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Prefrontostriatal Circuitry Regulates Effort-Related Decision Making

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The anterior cingulate cortex (ACC), the basolateral amygdala (BLA), and the dopamine in the nucleus accumbens (NAc) are part of a neural system that is critically involved in making decisions on how much effort to invest for rewards. In the present study, we sought to identify functional interactions between ACC and NAc regulating effort-based decision making. Rats were tested in a T-maze cost–benefit task in which they could either choose to climb a barrier to obtain a large reward (LR) in one arm or a small reward in the other arm without a barrier. Experiment 1 revealed that bilateral excitotoxic lesions of the core subregion of the NAc impaired effort-based decision making, that is, reduced the preference for the high effort–LR option when having the choice to obtain a low reward with little effort. Experiment 2 showed that disconnection of the ACC and NAc core using an asymmetrical excitotoxic lesion procedure impaired effort-based decision making. The present data provide evidence that effort-based decision making is governed by an interconnected neural system that requires serial information transfer between ACC and NAc core.

Keywords: anterior cingulate cortex, disconnection, nucleus accumbens, prefrontal cortex, rat

Decision making refers to the process by which humans or animals choose between competing courses of action based on the expected costs and the relative values of their consequences. Such costs may involve the risk that a reward may not be forthcoming or the investment of time or effort. Selecting an action from a set of available options on the basis of an evaluation of the potential costs and benefits is a fundamental capacity that is impaired in patients with many neuropsychiatric disorders (Paulus 2007). Although subject of intense research, the neural and neurochemical correlates of decision making are still poorly defined. Recent studies suggest that the anterior cingulate cortex (ACC), the basolateral amygdala (BLA), and the dopamine (DA) in the nucleus accumbens (NAc) are part of a neural system that subserves a particular form of decision making, that is effort-based decision making. For instance, in rats tested in a T-maze cost–benefit task, excitotoxic lesions of the ACC caused a bias away from the response option requiring more effort to obtain greater reward (Walton et al. 2003; Schweimer and Hauber 2005; Rudebeck et al. 2006). Likewise, in the same task, rats with DA depletion of the NAc no longer chose effortful but large reward (LR) action suggesting that mesostriatal DA fibers projecting to the NAc are critical for enabling an organism to overcome response costs to gain access to greater reward (Cousins and Salamone 1994; Salamone et al. 1994, 2007). Furthermore, not only inactivation of the BLA but also disconnection between the ACC and the BLA produced deficits in effort-based decision making indicating that a serial information transfer between both structures is essential to guide decisions requiring an assessment of costs and benefits (Floresco and Ghods-Sharifi 2007). However, a number of key questions on how these areas interact to calculate value and guide actions are still unresolved. First, although NAc DA is important, it is still open whether NAc medium–sized spiny neurons projected upon by DA neurons are part of the brain circuitry subserving effort-based decision. Second, it is not clear whether direct interactions between ACC and NAc are involved in effort-based decision making are crucial. In a series of experiments, we attempted to delineate functional interactions between ACC and NAc required for effort-based decision making in more detail. In Experiment 1, we analyzed the effects of bilateral cell body lesions of the NAc core subregion that receives prominent input from the ACC (Brog et al. 1993) in effort-based decision making in a T-maze cost–benefit task. In this task, subjects could either choose to climb a barrier (30 cm) to obtain an LR (4 pellets) in one arm or a small reward (SR) (2 pellets) in the other arm without a barrier (Salamone et al. 1994; Cousins et al. 1996; Walton et al. 2003; Schweimer and Hauber 2005). In Experiment 2, we examined the effects of disconnection of the ACC and NAc core on effort-based decision making using asymmetric cell body lesion procedures. Results of these experiments provide evidence that a serial interaction between ACC and NAc is required to make decisions how much effort to invest for rewards.

Materials and Methods

All animal experiments were conducted according to the German Law on Animal Protection and approved by the proper authorities in Stuttgart, Germany.

Experiment 1

Subjects

Male Sprague–Dawley rats (Charles River, Sulzfeld, Germany) were used weighing between 240 and 340 *g* at the time of surgery. They were housed in transparent macrolon cages (type IV; 35 × 55 × 10 cm; Ebeco, Castrop-Rauxel, Germany) in a 12:12-h light–dark cycle (lights on at 8.00 AM) with ad libitum access to water; food was restricted to 15 *g* per animal and day (standard maintenance chow; Altromin, Lage, Germany). Temperature (20 ± 2 °C) and humidity (50 ± 10%) were kept constant in the animal house.

