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ADULT CLINICAL NEUROPSYCHOLOGY: Lessons from Studies of the Frontal Lobes

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■ **Abstract** Clinical neuropsychologists have adopted numerous (and sometimes conflicting) approaches to the assessment of brain-behavior relationships. We review the historical development of these approaches and we advocate an approach to clinical neuropsychology that is informed by recent findings from cognitive neuroscience. Clinical assessment of executive and emotional processes associated with the frontal lobes of the human brain has yet to incorporate the numerous experimental neuroscience findings on this topic. We review both standard and newer techniques for assessment of frontal lobe functions, including control operations involved in language, memory, attention, emotions, self-regulation, and social functioning. Clinical and experimental research has converged to indicate the fractionation of frontal subprocesses and the initial mapping of these subprocesses to discrete frontal regions. One anatomical distinction consistent in the literature is that between dorsal and ventral functions, which can be considered cognitive and affective, respectively. The frontal lobes, in particular the frontal poles, are involved in uniquely human capacities, including self-awareness and mental time travel.

CONTENTS

INTRODUCTION 402
A BRIEF HISTORY OF ADULT CLINICAL NEUROPSYCHOLOGY 403
Neuropsychology, Behavioral Neurology, Neuropsychiatry 403
Clinical Neuropsychological Assessment Approaches 403
Modern Clinical Neuropsychology: Integration of Cognitive and Clinical Neurosciences 406
The Focus of This Review: The Frontal Lobes 407
COGNITIVE FUNCTIONS ASSOCIATED WITH THE PREFRONTAL CORTEX (DORSOLATERAL) 409
Frontal Lobe Language Functions 409
Control of Memory 410
Working Memory 412

Anterior Attention Functions 413
Overall Summary 416
EMOTIONS, SELF-AWARENESS, AND SOCIAL BEHAVIOR:
VENTRAL AND POLAR FRONTAL CORTEX 417
Emotions, Reinforcement, Self-Regulation, and Decision-Making 417
Episodic Memory, Self-Awareness, and Autonoetic Consciousness 420
Empathy, Sympathy, and Humor 422
Clinical Implications 423
CONCLUSIONS 424

INTRODUCTION

The field of adult clinical neuropsychology is not only beyond the scope of a single paper, it also exceeds the limits of most books. We therefore start with a panoramic view to provide a historical and anatomical context to adult clinical neuropsychology, present a framework for adult neuropsychological assessment in general, and proceed to a more narrow focus on one facet of adult clinical neuropsychology, the functions of the frontal lobes. Why have we narrowed our focus thus? The executive functions mediated by the frontal lobes are highly sensitive to brain damage, and executive dysfunction is therefore the most common presenting problem in neuropsychological practice. With the recent explosion in research on frontal lobe functions, it has become increasingly clear that they are involved in nearly every aspect of human neuropsychology. Indeed, as we argue later, they may be what define us as human. In comparison to other cognitive functions such as memory, language, and perception, where many clinical measures have emerged from detailed experimental analysis, few clinical measures reflect recent empirical work on frontal functions. In this sense, the frontal lobes may be considered the final frontier of neuropsychology.

Even with these restrictions, our mandate is not inconsiderable, and further limits have been self-imposed. First, we have limited ourselves to an anatomical/behavior functional relationship to avoid the confusion of multiple terms such as executive functions, the dysexecutive syndrome, the supervisory system, and frontal lobe functions. Second, the focus is on the revelation of fractionation of specific processes and systems within the frontal lobes (Alexander et al. 1986, Cummings 1993, Saint Cyr et al. 2002). Third, our focus is clinical, but the emphasis is on the newest frontal brain-process relationships. The use of clinical frontal lobe tests in various populations is reviewed as much for the information they have provided in relation to frontal localization of function as for their construct validity as individual tests. Indeed, one hoped-for byproduct of this review is that the knowledge of more experimental research in patients with focal lesions might alter the use of such clinical tests. To help us achieve this goal, functional neuroimaging data are presented where possible to support, extend or challenge the more classical clinical neuropsychological lesion research.

A BRIEF HISTORY OF ADULT CLINICAL NEUROPSYCHOLOGY

Neuropsychology, Behavioral Neurology, Neuropsychiatry

Clinical neuropsychology, in its broadest definition, is the understanding of brain-behavior relations and the clinical use of this information. The first noted cortical "localization" of function after brain injury probably was the Edwin Smith Surgical Papyrus, dated sometime around the seventeenth century BC (Walsh 1987). In a real sense, however, the history of neuropsychology started in the nineteenth century, with Carl Wernicke (1874) possibly being the father of neuropsychology. Renewed attention to his work on aphasia and apraxia was a major force that fanned the flames of the burgeoning of interest and activity in neuropsychological issues in the mid- and later twentieth century.

The roots of neuropsychology lie in neurology and psychology, with no real separation existing among these interests in the initial stages. Kurt Goldstein (1934/1995), for example, was an expert in neurology, psychology, psychiatry, and rehabilitation. The psychological basis of neuropsychology began to disengage from medicine in the 1940s, at least in North America (Lezak 1983), the separation occurring to a greater or lesser degree in different regions. Today, three related and relatively new subdisciplines play important interactive and somewhat different roles in brain-behavior studies. Behavioral neurology assumes that at least certain aspects of behavior, even complex behaviors to some degree, are hardwired in the adult central nervous system (Heilman & Valenstein 1985). This assumption provides the framework for behavioral neurology research: In most cases, brain damage in a specific area will result in a certain kind of functional deficit. Neuropsychiatry uses similar assumptions as behavioral neurology, but the emphasis is on the psychiatric manifestations of neurologic disease. Finally, clinical neuropsychology focuses more on psychological testing procedures. Where an individual scientist falls on this spectrum is often an accident of training rather than a result of knowledge, skills, or interest.

Clinical Neuropsychological Assessment Approaches

In the early years of neuropsychological assessment, clinicians would have a sense of "normal" performance, and anything below that indicated a pathological deficit. This dichotomous approach allowed little sense of normal variability. To remedy this, some clinics developed local quantitative procedures, but these usually had no real empirical standardization and no clear generalizable clinical use (Benton 1967). Some clinicians diagnosed "organicity" (meaning brain pathology of some kind) based on "pathognomonic" signs discovered in a patient's response to a test. These early forays in clinical assessment were dramatically altered by Binet and the Stanford-Binet test of psychometric intelligence. Binet developed tests that were objective (procedures were clear and there were precise criteria for satisfactory performance), standardized (the tests were given to samples of different ages, and tests were finally chosen based on specific criteria from these results), and had demonstrable usefulness (Benton 1967).

Binet's transformative method set the stage for the psychometric test battery approach advocated by many neuropsychologists. There was a move from the more dichotomous classification supposedly associated with behavioral neurology to "the measurement of continuously distributed variables within a psychometric tradition that attempts to achieve at least equal interval scaling of the operations in question" (Rourke & Brown 1986. p. 5). Halstead (1947) was a key figure in this shift, with his attempt to use a battery of objective tests to diagnose brain damage and general categories of brain damage. There was a growing desire to create an empirical base to assessment and to make neuropsychology more scientific, with standardized tests for validation, cross-validation, and replication. Within this psychometric approach, a battery of tests was considered superior to individual tests for several reasons (Rourke & Brown 1986). Addition of certain tests improved the rate of accuracy of diagnosis of brain damage. A fixed battery of relatively well-normed standardized tests provided more data on different functions to assist decision making. Individual and global scores could be used. With a fixed battery, issues of generalizability, assessment of different types of validity, and the presence of differential sensitivity of test items all were considered to improve the accuracy of diagnoses. Most importantly, a battery helped avoid the powerful effects of base rates of the condition in the population to which the patient belonged.

Gradually, different procedures were developed to maximize the use of the battery of tests: norms (Reitan & Davidson 1974), keys or decision rules (Russell et al. 1970), and patterns of scores (Golden 1981). The application of multivariate statistics maximized the value of the battery approach by combining information, minimizing variability among groups, and grouping patients by behavioral characteristics (Crockett et al. 1981). For example, factor analysis helped differentiate variables into functional representative groupings and provided a means of examining shared and independent variance to maximize brain-behavior understanding. Discriminant function analysis was an excellent tool for classification of subjects into their proper groups, a major tool of validation of the battery approach (Stuss & Trites 1977).

