Cerebral Cortex April 2007;17:826-838
doi:10.1093/cercor/bhk031
Advance Access publication May 12, 2006

Effects of Focal Frontal Lesions on Response Inhibition

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This study examined the performance of 38 normal subjects and 43 patients with focal lesions of the frontal lobes on a simple go–nogo task where the probability of the nogo stimulus was either 75% or 25%. Patients with lesions to the superior medial parts of the frontal lobes, in particular to the left superior portion of Brodmann area 6 (which includes the supplementary motor areas and the premotor areas for the right hand) had an increased number of false alarms (incorrect responses to the nogo stimulus). These results indicate that area 6 is specifically involved in the inhibition of response. Patients with lesions to the right anterior cingulate (areas 24 and 32) were slower and more variable in their reaction time. These findings could be explained by an inability to sustain stimulus-response contingencies. Lesions to the right ventrolateral prefrontal cortex (Brodmann areas 44, 45, 47) also increased the variability of response, perhaps by disrupting monitoring performance.

Keywords: anterior cingulate, lesion localization, nogo paradigm, premotor cortex, supplementary motor areas

Introduction

The prefrontal cortex controls our actions, deciding when to initiate and when to withhold response. Luria (1966) postulated that the human frontal lobes support the verbal regulation of behavior and that patients with frontal lesions are often unable to use task instructions to direct behavior even when clearly able to comprehend their meaning. Drewe (1975a, 1975b) evaluated this theory in 24 patients with frontal lobe lesions and an equal number of patients with nonfrontal lesions. She found that dissociations between verbal and motor behavior only occurred for some tasks. One of these was a simple go–nogo task in which the subject responded to one stimulus and not to another. Patients with frontal lobe lesions had a significantly greater number of false-positive responses (10%) to the nogo stimulus than patients with nonfrontal lesions (6%). The high false-positive rate in this simple go–nogo task was particularly associated with medial lesions of the frontal lobe (Drewe 1975b). Drewe pointed out that a similar inability to inhibit responding occurred in animals with lesions of inferior and medial frontal cortex (e.g., Brutkowski and Mempel 1961). However, later studies of the effects of frontal lesions in animals stressed the role of the ventral and lateral frontal cortex in preventing inappropriate responses or perseverative errors (e.g., Brutkowski 1965; Iverson and Mishkin 1970). Perhaps the medial frontal regions controlled the drive to respond and the more lateral regions the specificity of response.

Surprisingly, no subsequent study of the go–nogo task has used as large a group of patients as Drewe (1975a, 1975b). Patients with frontal lobe lesions generally show a high rate of false-positive responses (also known as false alarms or commission errors) in the go–nogo task, but there has been no consistent localization or lateralization of this deficit within the frontal lobes. Verfaellie and Heilman (1987) compared 2 patients with lesions to the right or left medial frontal lobe. The patient with a left-sided lesion had difficulty preparing for response, and the patient with a right-sided lesion had difficulty inhibiting responses. Décary and Richer (1995) studied 6 patients with frontal lobe excisions (involving the dorsolateral and medial frontal cortex) using 3 different probabilities of nogo stimulus (15%, 50%, and 85%) and a short interstimulus interval (1.2 s). The errors were significantly higher in frontal patients (3%) than in temporal patients (0.7%) but did not change with the probability of the nogo stimulus. Fellows and Farah (2005) reported that go–nogo behavior at 2 probability levels (12.5% and 62.5% nogo stimuli) was indistinguishable from normal in 4 patients with damage to the anterior cingulate cortex (3 left and 1 bilateral). Two studies produced some evidence for a more specific localization, which in fact tended to support Drewe's position. Leimkuhler and Mesulam (1985) reported that a patient with a large meningioma of the falx involving the medial portions of the frontal lobe had many commission errors in a go–nogo task and that performance returned to normal after excision of the tumor. Godefroy and Rousseaux (1996, see also Godefroy and others 1996) reported a much higher rate of commission errors in 11 frontal patients (22%) than in posterior patients (7%) or controls (8%) using equiprobable go–nogo stimuli presented at interstimulus intervals varying between 1 and 10 s. Stepwise regression analyses showed that commission errors depended on lesions to the left caudate and the medial regions of the frontal lobe. Lesion studies thus provide tentative support for nogo commission being related to medial prefrontal damage.

Early studies of the event-related potentials during the go–nogo task showed a frontal scalp topography on nogo trials (Hillyard and others 1976; Pfefferbaum and others 1985; Roberts and others 1994). More recent studies using many more scalp electrodes have shown that the N200 wave occurring on nogo trials is maximally recorded over the right frontal scalp (e.g., Schmajuk and others 2006). However, it is not clear what this means in terms of the underlying cerebral generators; source analysis (Kiefer and others 1998) has suggested bilateral inferior medial (IM) generators, but other source

configurations might have been possible. Several event-related potential studies associated monitoring of errors (or response conflict) with activation of the anterior cingulate (Gehring and others 1993; Dehaene and others 1994; Ridderinkhof and others 2004).

Initial functional magnetic resonance imaging (fMRI) studies evaluating the difference in activation between go–nogo tasks and simple go tasks found increased activation bilaterally in the anterior cingulate cortex and various other regions of the prefrontal cortex (Casey and others 1997) but were not consistent as to whether the activation was greater over the right (Kawashima and others 1996) or left (Rubia and others 2001) hemisphere. Event-related fMRI analyses were able to look more specifically at the error trials as opposed to correctly inhibited trials. These studies suggested that the anterior cingulate might be related to error processing (Kiehl and others 2000; Menon and others 2001) or to monitoring the response conflict associated with nogo trials (Braver and others 2001).

The fMRI studies also indicated that response inhibition was associated with activation of widespread areas of the prefrontal cortex. The first study reported specific activation around the right inferior frontal sulcus (Konishi and others 1998). The right-sided lateralization and the particular importance of the right frontal operculum were also found by Garavan and others (1999, 2006; Kelly and others 2004). However, other studies have reported activation of the prefrontal cortex bilaterally (Menon and others 2001) and (in addition to bilateral middle frontal gyrus) the left premotor (PM) region (Watanabe and others 2002). Sometimes the studies do not show focal localization. For example, Menon and others (2001) reported that response inhibition was associated with bilateral activation of dorsolateral (Brodmann areas 9/46), inferior frontal (45/47), and PM (6) regions as well as regions of the parietal cortex and the caudate nucleus. Liddle and others (2001) showed significant activation of 23 areas of the brain when comparing successful nogo inhibition with normal go response: the frontal regions showed activation of the left middle and superior frontal gyri (Brodmann area 6) and the right middle and inferior frontal gyri (Brodmann areas 9 and 47) and several other areas. Such widespread activation may indicate that inhibition requires a complex network of interacting brain regions. Another possibility is that behavioral inhibition involves several attendant processes such as sustained attention, response selection, and action monitoring in addition to those specific to response inhibition.

Some of the variability of the results may derive from differing cognitive requirements during the go–nogo paradigms. Mostofsky and others (2003) therefore conducted a neuroimaging study of the go–nogo paradigm involving 48 right-handed subjects performing a go–nogo task using either a very simple format (18% nogo) or one that also required counting the different stimuli in order to make the go–nogo decision. The simple paradigm used a highly engrained stimulus-response mapping (green go and red nogo) to minimize requirements for setting up and maintaining the task set. In an event-related analysis of the simple task, go trials showed activation of the left sensorimotor areas, the cerebelleum, and the left superior frontal gyrus (Brodmann area 6), whereas nogo trials involved the left superior frontal gyrus, a little anterior to the area activated during the go trials, and the cerebellum. The counting go–nogo task showed additional activation of the right middle frontal gyrus (probably Brodmann areas 9/46). The authors concluded that the motor response with the right hand is controlled by the left supplementary motor area (SMA) and the sensorimotor regions, that withholding a response requires activation of the left pre-SMA, and that the working memory load involved in counting the stimuli involved the right dorsolateral prefrontal cortex.

