Published in final edited form as:

Behav Neurosci. 2011 June ; 125(3): 360–371. doi:10.1037/a0023250.

Attentional effects of lesions to the anterior cingulate cortex: how prior reinforcement influences distractibility

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Abstract

Morphological changes in the anterior cingulate cortex are found in subjects with schizophrenia, attention deficit hyperactivity disorder, and obsessive compulsive disorder. These changes are hypothesized to underlie the impairments these individuals show on tasks that require cognitive control. The anterior cingulate cortex has previously been shown to be active in situations involving high conflict, presentation of salient, distracting stimuli, and error processing, i.e. situations that occur when a shift in attention or responding is required. However, there is some uncertainty as to what specific role the anterior cingulate cortex plays in these situations. The current study used converging evidence from two behavioral paradigms to determine the effects of excitotoxic lesions in the anterior cingulate cortex on executive control. The first assay tests reversal learning, attentional set formation and shifting. The second assesses sustained attention with and without distractors. Animals with anterior cingulate cortex lesions were impaired during reinforcement reversals, discriminations that required subjects to disregard previously relevant stimulus attributes and showed a more rapid decline in attentional ability than Sham-Lx subjects when maintaining sustained attention for extended periods of time. These results are consistent with the hypothesis that the anterior cingulate cortex is involved in attending to stimulus attributes that currently predict reinforcement in the presence of previously relevant, salient distractors and maintaining sustained attention over prolonged time on task.

Keywords

prefrontal cortex; cognitive control; executive function; selective attention; cingulated

Introduction

Previous research has supported the hypothesis that the anterior cingulate cortex (ACC) is only involved when behavioral responses are in conflict (Erickson et al., 2004). Others have demonstrated that ACC is critical to determining the relevance of stimuli, ignoring irrelevant stimuli (Ahnaou, Nayak, Heylen, Ashton, & Drinkenburg, 2007; Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; Lee, Rushworth, Walton, Watanabe, & Sakagami, 2007) and reversal learning (Ragozzino & Rozman, 2007). Dysregulation of the ACC is hypothesized to produce a disturbance in processing incoming information or ‘cognitive

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dysmetria' that leads to increased distraction and inefficient attention to relevant stimuli. This type of impairment has been reported in patients with schizophrenia (Laurens, Kiehl, Ngan, & Liddle, 2005; Liddle, Laurens, Kiehl, & Ngan, 2006; Stark, Uylings, Sanz-Arigita, & Pakkenberg, 2004). Children and adults with obsessive/compulsive disorder show increased error related activity and greater functional activation of the ACC during error processing and conflict situations (Aouizerate *et al.*, 2004; Santesso, Segalowitz, & Schmidt, 2006). This dysregulation may lead to the inability to disengage from a negative thought or action pattern (Sachdev & Malhi, 2005). Patients with attention deficit disorder have significantly less gray matter and hypoactivity in the ACC (Dickstein, Bannon, Castellanos, & Milham, 2006; Makris *et al.*, 2007; Seidman *et al.*, 2006). Attention deficit disorder patients also show poor attentional control in paradigms where response conflict is present or when task switching is required (King, Colla, Brass, Heuser, & von Cramon, 2007; Shallice *et al.*, 2002; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007). As dysfunction in the ACC has been hypothesized to be involved in producing vulnerability to distraction, the present series of experiments was aimed at better understanding what attributes of stimuli are most likely to produce distraction in rats with ACC damage.

In the first experiment of the effects of lesions to the anterior cingulate cortex were assessed using an attentional set shifting task (ASST) previously validated for use in humans (Jazbec *et al.* 2007; Owen *et al.* 1991; Pantelis *et al.* 1999), non-human primates (Dias, Robbins, & Roberts, 1997) and rats (Birrell & Brown, 2000; McGaughy, Ross, & Eichenbaum, 2008; Newman, Darling, & McGaughy, 2008). Subcomponents of this task assess proficiency in conditional discriminations with and without distractors, reversal learning, formation and shifting of attention set. Preliminary data from this study suggested lesions of the ACC impaired performance on trials where irrelevant stimulus attributes were present. As a result, we tested the ability of rats with or without ACC damage to perform simple discriminations and reinforcement reversals using stimuli that differed on only one dimension. This eliminated the influence of irrelevant stimuli during tests of reversal learning.

Subsequently, we tested the same subjects in a previously validated test of sustained attention task (SAT) with visual and auditory distractors. (Birrell & Brown, 2000; McGaughy & Sarter, 1995a; Newman & McGaughy, 2008). Previous work has shown that cholinergic deafferentation of the prelimbic cortex produces vulnerability to distraction caused by salient, task irrelevant stimuli (Newman and McGaughy 2008). In the present study we assessed the effects of distracting stimuli, i.e. flashing the houselight or intermittent tones that have not been explicitly paired with reinforcement, to determine if rats with ACC damage were distracted by salient stimuli not previously associated with reinforcement. As prior reinforcement history was hypothesized to influence susceptibility to distraction in the ASST, we hypothesized that the performance of ACC-Lx rats would be similar to that of intact subjects in the SAT with and without distraction. Previous research has shown greater activity in the ACC in tasks that require cross-modal divided attention than tasks that require unimodal divided attention (Vohn *et al.*, 2007). As a result distracting stimuli were presented in the same and different modality of targets to determine if ACC-Lx rats were more susceptible to the detrimental effects of cross-modal distractors than Sham-Lx rats.

Experiment 1

Method

Subjects—The subjects were 16 adult, male Long-Evans rats (Charles River, Boston, MA). Each rat weighed at least 275 grams upon arrival. Animals were allowed one week to habituate to the vivarium and daily handling. All rats were subjected to moderate food restriction (18 g/day) to allow them to maintain weights at approximately 90% of age-

matched free fed rats. Access to water was *ad libitum*. Animals were kept on a 12 hr light/dark cycle (on 7:00 am) and tested during their light period between 11 am and 5 pm. All procedures described were approved by the University of New Hampshire Institutional Animal Care and Use Committee in accordance with the *Guide for the Care and Use of Laboratory Animal*.

Apparatus and materials—All training and testing was performed in a plastic testing box (91.44 × 45.72 × 25.40 cm; L × W × H, Sterilite Corporation, Townsend, MA; Figure 1A).

Training to dig for reinforcement—All rats were trained to dig in a terra cotta pot with a height of 10 cm and an internal diameter of 10.2 cm to retrieve a food reward. Rats were given a limited hold of 90 sec on each trial to retrieve reinforcement. After animals successfully retrieved 10 pellets in a row, they were considered eligible for surgery.

