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Deficits in visual cognition and attention following bilateral anterior cingulotomy

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Abstract

A series of eight tests of visual cognitive abilities was used to examine pre- to post-operative performance changes in a patient receiving bilateral anterior cingulotomy. Compared with a set of eight matched control participants, post-operatively, the patient exhibited deficits in (a) the ability to sequence novel cognitive operations required to generate multipart images or rotate perceptual stimuli; (b) the ability to search for, select, and compare images of objects when the instructions did not specify precisely which objects should be visualized; and, (c) the ability to select a controlled and unpracticed response over an automatic one. Other imagery and cognitive tasks were not affected. Results are consistent with the hypothesis that anterior cingulate cortex is a component of an executive control system. One of the anterior cingulate's roles may be to monitor on-line processing and signal the motivational significance of current actions or cognitions. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Deficits in visual cognition and attention following bilateral anterior cingulotomy

The ability to regulate behavior effectively is thought to rely on a network of brain systems that includes regions of the frontal lobes as well as the anterior cingulate cortex (ACC) [6,9,11,34,39]. The idea that ACC plays an important role in executive control developed primarily in response to numerous functional neuroimaging studies showing ACC activation in a wide range of cognitive, motor, and affective tasks ([9,36,37,39,47]. Electrophysiological studies of error processing in humans [18,19] and non-human primates [7] is consistent with this view, as are studies of motor learning in non-human primates [45,48].

Studies of the cognitive deficits shown by patients with lesions of ACC have provided equivocal support for the role of ACC in executive control, however, partly because such studies have been relatively rare. A handful of clinical reports has indicated that extensive ACC damage following stroke may result in akinetic mutism [16,26] or disruptions of consciousness and self-awareness [33]. Although these findings generally are consistent with the executive control hypothesis, damage in these cases has not been limited to ACC, and observed that behavioral deficits could be at least partly due to damage to other areas (such as the supplementary motor area [26,27,32]). A case report of a patient with damage restricted to ACC did, however, show deficits on attention and response selection tasks [50].

Equivocal results have also been obtained by studies of patients who received cingulotomy, a psychosurgical procedure that selectively lesions ACC bilaterally. Cingulotomy is performed currently on either patients with

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chronic pain due to injury or illness [12,38], or psychiatric patients with intractable obsessive-compulsive disorder and/or major depression [1–3,44] in order to relieve their clinical symptoms [1–3,38,44,49]. Across a broad spectrum of standard neuropsychological tests, cingulotomy has been found to cause either no cognitive deficits [13,14], slight deficits confined to older patients (above 40-years-old) on tasks requiring visual-spatial processing [15,16,28,52] or simple motor skills, or deficits on tasks tapping high level attention, planning or intention. These deficits typically improve substantially [12] or completely [22] weeks or months post-operatively.

Although it is not clear why studies of the cognitive sequelae of cingulotomy have produced such divergent results, it is possible that performance deficits following cingulotomy are relatively subtle and short-lived, and standard neuropsychological measures of performance may not be sensitive enough to detect them [22]. In addition, some studies of psychiatric patients have included only post-operative testing and could not evaluate performance changes relative to a pre-surgical baseline to determine whether pre-operative performance was or was not abnormal.

At present, there remains a gap between neuroimaging studies which suggest that ACC plays an evaluative role in an executive control system, and lesion studies whose support for this conclusion has been equivocal. The present report provides additional data in support of the executive control hypothesis of ACC function. We compare pre- and post-operative performance of a psychiatric cingulotomy patient on a battery of attention and visual cognition tasks that require different degrees of controlled processing. Our selection of sensitive response time tasks was guided in part by functional imaging studies that have shown ACC activation during visual mental imagery [24]. Compared with visual perception, visual mental imagery draws more heavily on higher cognitive functions that guide the retrieval of information from long-term memory and the sequential construction and transformation of images in working memory [23,24]. These controlled processes depend upon the executive functions that seem to involve ACC.

Our testing procedure included eight different cognitive tasks. Seven tasks were presented in two different versions. The *perception* version required that participants only inspect and compare stimuli presented on a computer screen. In contrast, the *imagery* version required participants to generate, transform and/or maintain visual mental images of the same type of stimuli. The final Stroop task pitted automatic (word reading) and controlled responses (color-naming) against one another and required selection between them.

We reasoned that if ACC is a component of a system important for executive control, then cingulotomy should impair performance on a given task to the extent that it demands controlled processing. According to current theories, controlled processing is necessary when tasks require one or more of the following — (1) the inhibition of prepotent responses or the mediation of response competition; (2) selection of underdetermined, novel, poorly learned, or technically difficult cognitive or behavioral responses or response sequences; (3) planning and decision making; and, (4) error correction and/or 'trouble shooting' [6,9,34,39,42]. As noted by Posner and DiGirolamo [39], ACC activation has been observed in all of these situations.

The tasks we selected varied in the extent to which their performance relied on these four types of controlled processing. For some tasks we expected that performance of the imagery version would be impaired after cingulotomy because generating or transforming an image requires a novel sequence of mental operations, or the instructions did not precisely specify which images to generate thereby making judgments of them less certain. For two tasks, we expected that cingulotomy should not affect performance of either the imagery or the perception versions because the task required only simple maintenance of an image, the objects to image were precisely specified, and the nature of the judgments upon them was clear. Finally, we expected that cingulotomy should impair performance on Stroop task trials that require mediation of response competition.

