The Effect of Cingulate Cortex Lesions on Task Switching and Working Memory


Abstract

Anatomic interconnections between the prefrontal and anterior cingulate cortices suggest that these areas may have similar functions. Here we report the effect of anterior cingulate removal on task switching, error monitoring, and working memory. Neuroimaging studies have implicated the cingulate cortex in all these processes. Six macaques were taught task switching (TS) and delayed alternation (DA) paradigms. TS required switching between two conditional response tasks with mutually incompatible response selection rules. DA required alternation between two identically covered food-well positions. In the first set of experiments, anterior cingulate lesions did not consistently impair TS or DA performance. One animal performed worst on both TS and DA and in this animal the cingulate sulcus lesion was most complete. In the second set of experiments, we confirmed that larger anterior cingulate lesions, which included the sulcus, consistently impaired TS but only led to a mild and equivocal impairment of DA. The TS error pattern, however, did not suggest an impairment of TS per se. The consequence of a cingulate lesion is, therefore, distinct to that of a prefrontal lesion. TS error distribution analyses provided some support for a cingulate role in monitoring responses for errors and subsequent correction but the pattern of reaction time change in TS was also indicative of a failure to sustain attention to the task and the responses being made.

INTRODUCTION

The anterior cingulate and adjacent medial frontal cortices have extensive connections with the lateral prefrontal cortex (Paus, Castro-Alamancos, & Petrides, 2001; Wang, Shima, Sawamura, & Tanji, 2001; Morecraft & Van Hoesen, 1993; Lu, Preston, & Strick, 1994; Bates & Goldman-Rakic, 1993) suggesting that they may be implicated in similar cognitive functions. Blood flow increases in cingulate and dorsolateral prefrontal regions are correlated in human neuroimaging experiments as might be expected of functionally co-operating areas (Koski & Paus, 2000). In this report, we consider the role of the cingulate cortex in three cognitive processes known to depend on the prefrontal cortex (Roberts, Robbins, & Weiskrantz, 1998; Dias, Roberts, & Robbins, 1996; Passingham, 1993) and with which the cingulate and the wider medial frontal region have been associated in recent neuroimaging experiments (Paus, 2001): (i) task switching (TS) and response competition; (ii) error detection; (iii) working memory. Unusually, theories of primate cingulate cognitive function depend strongly on evidence from functional imaging studies while few experimental lesion investigations have considered the primate cingulate cortex (Meunier, Bachevalier, & Mishkin, 1997; Parker & Gaffan, 1997; Stern & Passingham, 1994, 1996; Thaler, Chen, Nixon, Stern, & Passingham, 1995; Murray, Davidson, Gaffan, Olton, & Suomi, 1989; Pribram & Fulton, 1954; Pribram, Wilson, & Connors, 1962). In another report, we discuss the effect of cingulate lesions on social and emotional behavior (Hadland, Rushworth, Gaffan, & Passingham, in press).

There is evidence that the cingulate cortex is important for attention/task switching. Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have recorded blood flow and blood oxygenation level dependent (BOLD) signal changes (“activations”) in the cingulate cortex in attention demanding situations, such as versions of the Stroop (1955) task (Barch et al., 2001; Bush et al., 1998; Bush, Luu, & Posner, 2000; Carter, Mintum, & Cohen, 1995; Carter et al., 2000; Taylor, Kornblum, Lauber, Minoshima, & Koepppe, 1997; Pardo, Pardo, Janer, & Raichle, 1990), dual task paradigms (Adcock, Constable, Gore, & Goldman-Rakic, 2000), and TS (Rushworth, Hadland, Paus, & Sipila, 2002; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Koechlin, Corrado, Pietrini, & Grafman, 2000; MacDonald, Cohen, Stenger, & Carter, 2000). The cingulate role in such paradigms is not clear (MacLeod & MacDonald, 2000). One possibility is that the cingulate cortex is part of an executive circuit, together with the dorsolateral prefrontal cortex, which selects and sets the currently required task set or
strategy. A second possibility is that the cingulate cortex is not an executive area that selects task set and strategy but that it is concerned with the response competition that follows once a novel task set has been selected (Carter et al., 1998, 2000; Casey et al., 2000; MacDonald et al., 2000; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Taylor, Kornblum, Minoshima, Olivers, & Koepppe, 1994; Paus, Petrides, Evans, & Meyer, 1995). Response competition accounts can also accommodate increased cingulate activation during the Stroop task; the Stroop task’s difficulty may be a consequence of the competition between the different possible responses that a given stimulus can instruct (MacLeod, 1991).

A third and related hypothesis is that the cingulate cortex may have a role in error detection (Bush et al., 2000; Shima & Tanji, 1998; Gemba, Sasaki, & Brooks, 1986; Niki & Watanabe, 1979). According to this interpretation, cingulate activation during response conflict reflects the fact that response conflicts are likely to be associated with errors (Braver, Barch, Gray, Molfese, & Snyder, 2001; Carter et al., 1998, 2000). If the cingulate cortex is crucial for error detection, then lesions would be expected to cause monkeys to fail to correct their own performance and to make one error after another (“consecutive errors”). We therefore conducted error analyses to examine whether cingulate lesions caused monkeys to make more consecutive errors. The rate of consecutive errors might increase postoperatively simply as a consequence of the overall increase in errors. What is at issue, however, is whether the error rate on trials subsequent to previous error trials is higher than the error rate otherwise. We therefore tested whether the error rate was higher on trials after an error trial (error + 1 trials) than it was on trials after a correct trial (correct + 1 trials) after cingulate removal. Human subjects sometimes respond more slowly on the trials that follow an error (Luce, 1986; Rabbit, 1966). Such “post-error slowing” is usually taken as indicative of an attempt to reduce the possibility of further errors. We therefore looked for evidence of any change in post-error slowing by comparing reaction times (RTs) on error + 1 and correct + 1 trials. It is not clear if monkeys also show post-error slowing. Many current monkey testing paradigms tend to reward animals for every correctly performed trial. Error trials are therefore associated with an absence of reward and may be particularly

Figure 1. TS procedure. (A) Each column shows three stages in a typical trial. The beginning of the trial is shown at the top when a cue appears either at the top or at the bottom of the screen. The middle row shows the presentation of the two response choices, which occurs immediately when the cue is touched. The correct choice was to touch the left and the right positions when the cue was presented at the top and at the bottom positions, respectively. (B) Trials presented against a different background pattern required the opposite response selection rules—to the right and left, respectively, if the cue was presented at the top and bottom positions, respectively.

