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Lateralization of functions in the prefrontal cortex: Cognitive stability vs. cognitive plasticity

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LATERALIZATION OF FUNCTIONS IN THE PREFRONTAL CORTEX: COGNITIVE STABILITY VS. COGNITIVE PLASTICITY

by

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

LATERALIZATION OF FUNCTIONS IN THE PREFRONTAL CORTEX: COGNITIVE STABILITY VS. COGNITIVE PLASTICITY

by

Kenneth Podell

Adviser: Professor Elkhonon Goldberg

The role of hemispheric specialization is well defined for posterior cortices. However, it has not been sufficiently studied in the frontal lobes. The lateralization of frontal lobe functioning is traditionally characterized only by the language/non-language dichotomy. The language/non-language distinction, however, can be viewed as a specific example of a more fundamental process. Based on the theory developed by Goldberg and Costa (1981) it is hypothesized that the left prefrontal cortex (PFC) is critical for cognitive stability (maintaining an internalized plan or strategy), while the right PFC is important for the maintenance of cognitive plasticity (switching between cognitive strategies and processing novel information).

A group of 20 subjects with well lateralized left and right PFC lesions (5 of each sex having left and right lesions) were administered two novel tasks (SP1 and SP2) and a set of standard neuropsychological tests (WAIS-R and Raven's Standard Progressive Matrices [RSPM]). A group of 34 healthy controls (17 males and females) were also administered SP1 and

SP2 and a personality questionnaire measuring traits similar to cognitive stability and plasticity.

The psychometric properties of SP1 and SP2 in the healthy controls revealed high test/retest reliability and substantial convergent validity with the Extroversion scale from the Eysenck Personality Questionnaire.

A significant gender difference in both healthy controls and lesion subjects was found. Healthy control females responded in a plastic fashion (target independent), while healthy control males responded in a more stable (target dependent) manner.

There was a diametric effect in males with lateralized PFC lesions: a left PFC lesion produced a bias toward plasticity, while a right PFC lesion produced a bias toward stability, relative to matched healthy controls. Unexpectedly, females with left or right PFC lesions had a bias toward cognitive stability, relative to matched healthy controls. Possible explanations for the occurrence of the results and their implications in understanding hemispheric specialization in the PFC, and gender differences, were presented.

Dedication

I would like to dedicate this work to my parents, Dr. & Mrs. Arnold Podell. Without them I would have never had the educational opportunity that I had. They devoted themselves to making sure that I had all I needed to complete my graduate education with minimal hardship. Their love and devotion for their children is unyielding and unending. I can only hope that some day I am as good a parent to my children as my parents were to me.

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I would have never been able to complete this project without the help of numerous people. My gratitude and thanks will never be complete. I am thankful for having had the opportunity to have worked with Gerald Turkewitz, whose expertise and wisdom served as a shining example. I am grateful to Joseph Jaffe for his keen insights and generosity.

I will never forget the insightfulness of Jason Brown. His comments were very challenging and helpful. Without the ingenuity and generosity of Allan Mirsky this project would have never been completed. I will always be thankful to Richard Harner, a gentleman and a scholar; he was instrumental during every stage of this project. I am grateful to Michael Miller, for taking time from his hectic schedule to help me analyze date.

To my mentor, and friend, Elkhonon Goldberg, I will always owe him the world of thanks. He was there at every turn guiding me through the darkness. His profound wisdom and knowledge will always serve as food for thought.

Trying to find appropriate subjects was comparable to looking for a needle in a haystack. I would like to thank Mark Lovell, Allan Mirsky, James Rebeta, Jason Brown, William Barr, and Stephen Sparr for supplying me with those needles. A special thanks to Robert Bilder, who diffused my fears and

anxiety countless times. His generosity and friendship will never be forgotten.

Michael Zimmerman, Michelle Sovastion, and Eric Rosenwinkle were extremely helpful in data collection and subject recruitment. The help of Ida Pearson cannot go unmentioned. If not for her I would still be in a bureaucratic quagmire.

Last and most importantly to Kathy, my wife, and life long companion. I cannot tell you how fortunate I was to have you by my side during the past few tortuous years. You were unselfishly devoted, and were always there when I needed. Now we can start to spend the rest of lives together.

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Much research shows that the two cerebral hemispheres have substantially different modes of cognitive processing. These lateralized differences are described, for example, as verbal/nonverbal (Sperry, 1966), sequential/parallel (Bradshaw and Nettleson, 1981), propositional/appositional (Bogen, 1969), and analytic/global (Nebes, 1978). At present, the language/non-language dichotomy is still tenaciously regarded by many as the fundamental aspect of human hemispheric specialization (Corbalis, 1983; Kosslyn, 1987; Levy, 1974; Sperry, 1966; see Sherman, Galaburda and Geschwind, 1982). If this is true then it invokes the notion of evolutionary discontinuity (Carlson and Glick, 1989; Goldberg, 1990). It suggests that because sub-human species do not produce language like humans, that lateralization in sub-humans is minimal, if present at all. This does not appear to be the case. There is a large body of literature showing that sub-human species have well lateralized cognitive processes: birds (Arnold and Bottjer, 1985; Nottebohm, 1977, 1979), chicks (Rogers, 1980), rodents (Carlson and Glick, 1989; Denenberg, 1981) and non-human primates (Dewson, 1977; Dewson, Cowey and Weiskrantz, 1970; Hamilton, Tieman and Farrell, 1974; Hamilton and Vermeire, 1988; Hamilton and Vermeire, 1991; Petersen, Beecher, Zoloth, Moody and Stebbins, 1978).

Although other continua/dichotomies are used to describe the role of the two cerebral hemispheres, they are unable to account adequately for the large body of data (see Bradshaw and Nettleton, 1981). They all appear to focus on a specific

aspect, or example, of a more fundamental process of hemispheric specialization. This more fundamental principle of hemispheric specialization is advanced by the theory of Goldberg and Costa (1981). Goldberg and Costa present a strong argument suggesting the fundamental principles underlying cerebral lateralization are as follows: The left cerebral hemisphere is specialized for processing information based upon well established, routinized codes. The complementary, right cerebral hemisphere is specialized for processing novel information for which the individual's well routinized codes are not applicable. The language/non-language distinction is then but a specific example of this more fundamental process.

There has been an extreme paucity of research studying the lateralization of frontal lobe functions. The overwhelming bulk of hemispheric specialization studies has incorporated paradigms or tasks that heavily depend upon the functioning of posterior cortices. Most hemispheric specialization studies ask subjects to make a response based upon higher order sensory/perceptual processing. The best examples of such paradigms are tachistoscopically presented material or dichotic listening.

The majority of work looking at lateralized functions within the frontal lobes is based upon the language/nonlanguage distinction. I will argue that this is not the fundamental aspect of hemispheric specialization.

There must then exist a more fundamental attribute of lateralization within the prefrontal cortex.

The aim of this study is to investigate the functional dissociations of the left and right prefrontal cortex (PFC). The left and right PFC are responsible for different, yet interrelated, complementary functions. Four areas suggest functional differences within the PFC: 1) neuroanatomy, 2) neurochemical substrates of cognition, 3) theories of hemispheric specialization and 4) neuropsychological studies.

Neuroanatomical Asymmetries

As with cognitive processes, anatomical asymmetries of the frontal lobe have not been studied as extensively as posterior cortices (e.g., various temporal and parietal lobe regions). However, a generally consistent pattern of neuroanatomical asymmetry does appear when examining studies that looked at both macro- and microscopic asymmetries within the frontal lobe (for reviews see Witelson and Kigar, 1989 and Goldberg and Costa, 1981).

The macroscopic evidence suggested that the right frontal pole, compared to the left, had a greater anterior extension (Bear, Schiff, Saver, Greenberg and Freeman, 1986; LeMay, 1976; Weinberger, Luchins, Morihisa and Wyatt, 1982). Several authors reported a wider right frontal lobe in right handers (Bear et al., 1986; Chui and Damasio, 1980; Galaburda, LeMay, Kemper, and Geschwind, 1978; Kertesz, Black, Polk and Howell,

1986; LeMay, 1977; LeMay and Kido, 1978). Studies of impressions on the vault (petalia) resulting from local protuberances of the brain are consistent with the above findings. An enhanced right petalia was the pattern most frequently seen in the prefrontal cortex of right handed subjects (Chui and Damasio, 1980; Hadziselimovic and Cus, 1966; Hadziselimovic and Ruzdic, 1966; LeMay, 1977; LeMay and Kido, 1978).

Most of the frontal asymmetry research was confined to Broca's area - typically defined as the combination of pars opercularis, pars triangularis and to a lesser extent, pars orbitalis (Galaburda and Habib, 1987). When defined by gross, convexital landmarks there was no consistent asymmetrical finding in Broca's area (Galaburda and Habib, 1987; Witelson, 1988).

A distinct pattern emerged when cytoarchitectonic regions or infrasulcal patterns were used. A greater representation was found in the left hemisphere for Brodmann areas 44 and 45 when intra- and infrasulcal patterns were used in defining the cortical area (Falzi, Perrone and Vignolo, 1982). This contrasted the finding of Wada, Clarke and Hamm (1975) who felt that Brodmann's area 44 and the posterior portion of Brodmann's area 45 was greater in the right. Wada et. al., only used convexital landmarks and the posterior portion of area 45. This probably led them to miss some of the area to be included - in particular, the infrasulcal region. In fact,

Wada et. al., suggested much of the area might extend deep into the sulci. When Brodmann's areas 44 and 45 were defined strictly by cytoarchitectonics, a greater expansion in the left hemisphere was again found (Kononova, 1935 cited in Adrianov, 1979). Similarly, Galaburda (1980) found that pars opercularis alone (Brodmann's area 44), was larger in the left.

Differences in columnar organization have also been found in Brodmann's region 44, 45, 47, 4 and 6 (Bogolepova, 1985; Kesarev, 1978 and Kononova, 1935 both cited in Adrianov, 1979). A greater degree of vertical organization of pyramidal cells was reported in these regions of the left hemisphere. Bogolepova also found differences within various neocortical layers. The pyramidal cells of layers III and V had a larger representation in the left hemisphere.

The advent of modern technology has allowed us to study in vivo changes in the physiological processes of brain functioning. This in turn allowed us to infer function or the regional effect different types of stimuli have on the brain. One such measure, regional cerebral blood flow (rCBF), has found a striking asymmetry in the cerebral hemispheres, especial in frontal regions. Gur, Packer, Hungerbuhler, Reivich, Obrist, Amarnek and Sackheim (1980) found that the left prefrontal cortex was characterized by a greater grey/white matter ratio, while the right prefrontal cortex had a much lower grey/white matter ratio. This suggested that the

neuronal organization of the left prefrontal cortex consists of dense, unmyelinated neurons. This type of organization is designed for short, intra-regional connectivity (Goldberg and Costa, 1981; Gur, et. al., 1980). This was consistent with the findings of Bogolepova (1985) and Kesarev (1978). The right prefrontal cortex had relatively more long, myelinated fibers that were best for inter-regional connectivity (Goldberg and Costa, 1981; Gur et. al., 1980).

The above findings and interpretation were consistent with the work of Woodward (1988) and Semmes (1968). Woodward showed that the local pyramidal cell connectivity of the left hemisphere is characterized by vertically arranged, well packed, "columnar" circuitry, while the right hemisphere consisted of horizontal circuitry. Semmes (1968) predicted, based upon sensorimotor deficits in unilateral lesions, that the left hemisphere was comprised of a tightly packed neuronal organization and suited for unimodal processing (e.g., language). The right hemisphere had a diffuse neuronal organization that was best for multi-modal processing (e.g., spatial integration).

Neuroanatomical asymmetries exist within the prefrontal cortex. The evidence suggests that the left hemisphere has a greater representation of Broca's area (Brodmann's areas 44 and 45), which is characterized by short, intraregional, neuronal connectivity. This type of organization is best for

modality specific processing, e.g., language (Goldberg and Costa, 1981; Gur et. al., 1980).

Most asymmetries described up to date are confined to Brodmann's Areas 44 and 45. Unfortunately, the same degree of attention has not been addressed to neuroanatomical asymmetries in more anterior regions, (e.g., the frontal polar region corresponding to Brodmann's areas 10 and 46). The only asymmetry found in the frontal pole is a greater extension and width in the right frontal pole. This would suggest that the right prefrontal region, relative to the left, contains a greater degree of association cortex. Association cortex consists of long, myelinated fibers, which have been considered best suited for multi-modal integration across regions (Goldberg and Costa, 1981).

Neurotransmitter Asymmetry

Paralleling the neuroanatomical findings are data suggesting that the relative ratios of the catecholamines, norepinephrine (NE) and dopamine (DA), are asymmetric within the prefrontal cortex. It appears that NE and DA have some of their greatest concentration of terminals and receptors in the prefrontal cortex (PFC). There is one exception for each: NE has its absolute highest concentrations in the postcentral, somatosensory region, while cortical DA is ultimately greatest in the premotor and motor regions (Bjorklund, Divac and Lindvall, 1978; Brown, Crane and Goldman, 1979; Brown and

Goldman, 1977; Levitt, Rakic and Goldman-Rakic, 1984; Lewis, Campbell, Foote and Morrison, 1986; Morrison and Magistretti, 1983).

Both NE and DA, in rats and monkeys, are highly prevalent in PFC. Cortical NE pathways enter through the frontal pole and run caudally (Emerson and Lindvall, 1974; Fallon and Loughlin, 1987; Morrison and Magistretti, 1983; Morrison, Moliver and Grzanna, 1979). The PFC is the cortical region richest in DA terminals (Bannon and Roth, 1983; Berger, Thierry, Tassin and Moyne, 1976; Bjorklund et al., 1978; Brown et al., 1979; Deniau, Thierry and Feger, 1980; Felten and Sladek, 1983; Kehr, Linquist and Carlsson 1976; Lindvall, Bjorklund and Divac, 1978). The density of NE and DA receptors and terminals follows a general rostrocaudal pattern - highest in prefrontal and lowest in occipital - with the exceptions stated above (Bjorklund et al., 1978; Brown and Goldman, 1977; Brown et al., 1979; Descarries and Lapierre, 1973; Levitt et al., 1984; Lewis et al., 1986; Morrison, Foote, O'Connor and Bloom, 1982; Morrison and Magistretti, 1983; Saledate and Orrego, 1977).

