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Multiple frontal systems controlling response speed

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Abstract

This study evaluated a model of attention that postulates several distinct component processes, each mediated by specific neural systems in the human frontal lobes. A series of reaction time (RT) tests (simple, choice, and prepare) examined the hypothesis that different attentional processes are related to distinct regions within the frontal lobes. These tests were given to 38 patients with frontal lesions and 38 age-matched control subjects. Lesions were localized both by general regions (superior medial, inferior medial, left and right lateral) and by individual architectonic areas. Lesions in the superior medial (SM) frontal lobes, particularly involving areas 24 and 32 on the right, were associated with slow RT in all tests and with failure to decrease RT after a warning signal. Lesions in the right lateral (RL) frontal lobe, centred in area 9/46v, prevented the decrease in RT with increasing foreperiod that was seen in normal subjects and in patients with lesions elsewhere in the frontal lobes. The ability to energize a response for rapid RT, either generally or specifically following a warning stimulus, is sensitive to lesions of the right SM. Monitoring of stimulus occurrence and response behaviour in order to enhance the speed of response to upcoming stimuli is sensitive to RL lesions.

Keywords: Frontal lobes; Reaction time; Right frontal lateral; Activation; Monitoring; Preparatory signal

1. Introduction

1.1. The general context

Attention functions to facilitate information processing in selected neural systems. Most models of attention emphasize the supervisory activity of an anterior attentional component, a network of different functional sites linked to the frontal lobes (e.g., Mesulam, 1985; Posner & Petersen, 1990). The details of this frontal attentional system have not been fully elaborated, although proposals have been made in both the lesion (e.g., Stuss et al., 2002a; Stuss, Binns, & Alexander, 2003) and the imaging (e.g., Paus et al., 1997; Sturm & Willmes, 2001) literature.

In 1995, in an attempt to specify the frontal attentional system, we (Stuss, Shallice, Alexander, & Picton, 1995) proposed an elaboration of the Supervisory System model of Norman and Shallice (Burgess & Shallice, 1994; Norman & Shallice, 1986; Shallice, 1982). The original model proposed that routine mental procedures are handled using processing modules, schemata linking these modules together for a particular task, and a "contention scheduling" process allowing multiple routine processes to occur in an efficient way.

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For non-routine activities a supervisory system is required to control schemata and contention scheduling. What had been incompletely elaborated were the potential functions of the supervisory system.

Our approach made two key assumptions. The first was that using a set of related tests would allow a critical analysis of the different processes required in the tests. We then reviewed tasks that have been frequently related to the anterior attentional system (Stuss et al., 1995). Patients with lesions of the frontal lobes show deficits on a variety of tasks. We suggested that these tasks could be collapsed into seven basic types of "anterior attentional" tasks (Stuss et al., 1995). *Sustaining attention* is required for tasks when targets occur at a relatively slow rate over a long period of time. *Concentrating attention* is necessary for demanding tasks involving rapidly occurring stimuli. *Sharing attention* is necessary when two or more unrelated tasks have to be carried out at the same time. *Suppressing attention* is required when automatic responses need to be inhibited. *Switching attention* demands shifting attention between tasks requiring different stimulus–response pairings. *Preparing attention* involves getting ready for a task that follows soon after a warning signal. Finally, *Setting attention* requires establishing a set (and a sequence) of appropriate processes to complete an up-coming task. The literature often confuses the task identification with the putative cognitive processes required to complete the task. They are not necessarily inter-changeable terms.

Our new proposal was that the Supervisory System recruited at least five different component processes to perform the seven attentional tasks we had described. These processes are energizing schemata, inhibiting task-irrelevant schemata, adjusting contention-scheduling so that the automatic processes can work more smoothly, monitoring the level of activity in schemata, controlling the "if this, then that" logic required to move through the steps of a task until completed. Based on more recent findings, we also now postulate that Task Setting is a sixth component process occurring in anticipation of, or early in, task performance (Alexander, Stuss, & Fansabedian, 2003; Stuss, Binns, Murphy, & Alexander, 2002b).

The second assumption was that precise localization of lesions in the frontal lobes would clarify exactly how frontal lesions disrupted these processes. We chose lesion research since it allows us to determine regions that are not just functionally but also necessarily involved in the sense that the process does not work when the region is lesioned. The approach proposed several steps of analysis. The first step was to devise tests that might exemplify more precisely the anterior attentional cognitive processes we had hypothesized based on our review of the seven categories of tasks. The second step was to specify both the overlapping and unique processes required for these different tests. The third step was to analyse the effects of focal frontal lesions on the various tests. This required examining enough patients to give reasonably representative samples of different regions of the frontal lobes. The final step was to deconstruct test performances to identify the fundamental attentional processes recruited for each test and the locations of lesions that specifically disrupt these processes.

In order to evaluate this model of attention, we constructed a battery of eleven tests that would comprehensively assess the seven categories of tasks and that, most importantly, could also be defined by the six proposed supervisory processes. The eleven tests (Table 1) were combined together

Table 1
Definitions and hypothesized processes for the ROBBIA reaction time tests

ROBBIA tests	Definition	Hypothesized component processes
Simple RT	Detection of and response to one stimuli that occurs over a prolonged period of time at a relatively infrequent rate	Energizing
Choice RT	Similar to Simple RT but with the additional condition of making a second response to non-target stimuli	Energizing, monitoring, inhibiting
Prepare RT	Same task as given for Choice RT but with the addition of a preparatory signal presented at variable time lengths preceding the stimulus	Energizing, monitoring, inhibiting
Concentrate	Serial choice reaction time task where responses are made to stimuli occurring at a rapid rate	Energizing, adjustment of contention scheduling, (inhibiting)
Count	Counting of stimuli presented at different rates	Energizing, monitoring, task setting
Divide	Responding to two separate and unrelated tasks that are occurring at the same time	Energizing, monitoring, adjustment
Tap	Simple motor task involving a tap response at a fixed rate both with and without an external cue	Energizing, monitoring
Switch	Switching between two different tasks within the same block of stimuli	Energizing, inhibiting, control of logic
Nogo	Suppression of a response to a particular stimulus or class of stimuli	Inhibiting control of logic
Suppress	Suppressing a response to a nontarget stimulus that shares characteristics with a target stimulus	Inhibiting, control of logic, task setting
Set	Establishing a response mode (task setting) when response requirement changes from one block of stimuli to another	Energizing, monitoring, control of logic, task setting

as ROBBIA (ROtman-Baycrest Battery to Investigate Attention). To isolate distinctions between tasks the tests proceeded by stepwise elaborations of the same basic reaction time (RT) paradigm.

This initial paper presents the results of three closely related ROBBIA tests on a large group of patients with precisely localized frontal lesions: simple reaction time (Simple RT), choice reaction time (Choice RT), and prepare reaction time (Prepare RT). We start with these three paradigms, since they provide the opportunity to isolate the most basic processes related to the anterior attentional system. These data will be relevant in understanding performance on more demanding tasks such as switching attention. From a practical viewpoint, they also represent the types of tests that have been most commonly used in lesion studies. Simple RT required a rapid and unvarying response to a constant target occurring at random intervals over a relatively long time. Choice RT required the same response to the same target, but the target appeared randomly mixed with other stimuli requiring a different response. Our Choice RT paradigm differed from other Choice RT paradigms. It was selected since it had proven a sensitive measure of task complexity in patients with traumatic brain injury (Stuss et al., 1989) including mild concussion (Hugenholtz, Stuss, Stethem, & Richard, 1988), and focal frontal lobe damage (Stuss et al., 2002b). The intent of our paradigm was to assess whether this level of complexity affected the component processes involved in Choice RT differentially in frontal lobe subjects compared to controls. Prepare RT required the exact same responses to the same stimuli as Choice RT with a warning signal occurring either 1 or 3 s before the stimulus to be discriminated.

These three tests mainly involve the energization process [initiation and constant activation of the strength of the selected response mode], but hypothetically other processes. If ISI is unpredictable (variable foreperiod), subjects also should benefit from modulating expectancy to anticipate changes in the conditional probability of the stimulus occurring, leading to a decrease in RT as the interval lengthens. We will argue later that this modulation is a form of monitoring (to evaluate the timing of the stimulus) process (Sanders, 1998). Simple RT depends solely on energizing while choice RT also requires substantial monitoring (Bloxham, Mindel, & Frith, 1984) and potentially inhibition to prevent wrong responses (Stuss et al., 2002b). In frontal patients the effect of task complexity in RT tasks has not been consistent. Medial frontal lesions have been associated with deficits in various complex RT tasks (Drewe, 1975; Leimkuhler & Mesulam, 1985; Luria, 1973). In a feature integration task (Stuss et al., 2002b), adding one level of processing complexity resulted in a significant slowing in RT – but only for the patients with left dorsolateral lesions, although a slowing trend was observed for patients with pathology in medial frontal regions. The more complex choice task also resulted in a significant impairment in sensitivity (errors related to the inability to easily differentiate targets from non-targets) for the right lateral patients.

Prepare RT provides the opportunity to assess the benefit of a warning signal at different intervals to assist putative energization and monitoring deficits. Clinical studies of preparation of attention using a warning signal, i.e., the most basic preparation paradigm, have been controversial (Alivisatos & Milner, 1989; Audet, Mercier, Collard, Rochette, & Herbert, 2000; Tartaglione, Bino, Manzino, Spadavecchia, & Favale, 1986). A warning signal speeds reaction time by increasing phasic alertness (Posner, 1978), but optimal alertness can only be held for a brief time (Gottsdanker, 1975). A preparatory signal may facilitate intentional, voluntary, strategic processes for rapid production and response, although the role of intention after preparation is controversial (De Jong, 2000; Meiran, 1996; Rogers & Monsell, 1995). The requirements for preparatory tasks might then be either phasic increased energizing or facilitated contention scheduling. A second factor, not directly related to attention, may be involved in optimal preparation. Time estimation may assist RT when a fixed warning interval is used. RT decreases in normal subjects with the length of the warning interval until an optimal value is reached, usually considered to be between 200 and 500 ms (Bertelson, 1967; Posner & Boies, 1971). If the interval is longer, facilitation is diminished (slower RT) though still evident for up to at least 5 s (Posner & Boies, 1971). We selected 1 and 3 s for the time between the warning signal and the stimulus response signal to be at least partially consistent with previous lesion literature and to take into account the difficulty patients might have if the time were too short. More importantly, these intervals allowed us to test the hypothesis that increasing the difficulty of time estimation with longer intervals contributes to the loss of preparatory effect which, in turn, may prove to be a sensitive indicator of performance associated with particular lesion sites.

To test these claims about tasks and processes, we contrasted Simple RT and Choice RT using a common foreperiod paradigm involving intervals from 3 to 7 s. This range of durations avoids the intervals at which variable foreperiod effects attributed to conditioning have been found, such as those investigated by Los and Van den Heuvel (2001). We used these intervals for two reasons: to provide adequate time intervals to evaluate monitoring and to assure that the patients could do the tests. For Prepare RT pilot studies demonstrated the strongest effects at shorter intervals, and durations of 0–3 s were used.