Figure 2. TS procedure. Trials of the same type were presented until the monkey obtained 10 rewards. A pseudorandom algorithm was then used to determine if the background pattern should change or stay the same.
frustrating. If frustration leads to higher arousal, then it is possible that an error trial will be followed by very quick responses.

In Experiment 1, we report how we taught six monkeys a TS paradigm which required them to alternate between two tasks with mutually incompatible response demands (Figure 1). The monkeys were taught two different spatial conditional response tasks on a touch screen. In Task 1 (Figure 1A), monkeys were presented on each trial with a cue at either the top or the bottom of the touch screen. Touching the cue triggered the presentation of a choice of two different response options to the left and right of the screen. The rule was that the monkey was to respond to the left when the cue had appeared above and to the right when the cue had appeared below. As can be seen in Figure 1, the cues were always presented against a distinctive background pattern. On other trials (Figure 1B), however, a different background pattern was used and the response selection rule was reversed; now cues in the top and bottom positions instructed monkeys to respond to the right and left, respectively. The monkeys performed trials of one task type, against a particular background pattern, until they managed to get 10 trials correct. A pseudorandomization procedure was then used to either change to the other task or to continue with the task that had already been performed (Figure 2). The pseudorandomization procedure prevented any given task being presented for more than 30 correctly performed trials. We tested the hypothesis that the cingulate lesion might impair performance particularly at the time of TS.

The cingulate cortex has been associated with working memory. In the monkey, the activity of single cells in the cingulate cortex is modulated during the delays of working memory tasks (Procyk & Joseph, 2001; Niki & Watanabe, 1976). There are activations in the cingulate cortex and adjacent areas, such as the pre-SMA, during working memory tasks (Petit, Courtney, Ungerleider, & Haxby, 1998). The task used by Petit et al. (1998) required subjects to memorize the identities or locations of face stimuli over delays of between 9 and 15 sec. On the basis of a meta-analysis of 108 PET studies, Paus, Koski, Carmanos, & Westbury (1998) concluded that working memory was one factor that determined blood flow in the cingulate region. How central and essential the cingulate cortex is to sustaining memory through such delays, however, is not clear. While large lesions that include the orbital frontal tissue in addition to the cingulate cortex have been shown to impair spatial working memory in the monkey (Bachevalier & Mishkin, 1986), it has been claimed that smaller lesions of just the cingulate cortex cause no significant impairment (Murray et al., 1989) or only mild and variable impairment (Meunier et al., 1997). In Experiment 2, we therefore examined the importance of the cingulate cortex for correct performance of a delayed alternation (DA) task (Figure 3).

Figure 3. DA task. Monkeys chose between two identical food-well positions on the left and right. Both positions were baited on the first trial. On the second trial, the position that was not previously chosen was baited. The food position was alternated on each trial unless a mistake was made (e.g., fourth panel). On such trials the food stayed in the same position. This meant that the monkey always had to alternate its responses on every trial regardless of whether a correct response or an error had been made.

RESULTS
Experiments 1 and 2

The lesion histology is shown in Figure 4 and is described in more detail in Methods.

Experiment 1: Task Switching—Part I

Each animal had longer RTs on switch trials (the first trials of each block) than on subsequent block trials at the time of both the preoperative and postoperative tests (Table 1). A t test showed that RTs were significantly longer on switch than block trials at the time of the preoperative test ($t = 2.305, df = 5, p = .035$). At the time of the postoperative test, although the RT difference was still observed for each animal, its extent was now more variable and the effect was just marginally significant on testing with a $t$ test ($t = 1.818, df = 5, p = .065$).

Despite the evidence that all animals were slower to respond at the beginning of each task block, there was no evidence that the impact of set switching on RT was enhanced by the lesion. The RT difference between switch and block trials decreased for two of the animals.
after cingulate lesion and it increased in the other individual, CING2.

There was no evidence that the lesion led to a basic impairment in task performance after the lesion (Table 1). Lesion animals CING1 and CING3 were very slightly worse than preoperatively. A similar level of performance variation, however, was also seen among the control animals. The other animal, CING2, however, was clearly affected by the lesion. This animal made more than twice as many errors on both switch and block trials in the postoperative test than had been made in the preoperative test. Although not the slowest, the speed of CING2’s responses decreased more than other animals postoperatively.

