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Fractionation and Localization of Distinct Frontal Lobe Processes: Evidence from Focal Lesions in Humans

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The frontal lobes, comprising 25% to 33% of the human cortex (Stuss & Benson, 1986; Rademacher et al., 1992), most readily differentiate a primate brain from the brains of other mammals (Fuster, 1997). The functions of this region are also considered those that most strongly identify a human as human. Despite the general acceptance of the importance of frontal lobe functions, the study of these abilities has been difficult for theoretical, experimental, and clinical reasons (Stuss et al., 1995). For example, concepts such as executive control or supervisory system are difficult to make operational in experimental paradigms. In addition, even if separable processes can be defined, the relationship of these to potentially specific frontal lobe regions has been difficult to determine because of the relative infrequency of patients with limited focal frontal lobe lesions.

In this chapter, we summarize a decade or more of research on the functions of the frontal lobes through the study of patients with pathology restricted to that region (Alexander & Stuss, 2000; Stuss & Alexander, 2000). We started with one assumption: there is no unitary frontal lobe process, no central executive (Stuss & Benson, 1986; Shallice & Burgess, 1991). Rather,

> the frontal lobes (in anatomical terms) or the supervisory system (in cognitive terms) do not function (in physiological terms) as a simple (inexplicable) homunculus. . . . The different regions of the frontal lobes provide multiple interacting processes. Because the level of processing allows the interaction of information from other brain regions and because of the complexity of the frontal structures, the interacting processes can provide a sophisticated control. . . . The understanding of this, however, can be completed only at the level of processes and mechanisms (Stuss et al., 1995).

In the next section, evidence will be presented from research using neuropsychological tests of frontal lobe function to demonstrate that different cognitive processes can be related to distinct regions of the frontal lobes. A very brief review of the relation of less cognitive human abilities, such as humor appreciation and theory of mind, provides some support that even higher human abilities depend on the interaction of more distinct localizable functions. We then move from the location of distinct processes to the interaction of these in networks and cognitive systems. In the final section, we will present the implications of our review.

DISTINCT PROCESSES: EVIDENCE FROM NEUROPSYCHOLOGICAL TESTS

AN APPROACH

To refine frontal lobe brain–behavior relations, we simultaneously improved our differentiation of cognitive processes, and refined the localization of regions within the frontal lobes. For cognitive processes, we tried to isolate the different components that were necessary to complete a task, or devised tests that would more directly be related to a specific cognitive function. These efforts to differentiate frontal lobe processes are exemplified below, and described in detail in the original publications.

There were several steps required to improve the identification of functionally relevant gyrus-specific frontal lobe lesions. Since lesions do not usually respect defined Brodmann's areas, we decided that it would be necessary to test as many patients as possible who might have lesions involving, and restricted to, any region of the frontal lobes. Although patients would have pathology that affected different frontal lobe areas, it was hypothesized that, if a particular region was relevant to a specific function, those individuals who had involvement in that distinct area would be impaired in that function, regardless of brain damage in other surrounding areas. In finding patients whose lesions might represent different regions of the frontal lobes, various etiologies other than single infarctions (the preferred sample) would have to be considered. Thus, patients with resected meningiomas or benign gliomas are acceptable research participants, provided that the damage from this etiology can be demonstrated to be truly focal and limited, and that such patients would be reasonably represented in all subgroups. Patients with bifrontal contusions are necessary to provide an adequate sample of subjects with inferior medial and/or polar pathology. However, such patients should not have evidence of significant diffuse axonal injury. The challenge here is that patients with restricted frontal lobe lesions fitting our inclusion and exclusion criteria are not common, and completing projects of this magnitude would take 5 to 10 years. The gamble is that the lengthy effort would be for naught, or that theoretical assumptions would no longer be relevant when the study was completed.

Over the years, we used the greater numbers of patients to evolve different approaches to localize functions within the frontal lobes. We moved from comparison of frontal versus posterior lesions to what we called the standard anatomical classification within the frontal lobes: right frontal, left frontal, and bifrontal (Della Malva et al., 1993). A somewhat more sophisticated approach can be considered "backwards engineering." That is, rather than using an a priori anatomical classification, we started from differences in performance as a means of classifying individuals. The overall goal was to reduce even further the group performance variability commonly found in patient studies by developing anatomical groupings that would be more specific than the standard anatomical classification. The grouping factor would be driven by performance itself. This is a modified case study–group approach (Shallice, 1988). As illustrated below, this method of grouping patients can be accomplished in different ways.

The success of this lesion specificity approach depends not only on the ability to separate cognitive processes but also on the precision in brain area delineation. Our anatomical classification has gradually improved with the accumulated experience of several studies. We currently use an anatomical classification based on the Petrides and Pandya (1994) architectonic divisions. The rendering of these architectonic areas onto an adult human brain is illustrated in Figure 25–1. We have also grouped these architectonic areas into more specific subgroupings, which can be further clustered into four major anatomical regions (polar, inferior medial, superior medial, and lateral). This cascade of anatomical groupings is depicted in Figure 25–2. The different levels of alignment allow flexibility in the precision of lesion identification, depending on the specificity of the available imaging data.