Buchsbaum and others (2005) conducted a meta-analysis of response inhibition in 18 go–nogo fMRI studies. Imaging meta-analyses are difficult to interpret because it is not clear how to weight studies that can contribute as few as 3 (Mostofsky) or as many as 23 (Liddle) loci to the analysis or how to interpret the size of a significant cluster (does a larger cluster mean more or less specific localization?). They found significant clusters of activation in 14 regions of the brain. In the frontal regions, the largest clusters were in the right middle and inferior frontal gyri (Brodmann areas 44/46), both medial frontal gyri (Brodmann area 6), and the right cingulate gyrus (Brodmann areas 39/40). Garavan and others (2006) performed a meta-analysis of their own 5 fMRI studies of the go–nogo paradigm and found that the right dorsolateral prefrontal cortex (Brodmann areas 9, 10, 44, and 46) and right anterior cingulate (Brodmann areas 6 and 32) were most commonly activated but that areas of the left prefrontal cortex (particularly areas 6, 9, and 46) were also involved.

The stop-signal paradigm (Logan and others 1984) has also been extensively used to study response inhibition. fMRI studies of this paradigm have specifically implicated the opercular region of the right frontal lobes in response inhibition (Rubia and others 2001, 2003). Furthermore, patients with lesions to the right inferior frontal region show abnormal stopping parameters with the amount of abnormality correlating with the amount of damage (Aron and others 2003). Disruption of the functioning of the right inferior frontal region by means of transcranial magnetic stimulation (TMS) has shown decreased response inhibition in the stop-signal paradigm (Chambers and others 2006). Li and others (2006), however, evaluated the fMRI findings related to individual differences in the stop-signal paradigm in order to distinguish response inhibition from other cognitive and affective processes. They found that more efficient response inhibition was associated with activation of the left superior frontal gyrus (Brodmann area 8) and the left precentral gyrus (Brodmann area 9).

Robertson and others (1997, also Manly and others 1999) have used a variant of the go–nogo task called the sustained attention to response task (SART) wherein numbers from 1 to 9 are randomly presented at a regular rate, and the subject requested to respond to all stimuli except one. Fassbender and others (2004, also Hester and others 2004) studied fMRI action during the SART and found that correct inhibition (not responding to the improbable nogo stimulus) was associated with activation of left and right dorsolateral frontal regions as well as the left PM cortex (Brodmann area 6), whereas false alarms activated the anterior cingulate regions. They proposed several active networks during the task: an inhibitory network involving the right inferior prefrontal cortex, a task-setting network involving the left prefrontal cortex, and an error-monitoring network centered on the anterior cingulate.

Precise lesion studies might complement imaging studies by indicating whether an activated area is necessary for task performance (discussed by Shallice 2003). We have been examining the behavior of patients with focal lesions of the frontal lobe with a battery of simple stimulus-response tests (Alexander and others 2005; Stuss and others 2005; Picton and others 2006). Our intent was to discover whether distinct

deficits occur in patients with lesions to different regions of the prefrontal cortex. We postulated that these deficits might involve specific cognitive processes (Stuss and others 1995). One of these processes was inhibition, and we used the go–nogo task as a simple test for examining this process. Four equiprobable stimuli were presented, and the test was run under 2 different conditions. In one, the subject responded to one stimulus and not to the others. In the other, the subject responded to all stimuli except one.

Our main hypotheses were that false alarms would be more frequent in the nogo improbable condition and that patients with frontal lobe lesions would be more prone to these errors than normal controls. When we initially began this study a decade ago, we hypothesized that the increase in false alarms would be most evident in patients with lesions to the dorsolateral (as opposed to ventromedial) regions of the frontal lobes, but at the time of the initial hypotheses, we were not any more specific about localization or lateralization (Stuss and others 1995). The literature published in the intervening years justified more specific hypotheses concerning the false alarms—that response inhibition was related to the right inferior frontal region or to the left superior medial (SM) and PM regions. Our simple go–nogo paradigm also allowed us to evaluate the speed and variability of reaction time (RT) and the incidence of missed responses.

Methods

Subjects

We examined 43 patients with focal lesions to the frontal lobes and 38 age-matched normal control (CTL) subjects. The frontal lesions localized using magnetic resonance imaging (MRI) (13) or computerized tomography (CT) (30) scans and a standard anatomical template (Stuss, Alexander, and others 2002) were predominantly left lateral (LL) in 11, right lateral (RL) in 6, IM in 15, and SM in 11. The exact locations of the lesions, etiologies, and time since injury for the patients together with the results of basic neuropsychological testing are presented in a parallel paper (Alexander and others 2005). All patients were right handed except for 1 left-handed patient, 2 ambidextrous patients in the IM group, and 3 ambidextrous patients in the SM group. Of the 38 control subjects, 33 were right handed and 5 left handed.

Paradigm

This experiment occurred within the Rotman-Baycrest Battery to Investigate Attention (ROBBIA) (Stuss and others 2005). The battery took a full day to administer, and this particular experiment occurred at the end of the morning.

On each trial, one of the letters A, B, C, or D (each subtending a visual angle of 2 degrees) was presented for 300 ms in yellow at the center of a dark video screen. Each of the stimuli occurred equiprobably in a pseudorandom sequence (adjusted so that each stimulus was truly equiprobable, so that 2 of the same stimuli occurred in a row with a probability of 1/16, and so that 3 of the same stimuli did not occur in a row). Each subject received exactly the same sequence of stimuli. Stimulus onset asynchrony was between 1.9 and 2.1 s.

In the first half of the experiment, the subject was asked to respond to the letter A and not to respond to the letters B, C, and D. In the second half of the experiment, the subject was asked to respond to the letters B, C, and D and not to respond to the letter A. These 2 conditions were called the "improbable go" and the "improbable nogo." Subjects were instructed to respond as quickly and as accurately as they could. This paradigm ensured that in the second half of the experiment, the subject had to inhibit an infrequent prepotent response, the prototypic nogo situation.

Each half of the experiment consisted of 3 blocks of stimuli. The first block was a practice block, wherein the subject received direct visual feedback about whether their responses were correct or incorrect (and the stimulus onset asynchrony was therefore slower than in the experimental blocks). The practice block continued until 10 correct trials were performed. The practice block was then followed by 2 experimental blocks, each containing 50 stimuli. In these blocks, the subject did not receive any feedback. The patients had little difficulty learning the response requirements or changing their behavior between conditions, with an average of 10.2 trials for the first practice block and 10.8 trials for the second.

We decided not to randomize or balance the order of the blocks. This, together with the intervening practice condition, decreased the liability of confusion between the 2 experimental conditions. The pseudorandom stimulus sequences were exactly the same for each of the 2 halves of the experiment. Maintaining these sequences across the experimental conditions and the subjects prevented interactions between unusual sequences and patient groups.

The paradigms were programmed using Micro Experimental Lab (MEL2, Psychology Software Tools, Inc. Pittsburgh, PA) and run on a PC computer. Subjects responded by pressing the first (leftmost) button on a MEL s200A serial response box with the index finger of their preferred hand (the right in 40 of the 43 frontal patients and in 33 of the 38 normal subjects).