Attentional deficits are frequent in patients with frontal lobe damage: “From the first examination of the patient, the disorder of attention is noticeable” (Hécaen & Albert, 1978, p. 368). Our goal, using three basic RT tasks – Simple RT, Choice RT and Prepare RT – was to demonstrate the potential dissociations of attentional processes within the frontal lobes with finer anatomical and experimental precision. The inconsistent results in previous studies could be secondary to the substantial disparities in lesion locations in different studies. We assessed frontal groups with more precise differentiation (left lateral frontal, right lateral frontal, inferior medial,

and superior medial) than most previous research, and used a correlation technique to examine finer localizations within the frontal regions.

2. Methods

2.1. Subjects

Thirty-eight patients with a focal lesion predominantly involving the frontal lobes were assessed. Patients were examined between 2 and 109 months post onset (mean = 25 months). Other inclusion and exclusion criteria were absence of severe aphasia, no clinically detectable neglect, no other significant neurological or psychiatric disorders, and an IQ within the normal range (mean = 110.32; in addition, all scores were >90). The etiologies were all acute, acquired disorders: infarction, hemorrhage (including ruptured aneurysms), trauma, and resection of a benign tumour, with no evidence of diffuse brain pathology. The use of varied etiologies enhances the localization differences within the frontal lobes because different etiologies have predispositions for different regions (Stuss et al., 1995). Moreover, the localization of the lesion is more relevant than the etiology (Burgess & Shallice, 1996; Elsass & Hartelius, 1985; Stuss et al., 1994).

The patients were divided into the following anatomical classifications based on our previous research (Stuss et al., 1998, 2000): left lateral frontal (LL, n = 10); right lateral frontal (RL, n = 6); inferior medial (IM, n = 14); and superior medial (SM, n = 8). The lateral groups could include lateral subcortical lesions involving deep frontal white matter and the dorsal caudate (see Stuss et al. (1994) for rationale). Although patients with SM lesions may have had extension into the IM region, no IM patients had lesions involving the SM area (see Stuss et al. (1998) for rationale). In six patients, the pathology extended to nonfrontal structures. In five of these cases (4 RL, 1 SM) the nonfrontal extension was less than 10% of the entire lesion (range: 3.3–8.1, mean = 6.1%). For one patient, in the IM group, the nonfrontal extension was 35%.

All lesions were localized with a standard template (Stuss et al., 2002a), deriving from the methods of Damasio and Damasio (1989). Lesion size was quantified by superimposing the lesion contour for each axial slice on a constant pixel diagram and counting the number of pixels within the lesion area. The percentage of total brain area damaged was obtained by dividing the lesion count by the total pixel count for all axial slices.

The lesions for each patient in this anatomical classification schema are depicted in Fig. 1. The figure shows only 36 patients since the scans of two IM patients had been available for lesion documentation but were lost prior to quantification. The etiology, lesion location, lesion size, chronicity of lesion to time of testing, and handedness of the patients are presented in Table 2.

The patients were compared to 38 non-patient control (CTL) participants, matched as closely as possible to the patients for sex, age, and education (Table 2). All subjects, including the patients, responded with their dominant hand. In the patients with lateral pathology, all were right handed. In the medial frontal group, where handedness was likely not a factor, four were ambidextrous (two in each of the two medial groups) and one left handed (IM). None of the patients had significant motor weakness. All subjects reported normal colour vision. Measures of neglect (line bisection and double simultaneous stimulation) were normal in all groups. The National Adult Reading Test-Revised (NART-R; Blair & Spreen, 1989) provided a measure of general intellectual ability. Other neuropsychological test measures were the Digit Span forward and backward (Wechsler, 1981), Token Test of language comprehension (De Renzi & Vignolo, 1962), Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), Judgment of Line Orientation (Benton, Hamsher, Varney, & Spreen, 1983), and the Beck Depression Inventory (Beck & Steer, 1993). The results of these tests are presented together with the demographic data in Table 3. The project was approved by the University of Toronto/Baycrest Centre Human Subjects' Research Ethics Committee and consent for participation in the project was obtained for each participant according to the declaration of Helsinki.

3. Experimental procedures

3.1. Apparatus

The stimuli were presented on a 14 or 15 in. colour monitor, controlled by a personal computer (486 or Pentium). The subject sat approximately 40 cm from the monitor. The stimuli subtended a visual angle of 2.1°. Programming was carried out using MEL2 (Psychology Software Tools, Inc.), and responses were made on a MEL s200A serial response box, with five buttons (numbered 1–5 from left to right) aligned horizontally at 0.5 cm spacing.

3.2. General instructions and procedures

Subjects were instructed to respond as quickly and accurately as possible. For all RT test analyses, the first two trials of each block were eliminated to minimize variability due to lack of preparation or initial inattentiveness. Where possible, conditions were repeated either within the task or, in some cases, at different times of day, to measure response stability. Before each test, practices were held to ensure that participants understood the demands, and could perceive all the stimuli. None had difficulty.

The three tests reported in this paper were part of the larger reaction time battery, which was administered over approximately 5–6 h of testing, intermixed with general history, neuropsychological tests, measures of inclusion and exclusion (such as colour identification, naming, and neglect) and

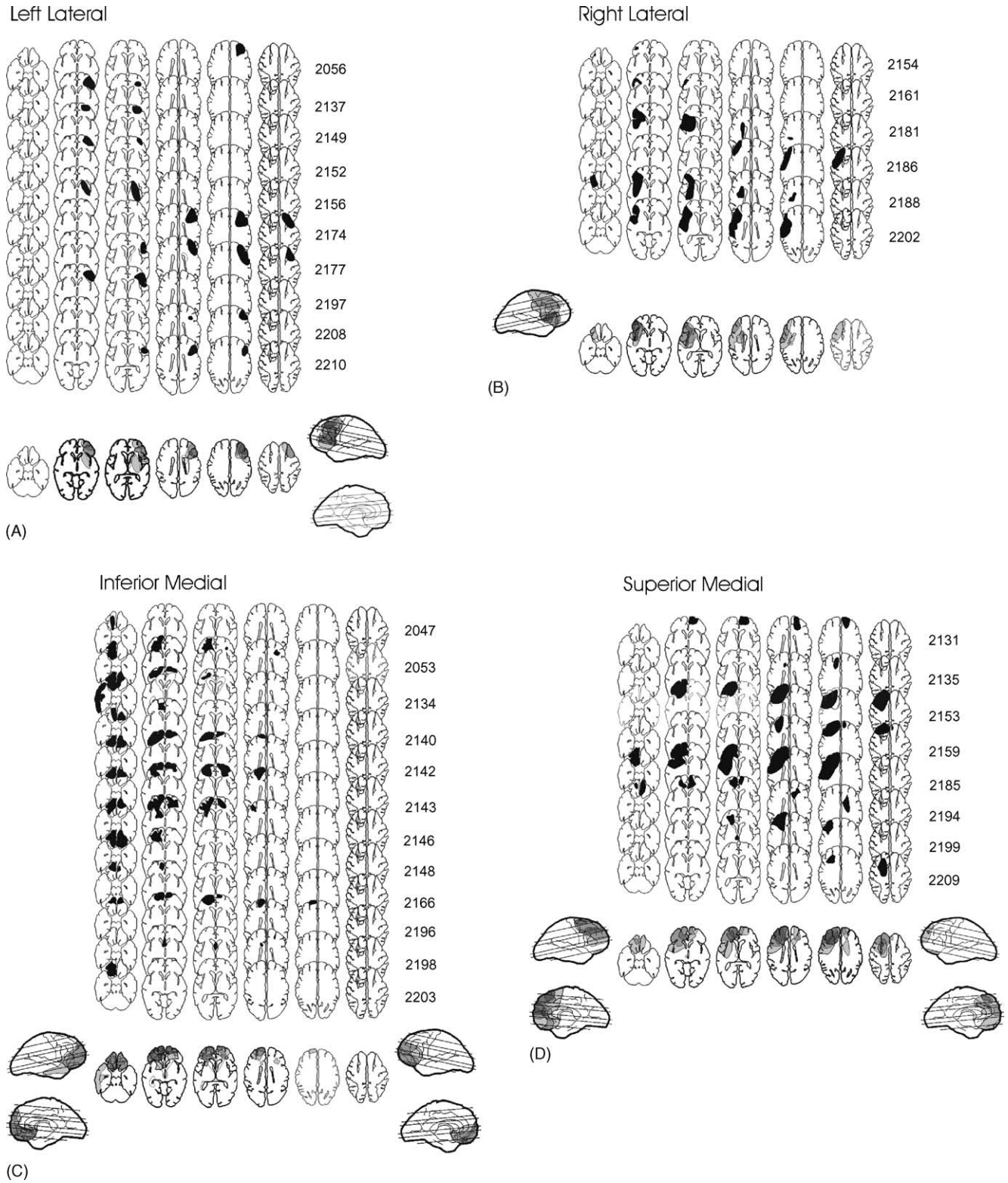

Fig. 1. (A–D) Lesion location of each subject within the four patient groups. (A) Left lateral frontal (LL); (B) right lateral frontal (RL); (C) inferior medial (IM); (D) superior medial (SM). Overlaps of the lesions of all subjects in each group are also presented. Lesion scans for subjects 2069 and 2160 in the inferior medial group had been available for lesion documentation and lost prior to depiction and quantification. Descriptions of lesion locations for all patients are listed in Table 2.