Surgery—Animals were matched by the number of trials needed to successfully retrieve 10 pellets in a row and response latency. One from each pair was randomly assigned to either receive the excitotoxin, ibotenic acid (0.06 M), or its vehicle, 0.1 M phosphate buffer, by infusion into the ACC. Rats were anesthetized using ketamine and xylazine (85 mg/kg ketamine and 8.5 mg/kg xylazine). Infusions were made into the ACC via a 10 µl, 26 gauge beveled tip microsyringe mounted on a stereotaxic frame. For each infusion the beveled tip was positioned so the opening was pointing towards the midline. A small volume of the toxin or vehicle (0.2 µl/site) was infused bilaterally at a rate of 125 nl per minute using an electronic infusion pump (Micro 4, Microsyringe Pump Controller, World Precision Instruments, Sarasota, FL). The needle was left in place for 4 minutes prior to and subsequent to infusion to minimize bleeding and undesired diffusion of the toxin. The following coordinates were used: AP: +2.7, ML: ±0.6, DV: -2.4; AP: +2.2, ML: ±0.6, DV: -2.2 with anteroposterior (AP) measurement relative to Bregma and dorsoventral (DV) measurement relative to the skull and the toothbar at -3.0 mm (Chudasama et al., 2003). All animals were monitored daily in the week following surgery to ensure they were healthy. Analgesic and antibiotics were administered as needed. Animals received 4 days of *ad libitum* food and water before food restriction was reinstated. An additional 3 days of food restriction (~18 g/day) were established before postoperative training commenced.

Postsurgical training—After recovery from surgery, the animal began testing in the attentional set shifting task. Pots of identical dimensions to those used to shape digging behavior were used for testing during the ASST. The outer surfaces of the pots were covered with textures and the inside of the pots were filled with digging media which were scented using diluted aromatherapy oils (essential oils diluted 1:100 in canola oil). Test stimuli were placed in either end of the testing box with access to these sections prevented by a divider while stimuli were placed prior to the onset of a trial. Reinforcement for both training and testing was a 45 mg food pellet (Dustless Precision Pellets, Bio-serv, Frenchtown, NJ). For all stages of training and testing, the unbaited pot contained an equal, but crushed amount of reinforcer to prevent the rats from using the scent of cereal to identify the correct stimuli.

Exemplar training: Rats were trained to perform conditional discriminations using three sets of exemplar pots, i.e. one in each of the dimensions the rat would be required to attend to during the conditional discrimination tests. The pots were wrapped in fabric to give different textures (fake fur vs. reverse of fake fur), filled with different digging media (white vs. green shredded paper), or scented with different odors (cherry vs. pine). A pair of pots was placed in the box behind a divider to prevent the rat's access to testing stimuli prior to the onset of a trial. The experimenter removed the divider and started the timer. If the rat

displaced the digging medium with his nose or paw, this was considered a response. After a response was made, the timer was stopped and the response latency and accuracy were recorded. The first four trials of every discrimination were discovery trials. In these trials, the animal was given 90 seconds to respond. If they responded incorrectly the latency was recorded, the trial was scored as a miss, and they were allowed to explore the correct pot. For the first discovery trial, a pellet was placed on top of the digging medium to ensure the rat recognized one of the pots was reinforced. On later trials, the pellet was wholly buried. On trials subsequent to the discovery trials, the limited hold was reduced to 60 seconds and the animal was no longer allowed to explore the correct pot if an incorrect choice was made. Once the rat achieved six correct responses in a row on each exemplar, it was eligible to move on to testing in the ID/ED task. The exemplars were not used again.

Attentional set shifting

Simple discrimination: The first discrimination in the attentional set shifting task was a simple discrimination (SD) where the pots differed on one dimension (texture, digging medium, or odor; see Figure 1B). The animal was again given four discovery trials in which they were permitted to dig in both pots, and again only one pot was baited (e.g. patchouli scented pot). As before, once the animal emitted six consecutive correct responses, the next discrimination was started. The same criterion was applied to every stage of testing.

Compound discrimination: The next discrimination was a compound discrimination (CD) where the other two dimensions e.g. texture and digging media were introduced but the rat was still rewarded for attending to the previously reinforced dimension (e.g. patchouli). In order to minimize the number of pairs of pots needed, the dimension that was irrelevant to ID and ED performance in the first session was held constant across both pots (e.g. texture). In other words, rats trained to attend to odor in tests of the SD→REV2 that shifted responding to digging media in the ED→REV3 received two pairs of pots with identical texture cues. Any deficits seen at the CD would suggest deficits in ignoring new irrelevant stimuli similar to deficits found in patients with frontal lobe damage or schizophrenia (Jazbec *et al.*, 2007; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; Pantelis *et al.*, 1999).

First reversal: After completion of the CD, the reinforcement contingencies within a modality were reversed (i.e. cinnamon, not patchouli, scented pot was rewarded, REV 1). Deficits on reversal learning have been demonstrated after damage to orbitofrontal and anterior cingulate cortices (Dias *et al.* 1997; McAlonan and Brown 2003; Tait and Brown 2007).

Intradimensional shift/reversal 2: Upon successful completion of the reversal, a new set of stimuli (new odors, digging media, textures) was introduced using a total changeover design. The animal was reinforced for attending to the same dimension as the previous discrimination (e.g. lilac scented pot). This discrimination was known as the intradimensional shift (IDS1). Learning at this stage should have been facilitated by the animal maintaining attentional focus on the previously rewarded stimulus dimension so that fewer trials were required to reach criterion performance on the IDS than the CD. After the successful completion of six consecutive trials on IDS1, another reinforcement reversal was performed (REV 2; e.g. reinforced for digging in rose scented pot).

Extradimensional shift/reversal 3: The next discrimination was the extradimensional shift (EDS1) which used another novel set of stimuli, and the animal was reinforced for attending to a previously irrelevant dimension, i.e. shifting attentional set (digging medium; e.g. metallic beads). If the animal had formed an attentional set, then they should require

significantly more trials to achieve criterion performance on the EDS than on the IDS. Previous research has suggested excitotoxic lesions (Birrell & Brown, 2000; Ng, Noblejas, Rodefer, Smith, & Poremba, 2007) and noradrenergic lesions (McGaughy et al. 2008; Newman et al. 2008a; Tait et al. 2007) of the prelimbic cortex impede the ability to shift attentional set. After successful completion of the EDS, the final reversal of the session was given with the alternate stimuli of the discrimination pair reinforced (REV 3; plastic beads).