Not all neuropsychologists followed the psychometric development path for adult clinical neuropsychology. Russian neuropsychology, under the guidance of Luria (1973, 1980), who had training in neurology, psychoanalysis, and psychological testing through his relationship with Vygotsky, was a proponent of a more clinical approach, adapting and improving rather than rejecting neurologists' tools. He emphasized sensitivity to individual differences, including variables such as lesion location, age, sex, handedness, and the individual's history. The approach was more flexible in the assessment of the patient's behavior, with rapid screening, and then focusing on the salient problems. If necessary, new measures would be developed to investigate these deficits; tests would be changed to test limits of abilities, or to provide a more thorough evaluation. Luria developed much of his theory from the investigation of individual patients; that is, he depended to a great degree on what has been a cornerstone of neuropsychology and a major tool of neurologists from the earliest days—case studies. The value of case studies is clear (Crockett et al. 1981). The patient and the deficits can be examined in exquisite detail. Hypotheses about the patient can be developed, tested, and refined, with control over virtually all variables. The case study is rapid and relatively inexpensive, with an ability to deploy and direct resources as required. It is clinically useful, because therapy can be developed based totally on the knowledge of the individual patient.

Luria & Majovski (1977) criticized the battery approach for not having a brain theory on which to base its conclusions. Russell (1986) disagreed, arguing that the battery approach does have many sources for theory: (*a*) a neurological basis, (*b*) its own clinical lore from the use of the battery and (*c*) psychometrics itself. Russell's response clearly demonstrates the key difference between the clinical and psychometric approaches: "In fact, the unique contribution of psychology to neuropsychology, a contribution that cannot be duplicated by neurology or behavioral neurology, can be summarized in one word: psychometrics" (p. 46).

The more clinical approach to neuropsychology can also be seen in a different form in what has been termed the "process" approach, pioneered by neuropsychologists in Australia (Walsh 1987), Denmark (Christensen 1979, who standardized Luria's approach while maintaining the qualitative hypothesis testing nature), and the United States (Kaplan 1988). A major difference of the process approach from the general clinical approach was the push for greater standardization. Qualitative aspects of behavior are identified and quantified and subjected to statistical analyses rather than the method just described. Testing of clinical limits is operationally defined, repeatable, and quantifiable. Whereas diagnosis of brain damage is still a goal in this approach, the questions are different (Milberg et al. 1986). What do the test results mean psychologically and cognitively? How did the patient achieve the final score? The premises underlying the need for this process analysis, at least as presented for the Boston Process Approach (Milberg et al. 1986), are several. Solutions to a test may be achieved by different processes, and each of these may be related to different brain structures. The unfolding of cognitive acts over time provides the opportunity for careful observation of behavior along this temporal continuum, providing a richer source of information than just right or wrong scores. That is, the way a patient responds is as, or more, important than the achievement itself. Because most categories of cognitive function consist of many components, a process approach provides the means to separate and assess these components in a manner not easily achieved by the pure psychometric or battery approach. This is particularly true if you adapt tests to isolate some of the processes. For example, comparing a Digit Symbol copy result to the regular Digit Symbol subtest of the Wechsler Adult Intelligence Scale allows dissociation of the effect of motor speed on Digit Symbol performance.

The strengths of the qualitative and quantitative approaches could be combined. "It is clear that failure to appreciate the appropriate role of qualitative dimensions in the measurement of brain-behavior relationships can lead to a vapid and meaningless generation of irrelevant data" (Rourke & Brown 1986, p. 15).

Modern Clinical Neuropsychology: Integration of Cognitive and Clinical Neurosciences

Our conceptual basis determines how we construct tests (Benton 1967). In the field of intelligence assessment, for example, certain tests were developed based on whether one considered IQ to be a general ability, or to consist of multiple primary abilities. Interestingly, Binet, whose method was a major push for the psychometric approach, avoided the issue—IQ is what the test measures. In this psychometric view the most important criteria are the effectiveness of the test and whether the test meets the critical conditions of objectivity, standardization, and usefulness. Russell (1986) stated that one could not know a function exists unless a test for that function has been developed. Whereas the psychometric approach is truly essential in understanding variability across individuals, the ossification of tests in a fixed battery and the emphasis on the psychometric criteria rather than conceptual bases have limited the ability of neuropsychologists to update the theoretical framework of brain-behavior relations.

The conceptual basis of cognitive and affective faculties derives from modern psychological theory. Clinical neuropsychology therefore should take advantage of current cognitive (and increasingly social) psychological thinking. Furthermore, it must also incorporate the newest neuroanatomical findings in the discovery and dissociation of cognitive processes; in turn, neuropsychology can inform cognitive and affective theory. Moreover, truly understanding the individual cognitive and affective processes of the brain, and their disturbance in brain damage of various types and lesion locations, is a sine qua non for diagnosis and rehabilitation. We also believe that this must be understood in the psychological, psychosocial, and environmental context of the individual, but that is another level of complexity to the clinical story.

The differences in the approaches described above appear to have derived from the background training of the proponents, and by the questions they asked. Take, for example, the following different questions: What is the difference between biological and psychometric intelligence (Halstead 1947); can the presence/absence of brain dysfunction be identified in a particular individual, and with what level of accuracy; what specific cognitive process is impaired in this patient for the purpose of establishing an individualized rehabilitation program; what are the cognitive structure and anatomical underpinnings of, for example, the anterior attentional system? Each of these questions may not only lead to the establishment of different approaches; each may still necessitate the use of a particular approach to answer the question.

In many regards, facets of different approaches are being used in a combined way in modern clinical neuropsychology. For example, case studies (the importance of which is typified in journals such as *Neurocase*) are being directed by sophisticated cognitive theory and assisted by new structural and functional imaging methodologies. Multivariate covariance-based techniques such as structural equation modeling are being used not to differentiate brain damage from non–brain damage but to understand the dynamic interactions of different focal functional brain units (localizationist, brain as a mosaic of separate skills related to distinct areas) in a large neural network (generalist, the hierarchical, sequential, and interactive nature of brain functioning). Methods from case studies and group studies are being combined to enhance the group study approach by providing more in-depth investigations, but also immediate replicability. Our research into the functions of the frontal lobes has benefited from all of these approaches.

The Focus of This Review: The Frontal Lobes

Executive functions are high-level cognitive functions that are involved in the control and direction of lower-level functions. For the purposes of consistency with prior literature, we use the terms "frontal" and "executive" interchangeably when referring to broad classifications of tests, but it will be clear that we adopt a much more specific approach when trying to understand and explain the true functional localization of these processes.

One very general method of separating the different facets of frontal lobe functioning is based on a fundamental neuroanatomical distinction (see Figure 1). The ventral prefrontal cortex (VPFC) is functionally dissociated from the dorsolateral prefrontal cortex (DLPFC), a distinction supported by evolutionary theory of cortical architectonics (Pandya & Yeterian 1996). The DLPFC is part of the archicortical trend originating in the hippocampus. It is involved in spatial and conceptual reasoning processes. Much of what is known about frontal functions in neuropsychological studies is based on patients with DLPFC dysfunction. These cognitive processes form the basis of what is referred to as executive functioning (Goldman-Rakic 1987, Milner 1963).

The VPFC is part of the paleocortical trend emerging from the caudal orbitofrontal (olfactory) cortex. It is intimately connected with limbic nuclei involved in emotional processing (Nauta 1971, Pandya & Barnes 1987), including the acquisition and reversal of stimulus-reward associations (Mishkin 1964, Rolls 2000). The involvement of the ventral medial/orbitofrontal region in inhibition, emotion, and reward processing suggests a role in behavioral self-regulation, as shown in numerous case studies of patients with pathology in this area (Eslinger & Damasio 1985, Harlow 1868). In spite of the obvious importance of these processes to human behavior, they are not adequately assessed by standard neuropsychological assessment.