Surgery

For stereotaxic surgery, animals were anaesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally) (Narcoren, Merial, Hallbergmoos, Germany) following pretreatment with atropine sulfate (0.2 mg, subcutaneously, WDT, Garbsen, Germany) and secured in a Kopf stereotaxic apparatus with atraumatic ear bars (Kopf Instruments,

Tujunga). The skull was exposed, and standard stereotaxic methods were used for bilateral quinolinic acid (QA; 2,3-pyridinedicarboxyic acid, Sigma-Aldrich, Taufkirchen, Germany) injections into the NAc core at the following coordinates from skull surface at bregma: AP +1.2 mm, ML ±1.8 mm, and DV −7.1 mm (tooth bar at −3.3 mm below the interaural line) with reference to the 3atlas of Paxinos and Watson (1997). QA (0.09 M) was dissolved in 0.1 M phosphate buffer (0.07 M Na_2HPO_4, 0.028 M NaH_2PO_4 in bidistilled water, sterilized by filtration) adjusted with NaOH to a final pH of 7.2–7.4. Sham lesions were made by infusing the phosphate buffer only. Infusions were made with a 1 μL Hamilton syringe through a 25-gauge injection cannula. Infusion volume per injection was 0.5 μL. Infusion time was 2 min, and the injector was left in place to allow diffusion for 5 min. After surgery, rats received a subcutaneous injection of 2.5 mL saline. After surgery, animals of all treatment groups showed a transient and small decrease of body weights. Animals were allowed to recover for at least 7 days.

Apparatus

A T-maze task involving effort-based decision making (Salamone et al. 1994; Walton et al. 2002) was used. The elevated T-maze consisted of a start arm and 2 goal arms (17 cm wide and 70 cm long) made of laminated wood; the walls were 30 cm high. A food well was placed at the end of each goal arm. On "forced" trials, a solid block was used to prevent entering one goal arm. The barriers that the animals had to surmount were made of wire mesh in shape of a 3-dimensional right-angled triangle. The rats had to climb the vertical side of the triangle and to descent down the slope to attain the reward. The height of the barriers was increased during training from 15 cm at the beginning to a final height of 30 cm (final steepness ~50°).

Training and Experimental Procedure

The experimental procedure corresponds to the schedule described by Walton et al. (2002). In brief, after habituation to the maze for 1 day, animals learned to discriminate a goal arm with LR containing 4 food pellets (45-mg dustless precision pellets, Bioserv, Frenchtown, NJ) from a goal arm with an SR containing 2 food pellets. For one half of the group, the LR was on the right, for the other half on the left. Animals were trained until choosing the LR in ⩾80% of trials, before a 15-cm barrier was introduced into the LR. When animals selected the LR in the majority of trials (⩾70%), the height of barrier was increased in steps of 5 cm to a maximum of 30 cm. On the first 2 trials each day, the animals were forced to run in opposite directions. An animal had 10 choice trials each day with a minimum intertrial interval of 4 min. The experiment consisted of 4 testing blocks of 3 consecutive testing days. During the prelesion block as well as the first and third postlesion block (blocks A, B, and D), there was a 30-cm barrier in the LR only. During the second postlesion block (block C), identical 30-cm barriers were present in each goal arm to assess whether the lesions caused any motor or spatial deficits or an inability to remember the reward size in the goal arms. Training was given over 16 consecutive days followed by the prelesion block A (3 days). Thereafter, animals were subjected to surgery. After recovery, animals were tested in blocks B–D (9 days).

Data Analysis and Statistics

Choice of the LR arm on each testing day was counted and given as means ± standard error of the mean. The data were subjected to a repeated measures analysis of variance (ANOVA) with 2 within-subject factors (days of testing, 3, and testing blocks, 4) and 1 between-subject factor (treatment, sham vs. lesion). Results were calculated using a Greenhouse–Geisser correction to compensate for problems caused by violations of the sphericity assumption when using an *F*-test. All statistical computations were carried out with STATISTICA (version 7.1, StatSoft, Inc., Tulsa, OK). The level of statistical significance (α-level) was set at $P < 0.05$.

Histology

After completion of behavioral tests, animals were killed by an overdose of Ethrane (Abbott, Wiesbaden, Germany) and perfused transcardially with 0.01 % heparin sodium salt in phosphate-buffered saline (PBS) followed by 4% paraformaldehyde in PBS. The brains were removed and postfixed in paraformaldehyde over night and dehydrated in 30% sucrose for cryoprotection. The brains were sectioned coronally (30 μm) with a cryostat (Mikrom, HM-550, Heidelberg, Germany). Every third section was mounted on coated slides and stained with cresyl violet.

Experiment 2

The general procedures for this experiment were identical to those described for Experiment 1 unless otherwise noted.

Subjects

Male Sprague–Dawley rats (Charles River) were used weighing between 250 and 340 *g* at the time of surgery.

Surgery

Standard stereotaxic methods were used to make either contralateral ACC–NAc disconnection sham lesions or contralateral ACC–NAc disconnection QA lesions according to a protocol by Parkinson et al. (2000). In addition, unilateral ACC or NAc QA lesions as well as ipsilateral ACC + NAc were performed. The sides of the lesions were balanced, such that there were approximately equal numbers of rats with lesions in the left or right hemispheres.