Figure 4. Coronal sections showing the cingulate lesion in all three animals that received surgery in Experiments 1 and 2 (CING1, CING2, CING3). The sections are reproduced at 70% original size. The third section from the bottom is taken at the level of the bow of the arcuate sulcus. The more caudal sections are shown below and the more rostral sections are shown above. There is a distance of 2 mm between each section and the next. The rostral CMA is normally taken to extend from just behind the level of the bow of the arcuate sulcus (third section from bottom) to the level of the rostral tip of the superior limb of the arcuate sulcus (between the top and the second sections). Although the lesion in the anterior cingulate gyrus is complete the lesion in the cingulate sulcus in the region of the rostral CMA is only complete in CING2. The arrow in each case indicates the caudal-most bilateral extent of the sulcal lesion in each animal. CING2 was the most impaired animal on both DA and TS.
Table 1. Task Switching in TS Paradigm (Experiment 1)

<table>
<thead>
<tr>
<th></th>
<th>Preoperative Test</th>
<th>Postoperative Test</th>
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<tr>
<td></td>
<td>Errors</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>Sw</td>
<td>Bl</td>
</tr>
<tr>
<td>CING1</td>
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<td>CING2</td>
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<td>73</td>
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<td>CING3</td>
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<td>40</td>
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<td>CING4</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>CING5</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>CING6</td>
<td>7</td>
<td>102</td>
</tr>
</tbody>
</table>

Errors and RTs (msec) are on the first trials after a switch (Sw) and the other trials of the block (Bl) are shown for the animals with anterior cingulate lesions (CING1, CING2, CING3) before and after surgery at the top of the table. Data for the same periods for the control group (CING4, CING5, CING6) are shown at the bottom of the table.

There was an increase in consecutive errors after the lesion (Table 2). Error rates on error + 1 trials and correct + 1 trials were not different at the first testing period ($t = -7.64, df = 2, p > .05$). After the lesion, this remained the case in the control group ($t = .314, df = 2, p > .05$) but the error rate was significantly higher on the error + 1 trials in the lesion group ($t = 3.706, df = 2, p = .066$). The significant change in error distribution was also manifested as a three-way interaction between Group, Testing Period, and Error type ($F = 15.295, df = 1, 4, p = .017$). CING2, the animal that appeared most affected by the lesion in Table 1, showed the most pronounced change in error distribution; preoperatively, only 8% of errors were followed by further errors, but postoperatively, 42% of errors were followed by further errors. There was no clear evidence of post-error slowing in RT in the monkeys nor was there clear evidence that this was affected by the lesion.

Table 2. Error Effects in the TS Paradigm (Experiment 1)

<table>
<thead>
<tr>
<th></th>
<th>Preoperative Test</th>
<th>Postoperative Test</th>
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<tbody>
<tr>
<td></td>
<td>Error Rate</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>E + 1</td>
<td>C + 1</td>
</tr>
<tr>
<td>CING1</td>
<td>4.65</td>
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<td>CING2</td>
<td>7.95</td>
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<td>CING3</td>
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<td>10.50</td>
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<td>CING4</td>
<td>5.88</td>
<td>6.86</td>
</tr>
<tr>
<td>CING5</td>
<td>5.26</td>
<td>3.43</td>
</tr>
<tr>
<td>CING6</td>
<td>26.61</td>
<td>17.98</td>
</tr>
</tbody>
</table>

Error rates (%) and RTs (msec) were measured on the trials following previous errors (error + 1 trials [E + 1]) and the trials following previous correct responses (correct + 1 trials [C + 1]). Data for animals with anterior cingulate lesions (CING1, CING2, CING3) before and after surgery are shown at the top of the table. The same data are shown for the control group (CING4, CING5, CING6) at the bottom of the table.

Experiment 2: Delayed Alternation—Part 1

There was no clear evidence of any impairment on the DA task after cingulate lesions were made (Table 3). The performance of two lesion animals actually improved postoperatively. The other animal, CING2, however, made twice as many errors on the postoperative test than on the preoperative test.

There was no clear evidence of impairment when the animals were tested with longer delays of 10 and 15 sec (Table 3). It was noticeable, however, that CING2 always made the most errors at each testing delay.

Discussion—Experiments 1 and 2

The TS manipulation in Experiment 1 caused monkeys to respond more slowly on the first trials of each block. Despite the difficulty imposed by the TS manipulation, there was no evidence of a general impairment or, more specifically, an impairment of TS after the cingulate lesion (Table 1). There was, however, some evidence of a change in error distribution, consistent with a change in error sensitivity, after the lesion (Table 2). There was no evidence of impairment on DA (Table 3).

The postoperative performance of one animal with a cingulate lesion, CING2, was always worst. Postoperatively in Experiment 1, CING2 made many more errors than any other animal and made twice as many errors as it had made preoperatively (Table 1). The RT switching cost for CING2 increased after the lesion. There was a dramatic change in the proportion of consecutive errors made by CING2 postoperatively. Postoperatively in Experiment 2, CING2 also made the most errors at all three delays. Histologic analysis showed that CING2’s lesion included the whole of the cingulate sulcal region as far caudal as the level of the spur of the arcuate sulcus while this was not the case in CING1 or CING2. The posterior limit of the cingulate sulcal...
lesion is indicated by arrows in each animal in Figure 4. The area rostral to the level of the caudal-most parts of the arcuate sulcus (third section from bottom) and caudal to the rostral tip of the superior branch of the arcuate sulcus (top section) is generally agreed to contain the more rostral CMA (CMAr, 24c, or 24c0), which has connections with the both the spinal cord and the primary motor cortex (Dum & Strick, 1993; Van Hoesen, Morecraft, & Vogt, 1993; Vogt, 1993; Matelli, Luppino, & Rizzolatti, 1991).

We therefore conducted Experiments 3 and 4 to test whether TS and DA are consistently impaired by anterior cingulate lesions that include the sulcus as far caudally as the level of the genu of the arcuate sulcus and which therefore incorporate the rostral CMA. The TS and DA tests were conducted in the same manner as previously, except that now the animals were also tested preoperatively (as well as postoperatively) at all three delay lengths (5, 10, and 15 sec) of the DA procedure. Lesions were made in the three animals that had served as controls in Experiments 1 and 2 and pre- and post-operative performances were compared.

Experiments 3 and 4

The lesion histology is shown in Figure 5 and is discussed in Methods.