The identification of pathology in specific architectonic areas would be useful as an anatomical grouping method only if a very large number of patients with lesions in such areas

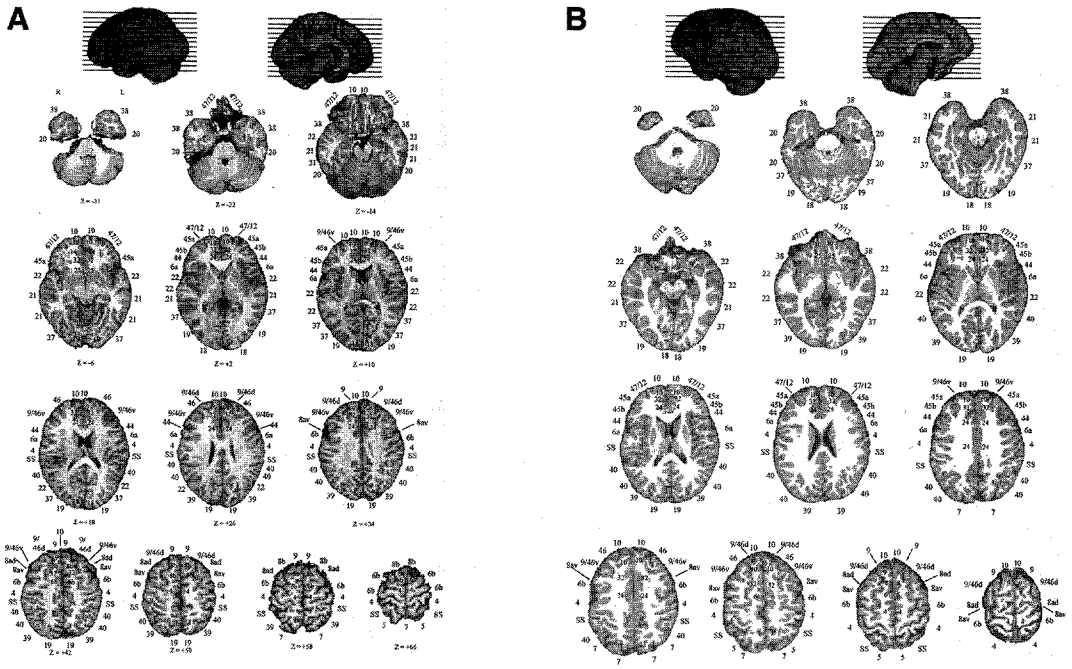

Figure 25–1. A fast T1°-weighted MRI of a young adult human brain is transformed into Talairach space (Talairach & Tournoux, 1988), enabling comparison to imaging data. On this brain, the frontal architectonic divisions of Petrides and Pandya (1994) are rendered in a manner similar to that of Damasio and Damasio (1989). For posterior areas where new architectonic divisions are not available, we continue to use Brodmann divisions on the lateral surface only. *A:* the brain is sliced in the axial plane parallel to the AC-PC line. *B:* the brain is sliced in the axial plane parallel to the orbitomedial line. Each slice is approximately 1 mm in thickness. Data from patient scans can be transferred onto the axial slices, providing a template for localizing lesions, at least in a general way, to the defined Petrides and Pandya specific architectonic areas. The subdivision of premotor area 6 is based on the Petrides and Pandya verbal descriptions of ventral and dorsal sections which we have labeled 6A and 6B, respectively.

were available. However, if a reasonable number of patients have pathology in regions of interest, then the relationship between a defined performance measure and each specific region could be calculated using various statistics, depending on the distribution of the performance measure.

Examples of these approaches are provided in the following section.

LOCALIZATION OF COGNITIVE FUNCTIONS WITHIN THE FRONTAL LOBES

An early success in discovering more precise frontal lobe–functional relationships was in a study of word list learning (Stuss et al., 1994; see also Janowsky et al., 1989). Standard analysis of variance (ANOVA) indicated that, using the standard anatomical classification, the left frontal and bifrontal groups had a significant impairment in recognition performance. Since this was contrary to accepted wisdom at that time (see Wheeler et al., 1995, for a meta-analysis of frontal lobe memory research), we were curious about the reason for this unusual finding. All patients with frontal lobe damage were ranked in order of performance, from the best to the worst, and compared to the performance of the control group. We then used a standard criterion (2 standard deviations from the control group mean) to differentiate the good from the impaired performers. Some of the frontal pa-

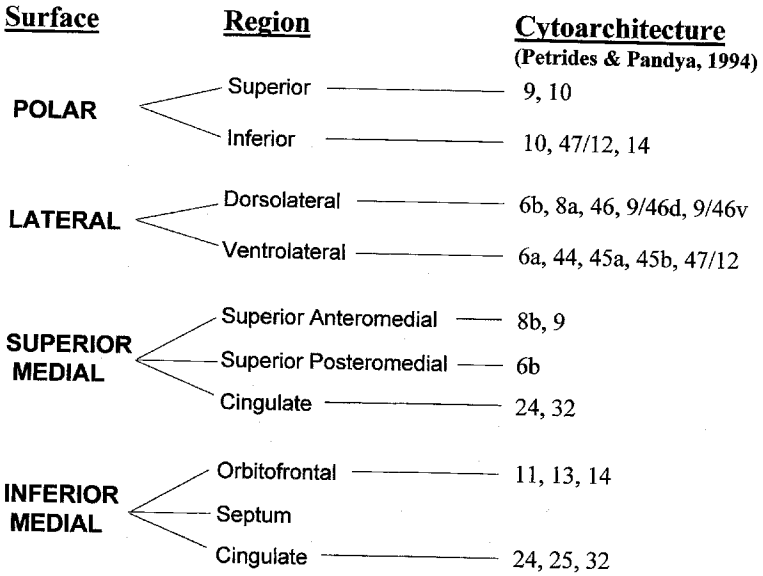

Figure 25–2. Four major regions of the frontal lobes (which can be separated into right or left frontal areas) are depicted: polar, lateral, superior medial, and inferior medial. Each of these divisions is segmented further. The polar area can be superior polar or inferior polar, the division approximately between the 6th and 7th axial slices in Figure 25–1a. The lateral frontal lobe is divided into the dorsolateral and ventrolateral (inferior) sections at this same level with minor overlap of dorsolateral and ventrolateral cytoarchitectonic areas on the 6th and 7th slices. The superior medial division is divided into three sections: the superior medial region continuous with the polar area; the more posterior superior medial area; and the more caudal portions of the anterior cingulate gyrus. Three sections comprise the inferior medial region: the orbitofrontal gyri; the posterior inferior medial region involving the septum; and the parts of the anterior cingulate cortex somewhat inferior to the corpus callosum. All of these divisions can be further classified into the Petrides and Pandya architectonic areas as indicated, but separating these in a practical way in human pathology research is difficult. This information can be used in correlational analyses, as described in the text.

