable behavioural effects. Remarkably, intra-NAc infusion of cocaine elicited hyperlocomotion, while the local anaesthetic drugs procaine and lidocaine had no overall effect on locomotor activity (Delfs *et al.*, 1990), thus paralleling, to some extent, our present results.

There is compelling evidence that transient lidocaine inactivation produces behavioural impairments in a number of tests (e.g. Seamans and Phillips, 1994; Floresco *et al.*, 1996, 1997). However, the studies presented suggest that, at least in some cases, transient (present study) or permanent inactivation of the NAc by cell-body lesions (Brown and Bowman, 1995) are devoid of behavioural effects, while other pharmacological manipulations produce behavioural impairments. One possible explanation for this discrepancy is provided by clinical findings that inactivation of the internal part of the globus pallidus, a major basal ganglia output structure, paradoxically ameliorates both parkinsonism and dyskinesia in parkinsonian patients, but produces few deficits on its own (Marsden and Obeso, 1994; Brown and Marsden, 1998), contrasting predictions derived from current models of the basal ganglia functions (Albin *et al.*, 1989). These findings have been suggested to indicate that, for some aspects of motor control, it might be better to have no basal ganglia output signals to the thalamus than 'noisy' ones (Marsden and Obeso, 1994; Brown and Marsden, 1998). A similar mechanism might account for the present findings. That is, permanent or transient lesion of the NAc might almost completely inhibit NAc output signals, allowing alternative routes, other than via the NAc, to be used to control behaviour in the task investigated here. By contrast, pharmacological manipulation, such as ionotropic glutamate receptor blockade, inhibits only specific components of NAc neurotransmission, probably resulting in 'noisy' output signals interfering with task performance.

Taken together, the present data suggest that transient lidocaine inactivation of the NAc does not necessarily disrupt aspects of RT performance in the task used here, unlike manipulation of dopamine or glutamate neurotransmission in the NAc. It is speculated that transient, as well as permanent, inactivation almost completely inhibits NAc neuronal output, thus allowing alternative routes to be used to effectively control behaviour, at least in the task employed here.

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