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Nucleus accumbens core lesions enhance two-way active avoidance

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Abstract

The majority of work examining nucleus accumbens core (NAc) has focused on functions pertaining to behaviors guided by appetitive outcomes. These studies have pointed to NAc as being critical for motivating behavior toward desirable outcomes. For example, we have recently shown that lesions of NAc impaired performance on a reward-guided decision-making task that required rats to choose between differently valued rewards. Unfortunately, much less is known about the role that NAc plays in motivating behavior when aversive outcomes are predicted. To address this issue we asked if NAc lesions impact performance on a two-way active avoidance task in which rats must learn to shuttle back and forth in a behavioral training box in order to avoid a footshock predicted by an auditory tone. Although bilateral NAc lesions initially impaired reward-guided decision-making, we found that the same lesions improved acquisition and retention of two-way active avoidance.

Keywords

striatum; nucleus accumbens; rat; escape; avoidance

INTRODUCTION

The ventral striatum is involved in decision-making guided by predictions about future outcomes (Mogenson et al., 1980, van der Meer and Redish, 2011). Most of the work leading to this hypothesis is derived from behaviors that are governed by appetitive outcomes. For example, we have shown that neural activity in nucleus accumbens core (NAc) is selective for cues that predict more valued reward (Roesch et al., 2009, Goldstein et al., 2012, Bissonette et al., 2013) and that bilateral NAc lesions make rats less accurate at choosing more valued options during performance of the same task (Burton et al., 2013).

Much less is known about the role NAc plays in motivating behavior away from aversive stimuli. Here, we examine this issue by asking how bilateral NAc lesions impact

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performance on a two-way active avoidance task. Previous work has shown that escape-avoidance depends on dorsal striatum (Kirkby and Kimble, 1968, Allen and Davison, 1973, Winocur, 1974, Prado-Alcala et al., 1975, Viaud and White, 1989, White and Viaud, 1991) and normal dopamine levels in striatum (Cooper et al., 1974, Neill et al., 1974, Jackson et al., 1977, Schwarting and Carey, 1985, Wadenberg et al., 1990, McCullough et al., 1993), but it is less clear what specific role NAc plays in these types of paradigms (Gal et al., 2005, Pothuizen et al., 2005, 2006). Original reports suggest that electrolytic lesions of the rat nuclei accumbens septi improves performance on conditioned avoidance (Lorens et al., 1970), but it is unclear if excitotoxic lesions to NAc will have the same effect during performance of a two-way active avoidance task. Thus, one motivator of this experiment is to determine if modern axon sparing excitotoxic lesions focused specifically at NAc would have a similar impact on avoidance behavior as electrical lesions.

A second motivator for this study spawned from the observation that reward-guided decision-making deficits after NAc lesions are transient (Burton et al., 2013). That is, lesioned rats recovered function over time. This suggests that other parts of brain might be compensating for loss of NAc. Consistent with this hypothesis we have shown that stimulus-response encoding in dorsal striatum was enhanced after NAc lesions and that additional recruitment of dorsal striatum (DS) might be sufficient to control behavior in the absence of NAc. If loss of NAc function enhances neural selectivity in DS as we are suggesting, then NAc lesions might also promote better performance on other DS dependent tasks. Thus, in addition to replicating results with modern lesion techniques, we set out to determine if rats that showed reward-guided decision-making deficits and recovery, also exhibited improved performance on two-way active avoidance. We found that rats with NAc lesions more actively avoided shock as compared to controls. We also show that the ability of lesion rats to outperform their sham counterparts in the current study was correlated with their inability to select more valued outcomes during performance of a reward-guided decision-making task.

MATERIALS AND METHODS

Subjects

Fifteen adult male Long-Evans rats obtained at 175–200g from Charles River Labs served as subjects. Data from these rats contributed to a previous publication in which they participated in a different paradigm (Burton, 2013). Animals were housed individually on a 12-h light/dark cycle (lights on at 7:00 am) and had ad libitum access to food and water except during testing. Rats were tested at the University of Maryland, College Park in accordance with National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1996). All experimental procedures were approved by the University of Maryland Institutional Animal Care and Use Committee (IACUC).