Figures 25–1 and 25–2 are used practically as follows. Information from the available scans (preferably at least 3 months post-injury) are transferred to the axial and lateral/medial views. The presence (1) or absence (0) of pathology for each architectonic area is noted on a spreadsheet. The data can then be used for each architectonic area, or collapsed in a hierarchical manner. For example, patients with discrete damage to ventrolateral 45A may exhibit a definable performance pattern. On the other hand, such a specific pattern may not be observable. That is, patients with damage to different architectonic areas of the ventrolateral area may exhibit common behavioural results indicating that the logical grouping is by the ventrolateral area in general, not by architectonic division within the area. While this is still crude, it is a considerable improvement on past localization methods for human lesion research.

tients indeed showed good recognition performance, with many performing equivalent to or better than the control group. Since many of the impaired patients had bifrontal lesions, our first hypothesis to explain the impaired recognition performance was that the frontal lobe damage in the impaired patients involved the septal–limbic memory area. This lesion location was evident in many, but not all, of the impaired patients. Further investigation revealed that the remaining individuals with impaired recognition had mild language impairment, and their pathology was in the left lateral frontal region. Thus, two separate reasons, and two distinct anatomical areas, could explain the same recognition performance deficit: left dorsolateral frontal pathology, with mild residual language impairment; and posterior inferior medial frontal damage involving the septal–limbic memory system. The implication is that the two areas are related to a verbal learning memory–encoding neural system.

This performance-based clinical approach

was completed in a more formalized manner in a study on verbal fluency (Stuss et al., 1998). For each patient, each frontal region of interest that we had defined at that time (see Stuss et al., 1995) was coded as 1 (damaged) or 0 (not damaged). Using the performance on the verbal fluency task, the Classification and Regression Tree (CART; Breiman et al., 1984) statistical procedure was used to divide patients into anatomical groups that were maximally different in terms of their performance. The standard frontal lobe anatomical classification (right, left, bifrontal) was then compared to these new anatomical groupings by fluency performance (Fig. 25–3). The original coarse anatomical classification for the frontal lobes was refined from three groups into four (left and right dorsolateral, superior medial, and inferior medial). Pathology in the right dorsolateral frontal cortical or striatal areas, or the medial inferior lobe of either hemisphere, did not result in impaired performance in phonological fluency. Damage to the right *or* left superior medial areas, and left dorsolateral and/or striatal lesions, as well as left parietal pathology, did cause a significant deficit. These new anatomical classifications were subsequently used to assess differences in strategy performance on verbal fluency tasks (Troyer et al., 1998). In the semantic fluency task, damage to the right dorsolateral and inferior medial areas also resulted in impaired performance, suggesting that this task required other processes related to other brain regions (see Fig. 25–3).

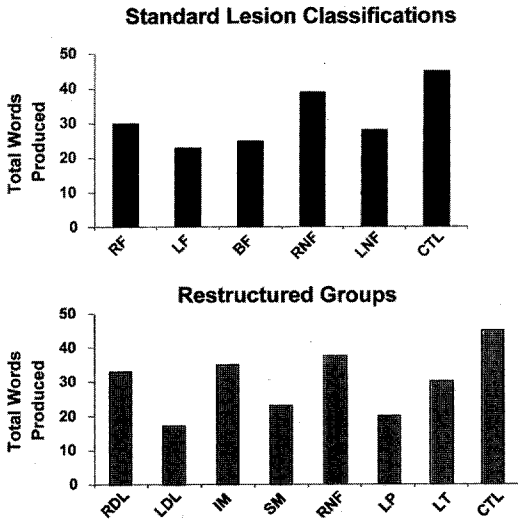

Figure 25–3. Verbal fluency results (total words produced starting with either *F, A,* or *S,* over a 1-minute period) are compared for the standard anatomical groupings (*top*) based on right frontal (RF), left frontal (LF), bifrontal (BF), right nonfrontal (RNF), and left nonfrontal (LNF) lesions to the restructured groups (*bottom*) based on Classification and Regression Tree analysis. The left nonfrontal group is now divided into left parietal (LP) and left temporal (LT) groups. The major difference for the frontal patients is the division of most of the original bifrontal group into inferior medial (IM) and superior medial (SM) groups. CTL, control.

This study exemplifies how a distinct frontal region can be demonstrated to be important for a process, regardless of the presence of brain damage in other surrounding areas. The inferior medial group who performed within the normal range on the letter fluency task tended to have pathology restricted to the inferior medial frontal area. Patients in the superior medial group, who were significantly impaired, occasionally had damage extending to the inferior medial region. The comparison of the two groups suggested that the superior medial area was most relevant for successful performance on the letter fluency task, and that the extension of pathology to the inferior medial frontal area for that group was likely not relevant to their performance.

The use of the CART to separate 35 patients with frontal lobe damage on the Wisconsin Card Sorting Test (WCST) also resulted in four different groupings: left dorsolateral, right dorsolateral, superior medial, and inferior medial (Stuss et al., 2000a). With these new groupings we were able to clarify previous results using the WCST, which tended not to emphasize the role of the medial regions. Damage to the inferior medial frontal area did not result in a deficit on the WCST (the now common finding that such patients are normal on "frontal lobe" tests), with one exception. If these patients were given the categories, they had no trouble changing categories of responses, but tended to lose set (see also Stuss et al., 1983). Patients with superior medial damage, right or left, tended to be the most impaired on all measures (categories achieved, perseverations of

the preceding sorting category), except for loss of set. Right and left lateral–damaged patients were also significantly impaired, although usually somewhat less than the superior medial group. There was one contrast between the right and left lateral groups: only those with right lateral damage had high set loss, even when further instructions were given to assist performance.

