"A REVIEW OF RECENT EVIDENCE CONCERNING THE FUNCTIONS OF THE HUMAN FRONTAL CORTEX"

Mary Rees NISHIO

Faculty of Liberal Arts and Science
Okayama University of Science
1-1 Ridai-cho Okayama, 700 Japan
(Received September 30, 1993)

ABSTRACT

The most recent experimental findings involving the frontal lobes of the human brain are reviewed. When these findings are viewed as a whole, the conclusion is reached that more and more mental abnormalities are being found to arise from dysfunction of the frontal lobes or the interconnections of the frontal lobes with other subcortical areas. Though scientists have developed many sophisticated noninvasive techniques for viewing frontal lobe activity both in healthy and impaired individuals, our standardized neurpsychological tools are still quite crude and fall short in measuring the more sophisticated abilities which clinical evidence has shown that the frontal lobes support. The issue of the long-term effects of chronic drug and alcohol use on the frontal lobes is briefly discussed. Our knowledge concerning the frontal lobes is still quite rudimentary, however, a full understanding of this complex area may open the possibility of finding true cures or preventive measures for many types of mental disease.

I. INTRODUCTION

Over the last century, the attitudes of scientists toward the frontal lobes have ranged from their designation as the seat of human intelligence to the position that they have nothing to do with intelligence. Early investigators who compared the frontal cortex with other cortical regions found that not only was this area the largest cortical area, but that the human frontal lobes were also the largest proportionally when compared with those of other species. Since we generally consider ourselves to be the smartest species on the earth, it was not unusual that these early specialists concluded that this area must certainly be the source of our intelligence. In the 1930's and 1940's, doctors performed numerous lobotomies, due partly to the fact that patients showed no change in their intelligence test scores after disconnection or removal of large parts of the frontal lobes. Unfortunately , these doctors failed to note that there were two possible

interpretations to the phenomenon of unchanging test scores. One was that intelligence did not change; the other interpretation was that the "intelligence" tests of the time were not measuring the highest forms of human intelligence.

Our understanding regarding the functions of the frontal lobes has been slowly increasing. Clinicians have long known that frontal lobe injury often causes subtle, but devastating changes in the individual. The person with frontal lobe injury may still be capable of speech, reading, and writing, but may be grossly impaired in a number of areas including emotional responding, judgment, impulsivity, planning, aspects of memory, etc.

Slowly researchers have begun to develop tests which can measure those abilities supported by the frontal lobes. In additon, the recent advances in brain imaging technology have allowed us to directly observe which specific areas of the frontal lobes are functioning during certain types of tasks. Our knowledge is still rudimentary, but as this review of current evidence concerning the frontal lobes shows, we are beginning to unravel many of the conditions which have long puzzled our greatest minds-schizophrenia, attention deficit hyperactivity disorder, effects of alcoholism, autism, etc.

The purpose of this paper will be to review the most recent research concerning the frontal lobes and, to summarize the implications of these findings.

II. THE FUNCTIONS OF THE FRONTAL LOBES & DEFICITS RESULTING FROM INJURY

A. ANTISOCIAL BEHAVIOR

Meyers et al. (1992)[1] have recently reported the case of a man who developed personality changes resembling antisocial personality disorder following surgical resection of a pituitary tumor which resulted in damage to a circumscribed area of the left orbitofrontal cortex. The behavioral change was quite clear to all observers, but no specific cognitive deficit or psychopathology was evident when he was tested with formal neuropsychological and personality tests. The sgnificance of this report lies in the fact that the personality changes resulted from *unilateral* frontal lobe damage alone (previous reports had ascribed this type of personality change to bilateral damage).

It has recently been suggested that conduct disorders may be related to the disinhibition deficit seen in frontal lobe impairment. Lueger & Gill (1990)[2] compared the performance of 21 conduct disorder adolescents with matched controls on measures of cognitive processing associated with frontal lobe functions. They found that the conduct disorder adolescents performed more poorly on measures sensitive to frontal lobe dysfunction (conceptual perseveration, poorly sustained attention, impaired sequencing on memory and motor tasks), but not on non-frontal lobe specific cognitive measures. They interpreted their findings as supporting a neurobehavioral explanation of antisocial behavior.

B. BEHAVIORAL DISINHIBITION

Miller et al. (1991)[3] studied the clinical, neuropsychological, and cerebral blood flow (CBF) characteristics of 8 patients with frontal lobe degeneration. The earliest and most common symptoms were social withdrawal and behavioral disinhibition. Relative sparing of attention, language, and visuospatial skills and selective impairment on frontal lobe and memory tasks during neuropsychological testing were found.

C. CALCULATION

Difficulties in calculation have been found in a patient with an infarct in the medial cortex of the left frontal lobe by Lucchelli & De Renzi (1993)[4]. Retrieval of basic, over-learned facts was found to be mildly impaired and execution of calculation procedures was severely impaired. The investigators interpreted the data from this case as suggesting participation of the (left) medial frontal areas in calculation processes.

D. COGNITIVE FLEXIBILITY

In order to study the contributions of the frontal lobes and frontal-striatal connections to human cognitive flexibility, Eslinger & Grattan (1993)[5] examined patients with focal ischemic lesions in the frontal lobes and basal ganglia and compared them on two forms of cognitive flexibility: shifting response set (termed "reactive flexibility" by the researchers) and producing a diversity of ideas (called "spontaneous flexibility"). The frontal and basal ganglia lesioned patients performed similarly in shifting response set with both groups being significantly lower than posterior cortical lesioned patients. However, when compared with the basal ganglia lesioned patients as well as posteriorly lesioned patients, the frontal lobe patients showed markedly disturbed spontaneous flexibility. These finding were interpreted as indicating that the frontal lobes and basal ganglia participate differently in cognitive flexibility. They suggested that the generation of diverse ideas may require direct cortical-cortical interactions "in order to access knowledge systems with novel strategies that transcend the most common semantic linkages." Based on the accumulated evidence, Eslinger & Grattan suggested that shifting response set is dependent upon the frontal lobes, basal ganglia, and their interconnections.

Vilkki (1992)[6] investigated the relationship between closed head injury and the frontal lobe deficits of cognitive inflexibility and mental programming impairment using a Category Identification and Sorting test and a Spatial Learning task. They concluded that the diffuse axonal lesions in closed head injury cause deficits similar to those following frontal lobe excision.

E. EXECUTIVE FUNCTIONS/PLANNING

Twenty-six patients with unilateral or bilateral frontal lobe excisions and matched controls were examined by Owen et al. (1990)[7] using computerized tests of spatial working memory and planning. The patients were found to be significantly impaired

on the test designed to access spatial working memory and were also found to be less efficient than controls in their usage of a strategy for improving performance on the test. They required more moves to complete the problems and a yoked motor control condition revealed that their movement times were significantly increased.

Vilkki & Holst (1991)[8] investigated the question of whether the inability to set adequate sub-goals is a sensitive indicator of the programming deficit after frontal lobe lesion. A modified Digit Symbol task was used to examine 61 patients with focal lesions and 25 control subjects. The results were interpreted by the researchers as confirming their prediction that patients with anterior lesions set less adequate sub-goals than patients with posterior lesions. It was also felt that unlike patients with posterior lesions, those with frontal lesions (especially left frontal lesions) underestimated their capabilities in relation to the task requirements.

The case of a 51-year-old man who had 5 cm of his left frontal lobe removed due to cancer who experienced changes in behavior has been reported by Goldstein et al. (1993)[9]. Although the man had intact performance on numerous neuropsychological tests, he was found to be impaired on a test of "strategy application" which required goal articulation, plan specification, self-monitoring, and evaluation of outcomes. His impairment on this test also extended to failure to establish mental "markers" to trigger specific behaviors. The researchers concluded from their study of this case that strategy application disorder can be produced by unilateral circumscribed frontal lobe lesions.