NAc lesions and histology

Rats were randomly assigned to receive either bilateral NAc lesions ($n = 9$) or sham lesions ($n = 6$). Before surgery, rats were anesthetized with isoflurane and bilateral NAc lesions were made with a 2 μ l Hamilton syringe, beveled edge facing the posterior direction, using 0.11M quinolinic acid, pH 7.4 (Sigma, St. Louis MO, USA) in Dulbecco's PBS (Sigma, St. Louis, Mo, USA). Quinolinic acid (0.3 μ l) was delivered at 0.15 μ l/min at coordinates: AP +1.9mm, ML $\pm$ 1.9mm, DV -7.3 mm relative to bregma. A similar procedure was used for the sham controls, during which the Hamilton syringe loaded with saline was lowered to the same coordinates, and no saline was injected. Brains were removed and processed for histology using standard techniques at the end of the experiment. Four rats were removed

from the study because of poor lesions. One of these rats showed no signs of a lesion, possibly due to a clogged needle, whereas the other three had damage in more dorsal regions of striatum.

Reward-guided decision-making task

Before avoidance training all rats were trained on the odor-guided delay/size choice task in an entirely different behavioral box. The full description and analysis of these data can be found in Burton et al., 2013. For this task, nose poke into the odor port after house light illumination resulted in delivery of an odor cue to a hemicylinder located behind this opening (Bryden et al., 2011, Roesch and Bryden, 2011). One of three different odors (2-Octanol, Pentyl Acetate, or Carvone) was delivered to the port on each trial. One odor instructed the rat to go to the left to receive reward, a second odor instructed the rat to go to the right to receive reward, and a third odor indicated that the rat could obtain reward at either well. Odors were presented in a pseudorandom sequence such that the free-choice odor was presented on 7/20 trials and the left/right odors were presented in equal proportions.

During probe sessions after surgery, either the length of the delay preceding reward or the size of the reward varied in different trial blocks. Rats prefer immediate reward delivered after short delays as opposed to reward delivered after long delays. In delay trial blocks, during the first block of trials, one well was randomly designated as short (500 ms) and the other long (1–7s) at the start of the session. In the second block of trials, these contingencies were switched (Block 2). Finally, in the third block, contingencies reverted back to the first block. In blocks where reward size was manipulated, we held the delay preceding reward delivery constant (500 ms) while manipulating the size of the expected reward. The reward was a 0.05 ml bolus of 10% sucrose solution. For big reward, an additional bolus was delivered 500 ms after the first bolus. Again, at the start of the session, one well was randomly designated as big and the other small. Contingencies reversed in the second block and then reverted back to the original during performance of the third block of trials. The location of the high value outcomes (i.e., short delay to reward and large reward) switched every 60 correct trials. There were a total of 3 blocks each day. Delay (4 days) and size (4 days) manipulations alternated daily. Rats were given 3 days rest before starting avoidance training.

Two way active avoidance training

Rats were trained on two way active avoidance (Choi et al., 2010) in a shuttle box apparatus (20.3 cm x 15.9 cm x 21.3 cm) (Med Associates). The box was divided in half by a white opaque wall with a guillotine door opening situated at floor level allowing passage from one side of the shuttle box to the other. The floor of the apparatus was made of stainless steel bars. Infrared photobeam source/detector arrays were located on the side walls in each section of the shuttle box in order to monitor movement of the animal.

Prior to training on the active-avoidance paradigm, all rats underwent testing on the odor-guided delay/size choice task as described above (Burton, 2013). Only lights and odors were used as cues in the odor-guided delay/size choice task, thus the first time rats experienced the auditory stimulus was during avoidance training. Four days after completion of that study, rats were habituated to the shuttle box for 1 hour on the day prior to avoidance training. Each rat was first given a 5 min stimulus-free acclimation period prior to starting the behavioral task each testing day. On the first day of testing, a Pavlovian conditioning trial was administered. A 3150 Hz tone (CS) (80dB) and a 0.7 mA scrambled shock (US) was presented for 15s while the subjects were locked on one side of the chamber. After this single Pavlovian trial the guillotine door was opened and testing commenced.