We noted parallel findings with an experimental concept generation task modeled after the California Card Sorting Test (Delis et al., 1989; Levine et al., 1995a), which also involves successively increasing instructions. Dorsolateral and superior medial patients were more impaired than inferior medial patients were. While all patients improved with additional instructions, the superior medial patients improved the least (Levine et al., 1995b).

The incongruent condition of the Stroop Test (Stroop, 1935) is one of the most commonly accepted measures of frontal lobe functioning, with different frontal regions considered relevant. Investigators using functional imaging have proposed a variety of frontal sites as key: left inferior lateral (Taylor et al., 1997), left superomedial (Pardo et al., 1990), right frontal polar (Bench et al., 1993), and bilateral anterior cingulate, perhaps with right predominance (Pardo et al., 1990; Bench et al., 1993). Lesion studies have also suggested different possible frontal regions: left lateral, which is the most common region (Perret, 1974; Golden et al., 1981; Corcoran & Upton, 1993); right lateral (Vendrell et al., 1995); and superomedial (Holzt & Vilkki, 1988). The orbital frontal region is apparently not essential for successful performance on the Stroop Test (Stuss et al., 1981).

Our approach in analyzing performance on different conditions of the Stroop Test (Stuss et al., 2001b) indicated that a speed performance measure was too variable to differentiate among patients with different frontal lesions. However, the number of errors for the color-naming (name patches of colors) and incongruent (read color words printed in a different color than the word itself) conditions yielded two distinct groups (see Figure 25–4). Subjects were coded 0 for good performers or 1 for poor performers, on the basis of whether the number of errors committed fell above or below 1.5 standard deviations above the control group's mean. Only 7 of 37 frontal-

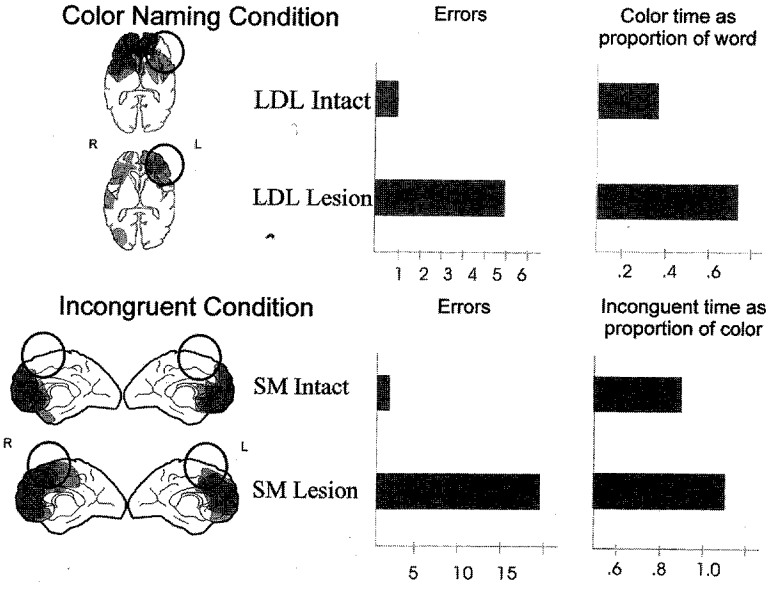

Figure 25–4. Patients with frontal lobe lesions are grouped by the number of errors they made on the Stroop test for both the color naming and incongruent conditions. The time to complete the different conditions is also presented for each group, as well as the overlaps of the lesions. In the color-naming task, the major anatomical difference was the involvement of the left dorsolateral (LDL) group. In the incongruent condition, damage in the superior medial (SM) region, particularly on the right, was the differentiating area. Since the individuals who were impaired in each condition were also slower, the difference in the errors could not be attributed to a speed–accuracy trade-off.

damaged patients were classified as poor performers on color naming, and their performance was highly related to their lesions in the left lateral area. Twelve of the frontal patients made many errors in the incongruent condition; the important pathology here was in the superior medial areas, particularly the right superior posteromedial region. The impaired patients in each condition were also generally slower, but some frontal patients who did not make errors were also slow. Time scores alone may not be the most effective measure of Stroop performance.

Our Stroop lesion study has several important implications. The Stroop is not just a "frontal lobe" test. Many patients with large frontal lobe lesions performed normally. Grouping by performance is effective, but sometimes the precise measure by which to group patients by performance to maximize information has to be sought. In addition to the information provided by the larger anatomical divisions, the correlational methods can yield reasonably precise gyral-specific relations. The previous lesion studies that suggested left frontal regions as being most relevant for performance of the incongruent condition were based on straight time scores. However, the incongruent condition also requires color naming (a condition in which the left frontal patients *were* impaired), and a speed measure would be confounded by the ability to color—name. If time scores are to be used, the incongruent time should be indexed relative to straight color-naming time. Our Stroop results dissociate the functional relevance of the left lateral and superior medial frontal regions.

The Trail Making Test (Army Individual Test Battery, 1944; TMT) has been considered by some to be a sensitive index of frontal lobe dysfunction, in particular the switching demands of Part B, but such claims were not based on studies assessing individuals with documented evidence of frontal lobe dysfunction. Stuss et al. (2001a) tested this assertion by administering the TMT to 62 patients with focal lesions in various frontal (n = 49) and nonfrontal (n = 13) brain regions. The time to complete TMT Part B seemed to suggest that this test was sensitive to frontal lobe damage. This result, however, was evident only when transformed scores were used and, if a proportional measure that accounted for the time taken to complete the processes required for Part A, no frontal-posterior differences were noted. The number of errors, however, was discriminatory. Only subjects with frontal lobe lesions made more than one error. Patients with right or left inferior medial frontal and/or anterior cingulate pathology made the fewest errors. Those who made the most errors tended to have dorsolateral pathology, although this was not significant.