Table 2
Etiology, lesion location, lesion size, time since injury, and handedness within patient groups

Subject	Etiology	Lesion location[a]	Lesion size[b] (%)	TSI (months)	Hand
Left lateral					
2056	Tumour	Dorsolateral	0.6	24	Right
2137	Trauma	Ventrolateral	1.3	95	Right
2149	Trauma	Dorsolateral	0.2	7	Right
2152	Trauma	Dorsolateral	0.2	8	Right
2156	Stroke	Caudate	1.1	6	Right
2174	Stroke	Dorsolateral, ventrolateral	2.0	24	Right
2177	Tumour	Dorsolateral, ventrolateral	3.3	7	Right
2197	Trauma	Dorsolateral, ventrolateral	1.3	2	Right
2208	Tumour	Dorsolateral	0.4	14	Right
2210	Tumour	Dorsolateral, ventrolateral	0.8	22	Right
			1.1	21	
Right lateral					
2154	Tumour	Ventrolateral	0.1	15	Right
2161	Tumour	Ventrolateral	0.4	6	Right
2181	Infarct	Ventrolateral, corpus callosum, caudate	2.5	6	Right
2186	Tumour	Dorsolateral	2.7	5	Right
2188	Infarct	Ventrolateral, corpus callosum, caudate	2.6	19	Right
2202	Infarct	Dorsolateral, ventrolateral	3.9	30	Right
			2.0	13	
Inferior medial					
2047	Stroke	Inferior medial (R)	0.4	4	Right
2053	Trauma	Polar (R), Inferior medial (R), dorsolateral (L), ACG (R)	2.4	25	Right
2134	Trauma	Polar (L & R), inferior medial (L & R)	3.9	91	Right
2140	Stroke	Inferior medial (L & R), ACG (L)	1.2	48	Right
2142	Trauma	Polar (L & R), ventolateral (R), dorsolateral (R), inferior medial (L & R)	3.2	21	Right
2143	Trauma	Polar (L & R), inferior medial (L & R), ventrolateral (R)	3.7	27	Both
2146	Trauma	Polar (L & R), inferior medial (L & R), ventrolateral (R), corpus callosum (L & R), caudate (R)	4.6	48	Right
2148	Trauma	Polar (L & R), inferior medial (L & R)	3.3	11	Both
2166	Tumour	Polar (R), inferior medial (L & R)	0.6	6	Right
2169	Stroke		No scan	109	Right
2180	Stroke		No scan	28	Right
2196	Trauma	Polar (R), dorsolateral (R), inferior medial (L & R)	2.4	14	Right
2198	Stroke	Inferior medial (L & R)	0.3	10	Right
2203	Trauma	Inferior medial (R)	1.0	12	Left
			2.3	32	
Superior medial					
2131	Trauma	Polar (L), superior medial (L)	1.7	52	Both
2135	Trauma	Superior medial (R)	0.6	6	Right
2153	Trauma	Ventrolateral (R), superior medial (R), dorsolateral (R)	7.0	37	Right
2159	Stroke	Corpus callosum (L & R), superior medial (R), dorsolateral (R)	4.2	31	Right
2185	Infarct	Polar (R), inferior medial (R), ventrolateral (R), corpus collosum (R), superior medial (R)	11.0	6	Right
2194	Stroke	Polar (L & R), inferior medial (L & R), superior medial (L & R)	3.2	20	Right
2199	Stroke	Dorsolateral (R), superior medial (R)	2.1	28	Both
2209	Tumour	Corpus callosum (R), superior medial (R)	1.8	10	Right
			3.9	24	
Mean of all groups			2.7	25	

[a] Only areas of maximum pathology are identified.
[b] Percent of whole brain.

Table 3
Demographic characteristics and neuropsychological test[a] results of patient groups and matched control subjects

Group	Sex		Age		Years of education		NART-R		DSF		DSB		Token		BNT		JOL[b]		BDI	
	M	F	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.
LL	8	2	42	12	13	2	102	9	6	1	5	2	43	2	54	4	26	4	9	8
RL	4	2	47	12	16	2	113	10	6	1	5	1	44	1	57	3	25	4	11	12
IM	9	5	46	16	14	2	109	7	6	1	5	1	43	1	53	9	27	3	9	9
SM	4	4	48	17	14	2	110	8	7	2	5	1	42	2	52	4	23	6	6	5
CTL	16	22	49	16	15	2	112	7	7	2	6	1	42	3	56	4	28	3	6	6

[a] NART-R, National Adult Reading Test-Revised; DSF, Digit Span Forward; DSB, Digit Span Backward; Token, Token Test; BNT, Boston Naming Test; JOL, Judgment of Line Orientation; BDI, Beck Depression Inventory.
[b] JOL scores are corrected for age and gender.

repeated measures of motivation and sleepiness. The three tests are Simple RT (SRT), Choice RT (CRT), and Prepare RT (PRT). The Choice RT paradigm included a Simple RT test as a control and the Prepare RT paradigm included a Choice RT test as a control.

3.3. Measures of motivation and sleepiness

To assess if the patient groups were affected by attitude or sleepiness, the motivation measure was administered three times and the sleepiness measure (Stanford Sleepiness Scale – Hoddes, Zarcone, & Dement, 1972) six times during the day. For the motivation measure subjects listened to six statements read by the experimenter describing various degrees of motivation, and were asked to choose one that best described how they felt at that moment. Similarly, for the sleepiness measure, subjects listened to seven statements describing various degrees of sleepiness and were asked to choose one that best describes how they felt at that moment.

3.4. Simple reaction time

The capital letter "A" was presented in a block of 50 trials. Subjects responded by pressing button 1 as soon as the letter was presented. The response turned off the stimulus. Interstimulus intervals (ISI) were at 3, 4, 5, 6, or 7 s, with each ISI occurring 10 times in a random order. The ISI was defined as the time from the offset of one stimulus (at the response) to the onset of the next (and is equivalent to response-to-stimulus interval). Reaction time was measured from the onset of the stimulus to the button press. The Simple RT test was administered three times during the day, twice as control for the Choice RT test in the morning (SRT1 and SRT2), and once independently in the afternoon (SRT3).

3.5. Effect of choice

To examine the effect of choice in reaction time, Simple RT was compared to Choice RT. In the CRT test, the subject pressed button 1 when the letter "A" was presented, and button 2 when any of the letters "B", "C", or "D" was presented. Each of the four stimuli occurred with a probability of 0.25. This test was presented twice – CRT1 and CRT2. These tests were presented in mid-morning in the following order: SRT1, CRT1, CRT2, SRT2, with 50 trials each. Again, ISI ranged from 3 to 7 s, as described for the SRT test. RTs were collapsed across the letters.

3.6. Effect of warning stimulus and preparation time

The Prepare RT test was identical to the CRT, apart from the addition of a warning stimulus (a star lasting 200 ms) that was presented with an onset either 1 or 3 s (consistent through the block) before the onset of the letter. These were compared to the CRT test (no warning). These tests were presented in this order: CRT3, PRT1 (1 s), PRT2 (3 s), PRT3 (3 s), PRT4 (1 s), and CRT4. Because of the warning stimulus in the PRT test, ISI was restricted in all blocks to the range of 4–7 s. For analysis of the effect of the warning stimulus and preparation time, the following replications were combined – no warning: CRT3, CRT4; 1 s warning: PRT1, PRT4; 3 s warning: PRT2, PRT3. Again, the RTs were collapsed across the different letters.

4. Statistical analyses

4.1. Demographics, sleepiness, motivation, and structural lesion overlap

Analysis of variance was used to determine whether the five groups (LL, RL, IM, SM, and CTL) differed on demographic, neuropsychological, sleepiness, and motivation measures. Since some values are missing on some measures (see below), the denominator degrees of freedom vary from 74 down to 67. Tukey's post hoc test was used to follow-up significant group effects.

4.1.1. Reaction times

The major dependent variable was the average reaction time (RT). Trials with RT less than 150 ms were excluded on the basis that they would be too fast to reflect a real response to the stimulus. Only one trial was faster than this criterion. The exclusion of slow trials was based on the distribution of

RTs of each group of subjects on each particular test, using the criterion of the group mean plus 4 S.D.s. This led to an average exclusion of less than 2% for each group for each test. Occasionally there are missing data points for reasons such as computer failure. These are noted in the degrees of freedom.

Analyses for the CTL group were completed first to determine the normal response to the experimental manipulation. Then, each of the five groups was compared to the CTL group using five separate two-way ANOVAs (experimental manipulation versus patient group) with repeated measures across the experimental manipulation to test the null hypotheses that, pooled across all replications, each of the four groups had equivalent performance compared to the control group. In a similar manner we examined whether performance was equivalent across a within subject factor. Significant differences between levels of within subject factors were further evaluated with Tukey's post hoc procedure. For example, in the SRT task one experimental manipulation was the ISI. The analysis would show whether the RT of one group of patients was slower than controls (main effect of group), whether the RT changed with ISI (main effect of experimental manipulation) or changed differently with ISI in the patients and the controls (an interaction between group and the experimental manipulation).

4.1.2. Main experimental manipulations

4.1.2.1. Replication. To investigate the effect of replication, the levels of the within subject factor were SRT1, SRT2, and SRT3 for the Simple task and CRT1, CRT2, CRT3, and CRT4 for the Choice task.

4.1.2.2. Choice. To investigate the effect of adding choice in response selection, the levels of the within subject factor for these analyses were the combined RTs for SRT1 and SRT2 contrasted to the combined RTs for CRT1 and CRT2.

4.1.2.3. Preparation. To investigate the effect of adding a warning stimulus, the levels of the within subject factor were no warning (CRT3, CRT4), 1 s warning (PRT1, PRT4), and 3 s warning (PRT2, PRT3).

4.1.2.4. Inter-stimulus interval. To investigate the effect of ISI, trials were classified as either following a short (3 or 4 s) or long (6 or 7 s) interval and reaction time was averaged for each subject within these two levels.

4.1.2.5. Trials. To investigate the effect of repetition (within a block of trials during one replication of the task), trials were classified according to the quarter of the task in which they occurred, and reaction time was averaged for each subject within each of these four quarters.

4.1.3. Secondary analyses

In addition to the above, total errors for each group within each condition were compared, and the sleepiness and motivation measures administered most proximally in time to the RT task were correlated with RT speed.

4.1.4. Architectonic localization

In addition to the analysis based on the standard anatomical groupings, we related performance to anatomy using a more precise mapping of the lesions. First, we identified which particular brain regions within the frontal lobes were damaged for each patient. This was achieved by superimposing the scan of each patient on a brain template based on the Petrides and Pandya (1994) architectonic division (P & P areas) of the frontal lobes (see Stuss et al. (2002a) for a description). This procedure was similar to that of Damasio and Damasio (1989), but used the more refined Petrides and Pandya architectonic divisions of prefrontal cortex rather than the standard Brodmann areas. Other brain regions were also identified: the septal region and the anterior cingulate (which was divided into superior and inferior sections). Each of the 62 P & P areas (right and left) in the frontal lobes and seven other regions (septum; thalamus, globus pallidus, caudate – right and left) were then used as an independent dummy variable that identified the specific architectonic area. If an individual patient's lesion involved a defined architectonic region, it was coded as 1 for damaged; if not damaged, it was coded as 0. Only areas that were involved in three or more subjects were evaluated. Our goal using this method was to detect which P & P areas were most related to the abnormal findings. For example, to look at abnormal slowing in the SRT task, for each P & P area we identified all the patients who had lesions in that area and compared their RT to all patients who had no damage to that area using a simple *t*-test. We considered all areas with a one-tailed $P < .10$ – where patients with damage in that area were slower – as potentially involved in the processes that determined the measurement (in this example, the slowed SRT) and considered areas with a one-tailed $P < .05$ to be critical areas.