2. Methods

2.1. Participants

2.1.1. Cingulotomy patient

The patient (M.T.) was a 41-year-old, right-handed female college graduate who had completed 1 year of graduate professional training. She was diagnosed with obsessive compulsive disorder and co-morbid major depression and had a history of anorexia nervosa that had been stable for 4 years prior to cingulotomy. At age the 5, she was struck by an automobile in a pedestrian accident and suffered a head injury that resulted in loss of consciousness and one grand mal seizure. She took anti-seizure medication until age of 9, and since has had no history of abnormal EEG or CT or MRI scans. M.T. was recommended for cingulotomy after her OCD symptoms proved refractory to an exhaustive array of non-surgical interventions including behavioral therapy, electroshock therapy, and pharmacotherapy. She was on standing doses of Ritalin (10 mg, four times a day) and Prozac (40 mg, twice daily) that continued throughout her hospital stay. Pre-operative sedation included low doses of narcotic analgesics, some of which (droperidol and acetominophen with codeine) also were given for nausea the first day post-operatively. These drugs were last taken at least 48 h before post-operative testing. As shown in Figs. 1 and 2, her cingulotomy comprised three lesions per hemisphere. The second lesion was placed immediately superior, and the third was placed immediately lateral, to the first lesion. Lesions were located approximately 2.5 cm caudal to the genu of the corpus callosum. Although the precise Talairach coordinates for M.T.'s lesion are not available, analysis of morphometric MRI data from 9 cingulotomy patients collected 9 (± / − 6) months post-operatively showed that the centroid of the lesion volume in the right hemisphere was located at coordinates 9, 18, 30 in Talairach space. These coordinates should be taken as an approximation of the lesion location in M.T., and represent only one of her bilateral lesions, which were placed approximately symmetrically [40]. In addition to ablating portions of Brodmann areas 32 and 24, cingulotomy severs fibers of the cingulum bundle, which may disrupt communication between anterior and posterior regions. Two days before cingulotomy, she had a Yale–Brown Obsessive Compulsive Scale [21] score of 17 and a Beck Depression Inventory [5] score of 29, both of which were in the clinical range. At this time, M.T. also completed a battery of neuropsychological tests, which showed normal cognitive functioning. Her Full Scale WAIS-R [54] IQ of 97 (Verbal IQ = 99; Performance IQ = 93) was normal as was her performance on the Wechsler Memory Scale (Verbal = 97; Visual = 114; Delayed Recall = 118). On the Wisconsin card sorting task, she achieved five categories and made five perseverative errors. She scored 58 of 60 correct on the Boston Naming test and showed normal recall with no decay over a 30-min delay on the Rey Auditory–Verbal Learning test. Copying of the Rey–Osterreith figure showed attention to detail but some loss of overall form, which is typical of patients with obsessive compulsive disorder [41]. Finger tapping performance was normal with her dominant right hand but one standard deviation worse than the mean with her left hand. Her performance on the Trails B test was normal but one standard deviation worse than the mean on the Trails A test. EEG 1 year prior to cingulotomy and MRI 4 months pre-operatively were normal. Neurological exam 2 days pre-operatively also was normal.

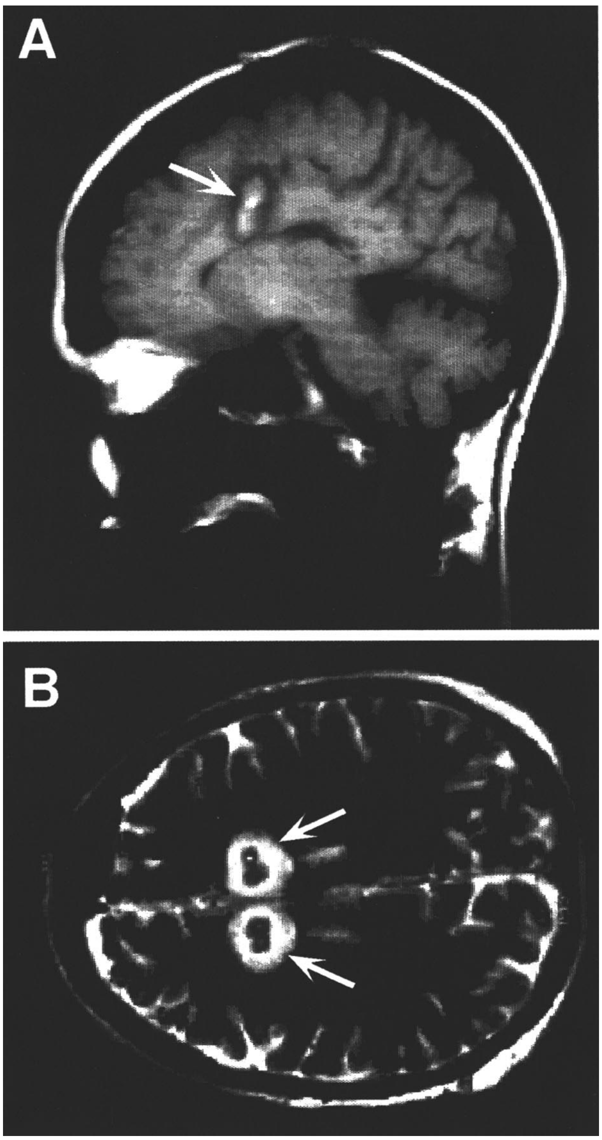

Fig. 1. Structural MRI scan of M.T. after bilateral anterior cingulotomy. Arrows indicate lesion location. (A) T1-weighted parasagittal section 7 mm to left of midline showing extent and location of lesion. (B) T2-weighted axial section showing bilateral cylindrical lesions.

2.1.2. Control participants

Normative data were obtained from eight right-handed female control participants, ages 35–42 years ($M = 38.9$, S.D. = 4.25), with an average of 15.9 years of education (range 14–18, S.D. = 1.26). All control participants denied a personal or family history of psychiatric illness or head injury resulting in loss or alteration of consciousness and were not taking prescription medications at the time of testing.

2.2. Task descriptions

The seven visual cognition tasks shared a common trial format (see Fig. 2). Each trial began when an exclamation point appeared in the center of the screen to alert participants that they should get ready for the next trial. Participants were instructed that when the exclamation point was present, they could press the spacebar to proceed, but should do so only if they were attentive and prepared for stimulus presentation. The stimulus was presented in the center of the screen 1 s after the spacebar was pressed and remained present until a response was made unless otherwise noted be-

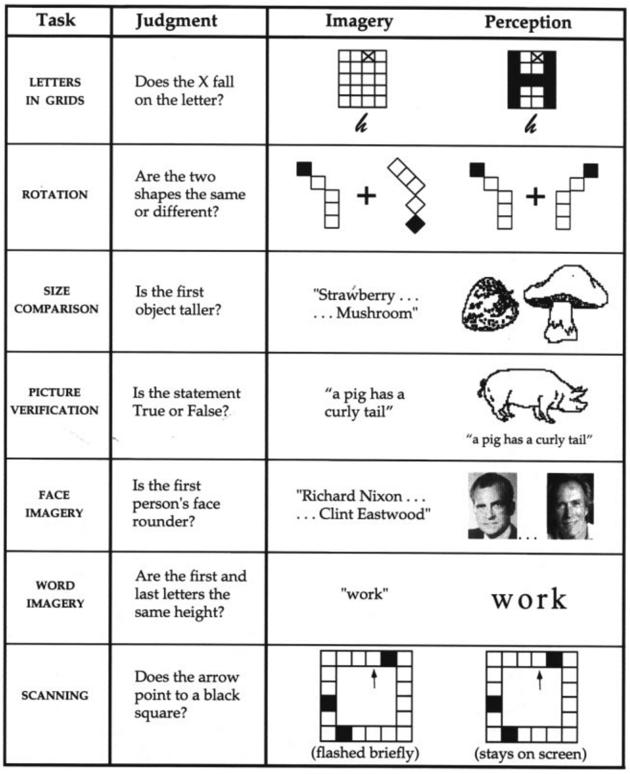

Fig. 2. Overview of stimuli and judgments for imagery and perception versions of the visual cognition tasks. Note that stimuli are not shown in their actual size and have been scaled down 50–70% for inclusion in this diagram.

low. Each task consisted of 16 trials with intertrial intervals of 1000 ms. Responses were a simple dichotomous choice (yes/no) made with the index and middle fingers of the right hand.

