Deficits in Selective Attention Following Bilateral Anterior Cingulotomy

Kevin W. Janer
Washington University

José V. Pardo
Washington University School of Medicine

Abstract

■ Positron emission tomographic (PET) studies of normal humans undergoing specific cognitive activation paradigms have identified a region of the anterior cingulate cortex as a component of an anterior, midline attentional system involved in high-level processing selection. However, deficits in attention have not been demonstrated in patients following bilateral anterior cingulotomy, a procedure that results in lesions of adjacent anterior cingulate cortex. Task paradigms used in PET studies that recruit the anterior cingulate cortex were applied to normal, control subjects and to a patient before and after cingulotomy to provide highly sensitive and functionally targeted reaction time measures of attentional performance. In contrast to unchanged performance in several neuropsychological measures, this patient demonstrated specific deficits in attention during the subacute postoperative period, which resolved spontaneously several months after surgery. Such impairment is consistent with the evolving view of the anterior cingulate's involvement in high-level processing selection. These data show the feasibility of using information from PET activation studies of normals in the design of novel chronometric tasks useful for probing abnormalities in specific cognitive operations associated with discrete cortical regions. ■

INTRODUCTION

The anterior cingulate (Brodmann areas 24 and 32) is an extensive cortical region defined traditionally as paralimbic and implicated vaguely in various aspects of higher brain function such as affect, attention, memory, and higher order autonomic integration (Mesulam, 1985). Neurophysiological studies of the primate anterior cingulate cortex identify an important role in the cerebral organization of emotional utterances (Jürgens, 1986). Stimulation of the human anterior cingulate cortex can result in involuntary movements (Talairach, Bancaud, Geier, Bordas-Ferrer, Bonis, Szikla, & Rusu, 1973) reminiscent of the motor tics seen in Tourette's disorder; preliminary functional neuroimaging studies of Tourette's patients show anterior cingulate hypometabolism (Chase, Geoffrey, Gillespie, & Burrows, 1986). Case reports of limited bilateral anterior cingulate infarctions suggest impairments in attention; more extensive anterior cingulate infarctions produce akinetic mutism (Laplane, Degos, Baulac, & Gray, 1981; Németh, Hegedüs, & Molnár, 1988). However, neuropsychological studies of patients with selective, stereotactic, bilateral anterior cingulotomies—performed occasionally for intractable depression, obsessive-compulsive disorder, or pain syndrome—are notable for the sparing of damage to higher brain functions (Ballantine, Levy, Dagi, & Giriunas, 1977; Corkin, Twitchell, & Sullivan, 1979; Vasko & Kullberg, 1979). The most consistent deficits are difficulties in visuospatial processing during postoperative periods ranging from 1 week to several months. There are no lasting neurological or behavioral deficits (Corkin et al., 1979). The personalities of these patients are preserved and the level of function is often much improved following amelioration of the underlying symptomatology (Ballantine et al., 1977).

Several recent positron emission tomographic (PET) studies of normal subjects performing cognitive activation paradigms have detected robust activation in a region of the anterior cingulate cortex (Pardo, Pardo, Janer, & Raichle, 1990; Petersen, Fox, Posner, Mintun, & Raichle, 1988, 1989; Posner, Petersen, Fox, & Raichle, 1988). To date, this area of the anterior cingulate, overlying the anterior one-third of the corpus callosum, has been activated only in tasks demanding the highest levels of processing selection. For example, reading of visually presented words does not significantly activate the areas of the anterior cingulate that are recruited during the generation of verbs to the same visually presented nouns; the latter task would represent higher level processing selection. The evolving perspective from the neuroimaging work is that at least part of the anterior cingulate appears to be a component of an anterior, midline attentional system involved in selective attention (Pardo et al., 1990; Posner, Petersen, Fox, & Raichle, 1988); more specifically, the anterior cingulate has been hypothesized to be involved in the selection of cognitive procedures. How, then, can cingulotomy patients be so unimpaired during postoperative periods ranging from 1 week to several months?

One possibility is that the typical cingulotomy might not lesion the specific region of the anterior cingulate cortex that is involved with attention. The PET studies of attention in normals, which are based on data averaged across several individuals, demonstrate activation of several foci spanning at least 20–30 mm and overlying the anterior one-third of the corpus callosum—areas usually lesioned by anterior cingulotomy. However, whether these foci reflect anatomical heterogeneity of attentional processing regions across individual subjects is unknown. Alternately, patients may develop recovery of function. Regardless of mechanisms, recovery is more likely with small lesions particularly if spaced temporally apart—the usual approach when cingulotomies are performed (Finger & Stein, 1982). Finally, classical neuropsychological measures may not be sensitive enough to detect specific, subtle processing impairments associated with small, focal lesions.

Among the most sensitive measures of cognitive processing performance are chronometric, or reaction time, techniques (Posner, 1986). These methods can detect significant processing deficits in the range of tens of milliseconds. For example, schizophrenic patients show right visual field hemineglect as assessed in this manner; yet, such deficits were not evident previously using traditional neurological and neuropsychological examinations (Posner, Early, Reiman, Pardo, & Dhawan, 1988).

This report describes the modification of several PET task paradigms known to activate the anterior cingulate so as to probe sensitively, and in a targeted approach, selective attentional processing of a patient before and after bilateral anterior cingulotomy. The data demonstrate that during the subacute postoperative period, the patient does have attentional processing impairments consistent with the anterior cingulate's role in high-level processing selection. These deficits resolve spontaneously several months after surgery. In contrast, the patient performed normally during both subacute and chronic postoperative periods on a variety of other cognitive and behavioral measures. The patient's attention deficits cannot be explained as a nonspecific effect of surgery since a subsequent second cingulotomy directed more anteriorly within the anterior cingulate did not result in performance decrements.

The strategy used here illustrates the potential for developing sensitive chronometric neuropsychological probes of targeted cognitive operations and their associated cortical regions, based on information from PET activation studies of normals. This approach permits the detection of subtle and transient forms of cerebral dysfunction at both anatomical and functional resolutions not readily achieved by existing, classical neuropsychological assessment techniques.

RESULTS

Statistical analyses on the anterior cingulate processing probes included analysis of variance (ANOVA) for repeated measures with Bonferroni post hoc means comparison t tests and paired comparisons t tests for examination of between subjects effects. Significant within subjects effects were further elucidated via post hoc analysis of variance of contrast variables. The factor "Status" represents the comparison of subjects from the first or preoperative testing (Time 1), which occurred 1 week prior to surgery, to the second or subacute postoperative testing (Time 2), which occurred 3 weeks later (i.e., 2 weeks postoperatively). The factor "Diagnosis" distinguishes the patient from the control subjects (N = 10).