F. GRASP REFLEX

One well-known consequence of frontal lobe injury is the appearance of the grasp reflex. De Renzi & Barbieri (1992)[10] studied a sample of 491 patients consecutively admitted to their neurological ward and found that the locus of the lesion was either in the frontal lobes or in the deep nuclei and subcortical white matter. Grasping never occurred when the disease was confined to the retrorolandic regions. In a subsequent aspect of this study, the researchers found grasping in 70% of the patients that had involvement of the medial frontal areas and that grasping was *always* associated with damage to the cingulate gyrus. They found that the supplementary motor cortex was less frequently encroached upon. Only 26% of those patients studied who had damage to the lateral motor and premotor areas demonstrated grasping. The most interesting aspect of this study was that analysis showed that even when the lesion was unilateral, it usually resulted in grasping motions of BOTH HANDS. They also found that this grasping was not a forced phenomenon, but could be modified at will. It did, however, show up again when the patients' attention was diverted. No hemispheric asymmetry was apparent.

G. IMPULSIVE BEHAVIOR

Miller (1992)[11] studied risk-taking and impulsivity in patients with unilateral frontal or temporal lobe lesions. Neither group obtained high risk-taking scores, but patients

with frontal-lobe lesions demonstrated impulsive behavior when manual responses were required.

H. INFORMATION SEARCH

Klouda & Cooper (1990)[12] investigated information search following focal damage to the frontal lobes in 5 adult patients using tests of planning, problem-solving, and decision making. They interpreted their results as indicating that damage to the frontal lobes impairs the ability to impose and utilize hierarchical organization in mental representations.

I. MEMORY

a. RECOGNITION MEMORY

Verbal recognition memory in young and elderly subjects was recently examined by Parkin & Walter (1992)[13] who found that explicit recollection declined with age, and familiarity-based recognition increased. In addition, they found that the extent to which older subjects relied on familiarity-based recognition correlated with neuropsychological indices of frontal lobe dysfunction. Research results of Shimamura et al. (1992)[14] indicate that patients with frontal lobe lesions exhibit normal levels of word-stem completion. They interpreted their findings as indicating that implicit memory (recognition memory) can operate normally despite damage to the prefrontal cortex and as being consistent with previous neuropsychological and PET findings which indicate that word priming depends critically on posterior cortical areas.

Further evidence to support the above finding comes from subsequent work by Parkin et al. (1993)[15] who report the case of a 20-year-old woman with Wernicke's Encephalopathy (a condition which has been shown to involve frontal lobe impairment). This patient was found to have remarkably well preserved recognition memory although she had a severe impairment of both verbal and nonverbal free recall.

b. TEMPORAL ORDER

Shimamura et al. (1990)[16] examined memory for temporal order in patients with frontal lobe lesions, amnesic patients with Korsakoff's syndrome, non-Korsakoff amnesic patients, and controls. Despite normal item memory (i. e. normal recall and recognition memory for the words and facts), the patients with frontal lobe lesions were impaired in placing the items in the correct temporal order. Both Korsakoff and non-Korsakoff amnesic patients were impaired not only on recall and recognition, but also on the temporal ordering task. The worst performers on the temporal order memory task were the patients with Korsakoff's syndrome (both diencephalic and frontal damage). The researchers interpreted their findings as indicating that frontal lobe lesioned patients have difficulty organizing information temporally.

c. WORKING MEMORY

Frisk & Milner (1990)[17] investigated the relationship of working memory to the

immediate recall of stories following unilateral temporal or frontal lobectomy. Although the temporal lobe group had transient deficits in working memory capacity, there were no deficits two weeks after the operation despite the fact that the story recall of the left temporal-lobe group was impaired. The authors explored the contribution of the hippocampus and of the frontal lobes using an additional group of patients, and found that the extent of excision of the hippocampus did not affect performance differentially on any of the tasks (working memory capacity, sentence comprehension, and rapid-naming ability). Story recall was impaired following left temporal lobectomy, whereas left frontal lobectomy impaired sentence comprehension and rapid-naming ability.

Petrides et al. (1993)[18] have recently conducted research using MRI & PET scans which showed that the human lateral frontal cortex is functionally heterogeneous and appears to contain areas equivalent to areas 46 and 9 in non-human primates which play a critical role in the performance of non-spatial self-ordered working memory and to area 8 which is critical for the learning and performance of visual conditional associative tasks.

The localization of working memory in the frontal lobes has recently been investigated using PET scans by Petrides et al. (1993)[19]. These researchers found strong bilateral activation in the mid-dorsolateral frontal cortex both while the person was maintaining self-generated numbers in working memory and while maintaining numbers generated by the experimenter in working memory. There was no evidence of additional activation during the self-generated condition.

J. METACONTROL

In a 1992 article, Jason & Pajurkova[20] reported the case of a right-handed man in whom an aneurysmal hemorrhage resulted in lesions in the genu and body of the corpus callosum and in the inferomedial frontal lobes bilaterally. This patient experienced a breakdown in behavioral unity which was characterized by conflict between the two sides of the body, actions inconsistent with verbalizations, and internal conflict over control of the left hand. The researchers interpreted this as indicating the importance of the medial frontal structures and the corpus callosum in maintaining metacontrol.

K. SOCIAL WITHDRAWAL

As mentioned earlier, Miller et al. (1991)[21] found social withdrawal (along with behavioral disinhibition) to be one of the earliest manifestations of frontal lobe degeneration.

L. WORD FINDING

Frith et al. (1991)[22] used PET scans to examine normal subjects during intrinsic (spontaneous) word generation (verbal fluency) and found an increase in the left dorsolateral prefrontal cortex (BA 46) with a corresponding decrease in activity in the auditory and superior temporal cortices. When subjects made lexical decisions about

heard words, an increase in the superior temporal area was observed and there was no change in Brodmann's area 46, The authors have suggested that the superior temporal area is the site of stored word representations and that "the inhibitory modulation of this area by the left prefrontal cortex is the basis of intrinsic word generation".

III. ACQUIRED FRONTAL LOBE DAMAGE

A. EARLY IN DEVELOPMENT

Two recent studies of patients who experienced frontal lobe damage early in life provide us with further information about the importance of the frontal lobes. Price et al. (1990)[23] studied two people who had suffered bilateral prefrontal damage early in life. These people subsequently developed severely aberrant behavior, and were found to have arrested social and moral development. The authors suggest that frontal damage acquired early in life affects the substrate of a special type of learning related to insight, foresight, social judgement, empathy, and complex reasoning.

Eslinger et al. (1992)[24] worked with a 33-year-old woman who had sustained damage to the frontal lobes at the age of seven. A lesion was evident in the left prefrontal cortex and deep white matter upon examination using magnetic resonance imaging (MRI). Cerebral blood flow (CBF) studies found an abnormal pattern in both the left and right frontal regions. She was found to have significant deficits in higher cognition especially in the self-regulation of emotion and affect and in social behavior. There appears to have been a delayed onset of the deficits and an arrest in development in adolescence. The auther noted that the long-term deficits were similar to those found in adult frontal patients, but that their patient differed from this type of patient in the delayed onset and the progression of the deficits.