Further functional/anatomical divisions within the frontal lobes can also be specified. Superior medial lesions can cause an apathetic syndrome, represented in the extreme by akinetic mutism (Cummings 1993, Stuss & Benson 1986). The functional basis of this impairment (i.e., lack of initiation) appears to be separate from more inferior medial frontal effects (Stuss et al. 1998). The superior medial

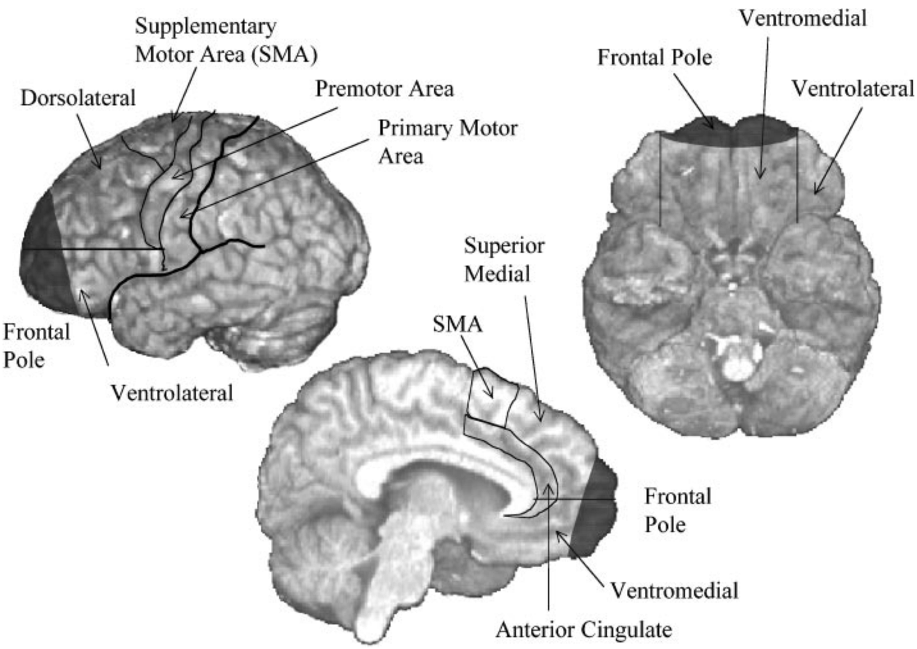


Figure 1 The major functional subdivisions of the human frontal lobes.

frontal region can exhibit dysfunction that at times mimics the lateral regions, and in other instances are unique.

Inferior (ventral) medial frontal regions have been functionally dissociated from ventrolateral and polar regions (Barbas 1995, Bechara et al. 1998, Elliott et al. 2000). Based on connectivity, Carmichael & Price (1995) divided the orbital and medial prefrontal cortex into three regional (and functional) divisions for behavior and emotional responses. The frontal poles, particularly on the right, are involved in more recently evolved aspects of human nature: autonoetic consciousness and self-awareness. The importance of polar regions in specific higher human functions has also been highlighted in studies of humor and theory of mind (Baron-Cohen et al. 1994; Shammi & Stuss 1999; Stuss et al. 2001c,d). We therefore consider the frontal polar region to be distinctly involved in processes that define us as human.

We present data on the effects of frontal lobe lesions, grossly divided into cognitive (DLPFC) and affective (VPFC) functions. As a means of maintaining a coherence of anatomy to function for the purposes of this review, our primary focus is on the DLPFC/VPFC separation, with additional separate consideration of the frontal poles. Whenever possible, these sectors are considered separately according to hemispheric lateralization. Although damage in our patients often crosses medial and lateral sectors, distinctions between these regions are noted where relevant.

COGNITIVE FUNCTIONS ASSOCIATED WITH THE PREFRONTAL CORTEX (DORSOLATERAL)

Our division of executive functions is functional, because this is the approach that would be followed in clinical neuropsychology. Standard tests have come into use through years of clinical practice and form the basis of the "frontal" part of neuropsychological assessment batteries. Some were developed in the context of focal lesion research, but most were classified based upon their face validity as executive measures. Whereas these standard tests have been used clinically with some validation in ancillary focal lesion and functional neuroimaging research, the origin of modern measures is theory-driven research on frontal functions, followed by clinical application.

We review the evidence from both the lesion and functional neuroimaging literature pertinent to the sensitivity and specificity of the standard "frontal" tests as contrasted with novel approaches based on recent cognitive neuroscience research. Our review is organized according to measures of higher-level language, attention, and memory processes. This organization is more pragmatic than theoretical; we acknowledge overlap of control operations across these domains. Owing to space constraints, we limit this review to those in wide usage and those with enough validity data upon which to base a meaningful evaluation. To foreshadow, there is evidence to support the validity of standard frontal tests, but this association depends on careful analysis of task parameters, lesion location, and the exclusion of patients with basic sensory and linguistic deficits from the posterior-lesion control groups. Novel approaches show considerable promise for improving assessment.

Frontal Lobe Language Functions

Excluding motor deficits (e.g., articulation problems), and Broca's aphasia, the language deficits related to the frontal lobes can be grouped globally under activation and formulation (paralinguistic) deficits (Alexander et al. 1989). Activation problems in speech output ("dynamic aphasia") are associated with medial frontal damage (anterior cingulate gyrus and supplementary motor area). Transcortical motor aphasia, with notably truncated spontaneous language as well as other deficits, may occur after damage usually to left DLPFC anterior and superior to Broca's area (Brodmann Areas 44, 46, 6, and 9) (Freedman et al. 1984).

Activation deficits can be tested by requiring the patient to generate a list of words beginning with a specific letter (phonological or letter fluency) or from a specific semantic category (semantic or category fluency). Next to the Wisconsin Card Sorting Test (WCST, see below), letter-based fluency is the most popular frontal test; its face validity derives from its lack of specification by external cues. It is traditionally considered to reflect left frontal function (Milner 1964, Perret 1974), although other areas of damage have been shown to produce impairment on this task (see Stuss et al. 1998 for review).

In our study of 74 focal lesion patients (Stuss et al. 1998), the left DLPFC patients were indeed the most impaired. Right DLPFC and VPFC patients were not impaired. However, patients with left parietal damage were also impaired and in fact could not be distinguished from the left DLPFC patients. Consistent with the role of superior medial regions in activation, superior medial damage on either side was also associated with impaired letter-based fluency. This left DLPFC, parietal, and superior medial frontal regional pattern is activated in functional neuroimaging studies involving word generation (Cabeza & Nyberg 2000). Posterior superolateral temporal regions are also implicated (Wise et al. 1991). We were not able to assess this effect, as our patients' temporal lesions were anterior. Semantic fluency was impaired in all patient groups except for right posterior. Further differentiation of frontal and temporal effects can be derived from process analysis of the size of semantically related clusters of words generated on semantic fluency (related to left temporal lesions) and switching between clusters on either letter-based or semantic fluency, related to left DLPFC or superior medial frontal lesions (Troyer et al. 1998).

The formulation problems, or disorders of discourse, are generative and narrative in nature. They reflect problems in planning and goal attainment. At the level of sentence generation and spontaneous utilization of complex syntax, deficits have only been described with left-sided lesions. At the level of story narrative, lesions in left dorsolateral and prefrontal regions may produce impairments. Left-sided lesions result in simplification and repetition (perseveration) of sentence forms, and omissions of elements. Right-sided lesions cause amplification of details, wandering from the topic and insertion of irrelevant elements, and dysprosody, all leading to loss of narrative coherence (Joanette et al. 1990).

Control of Memory

In considering the role of the frontal lobes in memory, it is useful to distinguish between basic associative processes of cue-engram interaction (mediated by medial temporal lobe/hippocampal structures), and strategic processes involved in the coordination, elaboration, and interpretation of these associations (mediated by the frontal lobes) (Luria 1973, Moscovitch 1992). The role of the frontal lobes on memory tasks is one of control and direction, hence the phrase "working with memory" (Moscovitch & Winocur 1992). Damage to the frontal lobes (other than extension to basal forebrain areas) does not result in clinically diagnosed amnesia.

Given traditional neuropsychology's strength in assessing medial temporal lobe amnesic syndromes, early clinical memory tests were more suited to the measure of associative than strategic processes. This imbalance has persisted. Whereas current clinical neuropsychological memory tests such as the Wechsler Memory Scale (Wechsler 1997b) tap both associative and strategic processes, few attempts have been made to quantify these skills separately, causing the clinical neuropsychologist to resort to qualitative analysis in the interpretation of frontal lesion effects on memory. A major development in this respect is the California Verbal Learning

Test (Delis et al. 1987), an excellent example from the Boston Process Approach of modern clinical neuropsychology, which draws upon cognitive science to improve the specificity of neuropsychological assessment. This test includes measures of serial position learning, semantic organization, interference effects, cued recall, recognition, and response bias. Although similar measures are incorporated into the latest Wechsler Memory Scale revision (Wechsler 1997b), the verbal learning test in this battery contains semantically unrelated words, precluding analysis of semantic clustering.

The effects of frontal brain damage on these and other measures were studied by Stuss and colleagues (1994), who showed that subjective organization (pair-frequency), was specifically affected by frontal damage, although the intrafrontal lesion location was not a factor. Right DLPFC patients had increased intralist repetitions, possibly owing to a monitoring deficit. Category clustering deficits were not found, although these have been reported elsewhere (Gershberg & Shimamura 1995). As expected, frontal damage (especially on the left) affected encoding and retrieval. Contrary to clinical lore, recognition was also affected by frontal damage. Analysis of this effect revealed that it was related to subtle anomia in left DLPFC patients and subtle associative mnemonic deficits in patients with medial frontal damage extending to septal regions. A subsequent meta-analysis confirmed a small but significant role for the frontal lobes in recognition memory (Wheeler et al. 1995), but only on tests that had an organizational component such as categorized lists.