Magnetic Resonance Imaging

The patient's preoperative MRI examination was normal. Her postoperative MRI examination, obtained 5 months after stereotactic cingulotomy, delineates the extent and location of the bilateral lesions of the anterior cingulate cortex, the cingulum, and the corpus callosum (Fig. 1). The anterior cingulate cortex lesions coincide with the regions activated during PET studies of attentional processing in normal subjects.

Semantic Monitoring (Task A)

Subjects performed a reaction time task in which they made dichotomous decisions as to whether a visually presented noun was or was not a dangerous animal (see Methods). A three-way analysis of variance (Diagnosis × Status × Word Category) was performed to compare the patient's performance with that of the controls from Time 1 to Time 2 (3 weeks later) for each condition. Figure 2 summarizes the performances of all subjects on this task. An interaction of Diagnosis by Status by Word Category, $F(3,27) = 4.75, p < .009$, indicates that the change in the patient's performance on this task from pre- to postoperative status differed from the change in performance for the normals. Two-way interactions of Diagnosis by Status, $F(1,9) = 13.4, p < .005$, and Diagnosis by Word Category, $F(3,27) = 4.8, p < .008$, further reveal that the patient's and normals' performances differ from each other from Time 1 to Time 2, as well as across the four Word Category conditions, respectively. A main effect of Word Category, $F(3,27) = 49.0, p < .0001$, is attributable to overall differences in reaction time between the four Word Categories. Dichotomous decision-making in the ambiguous category (possibly dangerous animal), which

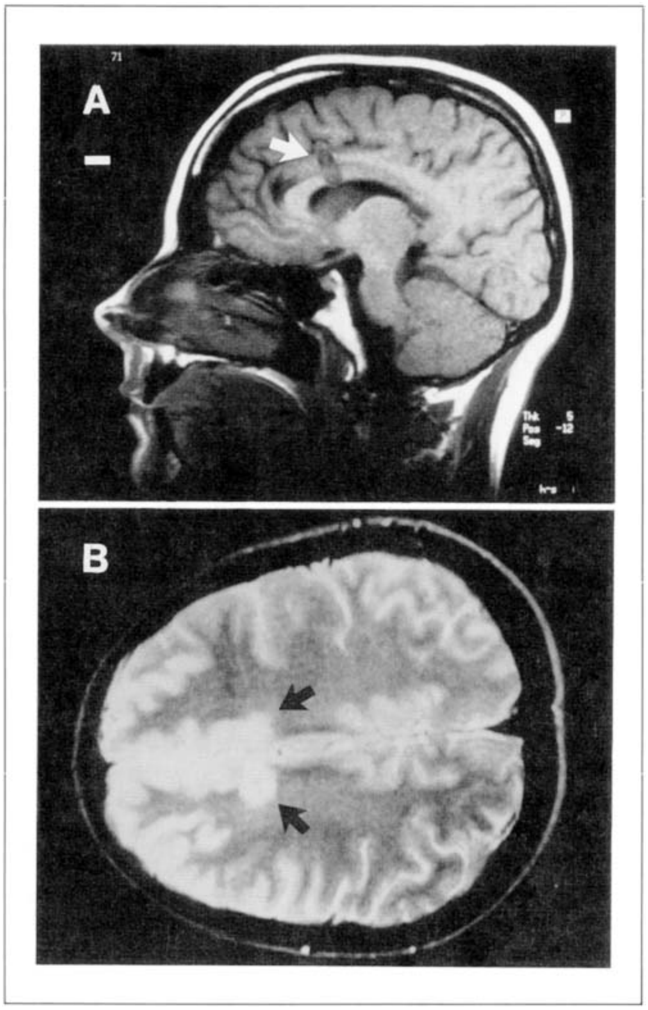


Figure 1. MRI scan of the patient after stereotactic, bilateral anterior cingulotomy. (**A**) Parasagittal section demonstrating lesion extent and location (arrow). (**B**) Axial section showing bilateral cylindrical lesions within the anterior cingulate cortex (arrows). Bar = 10 mm.

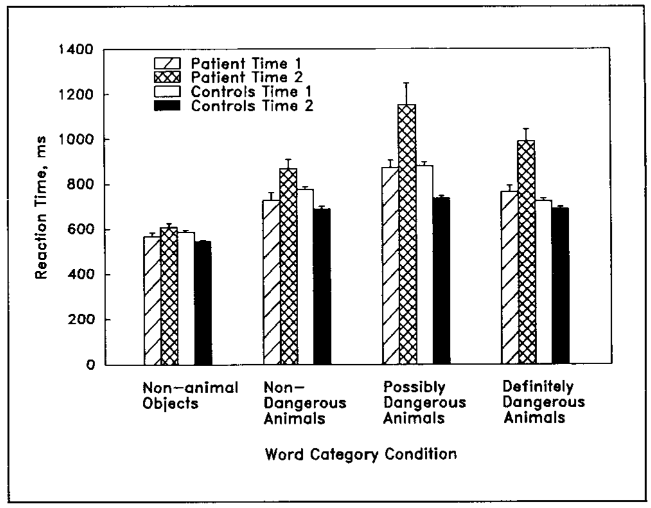


Figure 2. Task A. Reaction time means for dichotomous decisions about the "dangerousness" of various word stimuli presented to normal controls and to the patient before (Time 1) and 2 weeks after (Time 2) cingulotomy. Bars denote the standard error of the mean.

would be expected to require the greatest attentional processing demands, took the longest time for both the patient and the controls, while reaction times were the quickest in the nonanimal condition where there was no possibility of targets. The patient's performance remained unchanged in the nonanimal category (i.e., no possibility of targets) after the cingulotomy, as revealed by paired comparisons, $t = 1.54, p > .10$. The patient's reaction times increased significantly in all other conditions where there was a chance of targets, most notably in the possibly dangerous condition, $t = 2.89, p < .007$. Her postoperative performance in the ambiguous possibly dangerous category was worse than either the nondangerous or definitely dangerous categories. However, control subjects present a strikingly different pattern of change from Time 1 to Time 2.

Separate analysis of the control subjects' performance revealed a significant interaction of Status by Word Category, $F(3,27) = 6.81, p < .0015$, as well as main effects of Status and Word Category [$F(1,9) = 13.96, p < .0046$, and $F(3,27) = 72.19$, $p < .0001$, respectively]. Normal subjects demonstrate potent practice effects as seen in decreased reaction times in all four conditions. Post hoc comparisons reveal that the largest decreases in reaction time occurred in the nondangerous and possibly dangerous animal conditions. Unlike the patient, normals significantly improved their performance in the most difficult category, the possibly dangerous animals condition.

For the control subjects at Time 1, only three nonanimal targets were identified as dangerous animals, and at Time 2 only two nonanimal targets were similarly misidentified. The patient never misidentified any nonanimal targets as dangerous animals, nor did she ever misidentify nondangerous animals as dangerous. As seen in Figure 3, the number of reported targets progressively increased from nondangerous to possibly dangerous to definitely dangerous animal conditions for all subjects.