Rats received 30 signaled avoidance trials with an average intertrial interval (ITI) of 2 min. Trials consisted of a tone presentation that lasted a maximum of 15s, followed by a US footshock (0.7 mA) that also lasted a maximum of 15s. Shuttling during the tone caused immediate tone termination and no footshock (avoid trials). If no avoidance was performed during the 15s CS, the US was presented until the rat shuttled (escape trial) or for 15s. The CS and US were presented for a full 15s if the rat failed to shuttle during the US presentation (escape failure trial). Rats were trained on the task for 4 consecutive days and then tested again 72 hours later.

Behavioral measures and analysis of avoidance

For behavioral analysis we examined escape failures, escape latencies, percent avoid trials and avoidance latencies. Escape failure was when rats failed to move to the other side to terminate the shock. Escape latencies were how quickly, after the initiation of the shock, the rats moved to the other side. Percent avoid was the total number of trials during which rats moved to the other side after the onset of the tone and before the shock, divided by the total number of tone presentations. Avoidance latencies were how quickly, after the initiation of the CS, the rats moved to the other side. Multi-factor ANOVAs were used to quantify significant differences between lesions and controls. Factors included lesion (lesion vs sham), trial (1–30), and day (1–5). Post-hoc ttests were used to explore interactions.

RESULTS

Control and lesion rats were tested on a two-way active avoidance paradigm as described above. Rats that contributed to the subsequent analysis exhibited lesions that were mostly restricted to the core of nucleus accumbens (NAc) with minimal damage to shell and dorsal striatum (Fig. 1A). No part of olfactory tubercle or lateral NA shell were lesioned.

NAc lesions did not alter the ability of the rat to escape shock by jumping to the other side of the behavioral box. In only 0.8% and 0.3% of all trials did control and lesion rats fail to escape, respectively. Although percent escapes were not affected by lesion, the latency to escape was. A two-factor ANOVA (factors: lesion vs sham; day) on escape latencies produced a significant main effect of day ($F_{(4,290)} = 4.72$, $p < 0.05$) and a significant interaction between day and lesion ($F_{(4,290)} = 7.46$, $p < 0.05$). There was no main effect of lesion ($F_{(1,290)} = 0.35$, $p = 0.55$). During the first day of training, NAc lesion rats were significantly faster to escape compared to controls (Fig. 1B; day 1; ttest; $t_{(58)} = 4.06$, $p < 0.05$). This relationship reversed by day 3 (Fig. 1B; day 3; ttest; $t_{(58)} = 3.03$, $p < 0.05$). There were no significant differences between control and lesion groups on day 4 (Fig. 1B; day 4; ttest; $t_{(58)} = 1.07$, $p = 0.29$), or 72 hours later on day 7 (Fig. 1B; day 7; ttest; $t_{(58)} = 0.16$, $p = 0.87$).

NAc lesioned rats learned and retained the ability to avoid the shock better than controls. A two-factor ANOVA (factors: lesion vs sham; day) on avoids produced a significant main effect of day ($F_{(4,290)} = 10.3$, $p < 0.05$) and lesion ($F_{(1,290)} = 24.5$, $p < 0.05$), and a significant interaction between day and lesion ($F_{(4,290)} = 7.85$, $p < 0.05$). Lesioned rats avoided significantly more on day 2 (Fig. 1C; day 2; ttest; $t_{(58)} = 3.30$, $p < 0.05$). The two groups performed similarly on days 3 (Fig. 1C; day 3; ttest; $t_{(58)} = 0.48$, $p = 0.64$) and 4 (Fig. 1C; day 4; ttest; $t_{(58)} = 1.14$, $p = 0.26$). When retesting after 72 hours, lesioned rats were significantly better than controls (Fig. 1C; day 7; ttest; $t_{(58)} = 6.72$; $p < 0.05$). Although counts of avoids were impacted by lesions, avoid latencies were not (Fig. 1D; ANOVA; $F_{(4,249)}$'s < 1.65 , p 's > 0.16).

Further examination of the data illustrates that control rats exhibited little retention over the 72 hours of rest, returning to levels similar to those observed on the first day, exhibiting a

main effect of day (ANOVA; $F_{(4,145)} = 10.3$, $p < 0.05$) and no difference between days 1 and 7 (ttest; $t_{(58)} = 0.15$; $p = 0.88$). Unlike controls, lesioned rats were better on day 7 compared to day 1 (ANOVA; $F_{(4,145)} = 9.19$, $p < 0.05$; ttest; $t_{(58)} = 2.5$; $p < 0.05$). These results further suggest that lesioned rats learn and retain two-way active avoidance better than controls.