B. ADULTS—SPECIFIC LESIONS

a. LEFT FRONTAL RUPTURED CEREBRAL ANEURYSM

Acquired brain damage in adults often provides us with insights as to the relationship between schizophrenia and the frontal lobes. Hall & Young (1992)[25] recently reported the case of a 23-year-old male who was diagnosed as having a schizophreniform disorder after the sudden onset of blunted affect, looseness of associations, and auditory halluciations. The patient was found to have a ruptured cerebral aneurysm in the left frontal lobe, and the symptoms almost completely disappeared after removal of the hematoma.

b. MESIAL FRONTAL LOBE DAMAGE

Mochizuki & Saito (1990)[26] studied 26 patients with mesial frontal lesions. These patients commonly presented with depressed motivation. Those with mesial frontal motor cortex lesions demonstrated hemiparesis in the lower extremities. Long lasting hemiparesis was found in those with lesions in the supplementary motor cortex (but not involving the motor cortex). Left supplementary motor and superior prefrontal

damage resulted in verbal adynamia, and patients with large areas of damage bilaterally which included the cingulate presented with akinetic mutism. Two patients with intact supplementary motor cortex, but lesions in the superior prefrontal cortex showed transient mutism. Dementia and memory disturbance were related to damage to the anterior area of the superior prefrontal cortex. Motor neglect and dressing apraxia were related to lesions in the right hemisphere mesial frontal area.

c. THALAMIC INFARCTION

Further insight into frontal lobe function comes from work by Sandson et al. (1991)[27] who studied a 62-year-old woman who developed a dramatic change in personality and behavior subsequent to a discrete left-sided thalamic infarction involving the dorsomedial nucleus. Impairment of complex executive behavior (usually associated with frontal lobe impairment) was evident upon neuropsychological testing. Single photon emission computed tomography (SPECT) and electroencephalography (EEG) indicated dysfunction of the left frontal lobe. The authors interpreted this as indicating a "functional and physiologic thalamofrontal linkage as part of a broader cerebral network modulating complex human behavior."

Ⅳ. DRUGS

A. COCAINE

Volkow et al. (1992)[28] used PET to investigate glucose metabolism in the brains of neurologically intact, chronic cocaine users. Subjects were tested 1 to 6 weeks after last use of cocaine and again after a 3 month drug-free period. Although global cerebral glucose metabolism was not significantly decreased, they did find significantly lower metabolism in 16 of 21 left frontal regions and 8 of 21 right frontal regions. These decreases were found to be correlated with years of cocaine use. They have clearly shown that chronic cocaine users continue to experience decreased frontal metabolism several months after abstinence.

B. ALCOHOL

a. FRONTAL CORTICAL BENZODIAZEPINE RECEPTORS

Researchers examining postmortem cerebellar and frontal cortical membrane homogenates from human alcoholics, control subjects without neurological or psychiatric illnesses, and rats that chronically drank alcohol found that the binding of [3H] musimol, a GABAA agonist, tended to be higher in the frontal cortices of alcoholics. They interpreted their overall results as suggesting that no drastic changes occur through chronic alcohol abuse in the numbers of frontocortical benzodiazepine receptors in humans, however, they did feel that the data indicated that the alcoholics have either acquired or innate differences in classical benzodiazepine recognition sites of the cerebellum and in the coupling of these sites in GABAA sites in the frontal cortex.[29]

b. MEDIAL FRONTAL HYPOMETABOLISM & BEHAVIORAL CORRELATES

Gilman et al. (1990)[30] compared chronically alcohol-dependent patients with normal age- and sex-matched controls using positron emission tomography (PET) and found decreased local cerebral metabolic rates for glucose bilaterally in the medial frontal area of the cerebral cortex. The authors noted that the severity of the clinical neurological impairment was significantly correlated with the degree of hypometabolism in this medial frontal cortical area. The degree of atrophy found using computed tomography (CT) scans was significantly correlated with the local cerebral metabolic rates in this medial area.

In subsequent research, these same researchers investigated the possible behavioral deficits stemming from this medial frontal lobe glucose hypometabolism.[31] Anatomic imaging (CT or MR), functional imaging (PET), and two measures of abstraction known to be sensitive to frontal lobe disease or dysfunction [Wisconsin Card Sorting Test (WCST)] and the Halstead Category Test (HCT)] were used to examine 31 detoxified, medically stable, chronically alcohol dependent, male subjects and 18 age- and sex-matched control subjects. The concepts attained and the error scores on the WCST and HCT were significantly impaired in comparison with established norms. These severely alcohol dependent subjects were found to have significantly decreased local cerebral metabolic rates for glucose in a sagittal strip of the medial frontal cortex. The researchers found a significant relationship between the local cerebral metabolic rates for glucose in the medial frontal region of the cerebral cortex and the alcoholic patients performance on the WCST. No such relationship was found for the Halstead Category Test.

c. SPECIFIC DEFICITS

i. DELAYED RESPONSE TASKS

In a study by Oscar-Berman et al. in 1992 using 36 male alcoholics (of which 13 had been diagnosed as Korsakoff patients) and examining performance on visual and auditory delayed-response tasks, Korsakoff patients were found to be consistently impaired. Impairment in these Korsakoff patients was greatest when damands were placed on visual processing time and with increased demands on short-term memory.[32]

ii. PRESEVERATION & INEFFICIENT SORTING

In a study by Sullivan et al. (1993)[33] designed to examine the factor structure of the Wisconsin Card Sorting Test (WCST), the scores of schizophrenics. chronic alcoholics, and controls were entered into a principal components analysis which yielded three factors: Perseveration, Inefficient Sorting, and Nonperseverative Errors. The schizophrenic group and frontal lobe group were found to have the highest Perseveration factor scores, whereas the alcoholic group had the highest Inefficient Sorting scores.

iii. RETROGRADE AMNESIA

Kopelman (1991)[34] investigated the intercorrelation of 8 'frontal' tests in 32 patients with Korsakoff's syndrome and Alzeimer's disease as well as the relationship of frontal dysfunction to impoverished retrieval from retrograde memory. One of the findings of this study was that the defective retrieval of retrograde memories was correlated with frontal dysfunction in both groups. The conclusion of the researcher was that frontal dysfunction produces a disorganization of retrieval processes which contributes to the temporally-extensive retrograde amnesia of these two disorders.

iv. PLANNING & SPATIAL MEMORY

Joyce & Robbins (1991)[35] used traditional neuropsychological tests of frontal lobe function, and computerized tests of planning (the Tower of London task) and spatial working memory to examine groups of Korsakoff (KS) and non-Korsakoff alcoholics (ALC) and controls. The Korsakoff alcoholics demonstrated deficits on the planning task which could not be explained by abnormalities of memory (including spatial span), or by visuoperceptive disturbances. The authors interpreted the data as suggesting that in the alcoholic Korsakoff's syndrome there is a specific disturbance of frontal lobe function in addition to amnesia. They concluded that the impairment found in chronic alcoholics without Korsakoff's syndrome does not reflect specific frontal dysfunction.

v. VERBAL FLUENCY

Hewett et al. (1991)[36] investigated verbal fluency deficits in female alcoholics using Thurstone's Word Fluency Test (TWFT) and a category fluency test. They found that the controls' performance was superior to that of alcoholics on the category fluency test, but that the groups did not differ on the TWFT. The results were interpreted by the authors as indicating that the process of shifting rapidly between categories is more difficult than perusing a mental lexicon and as suggesting that the TWFT and category fluency test may be assessing different types of verbal fluency.

V. PSYCHIATRIC DYSFUNCTION

A. DEPRESSION

Various studies of adults and infants have shown the left frontal brain region to be specialized for approach emotions (joy) and the right frontal region to be specialized for withdrawal emotions such as distress. Dawson et al. (1992)[37] investigated the frontal lobe electroencephlographic (EEG) activity and affective behavior of infants of mothers with depressive symptoms and found that the infants of mothers with depressive symptoms exhibited left frontal brain activity (joy) during playful interactions with their mothers and did not exhibit the typical pattern of greater right frontal activity (distress) during a condition designed to elicit distress (maternal separation). These infants of symptomatic mothers also showed less distress during maternal separation.

Berman et al. (1993)[38] investigated whether depressed and schizophrenic patients have a common pathophysiological mechanism for hypofunction of the prefrontal cortex ('hypofrontality') and obtained results which suggested that the pathophysiological mechanisms underlying prefrontal hypofunction in depression and schizophrenia are different.

B. GILLES DE LA TOURETTE SYNDROME

In 1992, George et al.[39] investigated the possibility of orbito-frontal/basal ganglia dysfunction in Gilles de la Tourette syndrome (GTS), a condition where the person suffers from convulsive tics with echolalia, coprolalia (excessive foul language & swearing), and motor incoordination. The movements cease during sleep. The GTS patients and controls were examined with high-resolution single photon emission computed tomography (SPECT) and regional cerebral flow (rCBF). The Tourette syndrome patients showed significantly elevated right frontal/visual cortex activity.