2.2.1. Letters in grids task

ACC has been activated during the generation of visual mental images of letters [24] and we selected the tasks used in that imaging study. The *grids* image generation task used by Kosslyn et al. [24] began with a training phase in which participants learned to draw four upper-case block letters within 4×5 grids. Participants studied the letters and reproduced them from memory in empty grids until all four could be drawn without error. In the imagery version of this task, an empty grid appeared on the screen with a lower-case cursive version of one of the four letters printed underneath. The participant's task was to visualize the corresponding upper-case version of the letter in the grid and then decide whether an X printed in the grid would lie on or off of that letter. In the perception version of this task the upper-case block letter was already present in the grid and participants needed only to inspect it to make their response. Prior to beginning the tasks, participants learned the letters J, H, S, and U. Prior research has shown that the imagery but not perception versions of both tasks require the sequential placement of letter segments during the image generation process [25]. The sequential placement of letter segments in the imagery versions of this task requires making decisions about where segments should be put, and also may require error-checking to verify that they have been placed correctly. Thus, we infer that executive processes should be employed here.

2.2.2. Mental rotation task

In the perception version, pairs of shapes composed of five connected squares were shown with one on each side of fixation. The top of each shape was designated by a black square. Both shapes were shown upright, and the right shape was either identical to or the mirror image of the shape on the left. The participant's task was to decide whether the shapes were identical as shown on the screen (i.e. mirror images were given a 'no' response). In the imagery version, the shape on the right was rotated either 45 or 90° from upright. Shepard and Metzler [43] showed that judgments in the imagery version are performed by first rotating one of the shapes until it is congruent with the other. Participants typically rotate the 'shortest way around,' and thus, must make a decision about which way to rotate. We, therefore, expected that the perception version would require only simple perceptual comparisons whereas the imagery version would draw on executive processes used in decision-making and also used to generate sequences of novel cognitive operations.

2.2.3. Size comparison task

In this task, the stimuli were the pairs of common objects (e.g. an orange and a baseball) and the participant's task was to decide whether the first object shown on the screen (perception version) or whose name was pronounced by the computer (imagery version) was larger than the second object. We expected that the imagery but not perception version would require executive processing because the imagery version did not precisely specify which exemplar of each named object should be imaged. Thus, the imagery version should require decision making, error checking, and conflict mediation whereas the perception version should not. Participants were instructed to imagine seeing a prototypical exemplar of each named object and to respond accordingly.

2.2.4. Picture verification task

In the perception version of this task a picture of an object (could be living, such as a pig, or man-made, such as a table) appeared in the center of the screen as the computer read aloud a statement about the physical characteristics of the object. Each six-word statement could be true or false (e.g. 'a pig has a curly tail'). The participant's task was to decide whether the statement was true or false based on their inspection of the picture. In the imagery version, only the statement was played. The statements all involved subtle visual properties of objects of the sort that previous research has shown required visual imagery in order to verify [17]. As in the size comparison task, we expected that the imagery but not the perception version would require decision making and error monitoring to select the particular object exemplars to visualize.

2.2.5. Facial shape task

In the perception version of this task, grayscale pictures of the faces of two famous individuals of the same-sex were shown side-by-side. The first face appeared just to the left of fixation 1 s before the second face was presented just to the right of fixation. The computer read aloud the name of each individual as his or her face was shown. The participant's task was to decide whether the overall shape of the first individual's face was rounder than the face of the second individual. Faces were selected to be perceptibly, but not obviously, different in overall degree of roundness. In the imagery version, only the names of individuals were presented. We expected that both the perception and imagery versions of this task could be performed by simply comparing the stimuli shown on the screen or that participants specifically were instructed to image. Sixteen different pairs of individuals were used for each task, with assignment of individuals to task versions counterbalanced across participants.

2.2.6. Word comparison task

In the perception version of this task, lower-case four letter words were presented and participants decided whether the first and last letters were the same height. In the imagery version, spoken word names were read aloud by the computer and participants generated mental images of the corresponding words. For example, a yes response would be given for the word, 'worm' whereas a no response would be given for the word, 'work'. We expected that this task would require relatively minimal executive processing because images of words could be generated holistically (i.e. retrieved from memory all in one piece) and judgments of letter height were unambiguous. Janer and Pardo [22] found that comparisons of simple perceptual characteristics were unaffected by cingulotomy.

2.2.7. Scanning task

In the perception version, a square ring was shown whose sides were composed of six smaller light or dark squares. Three of the squares were black and all others were light. On each trial, the locations of the darkened squares changed randomly and participants could study the ring for as long as was necessary to familiarize themselves with the locations of these squares. When they had done so (typically about 1500 ms) they were instructed to press the spacebar. An arrow was then presented in the center of the ring. The distance of the arrow from the ring varied from trial to trial and its head always pointed outwards towards the center of one of the squares. The participant's task was to decide whether the arrow was pointing to a black square. In the imagery version, the arrow was shown for only 500 ms, at which time, both the arrow and ring disappeared. Previous research has shown that this decision is made by scanning a mental image of the ring, from the arrow to the indicated square [8]. Because this task requires judgments of readily discernible perceptual characteristics, and in the imagery version the maintenance (but not generation) of a specific image, we did not expect it to invoke executive control.

2.2.8. Stroop task

We used a variant of the Stroop [46] task that randomly intermixed equal numbers ($N = 30$) of congruent, incongruent, and neutral trials. On congruent and incongruent trials participants named the print colors of single words presented in the center of the computer screen. Single words were the color names black, blue, green, brown, yellow and red. On congruent trials, print color matched the word name and on incongruent trials, print color and word name did not match (e.g. 'red' was printed in black). Incongruent trials are thought to require controlled selection of the color-naming response over a relatively automatic tendency to name the word. On neutral trials, participants named the color of a solid rectangle whose dimensions were the same as a five-letter word and were intended to provide a comparison condition in which little or no response competition would occur [29]. Color naming times were recorded by a microphone attached to the microphone port on the computer, and stimuli remained on the screen until a response was made. The inter-stimulus interval was 500 ms. We expected that the incongruent trials would require executive control to mediate or monitor the conflict between the desired color naming and undesired word naming responses [6,20,35].

