Behavioral/Systems/Cognitive

Double Dissociation of Attentional Resources: Prefrontal Versus Cingulate Cortices

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Efficient attention to our environment facilitates the decisions that need to be executed in daily life. Filtering critical from noncritical information may require the neural organization of multiple brain regions. Combining lesion techniques and the rodent version of the Wisconsin card sorting task in humans, we show at least two types of attentional processing systems reside in the cingulate and prefrontal cortices depending on task demands requiring shifts of attention within or between sets of meaningful cues, respectively. This neural organization for shifting attention either within or between perceptual dimensions is task dependent, and this type of organization provides evidence of attentional systems that transcend separate modality processing systems while subdividing executive control of attention. The results suggest that the anterior and posterior cingulate cortices are critical when shifting attention to closely related meaningful cues (i.e., within a perceptual dimension or attentional set) by suppressing interference of irrelevant background information, whereas the prefrontal cortex is critical when shifting attention between disparate sets of meaningful cues (i.e., between perceptual dimensions or attentional sets) (Dias et al., 1996a,b; Birrell and Brown, 2000). Based on the theories of Mackintosh (1965, 1975; Sutherland and Mackintosh 1971), it is suggested that the cingulate cortex may be important for decreasing attention to irrelevant information. In general, attention deficit disorders affect both children and adults, and current medications may affect the prefrontal and associated parietal cortical systems more or less than the cingulate cortical system.

Key words: **anterior cingulate cortex; posterior cingulate cortex; attention set-shifting; olfactory; visual; discrimination**

Introduction

Attentional processing filters the rich incoming sensory information we have about the world by focusing energy on important life events through learning, memory, and decision making (i.e., executive control of behavior). Many theories suggest how attention might be organized [i.e., by sensory modality (Miller and Cohen, 2001) or by function (MacDonald et al., 2000; Corbetta and Shulman, 2002; Yantis et al., 2002)]. Multiple studies have demonstrated that the prefrontal cortices mediate attentional control over disparate sets of meaningful cues (i.e., attentional sets or perceptual dimensions), for example those in the Wisconsin card sorting task (WCST), and its modified versions of the set-shifting task for rats (Birrell and Brown, 2000), nonhuman primates (Dias et al., 1996a,b), and humans (Milner, 1963; Milner et al., 1968; Owen et al., 1991). The prefrontal, cingulate, and parietal cortices are involved in functional networks for attention, working memory, behavioral complexity, and executive control (Duncan and Owen, 2000; Kastner and Ungerleider, 2000; Miller and Cohen 2001; Corbetta and Shulman, 2002; Dalley et al., 2004).

Although much of the prefrontal, parietal, and cingulate cortices are demonstrably active during tasks requiring attention (MacDonald et al., 2000; Corbetta and Shulman, 2002; Yantis et al., 2002), their individual contributions to attentional processing are unclear (MacDonald et al., 2000; Wager et al., 2005; Haddon and Killcross, 2006). Controversy surrounds the attentional roles these areas play because of few human patients with circumscribed lesions. Although anterior cingulate cortex shows significant activation in humans and monkeys during many common attentional tasks, for example, the WCST, Stroop task, and conflict monitoring, etc. (Carter et al., 1998; Konishi et al., 1998; MacDonald et al., 2000; Kerns et al., 2004; Nakahara et al., 2004), specific deficits related to attention after damage to anterior cingulate cortex have not been found in human patients (Fellows and Farah, 2005).

Herein we use an attention set-shifting task (Birrell and Brown, 2000; Fox et al., 2003) modified from the human version of WCST to ascertain the role of anterior and posterior cingulate cortex. Animals learn six discrimination tasks using odors and digging media as stimuli forming two perceptual dimensions. Two primary discriminations include an intradimensional shift (IDS), wherein rats maintain an attentional set related to a particular perceptual dimension and then transfer their responses to a new stimulus pair within the same dimension, while ignoring a stimulus pair from an irrelevant dimension, and an extradimen-

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sional shift (EDS) relying on a shift of attention to a previously irrelevant perceptual dimension. In rats and monkeys, prefrontal cortex (Dias et al., 1996a,b; Birrell and Brown, 2000) and parietal cortex (Fox et al., 2003) are clearly involved when performing discriminations requiring an extradimensional shift of attention, and anatomical studies reveal reciprocal connections among medial prefrontal cortex, parietal cortex, and anterior and posterior cingulate cortices. This study tests the hypothesis that the functional attention network for shifting attention across perceptual dimensions extends beyond prefrontal and parietal cortices to include the anterior and posterior cingulate cortices.

Materials and Methods

Subjects. Fifty Long–Evans male rats (Harlan, Indianapolis, IN) weighing 230–300 g at the beginning of the study were individually housed in a 12 h light/dark cycle. Rats were randomly assigned to one of four groups, lesions of the anterior cingulate cortex (ACCx), lesions of the posterior cingulate cortex (PCCx), lesions of the medial prefrontal cortex (mPFCx), or cortical shams (sham). After lesion assessment, the final number of rats in each group was as follows: ACCx, $n = 9$; PCCx, $n = 10$; mPFCx, $n = 7$; and sham, $n = 9$. Fifteen rats were not included in the final analyses because of death or lesion misplacement.

Surgical procedures. Before surgery, each rat was anesthetized with Nembutal (sodium pentobarbital, 50 mg/kg, i.p.; Ovation Pharmaceuticals, Deerfield, IL). Treatment of the animals and surgical procedures were in accordance with the National Institutes of Health Guidelines and were approved by the University of Iowa Animal Care and Use Committee. Ibotenic acid (Sigma, St. Louis, MO; 5 mg/ml in PBS) was administered to several locations bilaterally in each of the designated lesion areas with surgical coordinates and nomenclature derived from Paxinos and Watson (1998). Rats recovered for 2 weeks before any behavioral training or food control occurred.

ACC lesions. Ibotenic acid was administered into both left and right hemispheres of the anterior cingulate cortex, specifically cingulate cortical area 1 (Cg1) and cingulate cortical area 2 (Cg2) (Lopez da Silva et al., 1990; Fisk and Wyss, 1999) with a 28-gauge beveled Hamilton syringe. A total volume of 0.3 μl was delivered at each injection site (six injections per hemisphere) at a rate of 0.1 μl/min. The brain coordinates for the ACC lesions were as follows: anteroposterior (AP) −1.2 mm from bregma, mediolateral (ML) ±0.4 mm, and dorsoventral (DV) −2.6 mm and −3.8 mm; AP −0.2 mm from bregma, ML ±0.4 mm, DV −2.6 mm and −3.4 mm; and AP +0.8 mm from bregma, ML ±0.4 mm, and DV −2.6 mm and −3.8 mm.