We have also explored intrafrontal heterogeneity with tests that have been developed more recently in the experimental literature. Conditional associative learning, requiring the acquisition of arbitrary paired associates, has been extensively studied in both human (Petrides, 1982, 1985, 1990; Martin & Levey, 1987; Molchan et al., 1994) and animal (Halsband & Passingham, 1982; Petrides, 1982; Rainer et al., 1998b; See Chapter 21) paradigms. In a comparison of patients with focal frontal and posterior lesions and healthy young and old adults, aging and focal frontal damage produced qualitatively similar deficits (Levine et al., 1997). These deficits, however, were not quantitatively similar; the magnitude of impairment was much greater in the patients with focal frontal lesions, even though they were younger than the older adults were. Consistent with prior work, frontal patients were not uniformly impaired. The test was sensitive to dorsolateral prefrontal dysfunction, but not inferior medial/orbitofrontal. This dissociation was notable in light of the fact that the original experimental work with this task was conducted with dorsolateral-lesioned animals and humans.

By limiting our conditional associative learning task to only four stimulus pairs, we minimized the role of basic medial temporal lobe–mediated memory processes. The specificity of the task to processes involving control over interference was further demonstrated by administering the stimulus pairs in a standard paired-associate learning paradigm (in which the examiner corrects errors rather than allowing the subject to generate their own errors through trial-and-error learning). By enhanc-

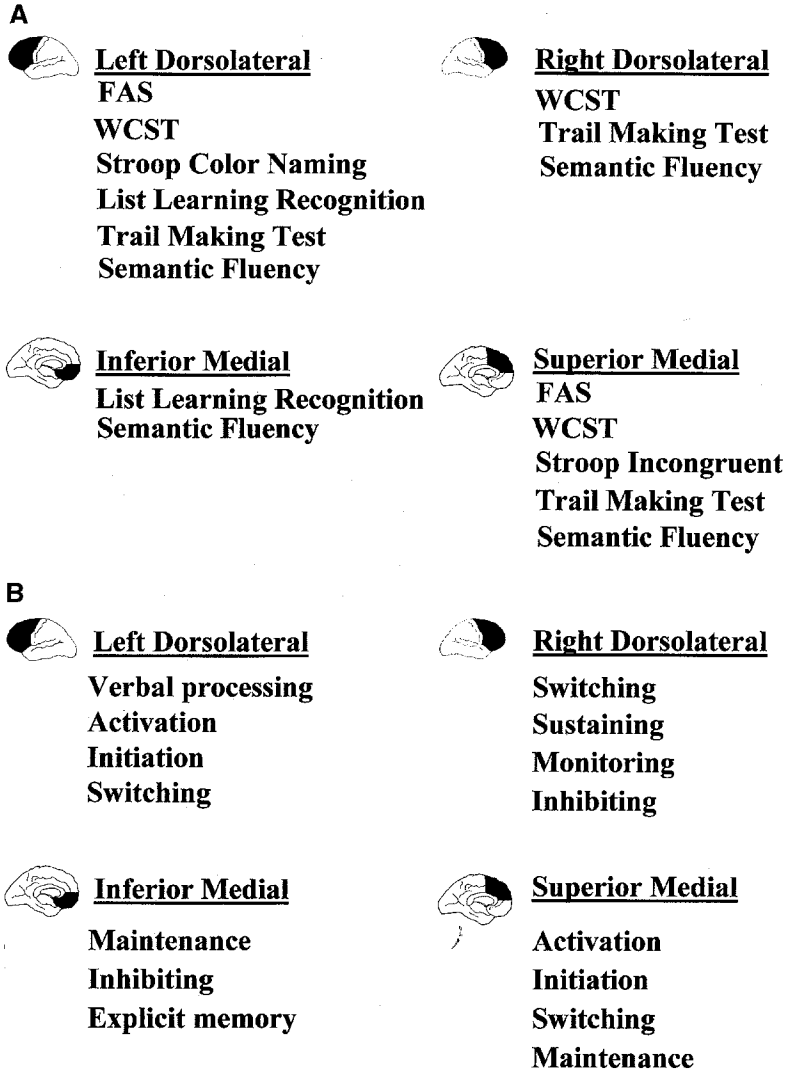

Figure 25–5. While our results have demonstrated that there are rather refined brain–behavior relationships within the frontal lobes, the major anatomical groupings that have been differentiated in our various studies are right and left dorsolateral, superior medial, and inferior medial. *A:* summarizes the relationship of the different measures from our various studies to these four groupings. *B:* Suggestions of which processes are related to those different tests. The inadequacies of our labels for the processes are evident. For example, the inhibition related to the inferior medial area is different from that to the right dorsolateral region.

ing structural support as in our work with the WCST, interference was reduced, and even the most impaired patients could acquire the stimulus pairs (Levine et al., 1997).

SUMMARY

The results to date suggest an anatomically and functionally discrete cognitive architecture to the frontal lobes (see Figure 25–5). At this stage, the architecture is truly an unfinished structure. Regardless, since lesion studies indicate which regions are necessary for a function, these results stand as a framework for more localized patient and imaging research in the future. In Figure 25–5a, the relation of the tests to the different frontal brain areas is presented. Figure 25–5b translates these tests into likely cognitive processes.