2.3. Procedure

Pre-operative testing for M.T. was completed 2 days before the cingulotomy, and post-operative testing was completed 3 days after the operation was performed. Testing sessions took place in a private office at Massachusetts General Hospital. The MacLab program controlled stimulus presentation and data collection on a Macintosh Powerbook 170, which was placed on a table approximately 50 cm in front of the participant. At the start of each session, a practice task that demonstrated the basic testing and key pressing procedures for the visual cognition tasks was completed. Then the tasks were administered in the following order — picture verification, word comparison, mental rotation, scanning, letter in grids, size, Stroop, and facial shape. Control participants were tested with a 6-day interval between sessions using the same task sequence. Testing of control participants was completed at the psychology department at Harvard University in a testing room comparable to the room used for testing of M.T. in the hospital.

3. Results

3.1. Clinical indices

M.T. reported subjective improvement in her symptoms within 1 week following cingulotomy and a post-operative follow-up 5 years later indicated at least 55% improvement on clinical measures of compulsions and depression (pre-operatively, YBOCS = 17 and BDI = 29; 5 years later YBOCS = 7; and BDI = 5).

3.2. Cognitive performance

Response times and error rates from the imagery and perception versions of each of the seven visual cognition tasks were analyzed separately using two factor analyses of variance (ANOVAs) with Time of test (Time 1 vs. Time 2, which is pre- and post-operation for M.T.) as the within-participants factor and Group (M.T. vs. Control) as the between-participants factor. For the Stroop task, Trial type (congruent, incongruent or neutral) served as an additional within-participants factor. Mean response times and error rates for each task are shown in Figs. 3–5 and summarized in Table 1. For each participant, outlier response times were defined as those shorter than 150 ms and more than 2.5 standard deviations greater the mean response time for that participant in a specific task condition. Outliers comprised less than 6% of trials for each task and were removed and replaced with the mean of the remaining trials for that task condition.

3.3. Letters in grids

The data for these tasks are shown in the top panel of Fig. 3. As predicted, the ability to perform the sequential mental operations required to generate images of letters was impaired following cingulotomy. Only in the imagery version of the grids task was the change in M.T.'s performance from Time 1 (T1) and Time 2 (T2) different than the change observed for the controls. Response times increased for M.T. whereas response times actually decreased for controls, $F(1,7) = 5.35$, $P = 0.05$ for the interaction between group and testing session; in contrast, this interaction was not significant in the perception condition, $F < 1$. Changes in error rates were not significantly different between groups for either the imagery, $F(1,7) = 2.96$, $P = 0.13$, or the perception, $F < 1$, conditions. It is noteworthy that the trend toward a significant drop in accuracy for M.T. in the imagery condition is consistent with her slower response times.

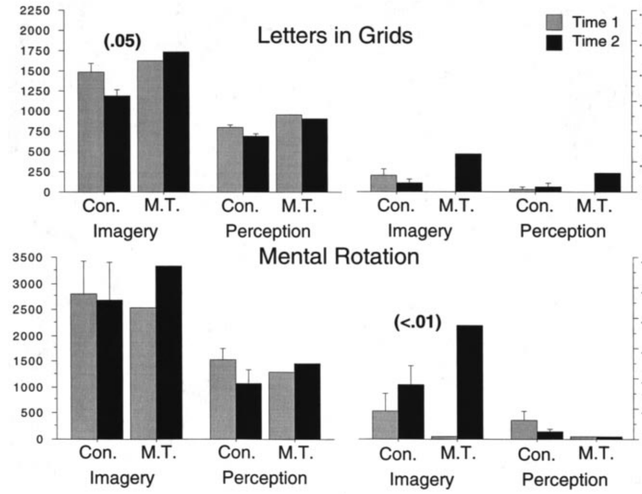

Fig. 3. Mean response times (in milliseconds) and mean accuracy as a function of Group (M.T. vs. controls), Time of test (T1 vs. T2), and task version (imagery or perception) for the letters in brackets tasks and mental rotation tasks. Bars show standard errors of the mean for control participants. Numbers in parentheses are significance values for the interaction of Group and Time of test for the imagery or perception version of the task. See text for details of analysis.

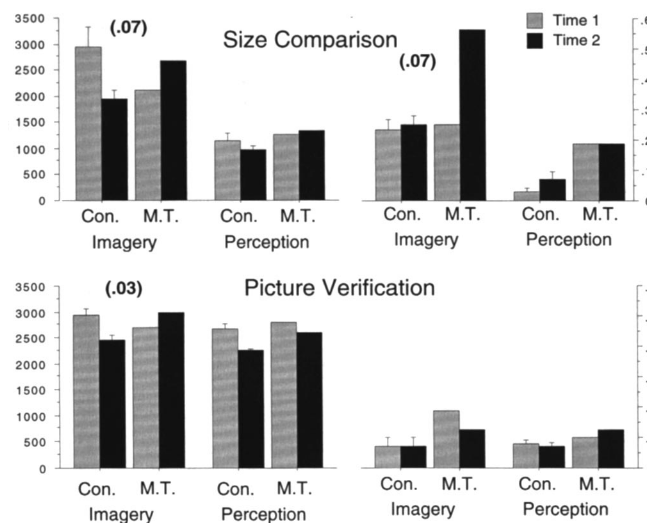

Fig. 4. Mean response times (in milliseconds) and mean accuracy as a function of Group (M.T. vs. controls), Time of test (T1 vs. T2), and task version (imagery or perception) for the size comparison and picture verification tasks. Bars show S.E.M. for control participants. Numbers in parentheses are significance values for the interaction of Group and Time of test for the imagery or perception version of the task. See text for details of analysis.