PCC lesions. Ibotenic acid was administered into both left and right hemispheres of retrosplenial agranular cortex (RSA) and retrosplenial granular b cortex (RSGb) (Lopez da Silva et al., 1990; Fisk and Wyss, 1999) with a 28-gauge beveled Hamilton syringe, with same rate and volume per injection site as for the ACC lesions. The bilateral PCC lesions were created by eight injections to each hemisphere. The brain coordinates for the PCC lesions were as follows: AP +2.30 mm from bregma, ML ±0.3 mm, DV −2.0 mm and −2.8 mm; AP +3.0 mm from bregma, ML ±0.4 mm, DV −2.0 mm and −2.7 mm; AP +3.8 mm from bregma, ML ±0.6 mm, DV −1.9 mm and −2.6 mm; and AP +4.5 mm from bregma, ML ±0.7 mm, DV −1.9 mm and −2.5 mm.

mPFC lesions. Ibotenic acid was administered into both left and right hemispheres of prelimbic cortex (PrL) and infralimbic cortex (IL) (Dalley et al., 2004) with a 28-gauge beveled Hamilton syringe. The bilateral mPFC lesions were created by six injections to each hemisphere, same rate and volume per injection site as the ACC lesions. The brain coordinates for the mPFC lesions were as follows: AP −4.2 mm from bregma, ML ±0.8 mm, DV −3.2 mm; AP −3.2 mm from bregma, ML ±0.6 mm, DV −5.0 mm, −4.2 mm and −3.4 mm; and AP −2.2 mm from bregma, ML ±0.6 mm, DV −4.4 mm and −3.6 mm.

Cortical sham lesions. After the same anesthetic and surgical procedures mentioned above, holes were drilled through the cranium either above the coordinates for the ACC lesions (six holes per hemisphere) or the PCC lesions (eight holes per hemisphere). The sham rats did not receive chemical injections and the injection needle was not lowered into the brain. The anterior and posterior cortical sham groups showed no behavioral differences and were combined to form one cortical sham group.

Postsurgery treatment. After 2 weeks of recovery from surgery, each rat was handled for three to 5 min per day, for 5 d. All subjects were then tested in an inhibitory avoidance task (0.3–0.75 mA, 1 s shock interval), and results to be reported at a later date. One day later, rats were tested on an open-field activity test. One week of food control followed before commencement of the habituation and acquisition phase of the attention set-shifting task. An 85% of *ad libitum* body weight served as the guideline for food control and rats had unlimited access to water at all times.

Open-field activity test. This test assessed general locomotor activity after surgery. The open field was a translucent purple polyethylene storage container (74 cm long, 42 cm wide, and 31 cm high) placed on the floor in the center of the testing room with various landmarks. The container was divided by orange lines, into eight equal segments ($18.5 \times 21\ cm^2$ each). The room was equipped with two light sources: (1) a floor lamp with three red light bulbs (25 W each) provided the only light source during the dark phase of the testing, and (2) a ceiling fluorescent lamp (90 W) and the red floor lamp together provided the light source during the light phase of the testing. The test was conducted at two different levels of environmental brightness (dark and light phases). Rats began with a dark phase for 4 min while the experimenter started scoring line crossovers, defined as the front and rear paws crossing one of the orange lines. The experimenter turned on the fluorescent light at the fourth minute and converted the task into the light phase for an additional 4 min.

Apparatus for the set-shifting task. The testing apparatus was a Plexiglas box ($50 \times 37.5 \times 25$ cm) with a black barrier dividing the box into one third for the start section and two-thirds for the testing area. The sliding door was raised allowing the rat to enter the test area, which contained two flowerpots, ~10 cm apart, for digging (Fig. 1). The rat was placed back into the start area for ~10–20 s before the next trial began. All stimuli used as digging medium were mixed and recycled by stimulus type so that odors from perfume oils, water solutions, and the tested rats were evenly distributed to prevent the rats from being able to effectively use any olfactory or other cues left by other previously tested rats.

Habituation and acquisition. Rats were trained to dig in terracotta flowerpots (10 cm deep, 10 cm internal diameter) filled with Sani-Chips bedding (Harlan), to retrieve one-half of a Honey Nut Cheerio (General Mills, Minneapolis, MN) food reward. The flowerpot rim was scented with perfumed oils or water solutions to produce a long-lasting odor. The odor was refreshed at the beginning of each training session. During habituation, parallel to the procedures used by Rodefer et al. (2005), each pot contained several Cheerios that the experimenter kept rebaiting until each rat showed reliable digging to retrieve food rewards (Fig. 1). Daily habituation sessions for each rat lasted from 30 to 45 min, across 3 to 5 d.

After habituation, the rats learned to perform simple discrimination (SD) on odors and digging media separately. The odor discrimination consisted of Exotic and Sensual (perfume oils; Body Shop, Wake Forest, NC) scented pots with normal Sani-Chips bedding. The digging medium discrimination consisted of pine shaving and vermiculite in nonscented pots. The order of the two SDs and the positive stimuli were balanced across subjects. In all discriminations, a valid dig was defined as a vigorous displacement of the digging medium by the paws. The reward was buried approximately one and a half inches (3.5 cm) deep to prevent visual or odor exposure of the Cheerios to the surface by any random routing of the animals' nose or paws. Digging media could be sampled by tactile or visual characteristics (or both) for choice discriminations. In all discriminations, the first four trials were the discovery trials in which the animal was permitted to dig in the correct pot after choosing an unbaited pot (i.e., correction trials). The incorrect choice was scored as an error. Starting with the fifth trial, the rat was no longer permitted to dig in the correct pot after making the wrong choice, and was immediately put back to the start area. The training criterion required animals to make six consecutive correct choices within the first 10 trials, on 2 consecutive days, before switching to the next discrimination.