NON-COGNITIVE CHANGES IN BEHAVIOR

The functions of the frontal lobes are far more than cognitive. A profound apathy, blunted social propriety, and a notable personality change often constitute the most striking observations in patients with frontal lobe damage, particularly bilateral orbitofrontal (ventral medial) pathology (Nauta, 1973; Stuss & Benson, 1986; Damasio et al., 1994; Stuss et al.,

2000b). The changes may be so significant that others may consider the individual not to be the same person, as in Harlow's (1868) classic description of Phineas Gage—"he was no longer Gage."

The frontal lobes also provide the individual self-awareness to use past personal knowledge to understand current behaviors, and to select and guide future responses to integrate the personal self into a social context. Stuss et al. (2001d) have proposed three interrelated hierarchical levels of self-awareness, with two of the three levels based on processes instantiated in the frontal lobes. Both of these levels appear to be related particularly to the right frontal region (Stuss, 1991; Stuss & Alexander, 1999). The highest level of self-reflectiveness has been called *autonoetic consciousness,* and is the basis for episodic memory, which is related to personal and emotionally relevant past episodes (Wheeler et al., 1997; Levine et al., 1998b). At the highest level, the self-referential abilities can be disturbed, despite normal executive or problem-solving capacities. This is a true disorder in self-reflection, a deficiency at the highest level of monitoring of behavior.

The importance of the right frontal lobe, and/or ventral medial frontal regions, in noncognitive emotional functions can be experimentally demonstrated. Patients with right frontal lobe damage, in particular the right frontal polar/medial region, could grasp slapstick humor but did not appreciate the subtleties of humor, as in jokes that depend on a "twist" at the end (Shammi & Stuss, 1999). Even when they recognized the humor, they did not show the appropriate emotional response. The right frontal lobe, certainly part of a much larger system of emotional modulation, is required for the subtle convergence of cognition and affect essential to humor.

These same types of patients, particularly if the pathology is (right) inferior medial, find it difficult to take the perspective of others to understand or guide their own behaviors (Stuss et al., 2001c). Making inferences about the actions of others requires the ability to "mentalize." Such patients may not grasp the implications of any faux pas they make (Stone et al., 1998). While such functions also require cognitive capacity of different kinds, these deficits do not seem to be reducible to cognitive impairment.

Problems in social decisions and interactions most often occur in real-life situations, not usually in highly constrained tasks designed to isolate a limited number of cognitive operations. Progress, however, has been made in study design and new methods demanding on-line monitoring, planning, and application of strategies for behaving have been developed (e.g., Burgess et al., 1998; Levine, 1999; Levine et al., 1998a, 2000; see Chapter 33). These tests comprise multiple subgoals that have to be completed in a relatively unconstrained environment. Patients with documented frontal lobe lesions, particularly in ventral regions, who may perform normally on traditional frontal lobe tests, show strategic deficits on these measures due to impaired self-regulation (Burgess et al., 1998; Levine et al., 1998a, 1999, 2000; see also Bechara et al., 1994; and Chapter 22). The performance of these patients is striking in that they may demonstrate full awareness of the task demands even when failing to execute them (although in everyday practice this dissociation is not always observed). They incur large penalties for their real-life misconduct, yet repeat the same mistakes again, with often devastating effects on their quality of life. Accordingly, we have demonstrated that the performance of patients with traumatic brain injury (which more selectively affects ventral frontal regions; Stuss & Gow, 1992) on our strategy application task is significantly related to measures of quality-of-life outcome (Levine et al., 2000). Grafman's concept of social knowledge units provides one mechanism of explaining these real-life failures (Grafman, 1995; see Chapter 19).

FROM LOCATION AND PROCESSES TO NETWORKS AND COGNITIVE SYSTEMS

Our research on the effect of focal frontal lobe lesions on separable cognitive and noncognitive processes revealed distinct roles for different regions of the frontal lobes. Careful

reading of the results leads to the conclusion that this is not a modern phrenology but a preliminary effort in the use of lesion research to understand integrated neural networks. Converging evidence from multiple methodologies compellingly argues for the regulatory role of the frontal lobes in networks involving posterior regions. The neural modeling of Cohen and Servan-Schrieber (1992) shows that the frontal lobes are capable of determining task context through excitatory connections with posterior association areas. Studies of event-related potentials (Knight, 1997), single-cell recording (Rainer et al., 1998a, 1998b), and functional neuroimaging (McIntosh et al., 1994) have each demonstrated that the frontal lobes regulate sensory cortex. The dynamic aspect of frontal lobe function within neural networks has also been captured. Event-related potential studies have demonstrated that not only are the frontal lobes involved in networks responsible for novelty detection (Halgren et al., 1998; Knight & Scabini, 1998) but frontal lobes can recruit posterior cortical areas for processing of novel events (Knight, 1996; Alain et al., 1998).

Our research focuses on how these networks can be uncovered and better understood through behavioral measures. The involvement of left dorsolateral and septal/hippocampal memory regions in recognition suggests a neural system for verbal encoding, different regions playing separate roles. In phonological fluency, for example, there were possibly several systems at work, including initiation and activation (superior medial, and possible left dorsolateral) and language-based process (left parietal and left dorsolateral frontal). Performance on the multicomponent nature of the WCST requires the functioning of a distributed neural network (superior medial and both lateral frontal regions for switching of categories; right lateral for sustained attention and monitoring; inferior medial for maintaining set under conditions of additional supervisory reflective efforts). In the Stroop Test, different regions of the frontal lobe were involved in color naming (left frontal) or maintenance of consistent activation of the intended response in the incongruent condition (bilateral superior medial frontal).