One or more areas might appear significant simply because contiguous regions were involved in the same patients, so a technique was devised to determine if significant areas were closely associated with each other in the same patients or if they were relatively independent. We grouped the cortical architectonic areas into the intermediate superordinate anatomical categories adapted from our earlier proposal for frontal lobe divisions (Stuss et al., 1995, 2002a – see Fig. 2). Although the level of subject division shown in Fig. 2 would be impractical for human lesion research because of the difficulty in obtaining an adequate sample size for each region, it provides a more detailed lesion specificity than the four areas (LL, RL, IM, SM). We then determined the conditional probability that a patient who had damage in one of the defined regions had damage in another. Two regions were classified as being dissociable if the sum of the two squared conditional probabilities was less than .25. When there are an equal number of patients with lesions in each of two regions, this threshold for lack

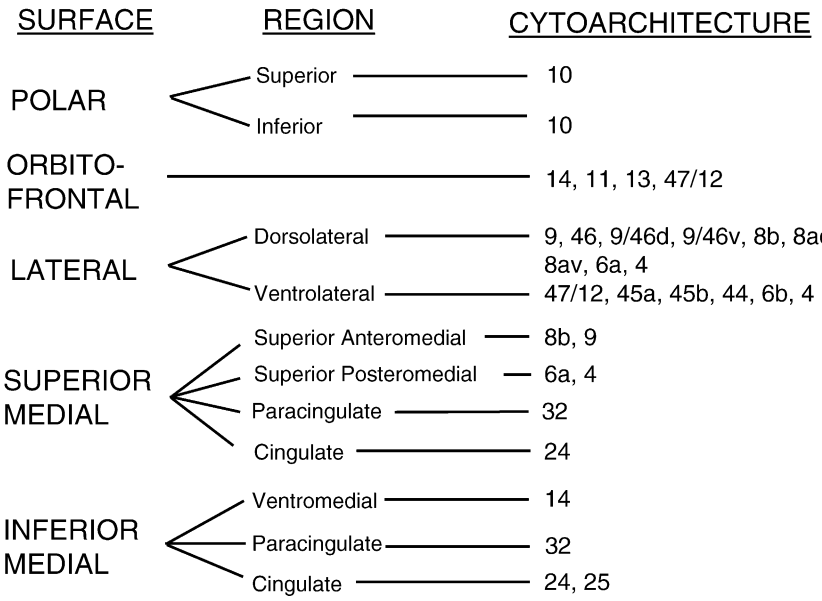

Fig. 2. Five major regions of the frontal lobes (separable into left and right frontal areas) are illustrated. These divisions can be segmented further. For example, the polar region can be superior polar or inferior polar. These divisions can also be further subdivided into architectonic regions based on the Petrides and Pandya (1994). From Principles of Frontal Lobe Function, edited by Donald T. Stuss and Robert T. Knight, copyright 2002 by Oxford University Press, Inc. Adapted by permission of Oxford University Press, Inc.

of association would identify pairs of regions where fewer than a third of the subjects with either region affected had the other region affected. We only used the lack of association between areas to determine the potential independence of different areas showing up on the architectonic analyses for each task. This was done within each hemisphere. Dissociability between areas indicated that different groups of subjects were contributing to the abnormality through different lesions.

5. Results

The means and standard deviations for all the groups, tests and conditions are presented in Appendix A.

5.1. Demographic variables

There were no significant group differences for the following variables: sex (P = .21); handedness (Fisher's exact test, P = .10); age (P = .79); Digit Span Forward (P = .30); Digit Span Backward (P = .06); Token Test (P = .26); Boston Naming Test (P = .15); or Beck Depression Inventory (P = .39). Significant group differences were observed for the following demographic variables: years of education [$F(4, 71) = 3.08$, P = .02], with the CTL group having more education than the LL group; NART [$F(4, 67) = 3.38$, P = .014], with the CTL group having a higher score than the LL group; Judgment of Line Orientation (corrected for sex and age) [$F(4,74) = 4.66$, P = .002], with the CTL group having a higher score than the SM group.

5.2. Sleep and motivation

For the sleepiness scale, there was a significant effect of time of day of assessment [$F(5,335) = 19.63$, $P < .0005$], but no significant difference between groups or interaction involving the different groups. All groups followed the same general pattern: most alert early in each half-day session and sleepiest later in the same session, with no other significant differences. The motivation measure also varied significantly [$F(2,142) = 17.96$, $P < .0005$], again with no group interaction. Motivation was highest at the beginning of the day, and lowest at the end of the day.

5.3. Simple reaction time

In the CTL group, the average RT across all three replications of the SRT test was 331 ms. The SM group was marginally slower than CTLs with all three replications combined (P = .059). The profile of the average reaction time across replications of the Simple RT test is presented in Fig. 3 for each of the groups.

5.3.1. Replication

In the CTL group, there was a significant replication effect [$F(2,74) = 16.67$, $P < .0005$], with SRT1 significantly faster than SRT2 and SRT3. There was a significant difference in the profiles across replication between the LL and CTL groups [$F(2,142) = 4.8$, P = .01]. This was due to a larger increase in RT from SRT1 to SRT2 and decrease from SRT2 to SRT3 for the LL group (Fig. 3).

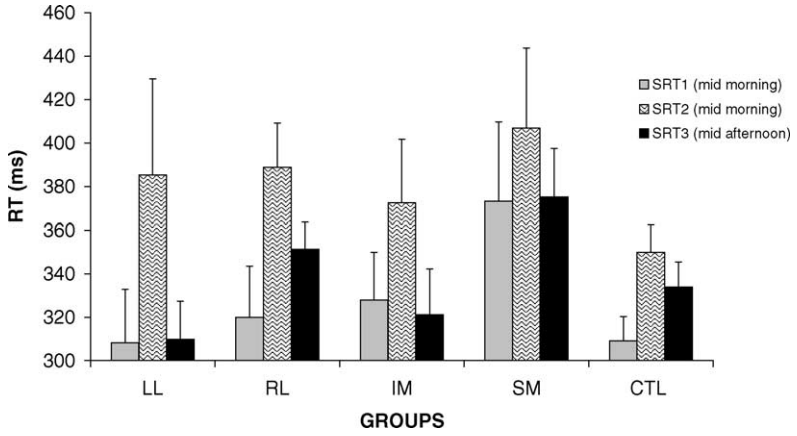

Fig. 3. The mean RTs for the four patient groups and the control (CTL) group are presented for the three administrations of the Simple RT task. Time of day is noted. Group definition as in legend of Fig. 1. Bars indicate 2 standard errors about the mean.

5.3.2. ISI

To analyze the effect of manipulating ISI, trials with short ISIs (3 or 4 s) were compared to those with long ISIs (6 or 7 s) for the three SRT replications combined. The CTL group exhibited a strong foreperiod effect for unwarned stimuli [$F(1, 37) = 98.67$, $P < .0005$], namely a gradual decrease in RT with increasing ISI. There was one significant group by ISI interaction [$F(1, 71) = 7.0$, $P = .01$]. The RL group exhibited an increase in RT with increasing ISI as opposed to the decrease in the control group (Fig. 4).

5.3.3. Trials

There was no main effect of trials for CTLs. There was a single significant interaction for the SM group [$F(3,213) = 3.02$, $P = .03$]. The SM group was significantly slower for the first quarter of a block compared to the second [$F(1, 71) = 5.36$, $P = .024$] and third quarters [$F(1, 71) = 5.93$, $P = .017$], but not quite when compared to the last quarter [$F(1, 71) = 2.34$, $P = .130$], relative to the CTL group.

5.3.4. Sleepiness/motivation ratings

The sleepiness measure of each subject was correlated with the RT score administered at a similar time of day. There were no significant correlations of SRT3 (in the later afternoon) with sleepiness rating no. 5. There was only a significant correlation of sleepiness with the morning SRT tests, the sleepier SM subjects responding more slowly ($r = .78$, $P = .021$). A similar pattern was observed for the motivation

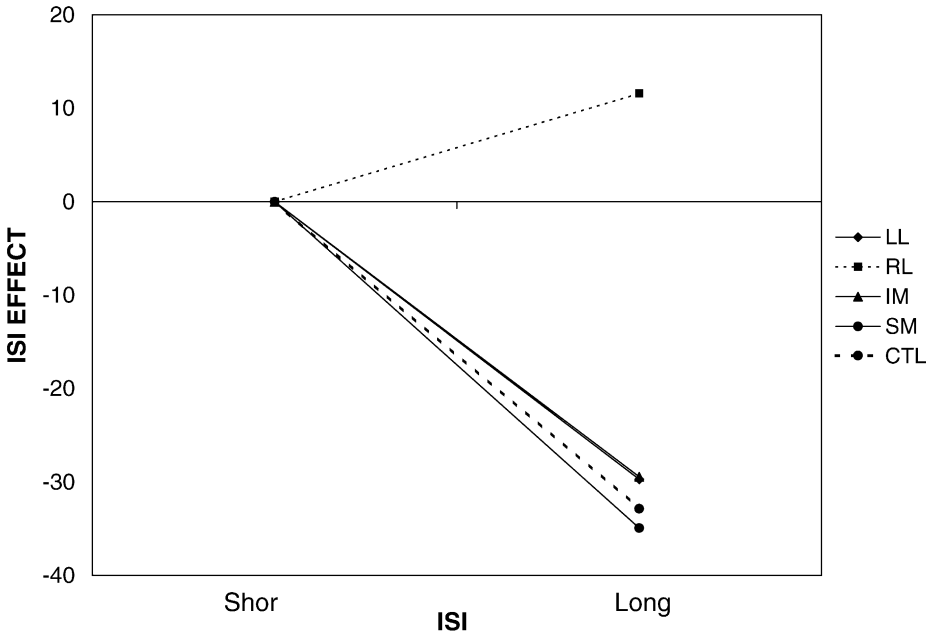

Fig. 4. The RTs in the Simple RT task for the short (3 and 4 s) and long (6 and 7 s ISIs) are illustrated for each group. For each group independently, the short ISI is set at 0, and the differences in RT for the long ISI contrasted to it. Negative RT indicates a faster RT, positive slower. Only the RL group fails to demonstrate the standard foreperiod effect; that is, the RT in the RL group is slower with a longer ISI, in contrast to all other groups. This is illustrated in the SRT2 which showed the largest effect. Group definition as in the legends of Figs. 1 and 3.