Focal lesion studies have demonstrated the importance of the frontal lobes on retrieval tasks in which monitoring, verification, and placement of information in temporal and spatial contexts are of critical importance (Milner et al. 1985, Stuss et al. 1994). Reduplication, confabulation, and focal retrograde amnesia, all disorders of faulty episodic retrieval, are associated with frontal lesions (Levine et al. 1998a, Moscovitch & Melo 1997, Moscovitch & Winocur 1995, Stuss et al. 1978). In the past decade, the role of the frontal lobes in memory has been greatly elaborated by functional neuroimaging studies (Cabeza & Nyberg 2000), which allow for separation of mnemonic processes not possible in straight behavioral research. Of particular importance is the role of the right frontal lobe in episodic memory retrieval (Tulving et al. 1994), which is consistent with the right lateralization often observed in neuropsychological patients with paramnestic disorders.

More recent imaging work has provided greater intrafrontal specificity in relation to retrieval success, retrieval monitoring, contextual recall, and material specificity (Cabeza & Nyberg 2000). In addition to the right hemispheric bias in retrieval, retrieval operations can also be distinguished according to relative DLPFC/VPFC involvement within the right hemisphere. VPFC is involved in retrieval cue specification, whereas DLPFC is involved in higher-level postretrieval monitoring operations (Fletcher et al. 1998, Petrides et al. 1995). This finding provided greater precision to the earlier patient work (Milner et al. 1991, Stuss et al. 1994) and later case studies (Schacter et al. 1996) on the nature and localization of right frontal executive control in memory retrieval.

Working Memory

Working memory is historically central to research on frontal lobe function (Fuster 1985, Goldman-Rakic 1987), beginning with the observation that monkeys with frontal lobe damage are deficient in making stimulus-guided responses after the stimulus is removed from view (Jacobsen 1936). After 65 years of research, however, the precise role of the frontal lobes in working memory tasks is still a matter of debate. Much of this debate is concerned with separation of working memory processes such as encoding strategies, storage/maintenance, rehearsal, interference control, inhibition, and scanning of working memory buffers (D'Esposito et al. 2000). These processes are addressed in experimental lesion or event-related functional neuroimaging research on working memory and attentional control.

For the purposes of clinical neuropsychological assessment, the important principles follow on those described for long-term memory above. As in long-term memory, the frontal lobes' primary role in working memory is in control and manipulation of information held on-line, hence Baddeley's notion of the "central executive" (Baddeley 1986). Whereas the frontal lobes are certainly involved in simple storage and maintenance, these operations are primarily mediated by posterior regions, such as the inferior parietal lobule ("slave systems") (Baddeley 1986, D'Esposito et al. 1995); frontal involvement increases as information held on-line is threatened by interference or exceeds working memory capacity (D'Esposito et al. 2000). The dorsolateral prefrontal cortex (DLPFC) appears to be preferentially involved in monitoring and manipulation (Owen et al. 1996). The role of the ventral prefrontal cortex (VPFC) is less clear, with hypotheses including maintenance, interference control, and inhibition (D'Esposito et al. 2000).

Working memory is important to many neuropsychological tests, but few widely used tasks seek to directly assess working memory per se. Digit span or spatial span tasks are important for determining working memory storage capacity, but do not provide information relating to rehearsal or executive control. Consistent with the neuroimaging evidence described above, a recent meta-analysis showed no evidence for an effect of frontal lobe lesions on digit or spatial span (D'Esposito & Postle 1999). Reversal of the sequences (e.g., digits backwards) does measure manipulation of information held on-line. Scoring methods that combine forward and backward span confound these capacity and manipulation measures. The latest updates of the Wechsler Instruments have added new tasks stressing manipulation and control (Wechsler 1997a,b) and even allow for a separate "working memory" composite score. This too combines the dissociable processes into a single measure, although the neuropsychologist is still able to examine the more demanding strategic subtests separately. The Brown-Peterson technique taps working memory control processes in the presence of interference (Stuss et al. 1982), and supraspan tests can be used to measure processing when working memory capacity is exceeded (see Lezak 1995 for description).

A modern approach would incorporate additional measures validated in the animal and human experimental literature. Delayed response tasks are among the most-studied tasks in the neuropsychological literature on frontal lobe functioning. Although they have been successfully transferred to clinical research (D'Esposito & Postle 1999, Oscar-Berman et al. 1991), there are many variations on these tasks and no standard administration procedures. The self-ordered pointing and conditional associative learning tests have been validated in both monkey and human focal lesion studies (Owen et al. 1990, Petrides 1989) and in functional neuroimaging studies of healthy adults (Owen et al. 1996; Petrides et al. 1993a,b). Self-ordered pointing requires the monitoring of past responses (such as which objects or spatial locations were selected in a spatial array) and planning of subsequent responses to prevent repetitions. Conditional associative learning requires the acquisition of arbitrary, fixed associations between members of a set of stimuli and a set of responses that are learned through a process of trial and error. Differences in functional localization of these tasks can be revealed through experimental lesion or functional neuroimaging studies, but both are sensitive to DLPFC dysfunction (albeit in different DLPFC regions) (Owen et al. 1990, Petrides 1989). In a sample of patients with focal DLPFC and VPFC lesions, we documented the specificity of conditional associative learning deficits to DLPFC lesions; patients with VPFC lesions were not impaired (Levine et al. 1997).

Anterior Attention Functions

The frontal lobes mediate attentional control in the top-down guidance and direction of other processes. Proper assessment of attentional deficits requires differentiation among distinct attentional processes that can be selectively impaired. Standard assessment is concerned with attentional switching, selective attention, and sustained attention, whereas modern assessment more finely fractionates anterior attentional systems.

ATTENTIONAL SWITCHING: THE WCST AND TRAIL MAKING TEST, PART B Tests of sorting or grouping have a long history in the psychological assessment of concept formation. Multiple processes contribute to performance on these measures, including generation and identification of concepts, hypothesis testing, maintenance of attention, resistance to interference, utilization of feedback to guide behavior, and when more than one concept is possible, switching categories and inhibiting perseveration of prior categories. In her classic 1963 study, Milner documented a specific effect of frontal cortical lesions on the Wisconsin Card Sorting Test (WCST). In this test the patient must determine the established sorting criterion (color, form, or number) through a process of trial and error, then shift to a new criterion according to a change in examiner feedback. The WCST has since become the most widely used behavioral measure of frontal lobe function (Heaton et al. 1993). However, posterior damage can affect WCST performance (Anderson et al. 1991). In addition, functional neuroimaging studies indicate frontal and posterior activation in association with WCST performance (Berman et al. 1995).

The WCST has been embedded in a larger context of problem-solving by Dias and colleagues (1997). In this framework WCST shifts are regarded as extra-dimensional (across perceptual dimensions, such as from color to form, on the basis of feedback) as opposed intradimensional (shifting within a dimension, such as from red to blue). Extra-dimensional shifting is specifically affected by dorsolateral prefrontal damage in monkeys (Dias et al. 1996) and humans (Owen et al. 1993) and is associated with DLPFC activity in healthy adults (Rogers et al. 2000). This brain-behavior association is consistent with the original development work on the WCST involving patients with DLPFC damage. We directly assessed this DLPFC/VPFC dissociation using the WCST in a large sample of patients with focal lesions (Stuss et al. 2000). Consistent with the monkey data, which indicated that VPFC damage does not affect extra-dimensional shifting, patients with DLPFC lesions were impaired, whereas VPFC patients were not impaired. As noted in earlier work (Stuss et al. 1983), the VPFC patients were prone to loss of set, possibly owing to susceptibility to interference. Set loss was also observed in right DLPFC patients, related to poor sustained attention.

In summary, the classification and use of the WCST as a frontal measure is justified, but with a number of caveats. Within the frontal lobes, the DLPFC is preferentially involved in the set-shifting aspect of the task. Patients with VPFC damage are relatively intact on this key aspect of the WCST, but they are prone to the less frequently reported set loss errors. Finally, the WCST is not completely resistant to the effects of posterior damage. As with any test, similar errors can occur for different reasons, such as comprehension deficits.