Attention set-shifting test day. After reaching the simple discrimination learning criterion as specified above, each animal was tested on a full set

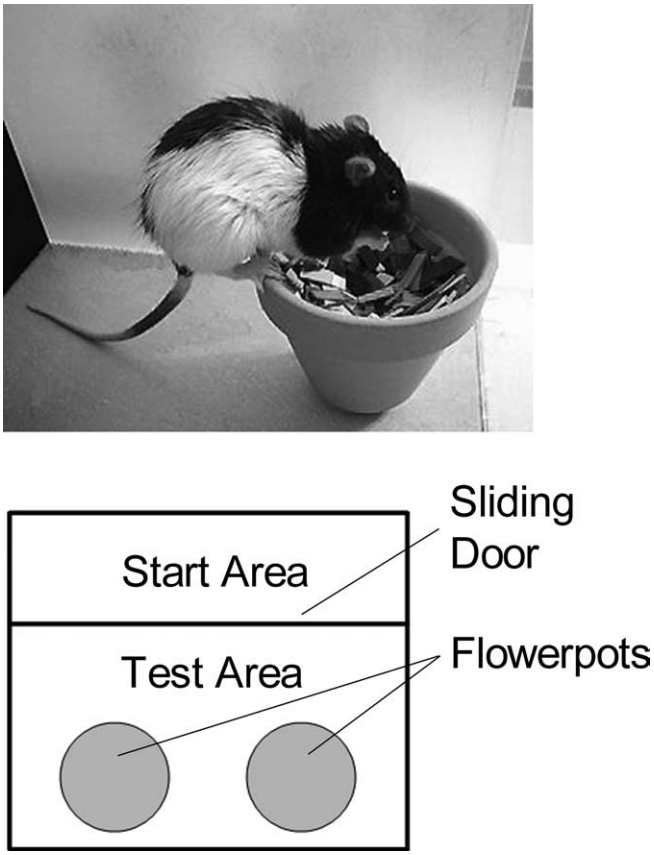

Figure 1. Physical testing apparatus. The photograph depicts a rat consuming a food reward during a training trial, on top of a clay flowerpot containing digging medium. The bottom diagram depicts a schematic top view of the set-shifting test apparatus. The testing area consists of a Plexiglas box containing two flowerpots with a combination of odors and digging medium for each discrimination problem.

of six discrimination problems within a single day (Fig. 2) (for one possible example). Novel odor and digging media stimuli were used on the set-shifting testing day and never repeated within subject. Digging medium consisted of shredded manila folders, aspen shavings, aquarium gravel, glass beads, foam rubber pieces, or plastic beads. Odors from perfume oils or water solutions were jasmine, vanilla, mulberry, patchouli, cinnamon, or gardenia. The set-shifting test day started with SD, and then preceded to the compound discrimination (CD), during which the positive stimulus was the same as during SD, although an irrelevant dimension, such as digging medium, was introduced. A discrimination requiring an IDS of attention was then presented. Two new stimuli of each perceptual dimension (odor and medium) were introduced to the animal; however, the learned solution of which relevant perceptual dimension would be rewarded remained unchanged. The IDS cues were then reversed (R1); the negative stimulus from the previous IDS now became the reliable predictor of the reward whereas another dimension still served as irrelevant information during the discrimination. Finally, the rat was exposed to an EDS discrimination, where the previous irrelevant dimension became the reliable one and the learned dimension was no longer the solution to the problem. The EDS cues were reversed (R2). Half of the rats in each group were assigned to start with shifting from odor to medium or vice versa during the full day of attention set-shifting problems. Figure 2 illustrates one possible combination of stimulus pairs for a rat shifting from odor to digging medium as the relevant dimension. The stimulus pairs of odor and digging media were maintained across all animals whereas the valence of each stimulus within a pair was counterbalanced across rats and groups. Therefore, in each of the six discrimination tasks, the positive stimulus of the relevant dimension was never paired with the same stimulus of an irrelevant dimension on more than two trials in a row.

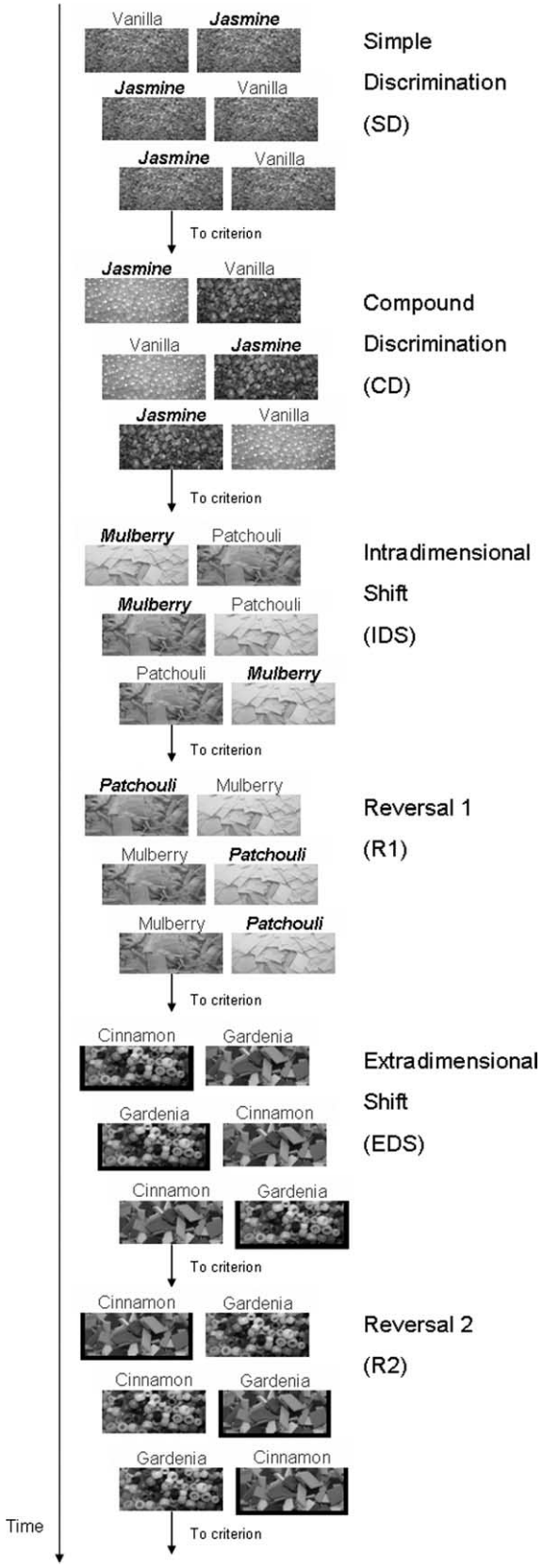

Figure 2. Possible set of stimulus pairings for attention set-shifting task, depicted is an example of one possible set of stimulus pairings (3 odor pairs, 3 digging medium pairs) for the six discrimination tasks on the full discrimination test day. This particular example uses odor cues first and then digging medium. The criterion is six correct choices in a row. The names of the odor cues are at the top of each picture of digging medium. Bolded text or pictures with black lines at the sides and bottom indicate cues paired with food reward.