Measurements

The experiment provided 2 main measurements: the accuracy of a response and the RT. The accuracy of response gave us 2 kinds of errors—either misses or false alarms. Beacuse subjects responded with one button to whatever stimuli were "targets," and withheld their response from the nontarget stimuli, RT measurements were only available for correct responses and for false alarms. We also calculated the individual standard deviation (ISD) of the RT on correct response trials in order to assess its variability (cf., the "dispersion" measurement of Stuss and others 2003). When expressed as a percentage of the RT for each condition and subject, this gave the coefficient of variation.

In addition to the average RTs over each block of trials, we also performed a sequential analysis of the RTs within a block. Because data for some trials were lost in 2 of the CTL subjects, we restricted this evaluation to the 36 CTL subjects with complete data sets. This analysis allowed us to obtain the average RT on trials immediately before and after an error in the improbable nogo blocks. Before-error trials that followed directly after a preceding nogo stimulus were omitted from this analysis. Because some subjects had no false alarms, these findings were evaluated only for the general pattern of results and not statistically analyzed.

Analyses

A sequence of analyses of variance (ANOVAs) evaluated the experimental effects (cf., Stuss and others 2005). An overall ANOVA compared the 5 separate groups of subjects, and 4 separate contrasts compared each of the patient groups with CTL. This analysis determined whether any patient group was behaving abnormally. If this occurred, a final ANOVA compared that patient group with all the other patients combined in order to determine if the abnormality was specific to the localization of the lesion. (This analysis would likely not show findings if more than one group of patients was abnormal.) All analyses of the RTs were performed using the basic simple RT to the stimulus A as a covariate (see Stuss and others 2005). This did not significantly change the results. We used a criterion for significance of $P < 0.05$.

If the group analysis based on large subdivisions of the frontal lobes showed significant effects, we also localized the abnormal behavior using more refined architectonic divisions (Stuss, Alexander, and others 2002). For each area of the frontal lobes (Petrides and Pandya 1994), we compared the performance of patients with lesions affecting at least one quarter of that area with the performance of patients who had no damage to that area (Stuss and others 2005). The frontal lobes were divided into 32 cortical areas (16 in each hemisphere) and 7 extra subcortical areas (thalamus, basal ganglia, septal region, etc). Because the actual lesions extended beyond the limits of our grouping (based on where the lesion was most prominent), the number of patients with lesions to one particular area often exceeded the number of patients in the group that contained that area. The comparisons were assessed using a *t*-test for the continuous variables (mean RT and coefficient of variation) and a Mann–Whitney *U* for errors. Significant comparisons were only accepted if the area was lesioned in 2 or more subjects (65 of

the possible 71). Areas showing significant differences at an alpha level of $P < 0.05$ were considered important to the performance being measured. Areas with $0.05 < P < 0.10$ were categorized as likely involved.

It is difficult to assess the actual false detection rate when performing these multiple tests. The probability of finding significant results depends on the number of tests, the distribution of the measurements, the distribution of the lesions, and the distribution of the overlap of the lesions. We modeled these effects using random permutations of the data set of observed measurements. A set of dummy architectonic areas was programmed, each area being lesioned in the same number (N) of patients as in the real data—4 areas affected in only 1 patient, 8 areas affected in 2, and so on up to 3 areas affected in 14 patients. The measurement data set comprised 43 observed values, one for each patient. The values of the patients with lesions to a particular area were then assigned by randomly permuting the data set, taking the first N values as the values for patients with lesions to that area, and making the remaining $43 - N$ values the measurements for those patients without a lesion to that area. This permutation process occurred 69 times, once for each area (2 of the 71 areas were not lesioned in any patient). Using alpha levels of 0.1, 0.05, 0.01, and 0.005, the comparison processes detailed in the previous paragraph then identified the areas in which patients with lesions to those particular areas had significantly different scores than patients without lesions to those areas. The whole procedure was repeated in several blocks of a thousand replications each to estimate the expected incidence of areas showing significant effects. This process did not specifically model the overlap among lesions (the fact that any one patient would have lesions in multiple areas) but gave a reasonable approximation of this overlap. These analyses indicated that demonstrating 1 or 2 areas significant at $P < 0.05$ was highly likely (occurring in more than half the randomized data sets). However, this proportion fell considerably when more than 2 areas were detected and/or when the probability for one or more areas was very low. When this occurred, the data set was essentially dividing itself between patients with abnormal measurements in one set of areas and patients with normal measurements in another set (an unlikely occurrence if the data were randomly allocated to areas). This "permutation probability" gave the likelihood that an equivalent localization pattern might have occurred by chance.

In light of recent work suggesting involvement of the right inferior frontal cortex or the left SM frontal region in response inhibition, we also performed some a posteriori tests of the number of false alarms in patients with lesions to these areas. The number of patients with lesions to particular architectonic regions often exceeded the number of patients within the group that included those areas. This was particularly true for the right inferior frontal cortex because patients with head trauma often had bilateral involvement of inferior frontal areas, and lesions of patients with mainly IM lesions often extended into this area. We grouped the patients with right inferior frontal lesions in several ways (extent of involvement of the affected area, predominance of lesion in that area) but found no significant differences in these groupings. The final analyses were based on 13 patients with lesions to right Brodmann area 44 and/or 45 (9 had lesions to 44), 4 patients with lesions to left Brodmann area 6A and/or 8 (all had lesions to 6A), 26 patients with lesions that spared all these areas, and 38 control subjects. Using Mann–Whitney U statistics, we evaluated intergroup differences in the incidence of false alarms in the nogo improbable condition, the go RT in the same condition, and the size of the lesion.

Results

Reaction Times

The average RT to go stimuli (Table 1) did not differ significantly between the 2 experimental conditions (improbable go and improbable nogo) and did not differ significantly between the first and second recordings within a condition. The RT of the SM patients was significantly slower than the CTL subjects ($F = 7.29$; df 1,76; $P < 0.01$) but was not significantly different from the other frontal patients taken together. In the improbable nogo condition, there were sufficient false alarms to show that the RTs for false alarms were significantly faster than for correct responses ($F = 32.8$; df 1,65; $P < 0.001$), whereas in the improbable go conditions, the false alarms were too few and too variable to examine. The trial-by-trial analysis in the improbable nogo condition showed that the RT speeded up until an error was made and then slowed down on the subsequent trial (Fig. 1). This general pattern was similar in all subject groups, with the SM patients showing relatively longer RTs for all trials.

Variability of RT

The SM patients were more variable in their RTs than controls. This showed in the significantly higher ISD ($F = 11.6$; df 1,74; $P < 0.01$) and coefficient of variation ($F = 7.1$; df 1,74; $P < 0.01$). Table 1 shows the means and standard deviations of coefficient of variation. Variability was not significantly affected by condition.

Errors

Table 2 gives the incidences of the different errors. There was no overall difference among the conditions for the number of misses. However, the SM group showed a much higher incidence of misses than the CTL subjects ($F = 9.58$; df 1,76; $P < 0.01$) and than the other patients combined ($F = 9.58$; df 1,41; $P < 0.05$). In addition, there was a significant group by condition interaction with the SM group showing an increased number of misses in the nogo improbable condition ($F = 10.4$; df 1,76; $P < 0.01$). A much greater number of false alarms occurred in the improbable nogo condition compared with the improbable go condition ($F = 18.0$; df 1,76; $P < 0.001$). The SM group of patients showed more false alarms than CTL subjects ($F = 4.48$; df 1,76; $P < 0.05$), but this rate was not significantly greater than the other frontal patients combined.