Evidence showing the lateralization of DA and NE (inter-hemispheric differences in DA-to-NE ratio) was found in rats and humans.[1] Relative to each other, there was greater DA in the left hemisphere, and greater NE in the right hemisphere.

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[1]Strangely, I have been unable to find any evidence of the relative lateralization of DA and NE in the non-human primate.

Denenberg (1981), in reviewing several studies, concluded that the direction of stereotypic rotation in rats (which is contralateral to the hemisphere with the greater amount of DA) indicated a left lateralization of DA. Denenberg's inference was supported by the greater amounts of left prefrontal DA, relative to NE (Slopsema, Van der Gugten and De Bruin, 1982) and higher DA metabolism in the left, compared to the right, frontal cortex of rats (Glick, Meibach, Cox and Maayani, 1979). Also, human levels of DA were higher in the left globus pallidus (Glick, Ross and Hough, 1982). Glick et al., did not measure cortical DA and NE.[2] Right, but not left, frontal lesions in rats impaired the bilateral distribution of NE (Pearlson and Robinson, 1981; Robinson, 1979). Higher right than left levels of NE have been found in the thalamus and striatum of rats (Oke, Lewis and Adams, 1980) and in human thalamus (Oke, Keller, Mefford and Adams, 1978).

Interestingly, there also was a difference in laminar distribution between prefrontal NE and DA within the same hemisphere. The difference was complementary. Where one was dense the other was scarce (Bjorklund et al., 1978; Bunney and

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[2] In this study the authors reanalyzed the data of Rossor, Garett and Iversen, 1980 who did not find any catecholamine asymmetry in post-mortem human brain. Rossor et al., used individual paired t-tests. Because handedness information was unknown Glick et al., reasoned that reversed handedness would obscure any significant differences when using a t-test. Therefore, using Chi-square and correlational analysis, Glick et al., found that there was, in fact, evidence for the asymmetrical distribution of DA in the striatum. Cortical DA and NE were not reliably measured in the study by Rossor et al.

Aghajanian, 1976; Levitt et al., 1984; Lewis et al., 1986, Lewis, Campbell, Foote et al., 1987; Morrison and Magistretti, 1983; Sawaguchi and Matsumura, 1985). This would also be consistent with the notion that DA and NE have separable yet interrelated functions.

Cognition subserved by Catecholamines

Tucker and Williamson (1984) reviewed the evidence for the lateralized distribution, prevalence within the prefrontal cortex, and the behavioral roles of DA and NE. Building upon the formulation of Pribram and McGuiness (1975) that there were two major regulatory systems for attentional control - arousal and activation, Tucker and Williamson concluded that "expansive", exploratory behavior, and response to novelty, was mediated largely by a noradrenergic arousal system, and "restrictive", redundant, stereotypic behavior by a dopaminergic activation system.

Norepinephrine. NE containing neurons in the Locus Coeruleus (LC) are responsive to poly-sensory input in general (Aston-Jones and Bloom, 1981; Bloom, 1979; Foote, Aston-Jones and Bloom, 1980) and critical for orienting to, and processing novel information, in particular. NE neuronal activity in the LC increased in response to novel (or interruptive) stimuli and decreased its activity with stimulus repetition (Aston-Jones, 1985; Aston-Jones and Bloom, 1981). Also, high activity in NE containing LC neurons leads specifically to

orientation to novel stimuli (Foote and Bloom, 1979; Watabe, Nakai and Kasamatsu, 1982). Rats with genetically high levels of NE concentration and turnover rates showed increased, non-purposeful, exploratory behavior (Kempf, Greilsamer, Mack and Mandel, 1974). Conversely, rats with lesions of the NE pathway repetitively, explored the same area (Mason and Fibiger, 1979) and were unable to attend to novel objects (Delini-Stula, Mogilnicka, Hann and Dooley, 1984; Martin-Iverson, Pisa, Chan and Fibiger, 1982).

Mason and Fibiger (1979) suggested that NE was critical in filtering out irrelevant cues, and helped the animal attend to novel information in the environment. NE increased the signal-to-noise ratio by attenuating activity to novel information and inhibiting responsivity to repetitive information (Mason and Fibiger, 1979; Oades, 1985; Tucker and Williamson, 1984).

Consistent with the findings that NE was important in the processing of sensory information was that NE depletion impaired habituation, extinction of simple learning during non-reinforcement, and avoidance learning (Kempf et al., 1974; Lorden, Rickert, Dawson and Pelleymounter, 1980; Mason and Fibiger, 1979; Mason and Iversen, 1975). All of these studies indicated an impairment in processing sensory information.

The idea that NE is critical in processing novel information inevitably presumes processing external, environmental stimuli (Tucker and Williamson, 1984). This is

consonant with NE having its highest concentration in the somatosensory region of the postcentral gyrus (Bjorklund et al., 1978; Brown and Goldman, 1977; Brown et al., 1979; Levitt et al., 1984; Lewis et al., 1986; Morrison and Magistretti, 1983).

Dopamine. DA is crucial for the redundancy or routinization of behavior in general, and the organization, integration and execution of motor action in particular (Fuster, 1990; Iversen, 1977; Oades, 1985; Tucker and Williamson, 1984). Increases in mesocortical DA levels correlate with, and even augment, motor activity (Cools and Rossum, 1970; Everett and Weigand, 1962). Increased mesocortical DA produces a restriction in the range of the animal's behavior causing repetitive responses (Lyon and Robbins, 1975). With incremental amounts of DA, successive restriction in the range of motor behavior occurs. With large amounts of DA, the animal continually repeats brief, highly stereotypic, motor sequences (Iversen, 1977). The role of DA in motor activation is consistent with having its greatest cortical concentration in premotor and motor cortices (Bjorklund et al., 1978; Brown and Goldman, 1977; Brown et al., 1979).

DA was also important in the sequential organization of responses (see Oades, 1985 for a review). Rats depleted of mesocortical DA are impaired in two-choice differential responding (Neil and Hendron, 1978). Cools (1980) found that

rats treated with a DA agonist performed the same unsuccessful, repetitive behavior when trying to escape a stressful situation (e.g., drowning) instead of trying various behavioral sequences as normal rats. From this, Cools suggested that DA helps to determine an individual's flexibility to cope with available sensory information.

The prevalence of NE and DA in prefrontal cortex, their complementary asymmetric distribution (NE greater in the right and DA in the left), and association with "expansive" vs. "restrictive" cognitive modes, suggest that the functions of prefrontal cortex are also lateralized along the lines of "exploratory" vs. "routinized" cognitive biases. NE is critical for orienting to perceptual novelty and the processing of new stimuli/information. It does this by increasing the signal (novel stimuli) and decreasing the attenuation to noise (repetitive stimuli/information). Oades (1985), in reviewing the functional roles of NE and DA in the CNS, concluded that "the noradrenergic system is particularly important for the formation of association and neural plasticity..." (p.261).

There too was evidence in humans suggesting that the right, relative to the left, prefrontal region was differentially involved in the "sustained" or "selective" attention of sensory stimuli. Roland (1982), found that during selective attention to a particular sensation (e.g., auditory, visual or somatosensory), right prefrontal rCBF was

always significantly higher than left prefrontal rCBF. This was especially evident when the subject was simultaneously stimulated with all three stimuli and asked to selectively attend to only one. During this particular paradigm there was an 80% increase in the right prefrontal region. Pardo, Fox and Raichle (1991) found that subjects had a consistent right prefrontal activation on PET, unrelated to laterality of presentation, when asked to sustain their attention to a particular sensory stimuli (visual or somatosensory). Nishizawa, Olsen, Larsen and Lassen (1982), found a non-significant trend for increased right prefrontal rCBF activation when the subject was told to "just listen" to auditorially presented words.[3]

Consistent with the above findings was the work of Mazziotta, Phelps and Halgren (1983). They found that the right, relative to the left frontal region, was more sensitive to the effects of sensory deprivation. As the degree of sensory deprivation became greater (e.g., the subjects went from having both eyes and ears open, to only ears open, to both eyes and ears closed) the decrease in metabolic flow was less in the left, relative to the right, frontal region. There was also a correlation between the degree of metabolism

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[3]Only lateralized prefrontal differences are presented. The authors also found lateralized posterior differences in activation. For example, when words are presented, a significant, lateralized activation of the left temporoparietal region occurs. The same is found for lateralized sensory stimulation and the appropriate posterior sensory regions.

of the cortical area along the anterior-posterior axis and the degree of sensory deprivation. Increased sensory deprivation produced the greatest reduction in the occipital region and the least reduction in the frontal region. The difference in flow reduction was significant between the occipital and frontal regions but not between the frontal and parietal regions. However, closer inspection of the data shows that the frontal reduction was always less than that in the parietal region. It was not apparent if this pattern of anterior-posterior reduction was asymmetric or not.

DA's function in cognitive processes is involved with behavioral response. The data shows that excessive DA decreases the range of response, and increases repetitive behavior. This suggests that one of the main functions of DA is to enhance an already well-established response. DA is also important in the function of the entire hierarchy of responding. Thus, DA's major role is the integration, organization and implementation of a behavioral response (Fuster, 1990; Oades, 1985; Tucker and Williamson, 1984) and the coordination between motor output and perceptual information (Ljungberg and Ungerstedt, 1976).

Hemispheric Specialization In Humans

Most of the evidence reviewed so far was obtained in animal models. Support for the lateralization of the left and right hemispheres along the lines of "routinized" vs.

"exploratory" cognitive bias, in humans, can be found in the hemispheric specialization model proposed by Goldberg and Costa (1981). Goldberg and Costa suggest that the right hemisphere is important in the processing and integration of novel sensory information for which none of the individual's pre-existing cognitive codes or strategies are applicable; or in the novel application of pre-existing codes and strategies. The complementary, left hemisphere is critical for processing information based upon pre-existing representations and well routinized cognitive strategies. The left hemisphere utilizes well established cognitive representations and strategies (on redundant, highly familiar information) that are used for specific classes of materials or tasks.

Support for Goldberg and Costa's (1981) "novelty/ routinization" hypothesis is supported by three lines of evidence: 1) hemispheric specialization studies in normal humans, which can be separated into two types of studies - those comparing task-naive with task-experienced subjects, and quasilongitudinal studies in which normals are presented with a new task having several trials, 2) the effects of early hemispherectomy on subsequent cognitive functioning, and 3) physiological (rCBF and PET) and electrophysiological measures of brain activity in healthy controls, while performing complex cognitive tasks.

Task-Naive vs. Task-Experienced Subjects. According to the theory put forth by Goldberg and Costa (1981) task-experienced subjects have a left hemisphere advantage, and task-naive subjects a right hemisphere advantage, for the task. Task-experienced subjects have a left hemisphere advantage because they have developed well-routinized codes for processing the information (Goldberg and Costa refer to them as descriptive systems). Conversely, since task-naive subjects have not been exposed to the task as long, or as often as the experienced subjects, they have not developed descriptive systems for processing the information. Thus, during lateralized presentation, naive subjects have a right hemisphere advantage.

Using PET, Mazziotta, Phelps, Carson and Kuhl (1982) found that on a test of same/different for sets of tonal pairs musicians showed a focal hypermetabolism in the left temporoparietal region, while nonmusicians had a diffuse right hemisphere increase in metabolism. Bever and Chiarello (1974) and Johnson (1977) reported a left-ear advantage (LEA) for musical discrimination in musical amateurs, but a right-ear advantage (REA) in trained musicians. In the analysis of the study by Gates and Bradshaw (1977) musicians had a consistent REA, and nonmusicians a LEA, for both familiar and non-familiar melodies. This finding was much stronger in males than females. This would be consistent with the findings that females were less lateralized than males (see McGlone, 1980).

The same pattern of findings was found for individuals familiar with vs. not familiar with Morse Code (Papcun, Krashen, Terbeek, Remington and Harshman, 1974). Also consistent with the above findings was a case study that found musical deficits in a musician following a left hemisphere stroke (Wertheim and Botez, 1961).

Another example of task-naive vs. task-experienced differences was when subjects were experimentally familiarized with the information or the information was well-known to them. When subjects viewed a set of unfamiliar faces before tachistoscopic presentation a left hemisphere advantage for discriminative reaction time appeared. In contrast, when a set of subjects were not allowed to preview the same set of unfamiliar faces a right hemisphere advantage appeared (Marzi, Brizzolara, Rizzolatti, Umilta and Berlucchi, 1974; Umilta, Brizzolara, Tabossi and Fairweather, 1985). Subjects with high spatial abilities had a left hemisphere advantage for tachistoscopically presented mental rotation tasks. Those with poorer spatial abilities had a right hemisphere advantage (Voyer and Bryden, 1990; Fischer and Pellegrino, 1988).

Right-to-Left Shift of Hemispheric Advantage. When learning a new task, or processing information in a novel way, Goldberg and Costa (1981) predicted that the initial acquisition was preferentially performed by the right hemisphere. Exposure to the stimuli over a certain amount of time, or repeated exposure to it, caused the formation of

descriptive codes, which the left hemisphere was best at processing.

This right-to-left shift of hemispheric advantage existed for both non-verbal stimuli, and in the novel processing of verbally based information. Although the extent of the effect varies - possibly because of differences between and within the experimental paradigms and differences in measurement, a consistent pattern does exist supporting the right-to-left hemispheral shift for non-verbal material (Gordon and Carmon, 1976; Holtzman, 1978; Reynolds and Jeeves, 1978; Kittler, Turkewitz and Goldberg, 1989; Ross and Turkewitz, 1982; Ross-Kossak and Turkewitz, 1984), as well as the processing of verbal material based on novel instruction (Holtzman, 1978; Hellige, 1976; Miller and Butler, 1980).

