The Cognitive Effects of Dopaminergic Lesions to Anterior Cingulate Cortex in Rats

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Introduction

Previous work has shown that excitotoxic lesions to the anterior cingulate cortex (ACC) increase distractibility to previously rewarded distractors (Newman & McGaughy, 2011). ACC lesions produced a specific distractibility to cues previously paired with reward. Here, we extend our prior work by assessing the effects of dopaminergic lesions to the ACC on distractibility using an attentional set-shifting task (ASST) and a test of sustained attention with distractors (SAT) to identify the neuromodulatory bases of these impairments. The SAT was also modified to assess the effects of DA lesions in the ACC on changes in response-reinforcement contingencies.

Surgical Methods

The ACC was injected with Anti-DAT-saporin (Advanced Targeting Systems, San Diego, CA), or Dulbecco's saline (0.2 µg/µL, 125 nl/min) using a 26 gauge syringe with the beveled edge towards the midline.

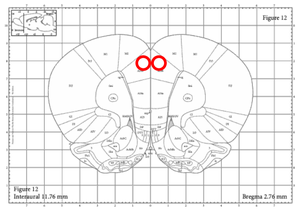

Figure 1A. Paxinos and Watson (2014) shows the rostral injection sites in the ACC, bregma +2.7.

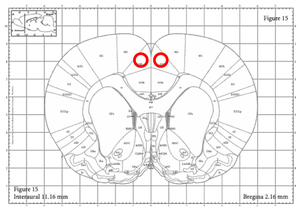

Figure 1B. Paxinos and Watson (2014) shows the caudal injection sites in the ACC, bregma +2.2

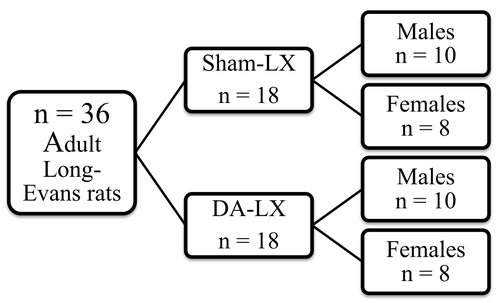

Figure 2. The subjects were 36 adult, Long-Evans rats (Charles River, Boston). All rats received injections at the locations indicated un figure 1A and 1B. Of those 36 subjects, 18 were injected with Dulbecco's saline, and 18 with an Anti-DAT saporin (Advanced Targeting Systems, San Diego, CA). Each lesion group was comprised of 10 male subjects, and 8 female subjects.

Behavioral Methods:
Attentional Set-Shifting Task (ASST)

Figure 3A. Each stage of testing begins with four discovery trials, in which rats are allowed to explore the baited pot after an incorrect response is emitted. Subsequent to these discovery trials, rats are not allowed to retrieve the reinforcer after an incorrect response and the limited hold is shortened from 90 to 60 sec. Rats are trained on a simple discrimination (SD; stimuli not shown) that one exemplar is reinforced e.g. light foam shapes. Subjects must displace digging media in the correct pot to receive reinforcement. An equal amount of crushed reinforcer in the incorrect pot prevents the use of an olfactory cue to identify the correct pot. At each stage, a subject must emit 6 correct, consecutive responses. Stimuli used in the compound discrimination (CD) and compound discrimination reversal (CDR) are shown to the left. Alternating pairs of stimuli are used on sequential trials. Subjects must respond to the exemplar reinforced in the SD (e.g, light foam shapes) and ignore novel, salient attributes (e.g. texture). Following achievement of criterion performance on the CD, all subjects began the CDR, where the alternate exemplar in the same modality (e.g. dark foam shapes) was paired with reinforcement.

Figure 3B. Stimuli used for the intra-dimensional shift (ID) and second reversal (IDR). The task uses a total changeover design by introducing novel stimuli for test of the ID. The attribute that predicts reinforcement on the ID and its reversal (IDR) is the same as the prior three testing stages (e.g digging media). Performance in the ID is facilitated in subjects who form an attentional set, so fewer trials are typically required to meet criterion performance on the ID than CD.

Figure 3C. Stimuli used for the extra-dimensional shift (ED) and third reversal (EDR). Subjects must inhibit responding to the previously relevant dimension, e.g. digging media, as it no longer predicts reinforcement. In these discriminations, a previously irrelevant attribute, e.g. texture, predicts reward. Normal subjects require more trials to learn this discrimination than the ID because of the increased cognitive demand required for a subject to inhibit responding to the previously relevant dimension and to learn a new attribute that predicts reinforcement. The dependent measure reported here is the number of trials to reach criterion performance. Response latencies were also recorded, but those data are not presented.