**Experiment 3: Task Switching—Part II**

The RT difference between switch and block trials was not significant at the time of preoperative testing; one of the three animals, CING4, was not slower on the switch trials. On postoperative testing, however, all animals performed the switch trials more slowly than the block trials and the difference was significant ($t = 4.788$, $df = 2$, $p = .021$). Moreover, the RT difference between switch and block trials was significantly augmented by the lesion ($t = 2.973$, $df = 2$, $p = .048$); the difference between switch and block RT was greater for all animals after surgery (Table 4).

All three animals made at least four times as many errors postoperatively as they had done preoperatively. There was no evidence, however, that the errors were mostly made on the switching trials at the beginning of blocks (Table 4). The data distribution was far from the ideal normal distribution; postoperatively, the distribution of errors was clearly positively skewed and the standard deviation increased in proportion with the mean. A logarithmic transform was therefore applied to the data before testing for statistical significance. A $t$ test showed that significant increases in errors occurred postoperatively on both switch ($t = 3.338$, $df = 2$, $p = .040$) and nonswitch trials ($t = 3.161$, $df = 2$, $p = .044$).

There was a clear trend for the error rate to be higher after a previous error trial than after a previous correct trial once the lesion was made (Table 5). There was no indication of a preoperative difference between error rates on error + 1 and correct + 1 trials ($t = .883$, $df = 2$, $p = .47$) but the postoperative difference reached a marginal level of statistical significance ($t = 2.212$, $df = 2$, $p = .079$). There was no evidence for post-error slowing in RT (Table 5).

**Experiment 4: Delayed Alternation—Part II**

All three animals made more errors on the longer two delays (10 and 15 sec) postoperatively than they had done preoperatively (Table 6). The effect of cingulate surgery was not significant ($F = 3.304$, $df = 1.392$, 2.784, $p = 1.84$) when scores from all sets of three delay length tests were considered together in a two-factor (delay and surgery) ANOVA. The scores from the first 5-day test with a 5-sec delay were particularly variable and so the results from each 5-day test at each delay length were considered separately. The postoperative increase in errors was significant at the 15-sec delay ($t = 4.964$, $df = 2$, $p = .017$) when two of the animals made twice as many errors postoperatively as they had preoperatively.

**GENERAL DISCUSSION**

It has been suggested that the cingulate cortex may be important for (i) error detection, (ii) TS, and (iii) working memory. The results of the present four experiments address each of these three hypotheses.

**The Anterior Cingulate and Error Monitoring**

The change in error distribution in the TS task (Experiments 1 and 3) after the anterior cingulate lesion (Tables 2 and 4) is consistent with the role of the

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**Table 3. DA Paradigm (Experiment 2)**

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<tr>
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<th>Preoperative Test</th>
<th>Postoperative Test</th>
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<tbody>
<tr>
<td></td>
<td>5-sec delay</td>
<td>10-sec delay</td>
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<tr>
<td></td>
<td>5-sec delay</td>
<td>10-sec delay</td>
</tr>
<tr>
<td>CING1</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>CING2</td>
<td>33</td>
<td>65</td>
</tr>
<tr>
<td>CING3</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>CING4</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>CING5</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>CING6</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>

Errors on the DA paradigm for animals with anterior cingulate lesions (CING1, CING2, CING3) before and after surgery are shown at the top of the table. The same data are shown for the control group (CING4, CING5, CING6) at the bottom of the table.
anterior cingulate in error monitoring. The error rate on trials immediately following errors (error + 1 trials) was higher than otherwise (correct + 1 trials). Human subjects tend to respond more slowly on the trial after an error has been committed (Luce, 1986; Rabbit, 1966). Such “post-error slowing” is normally taken as an indication that the subject is attempting to reduce the possibility of further errors by responding more cautiously and deliberately. We were not, however, able to observe any clear evidence for such “post-error slowing” at any stage of the present experiments. Error trials are associated with a lack of food reward for the monkey and the increased arousal that may be associated with the frustration of nonreward may have counterbalanced any tendency to respond more slowly on the next trial. It should also be remembered that the task designs often used in monkey experiments are unlikely to be the most sensitive to post-error

Figure 5. Coronal sections showing the cingulate lesion in all three animals that received surgery in Experiments 3 and 4 (CING4, CING5, CING6). The sections are reproduced at 70% original size. The same conventions are used as in Figure 4. Note that the lesion is complete even in the sulcus in all three animals.
slowing. As in many other experiments, the current task imposed a longer intertrial interval of 6 sec after an error than the 3-sec intertrial interval that followed a correct response.

Despite the absence of post-error slowing, it is widely acknowledged that monkeys are sensitive to error feedback. “Rerun correction” schedules, which involve the repetition of a trial until it is performed correctly, are often used when a monkey is first taught a task. Monkeys are even able to make strategic use of error feedback to minimize the number of different responses that are tested (Bussey, Wise, & Murray, 2001; Procyk & Joseph, 1996; Procyk, Tanaka, & Joseph, 2000).

Single unit and field potential recordings made in the cingulate cortex have identified responses when monkeys make errors (Procyk et al., 2000; Procyk & Joseph, 2001; Shima & Tanji, 1998; Gemba et al., 1986; Niki & Watanabe, 1979). Similar “error potentials” can be recorded with scalp electrodes from human subjects and dipole analysis has suggested an origin in the cingulate cortex (Bush et al., 2000). The behavioral significance of the cingulate error signal, however, has been difficult to ascertain. Shima and Tanji (1998) showed that muscimol injection into the cingulate cortex could be followed by a failure to reverse responses on the basis of changes in reward values, but the brevity of their report left it unclear as to whether such effects were found reliably or consistently. Moreover, the cingulate error signal is just one of many that has been identified in the brain and its importance for subsequent behavioral change might be questioned; error signals have also been recorded in the prefrontal cortex (Niki & Watanabe, 1979), the ventral tegmental area (Schultz, 2000), and the supplementary eye field (Stuphorn, Taylor, & Schall, 2000). Lesions of the dorsolateral prefrontal cortex can alter the error potential thought to be recorded from the cingulate cortex (Gehring & Knight, 2000). The present results confirm Tanji and Shima’s (1988) conclusion that cingulate lesions alter the normal pattern of corrective behavior after errors are made.