Unilateral lesions of the ACC were made by infusions of QA at the following coordinates with reference to the atlas of Paxinos and Watson (1997): AP +1.2 mm, ML ±0.5 mm, and DV −3.0 and −2.2 mm; AP +0.5 mm, ML ±0.5 mm, and DV −2.8 and −2.0 mm; AP −0.2 mm, ML ±0.5 mm, and DV −2.5 and −2.0 mm from skull surface at bregma with the tooth bar −3.3 mm below the interaural line. QA (0.09 M) (Sigma-Aldrich) was dissolved in 0.1 M phosphate buffer adjusted with NaOH to a final pH of 7.2–7.4. Sham lesions were made by infusing the phosphate buffer only. Infusion volume per injection was 0.5 μL at each site. Infusion time was 1 min, and the injector was left in place to allow diffusion for 1 min at the lower injection sites and 2 min at the upper injection sites.

Unilateral lesions of the NAc were made by QA infusions at the following coordinates from skull surface at bregma: AP +1.2 mm, ML 1.8 mm, and DV −7.1 mm (tooth bar at −3.3 mm below the interaural line) with reference to the atlas of Paxinos and Watson (1997). QA (0.09 M) (Sigma-Aldrich) was dissolved in 0.1 M phosphate buffer adjusted with NaOH to a final pH of 7.2–7.4. Sham lesions were made by infusing the phosphate buffer only. Infusion volume was 0.5 μL; infusion time 2 min. The injector was left in place to allow diffusion for 5 min.

The protocols for unilateral sham or QA lesions described above were used to produce contralateral disconnection sham and QA lesions as well as unilateral ACC and NAc QA lesions. Initially, they were also used to produce ipsilateral ACC + NAc QA lesions. However, in this case, large ipsilateral lesions including major parts of the dorsal striatum and an enlargement of the lateral ventricle were observed. Most probably, QA solution infused into the ACC diffused along the ipsilateral cannula track down to the Nac, thereby causing collateral cell loss within the dorsal striatum. Therefore, we modified the infusion procedure for intra-NAc QA infusion in those animals that received ipsilateral ACC + NAc lesions. In order to circumvent the ACC, QA infusions to the same target coordinates in the NAc as above were made in an angle. After surgery, rats received a subcutaneous injection of 2.5 mL saline. After surgery, animals of all treatment groups showed a transient and small decrease of body weights. Animals were allowed to recover for at least 7 days.

Training and Experimental Procedure

The training and testing procedures were the same as described in Experiment 1.

Results

Experiment 1

Histology

In sham-lesioned animals ($N = 12$), we observed minimal damage caused by the injection cannulae during vehicle

microinfusion. In animals with QA lesions ($N = 14$), neuronal loss and gliosis was prominent bilaterally in the NAc core (Fig. 1) as shown in previous studies (e.g., Parkinson et al. 2000) using similar infusion parameters, that is, dose and volume of QA, infusion speed, and stereotaxic coordinates. In some cases, minor damage to the NAc shell was observed.

Choice Behavior

In the prelesion testing block, all animals exhibited a strong preference to surmount the barrier to obtain the LR with an average of approximately 80–90% of the choices for the LR arm (Fig. 2). This preference was reduced postoperatively in QA-lesioned rats, if tested in the 1-barrier condition but not if tested in the 2-barrier condition. Repeated measures 3-way ANOVA revealed significant effects of treatment ($F_{1,24} = 5.78$, $P < 0.05$) and testing blocks ($F_{2.66,63.87} = 9.25$, $P < 0.0001$) but not of days ($F < 2$, not significant [n.s.]). Furthermore, there was a significant treatment × block interaction ($F_{2.66,63.87} = 3.11$, $P < 0.05$). For a detailed analysis, additional ANOVA was run on data from single blocks. In the prelesion testing block A (barrier in the LR arm), no significant main effects of group, days, or group × day interactions (Fs < 1, n.s.) were detected. By contrast, in the first postlesion block (block B, barrier in the LR arm), there was a clear, though not significant tendency for a main effect of treatment ($F_{1,24} = 3.53$, $P = 0.072$, n.s.) but no main effect of days or treatment × day interactions (Fs < 1, n.s.). In the subsequent postlesion block C (barriers in LR and SR arm), all animals preferred the LR arm; no significant main effects of treatment or treatment × day interactions (Fs < 1, n.s.) were detected but a significant main effect of days ($F_{1.88,45.2} = 5.18$, $P < 0.01$). After removal of the barrier in the SR in testing block D, the QA-lesioned animals did no longer prefer the LR. There was a significant main effect of treatment ($F_{1,24} = 8.75$, $P < 0.008$) but not of days and no treatment × day interaction (Fs < 1, n.s.).