In order to determine whether the deficits seen were consistent across time, the ASST was repeated on the following day. In the first discrimination of the second session, all animals were given the same discrimination used in REV 3 of the previous session. The animals were reinforced for responding to the same stimulus that was reinforced on the REV 3 e.g. plastic beads. Because the animal would be required to shift attention on the next ED to the previously invariant dimension (e.g. texture) the testing set was altered. On this test the previously invariant dimension was now varied between the pots and the other dimension (e.g. odor) was held constant. If animals have successfully learned that this previously constant dimension e.g. texture is irrelevant, there will be no difference in performance on REV3 and its repetition (learned irrelevance).

All animals were then given a novel set of pots and required to perform a second intradimensional shift (IDS2). The alternate exemplar of the relevant dimension, e.g. the other digging medium, was then reinforced (REV 4). The animals were again given a novel set of pots and required to perform a second EDS where attention to the previously relevant dimension must be inhibited and the subject must learn a new attribute predicts reward e.g. texture (EDS2). Finally the reinforcement was reversed within the relevant modality (REV 5). The dimension associated with reinforcement at each stage of testing e.g. SD-REV2 throughout testing was counterbalanced across subjects and matched across Sham-Lx and ACC-Lx rats. Testing order was designed so that the dimension shifted to on the second ED was not the same as the dimension that predicted reinforcement on the SD-REV2.

Serial reversals—Previous research has suggested animals with ACC inactivation have difficulty with reversal learning only in the presence of distracting stimuli (Ragozzino & Rozman, 2007). Preliminary data analyses from the ASST showed deficits in reversal learning, but it was unclear due to the complex nature of the stimuli used, whether the presence of irrelevant attributes contributed to the impairments found in ACC-Lx rats. Consequently, we conducted tests of serial reversals using pairs of stimuli that differed on only one dimension. These reversals were presented in each of the dimensions used in the ASST without the presence of the other dimensions. While the same modalities i.e. texture, odor and digging media were tested, the serial reversals used all new stimuli. Tests of conditional discriminations for digging media and textures were conducted in the same type of terra cotta pot used for the ASST. Odor discriminations and reversals were conducted using plastic testing cups (diameter: 7 cm, height: 6 cm, Glad Products Company, Oakland, CA). Testing was conducted in the same apparatus used in the ASST. All animals were assessed on three discriminations for each dimension: the acquisition of the simple discrimination, the reversal of the reinforced pot, and the reversion of the reinforcement to the originally reinforced pot. These three discriminations were given in one session. All animals were given two more sessions to complete the serial reversals for the other two dimensions. All orders of dimensions were presented and counterbalanced across subjects. Testing schedules were matched across Sham-Lx and ACC-Lx rats so the schedules tested did not differ based on lesion condition. All animals were given 60 seconds to respond and timing started upon removal of the barrier, similar to the methods used in the ASST.

Histology—After completion of testing, animals were given an overdose of Euthasol (6.5 mg/kg, i.p.). The rats were then trans-cardially perfused with 0.9% saline, followed by 4%

paraformaldehyde in phosphate buffer. Brains were removed, placed in a 30% sucrose solution until they sunk, and then sliced into 40 μ m coronal sections. Sections were thionin stained for Nissl bodies after they were mounted with gelatin solution on gelatin-coated slides. Histological assessment of cell loss was made on an Olympus Optical BX51 microscope (Optical Analysis Corporation, Nashua, NH) using the 4 $\times$ objective. Images of the sections were photographed using a SPOT Insight digital camera (Diagnostic Imaging, Sterling Heights, MI). Images were collected using Image Pro Plus version 6.0 software (Media Cybernetics, Silver Springs, MD), and the area of damage was outlined using ImageJ version 1.41 (National Institutes of Health, Bethesda, MD, USA). Using the nomenclature of (Paxinos & Watson, 2005) the percentage of ACC loss was then calculated at bregma +3.7, +2.7, and +1.7 mm similar to methods used previously (Bucci & Chess, 2005). The amount of damage to the surrounding areas was also noted.

Statistical analyses—All statistical analyses were performed with SPSS v. 17.0 (SPSS, Chicago, IL). Because performance at different stages of the task has been associated with functionally distinct areas of the frontal cortex and require unique cognitive skills, these stages were analyzed using separate mixed factors ANOVAs. The degrees of freedom in all analyses were corrected using the Huynh–Feldt correction in the case of a violation of sphericity. Epsilon (ϵ) values not equal to 1 are reported below. Alpha levels were modified using Bonferroni corrections when necessary. In order to ensure all animals were able to successfully discriminate in each modality, i.e. digging media, odor and texture, the number of trials needed to reach criterion performance in each exemplar discrimination was compared using a mixed factors ANOVA with a within subjects factor of Dimension (3 levels) and the between subjects factor Lesion (2 levels).

Attentional set shifting: In order to assess the initial acquisition of the ASST a separate ANOVA with Test (2 levels, SD, CD) as a within subjects factor and Lesion (2 levels) and Dimension (3 levels) as between subject factors was used. The CD was the first instance where the animal was required to focus attention in the presence of distracting, salient stimuli. Patients with schizophrenia have previously shown deficits at the CD which may be due to dysregulation of the ACC (Jazbec et al. 2007; Pantelis et al. 1999). This analysis will allow for the assessment of ACC in disregarding new, salient stimuli in the CD and dissociate impairments under these conditions from impairments due to an inability to discriminate two stimuli (SD). An assessment of the effects of ACC lesions on the number of trials to reach criteria on the first reversal in a session (REV 1 and REV 4) as compared to the second reversal of the session (REV 2 and REV 5) was done using a mixed factors ANOVA with Session (2 levels), and Test (1st REV vs. 2nd REV; 2 levels) as within subject factors and Lesion (2 levels) as a between subjects factor. Finally REV 3 and its repetition on the following session were compared with a mixed factor ANOVA with Repetition (2 levels) as a within subject factor and Lesion (2 levels) as a between subjects factor in order to determine the effect of changing the irrelevant dimension that was held constant and assess the subjects ability to retain information about a discrimination across testing sessions separated by 24 hrs.