From these results we conclude that bilateral NAc lesions improve performance on two-way active avoidance. Next, we asked if improved avoidance behavior was related to impaired reward-guided decision-making described previously. Prior to avoidance training these same rats performed a reward-guided decision-making task during which they chose between two different fluid wells that yielded either a high (reward after a short delay or a large reward) or low value (reward after a long delay or a small reward) reward (10% sucrose solution). Control rats chose the higher value reward significantly more often (Fig. 2A; $t_{(10)} = 7.7$, $p < 0.05$). Rats with NAc lesions showed impaired reward discrimination (Burton et al., 2013), selecting high and low value wells in roughly equal proportions (Fig. 2A; chi-square = 0.51; $p = 0.48$).

Here we ask if performance on the avoidance paradigm and the ability to accurately choose between the differently valued options were correlated. Figure 2B plots the strength of each rat's reward discrimination (as defined by the percent choice of high value reward minus the percent choice of low value reward) against the ability to learn and retain 2-way active avoidance (as defined by the percent choice on day 7 minus percent choice on day 1). Rats that performed better at avoidance (y-axis) tended to be worse at selecting more valued outcomes during the reward task (x-axis). Although this negative correlation only approached significance (Fig. 2B; $r^2 = 0.38$, $p = 0.056$), this result suggests that abnormalities in performance between the two tasks were related.

DISCUSSION

Given the importance of striatal nuclei in reward-learning, motivation, and fear-related learning (Kirkby and Kimble, 1968, Allen and Davison, 1973, Cooper et al., 1974, Neill et al., 1974, Winocur, 1974, Prado-Alcala et al., 1975, Jackson et al., 1977, Schwarting and Carey, 1985, Viaud and White, 1989, Wadenberg et al., 1990, White and Viaud, 1991, McCullough et al., 1993, Delgado et al., 2008, Darvas et al., 2011), we examined the effect of NAc lesions on two-way active avoidance. We demonstrated that NAc lesions facilitate the acquisition and retention of avoidance. To the best of our knowledge, this is the first study to report that neurotoxic lesions of striatum can actually promote, rather than hinder, active avoidance. Many studies have examined the role of the striatum in avoidance (Kirkby and Kimble, 1968, Allen and Davison, 1973, Winocur, 1974, Prado-Alcala et al., 1975, Viaud and White, 1989, White and Viaud, 1991), but the specific roles that subregions in striatum play in avoidance is not entirely clear, with most of the work focusing on the involvement of dopamine in this region or examination of subregions within DS (Cooper et al., 1974, Neill et al., 1974, Jackson et al., 1977, Schwarting and Carey, 1985, Wadenberg et al., 1990, McCullough et al., 1993).

Our work is consistent with the few interference studies examining this question in ventral striatum. It has been shown that electrolytic lesions to the nuclei accumbens septi in rats improves performance on a conditioned avoidance response task (Lorens et al., 1970). The current report improves on this finding through the use of more specific excitotoxic lesions to NAc. This previous report also suggests electrolytic lesions make rats more sensitive to footshock. We see no evidence of this in our study as suggested by similar escape latencies between lesion and control groups after learning (i.e., no main effect of lesion on escape latencies), however we did not systematically reduce shock to determine the threshold at

which rats stopped responding, thus we cannot directly address this issue. With that said, others have shown that neurotoxic lesions to NAc do not impair shock reactivity (Levita et al., 2002).

More recent research has examined the impact of nucleus accumbens core and shell lesions on avoidance focusing on the role that these regions play in latent inhibition (pre-exposure) and the importance of the shell in this paradigm (Gal et al., 2005, Pothuizen et al., 2005, 2006). Since it was not the focus of these papers, a direct comparison between core lesions and control animals during non-pre-exposure avoidance performance was never made, however with close inspection of Figure 3 in Pothuizen et. al., 2005 it does appear that core lesions made rats slightly better at avoidance than controls, consistent with the results we report here (Pothuizen et al., 2005).