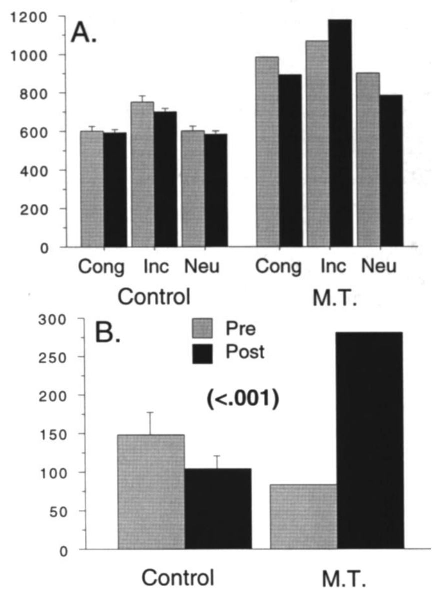

Fig. 5. (A) Mean response times (in milliseconds) a function of Group (M.T. vs. controls), Time of test (T1 vs. T2), and trial type (congruent, incongruent or neutral) for the Stroop task. (B) Mean amount of Stroop interference as a function of Group and Time of test. Interference is calculated by subtracting response times on congruent trials from response times on incongruent trials. Numbers in parentheses are the significance value for the interaction of Group and Time of test. See text for details of analyses.

3.3.1. Mental rotation task

We predicted that the necessity to decide which way to rotate and to perform a sequence of novel image transformations in the imagery version would be more difficult to perform after cingulotomy. In contrast to other tasks, this prediction was borne out not by response times, $F(1,7) = 1.09$, $P = 0.33$, but by an increase in errors for M.T. relative to controls, $F(1,7) = 12.52$, $P < 0.01$. Changes in response times and error rates in the perception condition were not significantly different between groups (both $F < 1$). The results from this task are shown in the bottom of Fig. 3.

3.3.2. Size comparison task

As predicted, the underdetermined search for objects to visualize in the imagery condition of this task had different effects for M.T. and controls — M.T.'s response times tended to be slowed whereas control response times tended to be speeded, $F(1,7) = 4.42$, $P = 0.07$. In addition, errors in the imagery condition were more frequent for M.T. than controls, $F(1,7) = 7.30$, $P = 0.03$, due to a drop in performance from T1 to T2 that was larger for M.T than for controls, $F(1,7) = 4.45$, $P = 0.07$. Performance in the perception condition also conformed to expectations — neither the change in response times, $F < 1$, nor the change in error rates, $F < 1$, was significantly different between groups, although overall M.T. made more errors than did controls, $F(1,7) = 7.58$, $P = 0.03$. The results from this task are shown in the top of Fig. 4.

3.3.3. Picture verification task

The underdetermined memory search required for the imagery version of this task became more difficult for M.T. after the operation. Relative to the change in performance shown by controls, her response times slowed significantly, $F(1,7) = 7.79$, $P = 0.03$, and the change in frequency of errors was no different, $F(1,7) = 1.57$, $P = 0.26$. Between-group changes in performance in the perception condition were not significant for response times, $F < 1$, or for error rates, $F(1,7) = 1.57$, $P = 0.25$. The results from this task are shown in the bottom of Fig. 4.

3.3.4. Facial shape task

The data for one control participant were lost due to computer error. Analyses of the data from seven controls confirmed our prediction that response times in neither the imagery $F(1,6) = 4.45$, $P = 0.08$, nor the perception, $F < 1$, conditions of the task would be slowed differentially for M.T. relative to controls. Changes in error rates for M.T. did not differ significantly from those for controls for either version of the task (both $F < 1$). The results from this task are shown in the top of Table 1.

3.3.5. Word comparison task

Performance on the word comparison task also conformed to expectations. This task was not expected to draw heavily on executive processing, and in neither the imagery nor the perception conditions did response times vary between groups (imagery, $F(1,7) = 1.27$, $P = 0.30$; perception, $F < 1$). Similarly, in neither the imagery nor the perception conditions did error rates vary between the two groups ($F < 1$ in both cases). These data are shown in the middle of Table 1.

3.3.6. Scanning task

Our expectation that performance on this task would be unaffected by cingulotomy was borne out in the imagery condition, for which response times and error rates showed similar changes for M.T. and controls (both $F < 1$). This prediction was not borne out, however, in the perception condition, for which M.T.'s error rates increased at T2 much more than did controls, $F(1,7) = 70.89$, $P < 0.0001$. On half the trials, the arrow cue appeared close (0.5 cm) to the ring and on half the trials, the cue was far (2 cm) from the ring. Inspection of error trials revealed that all incorrect responses were made when the arrow cue was far from the ring, suggesting a deficit in the ability to shift attention. Overall, M.T.'s response times ($M = 931.57$ ms, $SE = 101.57$) tended to be slower than those of the controls ($M = 809.34$ ms, $SE = 26.00$), $F(1,7) = 4.39$,

$P = 0.07$, and dropped at T2 to the same degree as did control's response times, $F < 1$ for the interaction of group and session. The results from this task are shown in the bottom of Table 1.

3.3.7. Stroop task

Incorrect color name responses were extremely rare for both M.T. and controls (2% of trials for M.T. and < 1% for controls) and these trials were excluded from analyses. The overall ANOVA on response times with Group, Time of test, and Trial type as factors indicated that M.T.'s response times ($M = 967$ ms) were generally slower than those of the controls ($M = 638$ ms), $F(1,7) = 28.17$, $P < 0.001$. A significant main effect of Trial type, $F(1,7) = 109.38$, $P < 0.0001$, indicated that response times were different for incongruent, congruent, and neutral trials. Planned contrasts showed the standard Stroop effects — response times were longer for incongruent ($M = 768$ ms) than either congruent ($M = 635$ ms), $F(1,7) = 114.04$, $P < 0.0001$, or neutral trials ($M = 620$ ms), $F(1,7) = 201.69$, $P < 0.0001$, and that congruent trial response times in turn were longer for than those for neutral trials, $F(1,7) = 12.41$, $P < 0.01$.

More importantly, the incongruent trials of the Stroop task were expected to place the greatest demands on executively-mediated selection among competing responses, and the results supported this prediction. A significant three way interaction of Group, Time of test and Trial type, $F(1,14) = 28.17$, $P < 0.001$, indicated that the change in response times from T1 to T2 was different for the two groups. To determine exactly how response time changes differed, difference scores were calculated for each trial type by subtracting response times at T2 from those at T1, and then conducting separate one way ANOVAS on the difference scores for each trial type with Group as the only factor. As shown by the top panel of Fig. 5, these analyses revealed that whereas response times in the incongruent condition decreased slightly for controls they actually lengthened for M.T., $F(1,7) = 7.34$, $P < 0.03$. In addition, whereas response times for controls on congruent and neutral trials also decreased slightly, response times for M.T. tended to decrease even more (congruent, $F(1,7) = 3.9$, $P = 0.09$; neutral, $F(1,7) = 4.36$, $P = 0.08$).