The analyses of performance revealed ACC-LX rats had large impairments on reversal learning. In order to determine the nature of the impairments during reversal learning, error analyses were conducted on reversal trials. Using methods similar to those described in previous studies, errors were categorized as either perseverative i.e. a result of a subject maintaining focus on previously reinforced exemplar and failing to explore the other stimuli or regressive i.e. the rat had received reinforcement for choosing the previously unreinforced stimuli but returned to responding to the stimuli that is no longer reinforced (Ragozzino et al. 2003; Ragozzino and Rozman 2007). All trials on a reversal discrimination were divided into blocks of four consecutive trials. Errors were categorized as perseverative if at least

three out of the four trials in the block were errors. If less than three errors were seen in a block of four trials these errors were considered regressive. After a rat chose an incorrect pot less than three times in a row, all errors made after this point were considered regressive. The first error was excluded from analysis as it is impossible for the animal to know reinforcement has shifted until after the first error. Independent samples t-tests were conducted to determine whether there were any differences between Sham-Lx and ACC-Lx animals on total errors, perseverative errors, or regressive errors.

The number of trials needed to reach criterion performance in the ID was compared to the ED in a separate mixed factors ANOVA with within subjects factors of Session (2 levels), Test (ID vs. ED; 2 levels) and between subjects factor of Lesion (2 levels) to determine whether animals were able to repeatedly form (IDS) and shift an attentional set (EDS).

Serial reversals: In order to assess the number of trials to criterion on acquisition and reinforcement reversal a mixed factor ANOVA was used in which the within subjects factors were Modality (3 levels) and Test (2 levels; acquisition vs. reversal) and the between subjects factor was Lesion (2 levels). Reversion back to the originally rewarded pot was assessed using a separate mixed factors ANOVA with Dimension (3 levels) and Test (2 levels; reversal and reversion) as within subject factors and Lesion (2 levels) as a between subjects factor.

Results

Histology—One ACC-Lx animal was excluded from the study due to a large amount of damage that extended beyond the ACC into the premotor cortex and prefrontal cortex. Four out of the seven remaining animals incurred some damage to the premotor and prefrontal cortex. Damage was concentrated on rostral portions of the ACC ($F_{2,12}=99.71$, $p<0.001$, $\epsilon=0.82$). Planned comparisons of the percent loss along the rostro-caudal axis in ACC-Lx rats revealed greater excitotoxic damage in the ACC of ACC-Lx rats at +3.7 and +2.7 mm from bregma than at +1.7 mm (3.7 vs 1.7: $t_6=10.91$, $p<0.001$, percent loss at 3.7: $90.90\% \pm 5.17\%$, 2.7 vs 1.7: $t_6=11.12$, $p<0.001$, percent loss at 2.7: $90.40\% \pm 5.38\%$, percent loss at 1.7: $49.63\% \pm 4.93\%$; corrected $\alpha = 0.017$; see Figure 2). No other significant interactions or main effects were present (all $p>0.1$).

Conditional discrimination with and without distractors—ACC-Lx animals took significantly more trials to reach criterion on the compound discrimination than Sham-Lx rats (Figure 3; Test: $F_{1,13}=21.44$, $p<0.001$; CD: $t_{13}=2.18$, $p=0.048$) and this difference was greater in ACC-Lx than Sham-Lx rats (Test $\times$ Lesion: $F_{1,13}=6.10$, $p<0.03$). There was no difference on SD performance as a result of lesioning ($t_{13}=1.43$, $p=0.18$). All animals took significantly more trials to reach criterion performance on the CD than the SD. All rats required fewer trials to reach criterion performance on the ID than the CD ($t_{14}=3.41$; $p=0.004$). There was no effect of the perceptual dimension on either test (Test $\times$ Dimension: $F(2,9) = .57$; $p = 0.59$; Dimension: $F(2,9)=0.19$; $p = 0.86$). The analyses of the simple discriminations performed during exemplar training showed that ACC-Lx and Sham-Lx rats performed similarly regardless of testing modality (all $p > 0.56$).

Affective shifting—Animals with lesions of the ACC also showed significant impairments on reversal learning (Lesion: $F_{1,13}=17.48$, $p=0.001$). This impairment was more severe on the first reversal of a testing day than the second (Figure 4; Test $\times$ Lesion: $F_{1,13}=26.78$, $p<0.001$). All rats showed significantly improved performance on second reversals relative to the first (Test: $F_{1,13}=81.41$; $p < 0.001$; Figure 4). ACC-Lx animals took significantly more trials to reach criterion than Sham-Lx rats on the first reversals of each session (REV 1: $t_{13}=5.48$, $p<0.001$, Sham-Lx: 22.13 ± 2.80 , ACC-Lx: 47.29 ± 3.73 ; REV 4:

$t_{13}=2.62$, $p=0.021$, Sham-Lx: 16.25 ± 1.62 , ACC-Lx: 23.71 ± 2.43 ; Figure 4) but were not significantly worse than Sham-Lx animals on the second reversal in a session ($p>0.05$). All rats showed improved performance on the first reversal of the second session, i.e. REV 4, relative to the first reversal of the first session, i.e. REV 1 (Session $\times$ Test: $F_{1,13}=128.41$, $p<0.001$) but ACC-Lx rats still required more trials than Sham-Lx rats to reach criterion performance on the first reversal of the second day (Session $\times$ Test $\times$ Lesion: $F_{1,13}=59.06$, $p<0.001$; Figure 4).

Error analyses were only done on the first reversals of each session because these were the only reversals where ACC-Lx animals showed significant impairments as compared to Sham-Lx animals. Error analysis conducted on the first reversals of the session reveal ACC-Lx animals committed significantly more errors on REV 1 (Figure 5A; $t_{13}=3.81$, $p=0.002$; Sham-Lx: 9.38 ± 1.59 , ACC-Lx: 19.57 ± 2.21) and REV 4 ($t_{13}=2.86$, $p=0.013$; Sham-Lx: 6.00 ± 1.12 , ACC-Lx: 7.57 ± 0.57). The groups did not differ in the number of perseverative errors committed on each reversal ($p>0.11$) but ACC-Lx animals did show more regressive errors than Sham-Lx rats (Figure 5B. REV 1: $t_{13}=4.45$, $p=0.001$, Sham-Lx: 2.63 ± 0.65 , ACC-Lx: 9.43 ± 1.46 ; REV 4: $t_{13}=3.00$, $p=0.010$, Sham-Lx: 2.00 ± 0.54 , ACC-Lx: 4.57 ± 0.69).

Retention of conditional discrimination and test of learned irrelevance—The second test session began with a test of learned irrelevance. Lesions of the ACC did not impair subject's ability to retain information between testing sessions nor did it impair the ability of rats to disregard irrelevant stimulus dimensions even when these dimensions were changed between testing sessions (all $p > 0.28$).