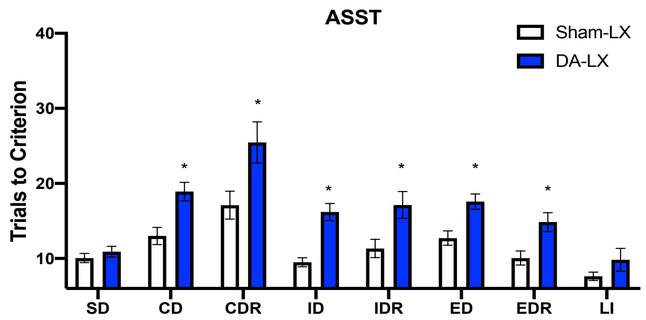

Figure 4. The trials needed to reach criterion performance of six trials correct in a row is shown on the ordinate. There was no difference between males and females so the data combines them. Both sham- and dopamine-lesioned subjects can discriminate stimuli differed on one stimulus dimension (SD). All subjects also showed an increase in trials to criterion with the first encounter of complex stimuli (CD). This effect was greater in rats with dopaminergic lesions (blue bars, n=18) than sham lesioned rats (white bars; n=18). Relative to sham-lesioned rats, dopamine lesioned subjects were impaired at reinforcement reversals (CDR, IDR, EDR), the forming (ID) and shifting of attentional set (ED). * = $p < 0.05$ compared to Sham-LX subjects.

Behavioral Methods:
Sustained Attention Task (SAT)

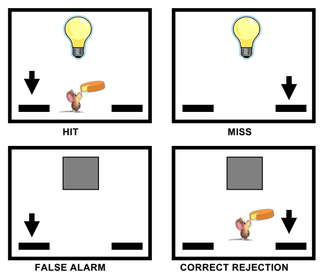

Figure 5: After completion of the ASST, rats were trained in a sustained attention task (SAT) as described in this schematic diagram. Rats must discriminate brief, temporally unpredictable lights of varying durations (500, 100 and 25 msec) from non-signals. After the levers extend into the box, rats are reinforced for responding on the left lever after a signal and the right after a non-signal trial. For explanation of distractor conditions, please select the audio file.

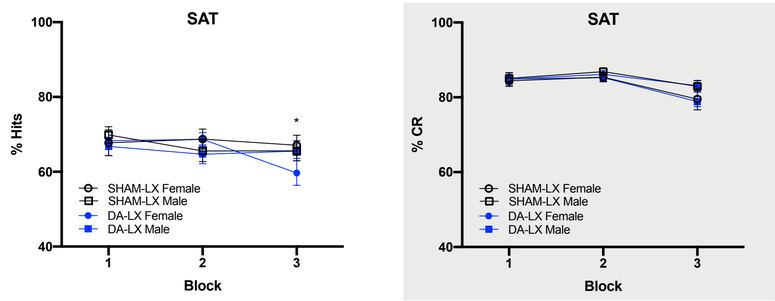

Figure 6. Dopamine lesions in females (blue circles; n=8) produced a vulnerability to the effects of time on task not found in other subjects during testing of the baseline task (left panel). All dopamine lesioned subjects showed the same performance as sham lesioned subjects on non-signal trials (right panel). All rats show stimulus length dependent performance (data not shown).

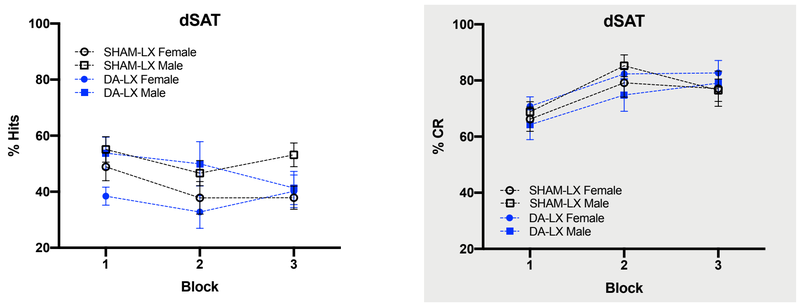

Figure 7. The presence of a visual distractor (0.5 Hz) impaired hits (left panel) and correct rejections (right panel) relative to performance in the baseline SAT (Figure 5). Rats with dopaminergic lesions (blue symbols; n=18) did not differ from sham lesioned animals (open symbols; n=18) in either the visual (left panel) or auditory distractor sessions (data not shown). Omissions were low in the both the baseline (SAT M = 9.33 ± 1.58), and the distractor condition SAT (dSAT M = 12.17 ± 2.63).