The traditional measure of interference in the Stroop task is the difference in response times between incongruent and congruent trials, and an ANOVA was per-

Table 1
Mean response times and error rates for controls and M.T. in the facial shape, word comparison, and scanning tasks[a]

Task, measure, group	Imagery		Perception	
	T1	T2	T1	T2
Facial shape				
Response times				
Controls	2361 (267)	1883 (184)	1525 (125)	1173 (115)
M.T.	1978	2183	1840	1612
Error rates				
Controls	0.26 (.05)	0.23 (.05)	0.11 (.04)	0.06 (.04)
M.T.	0.31	0.31	0.19	0.06
Word comparison				
Response times				
Controls	1921 (61)	1866 (111)	1091 (65)	1018 (63)
M.T.	1830	2100	1022	1174
Error rates				
Controls	0.15 (.06)	0.09 (.02)	0.07 (.03)	0.06 (.03)
M.T.	0.13	0.25	0.13	0.19
Scanning				
Response times				
Controls	753 (40)	652 (47)	890 (31)	729 (11)
M.T.	811	631	1033	830
Error rates				
Controls	0.07 (.03)	0.07 (.03)	0.01 (.01)	0.00 (0.0)
M.T.	0.06	0.13	0.01	0.19[b]

[a] T1, time 1; T2, time 2. Response times are in milliseconds. S.E.M. is shown in parentheses.

[b] Significant impairment of M.T. at T2 relative to controls, $P < 0.0001$; all other effects are non-significant.

formed using these response differences as the dependent measure and Group and Time of test as factors. As shown in the bottom panel of Fig. 5, this analysis revealed that whereas interference decreased across testing sessions for controls (T1 $M = 148$ ms, T2 $M = 104$ ms), interference increased for M.T. (T1 $M = 83$ ms, T2 $M = 282$ ms), $F(1,7) = 55.12$, $P < 0.0001$.

4. Discussion

The present results are consistent with the hypothesis that ACC is part of an executive system responsible for controlling behavior in a variety of domains. After cingulotomy, M.T.'s performance was impaired on a variety of tasks that required different kinds of controlled processing. Thus, M.T. showed post-operative impairments (1) when generating multi-part mental images (letters in grids task) and mentally transforming perceptual input (mental rotation task), both of which required generation of novel sequences of mental operations; (2) during the search for and selection of images to generate when this search was underdetermined by task instructions (picture verification and size comparison tasks); and, (3) when a novel response had to be selected over a prepotent one (incongruent trials of Stroop task). In general, following cingulotomy, there was neither impaired performance of tasks that required only the inspection and comparison of clearly defined stimulus characteristics, nor was there impaired performance of tasks that clearly specified which images should be generated and compared (facial shape, word comparison, scanning).

4.1. Relation to other findings

The present findings provide convergent evidence for theories of cingulate function derived from neuroimaging studies that have shown ACC activation in a number of situations that require controlled processing [6,9,31,34,39]. A strength of this study is that the theoretically significant cognitive effects of cingulotomy were detected against a backdrop of normal pre-operative task performance. The establishment of a normal pre-operative baseline was particularly important for M.T. because depressed patients may exhibit deficits in executive functioning [51]. These findings also fit with studies of non-human primates that suggest that ACC is important for the sequencing [45], self-organization [48], and error-driven acquisition [7] of motor responses.

It is noteworthy that M.T.'s performance of the Stroop task was slowed only on incongruent trials (response times were speeded for congruent ones), and that the overall amount of Stroop interference increased after the operation. This finding is exactly what would be predicted if ACC is part of an executive system responsible for mediating response competition. The only previously published case report of a psychiatric cingulotomy patient also included the Stroop task [22], but found slowing on only the congruent trials post-operatively. One reason for this discrepancy could be that they blocked congruent and incongruent trials separately whereas we intermixed them randomly. Blocking of trial types could reduce response competition on incongruent trials and promote speeding of responses on congruent trials [29]. If ACC not only helps mediate competing responses, but also facilitates congruent ones, then slowing on congruent trials could reflect a deficit in the latter process.

Recent work has shown that ACC may be divided into a number of distinct, but related, functional subregions, which suggests that discrepancies between the present results and those of Janer and Pardo [22] could be due to individual variability in the topography of ACC and the fact that M.T.'s cingulotomy lesioned a larger area of cortex. Patterns of neural connectivity in combination with functional neuroimaging and lesion studies indicate that dorsal, pregenual (anterior to the genu of the corpus callosum) and subgenual regions of ACC are involved in tasks tapping cognitive, affective and visceromotor functions, respectively [9,10,37,53,55]. A recent case study of patient with a right ACC lesion showed deficits on executive-related tasks when using manual but not vocal responses [50], which supports the idea that the effects of cingulotomy on performance may depend upon the particular subregion that is damaged. Although it cannot precisely be determined which subdivision(s) were damaged by M.T.'s cingulotomy, it is most likely that the operation lesioned the dorsal cognitive, and possibly portions of the affective, division of ACC [40].

4.2. The specific functional role of anterior cingulate cortex

Although the present results are consistent with theories of ACC function which suggest that it is part of an executive control system, they do not indicate which specific functions ACC carries out. Placed in a broader theoretical context, however, they fit with suggestions that ACC is important for monitoring on-going performance and determining whether one's behaviors or thoughts fit with current goals and needs [6,7,9,34]. This evaluative process serves the important function of indicating when control should be exerted [6,11,32,34]. From this perspective, ACC may monitor the goal-related significance of stimuli and signal when behavioral change and re-orientation of attention is required, but is not responsible for making those changes. Other components of the executive system, perhaps located in prefrontal cortex, interpret ACC signals to determine whether and how behavior in fact should be continued, changed, or stopped [6,18,30]. In this way, ACC signals may help to fine tune cognitive performance by keeping behavior 'on-track'. When ACC is lesioned, the rest of the executive system is not disrupted permanently and can learn to compensate for the loss of these signals, which could explain why behavioral deficits following cingulotomy often resolve over time [12,22].

4.3. Relationship between cognitive deficits and clinical improvement

As is observed commonly for cingulotomy patients [1–3,44], M.T. experienced a post-operative decrease in her obsessive-compulsive symptoms, depression, and other negative emotions in the weeks following cingulotomy and these improvements continued over time. Exactly how these emotional improvements relate to changes in executive control is not clear presently, but it is possible that they are experiential correlates of damage to the monitoring and evaluation process described above. The absence or decrease of signals indicating that behavior should change may be essential for facilitating improvement of emotional disorders (cf. [20]). The relationship between post-operative cognitive deficits and long-term clinical improvement observed here is, of course, correlational and not causal, but does suggest potential avenues for future research.