TASK COMPLEXITY AND NEURAL NETWORKS

The above studies led to considerations about how to test more actively neural networks through lesion research. We exploited the functional domain of attention, since a simple anterior–posterior dissociation of attentional abilities did not seem to encapsulate the potential complexities of the interaction between different brain regions. Patients with focal lesions in various frontal and posterior regions were compared on a location-based (select–what, respond–where) target detection task (Stuss et al., 1999). The test allowed measurement of three different attentional processes commonly linked to frontal function: *(a)* inhibiting attention to distracting information presented at the same time as the target (*interference*); *(b)* effect of previous inhibition of irrelevant information on subsequent processing (*negative priming*); *(c)* inhibition of motor responses to novel and previously processed locations (*inhibition of return*). These three attentional processes were measured under three levels of task difficulty.

Figure 25–6 summarizes our model of the regions involved in these tasks based on the

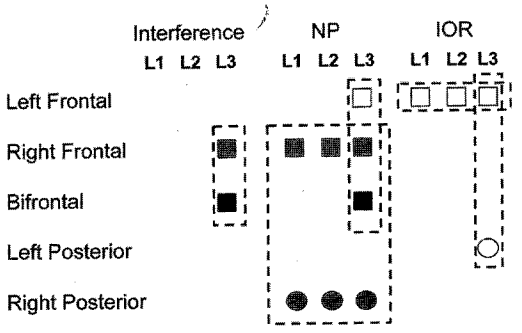

Figure 25–6. Performance of patients with right frontal, left frontal, and bifrontal lesions on a location-based (select–what, respond–where) target detection task is illustrated. There were three levels of difficulty in the task; three different attentional measures were taken (see text). The figure demonstrates that the different brain regions necessary for successful performance on the task varied depending on which attentional measure was taken, and the level of difficulty of the task. L1, lowest level of difficulty; L2, medium level of difficulty; L3, highest level of difficulty; NP, negative priming; IOR, inhibition of return.

Stuss et al. (1999) study. The presence of a symbol indicates abnormal performance for that specific attentional processes at that level of task complexity. The hypothesized neural systems are indicated by the dotted outlines grouping the task-relevant lesioned areas together.

Lesions in different brain regions affect different attentional processes. For some of the processes, impairment is found in both frontal and posterior regions, suggesting a functional neural system. Most importantly, the neural systems are dynamic and active, altering with the complexity of task demands. The functional process labeled *interference* is impaired by damage to the right frontal lobe (that is, unilateral right frontal and bifrontal damage, but not unilateral left frontal damage, results in impairment), but only at the highest level of complexity. The ability to withhold attention to irrelevant information as defined by this task appears to be a right frontal lobe function. In contrast, *inhibition of return* is affected by left frontal damage at all levels of complexity, although performance varies from abnormal facilitation to abnormal inhibition as task complexity increases. At the highest level of task difficulty there is also involvement of the left nonfrontal regions, suggesting that task difficulty or differing task demands now somehow recruit more posterior regions of left hemisphere. *Negative priming*, at the simplest level of task demands, is impaired after damage to either anterior or posterior regions of the right hemisphere, suggesting a right frontal–posterior neuronal system for inhibition of spatial selection. As difficulty increases, however, impairment is noted in all frontal groups, implying either the necessity of additional frontal lobe processes or resources.

There is no single frontal attentional deficit. A frontal supervisory attentional system is, in reality, an emergent interaction of different attentional processes, as proposed by Stuss et al. (1995). Different frontal regions support different attentional mechanisms, some in concert with posterior brain regions. These systems alter dynamically with changes in task demands or complexity. Functional neural systems are relative to the task, not absolute. The implications for theory and clinical neuropsychological assessment are obvious.

PARTIAL LEAST SQUARES

A major stumbling block to understanding the function of neural systems is the lack of process purity, or a one-to-one mapping between tasks and processes. Traditionally, the solution to this problem has been to either develop better tasks to isolate specific processes or look at post-hoc relationships between task measures and standard neuropsychological tests in multiple domains. These methods help to clarify the role of anatomical correlates across measures. More recently, novel statistical techniques have been applied in addressing this problem (Burgess et al., 1998, 2000; see Chapter 33). Burgess and colleagues (1998) proposed several distinct processes underlying performance in their multitasking procedure. A factor analysis of the measures taken from their task, together with several neuropsychological measures, identified five theoretical constructs that contribute to multiple performance measures. Later, Burgess and colleagues (2000) employed structural equation modeling to investigate the potential relationships between underlying processes and how these might combine to produce successful (or unsuccessful) multitasking in patients with focal brain lesions. In addition, they applied a lesion analysis technique similar to that described here to identify the relevance of lesion locations to the different measures of task performance. The cognitive and lesion analyses informed each other; the lesion location analyses constrained the cognitive model, which in turn suggested the structure of neural systems supporting the contributing processes.

We have applied a different multivariate statistical method, partial least squares (PLS), to understand the relationship between our lesion findings and our behavioral measures. A full description of the matrix operations involved in the PLS procedure has been provided elsewhere (McIntosh et al., 1996). For the current analysis, we covaried a brain matrix containing binary-coded lesion location data for nine areas (septal, and left and right

inferior medial, superior medial, lateral, and polar) with a behavior matrix containing age, education, and IQ-corrected scores for 24 patients with frontal lobe damage on several neuropsychological and experimental measures (see Fig. 25–7). The singular value decomposition of this covariance matrix produced sets of mutually orthogonal paired latent variables (LV). Each LV pair consists of a behavior profile across measures and a pattern of lesion locations that is optimally related to the behavior profile. The behavior profiles represent the structure of task performance most related to the pattern of lesion locations (lesion profile). The first and second LV pair accounted for 34% and 23% of the total covariance, respectively. When the analysis was subjected to a permutation test, only the first LV pair had a less than 5% probability that these relationships could have been found by chance. However, both LV pairs showed moderate correlations between the factor scores for the lesion latent variable with the factor scores for the behavior latent variable (first LV, $r = 0.61$; second LV, $r = 0.49$), which suggests that both LV pairs reflect relatively strong relationships.