Generation Paradigm (Task B)

Subjects' voice onset latencies were measured during vocal generation of verbs appropriate to visually presented nouns (see Methods). For this task, an interaction of Diagnosis by Status, $F(1,9) = 11.21, p < .009$, reveals the change in the patient's performance from pre- to postoperative status to be different from that of the normal subjects. Analysis of difference scores from Time 1 to Time 2 revealed that normal subjects had a mean change in reaction time of −89 msec (SD = 55); paired comparisons revealed this decrease in RT as a significant improvement in the normals' performance, $t = -5.10$, $p < .001$. However, the patient had a mean increase in reaction time of 105 msec, resulting in an absolute dif-

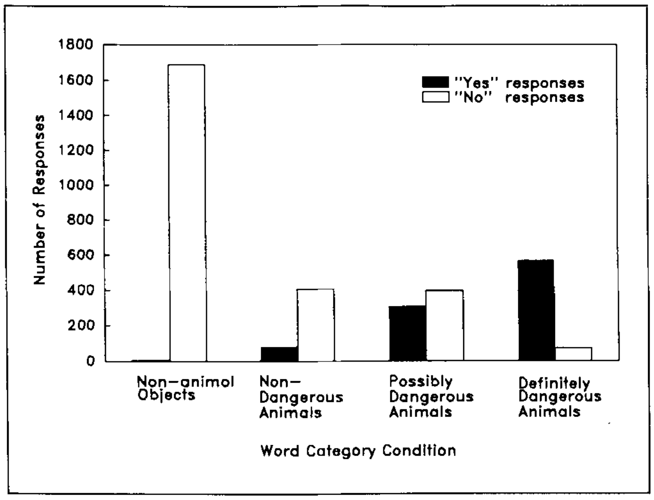


Figure 3. Task A. Responses ("yes" vs. "no") to dichotomous decisions about "dangerousness" of the various word stimuli (as in Fig. 2) for the normal subjects and the patient pre- and postoperatively.

ference of 194 msec between the patient and the controls. Thus, the patient's change in performance is approximately 3.5 standard deviation units away from that of the control subjects. Figure 4 illustrates the postoperative deterioration in the patient's performance (i.e., increased reaction time) as compared to the improvement in the controls' performance on this task.

The possibility of a speed–accuracy trade-off in the patient could not be discounted completely, as she made 13 errors preoperatively but only 5 errors postoperatively. Although the control subjects as a group made only one semantic error at Time 1 and then 12 semantic errors at Time 2, they had an extremely high number of invalid trials—101 at Time 1 and 32 at Time 2—due to vocalized hesitations when a subject would experience difficulty generating an appropriate verb. This type of hestitation error never occurred with this patient.

Stroop Paradigm (Task C)

Two conditions of the classic Stroop task (Stroop, 1935) were adapted for measurement of individiual voice onset latencies while subjects named the presentation colors of color words (see Methods). A three-way analysis of variance (Diagnosis × Status × Color–Word Congruence) was performed to compare the patient with controls from pre- to postoperative status by Stroop condition. A main effect of Color–Word Congruence was detected, $F(1,9) = 41.43, p < .0001$, due to longer reaction times when the color names and their presentation colors are conflicting (i.e., incongruent). An interaction of Diagnosis by Status reached borderline significance, $F(1,9) = 4.20, p < .071$, suggesting that the patient underwent a change in her performance from Time 1 to Time 2 that differed from the change seen in

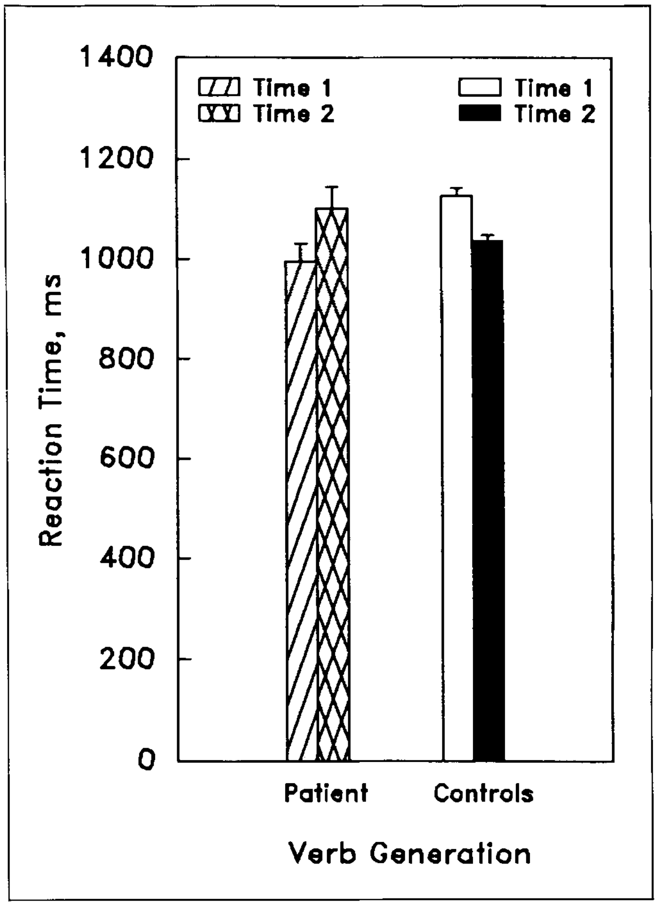


Figure 4. Task B. Reaction time means for generation of verbs appropriate to visually presented common nouns for the controls and the patient before and after cingulotomy. Bars denote the standard error of the mean.

the control subjects. Although this is only a statistical trend, a separate analysis of the control subjects' data revealed a significant main effect of Status, $F(1,9) = 17.21$, $p < .003$, confirming an improvement in performance for both Stroop conditions from Time 1 to Time 2 for normal subjects. Furthermore, post hoc paired comparisons of the patient's performance from Time 1 to Time 2 for each Stroop condition revealed that her overall performance pattern is quite unlike that of the controls (see Fig. 5). The patient's reaction times increased in the congruent condition from pre- to postoperative status, $t = 6.85, p < .0001$, but remained the same in the incongruent condition, $t = .62, p > .5$. However, the control subjects show equal degrees of improvement (i.e., decreased RTs) in both conditions from Time 1 to Time 2.