The change in error distribution after cingulate lesion may have been due to a fundamental insensitivity to a change in reinforcer value. Two other related possibilities should, however, be considered. First, it is possible that the cingulate lesion may have caused lapses in the monkeys’ attention to their own actions and their actions’ outcomes. A failure to attend to the responses being made would have left a monkey appearing more distractible and unable to change its behavior even when poor performance led to errors. Jueptner et al. (1997) argued that the cingulate cortex was crucial for attending to actions. Johansen-Berg and Matthews (2002) have reported a decrease in activation in cingulate and other motor association areas when human subjects are unable to attend to their responses. They also showed that under such conditions, RT variation increases. For this reason, we compared the log-transformed standard deviations of the RTs recorded in the TS paradigm. There was a significant

### Table 4. Task Switching in TS Paradigm (Experiment 3)

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<th>Preoperative Test</th>
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<th>Postoperative Test</th>
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<tbody>
<tr>
<td></td>
<td>Error Rate</td>
<td>RT</td>
<td>Error Rate</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>E + 1 C + 1</td>
<td></td>
<td>E + 1 C + 1</td>
<td></td>
</tr>
<tr>
<td>CING4</td>
<td>0.6 0</td>
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<td>11.90 10.63</td>
<td>783 642</td>
</tr>
<tr>
<td>CING5</td>
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<td>53.48 34.54</td>
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</tr>
<tr>
<td>CING6</td>
<td>3.6 18.18</td>
<td>1062 783</td>
<td>30.48 11.08</td>
<td>1025 976</td>
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</tbody>
</table>

Error rates (%) and RTs (msec) on error + 1 trials (E + 1) and correct + 1 trials (C + 1) are shown for the period before and after anterior cingulate lesions (CING4, CING5, CING6).
difference between the postoperative RT standard deviations in the control and cingulate animals in Experiment 1 ($t = 2.479$, $df = 4$, $p = .034$) and a significant difference between the preoperative and postoperative performance of the animals in Experiment 2 ($t = 5.996$, $df = 2$, $p = .014$). Interpreting the increase in consecutive errors as the consequence of a failure to attend to actions and their outcomes is similar to certain interpretations of cingulate activation in neuroimaging experiments (Braver et al., 2001; MacDonald et al., 2000; Carter et al., 1998). These authors have emphasized that high response competition conditions predispose subjects to make errors and therefore require more intense monitoring of responses and their outcomes.

The second related possibility to be considered is that the anterior cingulate lesion is disrupting the normal manner by which motivational changes influence responding (Paus, 2001). It might be expected that the frustration of not receiving an expected reward on an error trial would result in a change in arousal level. The change in arousal level might normally be instrumental in ensuring that performance improves after a mistake. It is clear that arousal levels modulate cingulate gyrus activation levels in human neuroimaging experiments (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Critchley, Elliott, Mathias, & Dolan, 2000; Critchley, Mathias, & Dolan, 2001; Paus et al., 1997).

The Anterior Cingulate Cortex and TS: The Critical Role of the Cingulate Sulcus

In Experiments 1 and 2, cingulate removal did not significantly impair basic performance of the TS or DA paradigms (Tables 1 and 3). There was no overall increase in errors on either of these tasks although there was some evidence for a change in error distribution (Table 2). Postoperatively, however, one animal, CING2, performed worse than the others. CING2 made more errors on the TS paradigm (Table 1), made a particularly high proportion of consecutive errors in the TS paradigm (Table 2), and made many errors in the DA task at longer delays (Table 3). It was only in CING2 that the tissue in the anterior cingulate sulcus region between the levels of the anterior tip of the superior limb of the arcuate sulcus and the spur of the arcuate sulcus was completely removed (Figure 4). In Experiments 3 and 4, we found that lesions that included all of this area in all three animals resulted in a more consistent impairment pattern (Tables 4, 5, 6).

The critical region of the anterior cingulate sulcus includes the most rostral of the cingulate motor areas, variously known as CMAr (Dum & Strick, 1991), 24c (Matelli et al., 1991), or 24c' (Vogt, 1993). The cingulate sulcal lesion extended further caudally in the lower bank and it is likely that parts of a more caudal cingulate motor area in the ventral bank of the cingulate sulcus (CMAv, Dum & Strick, 1991) was also removed (CING2, CING4, CING5, CING6). Both the CMAr and CMAv regions have connections with the prefrontal cortex, the spinal cord, and the primary motor cortex (Morecraft & Van Hoesen, 1993; Dum and Strick, 1993, 1996; He, Dum, & Strick, 1995; Luppino, Matelli, Camarda, Galles, & Rizzolatti, 1991; Luppino, Matelli, Camarda, & Rizzolatti, 1994; Van Hoesen et al., 1993; Murray & Coulter, 1981).

The finding that a restricted region of the cingulate sulcal cortex, known to contain the CMAr, had to be removed to produce TS impairment is consistent with the suggestion that the cingulate cortex’s role in attention-demanding situations is intimately related to its motor function (Turken & Swick, 1999; Paus et al., 1993). Jueptner et al. (1997) suggested that this region played a critical role in “attention to action.” It is also consistent with the claim that quite limited areas of cingulate damage can lead to impairment on Stroop tasks (Turken & Swick, 1999) and response reversal tasks (Paus et al., 1991; Paus, 2001) in some patients but not in others (Janer & Pardo, 1991).