Figure 25–7 illustrates the relationship between the behavioral measures and the pattern of lesion locations that was identified by the first two LV pairs. The direction of the bars represents how the behavior and lesion profiles correlate with one another. Bars that share the same direction (upward or downward) in both the behavior and lesion profiles within an LV pair are positively related to another. Bars that point in the opposite direction for the behavior and lesion profiles within an

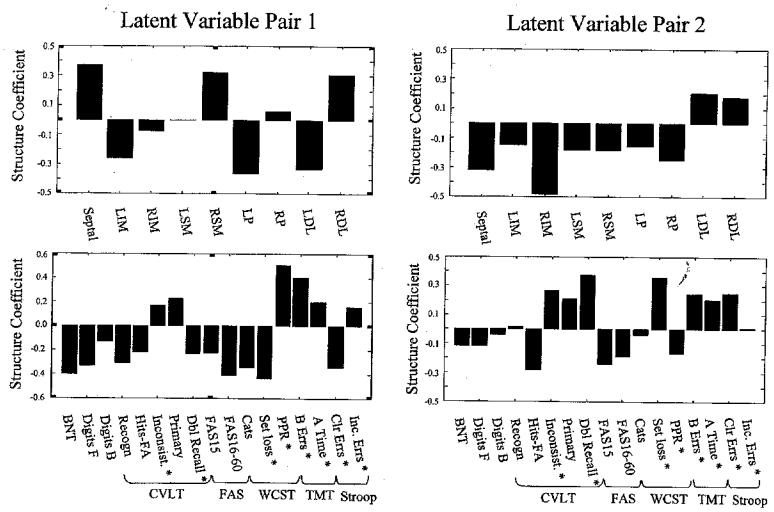

Figure 25–7. The first two orthogonal latent variable (LV) pairs identified in the partial least squares analysis. The *top* bar graphs represent the pattern of lesion locations related to each LV pair. The *bottom* bar graphs represent the profile of behavioral measures related to each LV pair. The length and direction of the bar represent the correlation of the measured variable with the LV that it contributes to. Within an LV pair, task and lesion location bars sharing the same direction (upward or downward) are positively related to one another, whereas bars that point in the opposite direction are negatively related to each other. Asterisks indicate variables for which a high score reflects poor performance. L, left; R, right; IM, inferior medial; SM, superior medial; P, polar; DL, dorsolateral; CVLT, California Verbal Learning Test; FAS, verbal fluency; WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; BNT, Boston Naming Test; Digits F, forward digit span; Digits B, backward digit span; Recogn, recognition measure of the CVLT; Hits-FA, CVLT hits minus false alarms; Inconsist, CVLT inconsistency of recall across learning trials; Primary, CVLT primary memory estimate; Dbl Recall, CVLT within-trial recall repetition; FAS15, output over first 15 seconds; FAS16–60, output over 16–60 seconds; Cats, categories achieved in the WCST; PPR, perseveration of the preceding response in the WCST; B Errs, number of errors on the TMT; A Time, time to complete Part A of the TMT; Clr Errs, number of errors in the color-naming condition of the Stroop Test; Inc Errs, number of errors in the incongruent condition of the Stroop.

LV pair are negatively related to each other. The output of the PLS is quite complex, but the aspect of this figure that is particularly relevant to the present discussion is that the pattern of lesion correlations for the first LV pair seems to reflect a left–right contrast, whereas the pattern of lesion correlations for the second LV pair seem to reflect a dorsolateral–other areas contrast. Notice that some of the task measures are related to both lesion patterns. For example, in the first LV pair, errors on Trails B covary positively with right-sided damage. In the second LV pair, errors on Trails B covary positively with dorsolateral damage. This same relationship is also true of performance measures on the California Verbal Learning Test, verbal fluency test, and the Wisconsin Card Sorting Test. In other words, within single measures, we were able to extract unique variance related to different lesion locations. Also, in general, the patterns of behavior–lesion relationships mirror those identified in the individual analyses discussed earlier. This analysis is the first of its kind and should be regarded as a preliminary attempt to separate processes within tasks using this method. The necessary next step is to cross-validate the patterns identified here in a larger sample of patients to determine the stability of these findings. The eventual goal would be to identify unique covariance across measures that represent neuropsychological dimensions that are represented to varying degrees in their relation to lesion location.

CONCLUSIONS

The frontal lobes clearly are not homogeneous anatomical or functional monolithic structures, but are composed of morphologically distinct areas interconnected with each other and with posterior and basal brain regions to constitute complex anatomical circuitries. Such systems are an anatomical (and certainly neurochemical) infrastructure allowing for the flexible and dynamic construction of functional networks necessary for a specific task. If one considers the posterior brain regions and their functions to be more modular and hard-wired, a major role of the processes related to the frontal lobes may be to serve the flexible and dynamic nature of such networks. Terms such as *supervisory system* or *executive control* are convenient labels to represent the sum of the processes recruited at any moment, for any task. We have identified some of the processes and marshaled evidence for their relationship to specific frontal regions.

Activation studies in neurologically intact individuals using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) also indicate that multiple regions are active during the performance of a specific task and identify how distinct frontal brain regions are related to particular elements of supervisory processes. However, such studies cannot normally differentiate all the different processes required for a complex task, since PET and fMRI are used to average results over time. Lesion research, by identifying that damage to a specific brain region impairs a relatively unique function, provides additional information related to the apparent necessity of a brain area for a specific function. In addition, functional imaging that provides temporal analysis, such as event-related potentials or magnetoencephalography, combined with source localization, would be an in vivo on-line method of dissociating processes related to brain localization. Newer methods of analysis of activation paradigms and complex networks, such as path analysis and partial least squares, may disentangle the supportive from the essential element of a brain network activated by specific supervisory processes.

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Principles of Frontal Lobe Function

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