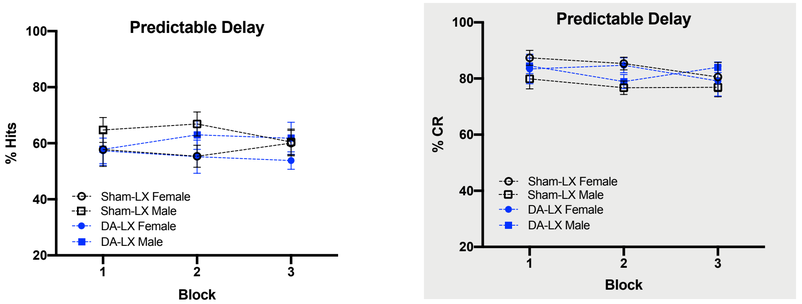

Figure 8. Imposing a 2 second delay of reinforcement after correct responses did not dissociate the performance of sham-lesioned subjects (open symbols) and dopamine lesioned subjects (blue symbols). Hits are shown in left panel and correct rejections are shown in the right panel. All subjects showed an increase in total omissions when the 2 second delay was imposed (Baseline omissions M = 4.15 ± 0.91; 2s M = 8.15 ± 1.93) and no change in side bias (M = 0.40 ± 0.01; 2s M = 0.39 ± 0.01).

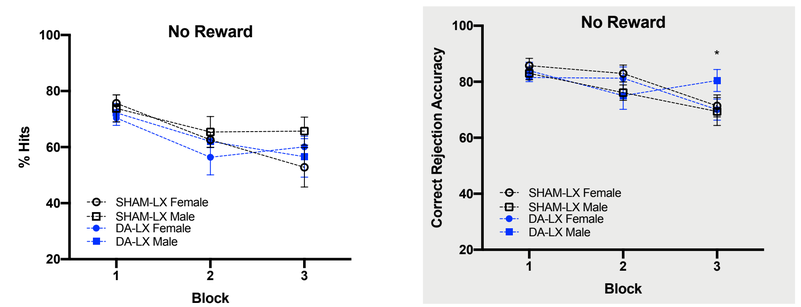

Figure 9. In sessions where no reward was given, there was no difference between sham-lesioned (open symbols) and dopamine lesioned subjects (blue symbols) on signal trials (left panel). On non-signal trials, dopamine lesioned males (blue squares) did not show a decline in accuracy over time like all other subjects (right panel). All subjects regardless of lesion showed an increase in omissions in block 3 when reward was removed (no reward: B1 M = 0.31 ± 0.07; B2 M = 1.70 ± 0.25; B3 M = 5.05 ± 0.43) and no change in side bias (baseline M = 0.42 ± 0.02; no reward M = 0.44 ± 0.01).

Conclusions

1. Dopamine lesioned subjects showed an increased susceptibility to distraction when attributes of a complex stimulus had a prior reinforcement history, as indicated by the impairment at the CD stage of the ASST. This was not a general susceptibility to distraction as there was no difference in performance when salient distractors with no prior reinforcement were tested in the SAT.

2. Dopamine lesioned subjects were impaired in several other stages of the ASST including reversals. As the reversal stages in the ASST include complex stimuli with a prior reinforcement history, further tests assessed changes to reinforcement contingences in the absence previously reinforced distractors and found no difference between the performance of sham- and dopamine-lesioned rats.

3. The present data, while qualitatively similar to previous work assessing excitotoxic lesions, is quantitively dissimilar. Dopaminergic lesions to ACC produced less severe deficits at the CD and CDR stages of the ASST, but resulted in more global deficits, including ID, ED, and all reversal stages. Together the data from both the ASST and SAT support the hypothesis that dopamine in the ACC is crucial for filtering distractors which have a prior reinforcement history, and less critical to updating responding when reinforcement contingencies are changed.

5. The effects of dopaminergic lesions to the ACC differed between sexes when subjects were tested in the SAT. The loss of dopamine in the ACC increased female rats vulnerability to prolonged time on task. In males, the loss of dopamine in decreased sensitivity to the removal of reinforcement. Additional analyses are required to understand these differences. Limitations of the current study include a lack of completed histological analysis which is currently underway.

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