C. OBSESSIVE-COMPULSIVE BEHAVIOR

Machlin et al. (1991)[40] measured regional cerebral blood flow with single photon emission computed tomography (SPECT) in 10 obsessive-compulsive patients and eight comparison subjects. The obsessive-compulsive patients had a significantly higher ratio of medial-frontal to whole cortex blood flow and this was correlated negatively with anxiety. No differences were found in orbital-frontal blood flow.

D. SCHIZOPHRENIA

a. HYPOFRONTALITY

Paulman et al (1990)[41] studied 20 medicated and 20 unmedicated chronic male schizophrenic patients and normal controls using Dynamic Single Photon Emission Computed Tomography (D-SPECT). Analysis revealed significant bifrontal and bitemporal rCBF deficits in the patient group. The researchers found that the frontal flow deficits were most prominent in paranoid patients whereas right temporal deficits were most prominent in nonparanoid patients. Reduced left frontal rCBF was associated with impaired performance on the Wisconsin Card Sorting Test and Luria-Nebraska Battery. Increased hemispheric CBF was correlated with the presence of positive schizophrenic symptoms. The researchers concluded that their findings demonstrate that hypofrontality has important implications for cognitive function in some schizophrenic individuals.

In a regional cerebral blood flow study of 39 Japanese schizophrenic patients receiving medication, Suzuki et al. (1992)[42] found the relative flow distribution to be significantly reduced only in the left frontal region when compared with controls. They found that the lower the left frontal blood flow in the schizophrenics, the more pronounced were the negative symptoms such as blunted affect, avolition-apathy, and inattention. The researchers interpreted their data as suggesting that the negative symptoms in schizophrenics are related to left frontal lobe dysfunction.

Rubin et al. (1991)[43] also found a significant activation deficit (reduced regional cerebral blood flow) in the left inferior-prefrontal region of schizophrenics during the Wisconsin Card Sorting Test. Their schizophrenic patients also showed impaired striatal suppression in the left hemisphere during the cognitive task. The researchers suggested that this inability to reduce striatal activity may be due to a lack of corticostriatal feedback during prefrontal activation.

In a study of the relationship between hypofrontality and negative symptoms of schizophrenia (marked poverty of speech or poverty of content of speech, affective flattening, inability to experience pleasure, few social contacts, lack of energy and impersistence at work or school, and attentional impairment), Wolkin et al. (1992)[44] used positron emission tomography and found a close relationship between negative schizophrenic symptoms and prefrontal hypometabolism, particularly in the right dorsolateral convexity. They state that this association was regionally specific.

Andreasen et al. (1992)[45] measured regional cerebral blood flow using single-photon emission computed tomography with xenon 133 as the tracer in neuroleptic-naive and nonnaive schizophrenic patients and normal subjects while performing the Tower of London task. They found this task in healthy normal volunteers to be a relatively specific stimulant of the left mesial frontal cortex (probably including parts of the cingulate gyrus), however both schizophrenic groups showed no activation of this area during the task. They state that decreased activation occurred only in the patients with high scores for negative symptoms, and concluded that the results suggest that hypofrontality is related to negative symptoms and is not a long-term effect of neuroleptic treatment or of the chronicity of illness.

One of the most convincing studies concerning hypofrontality in schizophrenics was conducted by Berman et al. (1992)[46]. In this study measuring regional cerebral blood flow in monozygotic twins who were discordant or concordant for schizophrenia or who were both normal, the authors found differences between affected and unaffected disordant twins only during a task which has been linked to the prefrontal cortex (Wisconsin Card Sorting Test). During this task, all of the twins who were schizophrenic were hypofrontal when compared with their unaffected co-twins. No difference was found between unaffected co-twins of schizophrenics and normal twins. This was interpreted as suggesting that nongenetic factors are important in the cause of the prefrontal physiologic deficit that appears to characterize schizophrenia. Another finding was that of the concordant twins who had received different doses of neuroleptics, the twin receiving the higher dose was more hyperfrontal thus suggesting that long-term neuroleptic treatment does not play a major role in hypofrontality.

The result of hypofrontality has also been found by Raine et al. (1992)[47] using MRI. These researchers also found significantly smaller prefrontal lobes in schizophrenics when they were compared with both psychiatric controls and normal controls. Schizophrenics also had more perseveration errors on the WCST and fewer correct responses on the Spatial Delayed Response Task used.

Hypofrontality has not only been found in schizophrenics, but also in those assessed

as having schizotypal personality disorder (SPD). Raine et al. (1992)[48] used magnetic resonance imaging (MRI) and the Wisconsin Card Sorting Task to examine a group of non-institutionalized, unmedicated normal subjects. The researchers found that high schizotypal scores were significantly associated with reduced prefrontal area activity and more WCST perseveration errors. No relationship was found between these prefrontal measures and measures of psychosis-proneness unrelated to SPD traits. The authors interpreted their data as providing support for a prefrontal explanation of individual differences in schizotypal personality in the general population.

The finding of hypofrontality in shizophrenics appears to be a fairly consistent finding. Akbarian at al. (1993)[49] examined the dorsolateral prefrontal area of schizophrenics and found a significant decline in nicotinamide-adenine dinucleotide phospate-diaphorase neurons in the superficial white matter and in the overlying cortex but a significant increase of these neurons in white matter deeper than 3 mm from the cortex. They interpret these findings as being consistent with a disturbance of the subplate during development in which the normal pattern of programmed cell death is compromised and accompanied by a defect in the normal orderly migration of neurons toward the cortical plate. This then may result in serious consequences for the establishment of a normal pattern of cortical connections leading to a potential breakdown of frontal lobe function in schizophrenics.

b. FRONTOLIMBIC SYSTEM DYSFUNCTION

Recent work has revealed both structural and behavioral deficits in the frontolimbic system of schizophrenics. Breier et al. (1992)[50] examined the morphologic characteristics of the amygdala/hippocampus, prefrontal cortex, and caudate nucleus in 44 chronic schizophrenics and 29 healthy volunteers using magnetic resonance. The researchers found that the schizophrenics had significantly smaller right and left amygdala/hippocampal complex volumes, smaller right and left prefrontal lobe volumes, and larger left caudate volumes. A secondary analysis revealed reductions in the right and left amygdala and left hippocampus. They also found that the prefrontal white matter, but not gray matter, was reduced in the schizophrenics. The schizophrenics right white matter volume was found to be significantly related to right amygdala/hippocampal volume. These results were interpreted as providing support for the hypothesis of abnormal limbic-cortical connections in schizophrenics.

Seidman et al. (1991)[51] administered the University of Pennsylvania Smell Identification Test (UPSIT) to test orbitofrontal (OF) and the Wisconsin Card Sorting Test (WCST) to test dorsolateral (DL) prefrontal lobe function. Schizophrenic patients were found to be significantly impaired on both tasks when compared with controls. The researchers found the two tasks to be uncorrelated and concluded that the two tasks may be tapping independent dysfunctions in schizophrenia and may reflect differential impairment in the fronto-limbic brain systems. Of the patients studied, 3 were found to have orbitofrontal dysfunction, 5 had dorsolateral dysfunction, and 7 had a generalized (OF and DL) frontal system dysfunction.