Architectonic Localizations

Figures 2, 3, and 4 show the localizations for the 4 measurements that were most significant in the group ANOVAs: the RT for correct responses across blocks, the coefficient of variability

Table 1
RT and its variability

RT	Condition	CTL	LL	RL	IM	SM
Correct RT	Improbable go	401 ± 69	394 ± 83	432 ± 78	409 ± 82	475 ± 136
	Improbable nogo	408 ± 67	377 ± 35	445 ± 77	421 ± 100	482 ± 118
False alarm RT	Improbable go	348 ± 37	342 ± 190		485 ± 224	370 ± 59
	Improbable nogo	298 ± 43	302 ± 30	325 ± 33	329 ± 64	355 ± 65
Coefficient of variation (%) (correct RT)	Improbable go	16 ± 4	19 ± 5	16 ± 5	17 ± 4	19 ± 9
	Improbable nogo	23 ± 6	20 ± 5	24 ± 9	22 ± 9	27 ± 9

Note: Means and standard deviations. The patients in the RL group had no false alarms in the improbable go condition.

of the RT across blocks, and the false alarm rate in the nogo improbable condition. Even though the group ANOVAs implicated the same SM group of patients, the localizations obtained by relating lesion site to behavior differed for each abnormality. The slowness of RT localized to the medial regions of the right frontal lobe, this degree of localization being significant on the permutation tests at $0.01 < P < 0.05$. The variability of the RT localized to both the right medial frontal lobe and the right ventrolateral frontal lobe. This degree of localization was highly significant on the permutation tests ($P < 0.001$) because it was highly improbable to randomly localize the high variability scores to about a quarter of the areas and not to the others. The false alarm rate localized to the left SM regions (particularly the dorsolateral part of area 6A where the probability of the comparison was $P < 0.004$). The permutation test of this localization showed $0.01 < P < 0.05$. The miss rate localized to several regions of the right frontal cortex including both the anterior cingulate ($P < 0.008$ for area 24s) and the adjacent dorsolateral region. This degree of localization only showed $0.05 < P < 0.10$ on the permutation test, probably because the increased incidence of misses only happened in a few subjects. Subcortical regions (not shown in the figures) were not specifically included in the localizations except for the right basal ganglia (caudate and pallidus) that were implicated in the variability at $P < 0.05$ and in the misses at $0.05 < P < 0.10$.

Right Inferior Frontal and Left Superior Medial Areas

The data for the patients with lesions to the right inferior frontal and left SM areas are summarized in Table 3. The incidence of false alarms was significantly greater in the patients with lesions to the left SM areas than in any of the other groups ($P < 0.01$ vs. controls, $P < 0.01$ vs. other patients, and $P < 0.05$ vs. right inferior). None of the other comparisons of false alarm rates was significant. There were no differences in the RT among the groups. The lesion size tended to be larger in the 2 selected patient groups ($P < 0.01$ for the right inferior frontal and $P < 0.06$ for the left SM) than in the other patients. The correlations within the patients between the incidence of false alarms and the RT ($r = 0.08$) or lesion size ($r = 0.19$) were not significant.

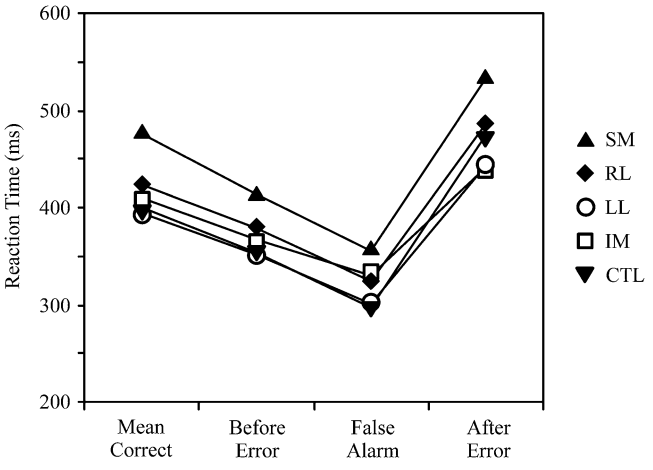

Figure 1. RTs during the improbable nogo condition. The first set of data represents the mean RTs for correct responses to the go stimuli. The subsequent 3 sets of data show the RTs on the trials immediately before a false alarm, for the false alarm response, and on the trials immediately after a false alarm. The SM group of patients shows longer RTs than the other groups. All subjects showed a speeding up of the RT before a false alarm, a faster RT for the false alarm, and a slowing down after the error.

Discussion

Our data replicate the increased false alarm rate that occurs during go–nogo tasks in patients with damage to the frontal lobes. This abnormality was most evident in patients with SM frontal lesions (i.e., our SM group). This fits with the localization originally suggested by Drewe (1975b) and the limited later lesion data. In addition to the increased false alarm rates, the SM group of patients also showed an increased rate of misses, a generally slow RT, and a greater RT variability.

Architectonic Localization

One of the difficulties of using patient groups is the inevitable heterogeneity within each group. Thus, patients within our SM group had lesions that may have been bilateral or unilateral, that may have been maximal on the left or the right, and that may have extended more or less to the superior regions of the dorsolateral cortex. The "architectonic localization" technique that compares the behavior of patients with lesions to particular regions of the frontal lobes with the behavior of patients in whom those regions are intact can help distinguish more specific localizations within the general region subsumed by the SM grouping. In this go–nogo paradigm, 3 different sublocalizations occurred—a right medial frontal localization for the RT slowing, a combination of right medial and right ventrolateral frontal localizations for the response variability, and a left SM localization for false alarms.

Prior to discussing these separate localizations, we should briefly consider the technique on which they are based. Lesion localization of neuropsychological deficits has usually relied on superimposing the lesions of a group of patients with a particular deficit. The deficit is then localized to the area of the brain that is common to all (or most) patients. This approach is illustrated by the important work of Kertesz and others in localizing the cerebral basis for different types of aphasia (Kertesz 1979). One problem with this approach involves the multi-dimensionality of the behavioral abnormality: for example, does lesion overlap in patients with Broca's aphasia indicates the cerebral source for fluency or syntax? As pointed out by Rorden and Karnath (2004), another problem is that the overlap is confounded by how often different regions of the brain are

Table 2
Errors

RT	Condition	CTL	LL	RL	IM	SM
Misses	Improbable go	0.0	0.0	0.0	0.3 (0–4)	1.1 (0–13)
	Improbable nogo	0.0	0.0	0.4 (0–3)	0.5 (0–5)	5.6 (0–39)
False alarms	Improbable go	0.2 (0–1)	0.8 (0–3)	0.0	0.5 (0–3)	0.2 (0–1)
	Improbable nogo	8.0 (0–29)	13.3 (4–38)	7.6 (0–17)	11.4 (0–46)	15.2 (4–46)

Note: Incidence of errors (expressed as a percentage of the total number of trials wherein each error was possible) shown for all subjects in each group in each condition. Numbers in brackets show the range of incidences within a group of subjects.