4.4. Limitations of the present study

The present results are qualified most significantly by the limited sample on which they are based. In addition, M.T. suffered a traumatic brain injury early in life, and was taking antidepressant medications at the time of testing. The facts that M.T.'s drug dosages remained constant, that she had no history of abnormal EEG, CT or MRI scans, and that she showed normal intelligence and memory as well as normal pre-operative performance suggest that these factors may not have had a significant impact on her cognitive performance. It also is worth noting that in some tasks, performance of the controls actually improved across testing sessions whereas M.T.'s performance either remained constant or declined. This suggests that inter-session consolidation of learning contributed to performance improvements for controls, but was disrupted by the surgical procedure for M.T. Although we cannot completely rule out any contribution of disrupted consolidation to our results, this account does not explain why M.T.'s response times decreased in the second testing session in both conditions of the scanning task and in the congruent and neutral blocks of the Stroop task. In addition, the selectivity of deficits on tasks predicted to show impairments and the absence of generalized increases in response times or error rates, argues against a generalized disruption of consolidation caused by cingulotomy.

4.5. Task difficulty

Another alternative interpretation of the present results is that cingulotomy selectively impaired performance of the more difficult versions or trials of each task. We consider this explanation unlikely for two reasons [4,9]. First, if cingulotomy simply impaired performance of the more difficult versions of tasks then performance in the imagery condition in the word comparison task should have been affected. However, performance of neither the imagery nor the perception conditions in this task were disrupted by cingulotomy, as was predicted on a priori theoretical grounds. Second, M.T.'s post-operative performance on the scanning task was less accurate in the perception condition but was unchanged in the imagery condition. This is noteworthy because the imagery version of this task places the additional demand of maintaining a visual image in working memory, which presumably would make it more difficult than the perception version. Furthermore, although the perception performance deficit was not expected, it is consistent with M.T.'s deficits on the Stroop task, which requires shifting attention away from one stimulus attribute and toward another. In the scanning task, participants were allowed to study the ring of squares prior to presentation of the arrow cue. When the arrow cue appeared, attention first had to be disengaged from the ring, then shifted to the arrow, and finally shifted back to the ring square indicated by the arrow. In the perception version of the task, M.T. may have been 'stimulus bound,' having trouble shifting attention away from the ring to the arrow cue — a problem which may have been eliminated in the imagery version because the ring disappeared from the screen. The fact that all of M.T.'s errors were made on trial, in which the arrow cue appeared far away from the ring is consistent with this account.

4.6. Conclusions

The present case study provides additional support for the role of ACC in executive control more generally, and evaluating the need for control more specifically. The dissociation among the different imagery tasks also provides support for the view that imagery is not a single, undifferentiated function, but rather relies on a host of neural processes — many of which are mediated by distinct parts of the brain. Future work with larger samples of patients are needed to extend and confirm these findings. Future research also could examine more closely the relationship between the cognitive and emotional effects of cingulotomy to determine whether damage to a common process is responsible for botheffects.

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References

[1] Baer L, Rauch SL, Ballantine HT, Martuza R, Cosgrove R, Cassem E, Giriunas I, Manzo P, Jenike MA. Cingulotomy for intractable obsessive–compulsive disorder: prospective long-term follow-up of 18 patients. Archives of General Psychiatry 1995;525:384–92.

[2] Ballantine HT, Cassidy WC, Brodeur J, Giriunas IB. Frontal cingulotomy for mood disturbance. In: Hitchcock E, Laitinen L, Vearnet K, editors. Psychosurgery. Springfield, IL: Charles C. Thomas, 1972:221–8.

[3] Ballantine HT, Bouckons AJ, Thomas EK, Giriunas IE. Treatment of psychiatric illness by stereotactic cingulotomy. Biological Psychiatry 1987;22:807–19.

[4] Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 1997;3510:1373–80.

[5] Beck AT, Steer RA. Beck Depression Inventory Manual. San Antonio, TX: Psychological Corporation, 1987.

[6] Botvinick MM, Braver TS, Carter CS, Barch DM, Cohen JD. Evaluating the demand for control: anterior cingulate cortex and cross-talk monitoring. Carnegie-Mellon University Technical Report, 1999.

[7] Brooks VB. How does the limbic system assist motor learning? A limbic comparator hypothesis. Brain Behavior and Evolution 1986;29:29–53.

[8] Brown HD, Kosslyn SM, Dror IE. Aging and scanning of imagined and perceived visual images. Experimental Aging Research 1998;24:181–94.

[9] Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL. The counting Stroop: an interference task specialized for functional neuroimaging — validation study with functional MRI. Human Brain Mapping 1998;6:270–82.

[10] Bush G, Luu P, Posner M. Cognitive and emotional influences in cingulate cortex. Trends in Cognitive Sciences 2000;4:215–22.

[11] Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex error detection and the online monitoring of performance. Science 1998;280:747–9.

[12] Cohen RA, Kaplan RF, Moser DJ, Jenkins MA, Wilkinson H. Impairments of attention after cingulotomy. Neurology 1999;53:819–24.

[13] Corkin S. Hidden-figures-test performance: lasting effects of unilateral penetrating head injury and transient effects of bilateral cingulotomy. Neuropsychologia 1979;17:585–605.

[14] Corkin S. A prospective study of cingulotomy. In: Valenstein E, editor. The Psychosurgery Debate. San Francisco: Freeman, 1980:164–204.

[15] Corkin S, Twitchell TE, Sullivan EV. Safety and efficacy of cingulotomy for pain and psychiatric disorder. In: Hitchcock ER, Ballantine HT, Meyerson BA, editors. Modern Concepts in Psychiatric Surgery. New York: Elsevier/North-Holland, 1979:253–72.

[16] Damasio AR, Van Hoesen GW. Emotional disturbances associated with focal lesions of the limbic frontal lobe. In: Heilman KH, Satz P, editors. Neuropsychology of Human Emotion. New York: Guilford Press, 1986:85–110.

[17] Eddy JK, Glass AL. Reading and listening to high and low imagery sentences. Journal of Verbal Learning and Verbal Behavior 1981;20:333–45.

[18] Gehring GW, Knight RT. Prefrontal–cingulate interactions in action monitoring. Nature 2000;3:516–20.