Histology. After all testing, rats were decapitated and brains extracted and frozen in hexane (Fisher Scientific, Fair Lawn, NJ) at −38°C for 15 min. All brains were sealed in a plastic bag and stored in a freezer at −80°C until sectioned coronally on a Leica (Bannockburn, IL) CM3050S cryostat at 40 μm. Every fifth section through the target or sham lesion area was mounted on glass slides, stained with thionin for visualization of Nissl substance, and then examined with a microscope to determine the location and size of the ibotenic acid lesions. Damaged brain areas were first outlined on the rodent atlas for each lesion type, based on that by Paxinos and Watson (1998). A grid transparency was placed on top of the lesion outlines from the atlas to count the numbers of squares occupied by the lesion. The percentage of lesion damage per brain area was calculated for each subject (total number of squares occupied by lesion were divided by the total numbers of squares per intact intended lesion area times 100).

Data analysis. For the open-field activity test, the number of crossovers provided an index of activity level for each rat. Activity levels were analyzed by repeated-measures ANOVAs with an α level of 0.05 for each experiment (SPSS 13.0; SPSS, Chicago, IL). Group was the between-subjects factor, with brightness (dark and light phases) and time period (four 1 min intervals) as within-subjects factors. *Post hoc* analysis by least significant difference (LSD) test was used if necessary.

In the set-shifting task, the number of trials to criterion for each discrimination problem was measured and analyzed by preplanned independent sample *t* tests for each experiment because the six discriminations (SD, CD, IDS, R1, EDS, and R2) varied with respect to level of difficulty. Planned comparisons were made to examine its contributions on the six discrimination tasks separately. The Bonferroni procedure was used with Keppel's modification, to correct for the "family-wise" error rate between group comparisons of *t* statistics (Keppel, 1982). For each lesion experiment, the six different discriminations were entered as the experimental treatment, the number of degrees of freedom for the treatment source of variance (6 − 1 = 5) was multiplied by the standard critical probability level (0.05), and the product was divided by the number of *t* test comparisons (i.e., 6), yielding the corrected, critical probability level of 0.042.

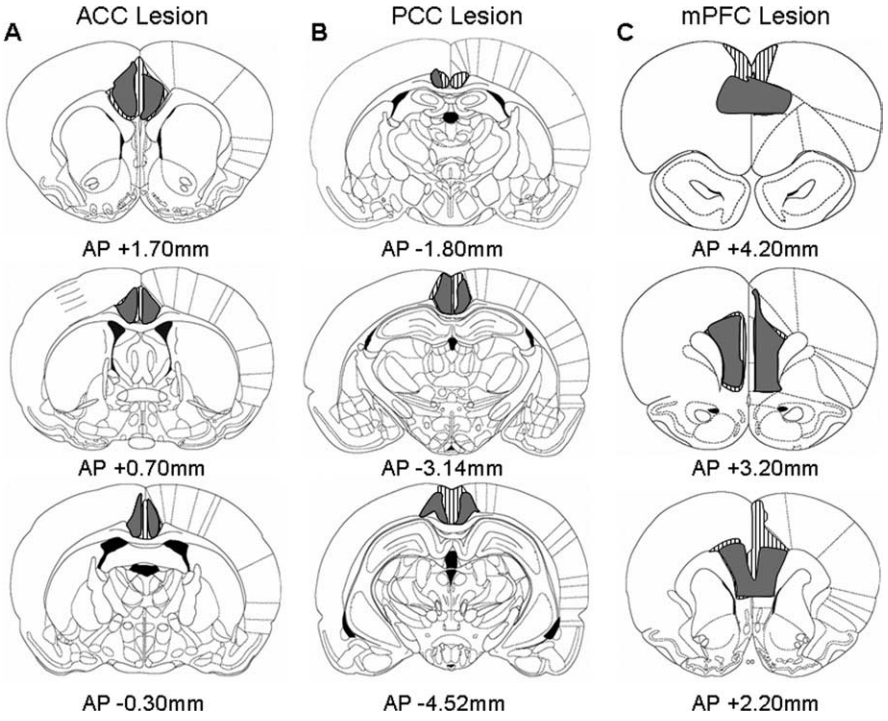

Figure 3. Lesion placements. Diagrams indicate the summaries of lesion assessments for the experimental groups that received ibotenic acid lesions. ***A***, Coronal sections with drawings of ibotenic acid lesions to the ACC shown at 1.7, 0.7, and −0.3 mm from bregma. ***B***, Coronal sections with drawings of ibotenic acid lesions to the PCC shown at −1.8, −3.14, and −4.52 mm from bregma. ***C***, Coronal sections with drawings of ibotenic acid lesions to the mPFC shown at 4.2, 3.2, and 2.2 mm from bregma. In all panels, shaded areas represent the extent of the damage in the rat with the largest lesion of the target region, and gray areas represent the extent of the damage in the rat with the smallest lesion of the target region. Coronal sections are adapted from Paxinos and Watson (1998).

Results

Lesion assessment

In Figure 3, shaded and black areas represent the area of lesion for each rat with the largest and smallest total lesion, respectively, for each of the three target regions. For the ACCx group, rats sustained bilateral damage to the anterior cingulate cortex (Fig. 3*A*) (adopted from Paxinos and Watson, 1998). The lesions were mainly located in Cg1 and Cg2, and the lesion damage ranged from 76 to 95% of the total target lesion ($n = 9$). In some cases, lesion damage extended laterally to a small portion of the secondary motor cortex (M2). For the PCCx group, rats sustained bilateral damage to the posterior cingulate cortex (Fig. 3*B*), with lesions mainly located in the RSA and RSGb (Vann and Aggleton, 2002; Vann et al., 2003). Lesion damage to the PCC ranged from 20 to 61% of the total target lesion. The actual lesion size was smaller than intended with most of the cortical damage located in the middle portions of the PCC anterior to posterior, primarily within AP +2.30 to +4.52 mm from bregma ($n = 10$). In most cases, the lesion extended laterally to small posterior portions (AP +1.8 to +3.0 mm from bregma) of M2 and M1, with extremely small portions (<2% of the total areas) of damage on the border with parietal association cortex and the mediomedial area of the secondary visual cortex. For the mPFCx group, rats sustained bilateral damage to the medial prefrontal cortex (Fig. 3*C*) ($n = 7$). The lesions were mainly located in PrL and IL, and the lesion damage ranged from 65 to 82% of the total target lesion. The mPFC lesions extended minimally into the frontal association area, M2, and/or the posterior portion of Cg1.