Further evidence to indicate that schizophrenia involves pathology of and dysfunction within a widely distributed neocortical-limbic neural network comes from research by Weinberger et al.[52] These researchers used magnetic resonance imaging and regional cerebral blood flow to study monozygotic twins discordant for schizophrenia. They found that the more an affected twin differed from the unaffected twin in left hippocampal volume, the more they differed in prefrontal physiological activation during the Wisconsin Card Sorting Test. The authors had previously reported that affected twins had a smaller anterior pes hippocampus and the current study showed that in the affected twins as a group, the prefrontal activation was strongly related to both left and right hippocampal volume.

c. FRONTOSTRIATAL SYSTEM DYSFUNCTION

Other researchers have found evidence of frontostriatal dysfunction in schizophrenics. Buchsbaum et al. (1992)[53] used positron emission tomography (PET) to scan 18 schizophrenics who had never received neuroleptic medication. Their findings confirmed previous reports of hypofrontality in schizophrenics, however, they also found diminished metabolism in the basal ganglia. They interpreted their research results as suggesting a combined frontostriatal dysfunction in schizophrenia.

d. COGNITIVE INFLEXIBILITY

Morice (1990)[54] used the Wisconsin Card Sorting Test to examine cognitive flexibility in schizophrenic and manic patients. Both groups demonstrated poor performance; the author interpreted this finding as suggesting that cognitive inflexibility and/or prefrontal dysfunction is not specific to schizophrenia.

In order to clarify the nature of the abnormality of mental processing associated with the psychomotor poverty and disorganization of schizophrenia, Liddle & Morris (1991)[55] administered a battery of neuropsychological tests sensitive to frontal lobe impairment. They found psychomotor poverty to be closely associated with slowness of mental activity, including slowness in generating words. The disorganization syndrome was found to be associated with deficits on tests in which the subject was required to inhibit an established but inappropriate response.

e. CAPGRAS SYNDROME

Interesting results have been obtained in connection with schizophrenic patients exhibiting Capgras Syndrome, a syndrome characterized by the person's belief that a closely related person has been replaced by a double. Joseph et al. (1990)[56] compared the computed tomographic (CT) scans of 12 schizophrenic patients with Capgras Syndrome and 12 matched controls and found that those patients with Capgras Syndrome had significantly more bilateral frontal and temporal atrophy. The authors have suggested that in some schizophrenic patients the presence of Capgras Syndrome may be a marker for the coexistence of a focal idiopathic neurodegenerative process that preferentially affects the anterior cerebrum bilaterally.

f. CELL DENSITY DECREASES IN FRONTAL LOBES

In a study of the density of pyramidal cells, interneurons, glial cells of the prefrontal, anterior cingulate, and primary motor cortex of the brains of schizophrenics, Benes et al (1991)[57] found the numbers of small neurons (interneurons) of the schizophrenics to be reduced in most layers of the cingulate cortex, with the differences being greatest in layer II. In the schizophrenic patients' prefrontal area, interneuronal density was also lower in layer II and, to a lesser extent, in layer I. Schizophrenic subjects with superimposed mood disturbances were found to have similar, though more significant differences. Pyramidal neurons did not differ between controls and schizophrenic patients except for the fact that there were higher densities of these in layer V of the prefrontal area. No difference was found in glial cell densities, thus suggesting that a neurodegenerative process did not cause the reduced interneuronal density observed.

E. SOCIOPATHIC BEHAVIOR

In a study of sociopathic behavior subsequent to brain damage, Damasio et al. (1990)[58] found that damage to the ventromedial frontal cortices in adults with previously normal personalities resulted in defects in decision-making and planning which were especially evident in abnormal social conduct which lead to negative personal consequences for the individual. The researchers proposed that this defect might be due to an inability to activate somatic states linked to punishment and reward through past experience.

In subsequent research aimed at exploring this issue experimentally, Saver & Damasio (1991)[59] investigated whether patients with lesions in the ventromedial frontal cortices retain the ability to recognize the entities and events that compose social situations, but lose the ability to generate an appropriate array of response options to social stimuli, and to conceptualize the future consequences of choosing a particular option. At least whithin the domain of the tasks used during the experiment, their hypothesis was not confirmed. The impaired subject exhibited normal or superior performance on the tasks provided that were thought to measure the ability to generate possible response options to social situations, to consider the future consequences of pursuing particular response options, to conceptualize effective measures to achieve given social objectives, to predict the likely outcome of a particular configuration of social stimuli, and to perform moral reasoning at an advanced developmental level. The researchers concluded that the base of social knowledge acquired during this patient's normal development was still intact and that his capacity to access and process components of such knowledge was also intact. They do not appear to have investigated whether the subject could use this knowledge and inhibit conflicting responses. It has been observed that frontally lobotomized patients can often verbalize a strategy, but are unable to translate these into action. The type of patient studied by Damasio may have access to previous moral knowledge, but is this knowledge capable of serving as an inhibitory influence when the subject must act.

VI ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

One interesting recent development in regard to the frontal lobes is the association of the Attention Deficit Hyperactivity Disorder (ADHD) with possible dysfunction of the frontal lobes. Heilman et al. (1991)[60] have suggested that ADHD may be due to dysfunction in the right-sided frontal-striatal system. They arrived at their conclusion after considering the deficits of ADHD (i. e. defective attention, defective response inhibition, motor restlessness) and the fact that this inattention, defective response inhibition, and impersistence are more commonly seen in adults with right (as opposed to left) hemisphere dysfunction. They cite further evidence for their hypothesis in the fact that ADHD children neglect the left side and have decreased activation of their right neostriatum. They have also proposed that the motor restlessness of these children may reflect frontal lobe dysfunction due to impairment of the mesocortical dopamine system. There is experimental evidence both to support and refute this suggested association between ADHD and frontal lobe dysfunction. Shue & Douglas (1992)[61] compared children with the attention deficit hyperactivity disorder and normal controls during tests which measured both frontal and temporal lobe activity. They found that ADHD children differed significantly from normals on measures of frontal lobe function but not on measures of temporal lobe activity. The authors concluded that the difficulty of these children is specific to the frontal lobes and does not reflect generalized cognitive impairment. Benson (1991)[62] reviewed evidence from research investigating diverse ADHD populations and frontal lobe dysfunction and concluded that the evidence to support the connection remains strong. Barkley et al. (1992)[63] reviewed 22 neuropsychological studies of frontal lobe function in ADHD children with and without hyperactivity, and found that some measures presumed to assess frontal lobe dysfunction were not reliably sensitive to the deficit occurring in either form of the attention deficit disorder. They found that tests of response inhibition more reliably distinguished ADHD children from normal children. They concluded after reviewing the results of one particular study which compared attention deficit children with and without hyperactivity, learning disabled children, and normal children that while attention deficit disorder children with and without hyperactivity share some similarities in deficits on a few frontal tests, the overall findings of this particular study suggested an additional problem with perceptual-motor speed and processing in the attention deficit children who were also hyperactive.

Loge et al. (1990)[64] compared performance on a battery of neuropsychological tests of 20 children with ADHD with 20 matched normal children. They found that the ADHD children performed nearly normally on measures of verbal and design fluency and on the Wisconsin Card Sorting Test, and interpreted these findings as suggesting that inability to control and direct attention is more central to the psychopathology of this disorder than the impulse dysfunction which has been suggested by others.

Ⅶ. CONDITIONS WITH GENETIC COMPONENT

A. AUTISM

Although not representing research findings per se, a recent article by Gedye (1991)[65] put forth an interesting hypothesis regarding the relationship between the frontal lobes and a condition which still defies our attempts at etiological explanation —autism. Gedye suggests that many of the symptoms characteristic of autism fit the clinical picture of frontal lobe seizures. He notes that the facial, vocal, and other body movements in autism are catalogued in parallel with facial, vocal, and body movements that occur during frontal lobe seizures.

B. DOWN'S SYNDROME

Bahado-Singh (1992)[66] compared the size of the frontal lobes in Down's syndrome fetuses and normal fetuses between 16 and 21 weeks gestation. They found the frontal lobe dimension to be significantly shortened in Down's syndrome fetuses.