The patient and the control subjects made no errors in the congruent conditions of the Stroop task at either Time. For the incongruent condition, the controls made seven and eight errors at Time 1 and Time 2, respectively. The patient made one error preoperatively and one error postoperatively in that condition, making her error rate

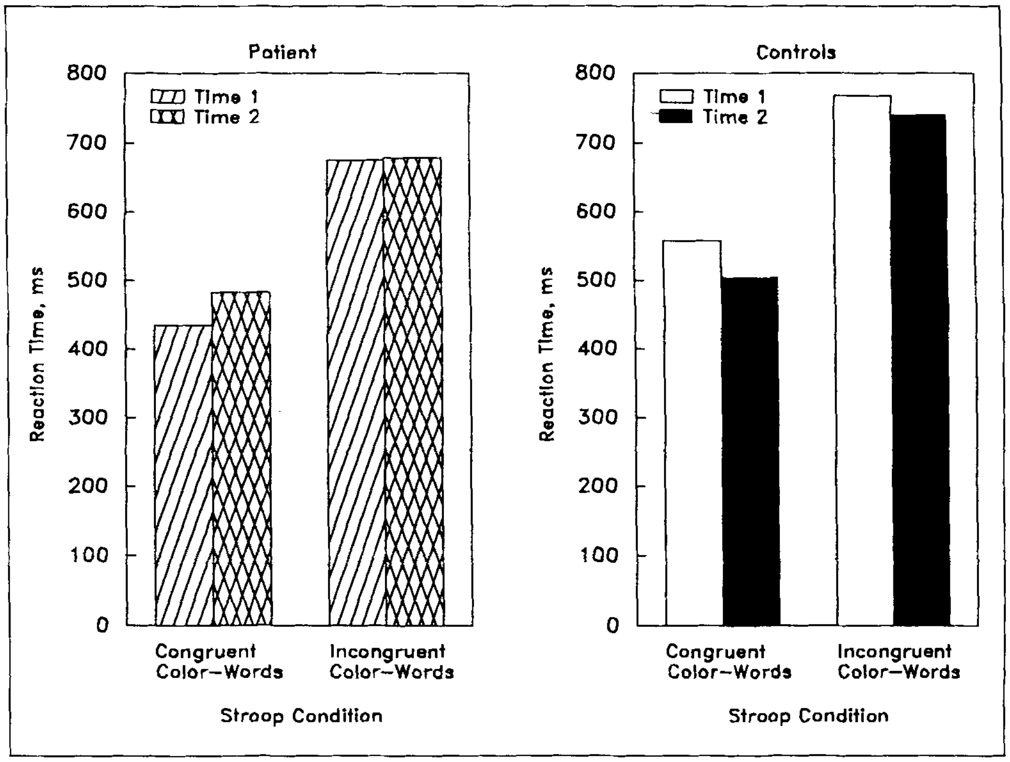


Figure 5. Task C. Reaction time means for congruent and incongruent Stroop conditions at Time 1 and Time 2. The patient's performance is displayed in the left panel and controls are displayed in the right panel.

similar to that of the controls. Consequently, speed–accuracy trade-off does not appear to play a role in the current Stroop findings.

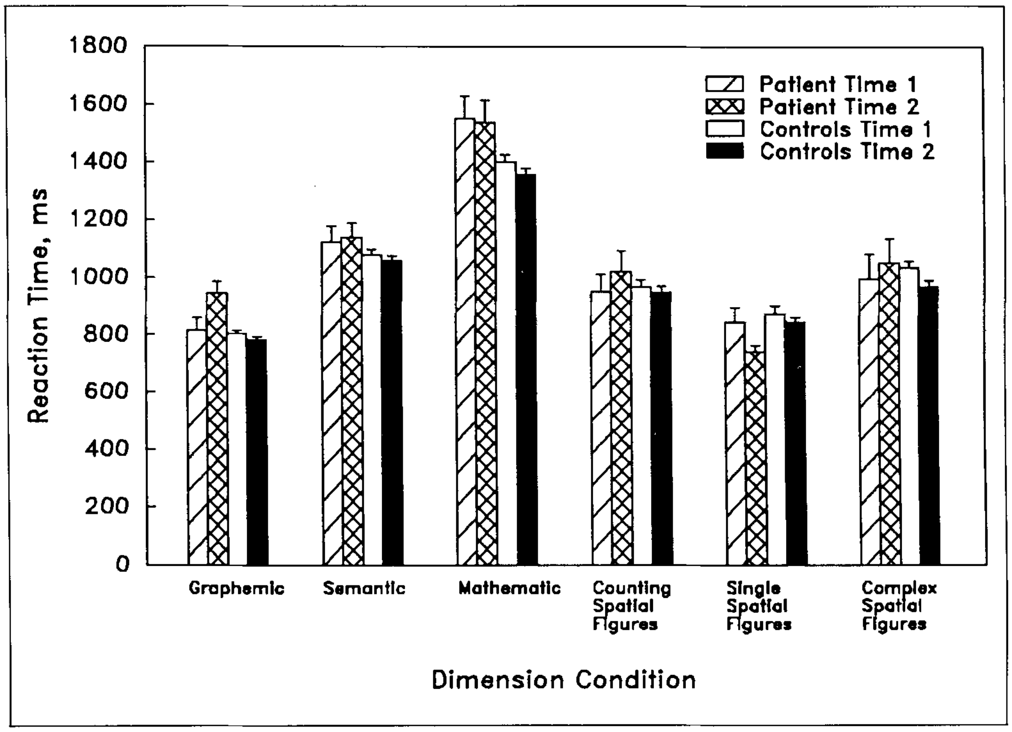
Dimensions Comparison Paradigm (Task D)

The degree of nonspecific, cerebral dysfunction associated with this stereotactically defined and limited surgery was studied using a reaction time paradigm not known to demand specifically anterior cingulate processing (see Methods). Figure 6 displays the control subjects' and the patient's preoperative and subacute postoperative performances on six conceptually related tasks evaluating speed of information processing for linguistic, mathematical, and visuospatial cognitive dimensions. A three-way ANOVA (Diagnosis × Status × Dimension) was performed on Task D to compare the patient's performance with that of the controls from pre- to postoperative status by condition. A significant main effect of Dimension, $F(5,45) = 20.7, p < .0001$, revealed differences in task difficulty, as demonstrated by reaction time, among the six task Dimensions. There were no differences between the diagnostic groups or between pre- and postsurgical status [$F(1,9) = .26, p > .6$, and $F(1,9) = .02, p > .8$, respectively]. Examination of the control subjects' performance separately revealed a trend toward improved overall performance for the six Dimension tasks from Time 1 to Time 2, $F(1,9) = 4.37, p < .07$, suggesting possible practice effects after repeat administration of this paradigm. Additionally, individual paired comparisons revealed that the only change in the patient's performance was an improvement from Time 1 to Time 2 for the single spatial figures condition, $t = -2.17, p < .05$. With this exception, the patient and the normal subjects retain the same pattern of performance after 3 weeks. In conclusion, the absence of an interaction of Diagnosis by Status suggests that the patient performed like the control group at both times, and this was confirmed via post hoc comparisons. Hence, there was no detectable effect of surgery on the patient's overall performance in this paradigm.