Another aim of this study was to extend upon our earlier work demonstrating stronger stimulus-response (S-R) encoding in the DS after unilateral NAc lesions (Burton, 2013). In that study, rats received chronically implanted electrodes in DS ipsilateral to the lesion. Animals were then trained and tested on an odor-guided delay/size choice task during which rats had to choose the more valued reward on free choice trials. We found that NAc lesions enhanced neural selectivity related to stimuli and responses. This enhancement likely compensates for loss of function observed after bilateral lesions during performance of that task.

Here, we show that shock avoidance, which relies on DS function, is improved after the same NAc lesions. This might reflect stronger encoding of stimuli and response in DS after NAc lesions. However, it is also possible that other brain areas might also be involved and that we will not know if neural representations related to avoidance in DS are enhanced after NAc lesions - as they were under the odor-guided reward paradigm - until the necessary single-unit study is conducted. Furthermore, actual performance on the odor-reward task may have shaped compensatory mechanisms induced by NAc lesions, and that without this training rats with NAc lesions may not have exhibited better performance on the avoidance task. Future work will have to examine this issue in naïve animals.

Of course, there are several other ways by which NAc lesions might enhance avoidance beyond heightened DS functionality. Most obvious is the explanation that NAc is critical for encoding signals that actually impede the ability to learn avoidance. Loss of such signals would promote learning, especially if they are in competition with performing the desired instrumental response.

To address this issue we must consider what NAc might be signaling during performance of this task. One possibility is that NAc might be critical for signaling context (i.e., shock occurs in this box). It has been reported that rats with NAc lesions exhibit deficits in retention of contextual conditioned freezing (Levita et al., 2002). This might explain why our lesion rats are more likely to return to the side of the box that they were shocked previously. That is, they don't recall that they were shocked in that context previously, making it easier to simply avoid the warning stimulus when it turns on during the session. This interpretation would suggest that rats should show faster avoid latencies; however there were no significant differences between the two groups.

Other studies have shown that that activity of NAc neurons reflect the value associated with expected outcomes and/or the motivational level associated with discrete cues (Setlow et al., 2003, Bissonette et al., 2013). Thus, one prediction is that during avoidance, activity in NAc represents the motivational level associated with avoiding the shock. This is an intriguing possibility, but it cannot explain why NAc lesions enhance avoidance learning; disruption of motivational or goal-directed neural signals would only hamper learning and performance.

Another possibility is that neural activity in NAc represents the association between the CS and the shock. Although this function is commonly ascribed to the amygdala (Choi et al., 2010), NAc does receive projections from amygdala and discriminative cue selectivity in NAc is dependent on these projections (Ambroggi et al., 2008). Furthermore, cues that come to predict aversive outcomes have been shown to modulate firing in NAc during decision-making, thus it is a possibility that NAc might signal predictions related to anticipated shock (Setlow et al., 2003, Bissonette et al., 2013). Predictions related to anticipated shock might serve in the computation of prediction errors critical for reinforcement learning as proposed by the actor-critic model. In this model, an actor (DS) learns to select actions based on current situation, in this case, jumping to the safe side of the shuttle box to avoid punishment (Maia, 2010). The critic (NAc) learns the value of states and calculates prediction errors thought to be signaled by dopamine neurons. In this framework, NAc might predict that a shock is imminent upon presentation of the CS. If the rat does not cross to the other side, shock is administered and the outcome is as expected. However, if the rat happens to cross to the other side, then the CS is terminated and no shock is delivered, which would elicit a positive dopaminergic prediction error signal because that event was better than expected. Consistent with this theory, it has been recently demonstrated that subsecond dopamine release, which supplies such a prediction error signal, is elevated when rats successfully avoid being shocked (Oleson et al., 2012).

All of this suggests a very important role for NAc during avoidance, thus it seems unlikely that NAc signals would impede performance. However, an alternative interpretation is that NAc is critical for other reactions that might work against avoidance, such as anxiety and conditioned fear, which may lead to elevated freezing (Fernandez-Teruel et al., 1991b, Choi et al., 2010). In light of this, it is important to note that our rats only partially acquired two-way active avoidance (~40%). It has been shown that in animals with only partial acquisition of two-way avoidance that anxiety and conditioned fear may act as prominent negative modulators of avoidance acquisition (Gray, 1982, Fernandez-Teruel et al., 1991b, Vicens-Costa et al., 2011). That is, anxiety and fear are inversely related to the ability to acquire the task as shown by manipulations that decrease context-conditioned fear and anxiety, such as septo-hippocampal lesions or administration of anxiolytic drugs (Gray, 1982, Gray and McNaughton, 1983, Pereira et al., 1988, Fernandez-Teruel et al., 1991a, Escorihuela et al., 1993, Vicens-Costa et al., 2011). Similarly, rats that show comparatively lower innate levels of fear have been shown to be better at escape-avoidance (Vicens-Costa et al., 2011, Diaz-Moran et al., 2012). On the opposite side of the spectrum, rats given anxiogenic drugs, or that have innately high levels of anxiety, exhibit impaired performance on avoidance acquisition (Fernandez-Teruel et al., 1991b, Vicens-Costa et al., 2011, Diaz-Moran et al., 2012).