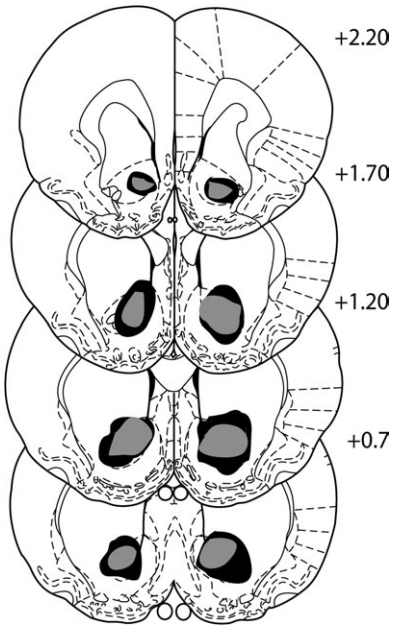

Figure 1. Schematic representation of the minimum (gray shading) and maximum (black shading) extension of NAc lesions ($n = 14$). Plates are adaptations from the atlas of Paxinos and Watson (1997); scales are relative to bregma.

Experiment 2

Histology

In ACC–NAc disconnection sham-lesioned animals ($N = 8$), we observed minor damage along by the injection cannulae tracks. By contrast, in animals with ACC–NAc disconnection lesions ($N = 7$) and animals with control lesions, that is, unilateral QA lesions of the NAc ($N = 4$) and ACC ($N = 4$) or combined ipsilateral ACC + NAc QA lesions, neuronal loss and gliosis was prominent in the ACC and/or NAc. A schematic representation is shown in Figure 3. Unilateral lesions of the ACC were comparable to those observed in one hemisphere using the same or similar infusion parameters for bilateral lesions (Walton et al. 2002, 2003; Schweimer and Hauber 2005) or disconnection lesions (Parkinson et al. 2000). Neuronal loss and gliosis was prominent in the fields Cg1 and 2 with a maximum extension from about +2.7 mm anterior to bregma to 1.3 mm posterior to bregma. Lesions included predominantly pregenual and perigenual parts of the ACC; minor damage of the prelimbic cortex was detected occasionally, and the corpus callosum was generally spared. Contralateral lesions to NAc core were also characterized by neuronal loss and gliosis. In some cases, minor damage to the NAc shell was observed. Animals with unilateral QA lesions of either the NAc core or the ACC as well as animals with combined ipsilateral QA lesions of the ACC + NAc showed similar lesions as observed with contralateral QA lesions of both structures (Fig. 3).

Choice Behavior in Animals with Control Lesions

Initially, we analyzed choice behavior of various control lesion groups, that is, animals with unilateral ACC QA lesions, unilateral NAc QA lesions, ipsilateral ACC + NAc lesions, and ACC–NAc disconnection sham lesions. In the prelesion testing block, animals of all groups exhibited a strong preference to surmount the barrier to obtain the LR with an average of approximately 80–95% of the choices for the LR arm. In the postlesion blocks, this preference remained largely unchanged in animals subjected to unilateral ACC QA lesions, unilateral

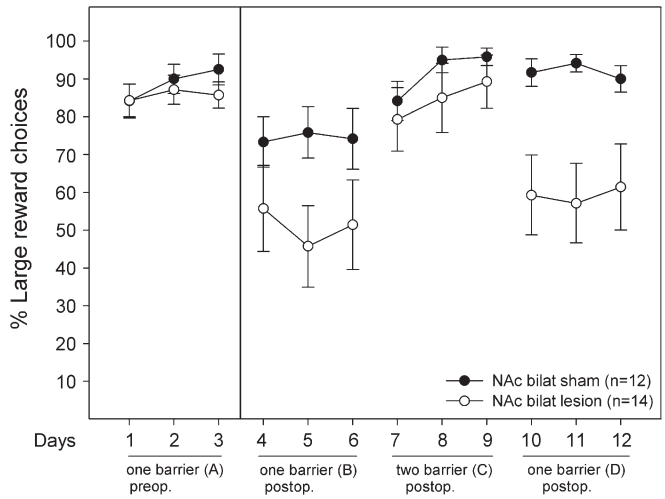

Figure 2. Effects of bilateral NAc lesions in a T-maze cost–benefit task. Mean (±standard error of the mean) percentage of LR arm choices per day in sham-lesioned ($n = 12$) and QA-lesioned ($n = 14$) rats are given. Testing block A was prelesion, blocks B–D postlesion. Each testing block consisted of 3 consecutive test days. On blocks A, B, and D, a 30-cm barrier was placed in the HR, on block C, identical 30-cm barriers were placed in each goal arm, respectively.