Early Hemispherectomy and Its Effects On Subsequent Learning. If the right hemisphere is best at intermodal information processing, and the left hemisphere is best at modality specific processing, then one could predict that the loss of either hemisphere at an early age would have differential effects on the subsequent development of different cognitive processes. Since, according to Goldberg and Costa, the right hemisphere is involved in the initial learning of information, early right hemisphere damage would impair all subsequent learning. Conversely, early left hemisphere damage would not impair initial learning. It would however, impair the individual's ability to process the

material in a quick and efficient manner. If an analogy would be useful, the right hemisphere is considered the jack of all trades and the master of none, while the left hemisphere is the master of a few specialized trades. Without the right hemisphere, the left hemisphere is unable to master any more trades, or masters them incorrectly with great difficulty. This suggests that during development severe left hemisphere damage or decortication would have less effect on subsequent learning and development then if the right hemisphere was involved.

According to Goldberg and Costa (1981) the right hemisphere is better at subserving the functions of both hemispheres. Since the right hemisphere is capable of multimodal processing, it is more flexible in the types of tasks it can perform. The left hemisphere, on the other hand, is much more rigid in the type of information it can process, and can not process information that has not developed into the proper format (i.e., fixed representations).

The differences between the two hemispheres is that the right hemisphere can process functions normally associated with the left hemisphere, albeit, not as efficiently. The left hemisphere is highly specialized in its type of information processing. Because it only uses highly specialized and refined descriptive systems, it can only process specific types of information.

Relative to each other, early right hemisphere damage is more detrimental to the subsequent learning of both verbal and non-verbal skills than left hemisphere damage. When compared to each other, groups with early left and right hemisphere damage have equivalent language development, but the early right hemisphere damage group has significantly worse non-verbal skills (Kohn and Dennis, 1974; Milner, 1974; Rasmussen and Miller, 1977).

The findings by Smith (1976) strengthen the notion that the right hemisphere is better at subserving the functions of both hemispheres. Either left or right hemispherectomy decreases Full Scale IQ (FIQ). However, the decrease in FIQ is greater in the right, compared to the left, hemispherectomy group. Although not significantly different, Kohn and Dennis (1974) find the same trend in a small group of early hemidecorticates. This indicates that if needed, the right hemisphere can process various types of information, while the left hemisphere is much more restricted in the types of information it can process.

Physiological and electrophysiological measures of lateralized PFC functioning

In addition to the evidence cited above, there were recent physiological studies consistent with the theory proposed by Goldberg and Costa (1981). A lateralized increase in the "activation" (e.g., PET or rCBF) of the superior, left

prefrontal region occurred when subjects performed a task based upon prior instructions (Larsen, Skinhoj and Lassen, 1978; Roland, 1984; Roland and Larsen, 1976; Roland, Meyer, Shibasaki, Yamamoto and Thompson, 1982; Roland and Skinhoj, 1981; Roland, Skinhoj and Lassen, 1981; Roland, Skinhoj, Lassen, and Larsen, 1980). Paralleling the work of Roland and his colleagues was more recent electrophysiological work done by Gevins and his colleagues (Gevins, 1990; Gevins, Cutillo, Bressler, Morgan, White, Illes, and Greer, 1989; Gevins, Morgan, Bressler, Cutillo, White, Illes, Greer, Doyle, and Zeitlin, 1987). Gevins and his colleagues found a consistently lateralized, left frontal "preparatory set" using sophisticated EEG measurement and analyses. Subjects were given verbal instructions and ample practice on a visuomotor task. Between the presentation of a stimulus (a slanted line presented on a computer screen) and the response of the subject (pressing a switch with either the left or right index finger) a consistent and focal activation of the left dorsolateral PFC region was consistently present regardless of which hand was used to respond.

Processing based upon a prior instruction, or a "preparatory set", implies a type of stable, routinized, cognitive process, which was what Goldberg and Costa and (1981) Tucker and Williamson (1984) predicted for the left hemisphere. Conversely, when subjects "just listened" or focused and sustained their attention on the sensation

(stimuli) a lateralized right prefrontal activation occurred on both PET (Pardo et al., 1991) and rCBF (Nishizawa et al., 1982). "Just listening" implied no prior "preparatory set" or internalized strategy - just attention to the external world/environment. Again, this was what Goldberg and Costa and Tucker and Williamson predicted.

Three additional features were found in the above studies. First, the selective activation of either the left or right prefrontal region was dependent upon what was asked of the subject - follow internalized instructions, or attend to sensory stimuli without any instructions. Second, whether the material was verbally based, or the left or right hand was used in responding, was <u>not</u> a factor in determining the laterality of activation. Thirdly, the degree of focality of activation was different between the two hemispheres. Roland and his colleagues typically found a much more focal activation in the left hemisphere (which appeared to be the superior portion of Brodmann Area 10 and/or inferior portion of area 9). Pardo et al., (1991) and Mazziotta et al., (1982) found a more diffuse activation in the right prefrontal region. Pardo et al., described it as, ". . . a variable coronal band of activity along the right dorsolateral convexity, corresponding to Brodmann areas 8, 9, 44, 46 (with concentration in area 9 . . .)" (p.63). It was interesting to note that Brodmann area 9 apparently was a crucial area for activation within the prefrontal region. The relative

difference in the focality of activation between the two hemispheres was consistent with the anatomical findings of Gur et al., (1980) and the predictions of Semmes, (1968).

Goldberg and Costa (1981) do not address how their model is expressed along the anterior-posterior axis of cortical functioning. To that end, the biochemical findings in animal models are applicable to prefrontal functioning. Considering the functional role and asymmetric distribution and prevalence of DA and NE within the prefrontal cortex, the physiological and electrophysiological studies, along with Goldberg and Costa's model of hemispheric specialization, it is proposed that the functions of the prefrontal cortex are lateralized in the following fashion: The right prefrontal cortex is critical in exploratory, plastic behaviors and responding to changing environmental contingencies, while the left prefrontal cortex is critical for redundant, stable behaviors and guiding behaviors by internal representations.

Functions of the prefrontal cortex

Before designing any test to assess the functional asymmetry of the prefrontal cortex, one needs to consider normal prefrontal functions, their disintegration, and how the two relate to the proposed exploratory vs. redundant distinction. The prefrontal cortex is vested with a special class of superordinate functions collectively called "executive control functions" (Luria, 1966/1980; Stuss and

Benson, 1984, 1986). Among these are functions ensuring: (1) stability of cognitive operations and the ability to maintain a cognitive set, and (2) plasticity of cognitive operations and the ability to shift cognitive sets (Luria, 1966/1980; see Stuss and Benson, 1986 for a review). The prefrontal cortex mediates both types of cognitive processes (Luria, 1966/1980) and serves to maintain proper equilibrium between the two. Accordingly then, two types of cognitive deficits are commonly found following prefrontal dysfunction: perseveration and stereotypies (Goldberg and Tucker, 1979; Luria, 1966/1980; Sandson and Albert, 1987) and field-dependent and echo-behaviors (Goldberg and Costa, 1985; Lhermitte, 1983; Lhermitte, Pillion and Sraru, 1985; Luria, 1966/1980).

Perseverations are defined as the inability to switch from a previous response, or the incorporation of a previously correct response into the present response (Goldberg and Bilder, 1987; Goldberg and Costa, 1985; Goldberg and Tucker, 1979; Luria, 1966/1980). Stereotypies, the inability to break a response pattern, are an extreme form of perseveration. Both can be considered secondary to exaggerated stability, or insufficient plasticity

Field-dependent behaviors are described as an inability to follow an internal cognitive set, distractibility from environmental stimuli, or the incorporation of irrelevant or conflicting stimuli into the current response (Goldberg and Costa, 1985; Lhermitte, 1983; Lhermitte et al., 1985; Luria,

1966/1980). Echo behaviors (e.g., echopraxia and echolalia) are extreme forms of field-dependent behavior. Both can be considered secondary to over-plasticity or insufficient stability.

The maintenance of cognitive stability and plasticity are complementary functions within the prefrontal cortex. Normal executive control functions are dependent upon the proper balance of the two. According to the findings stated above, it is predicted that the left prefrontal lobe is responsible for the stability of cognitive operations - the ability to maintain cognitive sets. The right prefrontal cortex is then responsible for the plasticity of cognitive operations - the ability to shift cognitive sets.

A deficit in one hemisphere (e.g., lesion) allows the other to function in an "unchecked" manner. The lesioning of one hemisphere disinhibits contralateral hemispheric functions (Denenberg, 1981; Sackheim, Greenberg, Weiman, Gur, Hungerbuhler and Geschwind, 1982). Specifically, I predict that a left prefrontal lesion allows the right prefrontal cortex to function "unchecked", leading to overly plastic, external, stimulus-driven behavior. This is hypothesized to lead to field-dependent behavior, and in extreme cases to echo-behaviors. Conversely, damage to the right prefrontal cortex allows the left prefrontal cortex to function "unchecked". I predict that this leads to overly stable, rigid behavior, which does not properly switch in response to

changes in the environment or instructions. This type of behavior is typically referred to as perseveration, and is probably the hallmark deficit associated with damage to the prefrontal cortex (Luria, 1966/1980; Stuss and Benson, 1986).

Neuropsychological Studies

Earlier studies driven by the traditional language vs. visuo-spatial distinction of hemispheric specialization provided direct evidence for a functional dissociation between the left and right prefrontal cortex. The most striking differences were found on "generation" tasks. Subjects were given specific rules to generate as many different responses as possible. Performance by subjects with lateralized left and right prefrontal lesions was impaired relative to normal controls in both the verbal and nonverbal generation tasks. The left prefrontal lesion group was more impaired than the right prefrontal lesion group on the verbal generation tasks (Hecaen and Ruel, 1981; Milner, 1964; Perret, 1974), while the right prefrontal lesion group was more impaired on nonverbal generation tasks (Glosser and Goodglass, 1990; Jones-Gottman and Milner, 1977).

There have been a few studies that lend more direct support to the lateralization of the stability/plasticity dimension within the prefrontal cortex. Two such studies involved the administration of the Wisconsin Card Sorting Test (WCST) to subjects with lateralized frontal lesions. Drewe

(1974) found that although both the left and right prefrontal lesion groups were inferior to normals on the number of categories sorted, the right prefrontal lesion group made more perseverative errors (median score), while the left prefrontal lesion group made more non-perseverative errors. Similarly, Robinson, Heaton, Lehman, and Stilson (1980) found that even though the left and right frontal groups were equated on the Halstead-Reitan Average Impairment Rating, the right frontal group made more perseverative responses. This was predicted by the stability/ plasticity model. The right frontal lesion group (intact left frontal cortex) was overly stable. They were unable to switch their pattern of responding when the feedback changed, hence perseverative responding. The left prefrontal lesion group (intact right prefrontal cortex) was overly plastic. They were unable to properly form and maintain the correct pattern of response - they kept switching between the different possible categories.

Also consistent with the stability/plasticity model of prefrontal functioning were the findings by Milner and Petrides (Milner, 1982; Milner and Petrides, 1984; Petrides and Milner, 1982). Through a series of recency memory tests and "subject ordering" tasks given to subjects with lateralized frontal lesions, they concluded that the left prefrontal cortex was important for "programming" internally ordered events, while the right prefrontal cortex was important for programming externally ordered events regardless

of the nature of the stimulus (verbal or nonverbal). In fact, in a review of frontal lobe functioning, McCarthy and Warrington (1990) determined that, "...failure on those tasks which require internal generation of strategies and/or control of motor-executive functions shows a greater tendency to be associated with damage to the left frontal lobe rather than the right." (p.356). The authors also concluded that very few tasks are strictly sensitive to unilateral right frontal lobe lesions.

The overwhelming majority of neuropsychological studies of the functional asymmetries within the prefrontal cortex were based on the traditional verbal/nonverbal distinction. They were uninformed of more current research and theories of hemispheric specialization. As stated earlier, current theories of hemispheric specialization indicated that the lateralized functions of the prefrontal cortex were likely to go beyond a verbal/nonverbal distinction. By considering more recent findings and theories pertaining to hemispheric specialization (e.g., Goldberg and Costa, 1981; Tucker and Williamson, 1984) this project was designed to study the expression of these more fundamental principles of hemispheric specialization within the prefrontal cortex.

In the current experiment the stability/plasticity model of prefrontal function will be directly tested in samples of patients with well lateralized left or right prefrontal lesions and their matched, healthy controls. It is

hypothesized that the left and right prefrontal lesion groups will significantly differ from each other and from their matched, healthy controls on the measures of stability/plasticity. In addition, the left prefrontal lesion group's performance will be characterized by overly plastic performance - inability to follow a consistent internalized strategy, while the right prefrontal lesion group's performance will be characterized by overly stable performance - rigidly following an internalized strategy.

METHODS

Subjects

Two types of populations were studied: (1) Subjects with lateralized, structural PFC lesions and (2) Healthy controls. Both males and females were used in each group. A subset of the healthy control group was matched to the lesion subjects according to age, sex and level of formal education. All lesioned subjects had well lateralized, CT or MRI verified, frontal lesions. The lesion area included at least damage anterior to the premotor region, while the total area of damage was confined to an area anterior to central sulcus. All subjects were between the ages of 18-65, inclusive, and completely right-handed without any evidence of first degree, familial left-handedness (based on part of handedness questionnaire). Personal and familial handedness was determined by a questionnaire developed after Briggs and Nebes (1975). A score greater than 40 (out of a possible 48) on the personal handedness section was considered completely right-handed. See Appendix 1 for a complete description of the handedness questionnaire. All subjects were without histories of drug and alcohol abuse based on DSM-III-R (1987) criteria.