Neuropsychological Assessments

There was no subacute postoperative effect on performance in the Wisconsin Card Sorting Test (WCST). Preoperatively, the patient performed normally, making only six perseverative errors and successfully completing all six categories; 2 weeks after surgery, the patient made five perseverative errors and again completed the six categories. On the preoperative administration of the Complex Figure Test (Taylor version), the patient obtained direct copy, immediate recall, and delayed recall scores (Osterrieth, 1944) of 35, 27, and 30, respectively. Her subacute postoperative scores were 36, 34, and 35. Thus, this patient evidenced no clinically detectable postoperative impairment for two-dimensional, visuospatial construction abilities or visuospatial memory. Finally, the patient's Beck Depression Inventory (BDI) score was 21 at the preoperative test session and 13 postoperatively.

Figure 6. Task D. Reaction time means for dichotomous decisions ("same" vs. "different") on linguistic, mathematical, and visuospatial stimulus dimensions. Performance of normal controls and the patient before and 2 weeks after cingulotomy is compared. Bars denote the standard error of the mean.



Eight-Month Follow-up Status

To evaluate for potential chronic effects of cingulotomy, the patient was reevaluated 8 months after surgery with a repeat administration of the Halstead–Reitan Battery (including the WAIS), the Wechsler Memory Scale, and the Benton Visual Retention Test. Once again, none of these clinical, psychometric assessments revealed cerebral dysfunction. The experimental and clinical tasks outlined above (Tasks A, B, C, D, WCST, Complex Figure Test, BDI, and MMPI) were also readministered 8 months after the cingulotomy. Performance on the Semantic Monitoring paradigm (Task A) revealed a return to the patient's preoperative baseline status for all four conditions. On the Stroop paradigm (Task C), she also improved her performance to a level equivalent to her original, preoperative status. However, her performance on the Generation probe (Task B) was unchanged from the postoperative subacute status; that is, there was neither a significant decrement nor an improvement in performance 8 months later on this task. Her performances on the remaining tasks (Task D, WCST, and Complex Figure Test) remained unchanged and well within acceptable limits for normal cognitive functioning. Her MMPI profile also remained unchanged from her initial evaluation prior to the surgery.

DISCUSSION

Advances in the clinical cognitive neurosciences have begun to dissect the computational architecture of the human neocortex. These efforts represent progressive elucidation of complex higher brain functions into more elementary cognitive operations associated with discrete cortical regions. In particular, PET studies of normal subjects performing tasks with definable and isolable cognitive operations allow visualization of the relevant functional neuroanatomy (Posner, Petersen, Fox, & Raichle, 1988). Thus, several recent PET studies of normals provide converging evidence that a region of the anterior cingulate cortex is part of the human attentional system associated with high-level processing selection (Pardo et al., 1990; Petersen et al., 1988, 1989; Posner, Petersen, Fox, & Raichle, 1988). These findings suggest that task paradigms recruiting the anterior cingulate might serve as sensitive reaction time probes for abnormalities in attention. A patient undergoing bilateral anterior cingulotomy provided the means by which to explore whether anterior cingulate lesions do affect high-level, selective attentional processing.

Before cingulotomy, the patient had no evidence of cerebral dysfunction, as assessed through several neuropsychological measures, and she performed normally compared to a reference control group on the Semantic Monitoring task, which is known to recruit the anterior cingulate cortex (Petersen et al., 1989; Posner, Petersen, Fox, & Raichle, 1988). The paradigm required decisions about stimuli that ranged from obvious nontargets (i.e., a form of vigilance processing known not to recruit the anterior cingulate cortex; Pardo, Fox, & Raichle, 1991), to ambiguous targets (which required high-level processing of the stimulus and selection of features relevant to target properties), to obvious targets. The subjects' slowest reaction times were in making decisions about ambiguous targets, suggesting that performance on this stimulus category demanded the greatest attentional processing capacity. The normal subjects and the patient (preoperatively) performed in like fashion across stimulus categories; thus, a similar strategy was probably used by all. Postoperatively, the patient was unimpaired in the condition with no possibility of targets, i.e. (the nonanimal stimulus category). This condition requires vigilance or sustained attention in the form of monitoring the stimuli for dangerousness despite the absence of any animal targets. Because her performance was unchanged in this condition, cingulotomy did not, therefore, impair the vigilance aspects of her performance. In contrast, at 2 weeks after surgery, the patient was most impaired in the ambiguous stimulus category. Furthermore, her subacute postoperative performance in the ambiguous stimulus category was worse than in any other condition, including the obvious target condition. Thus, her anterior cingulate was not so much involved in the perception of the target (Duncan, 1980), nor in the affective coding of the stimulus, but rather in the selection of processing appropriate for task execution.

The decrement in the patient's postoperative performance for semantic monitoring cannot be merely attributed to differences in task difficulty affecting response time. She performed normally after surgery on reaction time probes of cognitive speed of information processing (Task D) for linguistic, mathematic, and visuospatial dimensions, in which each condition represented a different level of task complexity and difficulty. The patient's and the controls' longest reaction times in these studies occurred in the mathematic condition of the cognitive speed paradigm (Task D). After surgery, the patient had no significant increase in reaction time for this condition, nor for the other two most difficult conditions (semantic comparisons and complex spatial figures).

The patient was also impaired 2 weeks after surgery in her ability to generate verbs appropriate to nouns (Task B), a paradigm that also recruits the anterior cingulate in normals (Petersen et al., 1988, 1989). If anything, she was expected to perform better given the effects of practice seen in the control subjects after 3 weeks. The possibility of a speed–accuracy trade-off could not be completely excluded, however. Her performance on the Stroop paradigm (Stroop, 1935), which also activates the anterior cingulate cortex (Pardo et al., 1990), was impaired 2 weeks after surgery. The finding of an increase in reaction time in the less difficult congruent condition but not in the more attentionally demanding incongruent condition argues less cogently for the detection of a specific impairment in selective attention by this task. The patient did nevertheless perform normally after surgery on reaction time probes (Task D) of cognitive speed of information processing for linguistic, mathematic, and visuospatial dimensions, as well as on a variety of other clinical, neuropsychological measures.

The reevaluation of this patient 8 months after surgery revealed a return to presurgical performance levels for tasks that had previously demonstrated impaired higher order selection processing during the subacute postoperative phase. Thus, although the procedure of stereotactic, bilateral anterior cingulotomy resulted in subacute postoperative effects on selective attentional processing—detectable only by sensitive chronometric assessment—such deficits resolved after a brief period of recovery. Such information is relevant to the conclusion that limited psychosurgical techniques, such as the bilateral anterior cingulotomy, result in minimal intellectual and cognitive changes for the patient, while still providing for the possibility of a reduction in the targeted symptoms (e.g., depression). The previous lack of evidence for attentional deficits in cingulotomy patients appears attributable to the limited sensitivity of classical neuropsychological probes of brain function, developed from study of patients with large lesions, as well as the current findings that the attentional deficits are extremely subtle and ephemeral.