The Anterior Cingulate Cortex and TS: Changing Set

It was clear that TS performance was impaired when the lesion included the complete removal of the anterior cingulate sulcus (CING2 in Tables 1 and 2; CING4, CING5, CING6 in Tables 4 and 5). It was, however, not clear that it was the process of task switching per se that caused the animals’ difficulties. Even when one just considers the four animals that were impaired on TS, there was no evidence for a greater predominance of errors at the time that the background pattern was renewed and animals began a new set. Very few errors were made on these trials and their number was not disproportionately increased (CING2 in Table 1 and all animals in Table 4). The RT difference between trials at the start of the blocks and other trials (the RT switching cost) was significantly greater after the lesion in Experiment 3 (Table 4). A similar increase in RT switching cost was also seen in the impaired animal, CING2, in Experiment 1 (Table 1). It was still the case that there was a significant augmentation in switching costs even when the results of all four impaired animals were considered together ($t = 3.791$, $df = 3$, $p = .016$). This aspect of the results is reminiscent of a report that a patient with a cingulate lesion was particularly slow to respond in the difficult incongruent response condition of the Stroop task (Turken & Swick, 1999, “word (manual)” condition).

Various considerations should, however, be borne in mind and set against the evidence that the increase in RT switching costs in the present experiments was consistent and statistically significant. It should be noted that the switching cost increase was only slight in size.
It could be argued that the increase in RT switching cost was dwarfed by the general increase in RT that could be seen even on standard block trials. If the increase in RT switching cost had been considered as a proportion of the baseline increase in RT on standard block trials, then it would not have been found significant. The evidence that cingulate lesions in human patients particularly impair conditions of high response conflict is, similarly, not clear. Janer and Pardo (1991) did not find that their cingulate patient’s RTs were disproportionately slowed in the Stroop incongruent condition and Turken and Swick (1999) found that their patient was not disproportionately slowed in some variants of the incongruent condition (“Arrow (manual)” condition). Like the monkeys in the present study, Turken and Swick's patient exhibited a general slowing on all trial types.

In summary, contrary to our expectations at the study's outset, the evidence that the cingulate cortex was particularly involved in TS was unclear. There was no evidence that trials at the beginning of blocks when response competition was greatest, as indexed by increased RT, were disproportionately more likely to be associated with errors after cingulate removal. There was, at best, equivocal evidence for an increase in switching costs after the lesion. This suggests an important difference between the effects of cingulate and prefrontal lesions. It has been claimed that both orbital and more lateral prefrontal lesions particularly impair performance on trials where the task changes. Different factors may explain the difficulty of task changes and the need for prefrontal involvement: the change in reinforcement association, the change in attentional set required, or suppression of a habitual response (Crofts et al., 2001; Roberts & Wallis, 2000; Dias et al., 1996; Dias, Robbins, & Roberts, 1997; Jones & Mishkin, 1972; Iversen & Mishkin, 1970). The present results suggest that increased cingulate activation on set switching and during high response competition cannot be interpreted as straightforward evidence that the cingulate cortex has a role in selecting and setting task set and strategy. Similar interpretations have been made of the neuroimaging data (Carter et al., 2000; MacDonald et al., 2000; Paus et al., 1993).

The Anterior Cingulate Cortex and Working Memory

The DA results of Experiments 2 and 4 task also clearly underlined differences between the prefrontal and cingulate cortices despite their anatomic interconnections. In Experiment 2, the performance of CING2, the monkey with the more complete sulcal lesion, deteriorated more than the other animals on the postoperative period test (Table 3). The performance of all three animals was worse postoperatively than preoperatively when larger lesions were made in Experiment 4, suggesting that tissue in the cingulate sulcus may also be important for DA performance (Table 6). Even in Experiment 4, however, the deficit was small and variable. For example, it should be noted that a similar degree of worsening was evident in the same animals between the two testing sessions when they acted as controls in Experiment 2. Studies have differed in whether they have concluded that cingulate lesions cause DA or delayed response (DR) impairments (Meunier et al., 1997; Pribram et al., 1962) or not (Murray et al., 1989; Pribram & Fulton, 1954). Although there has been variability in whether or not an impairment has reached the $p < .05$ level of significance, all the studies have been uniform in observing mild and variable performance decrements that are quite distinct to the profound deficits, even at short delays, that follow prefrontal lesions on similar tasks (Goldman, Rosvold, Vest, & Galkin, 1971). On the basis of cell recording data, Procyk and Joseph (2001) have also questioned the degree to which cingulate cells hold spatial information over working memory delays. Although signal changes may be recorded in this region during delays in neuroimaging experiments (Paus et al., 1998; Petit et al., 1998), it is clear that the maintenance of working memory is not central to this region’s function.

The DA procedure used in the present investigations is similar to the DA and DR tasks that have been shown to be impaired after prefrontal lesions in monkeys (Goldman & Rosvold, 1970; Goldman et al., 1971; Funahashi, Bruce, & Goldman-Rakic, 1993). Moreover, the task is not that dissimilar from the spatial DR paradigm that Petit et al. (1998) showed was associated with activation in the human cingulate cortex. It remains to be determined if the anterior cingulate cortex is essential for the more difficult working memory tasks, such as “n-back” tasks, which are used with human subjects (Cohen et al., 1997). In such tasks, responses are not determined just by the most recent stimulus in a list but by a stimulus that may have been presented 2, 3, or $n$ trials back in the list. That such tasks require subjects to update, monitor, and manipulate information, in addition to holding it in memory, may be an important determinant of the degree to which they recruit the prefrontal cortex (Owen et al., 1999).

Conclusion

In summary, the results suggest that anterior cingulate lesions impaired performance on a TS paradigm but it was not clear that the impairment was one of TS per se. There was some evidence that the lesion was associated with a tendency to produce consecutive incorrect responses suggesting that the lesion may have altered the normal pattern of corrective behavior after a lesion. A failure to sustain attention to responses could explain increases in RT variation seen after the lesion. The removal of the anterior cingulate sulcal region known to contain the CMAr is a prerequisite for the deficit and
this also highlights that response factors are determinants of impairment.