Formation and shifting of attentional set—Analysis of the trials to criterion on the IDS/EDS showed all animals took significantly more trials to reach criterion performance on the EDS than the IDS (Figure 6; $F_{1,13}=42.28$, $p<0.001$). Planned comparisons showed that SHAM-Lx rats took significantly more trials to reach criterion performance on the ED than ID in both sessions (ID1 vs ED1: $t(7) = 5.23$; $p = 0.001$; ID2 vs ED2: $t(7) = 5.04$; $p = 0.002$). There were no other effects of lesion on the formation or shifting of attentional set (all $p>0.06$) demonstrating both groups of animals were able to effectively form and shift an attentional set.

Serial reversal—Analyses revealed no significant interactions or main effects of lesion suggesting the performance of ACC-Lx animals did not differ from Sham-Lx animals on simple reversals (all $p>0.07$; Acquisition: Sham-Lx: 9.96 ± 1.24 trials, ACC-Lx: 7.62 ± 0.41 trials; Reversal: Sham-Lx: 9.17 ± 0.71 trials, ACC-Lx: 9.57 ± 0.80 trials; Revert: Sham-Lx: 7.67 ± 0.22 trials, ACC-Lx: 7.76 ± 0.33 trials). This finding is consistent with previous research examining the effects of anterior cingulate lesions on reversal learning in two-choice discrimination tests (Bussey et al. 1997; Dias and Aggleton 2000).

Response latencies—Response latencies were analyzed for all stages of the tasks (attentional set shifting task and serial reversals) however no significant differences were found between the groups (all $p > 0.1$ correct response latencies mean $\pm$ SEM: Sham-Lx: 7.1 ± 0.73 sec, ACC-Lx: 8.64 ± 1.02 sec).

Experiment 2

Effects of ACC lesions on a test of sustained attention with distractors. The results from experiment 1 supported the hypothesis that damage to the ACC leaves subjects susceptible to distraction as indicated by the poorer performance on the CD. Additionally subjects with ACC-Lx had problems with reversal learning when stimuli were complex i.e. contain

attributes of a different modality but were able to perform reinforcement reversals when stimuli differed on a single dimension. Study 2 was aimed at examining how the presentation of salient, irrelevant stimuli that coincided with target presentation influenced attentional performance of rats with damage to the ACC. The distracting stimuli used in study 2 had never been explicitly paired with reinforcement. If ACC rats showed attentional impairments similar to those found at the CD stage of the ASST, it would support the hypothesis that stimulus salience produced distraction in rats with ACC damage. On the other hand, if ACC-Lx rats were not impaired in the test of sustained attention in the presence of salient, but never reinforced stimuli, it would support the hypothesis that reinforcement history was critical to create susceptibility to distraction after ACC damage.

Method

Apparatus and materials—Operant chambers (Med Associates, St. Albans, VT) equipped with two retractable levers, a houselight (2.8 W), a 45 mg pellet dispenser, a 2900 Hz sonalert tone generator, and three panel lights (2.8 W) were used. The food dispenser, panel lights, tone generator, and retractable levers were all located on the same wall. The houselight was located on the opposite wall. Records of signal presentation, lever operation, and food pellet (Dustless Precision Pellets, 45 mg; Bio-serv, Frenchtown, NJ) delivery were maintained using a personal computer with Windows XP (Microsoft, Seattle, WA) and the Med-PC IV software (Med Associates).

Shaping—After completion of the ASST and serial reversals, rats were trained on a previously validated test of sustained attention (McGaughy & Sarter, 1995b), which required animals to discriminate between signal (panel light illumination) and non-signal (the absence of panel light illumination) trials presented in a temporally unpredictable manner (12 ± 3 seconds). Training and testing sessions consisted of a total of 162 trials. Subjects were placed in the operant chambers and given 1 min to acclimate to the environment. The animals were initially trained to discriminate between signal and nonsignal trials with the houselight on throughout the session. Signal and nonsignal trials were presented in a pseudorandomized sequence so that each block of 54 trials consisted of an equal number of signal and nonsignal events. For the first shaping task, signal trials consisted of illuminating the central and left panel lights for 1 second. The lights were not illuminated for nonsignal trials. Two seconds after the presentation of the signal or the nonsignal event, both levers were extended into the box and remained for 4 seconds or until a lever press occurred. Animals were reinforced for responding to the presence of the light stimuli by depressing the left lever (hit) and the absence of the lights by pressing the right lever (correct rejection). Incorrect lever presses were defined as misses when they occurred on a signal trial and false alarms when they occurred on a nonsignal trial. If the animal failed to respond or responded incorrectly, the levers were retracted and the ITI was reinstated. After an incorrect response, the trial was repeated up to three times (correction trials). If the animal failed to respond correctly after three correction trials, a forced-choice trial was initiated. In forced-choice trials, the event (signal or nonsignal) was repeated but only the correct lever was extended and remained active for 90 seconds. On forced-choice signal trials the lights remained illuminated for 90 seconds. These trials facilitated discriminative conditioning and blocked the development of a side bias. After the animals responded correctly to >70% of both the signal and nonsignal events for at least 2 consecutive testing days, they entered a second shaping task.

In this task, only the central panel light was illuminated for 1 second. All other aspects of the task were the same as the previous shaping task. After the animals responded correctly to >75% of both the signal and nonsignal events for at least 2 consecutive testing days in this phase of shaping, they entered the final task.

Sustained attention task: baseline task—In the final version of the task, the length of the signal duration was changed from 1 s to 25, 100, or 500 ms. Sessions consisted of 27 trials of each of the three signal lengths and 81 trials of the nonsignal trials, yielding a total of 162 trials per session. Because it was planned to analyze performance changes across three blocks of 54 trials each, the sequence of signal and nonsignal trials was pseudorandomized so that one block consisted of 27 signal and 27 nonsignal trials, with each signal length being presented nine times. The presentation of each signal length and non-signal trials was randomized within a block. In addition, both correction and forced choice trials were discontinued. Animals were trained to a criterion of >75% hits to 500 ms signals and >75% correct rejections to nonsignal trials for at least two consecutive sessions, at which point they were eligible to undergo testing with distractor stimuli. The presentation of all distractor sessions was counterbalanced across groups.