Potential confounds in these tasks require further discussion. First, lesions to the anterior cingulate cortex, traditionally defined as a limbic region, might be hypothesized to result in deficits in the assessment of emotionally laden concepts such as the dangerousness of animals. In fact, however, the patient demonstrated slower reaction times in the ambiguous rather than the definitely dangerous category (Fig. 2), despite her report of a greater frequency of dangerous targets in the latter condition. Thus, evaluations of dangerousness were not dependent on the affective quality of the targets. Second, anterior cingulate activation related to higher order attentional processing might be considered the result of increased, generalized arousal required to meet complex task demands. However, the anterior cingulate has been recruited during what subjects' considered to be a simple task of detecting obvious targets at frequencies of about 0.5 Hz (Petersen et al., 1988, 1989). Furthermore, PET studies of anxiety, a state of high arousal as evidenced by both subjective and autonomic measures, have not recruited the anterior cingulate (Reiman, Fusselman, Fox, & Raichle, 1989). Although the anterior cingulate is needed for limited capacity high-level processing that may sometimes be associated with high levels of arousal, arousal alone does not result in anterior cingulate activation. Third, the possibility that the postoperative deficits described here may be the result of nonspecific effects of stereotactic surgery (anesthesia, brain edema, surgical stress, etc.) or some involvement of immediately adjacent brain structures is unlikely. The patient has since undergone a second bilateral cingulotomy procedure immediately anterior to the first lesion site and with equivalent extension into the corpus callosum, cingulum, and anterior cingulate cortex. Her performance 2 weeks postoperatively was unchanged from her original preoperative baseline (K. W. Janer & J. V. Pardo, unpublished observations). Finally, measurement of reaction times, especially voice onset time, can be affected by word frequency, word length, the spectral characteristics of the initial syllable, various forms of priming, and so forth. The studies reported here, however, probe for changes in performance across a stable stimulus set thereby minimizing potential effects of such confounds.

In conclusion, sensitive reaction time studies that activate the anterior cingulate cortex in normals revealed defined deficits in attentional processing in a patient during the subacute postoperative phase following bilateral cingulotomy. These data provide further evidence for the role of the anterior cingulate in selective attention. The current finding of recovery of function over time on these sensitive chronometric tasks supports previous data that have indicated minimal changes in cognitive performance after bilateral anterior cingulotomy. The approach implemented here illustrates the utility of targeted neuropsychological probes of cognitive functions based on new information about human functional neuroanatomy made possible through PET imaging of normal subjects.

METHODS

Subjects

Report of a Case

The patient is a 34-year-old, right-handed, college-educated female with a history of severe, recurrent major depression (unipolar) beginning in her late teenage years. She has no recent history of drug or alcohol abuse. There is a family history of unipolar depression. She has made three serious suicide attempts. Her depression has been particularly severe, disabling, and unremitting during the last 3 years. All standard evaluations for depression refractory to treatment have been unremarkable and have included the following: general physical and neurological examination, magnetic resonance imaging, chest X-ray, serum chemistries including vitamins B_{12} and folate, complete blood count, VDRL, serum trace metals, urinalysis, T_4 index, thyroid-releasing hormone (TRH) stimulation test, dexamethasone suppression test (DST), and sleep-deprived EEG with nasopharyngeal leads. A clinical battery of standardized neuropsychological evaluations administered 1 month prior to surgery evidenced no cerebral dysfunction. These assessments revealed a WAIS (Wechsler, 1955) Full Scale IQ of 129 (Verbal IQ = 133; Performance IQ = 120), a Goldstein average impairment rating (Russell, Neuringer, & Goldstein, 1970) of 0.24 (superior), a Halstead impairment index (Halstead, 1947; Reitan & Davison, 1974) of 0 (normal), as well as normal performances on both the Wechsler Memory Scale (Wechsler, 1945) and the Benton Visual Retention Test (Benton, 1974). She has failed to respond to traditional interventions including adequate trials of tricyclic antidepressant medications, amoxapine, maprotilene, trazodone, bupropion, nomifensin, fluoxetine, monamine oxidase inhibitors (pargyline, phenelzine, tranylcypromine), lithium, pemoline, thyroid supplements, and electroshock therapy, including a course of weekly maintenance treatments. In addition, various combinations of these agents have also been inefficacious. Because of the severity of her illness, risk of suicide, and refractoriness to conventional treatments, she was referred to the Massachusetts General Hospital Cingulotomy Committee, Boston, Massachusetts. After consensus that surgery was indicated, Drs. R. L. Mortuza and H. T. Ballantine performed thermal, stereotactic, bilateral anterior cingulotomy without complications (Ballantine, Cassidy, Flanagan, & Marino, 1967). The patient gave informed consent for the surgery and psychometric assessments.

Control Subjects

Normative data on particular chronometric tasks (Tasks A, B, C, and D; see below) were obtained from subjects recruited from the university community. Ten right-handed females, ages 26 to 34 (mean = 30.4, SD = 3.2), with an average of 19.5 years of education (SD = 3.4) were screened for and denied any history of psychiatric or neurological illnesses, including head trauma or loss of consciousness for more than 2 min. None of the control subjects was on any medications, with the exception of birth control pills, and all gave informed consent.

Anterior Cingulate Processing Probes

Three task paradigms known to activate robustly the anterior cingulate cortex were adapted for reaction time performance studies (Pardo et al., 1990; Petersen et al., 1988, 1989; Posner, Petersen, Fox, & Raichle, 1988). No practice was permitted prior to task performance. Stimulus presentation and data collection of reaction times were performed on a Northgate Supermicro 286/12 computer (Northgate Computer Systems, Plymouth, MN) equipped with a Princeton Ultra 14 VGA Color Monitor (Princeton Graphics Systems, Princeton, NJ). Software from the Micro Experimental Laboratory, Pre-release System Version 120 (Psychology Software Tools, Inc., Pittsburgh, PA) was implemented for the programming of these experiments. Voice onset latency was measured using a Voice Operated Relay and Microphone, Model G1341T (Gerbrand's Corporation, Arlington, MA).

Task A: Semantic Monitoring Paradigm

Single nouns of one to three syllables were presented in random order on the video monitor with interstimulus intervals of 500 msec. Subjects made a dichotomous decision, by pressing either of two reaction time keys, as to whether the noun was or was not a dangerous animal. The investigators classified a priori the nouns as "nonanimal" (N = 77), "nondangerous animal" (N = 22), "possibly dangerous animal" (N = 32), and "definitely dangerous animal" (N = 29). Some assignments to a particular noun category were somewhat arbitrary but not crucial for the purposes of this experiment.