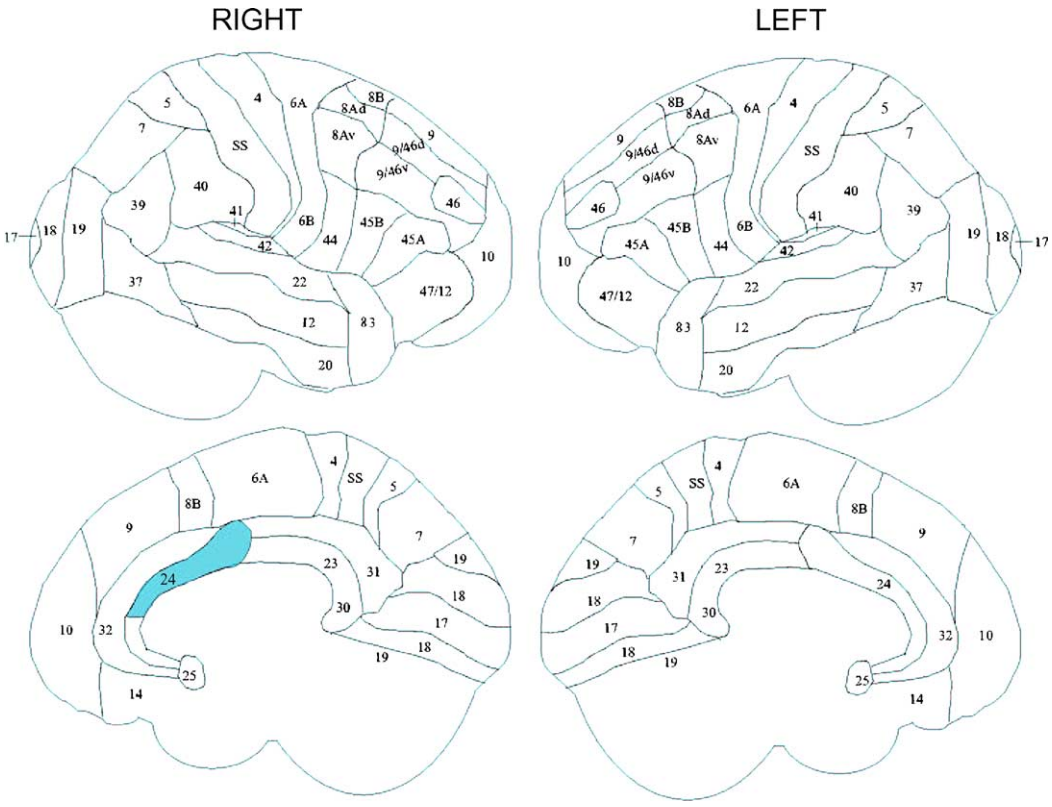

Fig. 5. This figure illustrates the lesion specificity analysis for SRT tests combined. This technique and results are described in the text. The light shading indicates a significant slowing in Simple RT ($P < .10$) related to that lesion compared to all other lesion areas.

ratings, the less motivated subjects in the SM group responding more slowly in the morning SRT tests ($r = .76$, $P = .024$).

5.3.5. Lesion specificity analysis

Only one frontal region (see Fig. 5) was identified with slow RT for the combined SRT1, -2, and -3 replications: the right superior cingulate, P & P 24. The right globus pallidus and caudate were also identified with slow RT. There was no significant correlation of lesion size with Simple RT ($r = .145$, $P = .398$).

5.3.6. Summary

(1) The group with SM lesions was slower, as well as right subcortical motor regions. (2) The group with right lateral lesions did not show normal foreperiod effects.

5.4. Choice reaction time

Two replications of Choice RT (CRT1 and CRT2) were administered mid-morning and two replications (CRT3 and CRT4) were administered at the end of the afternoon as part of the Prepare task (see Table 1).

There was a significant slowing of the SM group compared to the CTL group [$F(1, 44) = 7.9$, $P = .007$] for all four replications of the Choice RT test combined (see Fig. 6).

5.4.1. Replication

The CTL group did not show any significant changes in RT across Choice RT replications. There was a significant interaction between replication and group for the SM group [$F(3, 213) = 3.09$, $P = .028$]. For the SM group CRT4 was significantly slower than the other replications of this test (Fig. 6). This finding may be a time-of-day effect, as CRT4 was the last replication, late in the afternoon.

5.4.2. Choice

The CTL group was significantly slower on the CRT1 and -2 combined compared to SRT1 and -2 combined [$F(1, 37) = 370.94$, $P < .0005$]. There was a significant interaction between the effect of choice and group for CRT1 and -2 in the SM group only [$F(1, 71) = 5.6$, $P = .021$]. The SM group slowed more with the demands of choice than did the control group, all other groups being non-significantly different from the control group.

5.4.3. ISI

As in the SRT task, trials with shorter ISI were compared to those with longer ISI for CRT1 and CRT2 combined (ISI for CRT3 and CRT4 ranged only from 4 to 7 and were evaluated separately; see below). Controls show a standard foreperiod effect: declining RT with increasing ISI [$F(1, 37) = 17.51$, $P < .0005$] (see Fig. 7). All patient groups except the RL had

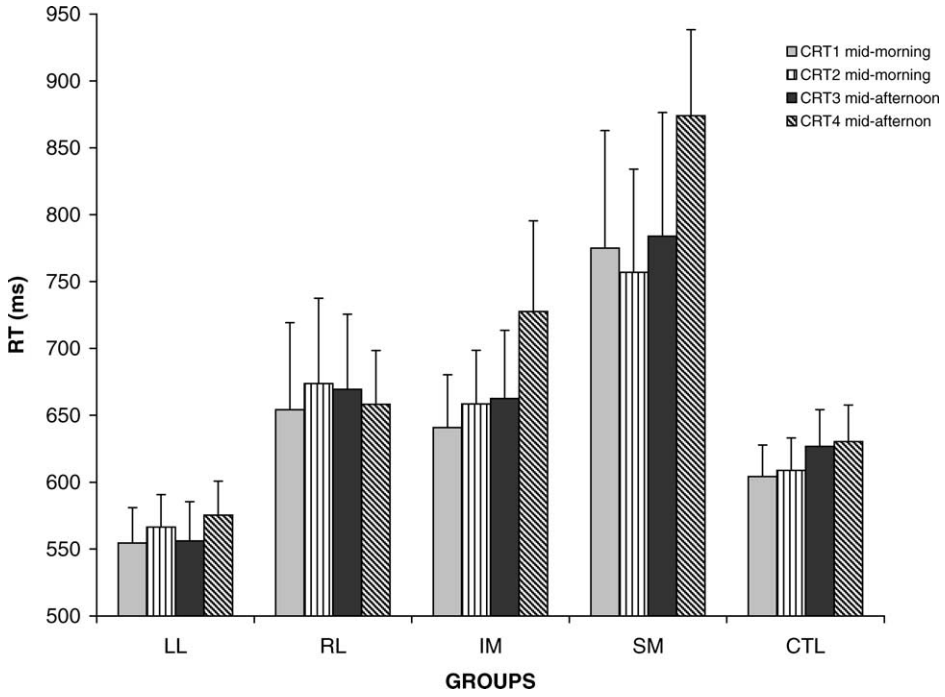

Fig. 6. The group mean RTs for all four Choice RT replications are presented for the five groups. Group definition as in legends of Figs. 1 and 3. Bars indicate 2 standard errors about the mean.

a foreperiod effect similar to CTLs. There was a significant group by ISI interaction for the RL group [$F(1, 71) = 13.75$, $P < .0005$], the RL group showing a reverse foreperiod effect of longer RT with increasing ISI. There were no significant control by patient group interactions for CRT3 and CRT4 combined.

5.4.4. Trials

There was a significant interaction of RL versus CTL with trials for CRT1 and -2 combined [$F(3, 213) = 3.24$, $P = .023$], with a gradual slowing of the RL group over the repeated trials, the third and fourth quarter being significantly slower than the second quarter of trials.

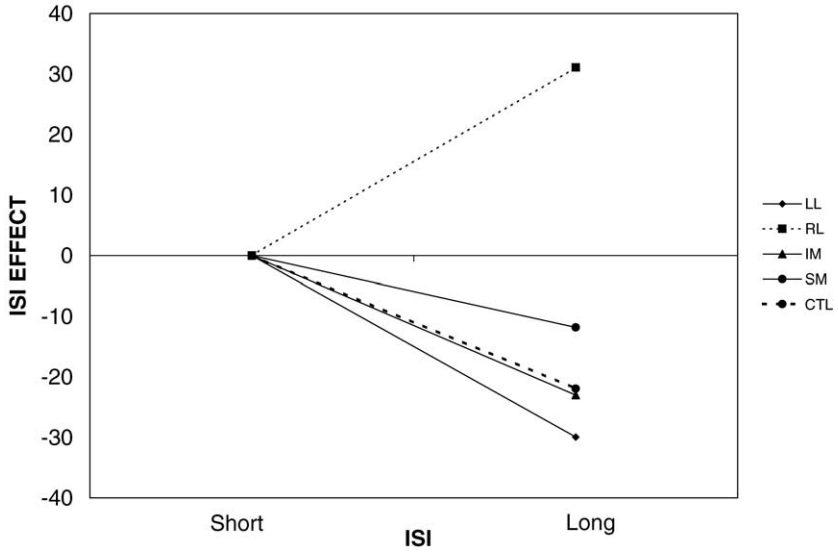

Fig. 7. The RTs in the combined Choice RT replications for the short (3 and 4 s) and long (6 and 7 s ISIs) are illustrated for each group. For each group independently, the short ISI for the first presentation of the Choice RT task is set at 0, and all other RTs are presented in relation to this arbitrary baseline. Negative RT indicates a faster RT, positive slower. The RL group again fails to reveal the standard forewarning effect, similar to the result in the Simple RT. Group definition as in legends of Figs. 1 and 2.

5.4.5. Sleepiness/motivation ratings

For the morning and afternoon replications of Choice RT, there were no significant correlations with the sleepiness or motivation measures. In the CTL group, there was a significant correlation of motivation for the morning CRT tests ($r = -0.383$, $P = .018$). The relation was negative; that is, the less motivated, the faster the RT.

5.4.6. Errors

There was no significant group difference ($P = .52$) in the number of errors in all of the Choice RT tests (less than 1.1% in all groups; range: 0.76–1.46%).

5.4.7. Lesion specificity

For the combined morning replications of CRT, the following regions were associated with slow RT: right superior cingulate [P&P 24 and 32 ($P < .05$)], right anteromedial [P&P 9 ($P < .05$)], right lateral [P&P 46 and 9/46v ($P < .05$); 6A and 45A ($P < .10$)], and orbitofrontal [P&P left 25 ($P < .10$)] (see Fig. 8). As in our other research with inferior and superior medial involvement (Stuss et al., 1998), patients with superior anteromedial pathology (in this case right) tended to have damage in the orbitofrontal (inferior medial) region, but the reverse was not necessarily true. Lesions in the right lateral region area 6 were dissociated from lesions in area 45a.

Summary: (1) The SM group was slower as in the SRT task, but with the demands of the CRT, the right lateral group also was slower. (2) The RL group again had loss of foreperiod alerting. (3) The RL group also slowed over the course of the trials although without increased errors.

5.5. Prepare reaction time

The Prepare task was presented toward the end of the afternoon in four blocks (two at each warning period). The RTs for each of the warning periods were combined across the two blocks for the analyses.

The SM group was significantly slower than the CTL group for all three conditions combined [$F(2, 142) = .395$, $P = .021$], this same group difference occurring for each of the conditions separately (see Fig. 9).

5.5.1. Effect of warning stimulus and preparation time

In the control group, RT was significantly faster with a preparatory warning signal 1 s prior to a CRT than without one [$F(1, 37) = 7.63$, $P = .009$]. RT increased minimally but not significantly with a 3 s warning interval compared to 1 s [$F(1, 37) = 3.5$, $P = .069$] or compared to no warning [$F(1, 37) = 3.04$, $P = .089$]. The SM group was the only group to show a statistically different effect of the warning stimulus compared to the control group [$F(2, 142) = 3.76$, $P = .026$].