Additional exclusion criteria for normal subjects were: history of psychiatric hospitalization or treatment, history of loss of consciousness, or any CNS disorder. None of the

lesion subjects had psychiatric histories predating the condition that produced the lateralized lesion. Lesion subjects were excluded if there was a history of loss of consciousness related to a previous injury, or a history of an additional CNS disorder.

All lesion subjects had demonstrable lesions (verified by CT or MRI). The definition of a lesion was the excision of, or destruction of parenchymal tissue. This excluded individuals with space occupying masses, such as intact tumors. Only lesioned subjects with adult onset diseases or injuries were included. For example, subjects with resected arteriovenous malformations, or lobectomies due to refractory infantile seizure disorders, were excluded. Table 1 shows lesion etiology broken down by lesion site and sex.

Table 1

Lesion Etiology By Group

		Lesion Etiology		
Group	n	Tumor Excision	Cerebro-Vascular	Post-traumatic Excision
Males				
Left Frontal	5	3	0	2
Right Frontal	5	3	1	1

continued

Table 1 (continued)
Lesion Etiology By Group

		Lesion Etiology		
Group	n	Tumor Excision	Cerebro-Vascular	Post-traumatic Excision
Females				
Left Frontal	5	1	4	0
Right Frontal	5	5	0	0
Totals	20	12	5	3

All lesion subjects, except for one, were tested no sooner than three months after the injury or surgery that produced the lateralized frontal lesion. There was no post-injury time limit for testing. The one exception was a male with a left frontal lesion tested 2 months and two weeks after a left frontal lobectomy for a large neoplasm. The patient was being discharged from a local rehabilitation hospital and moving to an area that would have made testing impractical at a later time. The range of time between onset of lesion and testing was 2.5 months to 8 years and 11.5 months.

There was one other criterion for the lesion subjects. They had to perform above predetermined cutoff scores on various neuropsychological tests before being given the experimental tasks. The cutoff values and rationale for using these tests are described below in the procedure section. One

lesion subject (left frontal female) was excluded from the study for failing to reach the predetermined cutoffs.

If electrophysiological (e.g., EEG or Brain Mapping) and/or metabolic/blood flow studies (SPECT, PET or rCBF) were available, they were used to determine if there were other areas (in particular, the non-lesioned hemisphere) of "focal" dysfunction. For example, if a subject had a focal, left frontal lesion and an electrophysiological or physiological study indicated focal, right frontal abnormality, or vica versa, then the patient was considered bilateral, and dropped from the study. If, however, the electrophysiological or metabolic/blood flow data was consistent with the side of lesion, or indicated diffuse, non-focal dysfunction, the subject was included. It should be noted that electrophysiological or physiological data were not available on all subjects.

Procedures

Subject Selection. A total of 22 lesioned subjects (males=11 and females = 11) were selected based upon CT or MRI findings. One male subject with a left frontal lesion was dropped from the study because of focal, right frontal abnormalities on EEG and Brain Map studies, and one female left frontal subject was dropped because she was unable to reach the cutoff values on standard neuropsychological tests (described below). Sixteen of the 20 lesioned subjects tested

and analyzed were outpatients (males=7, females=9) and 4 were inpatients (males=3, females=1).

All the CT or MRI films were analyzed by a senior neurologist familiar with the study, but not with the lesioned subjects, and by a neuroradiologist completely blind to both the study and subjects. Both were asked to verify three findings: the extent of the lesion, that the lesions were well lateralized, and that the prefrontal/frontal cortex was the only region lesioned. There was complete agreement between the neurologist and neuroradiologist.

Lesion analysis of all the CTs or MRIs was performed to determine which prefrontal regions were involved. The method used was that of Damasio and Damasio (1989). Each individual CT or MRI was matched by the senior neurologist to one of six standard templates. Using an X/Y plotting method, the lesions were transferred onto the templates. Using overlays, the different regions involved in the lesions could be determined. Table 2 shows the different prefrontal regions involved in all of the subjects.

Table 2
Localization of Lesions Using Brodmann's Area Classification

Group	Lesioned Brodmann's Area	Group	Lesioned Brodmann's Area
	Males		
Right Frontal		Left Frontal	
RFM1	6 8 9 10 12 24 32 44 45 46[a]	LFM1	6 8 10 11 24 32 44 45 46
RFM2	4 6 10 22 44 45 47[b]	LFM2	9 10 12 32 45 46
RFM3	6 8 9 24 32 44 45 46[a]	LFM3	9 10 12 24 32 44 45 46
RFM4	8	LFM4	10 11 45
RFM5	9 24 32 45 46[c]	LFM5	films unavailable[d]
	Females		
Right Frontal		Left Frontal	
RFF1	8 9 46	LFF1	6 9 44 45 46
RFF2	10 11 12[e]	LFF2	4 6 8 9 24 32
RFF3	9 10 24 25 32 45 46[f]	LFF3	4 6 9 44 46[b]
RFF4	6 8	LFF4	4 6 8 9 10 12 24 32 44 45 46[b]
RFF5	6 8 9 44 45 46	LFF5	6 8 9 10 12 32 44 45 46

Note: [a]minimal damage to Brodmann's area 8 on the left side
[b]minimal damage to Brodmann's area 22 on the same side
[c]minimal damage to Brodmann's area 24 on the left side
[d]CT report states a large area of encephalomalacia in the left frontal region without any other damage to the brain
[e]minimal damage to Brodmann's area 11 on the left side
[f]minimal damage to Brodmann's area 9 on the left side

If an individual met the criteria outlined above for normal subjects they were included. Since original, newly, developed, experimental tasks were used, psychometric properties of the task needed to be tested. Therefore, a large normal sample was tested. To better control for confounding variables, a subset of the normal population was matched to the lesioned subjects based upon age, sex and handedness. By controlling possible differences in cognitive functioning due to age, gender and education it was easier to looking at the effect lateralized lesion on test performance, rather than a combination of lesion effect and various confounding factors.

Test Material. Two types of paper-and-pencil tests are used: Standard neuropsychological tests (Wechsler Adult Intelligence Scale - Revised [1981], Raven's Standard Progressive Matrices [1958]) and a personality questionnaire - Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975) - and two newly developed experimental tasks - The Stability/Plasticity Tests 1 & 2 (SP1 and SP2). The Wechsler Adult Intelligence Scale - Revised (WAIS-R) is the most commonly used measure of general intellectual abilities. It yields a general IQ score which, is a composite of Verbal and Performance IQs. The Raven's Standard Progressive Matrices (RSPM) is a non-verbal problem solving test, which is also highly correlated with general intellectual functioning.

The WAIS-R was administered to control for general intellectual functioning. Lesioned subjects, depending upon the side of lesion, needed to obtain a VIQ or PIQ of at least 75. Subjects with left frontal lesions needed to obtain a PIQ of at least 75, while right frontal lesion subjects needed to obtain a VIQ of at least 75. This criterion determined if subjects were cognitively impaired in a global sense.

The RSPM was used to determine that subjects were not randomly responding on a multiple choice like test. Subjects needed to score above chance level to be included. Since the RSPM has a similar administration format (a target stimulus with multiple choice items below it) as SP1 and SP2 (see below), non-random performance on RSPM was deemed a sufficient indicator that performance on SP1 and SP2 was not secondary to purely random performance.

SP1 and SP2 measure the subject's bias toward cognitive stability or plasticity, based on their multiple-choice strategies over successive trials. Each stimulus is a geometric design characterized along five, binary dimensions: color (blue or orange), shape (circle or square), number (one or two), size (large - one inch, or small - 1/2 inch), and shading (outlined or filled). Thus, there are 32 different stimuli. Any two stimuli can be compared, and a "distance" between them numerically expressed: it may vary between 0 (for two identical stimuli) and 5 (for two stimuli different along all 5 dimensions).

On any given trial, a subject was presented first with a target card for approximately two seconds, then two vertically aligned choice cards were placed below it.[3] After looking at the target card the subject chose one of the two choice cards they liked the best. In comparing the dimensional differences between the target card and the two choice cards, one choice card was more similar (yielding a lower score), while the other was more different (yielding a higher score). Since there was no correct or incorrect response, the subject's bias, rather than an absolute performance, along the stability/plasticity continuum, was measured. The distance (0 - 5) between the target card and the subject's choice was summed across trials (SP1 had 60 trials and SP2 had 64 trials). Trials were arranged so that no two consecutive trials had the same possible pairs of dimensional differences.

SP1 and SP2 differed in their administration - SP1 was stochastic and SP2 was markovian. SP1 was a set of independent trials. A subject's response on trial i did not influence the possible choices for trial i+1. In SP2 the trials were "interlocked". On any given trial there were two sets of possible pairwise choices. The one employed was determined by the subject's response on the previous trial. It was felt that interlocking the trials might influence the

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[3]The choice cards have been vertically aligned under the target card to try and minimize any possible neglect caused by a field-cut or hemi-inattention.

subject's responding. By having the previous trial's response serve as the next trials target card, the subject may be preferentially biased towards a greater degree of target dependent responding.

The subject's range of responses were broadly categorized into three types: 1) consistently choosing the more similar choice, 2) consistently choosing the more different choice, or 3) inconsistently choosing the more similar and different choice. Consistently choosing similar or different throughout the entire test implies that the subject was performing in a stable fashion - being target dependent. The subject took into account the target's dimensional properties, compared them to those of the two choice cards, and then consistently applied the same strategy, i.e., choose the more similar or different choice card. In order to have this reflected in the dependent measure, all of the scores above the midpoint of SP1 and SP2 were converted to equivalent scores below the midpoint. In other words, the scale was folded in half at the midpoint - at 150 for SP1 and 163.5 for SP2. For example, on SP1 if a subject scored a 180 it was converted to 120.

Inconsistently choosing the more similar and different choice card was considered plastic responding. The subject's choice was either target independent, or, the subject did not consistently apply the same strategy. Responding in a target independent fashion implied that the subject only attended to the two choice cards. The subject disregarded the target

card, and may have only attended to a single salient perceptual feature (i.e., color or shape), or developed a novel strategy of responding. The other possibility was that the subject inconsistently chose between the more similar and different choices. Either method of responding produced a mid-range score.

Whether plastic behavior (mid-range score) reflected a distinct cognitive strategy, or was due to a pure aesthetic preference for a particular dimensional aspect, was not determined. However, it was apparent that a mid-range score indicated that the subject was performing in a target independent fashion - their choice was not based upon a comparison with the target card. It appeared that subject's who performed in a target independent fashion disregarded he target card a chose one of the choice cards based upon a bias for a particular dimensional property. In fact, choosing based on a purely aesthetic preference for a particular dimensional feature was still consistent with the hypothesis that plasticity refers to novel processing or attraction to perceptual novelty. See appendix 2 for a further detailed description of SP1 and SP2.

The printed instructions were placed in front of the subject and read to them. The instructions for SP1 were:

> You will see cards that have different designs on them. The designs may vary in several respects. You will see

one card at the top and two cards below it. Look at the top card, then choose one of the two cards below it that you **like the best.** There are no 'correct' or 'incorrect' responses. Your choice is entirely up to you. ' Please try to make your choices rather quickly. Do you have any questions?

The instructions for SP2 were:

You will see cards that have different designs on them. For the first trial choose one of the two cards you like the best. That card will be placed at the top and then two new cards will be placed below it. Look at the top card, then choose one of the two cards below it that you **like the best.** There are no 'correct' or 'incorrect' responses. Your choice is entirely up to you. Please try to make your choices rather quickly. Do you have any questions?

Order of Administration. All subjects gave signed consent before participation. Next, the Briggs and Nebes's Handedness Questionnaire was administered. Lesioned subjects were then given the WAIS-R, followed by the RSPM. Normal subjects were not administered the WAIS-R and RSPM. Next SP1 and SP2 were administered, in this order, to both the lesioned and normal subjects. For lesioned subjects, testing was

completed within four hours. There was a 10-15 minute break between the administration of the standard neuropsychological tests and the experimental tasks. Normal and lesioned subjects took approximately 30-35 minutes to complete SP1 and SP2. After completing SP1 and SP2, healthy controls were given the Eysenck Personality Questionnaire (EPQ) to complete, which took approximately 10-15 minutes.

Results

The results section is divided into three parts. The first section presents the psychometric properties of SP1 and SP2, where correlations with basic demographic variables (i.e., age and educational level), test/re-test reliability, convergent validity between the two tasks, correlations with the Extroversion scale from the Esyenck Personality Questionnaire (EPQ), and the scaling properties of SP1 and SP2 will be presented. The second section presents gender differences in healthy controls on SP1 and SP2. In the third section, two sets of comparisons will be made: between the four lesion groups, and each lesion group compared to their matched healthy control group. Two healthy subjects were matched to each lesion subject using sex, age, and education[4]. Comparisons between left and right frontal lesion groups, within gender, will also be presented.

All statistical analyses were conducted using the SPSS/PC+ statistical software package (Norusis, 1986). All significance levels used two-tail probabilities.

Psychometric Properties of SP1 and SP2

Some basic psychometric properties of SP1 and SP2 are presented, since they are newly developed tests. From a group

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[4]There is one exception. In the left frontal female group one subject was matched with three healthy controls. The three healthy controls all had the exact same age and education levels. Instead of randomly discarding one of the healthy subjects all three were included.

of 37 healthy controls, 34 (17 males and 17 females) are group matched on age and education level. Three healthy subjects (two 60 year old females with less than 10 years of formal education and one 20 year old male with 15 years of formal education) were discarded to give a better match. It is from this sample of 34 healthy controls that subgroups are used to determine the various psychometric properties of SP1 and SP2.

Test/re-test reliability for 15 subjects (7 males and 8 females) revealed a correlation of $r=0.88$ ($p<.01$) on SP1, and $r=0.73$ ($p<.01$) on SP2. When separated by sex, a difference between males and females in test/re-test reliability emerged. For males, test/re-test correlations for SP1 and SP2 were $r=0.97$ and 0.98, respectively ($p<.01$). However, in females, the correlations were not as high - $r=0.65$ and 0.20 for SP1 and SP2, respectively ($p>.05$). The sex difference in the correlations was significant for both SP1 ($Z=1.97$, $p<.05$), and SP2 ($Z=3.13$, $p<.01$).