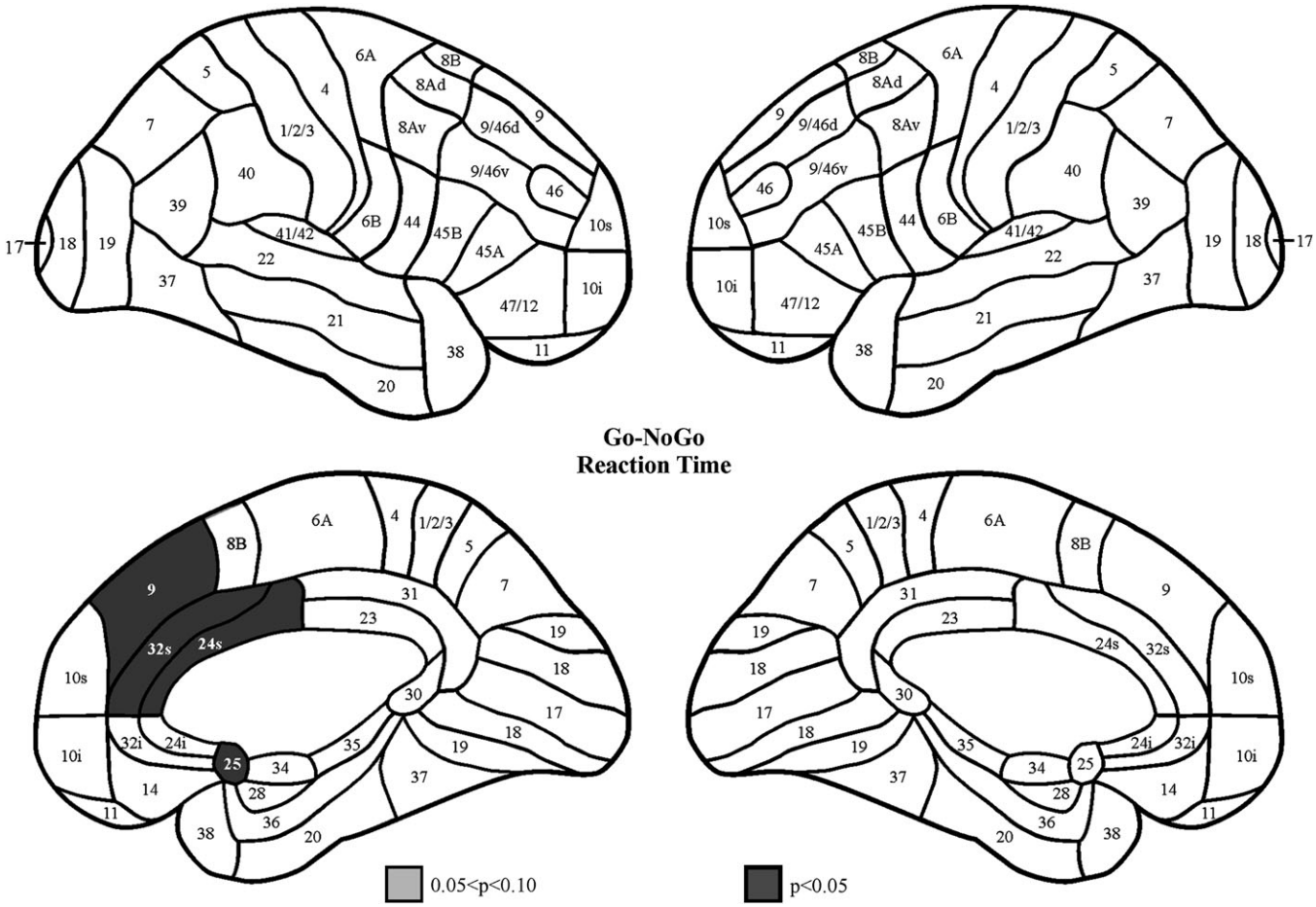

Figure 2. Localization of lesions related to slowness of the RT. The RTs for correct responses (collapsed across all experimental blocks) of patients with lesions to each architectonic area were compared with the RTs of patients without lesions to that area using a *t*-test. Areas where the *t*-test showed a significantly longer RT are shaded according to the criterion reached by the test.

affected by lesions—regions most frequently affected tend to show up in an overlap analysis whether or not they are essential to the behavior. In order to prevent this, Rorden and Karnath proposed that brain images from patients without a particular deficit should be subtracted from brain images of patients with the deficit. Their approach used a binary categorization—whether a deficit was present or not. Our approach involves a comparison of affected and spared regions but maps a full continuum of a behavioral variable (the latency of the RT or the incidence of errors) onto different areas of the brain and picks those brain regions where the variable is most abnormal (Stuss, Alexander, and others 2002). We have called this technique "architectonic localization" (Stuss and others 2005; Picton and others 2006) or "hot spot" (Alexander and others 2005). This technique maps lesions from MRI or CT scans onto a template based on architectonic classification of cortical regions (Petrides and Pandya 1994). Voxel-based lesion-symptom mapping (Bates and others 2003) uses a similar relation of behavioral abnormality to lesion location (and uses a similar set of *t*-test comparisons) but is based on voxels rather than architectonic regions.

The architectonic localizations proposed in this paper should be interpreted cautiously for several reasons. First, the localizations derive from a small number of patients (even though our numbers are greater than in most published lesion studies). Each architectonic area was involved in the lesions of between 2 and 12 patients (we did not consider regions lesioned in only 1). Larger numbers would clearly provide more power and probably give more focal findings. Second, statistical problems occur when performing such a large number of comparisons. We used permutations to model the data sets, but this did not fully evaluate such things as anatomical sizes and relationships of the different areas. However, we only considered architectonic localizations for the behavioral results that showed significant differences on an initial group ANOVA based on the locations of the most prominent lesion. The hot spot technique was used to indicate the probable sublocalizations of the mechanisms giving rise to the main results. Third, our localizations cannot be resolved beyond the architectonic resolutions we are using. For example, we cannot decide whether a lesion disrupts the SMA or the pre-SMA, both of which are located in the medial regions of Brodmann area 6 (Picard and Strick 1996). Fourth, the localization process depends on a reasonable distribution of lesions. If most of the lesions involve one particular area, comparisons of the behavior caused by lesions in that area with that caused by lesions in other areas become difficult to assess. If patients with lesions to a particular area are not available, the technique will not identify that area no matter how necessary it is to task performance. We selected patients as best we could to provide coverage of all the prefrontal regions (Stuss and others