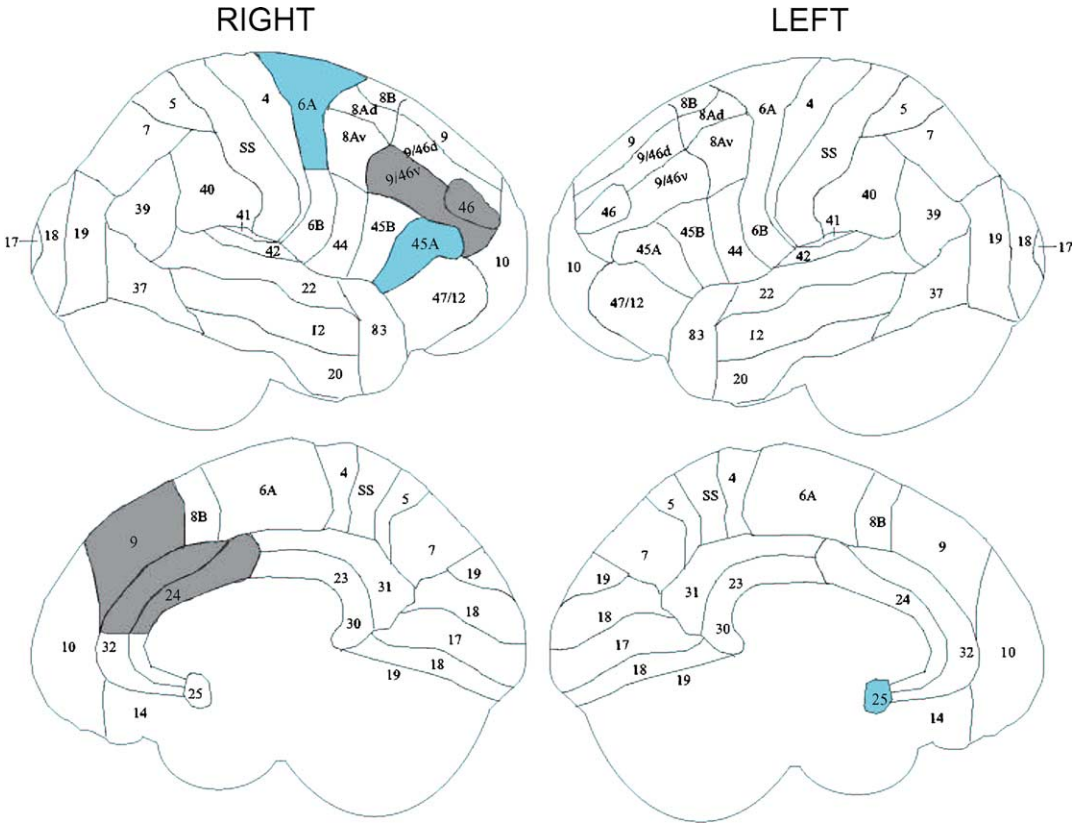

Fig. 8. Lesion specificity analysis for morning replications of CRT implicates right superior medial areas 24, 32 and 9 as well as right lateral 9/46v, 46, 45A and 6A with slower RT. The darker shading indicates a significant slowing related to that lesion area compared to all other areas at alpha level of 5%; the lighter shading corresponds to an alpha level of 10%.

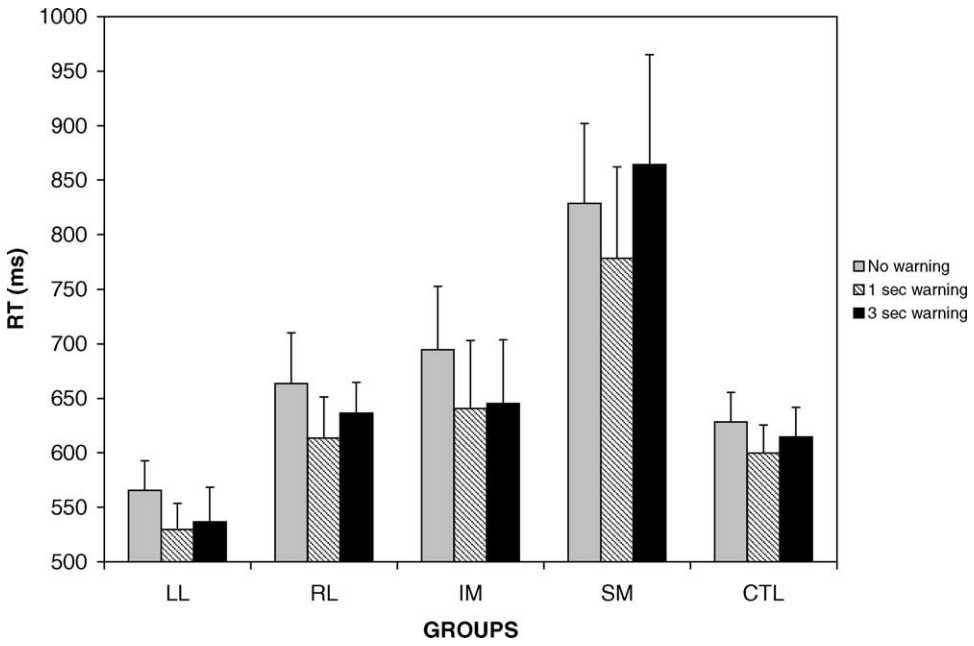

Fig. 9. For each group, the mean RTs for each condition (no warning, 1 s warning, 3 s warning) are illustrated. The slowing of the SM group to all other groups is most evident in this task. All groups are able to benefit from the presence of the 1 s warning (comparison of the no and 1 s warning conditions). While most groups demonstrate some benefit of the 3 s warning condition (comparison of the no and 3 s warning condition), the SM group alone is adversely affected. Group definition as in legends of Figs. 1 and 3.

For the SM group, the increase in RT between the 1 and 3 s warning was significantly greater than the control group's increase (P = .007). The SM group increased 86 ms (11%); the CTL group 15 ms (2.8%) (Fig. 9).

5.5.2. Trials

Since there were only 26 trials in total (two blocks of 13), the trial effect was not analyzed.

5.5.3. Sleepiness/motivation ratings

There were no significant correlations of motivation 3 (last in the day) or sleepiness 5 with any measures in the Prepare task (administered in late PM).

5.5.4. Errors

There were no significant group differences in the mean number of errors for the 0 s (P = .34), 1 s (P = .97) or 3 s (P = .86) warning conditions. Overall the percentage of errors within any group was less than 2.1% (in the SM group), the lowest being 0.65% (IM).

5.5.5. Lesion specificity

Analysis was completed for the 1 and 3 s warning PRT tests. For the 1 s warning (see Fig. 10a), the major regions identified with slowing were the right medial region (at P < .05) [superior cingulate region [P&P 24 and 32] and P & P medial 9], and at P < .10, the left superior anteromedial region [P & P 9], left orbitofrontal [P & P 25] and right lateral 6A. There were no separable regions among these areas. In the 3 s warning test (see Fig. 10b), there was involvement of a wider area, particularly in the right lateral region. The regions identified with slowing in this test at P < .05 were right superior cingulate [P & P 24 and 32], right superior anteromedial [P & P 9], and right lateral frontal [P & P 9/46 d and v, 45A, 46, and 6A]; at P < .10, the right globus pallidus. There were no dissociations among the regions identified for the 3 s warning PRT test. As in the CRT test, patients with right superior anteromedial pathology tended to have damage in the right orbitofrontal (inferior medial) region, but the reverse was not necessarily true.

In the 3 s warning replications, patients with larger lesions had slower RT (r = .341; P = .042), but the variance explained was relatively small. In the 1 s replications, the correlation was not significantly different from zero (P = .20).

Summary: (1) SM lesions, particularly right, were associated with a slower RT than normal controls in both warned conditions; lesion specificity also implicated the right lateral region. (2) In patients with lesions to the SM, the RT was particularly long when the preparatory interval was 3 s.

6. Discussion

One striking observation, contrary to the common beliefs about the attentional capabilities of frontal lobe patients, was that some patients with extensive lesions of the frontal lobes were able to perform quite normally on RT tasks. This finding might be due to the lesions being restricted to the frontal lobes and to the stability of patients seen on average 2 years after their lesion. The same protocol in more acute patients

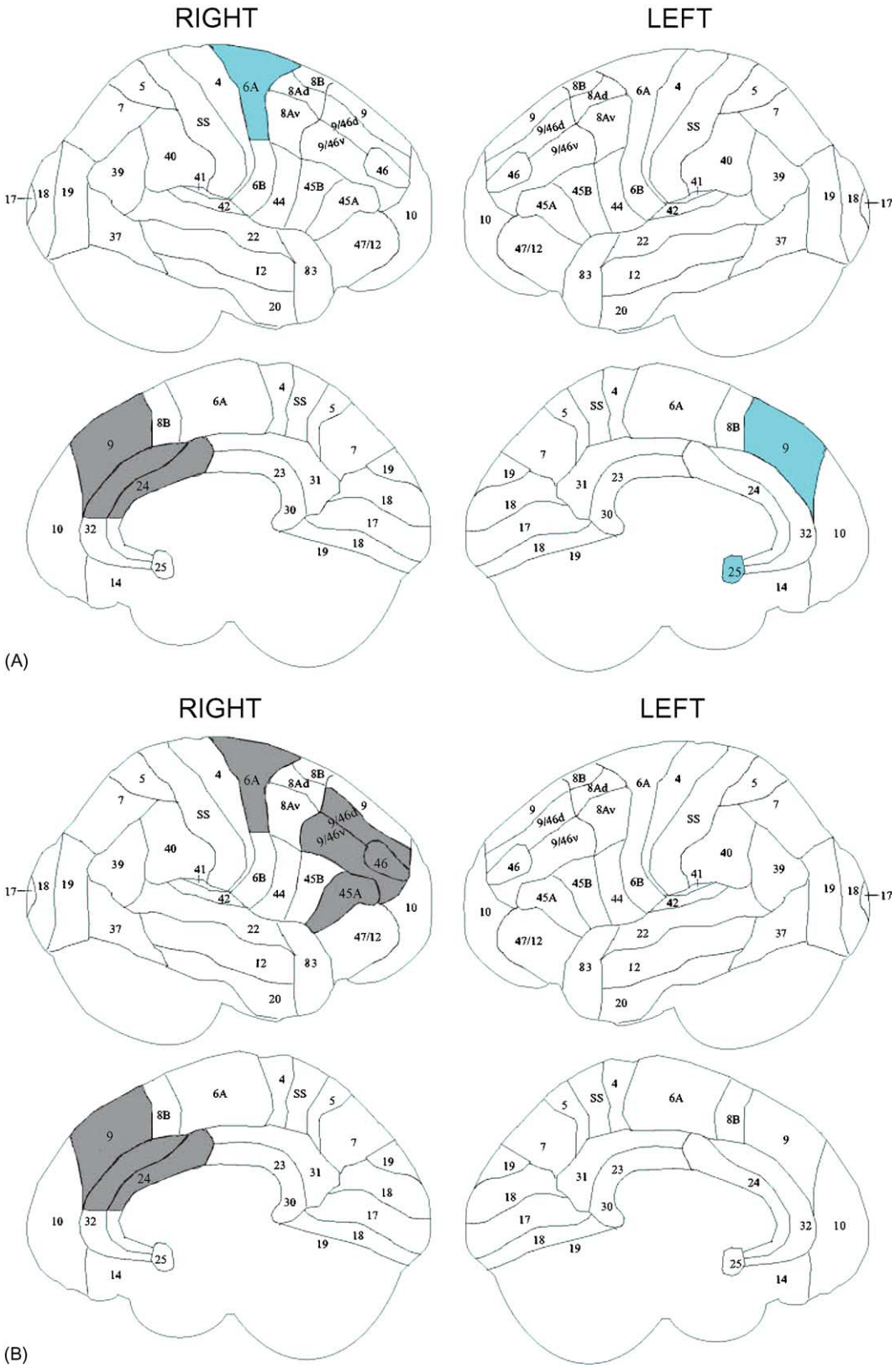

Fig. 10. Lesion specificity analysis relating to Prepare RT: (a) first and fourth replications of PRT with 1 s warning, and (b) second and third replications of PRT with 3 s warning. Shading is described in Fig. 8.

would presumably produce different results. Regardless, the negative findings are striking and put into marked relief those groups who stray from this pattern under specific experimental manipulations.