Thus, reduced anxiety and conditioned fear that might occur after NAc lesions could result in less freezing to conditioned stimuli that predict shock, which, in turn, could have promoted avoidance learning. Unfortunately, video was not recorded during the behavioral sessions, thus we cannot evaluate changes in freezing that occurred after NAc lesions. We do not think that freezing was an issue in this experiment because previous work has clearly shown that NAc lesions do not affect discrete-cue conditioned freezing during acquisition or retention (Levita et al., 2002). Furthermore, NAc lesions have no effect on acquisition of contextual conditioned fear or on sensory/motor processes, as measured by shock reactivity and spontaneous locomotor activity (Levita et al., 2002).

Lastly, it does not appear that rats with NAc lesions were freezing less in our study because rats with NAc lesions were not significantly slower on avoid trials (Fig 1D); if rats were freezing more, then they would have been slower to avoid. Thus, attenuated freezing after NAc lesions cannot explain the benefits observed during avoidance. Instead, NAc lesions

clearly improved acquisition and retention of two way escape-avoidance through some neural mechanism. We suggest that this might reflect enhanced stimulus-response encoding in DS observed after NAc lesions.

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- Lesions to nucleus accumbens core enhance escape avoidance.
- Lesions to nucleus accumbens core promote avoidance learning.
- Nucleus accumbens core lesions enhance retention of avoidance.
- Avoidance performance is correlated with inability choose valued reward.

Figure 1. NAc lesions improved performance on a two way active-avoidance paradigm
A Gray areas mark lesions for each animal. Shown are representative slices at 1.7mm, 1.0mm and 0.7mm anterior to bregma taken from Paxinos and Watson (1997). These rats were used previously to examine changes in reward-guided decision-making that occur after NAc lesions (Burton et. al., 2013). Rats in both groups were trained over four consecutive days (30 trials per day) to escape and avoid a shock that occurred 15 s after onset of a tone by moving through an open door to the other side of the chamber. Rats were retested on a 7th day which occurred 72 hours later. **B.** Escape latencies for controls (black square) and lesions (gray diamond) as defined by how quickly the rats moved to the other side after the shock initiated. **C.** Percent avoidance for controls and lesions as defined by the number of times the rats crossed to the other side within 15 s of tone onset divided the total number of tone presentations. **D.** Avoid latencies as defined by how quickly the rats moved to the other side after presentation of the CS. Asterisks indicate planned comparisons revealing statistically significant differences (t test, $p < 0.05$). Error bars indicate SEM.

Figure 2. Correlation between reward-guided decision-making deficits and avoidance retention
A. Height of each bar represents the percent choice of high (short delay to reward or a large reward; solid; black) and low (long delay to reward or a small reward; open; gray) during performance of the reward-guided decision-making task for controls (black) and lesions (gray). Data are from Burton et al., 2013. Control rats chose the higher value reward significantly more often (Fig. 1A; $t_{(10)} = 7.7$, $p < 0.05$). Rats with NAc lesions showed impaired reward discrimination, selecting high and low value wells in roughly equal proportions (chi-square = 0.51; $p = 0.48$). **B.** Values on the x-axis reflect the strength of each rat's reward discrimination on the reward-guided choice-task. Reward discrimination is defined by the percent choice of high value reward minus the percent choice of low value reward. Rats chose more immediate and larger reward over more delayed and smaller reward, respectively, thus values on the x-axis are mostly positive. Performance on this task (x-axis) is plotted against avoidance retention (y-axis), as defined by the percent avoidance on day 7 minus the percent avoidance on day 1.