Modern neuropsychological approaches to assessing task switching and other functions of sorting tests include the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al. 1994), which includes human analogues of the set-shifting paradigms described in the Dias et al. (1996, 1997) studies, and the California Card Sorting Test (CCST) (Delis et al. 1992). The latter presents a wider variety of verbal and visual sorting criteria (see also Levine et al. 1995b). The CCST incorporates standardized manipulations of environmental support, including identification of groupings executed by the examiner and generation of groupings according to cues. Similar cues can be applied in the WCST to investigate the extent to which deficits are due to self-initiated processes as opposed to a more basic deficit affecting perception or detection of the correct sorting criterion (Stuss et al. 2000). This information may be used to generate rehabilitation hypotheses.

The Trail Making Test, Part B (TMT-B), requiring alternating letter-number connecting, has also been used as a frontal test. Although it is interpreted as a measure of attentional switching, its functional and anatomical specificity is affected by several factors, including speed, visual search, and simultaneous maintenance of two sequences. Part A (TMT-A, number connection) is treated as a control for factors other than switching, but it is not well-matched to TMT-B in other respects (Rossini & Karl 1994). Interpretation is further complicated by the standard administration and scoring procedures in which errors and time are confounded. Early focal lesion studies failed to support the widely held claim that TMT-B is sensitive to frontal lesions (Reitan & Wolfson 1995, Stuss et al. 1981). In a direct test of this lesion-behavior relationship, we found that the timing measures were sensitive to frontal pathology, but the differential effect of frontal lesions on time to complete TMT-B was eliminated when this score was corrected for speed on TMT-A (Stuss et al. 2001a). Patients with DLPFC lesions, however, were distinguished from other patients on the basis of errors attributable to difficulties in attentional switching and maintenance of attention. VPFC patients were not impaired (Stuss et al. 2001a). TMT-B errors (but not time), therefore, are a valid measure of DLPFC dysfunction.

SELECTIVE ATTENTION: THE STROOP TEST Deficient selective attention results in omitted responses to important stimuli or enhanced reactivity to irrelevant information. The Stroop test (Stroop 1935) includes a key demand on selective attention of a given response characteristic (i.e., color naming) to the exclusion of a more dominant one (i.e., word reading). The Stroop interference effect is among the most extensively studied phenomena in experimental psychology (MacLeod 1991), although the experimental work has had no discernable effect on clinical versions of the test. Lesion studies have emphasized right or left DLPFC effects on this measure (Perret 1974, Stuss et al. 1981, Vendrell et al. 1995), whereas functional neuroimaging studies have emphasized the role of medial frontal (in particular anterior cingulate) regions in performance on the Stroop interference condition (Bench et al. 1993, Pardo et al. 1990). In a large sample of focal lesion patients, we recently found that the deficit associated with left DLPFC damage could be accounted for by impaired color naming (rather than interference) (Stuss et al. 2001b). Patients with frontal damage were slowed on all three conditions. Patients with superior medial lesions (especially on the right) committed the most errors, corresponding to this region's role in maintaining the strength of an activated (selected) intention (Devinsky et al. 1995, Goldberg 1985). Inferior medial patients performed normally. The inconsistency with prior lesion research could be explained by the fact that the prior studies did not correct performance in the interference condition for slowing in the color naming condition.

SUSTAINED ATTENTION There is a surprising lack of widely accepted measures for sustained attention (detection of targets over a prolonged time period) in traditional clinical neuropsychology. Whereas letter cancellation or other "vigilance" tasks are used (Lezak 1995), there are few data relating performance on these paper-and-pencil measures to frontal function. Continuous performance tests are sensitive to right frontal pathology, especially when the target complexity is increased (i.e., respond to "O" following "X"), as opposed to simple vigilance tasks (Reuckert & Grafman 1996, Wilkins et al. 1987) and are associated with right frontal activation in healthy adults (Deutsch et al. 1987, Pardo et al. 1991). Several investigators have highlighted the importance of dull, repetitive tasks in tapping top-down modulation of endogenous arousal (Robertson et al. 1997). Accordingly, slow sustained attention tasks are more sensitive to right frontal pathology than fast-paced ones (Reuckert & Grafman 1998, Wilkins et al. 1987). The Sustained Attention to Response Task (SART; Robertson et al. 1997) and the Elevator Counting Test

(Robertson et al. 1991) are modern neuropsychological tests of these sustained attention abilities stressing maintenance of endogenous arousal.

A COGNITIVE NEUROSCIENCE APPROACH TO ANTERIOR ATTENTION SYSTEMS The Supervisory Attention System as proposed by Norman & Shallice (1986) distinguished between routine tasks as mediated by contention scheduling and novel, nonroutine tasks in which unmodulated contention scheduling is likely to generate errors, requiring supervisory top-down control (Shallice & Burgess 1993). Although the Supervisory Attention System has been useful for framing problems in frontal lobe research, it is considered to be underspecified in its original form (Shallice & Burgess 1996). Stuss and colleagues (1995) refined an approach to anterior attentional systems by describing five independent supervisory processes: energizing schemata, inhibiting schemata, adjusting contention scheduling, monitoring schema activity level, and control of if-then processes. These control processes are demonstrated in seven attentional tasks: sustaining, concentrating, sharing, suppressing, switching, preparing, and setting.

Context is an important variable in assessing attention. In the WCST we demonstrated that a little information for patients with ventral damage was more destructive than no information (Stuss et al. 2000). We manipulated context by relatively small changes in task difficulty in a "select-what, respond where" attentional task (Stuss et al. 1999). Three different measures of attention were assessed (interference, negative priming, and inhibition of return) across three levels of task difficulty. In certain groups of patients, the brain areas impaired with each attentional measure varied with the task difficulty. For example, when task complexity was manipulated, inhibitory deficits (negative priming) were shown to be related to different regions of the frontal lobe. When the task was simple, deficits were more focally limited to right posterior and right frontal lobe damage. When the task became more complex, impairment was observed after damage in most frontal brain regions (but not all posterior brain regions, in contrast).

Overall Summary

Executive functions, higher-level cognitive functions involved in the control and regulation of lower cognitive operations, are clinically assessed by a small battery of tests that, on the basis of putative sensitivity to frontal damage, are referred to as "frontal." Support for the validity of this claim is variable. There is evidence for the sensitivity of these measures to right or left DLPFC, and in many instances to superior medial area lesions. In some cases this claim is supported by functional neuroimaging data. Because these tests are complex and multifactorial, they do not specifically assess frontal function. Both lesion and functional neuroimaging evidence indicate recruitment of posterior regions involved in the basic linguistic or perceptual operations of the task. Moreover, task complexity could affect which regions of the frontal lobes were involved. As a general rule for some processes, the more complex the function, the more frontal brain regions involved (Stuss et al. 1994, 1999).

In general, modern cognitive neuroscience findings have failed to penetrate clinical assessment of executive functions. The incorporation of measures with greater psychological and anatomical specificity into modern clinical neuropsychology would improve executive functioning assessment. Whether modern or standard, however, a very consistent finding is the relative insensitivity of these measures to VPFC damage.

EMOTIONS, SELF-AWARENESS, AND SOCIAL BEHAVIOR: VENTRAL AND POLAR FRONTAL CORTEX

Functions mediated by VPFC and polar frontal cortex can be considered superordinate for their role in defining human individuality and high level personal decision making and social behavior. Damage to these regions may result in changes so significant that the individual is considered not to be the same person, as in Harlow's classic description of Phineas Gage: "he was no longer Gage." These functions are not properly addressed in standard clinical neuropsychological assessment. Patients with VPFC damage can appear normal on frontal tests of DLPFC functions. Extensive experimental work on this region is important for understanding the basic operations contributing to self-aware behavior. This section suggests that the disorders of self-awareness can be dissociated and that different assessment approaches provide us with different information about the patient.

The critical regions for emotions are located in the subcortical medial wall of the brain: the hippocampal formation including the olfactory apparatus, the gyrus cinguli, mamillary body, hypothalamus, anterior thalamus, amygdala, substantia innominata, midbrain, basal ganglia, and their interconnections (Papez 1937, Watanabe 1998). The area most commonly and strongly related to human emotional and social behavior is the frontal lobes. Connections of the subcortical emotional regions with the prefrontal cortices (the biochemical substrate is admirably described in Arnsten & Robbins 2002) play a critical role in emotional reactions and responsiveness, representing the end point for the interpretation of external percepts (Nauta 1979, Pandya & Barnes 1987), merged with visceral input (Nauta 1973) and integrated with emotional states for the preparation and execution of responses (Mesulam 1985). It is in the frontal lobes, with perhaps a preeminent role of the right frontal lobe, that the complete integration of subjective experience in a fully self-aware person is achieved. We postulate that, at the clinical level, distinction can be made between the effects of ventral medial prefrontal cortex and frontal polar regions.