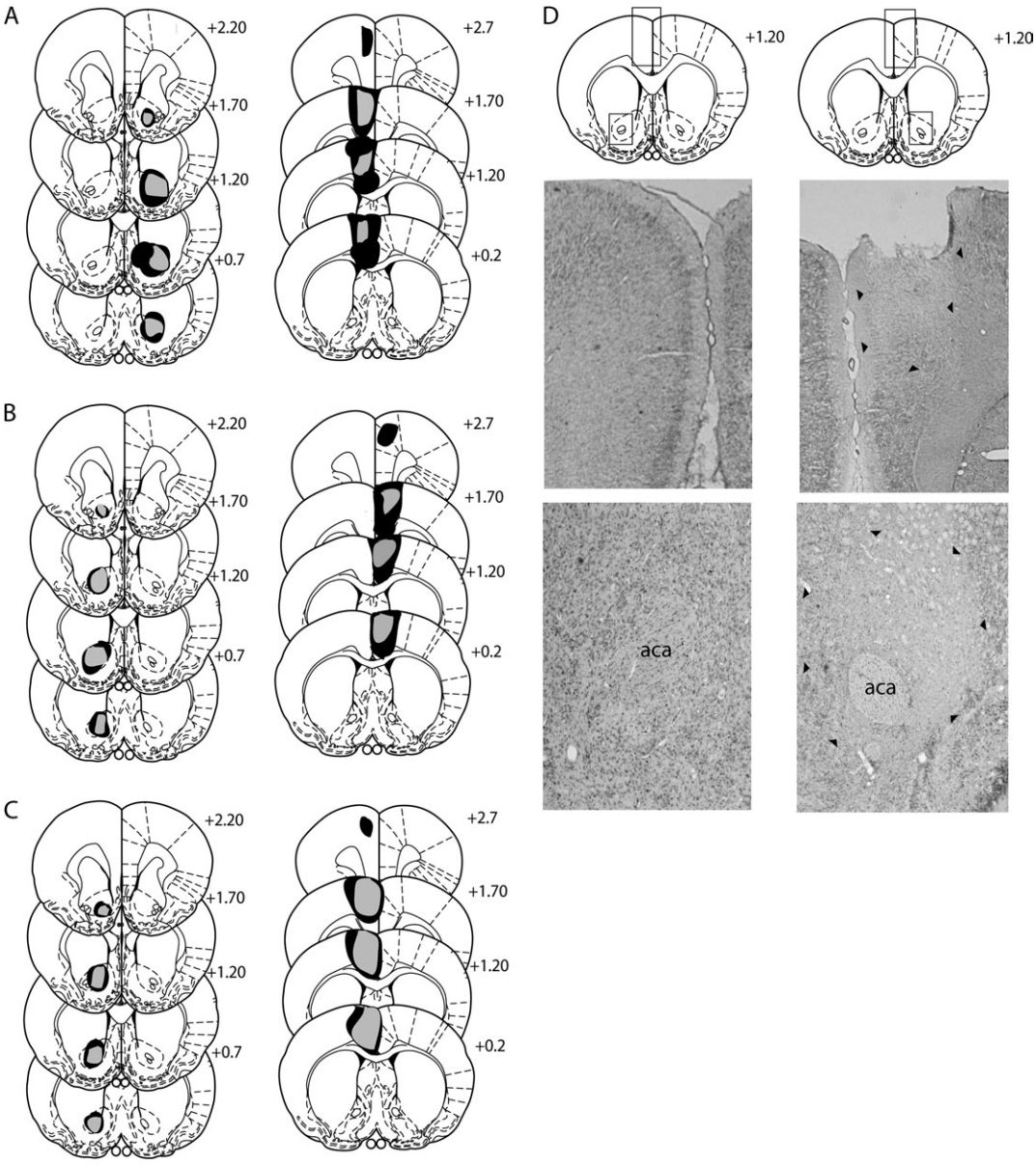

Figure 3. Schematic representation of the minimum (gray shading) and maximum (black shading) extension of (*A*) contralateral ACC–NAc lesions ($n = 7$), (*B*) unilateral ACC ($n = 4$) and NAc lesions ($n = 4$), and (*C*) ipsilateral ACC–NAc lesions. The sides of the lesions were balanced, such that there were approximately equal numbers of rats in each group with lesions in the left or right hemispheres; the shaded areas represent the smallest and largest extent of neuronal damage in a single representative rat. (*D*) Photomicrographs of coronal sections showing cell loss in animals subjected to ACC lesion (middle panel, right) and NAc lesion (bottom panel, right). The panels on the left side show the ACC and NAc of sham controls. The boxed regions in the top panel are shown at high magnification in the middle and bottom panels. Plates are adaptations from the atlas of Paxinos and Watson (1997); scales are relative to bregma.

NAc QA lesions, and ipsilateral ACC + NAc QA lesions. Furthermore, LR preference of uni/ipsilateral control lesion groups and the disconnection sham lesion group was similar as shown in Figure 4*A*. A repeated measures 3-way ANOVA of the LR arm choices in uni/ipsilateral lesion control groups and the disconnection sham lesion group confirmed this description. There was a significant main effect of block ($F_{3,48} = 6.88$, $P < 0.001$) but no main effects of group or day and no further interactions (Fs < 1, n.s.).