[19] Gehring WJ, Goss B, Coles MG, Meyer DE, Donhin E. A neural system for error detection and compensation. Psychological Science 1993;4:385–90.

[20] George MS, Ketter TA, Parekh PI, Rosinsky N. Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). Journal of Neuropsychiatry and Clinical Neurosciences 1997;9:55–63.

[21] Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale–Brown obsessive compulsive scale: development use and reliability. Archives of General Psychiatry 1989;46:1006–11.

[22] Janer KW, Pardo JV. Deficits in selective attention following bilateral anterior cingulotomy. Journal of Cognitive Neuroscience 1991;3:231–41.

[23] Kosslyn SM. Image and Brain: The Resolution of the Imagery Debate. Cambridge, MA: MIT Press, 1994.

[24] Kosslyn SM, Alpert NM, Thompson WL, Maljkovic V, Weise SB, Chabris CF, Hamilton SE, Rauch SL, Buonano FS. Visual mental imagery activates topographically organized visual cortex: PET investigations. Journal of Cognitive Neuroscience 1993;5:263–87.

[25] Kosslyn SM, Cave CB, Provost DA, von Gierke SM. Sequential processes in image generation. Cognitive Psychology 1988;20:319–43.

[26] Laplane D, Talairach J, Meininger V, Bancaud J, Orgogozo M. Clinical consequences of corticectomies involving the supplementary motor area in man. Journal of the Neurological Sciences 1977;34:301–16.

[27] LaPlane D, Degos JD, Baulac M, Gray F. Bilateral infarction of the anterior cingulate gyri and of the fornices. Journal of the Neurological Sciences 1981;51:289–300.

[28] Long CJ, Pueschel K, Hunter SE. Assessment of the effects of cingulate gyrus lesions by neuropsychological techniques. Journal of Neurosurgery 1978;49:264–71.

[29] MacLeod CM. Half a century of research on the Stroop effect: an integrative review. Psychological Bulletin 1991;109:163–203.

[30] McDonald AW, Cohen JD, Stenger VA, Carter CS. Dissociating the role of dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 2000;288:1835–8.

[31] Mesulam MM. A cortical network for directed attention and unilateral neglect. Annals of Neurology 1981;10:309–23.

[32] Nemeth G, Hegedus K, Molnar L. Akinetic mutism associated with bicingular lesions: clinicopathological and functional anatomical correlates. European Archives of Psychiatry and Neurological Sciences 1988;237:218–22.

[33] Nielsen JM, Jacobs LL. Bilateral lesions of the anterior cingulate gyri. Bulletin of the Los Angeles Neurological Society 1951;16:231–4.

[34] Ochsner KN, Feldman-Barrett L. A multiprocess perspective on the neuroscience of emotion. In: Mayne TJ, Bonnano G (Ed.). Emotion: Current Issues and Future Directions. New York: Guilford Press, in press.

[35] Pardo JV, Pardo PJ, Janer KW, Raichle ME. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proceedings of the National Academy of Sciences 1990;87:256–9.

[36] Paus T, Koski L, Caramanos Z, Westbury C. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience 1998;9:37–47.

[37] Petit L, Courtney SM, Ungerleider LG, Haxby JV. Sustained activity in the medial wall during working memory delays. Journal of Neuroscience 1998;1822:9429–37.

[38] Pillay PK, Hassenbusch SJ. Bilateral MRI-guided stereotactic cingulotomy for intractable pain. Proceedings of the American Society for Stereotactic and Functional Neurosurgery 1992;59:33–8.

[39] Posner MI, DiGirolamo GJ. Executive attention: conflict target detection and cognitive control. In: Parasuraman R, editor. The Attentive Brain. Cambridge, MA: The MIT Press, 1998:401–23.

[40] Rauch SL, Kim H, Makris N, Cosgrove GR, Cassem EH, Savage CR, Price B, Nierenberg AA, Shera D, Baer L, Caviness V, Jenike MA, Kennedy DN. Volumetric reduction in caudate nucleus following stereotactic lesions of anterior cingulate cortex in humans: a morphometric magnetic resonance imaging study. Journal of Neurosurgery (provisionally accepted, pending revision).

[41] Savage CR, Deckersbach T, Wilhelm S, Rauch SL, Baer L, Reid T, Jenike MA. Strategic processing and episodic memory impairment in obsessive compulsive disorder. Neuropsychology 2000;14:1–11.

[42] Shallice T, Burgess P. Supervisory control of action and thought selection. In: Baddeley AD, Weiskrantz L, editors. Attention: Selection, Awareness, and Control: A Tribute to Donald Broadbent. Oxford: Oxford University Press, 1993:171–81.

[43] Shepard RN, Metzler J. Mental rotation of three-dimensional objects. Science 1971;171:701–3.

[44] Spangler WJ, Cosgrove GR, Ballantine HT, Cassem EH, Rauch SL, Nierenberg A, Price BH. MRI-guided stereotactic cingulotomy for intractable psychiatric disease. Neurosurgery 1996;38:1071–6.

[45] Stern CE, Passingham RE. The nucleus accumbens in monkeys (*Macaca fascicularis*): I. The organization of behavior. Behavioural Brain Research 1994;61:9–21.

[46] Stroop JR. Studies of interference in serial verbal reactions. Journal of Experimental Psychology 1935;18:643–62.

[47] Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH. Multiple representations of pain in human cerebral cortex. Science 1991;251:1355–8.

[48] Thaler D, Chen Y-C, Nixon PD, Stern CE, Passingham RE. The functions of medial premotor cortex: I. Simple learned movements. Experimental Brain Research 1995;102:445–60.

[49] Tow PM, Whitty CWM. Personality changes after operations on the cingulate gyrus in man. Journal of Neurology Neurosurgery and Psychiatry 1953;16:186–93.

[50] Turken AU, Swick D. Response selection in the human anterior cingulate cortex. Nature 1999;2:920–4.

[51] Veiel HOF. A preliminary profile of neuropsychological deficits associated with major depression. Journal of Clinical and Experimental Neuropsychology 1997;19:587–603.

[52] Vilkki J. Changes in perception and memory after three different psychosurgical operations. Neuropsychologia 1980;19:553–63.

[53] Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cerebral Cortex 1992;6:435–43.

[54] Wechsler D. Manual for the Wechsler Adult Intelligence Scale — revised. New York: The Psychological Corporation, 1981.

[55] Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL. The Emotional Counting Stroop paradigm: an FMRI probe of the anterior cingulate affective division. Biological Psychiatry 1998;44:1219–28.