This general competence notwithstanding, we demonstrated some consistent abnormalities in RT and relate these to specific regions of the frontal lobes. This was achievable because of our approach. Although each task might involve multiple different neurocognitive processes, close examination of the abnormalities across tasks and within the different experimental manipulations of a task, and assessing patients with frontal lobe pathology in different regions, allowed us to determine which process was affected.

6.1. Activation and energization of responses

The second most notable finding was related to response speed, and our hypothesized role of activation and energization. Frontal lesions do not universally produce slowing, even in Simple RT. Most subjects were right-handed, and we expected an effect of left frontal lesions due simply to slow motor responsiveness. The group with left lateral damage was, however, slightly faster (not significantly) than the control group. We did not demonstrate a general effect of right lesions in the a priori defined anatomical groups, but the IM and SM groups as well as the RL group include patients with right-sided damage, and the lesion specificity analysis does support to some degree this suggestion (see below). Our data also support the conclusion that lesion volume in the frontal lobes at least has no association with simple RT. The SM group was the slowest by far, and there was no relation of lesion size to RT in this group (e.g., $P = .6$ to .9 for the different tasks). Lesion location is a better predictor of response slowing than lesion size.

In all three RT tasks, significant slowing was related primarily to the SM region, the effect largest with more demanding tests. How does a lesion in SM brain regions cause pervasive slowness in RT? Damage may produce inefficient, i.e., noisy, transfer of information about stimulus occurrence. The response could then be delayed because a high response threshold is needed to prevent responding to noise. This effect would increase with task complexity: more stimuli and more responses lead to more noise. This study provides some support for this hypothesis. All three levels of RT tests *did* produce significant slowing, and there *were* differences in significance depending on the test. In the Simple RT test, the significant difference between the SM and CTL groups occurred only for the first replication, but in the more complex Choice RT the SM slowing was observed for all replications. The effects on RT were strongest in conditions that were performed more slowly by other groups including controls.

We do not, however, believe that the noisy transmission hypothesis adequately explains all our data. In a previous study comparing three levels of complexity of feature integration and detection, increased complexity caused increased slowing for some frontal groups at one step of increased complexity, but no group showed disproportionate slowing with the next level of complexity (Stuss et al., 2002b). If noisy transfer of information plays a role, it did not explain all of the variance in that study. More critically, the noisy transmission account provides no explanation of the second key finding with the SM group: marked slowing when there was a fixed 3 s warning interval compared to the 1 s condition. The amount of information processed is identical in the two conditions.

Another possibility is that multiple different pathways activate even simple motor responses. Some of these may go through the supplementary motor areas on the medial frontal lobe. If these areas are lesioned, the response might have to be mediated by other slower pathways (e.g., involving the basal ganglia). However, a single pathway from sensory analysis to supplementary motor areas to motor cortex is unlikely. The connections for simple responses are more likely directly to motor cortex. The supplementary motor areas may be necessary to organize complex responses, facilitate speeded responses, activate unpractised motor patterns and maintain decision rules (Erdler et al., 2001; Humberstone et al., 1997; Picard & Strick, 1996).

We propose that the effect of SM lesions can be explained within the structure of the modified Supervisory System: decreased facilitation (energizing) of the neural systems that are needed to make the decisions (contention scheduling) and initiate the responses (schemata), a proposal with considerable similarity to the thresholding function proposed by Paus (2001) for the anterior cingulate cortex. Within different theoretical models, this deficit might be considered a disturbance in phasic alertness. Bilateral lesions of anterior cingulate and SMA produce akinetic mutism, certainly the most dramatic example of deficient energizing (Alexander, 2001; Plum & Posner, 1980). The anterior cingulate has been implicated in arousal, with changes in activity of the cingulate cortex as a function of sleep stages (Hofle et al., 1997), vigilance (Paus et al., 1997) and alertness (Luu, Collins, & Tucker, 2000; Luu, Flaisch, & Tucker, 2000). Loss of "energizing the schemata" in the SM patients might account for the rapid decline in preparatory activation from 1 to 3 s after a warning stimulus. This account is also consistent with the demonstrated effect of lesions in the SM region on the Stroop interference task: an inability to maintain an activated response mode (i.e., to name colours and not read the words), a state that may wax and wane along a gradient (Cohen, McClelland, & Dunbar, 1990; Kornblum, Stevens, Whipple, & Requin, 1999; Stuss, Alexander, Levine, & Katz, 2001b). In physiological terms, energization would cause excitation of the relevant cell assemblies (in parietal association areas, supplementary motor areas, or motor cortex) to give more rapid output when pertinent input is provided.

The role of the SM region in energization and activation is reinforced by the analysis of the general effect of the warning stimulus in Prepare RT. The presence of a non-specific warning stimulus [that is, the stimulus provides no informa-

tion about the content of the imperative stimulus (Los & van den Heuvel, 2001)] reduces RT (Bertelson, 1967; Niemi & Naatanen, 1981). This reduction in RT is affected by the time between the warning and imperative stimuli. The RT decreases from 0 to 500 ms with a superimposed brief facilitation near 150 ms (Bertelson, 1967). Facilitation is generally considered to be optimal at intervals between 200 and 500 ms, but though diminished, it can still be found with foreperiods of up to 5 s, provided that the foreperiod time is constant (Karlin, 1959; Klemmer, 1956; Posner & Boies, 1971; Zahn & Mirsky, 1999). We did not assess the shorter ISIs for several reasons: our desire to evaluate monitoring that would be necessary over longer foreperiods; the previous data suggesting that there might be some benefit for up to 5 s; and uncertainty about the patient's ability to do the task if the foreperiod were too short.

Most patient groups followed the expected pattern closely and performed like the control group; that is, the RTs were slowest with no warning, fastest with the 1 s warning, and in between for the 3 s warning. The 1 s warning improved the control and all patient groups regardless of lesion location. This improvement reached significance for the LL and IM groups. The effect of the warning stimuli is to reduce RTs by alerting and increasing expectancy of the imperative stimulus, thereby maximizing preparation (Niemi & Naatanen, 1981). Frontal lobe damage, of the location and size of our patients, does not appear to cause a deficit in "intentional action", at least of this type of intention, for RT (Gauntlett-Gilbert & Brown, 1998). Patients with frontal damage appear able to use advance information to improve response speed, although the efficiency in doing so may vary depending on lesion location.

This result extends the findings of Audet et al. (2000), who found that all patients with left and right hemisphere damage responded more quickly with a warning stimulus. Alivisatos and Milner (1989), on the other hand, reported that patients with frontal lobe lesions did not benefit from a neutral warning cue and benefited less than patients with temporal lobe lesions from an informative cue. Differences in methods and subjects between that study and ours may account for the discrepancy. Alivisatos and Milner did not compare warning to no warning. Approximately half of their patients were tested within the first 2 weeks after surgery, and they did not report any analysis of the effect of time post injury. Perhaps there is an early effect of frontal damage that clears with recovery. The most important factor may be lesion location; most patients in that study had superior medial lesions. In our study, patients with SM lesions showed a significantly greater loss of benefit from a warning stimulus when it was 3 s ahead. Both the 1 and 3 s warning alert the subjects. That activated state of alertness must be maintained. In normal subjects and most patients with frontal lesions, the activation ebbs slightly between 1 and 3 s. In SM patients, it is much less robust, and by 3 s has fallen substantially which we interpret as a failure of the energizing process.

6.2. Monitoring

The process of monitoring was evaluated with the different foreperiod effects and warning signals. The foreperiod effect is the change in response time with changes in the duration of the interval between the stimulus requiring a response and a preceding stimulus (either a warning stimulus or the preceding stimulus eliciting a response). The foreperiod effect may be due to different processes in warned (where a warning stimulus of some type precedes the imperative stimulus requiring a response) versus unwarned (where the imperative stimulus is presented without a warning stimulus) paradigms (see Karlin, 1959; Niemi & Naatanen, 1981). The foreperiod effect is also quite dramatically influenced by blocked versus unblocked ISI presentation.

When there is no warning stimulus and the ISIs are random, the standard foreperiod effect is decreasing RT with increasing ISIs (Niemi & Naatanen, 1981). In random (unblocked) ISI presentations, the longer ISI may allow better preparation for the impending response stimulus. On the other hand, when ISI is blocked, RT increases with longer ISI perhaps because of sustaining peak preparedness and the difficulty of timing peak preparation for longer intervals. This reflects different effects of modulating expectancy (monitoring) and of sustaining peak preparedness or time estimation. In the SRT and CRT tests with random ISI, only the RL group showed an abnormal foreperiod effect: RT increased with longer ISI. Thus, most patients with frontal lobe damage are able to use the longer ISI to prepare more fully for a fast response. In contrast to the control group, the RL group was significantly slower with increasing ISI, rather than faster. This pattern occurred in SRT2, CRT1, CRT2 and CRT3, indicating consistency of the effect that we believe is due to deficiencies in the monitoring process.

6.3. Inhibition

We had hypothesized that, in Choice RT compared to Simple RT, the process of inhibition would be required to overcome making erroneous choices. There were insufficient errors to study this hypothesis, perhaps due to our selection of an insufficiently demanding Choice RT test. Our hypothesis still stands, based on previous research, which demonstrated a significant problem in discriminating between targets and non-targets in a complex feature integration task, requiring choices related to the features involved in the target compared to the non-target (Stuss et al., 2002b). In this study, patients with right lateral pathology were most impaired.