Experiment 1: effects of ACC ibotenic acid lesions

Open-field activity test

Figure 4*A* depicts the average crossovers of the ACCx and sham groups during each minute of the dark and light phases of the open-field activity. There was a main effect of brightness ($F_{(1,16)} = 154.0$; $p < 0.05$) and a main effect of time periods ($F_{(3,48)} = 27.1$; $p < 0.05$). Regardless of group, rats showed a decreased number of crossovers within the 4 min period of each dark phase and light phase. There was an interaction effect between lesion and brightness ($F_{(1,48)} = 10.0$; $p < 0.05$). *Post hoc* LSD comparisons indicated that the ACCx group exhibited a higher activity level than the sham group only during the dark phase of the testing. Their activity reached similar levels relative to the sham group during the light phase.

Set-shifting task

The ACCx group was selectively impaired on the IDS phase of the task (Fig. 5*A*). The ACCx group required significantly more trials to reach criterion on the IDS discrimination phase than the sham group ($t_{(16)} = 2.49$; $p < 0.042$, two-tailed), but not on any other

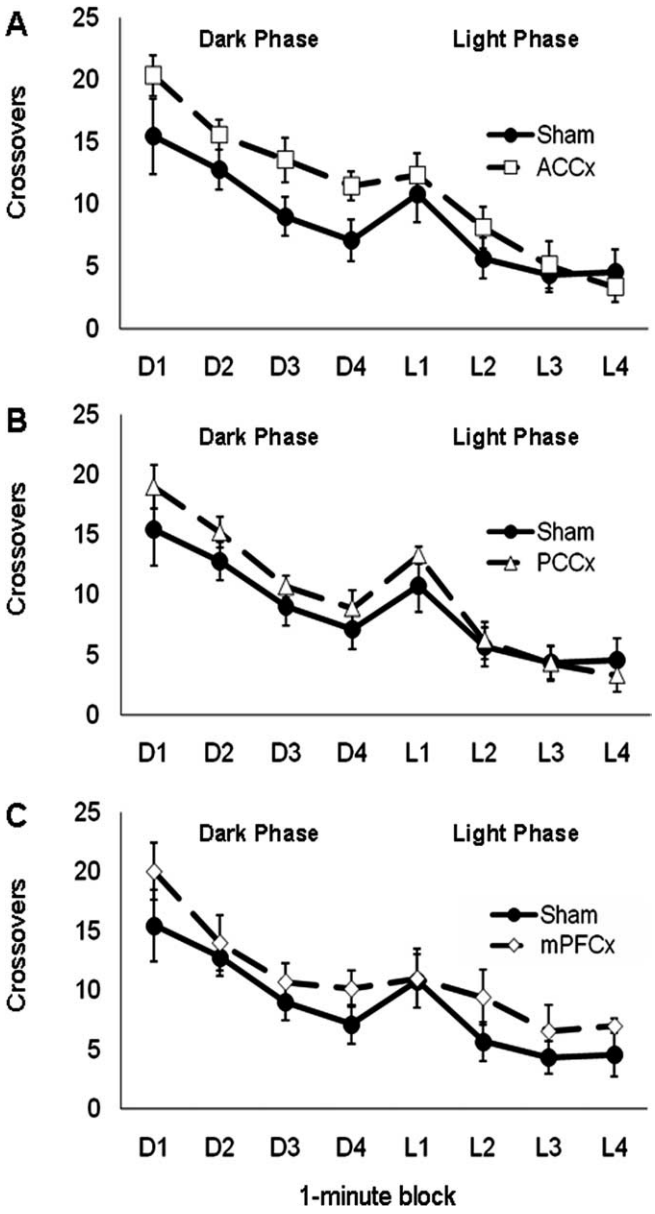

Figure 4. Performance during open-field activity test. During the activity test, rats were placed in a dark open field for the first 4 min (dark phase: D1–D4). A ceiling fluorescent lamp was then on for another 4 min (light phase: L1–L4). The solid line with filled circles always represents the numbers of crossovers displayed by the sham group. ***A***, Line graphs depict the results for the open-field activity test for the ACCx group ($n = 9$) versus the sham group ($n = 9$). The dotted line with open squares represented the numbers of crossovers displayed by the ACCx group. ***B***, Line graphs depict the results for the open-field activity test for the PCCx group ($n = 10$) versus the sham group ($n = 9$). The dotted line with open triangles represented the numbers of crossovers displayed by the PCCx group. ***C***, Line graphs depict the results for the open-field activity test for the mPFCx group ($n = 7$) versus the sham group ($n = 9$). The dotted line with open diamonds represented the numbers of crossovers displayed by the mPFCx group.

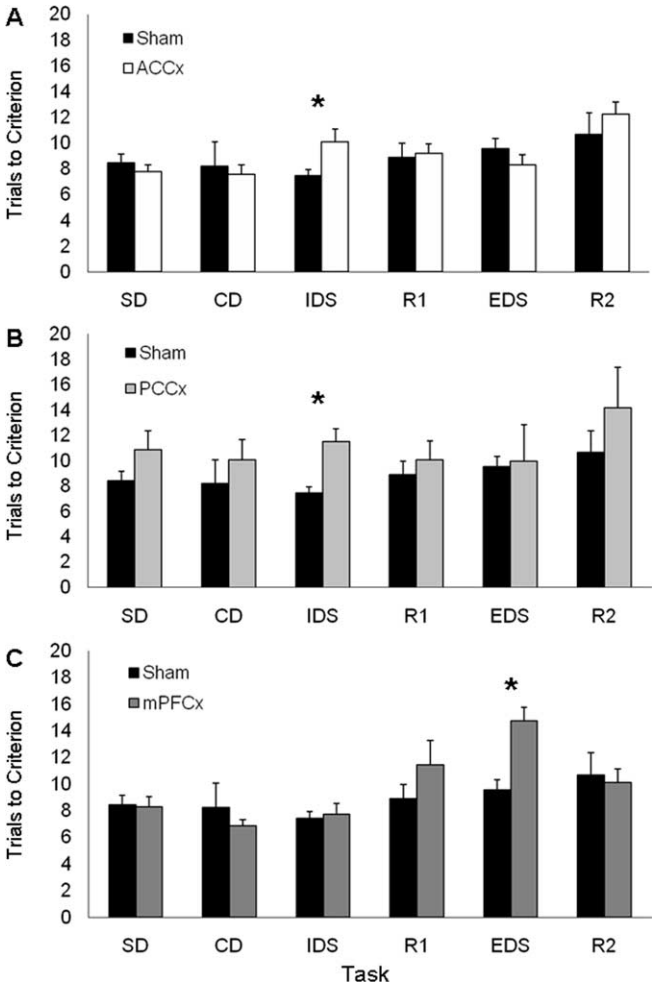

Figure 5. Performance during attentional set-shifting task. Bar graphs represent performance as the numbers of trials to criterion (means and SEs) during the six discrimination problems within a single test day. Solid black bars always represent performance of the sham group ($n = 9$) for each discrimination. Asterisks indicate a significant difference between lesion and sham groups, revealed by corrected independent sample *t* test analyses ($p < 0.042$). ***A***, Open bars represent performance of the ACCx group ($n = 9$). Rats with lesions to the ACC were selectively impaired on the discrimination requiring an IDS of attention. ***B***, Light gray bars represent performance of the PCCx group ($n = 10$). Rats with lesions to the PCC, like the rats with lesions to the ACC, were selectively impaired on the discrimination during IDS of attention. ***C***, Dark gray bars represented performances of the mPFCx group ($n = 7$). In contrast to the lesions of the ACC or PCC, rats with lesions of the mPFC were selectively impaired on the discrimination requiring EDS of attention.