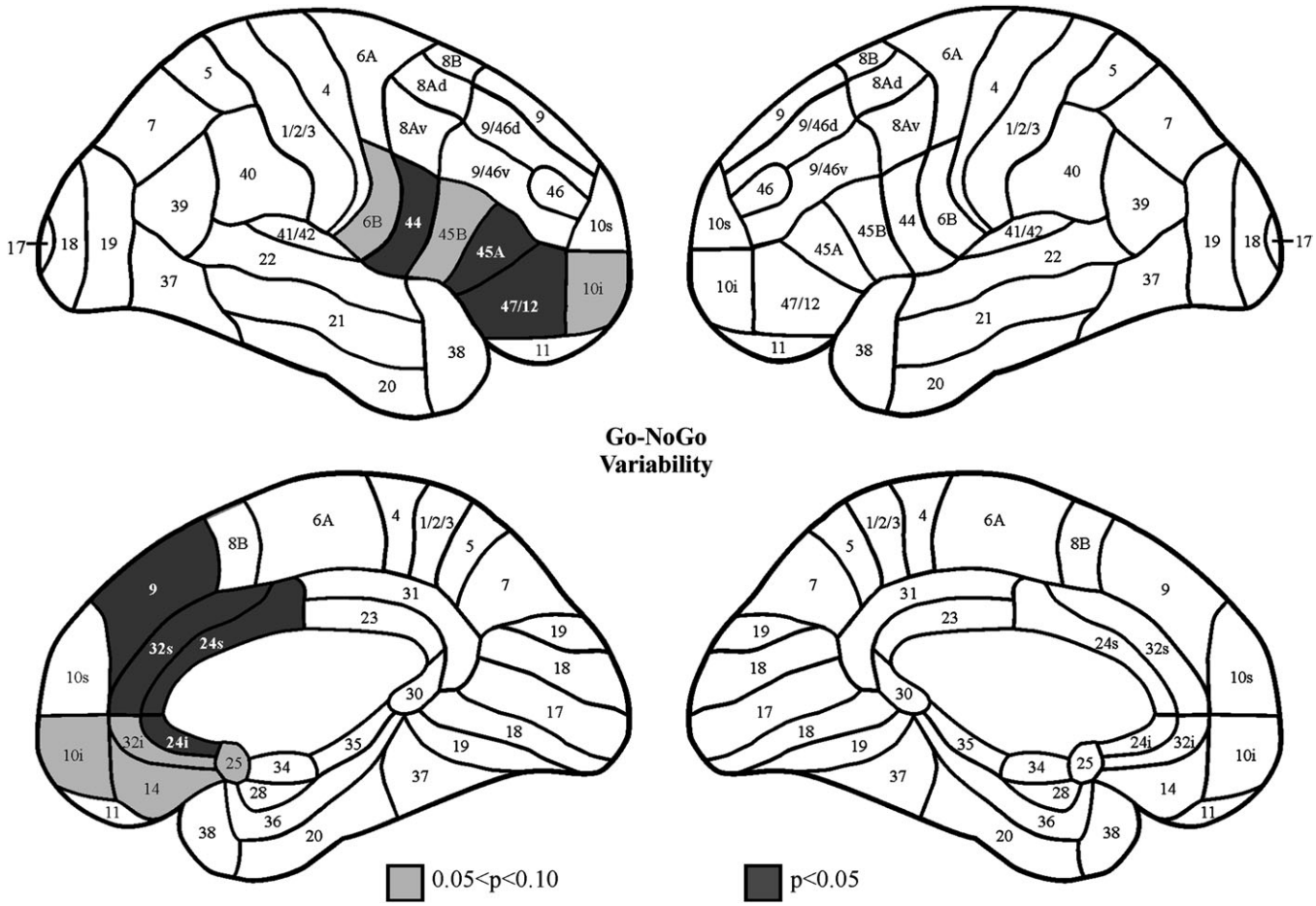

Figure 3. Localization of lesions related to variability of the RT. The comparison measurement was the coefficient of variability collapsed across all blocks.

1995). Finally, as is true of any lesion analysis, it is impossible to dissociate the effects of a cortical lesion from the effects of a concomitant disruption of fibers passing just beneath the cortex to connect to other areas of the brain. With these caveats in mind, we can nevertheless consider the results. We shall begin with the false alarms because the main orientation of the paradigm was to investigate their increased incidence in patients with frontal lesions.

Inhibition of Response

The cerebral processes that occur during the go–nogo task are not fully understood. Clearly, the brain must set up some connections between the visual areas that recognize the go stimulus (or stimuli) and the regions of the brain that initiate the finger movements that press the button. Withholding a response to the nogo stimuli may theoretically not require an active inhibitory process. The connections between recognizing the nogo stimuli and the response system could simply not be activated. If this were so, false alarms would probably never occur. However, this is not the case when inhibiting a response made prepotent by prior experience. In the go–nogo paradigm, the brain likely prepares to respond to any visual stimulus but specifically inhibits the ongoing response whenever a nogo stimulus is recognized. This setup readily explains why false alarms occasionally occur (when the inhibition is too little or too late). Measurements of peripheral motor excitability suggest that inhibition occurs during choice RT tasks (Burle and others 2004). This pattern of processes is similar to what must be happening in the stop-signal paradigm (Aron and others 2003) except that in the go–nogo paradigm, the same stimulus is both initiating and stopping the response. In our improbable nogo paradigm, false alarms were frequent because of the higher probability that any stimulus requires a response. In our particular experiment, false alarms were also prominent in this condition because the subjects had used the opposite stimulus-response mapping on previous trials, and a clearly prepotent response had to be inhibited.

Our major measurement of defective response inhibition is the incidence of false alarms. Our localization data suggest that left area 6A—which includes the SMAs and the PM regions for the hand—is crucially involved in the inhibition of response (Fig. 4). Other regions of the left frontal cortex may also be involved: area 8B, area 9/46, and area 14. The left lateralization of this effect is most easily explained by the relationship to the right hand used by the 40 of the 43 patients when responding. The motor response itself was not significantly affected: the RTs of patients with lesions involving these areas were not significantly different from the other patients. Further justification of a relationship to the response hand would require testing left-handed patients with PM lesions and/or testing right-handed patients responding with their left hand. Because Talati and Hirsch (2005) balanced out the effect of response hand and found greater fMRI activation of the left medial frontal region

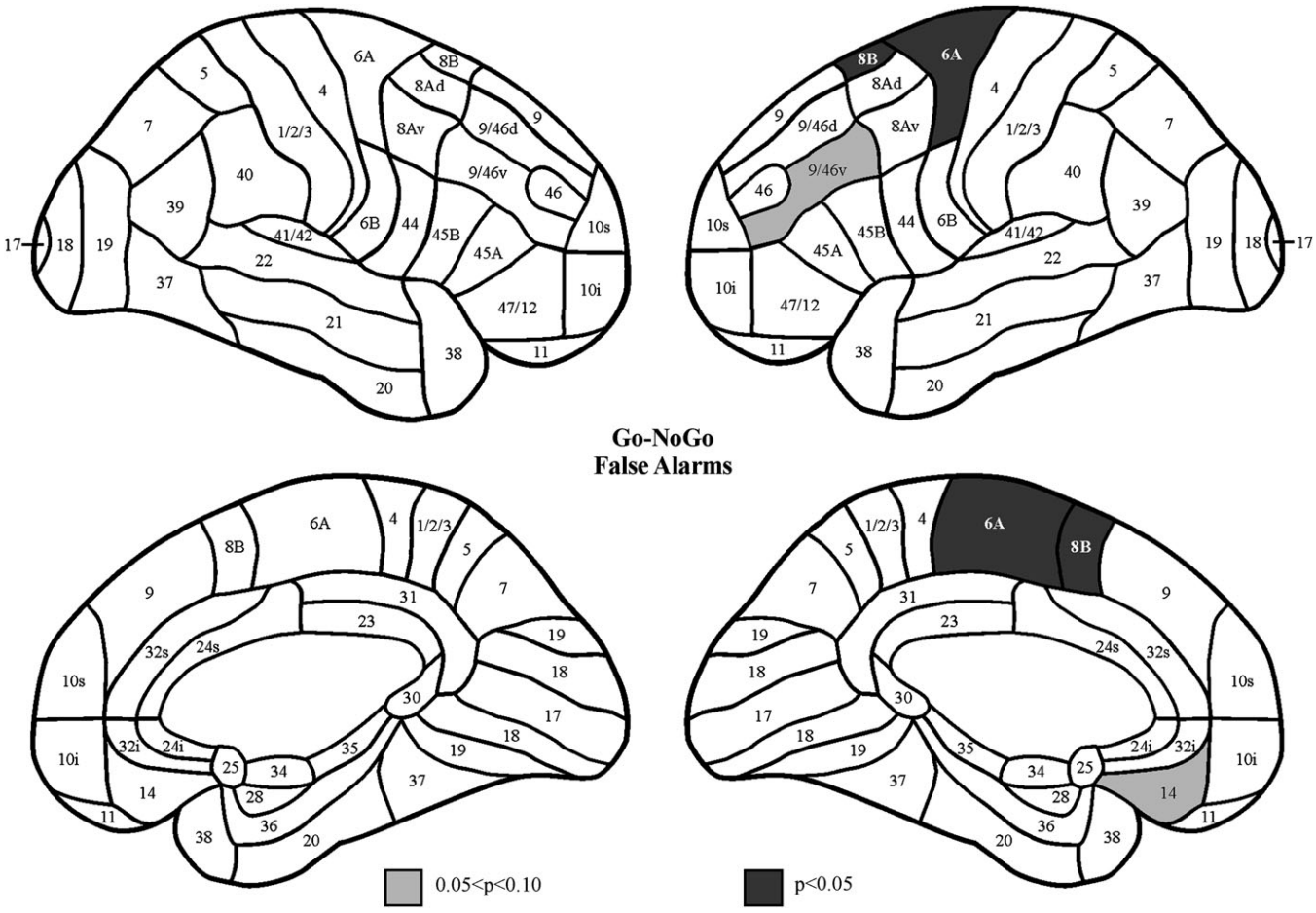

Figure 4. Localization of lesions related to false alarms. The comparison measurement was the incidence of errors in the improbable nogo blocks.