6.4. Effect of motivation and sleepiness

There were few correlations of sleepiness with RT. A significant correlation occurred with the SM group on only one presentation of the simple RT (SRT – C2, $r = 0.812$, $P = .014$). The sole significant correlation of motivation and RT was also found on one of the simple RT tasks (SRT – C2, $r = .799$,

P = .017). Slight declines in arousal, whether measured as alertness (sleepiness) or activation (motivation), might contribute to RT performance. If so, the effect could be limited to the patient group with the most impaired baseline arousal: the SM group. Poor motivation, poor endurance, early fatigue or other systemic factors affecting task engagement might affect RT performance, perhaps particularly on demanding or complex tasks (Chapman & Chapman, 1973, 1978). With only a single significant correlation with motivation, and that on a simple RT task, it is extremely unlikely that significant group differences on the more complex tasks were secondary to motivation or alertness deficits as the tasks unfolded (Godefroy, Cabaret & Rousseaux, 1994; Ward, Sharkey, Marston, & Brown, 1998).

6.5. Lesion specificity in anterior attentional functions

We defined lesion sites at two levels. First, patients were assigned to subgroupings of left lateral, right lateral, superior medial, and inferior medial based on previous research (see Stuss et al., 2002a, for a review). Even at this relatively coarse level, the four groups were based on more precise anatomical distinctions than used in most other lesion studies of the frontal lobes. Second, all lesions were mapped to specific architectonic regions, and the relationship between regions and impaired performance was analyzed.

At the first level – coarse regional groupings – the most prominent abnormalities in RT were seen in the group with SM lesions. Recall that these patients had lesions that were right, left and bilateral, and generally included damage to the IM region as well. Since patients with only IM lesions did not differ from controls, the critical areas of damage in the SM group involved the truly superior structures. Right-sided lesions were more frequently identified with slowing than left sided lesions (Figs. 5 and 8). This asymmetry should be interpreted with caution, since not all areas of the SM region were represented equivalently: 50% of the group had right SM lesions, 38% bilateral, and only 12% had a unilateral left SM lesion (Table 1). Supportive evidence for this right-sided preeminence may derive from our previous research which had more symmetric distribution of left and right SM lesions, and still implicated the right SM region in an activation process (Stuss et al., 2001a, 2001b).

Medial frontal lesions have previously been associated with deficits in various complex RT tasks by a number of authors (Drewe, 1975; Godefroy et al., 1994; Leimkuhler & Mesulam, 1985; Luria, 1973). The current research shows the specificity of this effect – medial but not lateral – and superior but not inferior medial. Our results particularly stress the importance of areas 24/32, as well as medial 9. PET and fMRI activation studies in normal subjects have suggested several possible functions of the anterior cingulate gyrus, in particular: response selection from a set of competing stimuli (Pardo, Pardo, Janer, & Raichle, 1990; Paus, Petrides, Evans, & Meyer, 1993; Posner & Petersen, 1990); monitoring and regulation of conflicting responses (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999); cortical modulation of autonomic function (Critchley, Elliott, Mathias, & Dolan, 2000). Disruption of any of these putative functions might affect choice RT, but only the last of these would be expected to give rise to problems in simple RT. Several studies have suggested a "presupplementary" motor area that is located on the medial frontal lobe anterior to the anterior commisure (e.g., Humberstone et al., 1997; Picard & Strick, 1996) that is related to decisions about motor responses rather than the initiation of these responses through the supplementary motor area and execution through the motor cortex.

The anatomical analyses showed a second relationship between behaviour and lesion site. The RL group showed a consistent loss of the normal foreperiod effect. This group had increasing RT with longer ISIs, compared to the opposite pattern in all other groups. This contrasted to the RTs with longer fixed warning intervals, when this group performed normally. The areas of the RL that were associated with slowing may interact with the SM regions to initiate or maintain phasic arousal. Lesions to either of these areas may thus generally slow responses. The normal foreperiod effect may represent a state of increased preparation to respond to the target stimulus as the conditional probability of its occurrence increases. A failure to show such a decrease in RT in variable foreperiods, contrasted to normally maintained energizing over a fixed warning interval, is most likely related to impairment in monitoring or checking. If the patients fail to notice that a stimulus has not yet occurred, they will not be able to increase their preparedness to respond. A similar explanation underlies the role of the region in vigilance experiments (Pardo, Fox, & Raichle, 1991; Wilkins, Shallice, & McMarthy, 1987) and in functional imaging studies of monitoring (Henson, Shallice, & Dolan, 1999; Shallice, 2002). Using a simple RT model but with many different parameters and patients who had been injured decades prior to testing, Rueckert and Grafman (1996) also demonstrated impaired monitoring in patients with right sided injuries. In their experiment the right lesion group had significantly more misses of targets. The exact manifestations of poor monitoring may be sensitive to small differences in subjects' expectations.

It is also possible that the RL group does not perceive time accurately. If so they could not perceive the ongoing passage of the ISI and increase their preparedness for the upcoming stimulus. Prefrontal lesions impair time perception (e.g., Mangels, Ivry, & Shimizu, 1998). However, the frontal involvement in time perception is also likely a monitoring deficit (a clock is monitored). Analysis of our Tap experiment, which evaluates how well patients can estimate intervals of 1.5 s, will shed light on this hypothesis.

6.6. Summary interpretations

For a set of tasks requiring 20–25 min of attention, even late in a tiring day, patients with frontal lesions show remarkably good performance with minimal errors and no decline over time. The strategy of assembling related tasks, analyzing

the underlying task demands, and correlating deficits in the tasks with impairments in the processes nevertheless demonstrated important lesion-specific effects that resolve much of the controversy in studies of attention.

Using three RT tests (Simple RT, Choice RT, and Prepare RT), we have dissociated different attentional processes within the anterior attentional system, each related to distinct frontal brain regions. It is unlikely that the significant group differences in the demographic variables impacted the results. The LL group had the lowest education and IQ scores, and the fastest RT scores. The SM impairment in Judgment of Line Orientation (JLO) would not explain the slowing on the SRT task. For the CRT, there might be processes, such as selection of response, that are shared with the CRT and JLO, but it seems unlikely that a process impaired in a slow task such as the JLO could be causal for the CRT. Moreover, the correlation between JLO and CRT in the SM group was not significant.

Energization of the Schemata (*target*) is sensitive to medial superior lesions, perhaps particularly right, regardless of whether the response is simple or complex. We obtained no evidence for any prepare or sustain processes in prefrontal cortex separate from energizing. However, when attention is activated by a warning stimulus, lesions of the right SM region reduce the capacity to sustain energization after the prompt, and so impair preparation. *Monitoring* the occurrence of stimuli over time, in anticipation of responding more quickly to upcoming stimuli, is sensitive to right lateral lesions.

That standard neuropsychological tests cannot demonstrate these distinctions is not surprising, as they are not constructed to be discretely sensitive to underlying processes. Their value as clinical tests for executive functions lies in their broad demands for attentional processes even when they are described as tests of switching (WCST) or inhibiting (Stroop). Only the "subtractions" possible with the tests utilized here, combined with the extractions of basic processes from those tasks, and precise lesion localization, can uncover the fundamental workings of the Supervisory System.

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Appendix A

		SRT1			SRT2			SRT3		
		Total	Short[a]	Long[b]	Total	Short	Long	Total	Short	Long
LL	Mean	308.0	318.6	297.5	388.4	403.3	373.6	311.8	326.7	296.9
	S.D.	78.0	85.4	71.2	141.7	146.1	139.1	56.2	54.8	58.9
RL	Mean	319.8	326.1	313.4	392.5	386.7	398.3	356.7	370.9	342.4
	S.D.	59.4	60.5	58.8	53.1	49.0	63.3	28.8	18.5	45.7
IM	Mean	332.2	349.0	315.4	375.6	390.3	360.9	321.6	338.7	304.5
	S.D.	82.3	82.5	83.8	110.2	113.9	108.6	75.6	73.6	79.1
SM	Mean	372.5	391.3	353.7	405.1	422.5	387.6	376.5	401.8	351.3
	S.D.	98.7	99.2	99.4	97.2	99.7	96.7	63.0	62.0	66.9
CTL	Mean	310.0	321.0	299.0	352.7	369.1	336.3	335.7	356.2	315.3
	S.D.	69.0	69.7	70.4	78.5	76.2	83.6	70.4	64.7	78.1

		CRT1			CRT2			CRT3			CRT4		
		Total	Short[a]	Long[b]	Total	Short	Long	Total	Short	Long	Total	Short	Long
LL	Mean	561.8	579.7	543.8	574.8	586.8	562.9	556.1	557.3	554.8	576.1	577.6	574.7
	S.D.	87.0	81.6	94.8	80.9	76.8	88.7	92.6	101.8	88.8	80.3	96.3	68.4

Appendix A (*Continued*)

		CRT1			CRT2			CRT3			CRT4		
		Total	Short[a]	Long[b]	Total	Short	Long	Total	Short	Long	Total	Short	Long
RL	Mean	649.1	630.4	667.8	668.1	655.7	680.5	667.8	638.4	697.1	658.5	674.3	642.7
	S.D.	147.7	137.9	159.3	149.9	164.6	136.0	134.0	93.8	179.8	98.2	96.6	111.7
IM	Mean	643.3	656.5	630.2	666.1	676.0	656.3	662.3	655.9	668.7	726.5	755.2	697.8
	S.D.	138.2	141.3	138.3	148.3	148.7	151.3	191.2	204.3	184.5	252.7	259.5	252.7
SM	Mean	773.5	773.0	773.9	765.6	777.9	753.3	782.6	795.7	769.5	876.9	871.9	881.8
	S.D.	254.1	268.6	242.6	212.2	209.2	218.0	261.6	268.4	259.0	183.4	200.6	183.6
CTL	Mean	609.9	620.6	599.3	621.4	632.7	610.1	626.4	637.2	615.6	630.3	638.8	621.8
	S.D.	139.4	132.8	149.0	150.4	151.3	153.2	168.2	167.4	174.1	168.8	177.2	164.6

		PRT1 total[c]	PRT2 total	PRT3 total	PRT4 total
LL	Mean	527.5	527.7	545.4	536.8
	S.D.	91.7	103.5	102.1	81.9
RL	Mean	628.5	623.4	648.5	618.1
	S.D.	119.8	75.3	81.1	98.7
IM	Mean	649.0	649.3	641.9	642.3
	S.D.	247.7	217.0	221.7	248.0
SM	Mean	774.7	829.8	895.0	785.8
	S.D.	281.3	252.1	321.9	224.2
CTL	Mean	589.8	608.8	620.5	605.5
	S.D.	170.9	175.3	163.9	159.0

[a] Average RTs for trials with 3 and 4 s ISIs.
[b] Average RTs for trials with 6 and 7 s ISIs.
[c] Average total RTs. PRT1 & PRT4 – 1 s warning; PRT3 & PRT 4 – 3 s warning.

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