Task B: Generation Paradigm

Single common nouns (N = 86) of one to three syllables were presented in random order on the video monitor with interstimulus intervals of 500 msec. Subjects were asked to verbally generate a verb appropriate to each noun, during which the subjects' voice onset latencies were measured. To ascertain the potential contribution of a speed–accuracy trade-off to overall performance, errors were noted and subsequently filtered from the data prior to statistical analysis. Errors included trials on which no response was given, as well as those trials when the subject gave a semantically inappropriate response (e.g., responding "ride" to the word "tree"). Inappropriate utterances, such as coughs or vocalized hesitations that prematurely triggered the voice relay interface, were also filtered prior to statistical analysis.

Task C: Stroop Paradigm

In the first block of the Stroop task (Stroop, 1935), subjects named the presentation color of a single word on the monitor. The words were the color names "red," "blue," "green," and "yellow," which were displayed in colors congruent to the color name (e.g., the word "red" displayed in red). In the second block, the subjects again named the display color of the words presented on the monitor. However, the words were color names that were incongruent to the presentation color (e.g., the word "blue" displayed in green). Each block contained 100 color–word presentations. Both the presentation order of the words and the display colors were randomized, with each word or display color not occurring consecutively across any two trials; the interstimulus interval was again 500 msec. Voice onset latencies were measured, and errors and inappropriate utterances were again noted and filtered from the data.

Cognitive Speed of Information Processing Probes

To serve as a control measure of general cognitive functioning, the subjects also performed a series of six conceptually related reaction time tasks of varying complexity and difficulty. The tasks were designed to explore relative cognitive speeds of information processing on verbal, quantitative, and visuospatial materials (Levine, Preddy, & Thorndike, 1987), but not requiring, at least by extant data, anterior cingulate processing. This "Dimensions Comparison" paradigm (Task D) required dichotomous decisions ("same" vs. "different") about whether two simultaneously presented stimuli differed on a particular perceptual, numerical, or linguistic dimension. Six blocks of 22 stimulus pairs (4 practice trials followed by 18 real trials) were presented in random order, preceded by instructions explaining the dimension of the task. Each block represented one of the following dimensions: graphemic word forms, semantic word forms, mathematical calculations, counting spatial figures, single spatial figures, or complex spatial figures (see Fig. 7 for stimulus examples). The stimuli were displayed on the video monitor with interstimulus intervals of 750 msec, and reaction times were measured via the subject's voice onset latency to stimulus presentation onset. Inappropriate utterances were noted and filtered from the data.

Neuropsychological Assessments

In addition to the separate administration of a traditional, standardized psychometric test battery (i.e., Halstead–

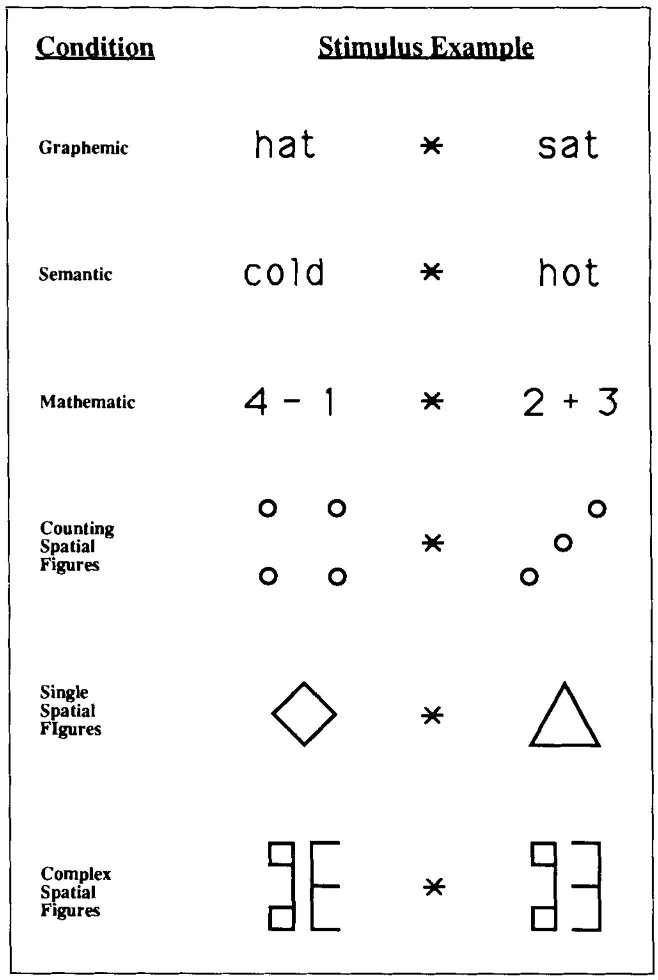


Figure 7. Examples of stimuli from each Dimension condition of the Cognitive Speed of Information Processing paradigm (Task D). All are examples of when a subject should respond "different." The star in the middle is the screen center point to which the subject attends between stimulus frames.

Reitan, Wechsler Memory Scale, and Benton Visual Retention Test; see above), the patient underwent further neuropsychological testing as a part of the present experimental evaluation. The Wisconsin Card Sorting Test (Heaton, 1981) was included because of its specific sensitivity to lesions of the frontal lobes and their associated behavioral sequelae (Drewe, 1974; Milner, 1963; Robinson, Heaton, Lehman, & Stilson, 1980). Because studies on groups of cingulotomy patients have revealed visuospatial abnormalities (Corkin et al., 1979; Vasko & Kullberg, 1979), the patient completed the Taylor version of the Complex Figure Test (Taylor, 1969) by direct copy, immediate recall, and delayed recall (25 min) administrations. To assess mood and general personality characteristics, the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and Minnesota Multiphasic Personality Inventory (Hathaway & McKinley, 1951) were administered, respectively.

Magnetic Resonance Imaging

Before and 5 months after the patient's first cingulotomy surgery, magnetic resonance imaging (MRI) was performed on a Siemens Magnetom Scanner (Erlangen, Germany) with a 1.0 tesla superconducting magnet. Sagittal images were obtained with a spin-echo sequence that was T1 weighted (TR = 600 msec. TE = 15 msec); axial images were obtained using a spin-echo sequence that was weighted for proton density (TR = 2400 msec, TE = 25 msec). The slice thickness was 6 mm with an interslice gap of 1.2 mm.

Procedure

The patient was kept free of psychoactive medications 1 month before the preoperative test session, which occurred 1 week prior to surgery. The patient was retested 2 weeks after the surgery during the subacute postoperative period. She remained free of any psychoactive medications until after that testing. To evaluate for more chronic effects of the cingulotomy, the patient was retested again 8 months after surgery while free of psychoactive medications for at least 3 weeks.

The control subjects were administered Tasks A, B, C, and D for the purpose of providing baseline data on normal performance for these tasks. The subjects returned for retesting on these identical tasks an average of 3 weeks later (mean = 23 days, SD = 4.9). This second testing provided a comparison group for the patient's subacute postsurgical performance and allowed for the investigation of possible practice effects. Because reliable normative data are available for the remaining clinically familiar neuropsychological tasks, the control subjects did not undergo the other test procedures. The various task paradigms were presented in the same order during all testing sessions.