C. FRAGILE X GENE

Mazzocco (1992)[67] investigated the relationship between the neurocognitive phenotype of Fragile X and its relation to cytogenetic expression in 10 fragile X women and 10 controls. Results showed that when controlling for the effects of IQ, the expressing Fragile X women exhibited deficits on measures of frontal lobe functioning, and enhanced performance on verbal, but not figural, memory. The authors concluded that frontal lobe deficits may account for the behavioral and cognitive manifestation of Fragile X. It is thought that behavioral abnormalities are present in 80% of Fragile X males including hyperactivity, violence, stereotypies, resistance to environmental changes, and self-mutilatory behaviors. Language and speech deficits include immature syntax, poor abstraction, expressive and receptive language deficits, articulation problems, and perhaps cluttering. Approximately 20 to 40 percent of Fragile X males have features of the autistic disorder, but less than 10 percent of autistic males have the Fragile X Chromosome syndrome.[68]

Ⅷ. AGING

Advances in brain imaging technology have provided valuable evidence concerning the functioning of the frontal lobes in both healthy and impaired individuals. Salmon et al.(1991)[69] compared frontal lobe activity with other cortical and sub-cortical areas in healthy elderly and young volunteers using measures taken using positron emission tomography (PET). They found the elderly subjects to have decreased frontal activity relative to other cortical areas when compared with healthy volunteers. They concluded that cortical atrophy and neuronal depopulation could not provide a full explanation of this phenomenon.

Oscar-Berman et al (1992)[70] found age-linked deficits when comparing male alcoholics and normal controls performing visual and auditory delayed response tasks sensitive to prefrontal cortical damage in nonhuman primates. These age-linked

deficits were found for normal subjects over 50 years old only when attempting the most difficult tasks and were mild when compared with the Korsakoffs' deficits.

Ⅸ. ASYMMETRY OF FRONTAL LOBES

A. ASYMMETRIES DURING LEARNING INVOLVING REWARD & PUNISHMENT

Various researchers have reported finding greater suppression of alpha power in the right hemisphere frontal lobe when experiencing negative emotions, whereas there is greater suppression of alpha in the left hemisphere frontal lobe when experiencing positive emotion. Sobotka et al. (1992)[71] have interpreted this asymmetry as reflecting specialization for approach and withdrawal processes in the left and right frontal regions. They tested this hypothesis experimentally and interpreted their results as supporting their hypothesis that approach-related processes can be differentiated from withdrawal-related processes on the basis of asymmetrical shifts in alpha power in the frontal region.

B. EMOTION

In research aimed at assessing whether individual differences in anterior brain asymmetry are linked to differences in the basic dimension of emotion, Tomarken (1992)[72] recorded electroencephalogram (EEG) activity from female adults and extracted mean alpha power asymmetry in mid-frontal and anterior temporal sites. The researchers found that groups demonstrating stable and extreme relative left anterior activation reported increased generalized positive affect (PA) and decreased generalized negative affect (NA) when compared with groups demonstrating stable and extreme relative right anterior activation.

C. IMMUNE SYSTEM

Kang et al. (1991)[73] recently investigated the relation between brain activity and the immune system by assessing immune responses in 20 healthy women who manifested extreme differences in the asymmetry of frontal cortex activation—either extreme and stable left frontal activation or extreme and stable right frontal activation. They found that the women with extreme right frontal activation had significantly lower levels of natural killer cell activity (at effector:target cell ratios of 33:1 and 11:1) than did left frontally activated individuals. Two other immune measures, lymphocyte proliferation and T-cell subsets did not show this difference. However, higher immunoglobulin levels of the M class were observed in the right frontal group. Results supported the hypothesis of a specific association between frontal brain asymmetry and certain immune responses.

Ⅹ. SUMMARY

For many years full understanding of the functions of the human frontal lobes has eluded experts as we have lacked the tools to unlock these secrets. Nature has

provided occasional natural experiments as in the case of Phineas Gage who had part of his frontal lobe removed by an iron rod over a hundred years ago, and we have been able to study the behavior of people in whom the frontal lobes were either removed or disconnected (frontal lobotomies). It is only very recently, however, that we have been able to directly study the functioning frontal lobes in normal people. Technology has enabled us to directly observe the activation of specific areas of the brain during specific tasks. Unfortunately we are still rather inept in our choice of tests. For example, the widely use Wisconsin Card Sorting Test which has been conidered a specifically frontal lobe task has been recently called into question by Anderson et al. (1991)[74] who found no significant difference in WCST performance between subjects with frontal versus those with nonfrontal damage. Some subjects with extensive frontal lobe damage did well on the test while others with damage outside the frontal lobes did poorly.

Clinicans are well aware of the difficulties that frontal lobe patients experience in their daily lives, but researchers have been very slow in translating these difficulties into standardized tests which can be used in the experimental setting. Despite this drawback, there is much interesting evidence which has been added to our knowledge of the functioning of the frontal lobes

One of the most interesting recent trends is the association of many psychiatric problems with dysfunction of the frontal lobes. Neurologists have long been aware that tumors, infarcts, and hemorrhages can cause symptoms mimicing certain psychiatric states. For example, catatonia, a condition where the patient becomes immobile for some time in one position or maintains the position in which placed by the observer (waxy flexibility), is often associated with schizophrenia, but can also occur due to organic brain disease. As reviewed in the section on schizophrenia, more and more evidence points to dysfunction of the frontal lobes in this puzzling mental disorder. Other psychiatric conditions have also been found to be associated with the frontal lobes including depression, the obsessive-compulsive disorder, sociopathic behavior, and Gilles de la Tourette syndrome. This association with the frontal lobes not only applies to frankly psychiatric conditions, but also to other types of aberrant or dysfunctional behavior including antisocial behavior, conduct disorders, and the Attention Deficit Hyperactivity Disorder (ADHD). The similarities between frontal lobe seizures and autism have been noted, and Down's syndrome fetuses have been shown to have decreased frontal lobe size. Persons with a genetic condition known as Fragile X appear to have many frontal lobe related difficulties (i. e. hyperactivity, stereotypies, resistance to environmental changes, poor abstraction ability, etc,). Decreased frontal activity has also been found in the normal elderly.

Certain drugs have also been shown to have long lasting effects on the functioning of the frontal lobes. As mentioned previously, research has shown that chronic cocaine users continue to experience decreased frontal lobe function even months after cessation of drug use. The exact way in which this dysfunction affects the user is, as yet, unclear, but failure to experience pleasure from the normally pleasurable activities of

life (i. e. sex, eating) is one of the most commonly reported symptoms. Of considerable importance to society are the affects of alcohol on the frontal lobes. Though time does not allow an in-depth consideration of this issue, scientists are now beginning to clarify the more subtle psychological changes which occur following chronic alcohol ingestion. Alcohol ingestion appears to differentially impair specific areas of the frontal lobe which may provide the basis for behavioral inhibition, insight, attention, social judgment, empathy , complex reasoning, motivation, normal affect, memory retrieval, certain types of calculation ability, foresight, cognitive flexibility, temporal ordering, working memory, planning, word fluency, etc. The physiological consequences of heavy alcohol use are well known, but these more subtle neuropsychological changes which can have devastating effects on the individual is functioning in society are generally not widely recognized.

Survey of the results concerning asymmetry indicate that there may be some lateralization of negative (right frontal lobe) versus positive emotion (left frontal lobe). Interestingly enough, it has also been found that women with extreme right frontal activation had significantly lower levels of natural killer cell activity. In other words, there appears to be brain asymmetry in the relationship between certain immune responses and the activity of the frontal lobes.

In summary, scientists are clearly making headway in clarifing what is probably the most important area of our brain. It appears that psychiatrists of the future will need to be frontal lobe and frontal/subcortical interconnection specialists. When the term mental illness arises, it seems, more and more, that the term "frontal lobe dysfunction" can be applied.

BIBLIGRAPHY

1) Meyers CA, Berman SA, Scheibel RS, Hayman A, "Case report: acquired antisocial personality disorder associated with unilateral left orbital frontal lobe damage". *Journal of Psychiatry & Neuroscience* 17(3) : 121-5, 1992.

2) Lueger RJ, Gill KJ. "Frontal-lobe cognitive dysfunction in conduct disorder adolescents". *Journal of Clinical Psychology* 46(6) : 696-706, 1990.