A binomial distribution was calculated to determine if there was any systematic change between the first and second administrations of both SP1 and SP2 (i.e., subject scores for the second administration of SP1 and SP2 were consistently higher or lower than the first administration). The change in score (delta) between the first and second administration was converted into a binary score - 0 if the change was negative, and 1 if the change was positive. Using a probability of 0.5, no systematic change from the first to

second administration (separate two-tail, binomial distributions for SP1 and SP2) was found ($p>.50$ for both SP1 and SP2).

Table 3 displays the correlations between performance on SP1 and SP2 and the variables age and education for the healthy control group, and the healthy controls separated by sex. The only significant product moment correlations were a negative correlation for the healthy control group between SP2 and education, and for the females only between SP2 and age.

Table 3

Correlations Between SP1 and SP2 With Age and Education In Healthy Subjects

		SP1		SP2	
Group	n	Age	Education	Age	Education
Males	17	.24	-.36	.07	-.32
Females	17	-.34	.12	-.77**	-.30
Males and Females	34	.01	-.24	-.27	-.34*

Note. Values are product moment correlations
*p<.05 **p<.01 (two-tailed)

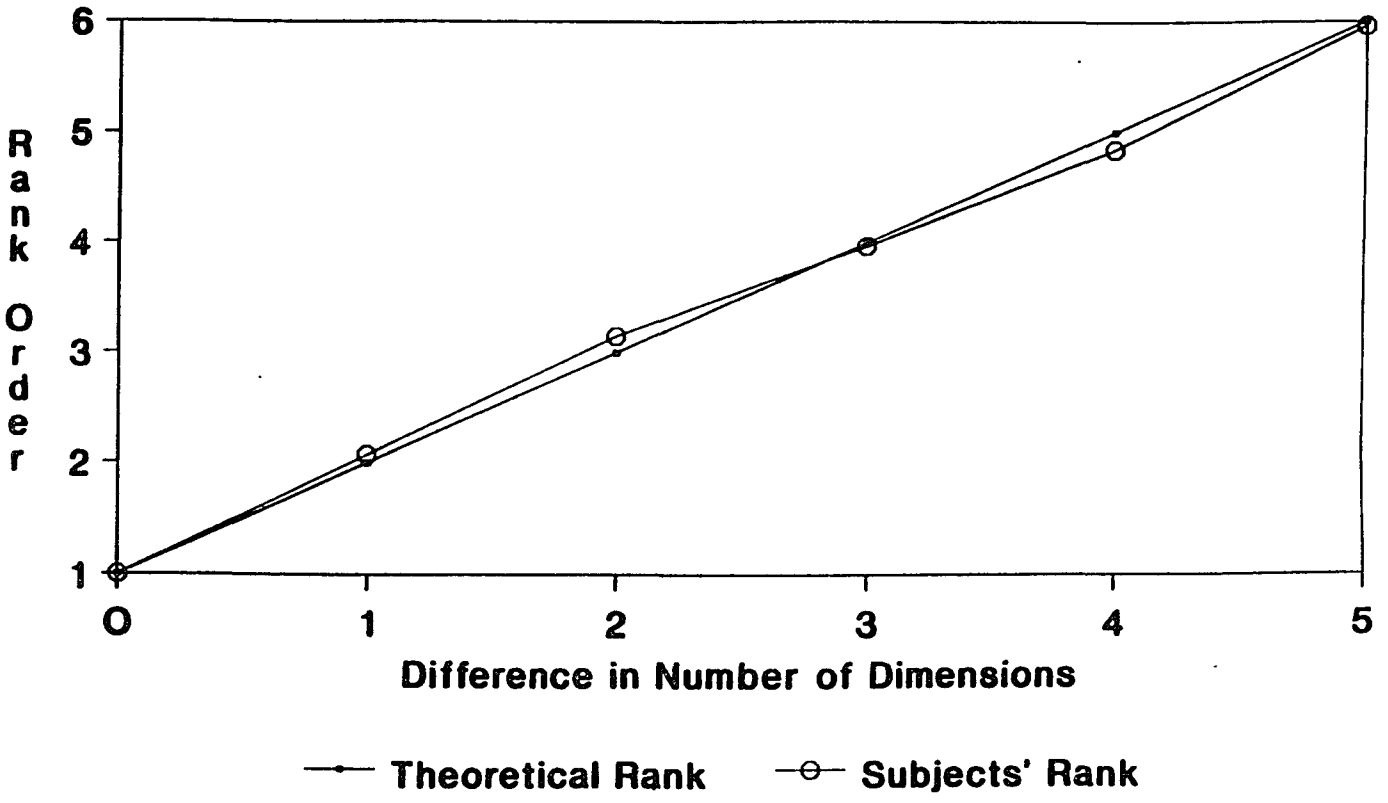
Since SP1 and SP2 were designed to tap into the same fundamental processes, but through different methods of administration, the correlation between the two served as a form of construct validity. The correlation between SP1 and SP2 was $r=0.66$ ($p<.01$), for females alone $r=0.51$ ($p<.05$), and for males alone $r=0.62$ ($p<.02$). The difference in the male and female's correlations was not significant ($Z=0.43$, $p>.10$).

As a way of looking at convergent validity, SP1 and SP2 were correlated with the Extroversion Scale (E) from the EPQ. Twenty-nine (16 females and 13 males) of the healthy control subjects completed the EPQ. The correlation between SP1 and the E scale approached significance ($r=0.33$, $p<.10$), while the correlation between SP2 and the E scale was significant ($r=0.42$, $p<.05$). When the sample was separated by sex, a difference between the correlations emerged. Significant correlations were found in the males between SP1 and SP2 with the E scale (for SP1 $r=0.73$, $p<.01$; for SP2 $r=0.79$, $p<.01$). For females, the correlations between SP1 and SP2 and the E scale were nonsignificant (for SP1 $r=-0.16$, $p>.50$; for SP2 $r=0.05$, $p>.50$). The differences in the correlations (SP1 and SP2 with E scale) between males and females were both significant - for SP1 $Z=5.48$ ($p<.01$), and for SP2 $Z=7.28$ ($p<.01$). This suggested that the construct validity of stability/plasticity was not found for females, but was present in males.

An important aspect of SP1 and SP2 which needed to be determined was whether the range of dimensional differences (0-5) represented a true interval scale. Were subjects able to determine the degree of dimensional differences between stimulus cards? To determine this a group of six judges (3 males and 3 females) were asked to arrange six stimulus cards in order of their dimensional difference(s) to a target card. In any given trial, a subject was presented with a target card placed in front of them. They were then given six stimulus cards (randomly ordered) that differed in dimensions (from the target) from 0-5. The subject was asked to place the six cards in decreasing order of similarity to the target card. Thus, the subject had to take the six stimulus cards and try to arrange them in the proper order of dimensional differences (0-5) from the target card. There were 32 trials (each possible design was used as a target). All dimensions were equally represented and counter-balanced across trials.

The subject's rank order of the stimulus cards served as the dependent measure. For example, if the subject correctly ordered the set of stimulus cards for a particular trial their rank order was 0,1,2,3,4,5. If the subject made one mistake (e.g., he/she placed the stimulus card that differed by three dimensional properties before the stimulus card that differed by two dimensional properties), then their score was 0,1,3,2,4,5. Figure 1 presents the mean rank order for all of the trials (a total of 192 - 32 trials for 6 subjects)

Fig. 1. RANK ORDERING OF DIMENSIONAL DIFFERENCES IN HEALTHY SUBJECTS



Note: n=6 (males=3; females=3)
Kendall's Concordance (W)=0.94
chi-square=906.38, p<.001

plotted against the theoretical rank order. The mean rank order was submitted to a Kendall's Concordance Correlation (W) and a chi-square distribution. This determined if the subjects' actual rankings were consistent, and if the mean ranks were significantly independent of each other. The correlation was very high (W=0.94) and the mean rank values significantly differed from one another (chi-square=906.38, p<.001).

Gender Differences in Healthy Controls

Table 4 presents the mean and standard deviation for age, education, and handedness score for the lesion groups, their matched healthy controls, and the healthy controls used in looking at gender differences in healthy subjects. It shows that healthy males and females were well matched on age, education and handedness. Significant gender differences were found on both SP1 (t=3.56, p<.001) and SP2 (t=3.06, p<.01).

Table 4
Demographic Variables For Lesion Groups, Their Matched Healthy Control Subjects, and Healthy Subjects

Group	n	Age	Education	Handedness[a]
			Males	
Left Frontal				
Lesion	5	42.0(9.2)	15.2(2.3)	48.0(0.0)
Matched Controls	10	43.8(8.6)	15.1(2.2)	47.1(1.9)

continued

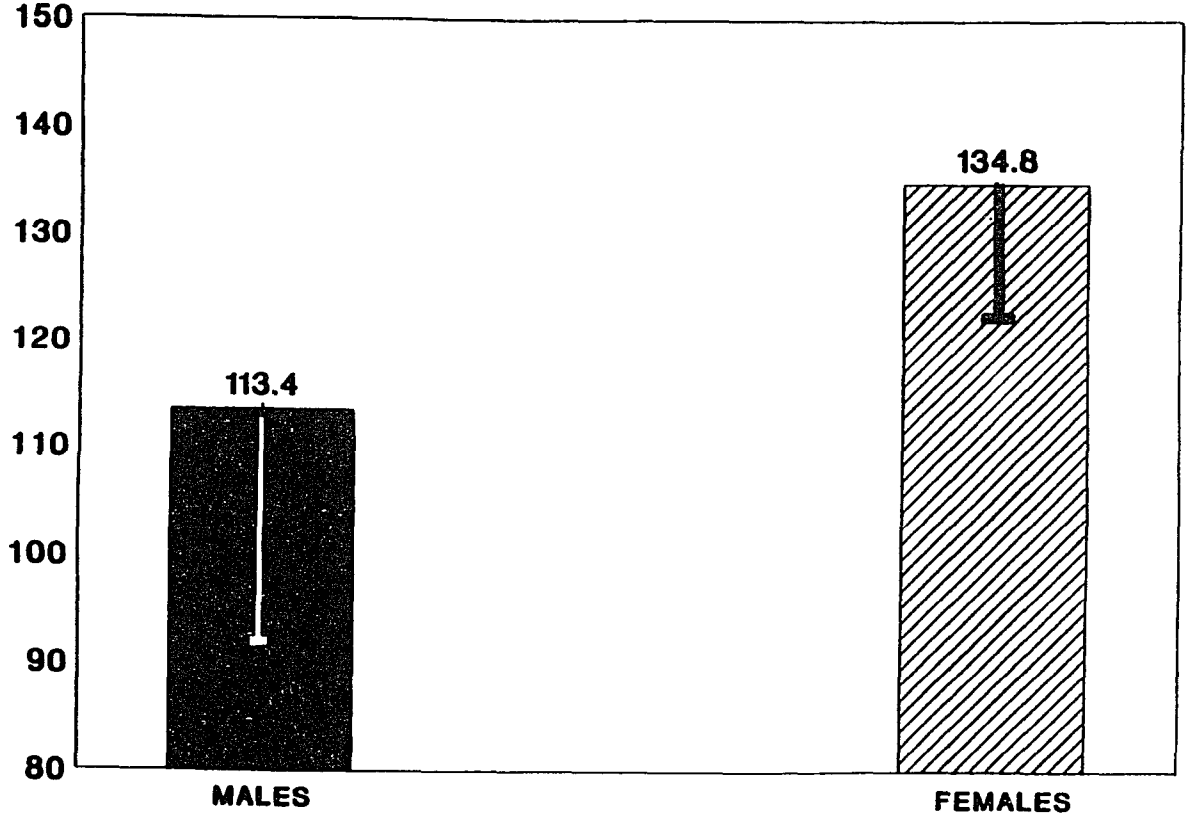
Table 4 (continued)
Demographic Variables For Lesion Groups, Their Matched Healthy Control Subjects, and Healthy Subjects

Group	n	Age	Education	Handedness[a]
Right Frontal Lesion	5	36.6(10.4)	13.2(2.7)	45.6(3.1)
Matched Controls	10	36.5(6.4)	13.4(2.0)	47.5(1.3)
Healthy Subjects	17	38.0(10.1)	15.1(2.4)	47.4(1.5)
			Females	
Left Frontal				
Lesion	5	40.4(15.4)	14.4(2.3)	45.4(2.9)
Matched Controls	11	39.5(13.5)	14.3(2.2)	47.6(1.2)
Right Frontal				
Lesion	5	33.6(11.5)	12.6(0.9)	46.0(2.8)
Matched Controls	10	36.7(11.1)	12.8(1.2)	48.0(0.0)
Healthy Subjects	17	38.6(11.9)	14.1(2.1)	47.8(1.0)

Note: Scores are group means with Standard deviations in parentheses.
[a]Range of score is 0-48. 48 is completely right-handed on all questions. Right-handedness is a score of 41 or above.

Figures 2 and 3 show that males score lower than females on both tasks.