task phase, including EDS discrimination and reversals (R1 and R2). To clarify whether initial relevant perceptual dimension (i.e., odors switching to digging media or vice versa) would confound performance of the ACCx group, independent sample *t* tests were used to examine the six discriminations (SD, CD, IDS, R1, EDS, and R2) divided into two groups by which dimension was relevant first, odor or digging medium. The findings indicate that the ACCx rats that had digging media as the initial relevant perceptual dimension took significantly more trials to criterion on the reversal of IDS (R1) than those having odors as the initial relevant perceptual dimension ($t_{(7)} = -3.25$; $p < 0.042$, two-tailed). However, this result does not obscure the evidence that lesions of the ACC induced the selective impairment on intradimensional shift, as both groups, separated by initial digging medium, were still impaired on IDS ($t_{(8)} = 2.649$; $p < 0.042$, two-tailed). The effect of the initial relevant perceptual dimension on learning appeared only after the observed IDS problems. Within the sham group, the initial relevant perceptual dimension did not differentially affect performance for the six discriminations ($p > 0.042$).

Experiment 2: effects of PCC ibotenic acid lesions

Open-field activity test

Locomotor activity did not differ between the PCCx and sham groups ($F_{(1,17)} = .681$; $p = 0.421$). Figure 4*B* depicts the average

crossovers of the PCCx and sham groups during each minute of the dark and light phases of the open-field activity test. There was a main effect of brightness ($F_{(1,17)} = 79.5$; $p < 0.05$) and a main effect of time periods ($F_{(3,51)} = 40.7$; $p < 0.05$) indicating that, as expected, both the PCCx and sham groups showed decreased numbers of crossovers within the four-min period of each dark phase and light phase.

Set-shifting task

Similar to the results of experiment 1 involving lesions of the ACC, analysis of the number of trials to criterion revealed that lesions of the PCC selectively impaired performance on the IDS discrimination (Fig. 5*B*). The PCCx group required significantly more trials to reach criterion ($t_{(17)} = 3.43$; $p < 0.042$, two-tailed) on the IDS discrimination than the sham group. There were no significant differences in any other task phase relative to the sham group. The initial relevant perceptual dimension did not differentially affect performance of the six discriminations within the rats of the PCCx group ($p > 0.042$).

Experiment 3: effects of mPFC ibotenic acid lesions

Open-field activity test

Locomotor activity did not differ between the mPFCx and sham groups ($F_{(1,14)} = 1.216$; $p = 0.289$). Figure 4*C* depicts the average crossovers of the mPFC lesion and sham groups during each minute of the dark and light phases of the open field activity. There was a main effect of brightness ($F_{(1,14)} = 65.1$; $p < 0.05$), and a main effect of time periods ($F_{(3,42)} = 18.8$; $p < 0.05$) indicating that, as expected, both the mPFCx and sham groups showed decreased numbers of crossovers within the four-min period of each dark phase and light phase.

Set-shifting task

Preplanned independent sample *t* tests revealed that rats with lesions of the mPFC were preferentially impaired during the EDS discrimination only, but not during IDS discrimination and reversals (R1 and R2) (Fig. 5*C*). The mPFCx group required significantly more trials to reach criterion ($t_{(14)} = 4.09$; $p < 0.042$, two-tailed) on the EDS than the sham group and the initial relevant dimension of odor or digging medium did not account for this difference. Our findings parallel those of Birrell and Brown (2000) that lesions of the mPFC result in selective impairment during the EDS discrimination, when the discrimination task requires subjects to switch to a solution relying on a previously irrelevant perceptual dimension.

General results

Within-group analysis of the sham performance indicated that our control animals did acquire the IDS discrimination faster than the EDS discrimination. EDS was significantly more difficult than the IDS (preplanned contrast: paired sample *t* test, $t_{(8)} = -2.33$; $p < 0.05$, one-tailed). These findings validate that the implementation of the set-shifting paradigm in rats by our laboratory produced comparable results to other laboratories using this task (Birrell and Brown, 2000; Fox et al., 2003; McAlonan and Brown, 2003; Rodefer et al., 2005).

The overall findings suggest a double dissociation between the contribution of the cingulate cortex and the prefrontal cortex to set-shifting performance. Lesions to either the ACC or PCC only impaired the IDS discrimination, without affecting the initial acquisition (SD and CD), discrimination reversals (R1 and R2), or the more difficult EDS discrimination. However, lesions to the mPFC impaired only the EDS discrimination, parallel with the findings of Birrell and Brown (2000).

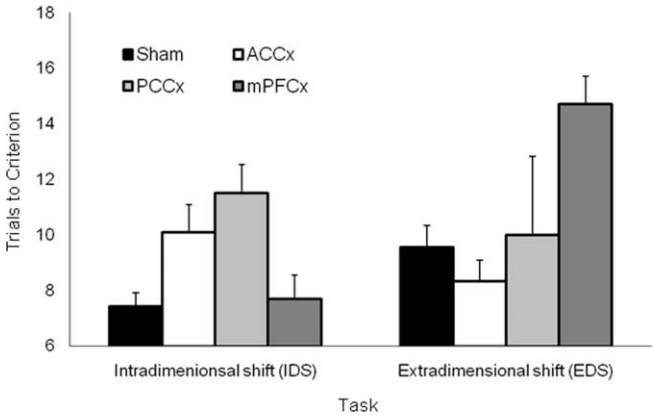

Figure 6. Summary of behavioral data. A clear double dissociation exists between IDS and EDS during attentional set-shifting for mPFC and ACC, wherein lesions of mPFC impair discrimination during EDS whereas lesions of ACC preferentially impair discrimination during IDS. This effect is not statistically significant for the PCC compared with the mPFC ($p = 0.09$), although individual behavioral results from experiments 2 and 3 alone are supportive of a double dissociation.