Houselight distractor—In the current study we assessed the effects of two visual distractors. The first, a 0.5 Hz flashing houselight, has been previously described in several studies (McGaughy, Kaiser, & Sarter, 1996; McGaughy, Sandstrom, Ruland, & Bruno, 1997; McGaughy & Sarter, 1995b; Newman, Darling, et al., 2008; Nuechterlein, Luck, Lustig, & Sarter, 2009) and has been shown to potently impair performance of intact subjects. The second distractor stimulus was chosen to determine if distracting stimulus presented for identical durations to targets but in a different spatial location would be more difficult to disregard than a distractor whose on/off cycle did not overlap with any target stimuli. In these sessions, the houselight flashed at a rate that corresponded with the target stimulus durations throughout the entire session (500, 100, 25 ms on/off pseudorandomly presented). Previous research has indicated as a distractor increases in similarity to the target stimulus it becomes increasingly difficult to disregard (Folk, Leber, & Egeth, 2008; Friedman-Hill, Robertson, Desimone, & Ungerleider, 2003; Newman, Hanson, Carter, & McGaughy, 2008) and in the present study was aimed at determining if ACC-Lx rats were more distracted by stimuli that are perceptually identical to targets.

Tone distractor—Previous research has shown that ACC activation occurs during presentation of cross-modal stimuli. As a result, tones (2900 Hz sonalert, Med Associates, St. Albans, VT) identical to houselight distractors were presented i.e. 0.5 Hz or 500, 100, 25 ms on/off. Increased activity in the ACC has been seen in response to task irrelevant, salient stimuli (Laurens, et al., 2005; Mohanty et al., 2007; Szucs & Soltesz, 2008) and to crossmodal stimuli (Vohn, et al., 2007). However, these findings are not consistent (Banich et al., 2000). The present experiment was designed to identify whether ACC is important for ignoring task irrelevant information and if cross-modal presentation of stimuli represents a unique cognitive demand that requires an intact ACC.

Statistical analyses—From each test session, the number of hits, misses, correct rejections, false alarms, and errors of omissions were recorded. Response latencies from the extension of the levers to when a lever was pressed were also recorded. The relative number of hits (hits/(hits + misses)) was calculated for each signal length. Furthermore, the relative number of correct rejections (correct rejections/(correct rejections + false alarms)) was computed. All statistical analyses were done on SPSS 17.0 for Windows.

Baseline sessions: All dependent measures were analyzed using separate mixed-factor ANOVAs. The degrees of freedom in all analyses were corrected using the Huynh-Feldt correction in the case of a violation of sphericity. Epsilon (ϵ) values not equal to 1 are reported below. The mean performance on the baseline days before each attentional variation test day were compared with each other to determine whether there was any difference in the performance of ACC-Lx and Sham-Lx rats in the standard task over time.

For the analysis of the effects of time on task (vigilance decrement), test sessions were divided in three blocks of 54 trials (see above). The effects of signal length and block over the days of baseline on hit accuracy were analyzed using a mixed factors ANOVA with one between subjects factor (Lesion, 2 levels) and three within subject factors (Day, 2 levels; Block, 3 levels; Signal, 3 levels). As preliminary data in our lab has shown that subjects with damage to the anterior cingulate cortex are more sensitive to the detrimental effects of prolonged time on task, we compared the performance of ACC-Lx and Sham-Lx rats over blocks of trials in a series of planned t-tests. Mean latencies on hits were also analyzed using a separate mixed factors ANOVA with one between subjects factor (Lesion, 2 levels) and two within subjects factors (Day, 2 levels, Block, 3 levels, Signal, 3 levels). The effects of block on correct rejection accuracy were analyzed using a mixed-factors ANOVA with one between subjects factor (Lesion, 2 levels) and two within-subject factors (Day, 2 levels; Block, 3 levels). A separate mixed factor ANOVA was used to analyze correct rejection latency using the same designs described for the correct rejection accuracy analysis.

Distractor sessions: All distractor sessions were compared to the baseline performance of the session immediately prior to the test day so that each ANOVA has a Session within subjects factor (2 levels), allowing a comparison of the mean baseline performance to the test session. The effects of varied attentional demand were assessed in independent, mixed-factors ANOVAs with one between-subjects factor (Lesion, 2 levels) and three within subject factors (Session, 2 levels; Block, 3 levels; Signal, 3 levels). The effects on correct rejection accuracy were analyzed using a mixed factors ANOVA with one between subjects factor (Lesion, 2 levels) and two within subject factors (Session, 2 levels; Block, 3 levels).

Results

Baseline sessions—As previously and consistently reported, the analyses of hits accuracy revealed that all subjects showed signal length dependent performance ($F_{2,26} = 147.01$; $p < 0.001$). Both groups showed similar signal-length dependent performance. Planned comparisons revealed that ACC-Lx showed a greater vigilance decrement than Sham-Lx rats. ACC-Lx rats were less able to detect signals in the second and third blocks of trials relative to the first (ACC-Lx: Block 1 vs. Block 2, $t_6 = 3.45$; $p = 0.014$, Block 1 vs. Block 3, $t_6 = 4.74$; $p = 0.003$) while the performance of Sham-Lx rats was consistent across testing blocks (all $p > 0.19$; Figure 7). ACC-Lx rats were as able as Sham-Lx rats to correctly reject non-signals (all $p > 0.14$).

Houselight distractor accuracy—While all subjects were less able to detect signals in the presence of the 0.5 Hz flashing houselight ($F_{1,13} = 39.53$, $p < 0.001$), there was no differential sensitivity to this distractor as a result of ACC lesions (all $p > 0.14$). The detrimental effects of the flashing houselight did not change with prolonged time on task, or the demands of the dynamic stimulus range (all $p > 0.25$) in either Sham-Lx or ACC Lx rats (all $p > 0.24$). There were no other main effects or interactions of the effects of ACC-Lx in the analyses of hits from the 0.5 Hz distractor session. There was no difference in non-signal trial accuracy performance between groups during the presentation of the 0.5 Hz distractor (all $p > 0.06$). All rats show an ability to disregard the distractor with prolonged exposure during the session (Session x Block: $F_{2,26} = 6.45$; $p = 0.005$; Baseline vs. 0.5 Hz Block 1: $t_{14} = 3.07$; $p = 0.008$; Block 2: $t_{14} = 0.21$; $p = 0.85$; $t_{14} = 0.42$; $p = 0.68$). The effects of the overlapping houselight were similar in both groups. Both ACC-Lx and Sham-Lx rats were less able to correctly identify targets in the presence of this distractor ($F_{1,13} = 8.82$, $p = 0.011$). Detection of both the 500 and 100 ms signal were impaired in this session relative to baseline ($t_{14} = 3.14$ and 3.04 , respectively, both $p < 0.009$). ACC-Lx rats showed no difference relative to Sham-Lx rats in any aspect of signal detection (all $p > 0.07$). Similarly, all rats showed an increase in false alarms when the houselight was flashed at durations that

overlapped with the target durations, $F_{1,13} = 14.63$; $p = 0.002$ and this effect was greater in the first block of trials than subsequent block ($F_{2,26} = 6.43$; $p = 0.005$). There was no other difference in the performance of ACC-Lx rats and Sham-Lx rats (all $p > 0.25$).