Choice Behavior in Animals with Disconnection Lesions

A comparison of choice behavior animals with disconnection sham lesions and disconnection QA lesions revealed that, in the prelesion testing block, animals of both groups exhibited a strong preference to surmount the barrier to obtain the LR with an average of approximately 80–95% of the choices for the LR arm. This preference remained largely unchanged in animals with ACC–NAc disconnection sham lesions. By contrast, the LR preference was reduced postoperatively in animals with ACC–NAc disconnection QA lesions, if tested in the 1-barrier condition but not if tested in the 2-barrier condition (Fig. 4*B*). Repeated measures 3-way ANOVA revealed significant effects of treatment ($F_{1,13} = 6.89$, $P < 0.05$) and testing blocks ($F_{1.90,24.72} = 13.20$, $P < 0.001$) as well as a significant block × treatment interaction ($F_{1.90,24.72} = 4.53$, $P < 0.05$). For a detailed analysis, additional ANOVA was run on data from

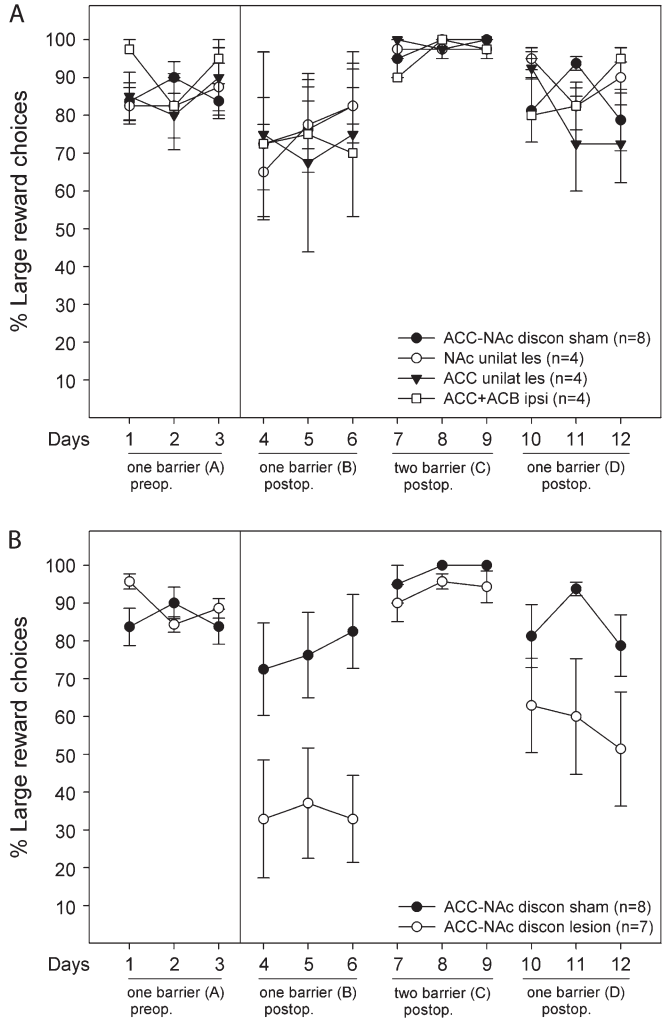

Figure 4. Effects of ACC–NAc disconnection lesions in a T-maze cost–benefit task. Mean (±standard error of the mean) percentage of LR arm choices per day in sham-lesioned and quinolinic acid-lesioned rats are given. Testing block A was prelesion, blocks B–D postlesion. Each testing block consisted of 3 consecutive test days. On blocks A, B, and D, a 30-cm barrier was placed in the HR, on block C, identical 30-cm barriers were placed in each goal arm, respectively. (*A*) Performance of animals with unilateral ACC QA lesions ($n = 4$), unilateral NAc QA lesions ($n = 4$), ipsilateral ACC + NAc QA lesions ($n = 4$), and ACC–NAc disconnection sham lesions ($n = 8$). (*B*) Performance of animals with ACC–NAc disconnection sham lesions ($n = 8$) versus ACC–NAc disconnection QA lesions ($n = 7$).

single blocks. In the prelesion testing block A (barrier in the LR arm), no significant main effects of group and days (Fs < 1, n.s.), but a significant group × day interaction ($F_{1.92,24.92} = 3.73$, $P < 0.05$), was detected. By contrast, in the first postlesion block (block B, barrier in the LR arm), there was main effect of treatment ($F_{1,13} = 6.60$, $P < 0.05$) but no main effect of days or treatment × day interaction ($F < 1$, n.s.). In the subsequent postlesion block C (barriers in the LR and SR arm), all animals preferred the LR arm; no significant main effects of treatment, day, or day × treatment interaction (Fs < 3.5, n.s.) were detected. After removal of the barrier in the SR in testing block D, the animals with ACC–NAc disconnection QA lesions showed a reduced preference for LR arm. There was a tendency for significant main effect of treatment ($F_{1,13} = 4.01$, $P = 0.063$), but no significant main effect of days and no treatment × day interaction (Fs < 2, n.s.) was detected.