Table 3
Right inferior frontal and left SM

Measurement	CTL	Right 44, 45	Left 6, 8	Other patients
Number	38	13	4	31
False alarms (% and range) (nogo improbable)	8.0 (0–29)	11.9 (0–25)	30.2 (12–46)	10.1 (0–46)
RT (ms) (nogo improbable)	408 ± 67	422 ± 76	410 ± 66	422 ± 108
Lesion size (% whole brain)		3.7 ± 2.8	4.9 ± 4.7	1.5 ± 1.2

(area 6) during a go–nogo task when the deciding information was object based (rather than location based), it is possible that the left area 6 may be involved in nogo motor control independently of the response hand.

The superior part of area 6 is active in multiple electrophysiologic (e.g., Ball and others 1999) and fMRI (e.g., Humberstone and others 1997; Kurata and others 2000; Sakai and others 2000) studies of simple motor behavior. Transcranial stimulation of the PM regions of the cortex can change motor excitability in the contralateral hand independently from direct stimulation of the motor cortex (Gerschlager and others 2001; Rizzo and others 2003). The different regions of the superior area 6 likely interact in many ways during motor responses (see reviews of Picard and Strick 1996, 2001). On the medial aspect, the pre-SMA may maintain the stimulus-response rules controlling the required behavior and select a response (or the inhibition of a response) as required by the presently perceived stimulus. The SMA may run the programs that actually initiate the response (once the stimulus has been recognized) and control the execution of the motor activity. The more lateral PM cortex may control such response requirements as its speed and force, particularly as these might relate to stimulus parameters. The resolution of our localization was insufficient to differentiate among these subcomponents of area 6.

We reviewed the lesion and neuroimaging literature associated specifically with go–nogo performance in the introduction to this paper. These studies reported many different regions of the frontal lobes to be involved in response inhibition. The most common are the right inferior frontal regions and the SM region of the frontal cortex (area 6, SMA, and pre-SMA). Our data (Fig. 4) compare reasonably well with the imaging data of Mostofsky and others (2003), who found selective activation of the left SM region of the frontal lobe (area 6) during nogo trials, and with the findings of Li and others (2006), who found that subjects

who were able to inhibit responses more effectively showed greater activation of the left superior frontal gyrus (area 8) and left precentral gyrus. Interestingly, Mostofsky and others (2003) found additional activation of right dorsolateral prefrontal cortex when the nogo task was made more complex.

Inhibition of response is also an essential part of the "stop-signal" tasks wherein the subject responds to certain stimuli unless a stop signal occurs at the same time as or immediately after these stimuli. Aron and others (2003) found that lesions to the right inferior frontal gyrus disrupted stop-signal inhibition and that the amount of disruption varied with how much this area was involved by the lesion. Other studies of the stop-signal paradigm have shown that patients with lesions to the right frontal cortex or bilateral lesions were more affected than patients with left frontal lesions (Rieger and others 2003). A recent study measured the effect of disrupting the right inferior frontal region of the brain using a 15-min period of TMS (Chambers and others 2006). This increased the stop-signal RT and the number of false alarms, whereas control TMS to more dorsal regions of the right frontal lobe or to the right parietal lobe had no effect. However, the effect was not present when the TMS was repeated suggesting that the networks underlying inhibition can functionally reorganize to allow other regions to take over the processes normally mediated by the right inferior frontal cortex.

Inhibition of response is an essential part of many other experimental paradigms: stimulus-competition tasks (such as Stroop or flanker tasks) wherein a subject must selectively respond to one aspect of a stimulus and not to others, response-compatibility tasks wherein the response is not the one that has been learned, negative priming tasks wherein a subject responds to a stimulus that was ignored or suppressed on a preceding trial, and task switching wherein previously successful stimulus-response connections must be changed. Negative priming (the slowed response to a target that was a distractor on the preceding trial) can be decreased (or even converted to positive priming) in some patients with frontal lobe lesions (e.g., Stuss and others 1999; Metzler and Parkin 2000; McDonald and others 2005) but not all (e.g., Dimitrov and others 2003). Stuss and others (1999) reported a right lateralization to deficits in negative priming, although when the tasks became more complex, left frontal lesions could also cause a deficit. McDonald and others (2005) reported that left medial frontal lobe excisions caused a deficit in negative priming in a task involving a verbal response. Aron, Monsell, and others (2004) have shown that greater damage to the right inferior frontal cortex is associated with larger switch costs on a task-switching paradigm. Aron, Robbins, and others (2004) and Aron and Poldrack (2005) reviewed these and other studies and proposed that inhibition is mediated by the right inferior frontal cortex.

Two studies have made fMRI recordings during several tasks involving inhibition in order to determine which areas were commonly active in all tasks. Rubia and others (2001) reported that go–nogo and stop tasks both activated several regions of the right frontal lobe (anterior cingulate, middle frontal gyrus, pre-SMA, and inferior frontal gyrus). Comparing the 2 tasks, they found that go–nogo tasks showed increased activation of the left dorsolateral prefrontal regions, medial, and parietal cortices. Wager and others (2005) used go–nogo, flanker, and stimulus compatibility paradigms to show common activation of the right dorsolateral prefrontal cortex (9/46), anterior cingulate, and right medial prefrontal cortex (area 8). The specific process of inhibiting a response is likely controlled by higher cognitive processes that show up as activation in other prefrontal areas.

Other stimulus paradigms involve inhibiting responses to which a subject has become predisposed in other ways. The Stroop paradigm, wherein a subject responds to the color of the word rather than the color named by the word, is the most widely studied. We have found that errors in color naming are frequent in patients with LL frontal lesions, but that incongruency effects (slowing and false alarms) were most evident in patients with medial frontal lesions (Stuss and others 2001). Barber and Carter (2005) found that several regions of the prefrontal cortex (left and right dorsolateral, anterior cingulate, and left anterior) were activated when subjects prepared to inhibit a prepotent response and that medial and superior frontal regions (Brodmann areas 6 and 32) were activated when the correct response was made (and the prepotent response inhibited). In paradigms in which the inhibition of response is not prominent, lesions to other areas of the brain might cause a higher incidence of false alarms: Stuss, Binns, and others (2002) suggested that the left dorsolateral frontal cortex might be concerned with setting the criterion of response during stimulus discrimination. If the criterion is not properly set, false alarms may result.

Although area 6 may be specifically concerned with the execution or inhibition of response, other areas of the prefrontal cortex are therefore likely involved in supervising these activities. One might speculate that the inhibition of a response made potent by past experience or present probability might involve the LL frontal cortex in setting up the task requirements, the RL frontal cortex in monitoring or changing the response setup, and the anterior cingulate in ensuring that the systems of control do not fade with time. The areas exerting control over the inhibition may be more widespread and less susceptible to the effects of focal lesions than areas specifically mediating response inhibition. This might explain the more restricted localization in lesion studies than in activation studies. Our patients with focal lesions to the frontal lobes were able to follow instructions and perform relatively well. However, lesions to area 6 still specifically interfered with response inhibition.