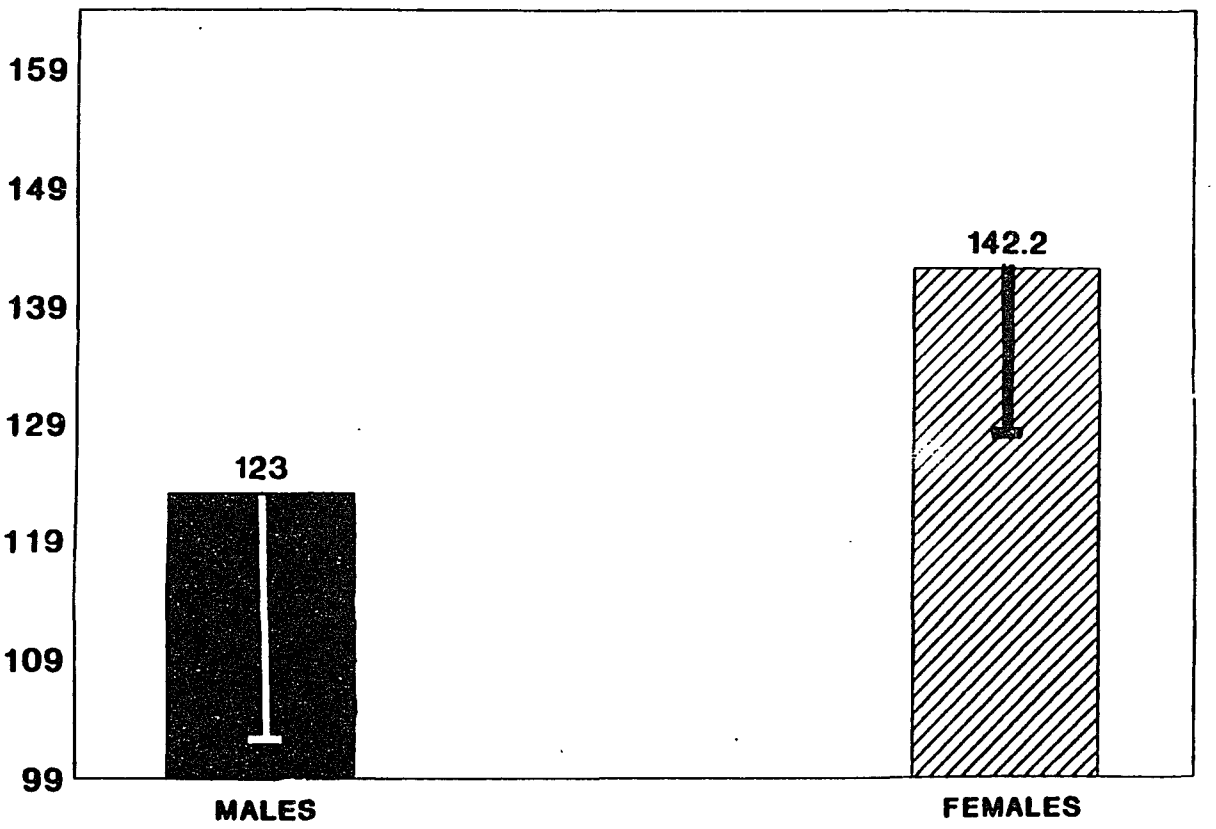
Fig. 2. MEAN SCORE COMPARISON ON SP1 BETWEEN HEALTHY MALE AND FEMALE SUBJECTS



Note: t=3.56, p=.001

low score indicates greater stability;
high score indicates greater plasticity

Fig. 3. MEAN SCORE COMPARISON ON SP2 BETWEEN HEALTHY MALE AND FEMALE SUBJECTS



Note: t=3.06, p=.004
low score indicates greater stability;
high score indicates greater plasticity

Comparison of lesion groups

Table 5 presents the mean, standard deviation, and range of scores on SP1 and SP2, for the male left and right frontal groups (LFM and RFM respectively), and their matched healthy controls (MHC). Male and female lesion groups' scores were submitted to a 2X2 (lesion group by sex) ANOVA to first determine if there were any main and interaction effects. Since significant sex differences were already found in healthy subjects, healthy control subjects were not added to the factorial design. It was felt that opposing scores between healthy males and females might nullify any main effects present in the lesion groups alone. Since male and female lesion groups were not matched, age and education were covaried in the ANOVA.

Significant main effects were present in SP1 for both sex (F=18.87, df=1,16, $p<.001$) and group (F=37.60, df=1,16, $p<.001$). The interaction effect (sex by group) was also significant (F=35.34, df=1,16, $p<.001$). For SP2 no significant sex effect was found (F=0.92, df=1,16, $p>.3$), but a significant group effect was found (F=25.62, df=1,16 $p<.001$). The interaction effect (group by sex) for SP2 was also significant (F=4.49, df=1,16, $p<.05$).

Table 5

Mean, standard deviation, and range of scores on SP1 and SP2 for Male and Female Left and Right Frontal Lesion Groups and Their Matched Healthy Controls

		SP1		SP2	
Group	n	Mean(S.D.)	Range	Mean(S.D.)	Range
			Males		
Left Frontal					
Lesion	5	137.0(4.2)	130-141	134.8(3.7)	130-140
Matched Controls	10	118.3(21.6)	85-144	124.2(20.8)	99-156
Right Frontal					
Lesion	5	85.0(2.2)	82-88	106.4(4.5)	99-111
Matched Controls	10	126.0(15.7)	106-148	130.2(21.3)	104-163
			Females		
Left Frontal					
Lesion	5	95.6(12.6)	85-112	130.4(13.8)	113-150
Matched Controls	11	135.2(12.0)	113-146	139.5(16.7)	99-154
Right Frontal					
Lesion	5	90.8(12.5)	83-113	118.4(10.3)	104-129
Matched Controls	10	136.9(9.2)	115-146	146.0(8.6)	134-161

Comparison of lesion groups with matched healthy controls

Since significant main and interaction effects were found in the lesion groups, comparisons between the lesion and MHC groups, and between same sex lesion groups, were undertaken to further delineate differences in performance.

Males. Significant differences were present when comparing performance on SP1 and SP2. Both LFM and RFM had smaller group variance - 5 to 6 times smaller - compared to their MHC (see table 4). Significant differences in group variance were found between LFM and their MHC on both SP1 (F=26.68, $p<.01$) and SP2 (F=31.26, $p<.01$). For the RFM vs. MHC, the same pattern emerged for SP1 (F=49.42, $p<.01$) and SP2 (F=22.33, $p<.01$).[5]

Because significant differences in the homogeneity of group variance were present, separate variance t-tests, instead of pooled-variance t-tests, were used. Separate-variance t-tests are considered more sensitive in analyzing mean differences when group variances differ significantly (see, Norusis, 1986).[6]

Figure 4 presents the mean scores on SP1 for the LFM and RFM vs. their MHC. The LFM group had a significantly higher

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[5]According to the SPSS/PC+ manual the F value is the ratio of the larger sample variance to smaller sample variance (p. B-122).

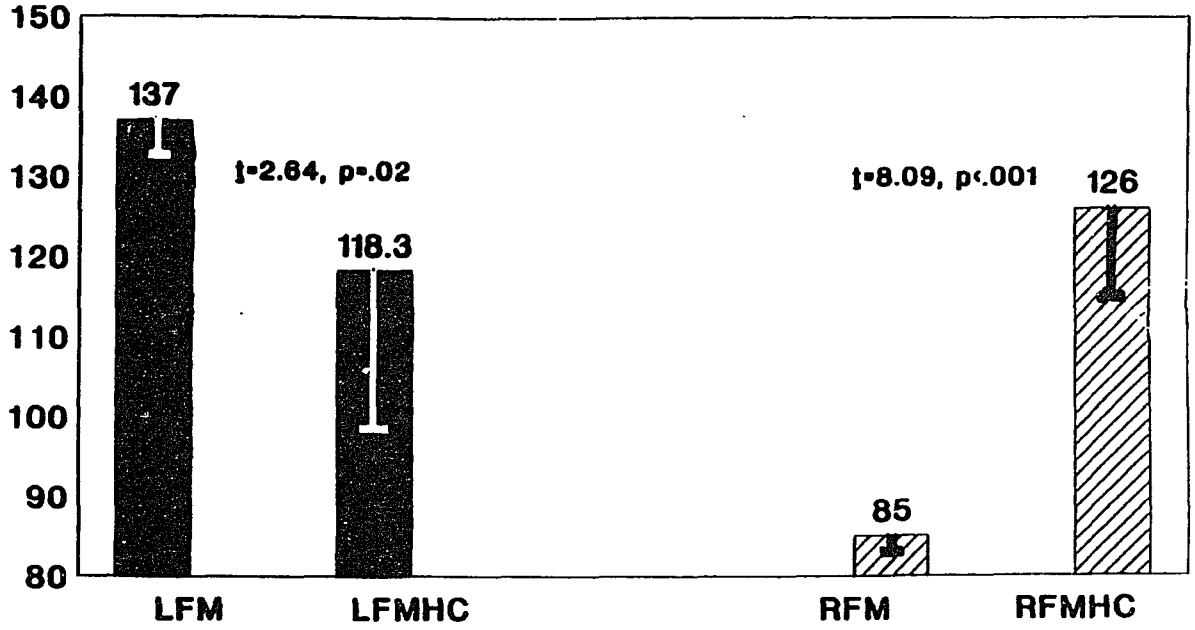
[6]For the subsequent separate variance t-tests degrees of freedom are given as integers. Since the groups had unequal cell sizes and group variances the resultant degrees are derived from a proportion of those factors.

score than its MHC (t=2.64, df=10.27, $p<.05$). The RFM, on the other hand, scored significantly lower than their MHC counter parts (t=8.09, df=9.71, $p<.001$). Figure 5 presents the mean scores on SP2 for the LFM and RFM vs. their MHC. On SP2 there was no significant difference between the LFM and their MHC (t=1.56, df=10.09, $p>.10$), while RFM had a significantly lower score on SP2 compared to their MHC (t=3.39, df=10.49, $p<.01$).

Since homoscedasticity was rejected, and the sample sizes were unequal, the use of a parametric t-test was questionable (Siegal, 1956; Boneau, 1960). However, Boneau has shown that the t-test is extremely robust even when certain underlying assumptions are violated. For example, even with significantly differing group variances, the t-distribution was accurate with equal sample sizes - even with samples as small as five.

In order to equate sample sizes between the LFM and RFM and their respective MHC, the mean score of each lesion subject's two MHC subjects was paired with it's lesion subject's score and submitted to a paired t-test. A significant difference was found on SP1 between the LFM group and their MHC (paired t=3.09, $p<.05$), while on SP2 the difference approached significance (paired t=2.39, $p<.10$). For the RFM group and their MHC the same pattern of results emerged - a significant difference on SP1 (paired t=27.18, $p<.001$), while the difference on SP2 approached significance (paired t=2.67, $p<.10$).

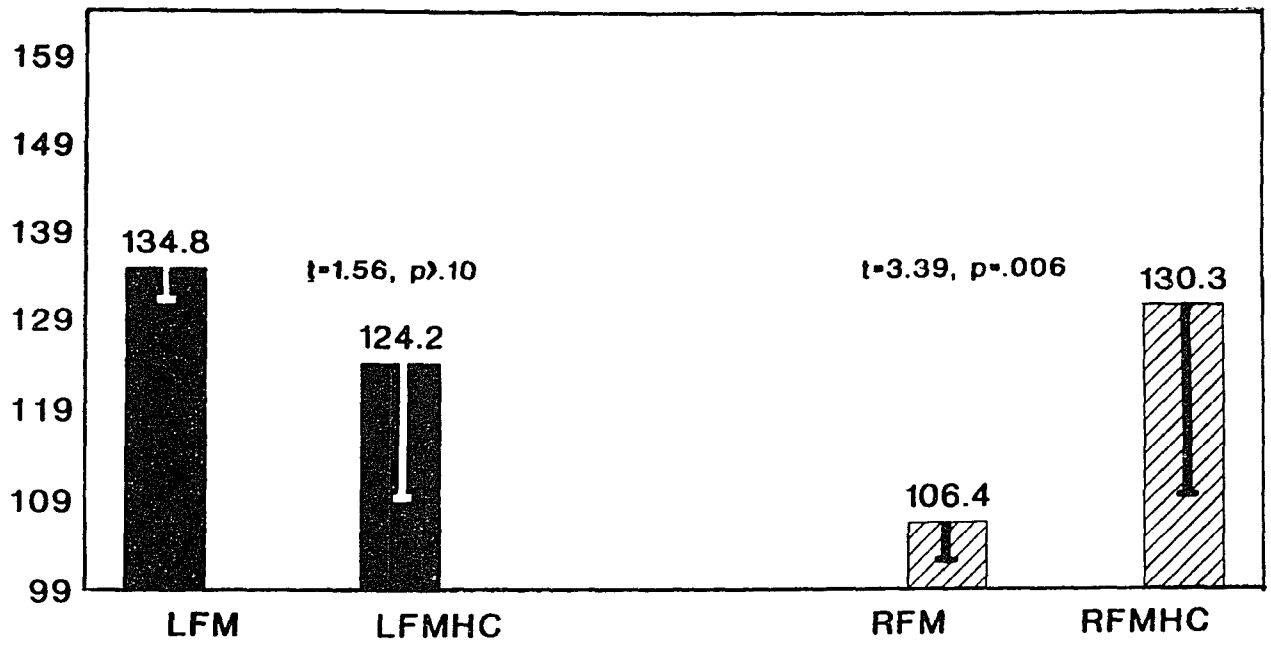
Fig.4. SP1 MEAN SCORE COMPARISON BETWEEN LEFT AND RIGHT FRONTAL LESION AND MATCHED HEALTHY CONTROL MALE SUBJECTS



Note: LFM = Left frontal males (n=5)
LFMHC = Left frontal matched healthy controls (n=10)
RFM = Right frontal males (n=5)
RFMHC = Right frontal matched healthy controls (n=10)

low score indicates greater stability;
high score indicates greater plasticity

Fig.5. SP2 MEAN SCORE COMPARISON BETWEEN LEFT AND RIGHT FRONTAL LESION AND MATCHED HEALTHY CONTROL MALE SUBJECTS



Note: LFM = Left frontal males (n=5)
LMHC = Left frontal matched healthy controls (n=10)

RFM = Right frontal males (n=5)
RMHC = Right frontal matched healthy controls (n=10)

Since the paired t-tests findings were consistent with those of the independent t-tests, the differences between the LFM and RFM and their matched controls were most likely true differences in performance, rather than spurious results from violations of the assumptions underlying the t-test.