Additional statistical analyses (repeated-measures ANOVAs) were used to clarify interaction effects between lesion type (between-subject factor) and discrimination task (within-subject factor). The analysis focused on how two important aspects of the set-shifting task, IDS and EDS, interact with lesions of discrete cingulate cortical regions (ACC or PCC), and mPFC. There was an interaction effect ($F_{(2,22)} = 20.29$; $p < 0.05$) of group by task for the comparison of the sham, ACCx, and mPFCx groups. *Post hoc* LSD tests indicated that lesions to the ACC significantly impaired IDS performance relative to the sham group, whereas lesions to the mPFC significantly impaired EDS performance relative to the sham group ($p < 0.05$). There was also an interaction effect ($F_{(2,23)} = 3.50$; $p < 0.05$) found for the comparison of the sham, PCCx and mPFCx groups. *Post hoc* LSD tests showed lesions to the PCC significantly impaired IDS performance relative to the sham group ($p < 0.05$); however, lesions to the mPFC did not significantly impair EDS performance relative to the sham group at a *p* value of <0.05 ($p = 0.09$). Because of large SE values originating from the PCC group (Figs. 5*B*, 6), the combined analysis failed to statistically establish a double dissociation between the posterior cingulate cortex and the medial prefrontal cortex. The large SE values for the PCCx group may be attributable to the variable size and relative smallness of the lesions in this group compared with the other lesion groups.

In summary, the double dissociation of set-shifting performance on IDS and EDS tasks was statistically significant for ACC versus mPFC, paralleling the separate performance results from experiments 1 and 3 (Fig. 6). Although statistically the double dissociation holds for mPFC and ACC, it is not as robust for PCC, which may be because of a smaller amount of lesion damage in this area compared with the relatively large lesions of the ACC and mPFC.

Discussion

The results do not support our hypothesis that lesions of cingulate cortex would impair discriminations requiring a shift to a new perceptual dimension (i.e., EDS); instead, the present study reveals a double dissociation for neuronal processing related to attention during set-shifting. Lesions of anterior or posterior cingulate cortices impair discriminations requiring an IDS (i.e., switching the solution to a new discrimination problem within a

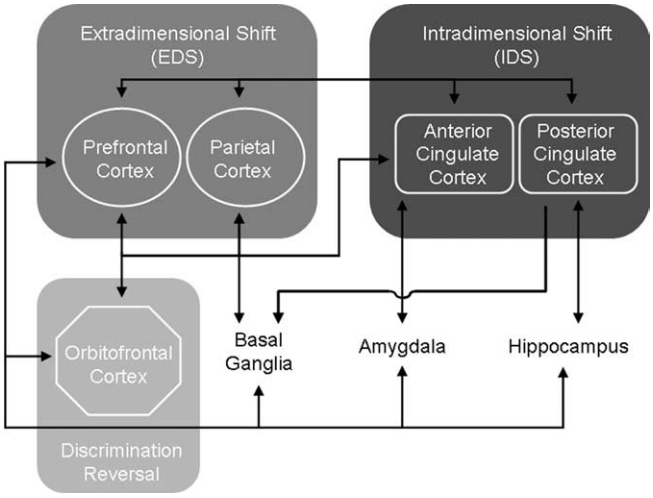

Figure 7. Cortical divisions for attention set-shifting. Depicted, based on nonhuman primate and rodent neuroanatomy, is the neural circuitry involved in various aspects of the attention set-shifting task as well as three highly connected subcortical structures which do not appear to be involved. The three neural circuits, as well as their contributions to the set-shifting task, are closely interconnected via corticocortical and subcortical connections [prefrontal and parietal cortices (Kolb and Walky, 1987; Vogt and Pandya 1987; Cavada and Goldman-Rakic, 1989; Ongur and Price 2000; Reep et al., 2004); cingulate cortices (Vogt and Miller, 1983; Barbas and De Olmos, 1990; Lopez da Silva et al., 1990; Kunishio and Haber, 1994; Reep et al., 2004); orbitofrontal cortices (Barbas and Pandya, 1989; Ongur and Price 2000; Reep et al., 2004)]. Prefrontal and parietal cortices mediate shifts of attention across different perceptual dimensions (i.e., EDS). The cingulate cortex is involved during intradimensional shifts within a well learned perceptual dimension (i.e., IDS) whereas the orbitofrontal cortex mediates reversal discriminations. Although the basal ganglia, amygdala, and hippocampus are involved in various aspects of learning and memory and they are closely connected to the cortical areas depicted, lesions of these areas do not impair attentional set-shifting (Owen et al., 1991; Crofts et al., 2001).

learned perceptual dimension), but these cingulate cortical lesions do not impair the perceived harder discrimination task requiring an extradimensional shift of attention. Rather EDS, involving shifts of attention between perceptual dimensions, but not IDS, is affected by lesions of the prefrontal cortex, as in experiment 3, replicating Birrell and Brown (2000). The results suggest at least two different subsystems are responsible for intradimensional and extradimensional shifts (Fig. 7). More than one cortical area (i.e., mPFC and cingulate cortex) may simultaneously mediate different types of complementary attentional mechanisms.

Animals with lesions of the cingulate cortex are not impaired in their ability to learn discriminations, form attentional sets, or acquire reversal learning. Generally, all baseline activity levels during the activity tests were the same with the exception of some transient hyperactivity for ACCx animals during the dark phase of testing. However, this small change in hyperactivity did not lead to a general deficit on the behavioral discrimination tasks, and is similar to previous rodent studies showing that lesions of the ACC can induce small changes in basic activity patterns (Bussey et al., 1996, 1997b; Weissenborn et al., 1997; Cardinal et al., 2002). The current results show that ACC lesions selectively impaired performance only during one particular discrimination task, IDS.

Animals with lesions of the anterior or posterior cingulate cortex are slower when learning a new discrimination within a previously learned dimension. Essentially, both IDS and EDS discrimination problems entail all new stimuli in both dimensions, odor and digging medium, the only difference being whether the newly rewarded stimuli are now from the same dimension or a different dimension. One possibility is that animals with lesions of cingulate cortex may have difficulties generalizing within dimension or increasing their learning set size, however all the lesion animals did eventually learn the new discrimination suggesting these are not the main deficits.