Emotions, Reinforcement, Self-Regulation, and Decision-Making

LOWER LEVEL OPERATIONS: VENTRAL FRONTAL INVOLVEMENT IN REWARD AND INHIBITION The ventral prefrontal cortex is intimately connected with more primitive limbic nuclei involved in emotional processing (Nauta 1971, Pandya & Barnes

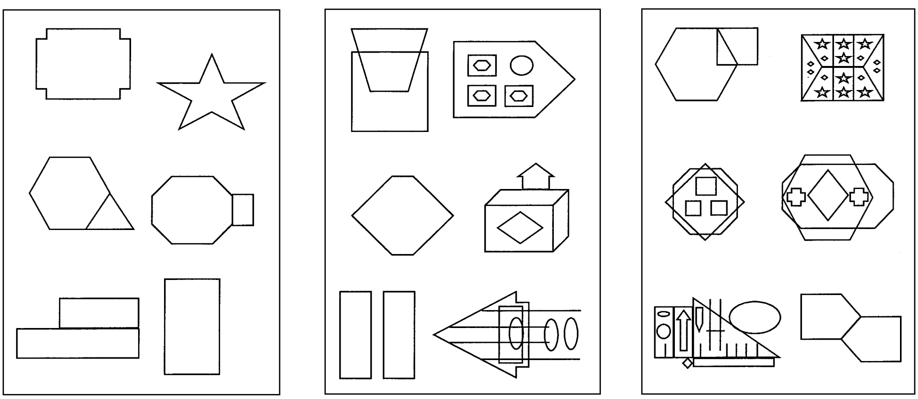
1987) and processes of information about basic drives and rewards that inform and direct high-level decision-making. Animal work stresses the VPFC's involvement in the acquisition and reversal of stimulus-reward associations (Fuster 1997, Mishkin 1964, Rolls 2000). A double dissociation between VPFC lesion effects on reversal learning (interpreted as affective) and DLPFC lesion effects on attentional (extra-dimensional) set-shifting was reported in the monkey research on set-shifting reported above (Dias et al. 1996, 1997). Similar dissociations have been reported in human research in both focal lesion studies (Freedman et al. 1998) and functional neuroimaging studies of healthy adults (Nagahama et al. 2001).

DECISION-MAKING More recently, the emphasis has shifted to higher level decision-making tasks involving reward processing in unstructured situations—tasks more in line with distinctly human capacities. One such example is the gambling task developed by Bechara and colleagues (1994) that is both sensitive and specific to VPFC lesions (Bechara et al. 1998). Performance on this task has been dissociated from deficits in working memory and inhibition (Bechara et al. 1998). The gambling results have been interpreted within the Somatic Marker Hypothesis (Damasio et al. 1991), which states that human reasoning is normally constrained by emotional biases acquired through previous conditioning, mediated by the ventromedial prefrontal cortex. Similar findings in patients (Rogers et al. 1999a) and healthy adults using functional neuroimaging (Rogers et al. 1999b) have been found using a different gambling task with parametric manipulation of reward ratios. Separate functional neuroimaging studies have also noted VPFC activation in response to tasks in which choices must be made in under-specified situations (Elliott et al. 2000).

STRATEGIC SELF-REGULATION The involvement of the VPFC in inhibition, emotion, and reward processing suggests a role in behavioral self-regulation, as shown in numerous case studies of patients with VPFC lesions (Eslinger & Damasio 1985, Harlow 1868). We have used the term "self-regulatory disorder" (SRD) as shorthand for the syndrome exhibited by these patients. SRD is defined as the inability to regulate behavior according to internal goals and constraints. It arises from the inability to hold a mental representation of the self on-line and to use this self-related information to inhibit inappropriate responses (Levine 1999; Levine et al. 1998a, 1999). SRD is most apparent in unstructured situations (e.g., child-rearing, making a major purchase, or occupational decision-making), in which patients fail to inhibit inappropriate responses in favor of those responses that might result in a preferential long-term outcome. This is contrasted with structured situations in which environmental cues or over-learned routines determine the appropriate response (Shallice & Burgess 1993), which is often the case for standard neuropsychological tests. As a result, many patients with SRD appear unimpaired in over-learned, structured situations in spite of significant real-life upheaval (Mesulam 1986, Stuss & Benson 1986).

Shallice & Burgess (1991) attained laboratory concordance of real life SRD in VPFC patients using naturalistic multiple subgoal tasks, setting a quantitative standard for deficits that had heretofore been limited to qualitative description. Subsequent studies in our laboratories and elsewhere have further established the use of such tasks in patients with brain damage (Burgess et al. 1998, 2000; Goel et al. 1997; Levine et al. 2000, 1998b; Schwartz et al. 1999).

Our Strategy Application Test, based on the Six Element Test of the Shallice & Burgess (1991) study, is a paper-and-pencil laboratory task of SRD that requires the selection of targets with high payoff to the exclusion of readily available, but lesser-valued, targets. Every patient with focal VPFC damage (particularly on the right) was impaired (Levine et al. 1998b), despite preserved performance on other tests described above that are sensitive to DLPFC damage (Levine et al. 1995a, 1997). We subsequently revised the test to increase its sensitivity to VPFC damage (Levine et al. 2000). This was accomplished by fostering a response (completion of all items in a sequential manner) applicable early in the task but not as the task progressed, forcing a shift in strategy (selective completion of certain items to the exclusion of other items) to maintain efficiency. In other words, efficient performance depended upon inhibition or reversal of the response pattern reinforced at the beginning of the test (see Figure 2). As in the more basic reversal learning paradigms, this process contrasts with attentional set-shifting (across stimulus dimensions, tapped by the



A B C

Figure 2 Sample items from the revised Strategy Application Task (R-SAT) (Levine et al. 1999, 2000). On the early pages (*A*), all items can be traced in 5–10 s. As the subject progresses through the task, items increase in duration to completion but not in difficulty of completion (*B* and *C*). Given limited time and an equal amount of points per item, the best strategy is to inhibit the tendency to do all items (established on early pages) in favor of selective completion of brief items on later pages. The test is constructed so that brief items are always available. Subjects are also to complete similarly constructed sentence copying and simple counting items (not shown).

WCST). Initial studies on the revised version of the test (R-SAT) have documented sensitivity and specificity to severe traumatic brain injury (Levine et al. 2000), which causes VPFC damage (Courville 1937). As tasks of this sort are designed to more closely approximate real-life situations than standard neuropsychological tests that are highly structured and examiner-guided, they should be related to real life SRD as measured by outcome questionnaires. In our sample of traumatic brain injury patients, R-SAT performance was significantly related to patients' endorsement of everyday problems in functioning on an outcome questionnaire (Levine et al. 2000; see Burgess et al. 1998 for a similar finding). Replication and extension of these findings in patients with focal lesions and frontotemporal dementia is ongoing.

Episodic Memory, Self-Awareness, and Autonoetic Consciousness

Solid evidence for the role of the frontal lobes in self-awareness derives from memory research. Tulving and colleagues (1994) proposed a hemispheric encoding-retrieval asymmetry model of memory based on functional neuroimaging studies in normal subjects. In simplest terms, left frontal lobe activation is primarily associated with memory encoding, and right frontal lobe activation is primarily associated with retrieval of episodic memories. Episodic memories are those temporally tagged memories that are personally relevant and emotionally salient to the individual. Such memories appear to depend on the autonoetic ("self-knowing") (Tulving 1985) processes—the mental models and self-reflectiveness of the right frontal lobe—that also underlie self-awareness (Wheeler et al. 1997).

Other research supports a preeminent role of the right frontal lobe for personal memory. For example, self-reflective memory is related to right frontal activation (Craik et al. 1999). The right prefrontal and other right hemisphere regions are activated when retrieving emotional memories from the past (Fink et al. 1996). False memories have been shown to be dependent upon subjective feelings that the false information had been previously learned (Loftus & Prickrell 1995). The occurrence of such false memories has been related to right frontal lobe damage (as well as medial temporal lobes) (Melo et al. 1999, Schacter et al. 1996) and right frontal functional imaging activation (Schacter & Curran 1995).