Discussion

Experiment 1 revealed that bilateral lesions of the NAc core impaired effort-based decision making, that is, reduced the preference for the high effort–high reward option when having the choice to obtain a low reward with little effort. Experiment 2 showed that disconnection of the ACC and NAc core produced an impairment of effort-based decision making similar to that observed after bilateral lesion or inactivation of the ACC (Walton et al. 2002, 2003; Schweimer and Hauber 2005; Floresco and Ghods-Sharifi 2007) or bilateral lesion of the NAc (Experiment 1). Impaired decision making seen in Experiments 1 and 2 cannot be attributed to changes in primary food motivation or appetite, to motor or spatial impairments, or to problems in reward magnitude discrimination because after introduction of a barrier into the SR arm, rats with bilateral NAc lesions or contralateral ACC–NAc lesions shifted back to select the high cost–LR option. Furthermore, as the time required to surmount the barrier was very short (<1.5 s), differential delays to obtain large versus SR might not bias responding in the 1-barrier situation. Taken together, the present data provide evidence that effort-based decision making requires serial information transfer between ACC and NAc core.

A number of studies implicated the ACC in effort-based decision making (Walton et al. 2002, 2003; Schweimer and Hauber 2005; Rudebeck et al. 2006; Floresco and Ghods-Sharifi 2007) though not in all categories of decisions requiring an assessment of costs and benefits (Schweimer and Hauber 2005; Rudebeck et al. 2006). The ACC subserves decision making as part of an interconnected neural system that includes the BLA (Floresco and Ghods-Sharifi 2007) and the DA in the NAc (Salamone et al. 1994; Cousins et al. 1996). Our present finding that after bilateral QA lesions of the NAc core, animals no longer preferred the high effort–LR response option implies that striatal projection neurons, a primary target of QA (Brickell et al. 1999), in the NAc core play a critical role in effort-related decision making. Furthermore, our data complement previous findings implicating NAc DA in effort-based decision making (Salamone et al. 1994; Cousins et al. 1996) and suggest that DA modulation of NAc core projection neurons is one important neurochemical mechanism to guide choice behavior. DA depletion of the NAc not only impaired effort-based decision making (Salamone et al. 1994; Cousins et al. 1996) but also reduced locomotor activity as well (e.g., Kelly et al. 1975). Remarkably, excitotoxic lesions of the NAc core that impaired effort-based decision making in the present study often produced locomotor hyperactivity (Maldonado-Irizarry and Kelley 1995; Parkinson et al. 1999). Together, these findings support the idea that impairments of effort-based decision making and suppression of locomotor activity are dissociable, although with some experimental manipulations such as NAc DA depletion (Salamone et al. 1994; Cousins et al. 1996) or systemic dopamine receptor blockade (Denk et al. 2005), they may occur together. Consistent with this notion, after NAc DA depletion, there was a differential recovery of impaired choice behavior and locomotor suppression, with the locomotor suppression recovering more rapidly (Salamone et al. 1994; Cousins et al. 1996).

Notably, recent studies suggest that the NAc core plays a critical role in behavioral choice on the basis of delayed or uncertain reward. For instance, Cardinal and colleagues (Cardinal

et al. 2001; Cardinal and Cheung 2005; Cheung and Cardinal 2005) observed that NAc core lesions reduced the preference for delayed LRs over small, immediate rewards without affecting processing of reward magnitudes. In addition, NAc core lesions induced risk-aversive choice behavior (Cardinal and Howes 2005), that is, when offered the choice between small and certain and a large and uncertain reward, rats with an NAc core lesions had a reduced preference for the uncertain response option (Cardinal and Howes 2005). Thus, it seems that the NAc core is a key structure in decision making that promotes the selection of delayed and uncertain rewards as well as the selection of rewards associated with higher effort. This account is compatible with human imaging studies showing that the ventral striatum/ventral pallidum among other basal forebrain structures are key nodes in a brain circuitry that enables expected rewards to energize behavior (Pessiglione et al. 2007). Furthermore, Kuhnen and Knutson (2005) observed that during the selection of high-risk response options, the NAc blood flow was increased.

Experiment 2 demonstrated that control rats with unilateral or ipsilateral QA lesions of either the ACC and/or NAc core were not significantly different from disconnection sham-lesioned animals, whereas subjects with ACC–NAc disconnection QA lesions were impaired in effort-based decision making. Notably, rats with ACC–NAc disconnection QA lesions had a reduced LR preference both in the first and second 1-barrier condition; however, the LR preference was markedly higher in the second (block D) relative to the first (block B). A recent study reported similar results with an even more pronounced increase in LR preference in the second relative to the first 1-barrier condition (Rudebeck et al. 2006). It was suggested that this behavioral effect was supported by NAc and BLA representations and governed by a response bias to the LR arm that emerged in the 2-barrier condition and persisted throughout the second 1-barrier condition (Rudebeck et al. 2006). In view of these findings, this idea is quiete plausible; however, we observed that ACC- (Schweimer and Hauber 2005) and NAc-lesioned (Experiment 1) can have a comparable low LR preference both in the first and the second 1-barrier conditions. The reasons for these discrepancies are not clear but might involve subtle differences in ACC lesion sizes, target coordinates, or baseline LR preferences.