Another possible explanation is that the irrelevant dimension needs to be ignored during IDS, whereas in EDS the opposite occurs, attention needs to center on the previously irrelevant dimension. Mackintosh (1965, 1975; Sutherland and Mackintosh, 1971) proposed a two-stage model of discrimination learning. One stage involves the animal learning what stimuli are relevant to the solution (thereby attention is paid to those stimuli) and a second stage involves the animal making a specific response in the presence of those specific stimuli (i.e., associative nature of response). In particular, it is the processing underlying the first stage that may be applicable to the interpretation of the current results as the capacity of attention is limited (Luck and Vogel, 1997), and paying attention to a particular set of stimuli means there will be less attention paid to other stimuli (Mackintosh, 1965, 1975; Sutherland and Mackintosh, 1971).

Applying Mackintosh's (1965, 1975; Sutherland and Mackintosh, 1971) theories to the attention set-shifting task, the effects of SD, CD, and IDS training may strengthen relevant cues although weakening irrelevant cues. Paying attention to a particular dimension (e.g., odor) will result in less attentional resources devoted to the other dimension (e.g., digging medium) and vice versa. Rats with lesions of the cingulate cortex seem to have no trouble with the relevant cues (rewarded dimension) being strengthened, but the valences of the irrelevant cues (unrewarded dimension) may not be weakened, thus leading to more trials to criterion. In IDS the irrelevant dimension needs to be ignored, whereas in EDS the opposite occurs, attention needs to now be paid to the irrelevant dimension. This can also explain why EDS problems are generally learned slower, as subjects are still attending to a previously relevant dimension; and why animals with cingulate cortical lesions, with less weakening to the irrelevant dimension, do not have difficulties during EDS.

The order of the current set-shifting procedures purposefully predisposes rats to focus on a particular perceptual dimension (i.e., the relevant dimension) in solving discrimination problems at the beginning. Approaching from SD, CD, to IDS, the relevant dimension remains the same, while introducing different stimulus pairs. According to the two-stage model, the sham group should learn faster from SD to IDS with repetition, as attention to the relevant dimension becomes stronger and that to the irrelevant dimension gets weaker. Other researchers show that with repeated IDS problems, the number of trials to criterion significantly decreases in rats (Shepp and Turrisi, 1969; Turrisi et al., 1969) and mice (Garner et al., 2006). The current experiment used only one IDS problem to compare these findings to previous results. Although there is no significant difference in trials to criterion across SD to IDS for the sham group, they did present a decreasing number of trials to criterion at each problem and the variance decreased between SD to IDS as expected, suggesting that attention to the relevant dimension became stronger. There is a slight increase in variance at the intermediate stage of CD as new stimuli are added, but this effect is not repeated when all the stimuli are changed at IDS suggesting that the irrelevant stimulus dimension was weakened in accordance with Mackintosh's (1965, 1975; Sutherland and Mackintosh, 1971) theories. Also supporting the idea that attention to the irrelevant dimension is weakened is that the sham group solved the problems well until

challenged with the EDS problem when the animals readjust attention to the new dimension, solving the problem, but taking more trials to do so while overcoming the previously weakened state of this dimension.

Like EDS, discrimination reversals were not impaired, implying that an attentional set is still formed after lesions of the mPFC (Chudasama and Robbins, 2006) or the cingulate cortex. Reversal, where no new cues are added, perpetuates the animal's attention within the previously learned, relevant perceptual dimension (Sutherland and Mackintosh, 1971). As described above, attention to the relevant dimension appears to be intact in animals with cingulate cortical damage despite their initial impairment in learning to ignore irrelevant cues.

Similar to previous set-shifting studies in rodents, nonhuman primates, and humans (Dias et al., 1996a,b; Birrell and Brown, 2000, Fox et al., 2003; McLean et al., 2004; Pantelis et al., 2004; Chudasama and Robbins, 2006; Jazbec et al., 2007), impairments during EDS for subjects with lesions of prefrontal cortex or parietal cortices, or brain degenerative diseases (e.g., schizophrenia), are unable to switch attention to a previously irrelevant dimension. Attention to the original relevant dimension remains strong in these subjects, and they are more vulnerable to perseveration to the stimuli of the previously relevant dimension, which becomes irrelevant when solving the EDS problem.

The present findings are compatible with the current theories of attention (e.g., bias competition, template matching, conflict monitoring, top down/bottom up, and response selection) (Desimone and Duncan, 1995; Bush et al., 2000; Botvinick et al., 2001; Corbetta and Shulman, 2002; Kan and Thompson-Schill, 2004), while further delineating the neural systems for attention and cognition (Fig. 7), rather than creating a different theory. The intradimensional cingulate cortical circuit is separated from both the extradimensional prefrontal/parietal circuit, and from individual modality attentional processing circuits (e.g., cortical area V4 for attention to color processing and V5 for motion) (Kastner and Ungerleider, 2000). In a previous study of humans by Watson et al. (2006), event-related potential correlates displayed differential cognitive/neural processing demands for IDS and EDS in a modified WCST task. Overall, the results suggest that intradimensional and extradimensional shifts of attention are independent of one another as demonstrated by the specificity of lesion effects and lack of impairment on the other discrimination problems. The lack of impairment on discrimination, in general, points to the involvement of other, yet to be determined brain areas involved in learning the original discriminations.

Based on current and previous findings, there are at least three neural circuits contributing to separate aspects of the attentional set-shifting paradigm (Fig. 7). Human, monkey, and rodent models of extradimensional shifts of attention are remarkably similar in their conclusions that prefrontal and parietal cortices are involved (Owen et al., 1991; Birrell and Brown, 2000; Dias et al., 1996a,b; Fox et al., 2003), whereas the orbitofrontal cortex is critical for shifting attention during discrimination reversals (Dias et al., 1997; McAlonan and Brown, 2003; Chudasama and Robbins, 2006) and, in similar paradigms, requiring reversal of the values attached to stimuli (Baxter et al., 2000; Chudasama and Robbins, 2003; Hornak et al., 2004). Now we can add to these closely interrelated circuits the anterior and posterior cingulate cortices that are critical for intradimensional shifts of attention. The cingulate cortex is anatomically relevant to many types of processing including attention, learning, and memory (Gabriel, 1990; Bussey et al., 1997a,b; Cardinal et al., 2003; Vann et al., 2003), with inputs coming from sensory systems after being processed by basic sensory systems and accessing the cingulate cortex via amygdala, limbic thalamic, and hippocampal connections (Lopez da Silva et al., 1990). It may be that anterior cingulate cortex, and sometimes posterior cingulate cortex, shows significant activation in so many different imaging tasks (Paus, 2001; Grosbras et al., 2005; Sarter et al., 2006), because many tasks involve a strong, although perhaps noncritical, intradimensional component.

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