**METHODS**

**Experiments 1 and 2**

**Subjects**

Six cynomolgus macaques were used, aged between 2 and 4 years and weighing between 3 and 5 kg. Lesions were made in three of the animals (CING1, CING2, CING3) and the other three animals (CING4, CING5, CING6) served as controls. All the animals were tested twice, before and after surgery. The studies were carried out under project and personal licenses from the British Home Office.

**Surgery**

All surgery was carried out under sterile conditions with the aid of a binocular microscope. Barbiturate anesthesia was used during surgery. The skin, galea, and muscle were first cut and retracted. A D-shaped bone flap was then made so that one hemisphere could be exposed up to the level of the midline. The dura was then cut and retracted. It was important to be able to see the spur of the arcuate sulcus and the precentral dimple as these were used to guide the placement of the lesion’s posterior limit. The lesion was made by aspiration with a fine gauge sucker. The lesion was first made in the exposed hemisphere. Veins on the medial surface that drained into the sagittal sinus were cauterized and cut. The cortex of the cingulate gyrus and sulcus was removed. The posterior limit of the lesion in the cingulate sulcus was an imaginary line drawn from the spur of the arcuate sulcus through the midpoint of the precentral dimple. The posterior limit of the lesion in the cingulate gyrus was extended by approximately 5–10 mm. The lesion continued anterior along the length of the cingulate sulcus. The anterior limit of the lesion was an imaginary line between the tips of the rostral and cingulate sulci. The posterior and supracallosal part of the lesion extended ventrally to the corpus callosum while the more anterior part of the lesion extended ventrally to the rostral sulcus. Strips of supporting tissue were spared underneath the ascending branches of the anterior cerebral artery using the method of Parker and Gaffan (1997). This ensured the blood supply to the tissue dorsal and lateral to the lesion. When the lesion was complete in the first hemisphere, the falx was cut and retracted dorsally. It was then possible to make a similar lesion in the second hemisphere.

**Histology**

Once the behavioral experiments were completed, the animals were deeply anesthetized and perfused transcardially with saline followed by formal saline. The brains were blocked in the coronal stereotaxic plane posterior to the posterior end of the central sulcus and allowed to sink in sucrose–formalin solution. The brains were then cut in 50 μm sections on a freezing microtome and every 10th section was retained and stained with cresyl violet.

The bow of the arcuate sulcus is often taken as a landmark and reference point for the cingulate sulcus. In Figure 4, for each animal, we have presented coronal sections at the level of the bow of the arcuate sulcus. We have then presented three more sections anterior to this level, at distances of 2 mm and two more posterior sections, again at distances of 2 mm. Because there is often some skewing of sections away from the true coronal plane, it was necessary to define the section containing the bow of the arcuate sulcus separately for each hemisphere. Thus, each section in Figure 4 is composed of two half sections taken from two different slides. In this way, it is possible to present histologic data for the same coronal position for each hemisphere in each row of Figure 4.

From Figure 4, it can be seen that the lesion in the cingulate gyrus was always complete. There was some variability in the degree of involvement of the cingulate sulcus. In CING2, the whole of the cingulate sulcus was removed as far posterior as the bow of the arcuate sulcus. The lesion extends further posterior in the lower bank of the cingulate sulcus. The lesion in CING2 is therefore likely to include both the cingulate motor regions, CMaR and CMaV, that receive a projection from the prefrontal cortex (Lu et al., 1994). In the case of CING1, the lesion in the right hemisphere extended back as far as the bow of the arcuate sulcus while in the left hemisphere only the most anterior 50% of the cingulate sulcus region between the bow of the arcuate sulcus and the most anterior of the superior limb of the arcuate sulcus was included in the lesion. In the case of CING3, only the most anterior 47% and 33% of the cingulate sulcus region between the bow of the arcuate sulcus and the most anterior of the superior limb of the arcuate sulcus was included in the lesion in the left and right hemispheres, respectively.

**Experiment 1: Task Switching—Part 1**

**Apparatus**

Visual stimuli were presented on a 20-in. color VDU, fitted with a touch-sensitive screen, which was fixed firmly to a table. Also fixed to the table were a centrally located metal receptacle for the delivery of reward pellets and a laterally located food box that was electronically controlled. The monkeys sat in a wheeled transport cage placed 20 cm from the VDU so that they could reach the visual targets easily through the bars of the cage. The tasks were controlled by computer.
**Task**

The monkeys learned to perform two spatial conditional tasks using the touch screen (Figure 1). For each task, the correct response was determined by the position of a cue. The rules for response selection in the two tasks were mutually exclusive. Different background patterns were present on the screen for each task.

Background pattern 1 (Figure 1A) was used when the rules for component task 1 were in effect. A single cue (red square) appeared at either the top or the bottom of the screen at the beginning of each trial. The monkey learned to touch the cue to make the two response choices (red squares) appear. The response choices always appeared on the left- or right-hand side of the screen. The monkey then selected the appropriate response given the position of the cue to gain a reward. Top and bottom cues instructed responses to the left and right. Background pattern 2 was used when the rules for component task 2 were in effect (Figure 1B). Now cues at the top and at the bottom of the screen indicated right and left responses, respectively.