Referring back to Figures 3 and 4 one can see that LFM, compared to RFM, had significantly higher scores on both SP1 ($t=24.51$, $p<.001$) and SP2 ($t=10.89$, $p<.001$). Table 6 presents the lesion groups' scores on the additional neuropsychological tests. There were no significant differences between LFM and RFM on Full Scale IQ ($t=1.32$, $p>.20$), Verbal IQ ($t=1.37$, $p>.20$), Performance IQ ($t=.38$, $p>.50$), nor on Raven's Standard Progressive Matrices ($t=.24$, $p>.50$). In addition, there were no significant differences between age ($t=.87$, $p>.40$) and education ($t=1.27$, $p>.20$).

Females. Table 5 contains the mean, standard deviation, and range of scores on SP1 and SP2 for the female left and right frontal groups (LFf and RFf, respectively) and their MHC.

As in males, the degree of homoscedasticity was determined between the lesion groups and their MHC. Neither LFf, nor RFf, significantly differed from their MHC in sample variance. For the LFf and their MHC the SP1 F value=1.1 ($p>.50$) and for SP2 the F value=1.46 ($p>.50$). For the RFf

Table 6

Group Means and Standard Deviations on The WAIS-R and Raven's Standard Progressive Matrices for Male and Female Left and Right Prefrontal Groups

		WAIS-R			
Group	n	FIQ	VIQ	PIQ	Raven's
			Males		
Left Frontal	5	84.8(7.0)	89.0(6.4)	85.4(10.5)	61.0(34.3)
Right Frontal	5	92.0(10.0)	96.4(10.2)	87.8(9.6)	56.0(31.7)
			Females		
Left Frontal	5	94.4(10.1)	96.6(11.0)	92.4(8.2)	60.2(28.8)
Right Frontal	5	86.6(4.4)	88.6(5.0)	86.2(3.7)	48.2(15.9)

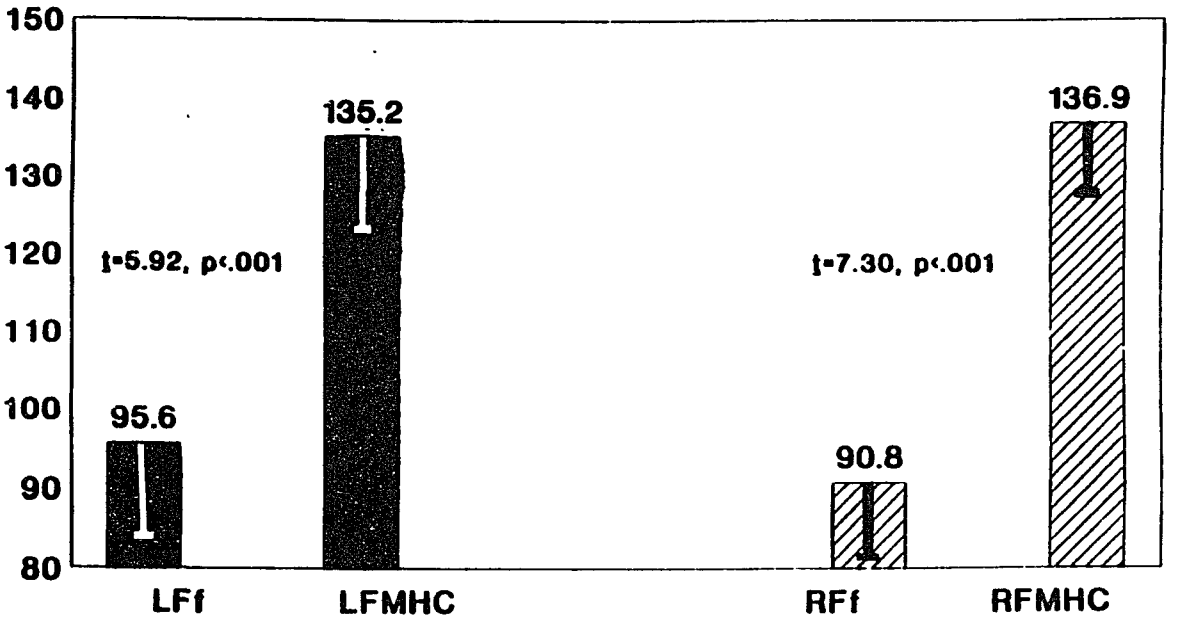
Note: Scores are group means with standard deviations in parentheses. Raven's score is percentile rank based upon normative data published in the manual.

and their MHC the SP1 F value=1.85 ($p>.50$) and for SP2 the F value=1.43 ($p>.50$).

Since the LFf and RFf groups and their MHC groups were homoscedastic, pooled-variance t-tests were used to analyze differences on SP1 and SP2. Figure 6 shows the mean scores of the LFf and RFf compared to their MHC on SP1. Both the LFf ($t=6.04$, $p<.001$) and RFf ($t=8.13$, $p<.001$) scores were significantly lower than their MHC. Figure 7 presents the mean scores on SP2 for the LFf and RFf and their MHC. The LFf scores were lower than their MHC, but not significantly lower ($t=1.04$, $p>.30$), while the RFf were significantly lower than their MHC ($t=5.49$, $p<.001$).

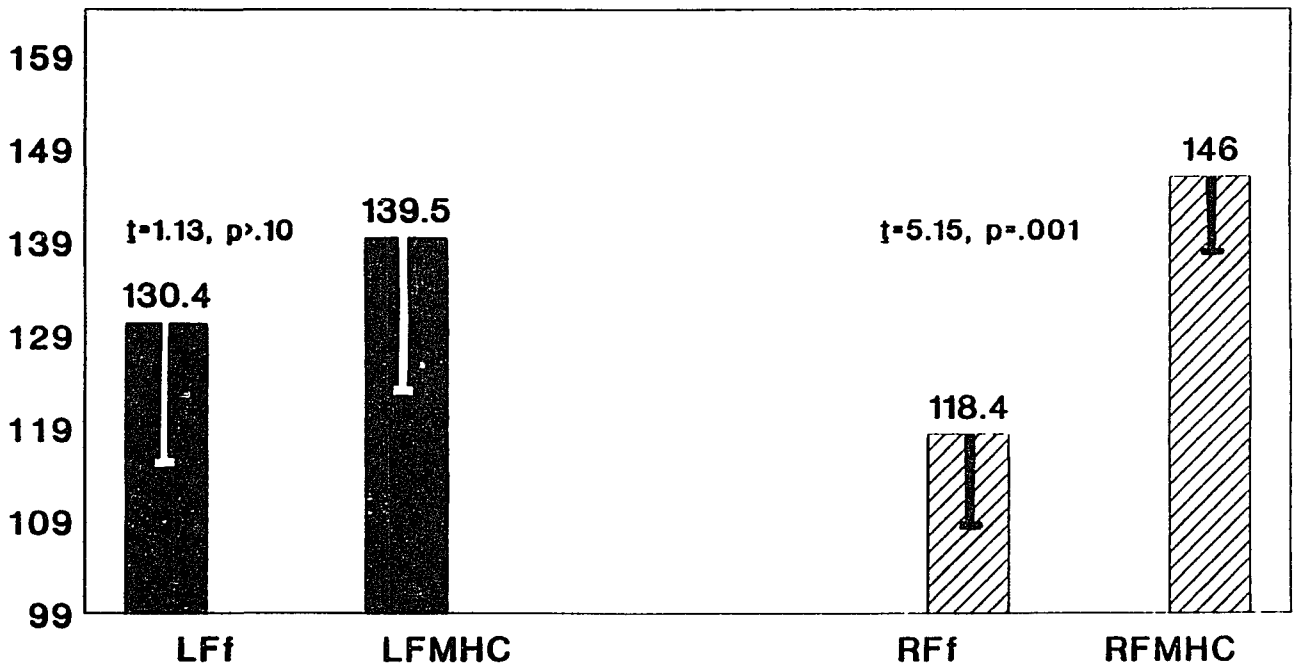
Looking at Figures 6 and 7, and comparing the LFf and RFf groups, there were no significant differences between SP1 ($t=0.60$, $p>.50$) and SP2 ($t=1.56$, $p>.10$). In addition, the two groups were not significantly different on age ($t=.79$, $p>.40$), education ($t=1.63$, $p>.10$), Full Scale IQ ($t=1.58$, $p>.10$), Verbal IQ ($t=1.48$, $p>.10$), Performance IQ ($t=1.54$, $p>.10$), and Raven's Standard Progressive Matrices ($t=.81$, $p>.40$).

Fig.6. SP1 MEAN SCORE COMPARISON BETWEEN LEFT AND RIGHT FRONTAL LESION AND MATCHED HEALTHY CONTROL FEMALE SUBJECTS



Note: LFf = Left frontal females (n=5)
LFMHC = Left frontal matched healthy contrpls (n=11)
RFf = Right frontal females (n=5)
RFMHC = Right frontal matched healthy controls (n=10)
low score indicates greater stability;
high score indicates greater plasticity

Fig.7. SP2 MEAN SCORE COMPARISON BETWEEN LEFT AND RIGHT FRONTAL LESION AND MATCHED HEALTHY CONTROL FEMALE SUBJECTS



Note: LFf = Left frontal females (n=5)
LFMHC = Left frontal matched healthy controls (n=11)

RFf = Right frontal females (n=5)
RFMHC = Right frontal matched healthy controls (n=10)

Discussion

In males, the results of this study supported the hypothesis that left PFC lesions produce plastic behavior and right PFC lesions stable behavior, relative to MHC. In addition, an unpredicted, significant, gender difference was found for both healthy and lesioned subjects. Healthy females were more plastic than males, and females with PFC lesions, regardless of the side, responded in a relatively stable fashion.

The gender difference indicates that cognitive functions in males and females differ, and is differentially effected by PFC lesions. Although unpredicted, the gender difference is consistent with a large body of literature showing gender differences in cognitive functioning. These results are discussed below. Possible explanations for the occurrence of the results and their implications in understanding gender differences and hemispheric specialization in the PFC, are presented.

Psychometric Properties of SP1 and SP2

Test/Re-test reliability. Since SP1 and SP2 were newly developed tests, some basic psychometric properties were examined. Even here, gender differences were present. In the overall healthy sample both SP1 and SP2 had high test/re-

test reliability. If, however, test/re-test reliability was evaluated separately by sex, a significant difference appeared. Males had near perfect test/re-test scores, while the females' test/re-test correlations were much lower. Although small sample sizes (7 males and 8 females) will affect the correlation, the significant gender difference between test/re-test correlations indicated that the consistency in performance was different for males and females - males were much more consistent across the two administrations.

The fact that females were less consistent between administrations of SP1 and SP2 was consistent with the idea that healthy female group performance on SP1 and SP2 was not driven by a stable internal representation or strategy. While males, as a group, tended to use the same strategy across administrations, the females, it appears, tended to apply different strategies.

There was no systematic change in scores for either males or females from the first to the second administration. This indicated that there was no "learning" of a particular strategy as might have been predicted by right-to-left shift theories of hemispheric specialization.

The only significant correlation in the entire healthy control group between SP1 and SP2 with age and level of formal education, was a negative correlation between SP2 and

education. When separated by sex, the females displayed a significant negative correlation between age and SP2. It appears then, that SP1 performance was not influenced by level of education and age. SP2 performance, on the other hand, might have been somewhat influenced by the subject's level of education. The higher the education the more stable the performance.

Validity measures. Since SP1 and SP2 were developed to test a novel construct, the validation of the tasks was required. This was attempted in two ways. The first was to develop two similar tasks, SP1 and SP2, which tap into the same construct through somewhat different methods. As a group, both the males and females had a reasonably high correlation between SP1 and SP2 indicated that the tasks were measuring the same fundamental principle, but were not redundant. There was no significant differences when the correlations between SP1 and SP2 were performed separately for each sex.

Another method used to validate the construct and its measurement was convergent validity. It was hypothesized that higher scores (plastic responding) would be associated with extroverted behavior (individuals who seek novelty and have an external locus of control [Eysenck, 1947]). Therefore, it was predicted that significant and positive correlations would occur between extroversion and SP1 and SP2. For the overall

healthy control group the correlations between SP1 and SP2 with the Extroversion Scale (E) of The Eysenck Personality Scale were both positive - SP1 approached significance, while SP2 was significant. As in test/re-test reliability, when the healthy control group was separated by gender, the correlations between SP1 and SP2 with the E scale were significantly different. In females the correlations were virtually non-existent, while in males both correlations were high.

The significant differences between the male and female convergent validity correlations suggested that the males showed good convergent validity while the females did not. However, the differences between the males and females night be accounted for by differences in group variance. When separated by sex small sample sizes were used. In addition, the male group had a larger group variance than the females. Smaller group variance along with a small group size might have accounted for the very low correlations in females, and thus the significant difference between the sexes in convergent validity. Therefore it is possible that the females' very low and significantly different correlations were artificial, and a due to restriction of the range of scores in females rather than a lack of convergent validity.

The above correlations suggest that SP1 and SP2 measure the same construct and have some degree of convergent validity

with a well established psychological test. The preferred method of validating the construct is to develop a completely new task different from SP1 and SP2 but measuring the same construct, and administer it along with SP1 and SP2 to another group of lesion subjects. It would be expected that the new task would yield the same pattern of results as SP1 and SP2.[7] The construct of cognitive stability/plasticity is a novel one, and the use of SP1 and SP2 is the first attempt to operationally define the construct.

Before explaining the gender difference found in healthy controls and lesioned subjects, one needs to consider the literature on sex differences in hemispheric specialization, and the role of gonadal hormones in the differentiation of the CNS, specifically the cerebral cortex. It is this body of literature that helps in explaining the gender difference found in this experiment.

