Dissociable attentional effects of dopaminergic and cholinergic lesions to the anterior cingulate cortex

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Introduction

Previous work has shown that excitotoxic lesions to the anterior cingulate cortex (ACC) increase distractibility when previously rewarded distractors were introduced into a complex stimuli (Newman & McGaughy, 2011). In contrast, ACC lesions did not increase distractibility to cues not previously paired with reward. Here, we extend our prior work by assessing the effects of neuromodulatory specific lesion to the ACC on performance in an attentional set-shifting task (ASST). We utilized a rat model to assess dopaminergic and cholinergic lesions to the ACC. The ASST assesses an animals ability to form and shift an attentional set. This task is also used to assess sensory processing, distraction to previously reinforced cues and reversal learning.

Subsequent to testing in the ASST, subjects were trained in a test of sustained attention (SAT). The SAT assesses the ability of rats to maintain attention to unpredictably occurring visual targets of varying durations, and to discriminate them from non-signals. Additionally, rats were tested in distractor sessions where distractors were in the same modality at the target stimulus (light) or cross modal to the target stimulus (tone) to provide greater insight into the attentional deficit produced by dopaminergic deafferentation of the ACC.

Surgical Methods

In the present study the ACC was injected with 0.2 µg/µL Anti-DAT-saporin, 192 IgG-saporin or Dulbecco's saline. For comparison to prior work, we also include data from rats who received 0.06 M ibotenic acid to produce non-specific damage to this region. Each site was 0.2 µl/site was infused at 125 nl/min using a 26 gauge syringe with the beveled edge towards the midline.

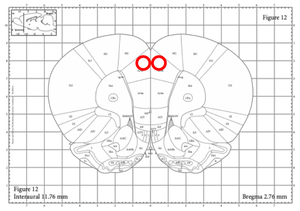

Figure 1A. Paxinos and Watson (2014) shows the rostral lesion locations in the ACC, bregma +2.7.

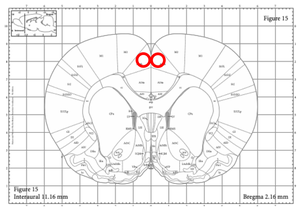

Figure 1B. Paxinos and Watson (2014) shows the caudal lesion locations in the ACC, bregma +2.2

Coordinates for ACC/A24b lesions

AP: Bregma +2.7	ML: ± 0.6	DV: skull -2.4
AP: Bregma +2.2	ML: ± 0.6	DV: skull -2.2

Behavioral Methods:

Attentional Set-Shifting Task (ASST)

Figure 2A. 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 2B. 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 2C. 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.

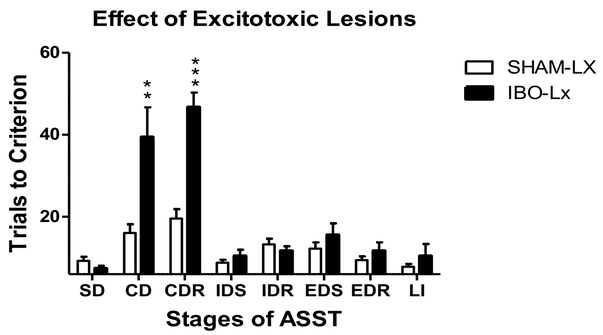

Figure 3. Excitotoxic lesions to the ACC (black bars; n=8) increased susceptibility to distractibility to cues previously paired with reward (CD). Lesioned rats also showed difficulty on the first reversal of the day, but not subsequent reversals. **indicates p<.01 ***indicates p<.001. For additional details see *Newman and McGaughy, 2011.*

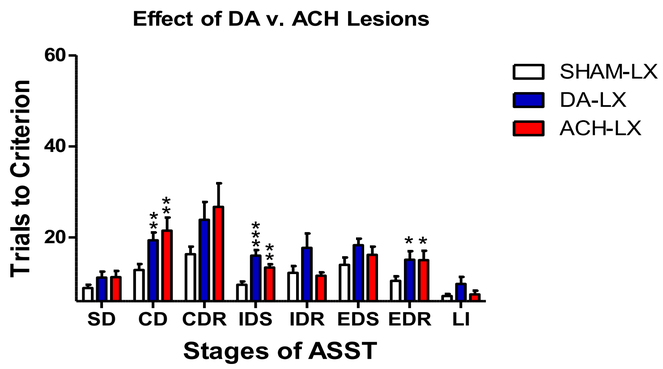

Figure 4. Rats with dopaminergic lesions to the ACC (blue bars; n=10) and cholinergic lesions (red bars; n=10) were more vulnerable than rats with sham lesions (white bars; n=13) to salient distractors as tested at the CD. Additionally, neither dopaminergic or cholinergic lesioned animals benefited from the formation of an attentional set tested at the IDS, as both groups took more trials to meet criterion than sham lesioned rats. **indicates p<.01 ***indicates p<.001.