Results from Experiment 2 provide strong support to the notion that the ACC and NAc core operate functionally and serially in effort-based decision making. Notably, Parkinson et al. (1999) showed that bilateral excitotoxic lesions of either the ACC or NAc core as well as disconnection of the ACC and NAc core impaired the acquisition of appetitive Pavlovian conditioning in an autoshaping procedure. These findings suggest that direct interactions of the ACC and NAc core are not only involved in making decisions on how much effort to invest for rewards but also contribute to other aspects of reward-directed behavior such as stimulus-reward learning. Importantly, the ACC is critical if 2 or more similar stimuli predicting different outcomes have to be discriminated suggesting that its contribution to stimulus-reward learning is highly specific (for review, see Cardinal et al. 2002). Furthermore, serial interactions in parallel prefrontostriatal circuits connecting the prelimbic/infralimbic cortex with the dorsal and ventral striatum are critically involved in functions such as attention (Christakou et al. 2001) or affective modulation of action (Christakou et al. 2004).

The question is which processes are mediated at different levels of such an interconnected circuitry between ACC and NAc core. The exact contribution of the ACC to effort-related decision making is still poorly defined. Neurons in the ACC receive input from structures that represent information about the reward magnitudes associated with response options such as the BLA (Pratt and Mizumori 1998) and encode increasing reward proximity through a series of work steps (Shidara and Richmond 2002). Thus, the involvement of the ACC to effort-related decision making may be related to its role in representing action-outcome contingencies (Hadland et al. 2003; Rushworth et al. 2004; Rudebeck et al. 2006). Accordingly, impaired effort-based decision making after BLA–ACC disconnection might reflect a compromised transfer of reward magnitude-related information from the BLA to the ACC (Floresco and Ghods-Sharifi 2007). As a result, integrative processes in the ACC that relate costs and benefits of the available response options may be disturbed and affect making decisions on how hard to work in a given situation. However, the involvement of the ACC to effort-related decision making may also be linked to its role in conflict monitoring (Botvinick et al. 2001, 2004). Relative to the 2-barrier condition, response selection in the 1-barrier condition may be viewed as a situation in which conflict is more likely to arise in the form of competition among the available responses. Therefore, the selective ACC lesion effect on decision making in the 1-barrier condition could reflect disturbed conflict monitoring during performance of a more complex task condition.

The NAc core has been implicated in several activational aspects of instrumental action, dependent on glutamatergic and DAergic mechanisms (e.g., Hauber et al. 2000; Giertler et al. 2003; Lex and Hauber 2008; for a review, see Salamone et al. 2005). Thus, the role of the NAc core in effort-based decision making may be to provide activation of a selected response option through DA modulation of NAc core projection neurons. Alternatively, as indicated by other empirical as well as computational accounts, the NAc and its mesostriatal DA input may be concerned with bridging internal states such as hunger to executive function, that is, governs the allocation of resources devoted to obtaining rewards (Phillips et al. 2007). According to this view, NAc DA modulation may represent one mechanism through which internal states might influence decision making by adapting the threshold cost to obtain reward. Recent findings further indicate that DA D1 receptor modulation of the ACC regulates effort-based decision making (Schweimer and Hauber 2006). This raises the question whether the DA modulation at different levels of the prefrontostriatal circuitry is redundant. Theoretical accounts indicate that prefrontal DA may be critical for appropriately updating goal representations by controlling the gating of afferent information into the prefrontal cortex (Montague et al. 2004). According to this hypothesis, ACC DA D1 receptor activity might be required to rely afferent information about the costs and benefits of the available response options to the ACC. Alternatively, ACC DA D1 receptor activity may be simply required to enable integrative processes in the ACC that relate costs and benefits of the available response options. Collectively, these studies suggest that effort-based decision making depends on an interconnected neural system including BLA, ACC, and NAc core and requires serial information transfer from the BLA to the ACC and from there to the NAc core. Furthermore, they suggest that effort-based decision making

requires DA modulation of this prefrontostriatal circuit through DA D1 receptor–mediated modulation of the ACC and a DA modulation of the NAc core. In line with this account, functional magnetic resonance imaging (MRI) in humans demonstrated that the ACC and the ventral striatum are key structures in a network of regions involved in guiding action selection for reward (Hampton and O'Doherty 2007) and in mental effort discounting (Botvinick et al. 2008). Likewise, imaging studies in human patients revealed that dysfunctions of the ACC-subcortical circuitry cause apathy (Cummings 1999) and further clinical evidence suggests that dysfunctions of central DA systems may contribute to psychomotor symptoms such as anergia or psychomotor slowing observed in depression and other psychiatric disorders (Stahl 2002; Salamone et al. 2007).

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