Missed Responses

We did not expect the patients with frontal lesions to miss responding to the go stimuli as well as incorrectly responding to the nogo stimuli. Nevertheless, the SM patients as a group missed responding more frequently than patients with lesions to other areas of the frontal lobes. Stuss, Binns, and others (2002) also found that SM patients made more errors of omission. The architectonic localization for the misses in our present data suggested involvement of the right anterior cingulate but this did not quite reach significance on the permutation tests. The misses were most frequent in the nogo improbable conditions. Because these conditions always occurred after the go improbable conditions, we cannot determine whether this increased frequency was related to the stimulus probabilities or to the passage of time in the experiment (and an increase in fatigue or boredom). In some of the other ROBBIA paradigms, patients with lesions to this area were unable to maintain their performance over time (e.g., responding in time with a pacing stimulus in Picton and others 2006),

but this was not true of others (e.g., a continuous RT test in Alexander and others 2005). We have proposed that the anterior cingulate region is responsible for energizing the necessary schemata that control stimulus-response connections. In the go–nogo paradigm, this would include maintaining the go-stimulus connections despite their continuous use.

Hemodynamic activation of the anterior cingulate occurs in almost any task that requires decision making and is greater when conflict is inherent in the decision. The general interpretation (e.g., Posner and Peterson 1990; Carter and others 2000; Paus 2001; Ridderinkhof and others 2004) has been that the anterior cingulate is involved in such processes as the allocation of attentional resources, target detection, cognitive control, or conflict monitoring. However, Fellows and Farah (2005) have recently shown that patients with lesions to the anterior cingulate (3 left and 1 bilateral) showed no obvious deficits in tasks such as the Stroop and go–nogo, which require ongoing cognitive control. Our patients with lesions specifically affecting the anterior cingulate did not show the increase in false alarms that would be expected with a deficit in cognitive control. They did show, however, an increase in misses, together with a slowing and an increased variability of RT.

Slow RTs

Patients with SM lesions showed significantly slower RTs than control subjects. This abnormality occurred for both correct and incorrect responses (Fig. 1) and was particularly related to the right anterior cingulate region (Fig. 2). Significant slowing occurred in this group of subjects in other ROBBIA paradigms that involve more than a simple RT (warned or unwarned choice RT in Stuss and others 2005; continuous choice RT in Alexander and others 2005). Fellows and Farah (2005) showed that patients with lesions to the anterior cingulate were significantly slower than matched controls by about 100 ms (their Table 3)—our difference was about 75 ms (Table 1). We have attributed this slowing to a deficit in the energization of stimulus-response schemata (discussed in Alexander and others 2005; Stuss and others 2005).

Variability of RT

Patients with frontal lobe lesions show inconsistency and variability of performance (Stuss and others 2003). In our present group of patients, this variability was most prominent in the SM group of patients, whereas in the study just mentioned, it was present in LL, RL, and SM patients. The abnormal variability was evident when measured either as the ISD or as the coefficient of variability. The coefficients of variation in the present paradigm (Table 1) are similar to those reported in the study of Stuss and others (2003). The architectonic evaluation (Fig. 4) suggested that lesions to either the right anterior cingulate or the right ventrolateral frontal cortex could increase the variability or performance. This raises the possibility that variability may come from disrupting either of 2 different processes. Consistency of performance requires that stimulus-response schemata be sustained so that they can continue to handle the incoming stimuli. It likely also requires some monitoring process that can trigger reenergization if performance begins to flag. Our previous studies (Alexander and others 2005; Stuss and others 2005) have suggested that the right SM regions are concerned with energization and the RL regions with monitoring. These processes would be more required in our task that used (and changed) novel stimulus-response maps than in the simple go–nogo task of Mostofsky and others (2003) that used deeply engrained stimulus-response maps (green go and red nogo). Bellgrove and others (2004) reported that intrasubject variability on the go RT in a go–nogo task was positively correlated with activation of both right and left midfrontal regions (Brodmann areas 44 and 46) and the right parietal region, suggesting that the right hemispheric attentional network is more active in variable subjects, perhaps because such control is more necessary to limit their intrinsic variablity. Some of these areas overlap with the lateral areas noted in our Figure 4.

Variability may indicate adaptability as well as inconsistency. The normal subject adapts the RT to the task, typically speeding up until an error occurs and slowing down immediately thereafter (Rabbitt 1966). All the groups of subjects in the present study did this (Fig. 1). This was striking because patients with frontal lobe lesions are often considered defective in their ability to adapt. Our previous work showed that some groups of patients with frontal lesions (particularly those with LL damage) did not show the usual posterror slowing (Stuss and others 2003). The different results may have been due to the longer interstimulus intervals or the more complex task in the earlier study. Unfortunately, the numbers of patients making more than a few errors in the present study was not sufficient to allow any more specific correlations of error-correction behavior to site of lesion.

Comments on Localization

The intent of this study was to study patients with focal lesions in order to localize regions of the brain that are essential to the performance of particular tasks. Although this approach has a long history, the logic of localization is still not completely clear. Because we do not fully understand how the brain works, we may not know what to look for in terms of the abnormalities that a lesion may cause. In our discussion, we have concentrated on the idea that particular cognitive processes might be localized in particular regions of the prefrontal cortices. Others such as Duncan and Owen (2000) have suggested that the prefrontal regions, or large parts thereof, might function as a nonspecific processor. Yet others such as Goldman-Rakic (1996, also Levy and Goldman-Rakic 2000) have suggested that the dorsolateral prefrontal regions are organized by the type or domain of information (spatial location, object identity, meaning) rather than the processes by which the information is handled. Prefrontal regions may also be organized by both type of process and type of information (Johnson and others 2003).

The methods of localization also vary with the way in which the brain operates. If information is processed in specialized regions, deficits caused by focal lesions should demonstrate the nature of the processing that occurs in these regions. However, if the brain functions as an interacting network, focal lesions may fail to demonstrate abnormalities whenever the network is redundant or plastic. This may explain some of the discrepancies between activation studies (which will demonstrate the various areas that are active during a task) and lesion studies (which are restricted to demonstrating regions essential to a task).

Regardless of how we finally map a model of cognition onto cerebral activity, the evidence of lesions will play a definite role. If focal lesions cause specific abnormalities, these lesions have disrupted processing. In our present study, we have shown that

lesions to the left superior frontal cortex (area 6) cause deficits in withholding responses and that lesions to the right cingulate area (areas 24, 32) cause slowness of response and inconsistency in both its timing and accuracy.

Notes

This research discussed in this paper was supported by grants MT-12853 and GR-14974 from the Canadian Institutes of Health Research. Two of the authors are supported by University of Toronto/Baycrest Chairs: TWP by the Anne and Max Tanenbaum Chair in Cognitive Neuroscience and DTS by the Reva James Leeds Chair in Neuroscience and Research Leadership. MPA receives support from the Posluns Centre for Stroke and Cognition at Baycrest Centre and the Heart and Stroke Foundation of Ontario Centre for Stroke Recovery. Many different clinicians referred patients for testing: D. Katz, D. Izukawa, and M. Mountain. Many research assistants and students helped to take the measurements from the patients: N. Arzumanian, S. Bisschop, B. Boucher, D. Derkzen, D. Floden, R. MacDonald, and A. Savas. Patricia Van Roon helped with the preparation of the manuscript. *Conflict of Interest*: None declared.

Funding to pay the Open Access publication charges for this article was provided by grant funds from the Canadian Institutes of Health Research.

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