3) Miller BL, Cummings JL, Villanueva-Meyer J, Boone K, Mehringer CM, Lesser IM, Mean I. "Frontal lobe degeneration : clinical, neuropsychological, and SPECT characteristics". *Neurology* 41(9) : 1372-82, 1991.

4) Lucchelli F, De Renzi E. "Primary dyscalculia after a medial frontal lesion of the left hemisphere". *Journal of Neurology, Neurosurgery & Psychiatry* 56(3) : 304-7, 1993.

5) Eslinger PJ, Grattan LM. "Frontal lobe and frontal-striatal substrates for different forms of human cognitive flexibility". *Neuropsychologia* 31(1) : 17-28, 1993.

6) Vilkki J. "Cognitive flexibility and mental programming after closed head injuries and anterior or posterior cerebral excisions". *Neuropsychologia* 30(9) : 807-14, 1992.

7) Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. "Planning and spatial memory following frontal lobe lesions in man". *Neuropsychologia* 28(10) : 1021-34, 1990.

8) Vilkki J, Holst P. "Mental programmig after frontal lobe lesions : results on digit symbol performance with self-selected goals". *Cortex* 27(2) : 203-11, 1991.

9) Goldstein LH, Bernard S, Fenwick PB, Burgess PW, McNeil J. "Unilateral frontal lobectomy can produce strategy application disorder". *Journal of Neurology, Neurosurgery & Psychiatry* 56(3) : 274-6, 1993.

10) De Renzi E, Barbieri C. "The incidence of the grasp reflex following hemispheric lesion and its relation to frontal damage". *Brain* 115 Pt 1 : 293-313, 1992

11) Miller LA. "Impulsivity, risk-taking, and the ability to synthesize fragmented information after frontal lobectomy". *Neuropsychologia* 30(1) : 69-79, 1992.

12) Klouda GV, Cooper WE. "Information search following damage to the frontal lobes". *Psychological Reports* 67(2) : 411-6, 1990.

13) Parkin AJ, Walter BM. "Recollective experience, normal aging, and frontal dysfunction". *Psychology & Aging* 7(2) : 290-8, 1992.

14) Shimamura AP, Gershberg FB, Jurica PJ, Mangels JA, Knight RT. "Intact implicit memory in patients with frontal lobe lesions". *Neuropsychologia* 30(10) : 931-7, 1992.

15) Parkin AJ, Dunn JC, Lee C, O'Hara PF, Nussbaum L. "Neuropsychological sequelae of Wernicke's encephalopathy in a 20-year-old woman: selective impairment of a frontal memory system". *Brain & Cognition* 21(1) : 1-19 1993.

16) Shimamura AP, Janowsky JS, Squire LR. "Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients". *Neuropsychologia* 28(8) : 803-13, 1990.

17) Frisk V, Milner B. "The relationship of working memory to the immediate recall of stories following unilateral temporal or frontal lobectomy". *Neuropsychologia* 28(2) : 121-35, 1990.

18) Petrides M, Alivisatos B, Evans AC, Meyer E. "Dissociation of human mid-dosolateral from posterior dorsolateral frontal cortex in memory processing". *Proceedings of the National Academy of Sciences of the United States of America* 90(3) : 873-7, 1993.

19) Petrides M, Alivisatos B, Meyer E, Evans EC. "Functional activation of the human frontal cortex during the performance of verbal working memory tasks". *Proceedings of the National Academy of Sciences of the United of America* 90(3) : 878-82, 1993.

20) Jason GW, Pajurkova. "Failure of metacontrol: breakdown in behavioural unity after lesion of the corpus callosum and inferomedial frontal lobes". *Cortex* 28(2) : 241-60, 1992.

21) Miller BL, Cummings JL, Villanueva-Meyer J, Boone K, Mehringer CM, Lesser IM, Mena I. "Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics". *Neurology* 41(9) : 1372-82, 1991.

22) Frith CD, Friston KJ, Liddle PF, Frackowiak RS. "A PET study of word finding". *Neuropsychologia* 29(12) : 1137-48, 1991.

23) Price BH, Daffner KR, Stowe RM, Mesulam MM. "The comportmental learning disabilities of early frontal lobe damage". *Brain* 113(Pt 5) : 1383-93, 1990.

24) Eslinger PJ, Grattan LM, Damasio H, Damasia AR. "Developmental consequences of childhood frontal lobe damage". *Archives of Neurology* 49(7) : 764-9, 1992.

25) Hall DP, Young SA. "Frontal lobe cerebral aneurysm rupture presenting as psychosis". *Journal of Neurology, Neurosurgery, & Psychiatry* 55(12) : 1207-8, 1992.

26) Mochizuki H, Saito H. "Mesial frontal lobe syndromes: correlations between neurological deficits and radiological localizations". *Tohoku Journal of Experimental Medicine* 161 Suppl : 231-9, 1990.

27) Sandson TA, Daffner KR, Carvalho PA, Mesulam MM. "Frontal lobe dysfunction following infraction of the left-sided medial thalamus". *Archives of Neurology* 48(12) : 1300-3, 1991.

28) Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP, Dewey SL, Handlesman L. " Long-term frontal brain metabolic changes in cocaine abusers". *Synapse* 11(3) : 184-90, 1992.

29) Korpi ER, Uusi-Oukari M, Wegelius K, Casanova M, Zito M, Kleinman JE. "Cerebllar and frontal cortical benzodiazepine receptors in human alcoholics and chronically alcohol-drinking rats". *Biological Psychiatry* 31(8) : 774-86, 1992.

30) Gilman S, Adams K, Koeppe RA, Berent S, Kluin KJ, Modell JG, Kroll P, Brunberg JA. " Cerebellar and frontal hypometabolism in alcoholic cerebellar degeration studied with positron emission tomography". Annals of Neurology, 28(6) : 775-85, 1990.

31) Adams KM, Gilman S, Koeppe RA, Kluin KJ, Brunberg JA, Dede D, Berent S, Kroll PD. "Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients". *Alcoholism* 17(2) : 205-10, 1993.

32) Oscar-Berman M, Hutner N, Bonner RT. "Visual and auditory spatial and nonspatial delayed-response performance by Korsakoff and non-Korsakoff alcoholic and aging individuals". *Behavioral Neuroscience* 106(4) : 613-22, 1992.

33) Sullivan EV, Mathalon DH, Zipursky RB, Kersteen-Tucker Z, Knight RT, Pfefferbaum A. " Factors in the Wisconsis Card Sorting Test as measures of frontal-lobe function in schizophrenia and in chronic alcoholism". *Psychiatry Research* 46(2) : 175-99, 1993.

34) Kopelman MD. "Frontal dysfunction and memory deficits in the alcoholic Korsakoff syndrome and Alzheimer-type dementia". *Brain* 114(Pt 1A) : 117-37, 1991.

35) Joyce EM, Robbins TW. "Frontal lobe function in Korsakoff and non-Korsakoff alcoholics: planning and spatial working memory". *Neuropsychologia* 29(8) : 709-23, 1991.

36) Hewett LJ, Nixon SJ, Glenn W, Parsons OA. "Verbal fluency deficits in female alcoholics". *Journal of Clinical Psychology* 47(5) : 716-20, 1991.

37) Dawson G, Klinger LG, Panagiotides H, Hill D, Spieker S. "Frontal lobe activity and affective behavior of infants of mothers with depressive symptoms". *Child Development* 63(3) : 725-37, 1992.

38) Berman KF, Doran AR, Pickar D, Weinberger DR. "Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Regional cerebral blood flow during cogitive activation". *British Journal of Psyciatry* 162 : 183-92, 1993.

39) George MS, Trimale MR, Costa DC, Robertson MM, Ring HA. "Elevated frontal cerebral blood flow in Gilles de la Tourette syndrome: a 99Tcm-HMPAO SPECT study". *Psychiatry Research* 45(3) : 143-51, 1992

40) Machlin SR, Harris GJ, Pearlson GD, Hoehn-Saric R, Jeffery P, Camargo EE. "Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: a SPECT study". *American Journal of Psychiatry* 148(9) : 1240-2, 1991.