Tone distractor accuracy—The predictable tone produced an improvement in the ability of ACC-Lx but not Sham-Lx rats to detect signals ($F_{1,13} = 7.61$; $p = 0.02$; Baseline vs. 0.5 Hz Tone Sham-Lx: $t_7 = 1.36$; $p = 0.22$; ACC-Lx: -2.41 ; $p = 0.05$). There was no other effect of this tone on signal detection nor were there any other differential responses of ACC-Lx rats to the presentation of this tone (all $p > 0.12$). The predictable tone did not alter the ability of either Sham-Lx or ACC-Lx rats to correctly reject non-signals and there were no effects of the lesion on correct rejections in these sessions (all $p > 0.27$). The presence of a tone presented at durations identical to visual targets did not alter the ability of either ACC- or Sham-Lx rats to correct reject non-signals or detect signals (all $p > 0.22$).

Discussion

The present results suggest that the ACC is critical to disregarding irrelevant information when stimulus attributes have previously predicted reinforcement. The complex stimuli used in the ASST vary on two stimulus dimensions from the CD stage through REV 3. Though all rats require more trials to achieve criterion performance on the CD than the SD, ACC-Lx rats are more susceptible to the detrimental effect of introducing irrelevant information than Sham-Lx rats. During the exemplar training, all rats learn that all stimulus attributes i.e. odor, texture and digging media may be predictive of reinforcement. At the SD stage of testing, only one stimulus dimension e.g. odor is present. Similarly, the simple serial reversals tested the effects of learning and reversing reinforcement contingencies with stimuli differing on only one dimension. ACC were as proficient on exemplar training, the SD and serial reversals as Sham-Lx rats. Together these data support the hypothesis that neither the demands of conditional discrimination nor simple reversal are sufficient to impede the performance of ACC-Lx rats but the addition of distracting attributes produces impairments subsequent to ACC damage.

Patients with schizophrenia are susceptible to novel, rarely presented stimuli (Laurens et al. 2005; Liddle et al. 2006). These patients were less able than controls to perform the CD suggesting that ACC dysfunction may be responsible for impairments in disregarding salient, novel stimuli (Jazbec et al. 2007; Pantelis et al. 1999). The CD is the first time irrelevant stimulus dimensions are introduced in conjunction with the target dimension. Moreover, these dimensions were associated with reinforcement in the exemplars. Therefore, adding these dimensions in the CD is not simply adding novel distractors but adding previously reinforced distractors. Though novel stimuli are presented at several other points in the testing procedure (IDSs and EDSs), the ACC-Lx animals are able to perform as well as Sham-Lx rats at all other stages of testing. This supports the hypothesis that the ACC is involved in the ability to disregard stimulus attributes that have previously predicted reinforcement.

ACC-Lx rats also had difficulty performing the first reversal after the CD. The larger impairment at this stage than the CD may represent the increase in cognitive demands as rats must inhibit responding to not only the previously reinforced stimuli within the same modality but also inhibit responding to irrelevant stimulus dimensions that could also be predictive of reward. Though ACC-Lx rats' ability to perform reversals improved within the testing session, the first reversal of the second testing day shows qualitatively similar results to day 1. This does not appear to be secondary to a mnemonic impairment as the repetition of reversal 3 used to test learned irrelevance on the same day did not impair performance in either group. The impairments on the CD and reversals are hypothesized to result from an

inability of ACC-Lx rats to maintain attentional focus on the exemplar that now predicts reinforcement as a result of being distracted by another stimulus dimension that previously predicted reinforcement. Moreover the data suggest that it is the varying, irrelevant dimension that impedes performance as there was no difference in the performance of Sham-LX and ACC-Lx rat in the test of learned irrelevance where changes in the constant, irrelevant dimension were introduced.

Error analyses on the first reversal showed that ACC-Lx rats committed more regressive than perseverative errors. This suggests that they were slow to learn the alternate exemplar within the same modality now predicted reinforcement but did not persist in responding to the previously reinforced attribute. Though the specific exemplars from the irrelevant modality had never been explicitly paired with reward, the subject had been exposed to stimuli within that modality that predicted reward during exemplar training. ACC inactivation produced problems in an odor reversal when subjects were given the opportunity to respond to a variety of odors including those that had never been explicitly paired with reinforcement (Ragozzino & Rozman, 2007). Rats made errors by choosing a variety of stimuli within the same modality as that previously predictive of reward even though these specific stimuli were not predictive of reward. In the present study, regressive errors may be due to the subject responding to the irrelevant stimulus attributes in a modality that previously predicted reinforcement.

The effects of the ACC lesions differ from those produced by excitotoxic lesions of the prelimbic cortex in rats which significantly increased trials to criterion on the EDS, i.e. impaired attentional set shifting (Birrell & Brown, 2000) or excitotoxic lesions of the orbitofrontal cortex which significantly increased trials to criterion on all reversals (McAlonan & Brown, 2003; Tait & Brown, 2007). There is some similarity to the deficits produced by excitotoxic lesions of the ACC and neuromodulator specific lesions to the orbitofrontal cortex. Following serotonergic (Clarke, Walker, Dalley, Robbins, & Roberts, 2007) and noradrenergic (Newman and McGaughy, unpublished data) lesions of the orbitofrontal cortex, rats require more trials to reach criterion on the first reversal of the day but not subsequent reversals in that testing session. This similarity may result from the interconnections of the ACC and the orbitofrontal cortex. Specifically the ACC may be involved in signaling that a change in reinforcement has occurred in order to engage the orbitofrontal cortex in preparing to perform the affective shift. It is possible that the loss of ACC leads to an inefficient processing of this error information in order for the animal to determine which stimuli is now reinforced. After reaching criterion performance on the first reversal, ACC-Lx rats are able to perform as well as Sham-Lx rats on the second reversal within a testing session. This suggests that if the animal has learned how to respond to a shift in reinforcement contingencies, the ACC is not as necessary to perform this action. In contrast to ACC lesions, serotonergic lesions of the orbitofrontal cortex cause perseverative errors suggesting that these subjects fail to learn new stimuli-reinforcement associations (Clarke, et al., 2007).