Several dramatic case studies demonstrate the value of the combined anatomical, theoretical, case, and group study approaches in evaluating the effects of right focal frontal lobe damage. Capgras Syndrome (Capgras & Reboul-Lachaux 1923) is defined as a selective and persistent delusion in which a familiar person has been duplicated by a patient (see also Pick 1903). Alexander et al. (1979) described a patient who had suffered a severe traumatic brain injury and, upon eventual recovery, insisted that his wife and four children constituted a new family different from his "first" family, albeit very similar. His neuropsychological test profile revealed no impairment on tests of basic cognitive functioning (memory, basic attention, IQ, etc.) but significant deficits in frontal cognitive tests. He had suffered significant right frontal and right temporal damage. If presented the scenario as if another person had described it, the patient concluded that the situation was "unbelievable." An in-depth review of the recovery course revealed that the reduplicative paramnesia surfaced after the patient had his first visits home about 10 months after the accident. At that time he had recovered sufficiently to be allowed home for a visit, although he still suffered from significant memory and attention deficits. His teenage children had grown notably, the family had a new car, and the wife had altered her hairstyle. It was hypothesized (Stuss 1991, Stuss & Alexander 1999) that the warmth, immediacy, and saliency of that visit home "affectively burnt in" these memories, becoming episodic past memories that define a person. When the patient recovered, he now had two episodic memories of two similar but different families that could not be reconciled owing to his significant and persisting frontal lobe deficits in judgment. The importance of the right frontal lobe in such patients has been repeatedly confirmed (e.g., Hakim et al. 1988, Malloy & Duffy 1994).

We described another patient who had lost all personal past memories after traumatic brain injury (Levine et al. 1998a). That is, he had virtually no episodic memory for pre-injury events, whereas semantic facts about his previous life were retained or relearned. The investigations were driven by theoretical knowledge of the characteristics and anatomical basis of episodic memory. Detailed structural magnetic resonance imaging (MRI) investigations demonstrated a right VPFC lesion that affected frontotemporal connectivity (uncinate fasciculus). New memories about his life after the injury were learned, but these were recalled without any affective valence; that is, they were not episodic in nature. This effect was quantified with the remember/know technique, a self-report measure proposed by Tulving (Tulving 1985; see also Gardiner 1988) to assess episodic reexperiencing. An $H_2{}^{15}0$ positron emission tomography (PET) study of cued recall revealed that, relative to carefully matched healthy controls and traumatic brain injury patients without retrograde amnesia, anterograde learning and memory were accomplished with reduced right frontal polar activation and increased left hippocampal activation, supporting the hypothesis of impoverished episodic and normal (or enhanced) semantic processes (Levine 1998a).

This case highlighted the need to assess autobiographical memory, including episodic reexperiencing. Lack of standardized assessment in this case led to delayed recognition of his syndrome and even accusations of malingering. The most widely used measure of autobiographical memory is the Autobiographical Memory Interview (Kopelman et al. 1989). This measure includes a thorough assessment of personal semantics (i.e., facts about oneself) as well as elicitation of personal episodes with a qualitative scoring system for separate quantification of autobiographical episodic memory. Moscovitch et al. (1999) described a more detailed protocol analysis.

Another level of self-awareness was revealed by our experience with two patients who had focal right frontal brain damage from two different etiologies (Stuss 1991, Stuss & Alexander 2000). In both there was excellent neurological, functional, and cognitive recovery with intelligence being normal or superior.

Performance on executive tests was normal/superior in one, and only mildly impaired in the other. Both patients could clearly identify their failings, exhibited concern about their problems, and could identify appropriate corrections to the problems. Neither, however, could return to their high-level executive work. The deficits in these patients were not at the level of executive control. Rather, they had a lack of real understanding of the implications of the problems and an inability to act in their own self-interest, despite knowing what to do and at least verbalizing an intent to change. These patients lack a mental model, not of the world, but of their own capacities and role in the world. The discrepancy between their mental model and their experience leaves them without a purpose or ability to organize perceptions and actions for future goals.

Empathy, Sympathy, and Humor

The important role of the right frontal lobe in emotional function suggested by the case studies can be demonstrated experimentally. For example, empathetic psychiatrists showed greater right frontal electrophysiological activation than those less empathetic in therapy (Alpert et al. 1980). During an event arguably associated with potent emotional responsiveness (orgasm), the greatest metabolic activation measured by PET was in the right frontal lobe (Tiihonen et al. 1994).

Two studies have emphasized the potential importance of more polar areas. The appreciation of humor requires the integration of cognition and emotions. When patients with focal lesions throughout the frontal and posterior brain regions were tested on their ability to appreciate jokes and cartoons and to rank how funny humorous sayings were, one group stood out as most impaired: those with right frontal lobe damage, in particular the more medial polar, somewhat more superior, region representing Brodmann Areas 8, 9, and probably parts of 10 (Shammi & Stuss 1999). Moreover, it was the same right frontal group that exhibited the least spontaneous affective responses. The significant correlation of performance with specific cognitive functions (e.g., verbal humor with verbal abstraction ability and mental shifting; cartoon humor with the ability to focus attention to details and to perform visual search effectively) strongly suggested that different systems were necessary for different tasks, but that there was a final common area necessary for humor appreciation. Event-related functional MRI data of normal individuals showed similar results (Goel & Dolan 2001). There were differential systems related to different types of humor tasks, and a "central reward" system with maximum activation in the ventral medial prefrontal region bilaterally and Brodmann Areas 10 and 11 (Goel & Dolan 2001). These imaging data suggest that the functions of the right frontal region may be "preeminent" rather than dominant in relation to self-awareness.

The concept of self-awareness implies a metacognitive representation of one's own mental states, beliefs, attitudes, and experiences. It is this self-reflecting ability that is the basis for understanding the relationship of one's own thoughts and external events, and to understanding the mental states of others. This ability to make inferences about the world, and to empathize with others, allows us to interpret mental states properly and to make social judgments. The neuropsychological basis of this "theory of mind" was tested in focal lesioned patients (Stuss et al. 2001c). On a simple perspective-taking task it was only patients with frontal lobe damage, with some suggestion of a more important role of the right frontal lobe, who were impaired. Detection of deception was impaired after medial frontal lesions, again with a preeminence of the right ventral region. Impairment of abstract awareness of emotions and expectations has been described after right hemisphere damage (Winner et al. 1998). Trauma to the right orbitofrontal region, including orbitofrontal cortex, resulted in significant social aberration in a case study, hypothesized to be based on the ability to generate expectations of others' negative reactions (Blair & Cipolotti 2000).

Functional imaging studies in neurologically intact individuals demonstrated specific right orbitofrontal activation in a task (Baron-Cohen et al. 1994). Whereas ventral and inferior medial damage are frequently observed, the preeminence of the right over the left is not always observed (Fletcher et al. 1995, Goel et al. 1995; see also Stone et al. 1998). Impaired theory of mind was reported in a patient treated with stereotactic anterior capsulotomy (Happe et al. 2001). These data suggest various possible explanations: roles of different brain regions in a functional/anatomical system, differences in processes required to complete the various tasks, variations in the areas of lesions represented among the patients tested, and possible preeminence rather than hemispheric dominance. Regardless, the overlap between the lesion and imaging data is still striking (Shallice 2001) (see Figure 3).

Clinical Implications

Disruption in self-regulation, self-awareness, and social cognition produces a profound alteration in real-life functioning and life quality outcome. These behavioral changes are not limited to the patient; they greatly affect families who must cope with their changed loved one. Although we have illustrated these concepts with dramatic case studies, less dramatic versions of these deficits are likely more common than is currently appreciated but are not revealed for lack of assessment methods (Levine 1999).