Acknowledgments

We thank the subjects for their cooperation and Michael I. Posner for support and invaluable discussions during the early phases of these studies. This research was supported through grants from the National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD); NIAAA AA03539 (to Samuel B. Guze); and Tourette's Syndrome Association. J.V.P. is a Pfizer Fellow. This work was performed in partial fulfillment of the requirements for the degree of Doctor of Philosophy (K.W.J.).

Reprint requests should be sent to Dr. José V. Pardo, Veterans Administration Hospital Medical Center, Psychiatry Service, 116A, 1 Veterans Drive, Minneapolis, MN 55417.

REFERENCES

Ballantine, H. T., Cassidy, W. L., Flanagan, N. B., & Marino, R. (1967). Sterotaxic anterior cingulotomy for neuropsychiatric illness and intractable pain. *Journal of Neurosurgery, 26,* 488–495.

Ballantine, H. T., Levy, B. S., Dagi, T. F., & Giriunas, I. B. (1977). Cingulotomy for psychiatric illness: Report of 13 years' experience. In W. H. Sweet, S. Obrador, & J. G. Martin-Rodriguez (Eds.), *Neurosurgical treatment in psychiatry, pain, and epilepsy* (pp. 333–353). Baltimore: University Park.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4,* 561–571.

Benton, A. L. (1974). *The Revised Visual Retention Test* (4th ed.). New York: Psychological Corporation.

Chase, T. N., Geoffrey, V., Gillespie, M., & Burrows, G. H. (1986). Structural and functional studies of Gilles De La Tourette syndrome. *Revue Neurologique, 142,* 851–855.

Corkin, S., Twitchell, T. E., & Sullivan, E. V. (1979). Safety and efficacy of cingulotomy for pain and psychiatric disorders. In E. R. Hitchcock, H. T. Ballantine, & B. A. Meyerson, (Eds.), *Modern concepts in psychiatric surgery.* Amsterdam: Elsevier.

Drewe, E. A. (1974). The effect of type and area of brain lesion on Wisconsin Card Sorting Test performance. *Cortex, 10,* 159–170.

Duncan, J. (1980). The locus of interference in the perception of simultaneous stimuli. *Psychological Review, 87,* 272–300.

Finger, S., & Stein, D. G. (1982). *Brain damage and recovery.* London: Academic Press.

Halstead, W. C. (1947). *Brain and intelligence: A quantitative study of the frontal lobes.* Chicago: University of Chicago Press.

Hathaway, S. R., & McKinley, J. C. (1951). *The Minnesota Multiphasic Personality Inventory* (Revised). New York: Psychological Corporation.

Heaton, R. K. (1981). *A manual for the Wisconsin Card Sorting Test.* Odessa: Psychological Assessment Resources, Inc.

Jürgens, U. (1986). The squirrel monkey as an experimental model in the study of cerebral organization of emotional vocal utterances. *European Archives of Psychiatry and Neurological Sciences, 236,* 40–43.

Laplane, D., Degos, J. D., Baulac, M., & Gray F. (1981). Bilateral infarction of the anterior cingulate gyri and of the fornices. *Journal of the Neurological Sciences, 51,* 289–300.

Levine, G., Preddy, D., & Thorndike, R. L. (1987). Speed of information processing and level of cognitive ability. *Personality and Individual Differences, 8,* 599–607.

Mesulam, M. M. (1985). *Principles of behavioral neurology.* Philadelphia: Davis.
Milner, B. (1963). Effects of different brain lesions on card sorting. *Archives of Neurology, 9,* 90–100.
Németh, G., Hegedüs, K., & Molnár, L. (1988). Akinetic mutism associated with bicingular lesions: Clinicopathological and functional anatomical correlates. *European Archives of Psychiatry and Neurological Sciences, 237,* 218–222.
Osterrieth, P. A. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie, 30,* 206–356.
Pardo, J. V., Fox, P. T., & Raichle, M. E. (1991). Localization of a human system for sustained attention by positron emission tomography. *Nature (London),* in press.
Pardo, J. V., Pardo, P. J., Janer, K. W., & Raichle, M. E. (1990). The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proceedings of the National Academy of Sciences U.S.A., 87,* 256–259.
Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M. A., & Raichle, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature (London), 331,* 585–589.
Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M. A., & Raichle, M. E. (1989). Positron emission tomographic studies of the processing of single words. *Journal of Cognitive Neuroscience, 1,* 153–170.
Posner, M. I. (1986). *Chronometric explorations of the mind.* New York: Oxford University Press.
Posner, M. I., Early, T. S., Reiman, E. M., Pardo, P. J., & Dhawan, M. (1988). Asymmetries in hemispheric control of attention in schizophrenics. *Archives of General Psychiatry, 45,* 814–821.
Posner, M. I., Petersen, S. E., Fox, P. T., & Raichle, M. E. (1988). Localization of cognitive operations in the human brain. *Science, 240,* 1627–1631.
Reiman, E. M., Fusselman, M. J., Fox, P. T., & Raichle, M. E. (1989). Neuroanatomical correlates of anticipatory anxiety. *Science, 243,* 1071–1074.
Reitan, R. M., & Davison, L. A. (1974). *Clinical neuropsychology: Current status and applications.* New York: Wiley.
Robinson, A. L., Heaton, R. K., Lehman, R. A. W., & Stilson, D. W. (1980). The utility of the Wisconsin Card Sorting Test in detecting and localizing frontal lobe lesions. *Journal of Consulting and Clinical Psychology, 48,* 605–614.
Russell, E. W., Neuringer, C., & Goldstein, G. (1970). *Assessment of brain damage: A neuropsychological key approach.* New York: Wiley.
Stroop, J. E. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18,* 643–662.
Talairach, J., Bancaud, J., Geier, S., Bordas-Ferrer, M., Bonis, A., Szikla, & Rusu, M. (1973). The cingulate gyrus and human behavior. *Electroencephalography and Clinical Neurophysiology, 34,* 45–52.
Taylor, L. B. (1969). Localization of cerebral lesions by psychological testing. *Clinical Neurosurgery, 16,* 269–287.
Vasko, T., & Kullberg, G. (1979). Results of psychological testing of cognitive functioning in patients undergoing stereotactic psychiatric surgery. In E. R. Hitchcock, H. T. Ballantine, & B. A. Meyerson (Eds.), *Modern concepts in psychiatric surgery.* Amsterdam: Elsevier.
Wechsler, D. A. (1945). A standardized memory scale for clinical use. *Journal of Psychology, 19,* 87–95.
Wechsler, D. A. (1955). *Manual for the Wechsler Adult Intelligence Scale.* New York: Psychological Corporation.