41) Paulman RG, Devous MD Sr, Gregory RR, Herman JH, Jennings L, Bonte FJ, Nasrallah HA, Raese JD. "Hypofrontality and cognitive impairment in schizophrenia: dynamic single-photon tomography and neuropsychological assessment schizophrenic brain function". *Biological Psychatry*27(4) : 377-99, 1990.

42) Suzuki M, Kurachi M, Kawasaki Y, Kiba K, Yamaguchi N. "Left hypofrontality correlates with blunted affect in schizophrenia". *Japanese Journal of Psychiatry & Neurology* 46(3) : 653-7, 1992.

43) Rubin P, Holm S, Friberg L, Videbech P, Andersen HS, Bendsen BB, Stromso N, Larsen JK, Lassen NA, Hemmingsen R. "Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizophreniform disorder. A regional cerebral blood flow study". *Archives of General Psychiatry* 48(11) : 987-95, 1991.

44) Wolkin A, Sanfilipo M, Wolf AP, Angrist B, Brodie JD, Rotrosen J. "Negative symptoms and hypofrontality in chronic schizophrenia". *Archives of General Psychiatry* 49(12) : 959-65, 1992.

45) Andreasen NC, Rezai K, Alliger R, Swayze VW 2d, Flaum M, Kirchner P, Cohen G, O'Leary DS. "Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London". *Archives of General Psychiatry* 49(12) : 943-58, 1992.

46) Berman KF, Torrey EF, Daniel DG, Weinberger DR. "Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia". *Archives of General Psychiatry* 49(12) : 927-34, 1992.

47) Raine A, Lencz T, Reynolds GP, Harrison G, Sheard C, Medley I, Reynolds LM, Cooper JE. "An evaluation of structural and functional prefrontal deficits in schizophrenia: MRI and neuropsychological measures". *Psychiatry Research* 45(2) : 123-37, 1992.

48) Raine A, Sheard C, Reynolds GP, Lencz T. "Pre-frontal structural and functional deficits associated with individual differences in schizotypal personality". *Schizophrenia Research* 7(3) : 237-47, 1992.

49) Akbarian S, Bunney WE Jr., Potkin SG, Wigal SB, Hagman JO, Sandman CA, Jones EG. " Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development". *Archives of General Psychitry* 50(3) : 169-77, 1993.

50) Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F. "Brain morphology and shizophrenia . A magnetic resonance imaging study of limbic, prefrontal cortex and caudate structures". *Archives of General Psychiatry* 49(12) : 921-6, 1992.

51) Seidman LJ, Talbot NL, Kalinowski AG, McCarley R, Faraone SV. "Neuropsychological probes of frontal-limbic system dysfunction in schizophrenia. Olfactory identification and Wisconsin Card Sorting performance". *Schizophrenia Research* 6(1) : 55-65, 1991.

52) Weinberger DR, Berman KF, Suddath R, Torrey EF. "Evidence of dysfunction of a prefrontal -limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins". *American Journal of Psychiatry* 149(7) : 890-7, 1992.

53) Buchsbaum MS, Haier RJ, Potkin SG, Nuechterlein K, Bracha HS, Katz M, Lohr J, Wu J, Lottenberg S, Jerabek PA, et al. "Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics". *Archives of General Psychiatry* 49(12) : 935-42, 1992.

54) Morice, R. "Cognitive inflexibility and pre-frontal dysfunction in schizophrenia and mania". *British Journal of Psychiatry* 157 : 50-4, 1990.

55) Liddle PF, Morris DL. "Schizophrenic syndrome and frontal lobe performance". *British Journal of Psychiatry* 158 : 340-5, 1991.

56) Joseph AB, O'Leary DH, Wheeler HG. "Bilateral atrophy of the frontal and temporal lobes in schizophrenic patients with Capgras syndrome: a case-control study using computed tomography". *Journal of Clinical Psychiatry* 51(8) : 322-5, 1990.

57) Benes FM, McSparren J, Bird ED, SanGiovanni JP, Vincent SL. "Deficits in small interneurons in prefrontal and cingulate cortices schizophrenic and schizoaffective patients". *Archives of General Psychiatry* 48(11) : 996-1001, 1991.

58) Damasio AR, Tranel D, "Individuals with sociopathic behavior caused by frontal damage fail to respond automatically to social stimuli". *Behavioural Brain Research* 41(2) : 81-94, 1990.

59) Saver JL, Damasio AR. "Preserved access and processing of social knowleige in a patient with acquired sociopathy due to ventromedial frontal damage". *Neuropsychologia* 29(12) : 1241-9, 1991.

60) Heilman KM, Voeller KK, Nadeau SE. "A possible pathophysiologic substrate of attention deficit hyperactivity disorder". *Journal of Child Neurology* 6 Suppl : S76-81, 1991.

61) Shue KL, Douglas VI. "Attention deficit hyperactivity disorder and the frontal lobe syndrome". *Brain & Cognition* 20(1) : 104-24, 1992.
62) Benson DF. "The role of frontal dysfunction in attention deficit hyperactivity disorder". *Journal of Child Neurology* 6 Suppl : S9-12, 1991.
63) Barkley RA, Grodzinsky G, DuPaul GJ. "Frontal lobe functions in attention deficit disorder with and without hyperactivity: a review and research report". *Journal of Abnormal Child Psychology* 20(2) : 163-88, 1992.
64) Loge DV, Station RD, Beatty WW. "Performance of children with ADHD on tests sensitive to fontal lobe dysfunction". *Journal of American Academy of Child & Adolescent Psychiatry* 29(4) : 540-5, 1990.
65) Gedye A. "Frontal lobe seizures in autism". *Medical Hypotheses* 34(2) : 174-82, 1991.
66) Bahado-Singh RO, Wyse L, Dorr MA, Copel JA, O'Connor T. "Fetuses with Down syndrome have disproportionately shortened frontal lobe dimensions on ultrasonographic examination". *American Journal of Obstetrics & Gynecology* 167(4 Pt 1) : 1009-14, 1992.
67) Mazzocco MM, Hagerman RJ, Cronister-Silverman A, Pennington BF. "Specific frontal lobe deficits among women with the fragile X gene". *Journal of the American Academy of Child & Adolescent Psychiatry* 31(6) : 1141-8, 1992.
68) Talbott JA, Hales RE, Yudofsky SC (Eds). *Textbook of Psychiatry,* The American Psychiatric Press, Washington. DC, 1988 p. 708.
69) Salmon E, Maquet P, Sadzot B, Degueldre C, Lemaire C, Franck G. "Decrease of frontal metabolism demonstrated by positron emission tomography in a population of healthy elderly volunteers. *Acta Neurological Belgica* 91(5) : 288-95, 1991.
70) Oscar-Berman M, Hunter N, Bonner RT. "Visual and auditory spatial and nonspatial delayed-response performance by Korsakoff and non-Korsakoff alcoholic and aging individuals. *Behavioral Neuroscience* 106(4) : 613-22, 1992.
71) Sobotka SS, Davidson RJ, Senulis JA. "Anterior brain electrical asymmetries in response to reward and punishment". *Electroencephalography & Clinical Neurophysiology* 83(4) : 236-47, 1992.
72) Tomarken AJ, Davidson RJ, Wheeler RE, Doss RC. "Individual differences in anterior brain asymmetry and fundamental dimension of emotion". *Journal of Personality & Social Psychology* 62(4) : 676-87, 1992.
73) Kang DH, Davidson RJ, Coe CL, Wheeler RE, Tomarken AJ. "Frontal brain asymmetry and immune function". *Behavioral Neuroscience* 105(6) : 860-9, 6991.
74) Anderson SW, Damasio H, Jones RD, Tranel D. "Wisconsin Card Sorting Test performance as a measure of frontal lobe damage". *Journal of Clinical & Experimental Neuropsychology* 13(6) : 909-22, 1991.