So what is today's neuropsychologist to do? Tests of reversal learning and inhibition sensitive to VPFC dysfunction can be readily administered in the laboratory. Tests mimicking real-life unstructured situations with no right or wrong answers (the Gambling test, the R-SAT, or the Six Element Test) are increasingly available. It is also possible to assess real-life functioning with outcome questionnaires, such as the Dysexecutive Questionnaire (Burgess et al. 1996), which includes parallel forms for self- and significant-other ratings. In the realm of memory, the remember/know technique (Tulving 1985) provides a useful self-report of the quality of autonoetic reexperiencing that defines episodic memory and can be easily applied to standard recognition memory tests. Autobiographical memory should be assessed, with emphasis on autobiographical reexperiencing in addition to personal

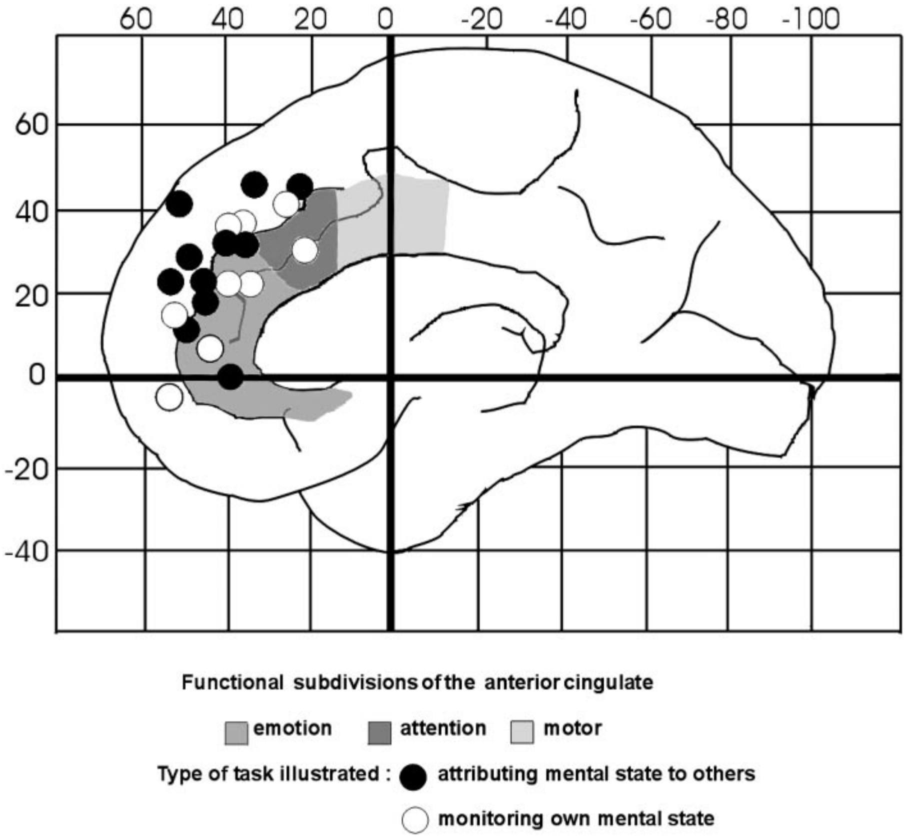


Figure 3 Location of peak activation in medial prefrontal regions during tasks in which subjects think about their own or others' mental states (C. Frith, personal communication, published in Shallice 2001). This is an updated version of the analysis presented in Frith & Frith (1999). (Reprinted with permission from the author and Oxford University Press.)

semantic knowledge. Finally, it is important to be aware of which patients are most likely to present with these deficits: those with VPFC and polar damage. The highest prevalence of this damage is in traumatic brain injury.

CONCLUSIONS

We have emphasized that adult clinical neuropsychology has evolved through many stages, with different approaches to assessment. Each school has had value, and each is still useful if the question being asked demands that approach. Through the example of recent findings about the frontal lobes, however, we hope we have illustrated that the future of adult clinical neuropsychology lies in an approach that is driven by current cognitive and affective psychological theories, is flexible in the design used (e.g., case study, group comparisons), and takes advantage of the most current methods (e.g., structural imaging for lesion location, various imaging modalities). The most recent findings on the role of the right frontal lobe being key to some of the highest human faculties required all of the above. This brain region has been notoriously nonresponsive to the probing of neuropsychological assessment, a fact considered by many neurosurgeons in their decisions about neurosurgical approaches.

There is an obvious clinical downside—the advocated approach when applied recklessly can lead to the use of tests that do not meet the psychometric criteria. As noted by Russell (1986), however, psychologists are well trained to contribute the psychometrics to the evaluation of brain and behavior. An important goal for future research will be to apply these skills to the analysis of not only the cognitive operations of the brain, but also the emotional and social processes that define us as human. Our contention, however, is not only that the "what" of assessment should not be lost at the expense of the "how," but that it should even precede the "how."

Functional imaging studies, and the lesion research using well-defined patients with damage in different regions, provide different information for use in adult clinical neuropsychology. Lesion research can indicate what brain regions are necessary for a task; imaging research informs us about what areas are involved. Both have clearly demonstrated that neuropsychological assessment must be done in the light of systems and processes (not just brain localization), and context (e.g., variations in task difficulty). In this light, the information provided on localization of processes is for theoretical purposes. The extension to clinical use must be made with caution.

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Annual Review of Psychology
Volume 53, 2002

CONTENTS

Frontispiece—*Endel Tulving* xvi

PREFATORY

Episodic Memory: From Mind to Brain, *Endel Tulving* 1

GENETICS OF BEHAVIOR

Genetic Contributions to Addiction, *John C. Crabbe* 435

BRAIN IMAGING/COGNITIVE NEUROSCIENCE

Child-Clinical/Pediatric Neuropsychology: Some Recent Advances, *Byron P. Rourke, S. A. Ahmad, D. W. Collins, B. A. Hayman-Abello, S. E. Hayman-Abello, and E. M. Warriner* 309

AUDITION AND ITS BIOLOGICAL BASES

Change Detection, *Ronald A. Rensink* 245

MEMORY

Remembering Over the Short-Term: The Case Against the Standard Model, *James S. Nairne* 53

JUDGMENT AND DECISION MAKING

Rationality, *Eldar Shafir and Robyn A. LeBoeuf* 491

BIOLOGICAL AND GENETIC PROCESSES IN DEVELOPMENT

Gene-Environment Interplay in Relation to Emotional and Behavioral Disturbance, *Michael Rutter and Judy Silberg* 463

DEVELOPMENT IN SOCIETAL CONTEXT

Socioeconomic Status and Child Development, *Robert H. Bradley and Robert F. Corwyn* 371

MOOD DISORDERS

Depression: Perspectives from Affective Neuroscience, *Richard J. Davidson, Diego Pizzagalli, Jack B. Nitschke, and Katherine Putnam* 545

PSYCHOPATHOLOGY: VARIOUS DISORDERS

Causes of Eating Disorders, *Janet Polivy and C. Peter Herman* 187

Insomnia: Conceptual Issues in the Development, Maintenance and Treatment of Sleep Disorder in Adults, *Colin A. Espie* 215

CLINICAL ASSESSMENT

Clinical Assessment, *James M. Wood, Howard N. Garb, Scott O. Lilienfeld, and M. Teresa Nezworski* 519

ADULT CLINICAL NEUROPSYCHOLOGY

Adult Clinical Neuropsychology: Lessons from Studies of the Frontal Lobes, *Donald T. Stuss and Brian Levine* 401

SELF AND IDENTITY

Self and Social Identity, *Naomi Ellemers, Russell Spears, and Bertjan Doosje* 161

ALTRUISM AND AGGRESSION

Human Aggression, *Craig A. Anderson and Brad J. Bushman* 27

INTERGROUP RELATIONS, STIGMA, STEREOTYPING, PREJUDICE, DISCRIMINATION

Intergroup Bias, *Miles Hewstone, Mark Rubin, and Hazel Willis* 575

CULTURAL INFLUENCES

Cultural Influences on Personality, *Harry C. Triandis and Eunkook M. Suh* 133

ORGANIZATIONAL PSYCHOLOGY OR ORGANIZATIONAL BEHAVIOR

Organizational Behavior: Affect in the Workplace, *Arthur Brief and Howard Weiss* 279

LEARNING AND PERFORMANCE IN EDUCATIONAL SETTINGS

Motivational Beliefs, Values, and Goals, *Jacquelynne S. Eccles and Allan Wigfield* 109

PSYCHOBIOLOGICAL FACTORS IN HEALTH

Emotions, Morbidity, and Mortality: New Perspectives from Psychoneuroimmunology, *Janice K. Kiecolt-Glaser, Lynanne McGuire, Theodore F. Robles, and Ronald Glaser* 83

PSYCHOPHYSIOLOGICAL DISORDERS AND PSYCHOLOGICAL EFFECTS ON MEDICAL DISORDERS

Effects of Psychological and Social Factors on Organic Disease: A Critical Assessment of Research on Coronary Heart Disease, *David S. Krantz and Melissa K. McCeney* 341

Analysis of Latent Variables

Latent Variables in Psychology and the Social Sciences,
Kenneth A. Bollen 605

Indexes

Author Index 635
Subject Index 679
Cumulative Index of Contributing Authors, Volumes 43–53 705
Cumulative Index of Chapter Titles, Volumes 43–53 709

Errata

Online log of corrections to the Annual Review of Psychology corrections:
Steven Regeser López and Peter J. Guarnaccia
Cultural Psychopathology: Uncovering the Social World of Mental Illness
Annu. Rev. Psychol. 2000, Vol. 51: 571–598.
http://psych.annualreviews.org/errata.shtml