On each trial, the presentation of the cue at the top or bottom position was determined by a pseudorandomization algorithm. If the monkey made a correct choice, a reward was delivered and the touched response square remained on the screen for 3 sec together with the stimulus square (bottom rows of Figure 1A and B). The stimulus and response shapes then disappeared but the background pattern remained on the screen for an intertrial interval of 6 sec. If the monkey made an incorrect response, the stimulus and response shapes disappeared immediately and a longer intertrial interval of 10 sec began. The background alternated after 10 correct responses had been made, regardless of the number of incorrect responses in the block (Figure 2). The background pattern disappeared immediately after the stimulus and response shapes disappeared on the last trial of the block. The presentation of the new background pattern was made salient by drawing it on the monitor over a 1-sec period. The typical 6-sec intertrial interval then began before the first stimulus of the new block was presented. Each day the animals performed enough trials to gain 100 rewards, that is, 100 correct trials. The number of correct responses was measured. Response shapes were presented immediately as the cue shape was touched and the response RT, the time between pressing the stimulus shape and the response shape, was also measured. For each animal, a median RT on switch trials and on all other trials was calculated.

**Training and Testing Procedure**

First shaping procedures were used to teach monkeys how to use the touch screen. These involved simple training to touch color patches to obtain food rewards. They were then taught a simple conditional task on which an upper cue meant go left and a lower cue meant go right, but without any background information until they reached a criterion of 85% correct over 2 days. The opposite rule set was then taught to the same criterion. Finally, the different background patterns were also presented and the monkeys were taught to alternate between rule sets until they reached a criterion of 90% correct over 2 days. A preoperative performance test was then conducted. Each animal was assessed over 5 days with 100 rewards per day so that an average measure of performance could be derived. After surgery, the animals were given an identical performance test for 5 days with 100 rewarded trials per day.

**Experiment 2: Delayed Alternation—Part I**

**Apparatus**

The monkeys sat in a wheeled transport cage in a Wisconsin General Testing Apparatus (WGTA) box. Here a screen could be raised and lowered by the experimenter to allow the monkey controlled access to the testing board. The testing board contained two food wells covered by two identical white plaques. When the screen was raised, the animals were reached out through the bars on the front of the cage to displace one of the plaques to gain food rewards.

**Tasks**

In the DA task, the animal was allowed to find a food reward by displacing the cover over the food well on the left- or the right-hand side of the testing board (Figure 3). The screen was then lowered so that the animal could no longer see the testing board. After a specified delay, for example, 5 sec, the screen was raised again and the animal could make its next choice. Each trial was initiated by raising the WGTA screen and was terminated by lowering the screen as soon as the monkey had responded. The rule was that if the reward was on the left side on one trial, it would be on the right side on the next trial; the correct side alternated from trial to trial (Figure 3). If a mistake was made then the food remained in the same location on the next trial. Thus, the correct response was always to alternate regardless of whether a previous response had been correct or incorrect.

**Training and Testing Procedure**

The monkeys were all first exposed to the same shaping procedures which involved simple training on displacing the covers to reveal the food wells and the hidden food rewards. The animals then learned the alternation procedure performing 50 trials per day with an intertrial delay of 5 sec, until reaching a criterion of 85% correct on two consecutive days. Once the task had been
learned successfully, a preoperative performance test was conducted. Here each animal was assessed over 5 days with 50 trials per day so that an average measure of performance could be derived. After surgery, the animals were given an identical performance test. Postoperatively, the animals were all tested on the DA task with longer intertrial delays. This was designed to see whether cingulate animals were impaired at holding information over extended periods. The animals performed 50 trials per daily session over a period of 5 days, first with a 10-sec intertrial delay and then with a 15-sec intertrial delay.

**Analyses**

Analyses of both experiments’ results were carried out using between-subject *t* tests to compare control and operated monkeys or within-subject *t* tests to compare the performance of the same group of animals in the preoperative and postoperative periods. In all cases, one-tailed, unidirectional *t* tests were used on the assumption that lesions would lead to behavioral impairment and deficits were taken to be significant when *p* < .05.

**Experiments 3 and 4**

**Subjects**

The three cynomolgus macaques that had previously served as controls in Experiments 1 and 2 were used in these experiments (CING4, CING5, CING6). Their preoperative and postoperative performances were compared.

**Surgery**

Removal of the cingulate cortex was carried out as previously. The sparing of cingulate sulcal tissue in the earlier experiments may have been due to our caution in attempting to preserve tissue beneath arteries supplying the superior frontal gyrus. In the second set of surgeries, we therefore attempted more complete removals of the cingulate sulcus even if that entailed the possibility of some damage to the adjacent superior frontal gyrus.

**Histology**

The histology was prepared as previously described in the methods for Experiments 1 and 2. Once again the lesion in the cingulate gyrus was complete and as intended. In addition, the cingulate sulcal region was removed completely as far posterior as the spur of the arcuate sulcus in all three animals. As expected, there was some unintended damage to the medial aspect of the superior frontal gyrus in all three animals. It is difficult to judge precisely how much of the medial frontal gyrus was damaged in each case because of movement of the tissue after the lesion.

**Experiment 3: Task Switching—Part II**

Experiment 3 was conducted with the same procedure and apparatus as Experiment 1 and the same analyses were used. The three nonoperated control animals were retrained on the TS procedure to the original criterion of 90% correct over two consecutive days. The animals were then trained to criterion on the DA procedure (see below) before a preoperative performance test was conducted. A similar time period elapsed between the end of training and the preoperative test as did between the pre- and postoperative tests.

**Experiment 4: Delayed Alternation—Part II**

Experiment 4 was conducted with the same procedure and apparatus as Experiment 2 and the same analyses were used. The nonoperated control animals were retrained preoperatively on the DA task to the original criterion of 85% correct on two consecutive days with an intertrial delay of 5 sec. The animals then carried out the preoperative test for the TS procedure (see above). A preoperative test of DA performance was then administered. A similar time period elapsed between the end of training and the preoperative test as did between the pre- and postoperative tests. The animals were given a 5-day performance test on the DA task for each of 5-, 10-, and 15-sec intertrial delays. They were then given cingulate lesions followed by postoperative 5-day performance tests at each of the delays.

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