Though data from the ASST support the hypothesis that the presence of irrelevant attributes in a complex stimulus causes impairment in performance, the ACC-Lx rats formed an attentional set as well as Sham-Lx rats as demonstrated by the lack of an impairment on the IDS. This finding is in contrast with those from Ng, et al. (2007) who found impairments on the IDS after ACC lesions. This difference may result from the exclusion of the reversal after the CD by Ng and colleagues. This may have led to a weaker attentional set as fewer discriminations were performed prior to the presentation of the IDS. The fragility of the attentional set may have produced impairments in ACC-Lx rats in this study. In the present study, the inclusion of the first reversal may have strengthened the attentional set. All animals required significantly more trials to reach criterion on the EDS than the IDS and

significantly fewer trials to reach criterion on the IDS than the CD. As the complexity of the stimuli and difficulty of the discrimination at each of these stages is the same, these data support the hypothesis that the formation of an attentional set facilitates performance on the ID and the demand to shift attentional set impedes performance on the ED.

Experiment 2 explicitly tested the hypothesis that ACC-Lx rats would be distracted by salient stimuli present in the same and a different modality as targets. Cross-modal distractors failed to impact the ability of ACC-Lx rats to maintain sustained attention. In contrast, the predictable tone improved signal detection in ACC, but not Sham-Lx, rats. In contrast to irrelevant dimensions in the ASST, tones were never paired with reinforcement. While all rats showed impaired performance in the presence of a visual distractor i.e. within the same modality as target stimuli, there was no unique susceptibility of ACC-Lx rats to these distractors. We hypothesize that this lack of impairment in the SAT with distractors after ACC lesions was because the task irrelevant stimuli were never paired with reinforcement prior to testing. Results from this experiment also demonstrate that the ACC is critical to maintaining attentional control during prolonged testing sessions as ACC-Lx, but not Sham-Lx, rats showed a significant decline in signal detection by the second block of testing. Collectively these data support the hypothesis that ACC is necessary to disregard irrelevant stimuli that may be predictive of reinforcement. Damage to the ACC produces a unique form of distractibility distinct from the effects of damage to prelimbic cortex which produces an inability to disregard salient, task-irrelevant stimuli not previously paired with reinforcement (Newman, Darling, et al., 2008; Newman & McGaughy, 2008).

Acknowledgments

Supported by NIMH MH087921 and MH074811.

This work was supported in part by a University of New Hampshire Dissertation Year Fellowship.

The authors wish to thank Emily Carter, Rebecca Misra, Colin White, Sandra Woodman, and Matt Gerding for their excellent technical assistance.

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Task	Testing Pair 1	Testing Pair 2	Not Relevant Attribute
SD	Cinnamon vs. Patchouli	Cinnamon vs. Patchouli	
CD	Cinnamon /Light Shapes vs. Patchouli/Dark Shapes	Cinnamon / Dark Shapes vs. Patchouli/Light Shapes	Fake Fur
Rev 1	Patchouli /Light Shapes vs. Cinnamon/Dark Shapes	Patchouli / Dark Shapes vs. Cinnamon/Light Shapes	Fake Fur
ID 1	Lilac /Gold Buttons vs. Rose/Black Buttons	Lilac /Black Buttons vs. Rose/Gold Buttons	Ribbed side Corduroy
Rev 2	Rose /Gold Buttons vs. Lilac/Black Buttons	Rose /Black Buttons vs. Rose/Gold Buttons	Ribbed side Corduroy
ED 1	Metal Beads /Gardenia vs. Plastic beads/Jasmine	Metal Beads /Jasmine vs. Plastic Beads/Gardenia	Terrycloth
Rev 3	Plastic Beads /Gardenia vs. Metal beads/Jasmine	Plastic Beads /Jasmine vs. Metal Beads/Gardenia	Terrycloth
New Session Rep Rev 3	Plastic Beads /Rough terrycloth vs. Metal beads/smooth terrycloth	Plastic Beads /Smooth terrycloth vs. Metal Beads/Rough terrycloth	Gardenia
ID 2	Light pompoms /Sequin fabric vs. Dark pompoms/Smooth fabric	Light pompoms /Smooth fabric vs. Dark pompoms/Sequin fabric	Pomegranate
Rev 4	Dark pompoms /Sequin fabric vs. Light pompoms/Smooth fabric	Dark pompoms /Smooth fabric vs. Light pompoms/Sequin fabric	Pomegranate
ED 2	Velvet fabric /Light yarn vs. Smooth fabric/Dark yarn	Velvet fabric /Dark yarn vs. Smooth fabric/Light yarn	Linen
Rev 5	Smooth fabric /Light yarn vs. Velvet fabric/Dark yarn	Smooth fabric /Dark yarn vs. Velvet fabric/Light yarn	Linen

Figure 1.

One example of the pairs of testing stimuli presented. While the schedule shown depicts a subject shifting from odor to digging media to texture, the order of shifting was counterbalanced across subjects. Additionally schedules were matched so one ACC-Lx and one Sham-Lx rat were tested on the same testing sequence. Rewarded stimuli are in bold.

Figure 2.

A series of coronal sections (adapted from Paxinos and Watson, 2005) at 3.7, 2.7, and 1.7 mm anterior to bregma. The maximum extent of any damage is shown in grey and the minimum extent is shown in black.

Simple/Compound Discrimination

Figure 3. ACC-Lx animals took significantly more trials to reach criterion on the CD than Sham-Lx animals. All animals took significantly more trials to reach criterion performance on compound discriminations (CD) than simple discriminations.

Figure 4.

ACC-Lx animals took significantly more trials to reach criterion on the first reversals in each session (REV 1 & REV 4) than Sham-Lx animals. Even though ACC-Lx animals were impaired compared to Sham-Lx animals on REV 4, they did take significantly less trials to reach criterion on the first reversal of the second session (REV 4) as compared to the first reversal of the first session (REV 1). Performance did not differ as a result of lesions on the second reversals of the testing day (REV 2 and REV 5). This suggests all animals were able to learn how to perform reversals efficiently within a session.

A

B

Figure 5.

A. ACC-Lx animals committed significantly more overall errors on REV 1 and REV 4 than Sham-Lx animals. B. ACC-Lx animals committed significantly more regressive errors at REV 1 and REV 4 than Sham-Lx animals suggesting they were unable to maintain new stimulus-reinforcement associations.

Figure 6.

All animals more trials to reach criterion on extradimensional shifts than intradimensional shifts in both sessions. There was no difference in the formation of shifting of attentional set as a result of damage to ACC.

Baseline Signal Detection Over Time on Task

Figure 7.

ACC-Lx animals were significantly impaired on the second and third blocks of trials when detecting signals as compared to the first block. This suggests a vigilance decrement due to ACC lesions.