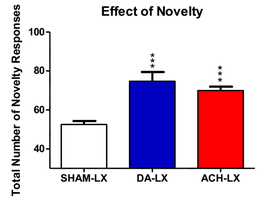

Figure 5. When the stages of the task where novel stimuli are presented were combined (SD, CD, IDS, EDS, and LI), both dopaminergic (*M*=74.70; *SD*=15.06) and cholinergic (*M*=69.90; *SD*=6.37) required significantly more trials to reach criterion on these tests than sham lesioned rats (*M*=52.54; *SD*=6.46). ***indicates p<.001.

Behavioral Methods:

Sustained Attention Task (SAT)

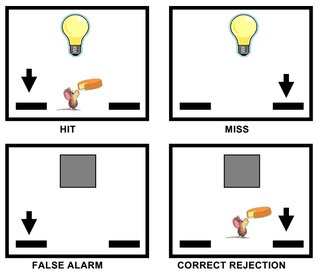

Figure 6: After completion of the ASST, rats were trained in a sustained attention task (SAT) as described in this schematic diagram. Rats must discriminate brief, temporally unpredictable lights of varying durations (500, 100 and 25 msec) from non-signals. After the levers extend into the box, rats are reinforced for responding on the left lever after a signal and the right after a non-signal trial. In the visual distractor condition, a light located in the back of the box flashed at 0.5 Hz. In the auditory distractor condition a 0.5Hz tone was present throughout the entire testing session. The order of testing was counterbalanced across subjects.

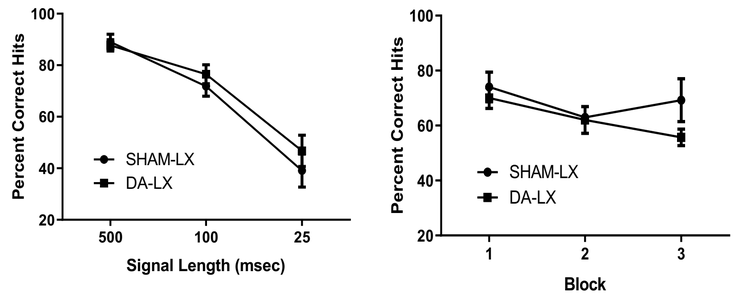

Figure 7. Rats with dopaminergic lesions (filled squares; n=10) did not differ from sham lesioned animals (filled circles) in the baseline version of the SAT. Both groups show stimulus length dependent performance (left panel) and decreased signal detection over the course of the testing session (right panel).

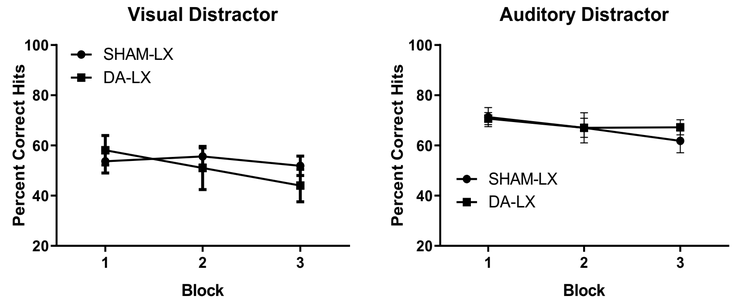

Figure 8. The presence of a visual distractor impaired target detection relative to performance in the baseline SAT (Figure 7, right panel). However rats with dopaminergic lesions (filled squares; n=10) did not differ from sham lesioned animals (filled circles) in either the visual (left panel) or auditory distractor sessions. (right panel).

Conclusions

1. Cholinergic and dopaminergic lesions of the anterior cingulate cortex (ACC) increased susceptibility to salient distractors in a test of attentional set shifting. Both lesions impaired formation of an attentional set. This deficit was supported by 1. the poorer performance of both ACH and DA lesioned rats on the IDS relative to sham-lesioned rats, 2. the absence of an improvement on the IDS relative to the CD and 3. the absence of an ID/ED difference.
2. A follow-up study in the DA lesioned animals showed that the increased susceptibility to distraction was found only with salient distraction, i.e. distractors in modalities previously paired with reinforcement. In contrast, the attentional performance of DA lesioned rats was not impaired by distractors that did not have previous reinforcement histories, e.g. the flashing houselight and tone in the SAT.
3. The similarity of effects of DA and ACH lesions on attentional performance requires further investigation. One possibility is that both lesions disrupt the interactions of these two neurmodulatory systems as nicotinic receptors act as heteroreceptors on catecholaminergic neurons.
4. Limitations of the current study include the absence of a full histological analyses and the inclusion of female subjects. Histological analyses is ongoing as is a parallel study with female rats.

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