Gonadal hormones and the sexual differentiation of the brain

One of the unexpected findings in the present study was a significant gender difference in healthy controls and lesion groups on both SP1 and SP2. Although this was an unpredicted finding, it can be sufficiently explained in a post hoc fashion by considering the role of gonadal hormones,

[7]This is currently being developed using pictorial stimuli.

specifically testosterone, in sexual differentiation of the brain. The following is a brief review of testosterone's effects on the sexual differentiation and functional development of the prefrontal cortex. For a more extensive review please refer to Appendix 3.

There are several areas that indicate that the cerebral cortex, in particularly the prefrontal cortex, is sexual differentiated by the gonadal hormone testosterone. These areas involve: receptor concentration; cortical thickness; cortical growth; and functional development. Table 7 is a summary of the findings showing the sex differentiation of the brain by the gonadal hormones.

Evidence has indicated that in males, rats have a larger concentration of estrogen receptors in the left PFC, and non-human primates have a larger concentration of right PFC androgen receptors. Female rats and non-human primates show no consistent left/right asymmetry for either estrogen or androgen receptors (Sandu, Cook, and Diamond, 1986; Sholl and Kim, 1990).[8]

Male rats showed a consistent asymmetry in cortical thickness. The male's left PFC was significantly thinner than

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[8]In the brains of rats and non-human primates, testosterone is aromatized into estradiol (an estrogenic compound). Estradiol is considered to inhibit cortical growth. In addition, testosterone has a direct androgenic effect in non-human primates facilitating cortical growth.

Table 7

Sex Differences In Gonadal Hormones and Their Effects on Brain Development

Findings:	Male	Females
Receptor Concentration	Show a consistently greater concentration of estrogen receptors in the left hemisphere of rats; particularly in PFC.	Show no consistent lateralization of estrogen receptor concentration in rats.
	Males have greater concentration of right frontal androgen receptors.	Females show no lateralization; have much fewer androgen receptors.
Cortical Thickness	Male rats have asymmetrically thinner left cerebral cortex especially in PFC region which is mediated be testosterone	Female rats show no asymmetry in cortical thickness
Cortical Growth	Male rats show greatest cortical development in frontal cortex during early post-natal development.	Female rats show greatest cortical development in posterior cortices during early post-natal development.
	Human male fetuses have greater right than left PFC cortical volume.	Human female fetuses have no PFC cortical volume asymmetry, or slightly larger left than right.
Functional Dev.	Male monkeys have functional orbito-frontal cortex 12-15 months before females (object reversal discrimination) task	Masculinized females perform like healthy males.

their right. In females there was no consistent asymmetry (Diamond, 1985; Diamond, Dowling, and Johnson, 1981; Diamond, Johnson, and Ingham, 1975; Diamond, Johnson, Young, and Sing, 1983; Papas, Diamond, and Johnson 1979). Consistent with these findings was the results of a study by de Lacoste, Horvath, and Woodward (1991). In measuring PFC volume (PFC pole to genu) in human fetuses, they found that males typically had a smaller left, than right, PFC volume, while females had no asymmetry, or a slightly larger left than right PFC volume. These findings were consistent with the estrogen and androgen receptor findings mentioned above.

In males rats and non-human primates the rate of PFC cortical and functional development is greater and occurs sooner, compared to females. Posterior cortical development, in female rats, is greater than PFC development. In non-human primates, females, compared to males, show a 15-18 month delay in their maturation of PFC functions. However, masculinized females show the same rate of PFC functional development as males (Clark and Goldman-Rakic, 1989; see Diamond, 1987; Goldman and Brown 1975; Goldman, Crawford, Stokes, and Rosvold, 1974).

All of these factors indicate that there are gender differences in the development of the cortex, particularly in the PFC, which are dependent upon gonadal hormones. This implies gender specific differences in cognitive functioning in general, and PFC functions, specifically.

Human Gender Differences In Cognitive Functioning

The gonadal hormones have a strong sex specific organizational effect on the brain. Are these sex specific organizational effects the foundation of gender differences in cognitive functioning? Does the gender difference found for the sex hormones support the findings of gender differences in cognitive functioning?

The two most commonly observed gender differences in cognitive functioning are: 1) males have a greater degree of hemispheric asymmetry and 2) males are better with spatial tasks and females with verbal tasks (see McGlone, 1980 and Springer and Deutsch, 1989). Two alternative views have been suggested in explaining sex differences in cognitive functioning - both of which implicated the role of gonadal hormones in gender differences. One view, developed by Kimura (1987; 1983; Kimura and Harshman, 1984), suggested that the axis of hemispheric specialization may differ between males and females: males were specialized on a left/right axis, while females were specialized along an anterior/posterior axis. The other view, developed by Brown (see Brown and Grober, 1983), suggested that males and females both have a left/right axis for hemispheric specialization, but that the effects of the gonadal hormones (both organizational and activational) produced "different rates of regional specification" (p. 433, Brown and Grober, 1983), within each

hemisphere. Both Brown and Kimura used the gender differences in aphasia rate in supporting their ideas (Brown also uses differences in age and aphasia type).

Gender difference in axis of hemispheric specialization. Kimura (1987, 1983; Kimura and Harshman, 1984) suggested that women were not necessarily less lateralized, but may have a different lateralization pattern. The finding that females were less likely to develop aphasia following a stroke (see Kimura, 1987; McGlone, 1978), was used to suggest that females were more likely to have bilateral speech representation. This implied that females with right hemisphere lesions should have had a higher frequency of aphasia than males. Males and females, however, had the same frequency of aphasia following right hemisphere strokes.

Kimura went on to show that females appeared to be more focally organized for left hemisphere speech than males. Males had an equal frequency of aphasia following anterior or posterior left hemisphere strokes. Women had aphasia more frequently following anterior strokes. The fact that stroke frequency was greater for posterior than anterior regions, explained why females with left hemisphere strokes (collapsed across anterior and posterior regions) had less frequency of aphasia.

The above findings indicate that the functional organization of male and female brains are different. The

male brain is possibly differentiated along a left/right axis, and the female brain along an anterior/posterior axis (Kimura and Harshman, 1984).

Gender effects for different rates of regional specification. Brown and Grober (1983) studied the effects of age and sex upon the rate of different classes of aphasia (fluent and nonfluent). They found that nonfluent aphasias (motor aphasia) were more common at a younger age, while fluent aphasias (sensory aphasia) were more common at a later age in life. Nonfluent aphasias predominated in both males and females at an earlier age. Starting in the third decade, differences were found between males and females in aphasia types. Males started to show both fluent and nonfluent aphasias, while females still mainly had nonfluent aphasias. As females got older (i.e., into their sixth decade) their aphasia type changed to predominately sensory aphasia, while in males both sensory and motor aphasias occurred equally.

Brown and Grober (1983) suggested that the gender difference in aphasia type across the life span was due to differences in both the organization and activational effects of gonadal hormones. Initially, language is bilaterally and diffusely organized in both males and females. However, during the third decade or so males became more lateralized and focally organized for language, while females progressed at a much slower rate - thus they still had bilateral representation. During the later decades of life males showed

equal occurrence of fluent and nonfluent aphasias, while females mainly developed fluent aphasias. This indicates that males either showed a decrease in regional specificity, and/or females had an increase in their rate of regional specification. This finding would be consistent with the fact that the level of testosterone in males decreases in age (see Goy and McEwen, 1980).

The gender difference found in the present study would be consistent with the findings of Brown and Grober (1983). Brown and Grober stated that it was in the third decade or so where males and females started to show a difference between aphasia types - implying that males were more lateralized and females where less lateralized. The majority of the lesion subjects were in their 30's or 40's (see table 4). This is precisely the age at which Brown and Grober stated that a gender difference emerged in aphasia type.

If one assumes that the gender difference found by Brown and Grober extends beyond aphasia, then one could assume that males would show lateralized differences, while females would not. This is consistent with the present findings.

The views presented by Kimura and Brown and Grober have substantially different implications for gender differences in cognitive functioning. However, they do share one communality. Both would predicate that in comparing males and females (at least in their third or fourth decade) with left and right PFC lesions, males would have a lateralized

effect, while females may not. This is consistent with the findings of the present study. It is important to remember that the present study does not differentially lend support to either Brown and Grober or Kimura. In order to further test their differences male and female posterior lesion subjects would have to be tested.

Levels of gonadal hormones and gender differences on cognitive tasks. The involvement of sex hormones in the sexual differentiation of the brain, and gender differences in cognitive functioning, suggests a possible relationship between levels of sex hormones and cognitive functioning. In males, the serum testosterone level, within the normal range, was positively correlated with visuo-spatial skills (Christiansen and Knussman, 1987; Tan 1990a,b). The pattern in females was more complicated, because of the frequent cycling of estrogen levels. In general, women's ability for spatial and verbal and articulatory/motor functions were reciprocal depending upon the stage of the women's menstrual cycle. When estrogen (estradiol) was high (preovulatory or midluteal) females were much better at verbal and articulatory/motor tasks than spatial tasks. When estrogen levels were low (menses) women were better at spatial tasks and poorer at verbal and articulatory/motor tasks (Hampson, 1990a, b; Hampson and Kimura, 1988).

Hampson also found that estrogen directly effects dichotic listening, especially in the right hemisphere. Left ear accuracy for monosyllabic word identification was much better when estrogen levels were low. The effects on the right ear were somewhat more mixed. High levels of estrogen facilitated right ear performance within subjects, but not between groups. This indicated that the activational role of estrogen suppressed right hemisphere functioning and possibly facilitated left hemisphere functioning.

This contradicts the previously cited evidence suggesting that estrogen or estradiol suppresses left hemisphere development. There are two possible explanations for this: 1) organizational vs. activational effects of gonadal hormones, and 2) gender. It is possible that the activational and organizational effects of hormones effect the functioning of the brain differently. Also, the interaction effect of gender and organizational effect of hormones could lead to the different behavioral effects a particular hormone has during development and adulthood. Nonetheless, it becomes quite apparent that the sex hormones play a significant role in the gender difference found in cognitive functioning.

Gender Differences in Healthy Controls On SP1 and SP2

A significant difference was found between healthy control male and female subjects. Males scored lower than females on both SP1 and SP2. This implies that males, as a

group, were stable - more likely to consistently choose the more similar choice card, while female subjects were plastic - less likely to consistently use the same strategy (inconsistently choosing either the similar or different choice), or they tended to choose in a target-independent fashion making their choice without regard for the target card. It appeared that males relied upon, and consistently followed, an internalized strategy. Females were less likely to follow an internalized strategy. They appeared to respond in a more target independent fashion. They disregarded the target card and chose one of the choice cards based upon a preference for a particular perceptual property (field dependent). On purely phenomenological grounds, when asked how they performed on SP1 and SP2, women tended to be drawn to the perceptual saliencies of the cards. They did not make their choices based upon a consistent strategy.

It should be mentioned that theories of hemispheric specialization, which advocate a right-to-left hemispheral shift of specialization (Goldberg and Costa, 1981; Kitler et al., 1989), may have predicted that subjects would switch their pattern of responding (e.g., from a non-consistent pattern to a consistent [similar or different] pattern, or from similar to different) at some point during the test. Although this was not systematically analyzed, there did not appear to be any subjects that even remotely responded as such.

The fact that females tended to make their choices based upon perceptual saliencies, or in an inconsistent fashion, agreed with the following evidence. In a review of the role of gonadal hormones in sensory processing, Gandelman (1982) found that females, compared to males, were more sensitive in overall, basic sensory processes. Although, this gender difference fluctuated depending upon the stage of the menstrual cycle. Gandelman indicated that females had better perception for pure auditory signals (pitch discrimination, judgement of loudness and annoyance of repetitive sounds) (see McGuiness, 1972). While males had better overall acuity, females had greater rod sensitivity to contrast, were better at visual persistence, and when matched for acuity, had better field position discrimination (McGuiness, 1976). Females were also more sensitive to two-point discrimination, taste and olfaction (see Gandelman, 1982). The fact that females were more sensitive to environmental stimuli suggests that when given a preference their choice may be guided by external perceptual properties rather than an internally guided strategy.

Potter and Graves (1988) found that right-handed females were better than right-handed males on an interhemispheric transfer test. Potter and Graves inferred from this that females had better interhemispheric transfer for, "...information about the external world..." (p.324). Also, testosterone (at least in males) is positively correlated with

a measure of field-independence (Embedded Figures Test) (Christiansen and Knussman 1987). Since males have higher levels of testosterone, this suggests they are more likely to be field-independent, which on SP1 and SP2 would be equivalent to consistently following the same internal strategy (low score). Finally, female rats are known to have higher levels of NE compared to males (Vaccari, Brothman, Cimino, and Timiras, 1977). If human females also have higher levels of NE, then it would be highly consistent with the idea that females are more field-dependant or perceptually bound because, as stated earlier, NE is related to orientation and processing of novel environmental stimuli (Aston-Jones, 1985; Aston-Jones and Bloom, 1981; Foote and Bloom, 1979; Mason and Fibiger, 1979; Oades, 1985; see Tucker and Williamson, 1984; Watabe et. al., 1982).

These findings support the notion that the healthy control females' higher scores on SP1 and SP2 are related to plastic behavior, and the males' lower scores are due to stable behavior (consistently following an internalized strategy). Females are more likely to respond to environmental stimuli rather than consistently follow an internalized strategy. This does not imply that females are better or worse at this task. Since, SP1 and SP2 are bias tasks, and not performance tasks, there is no correct or incorrect choice. The subject is free to choose either response card. I believe that it is this bias, or preference

to respond differently, that is one of the key factors accounting for the gender difference in healthy controls.

In unpublished data (Goldberg and Podell), when subjects were asked to specifically choose the more similar or more different response on SP1 and SP2 there was no gender difference. Both males and females were able to consistently follow an internalized instruction or plan (see appendix 3). Therefore, it appears that the gender difference exists in the "...readiness to deploy the major cognitive strategies of one or the other hemisphere, rather than in the degree of lateralization of the underlying mechanisms themselves." (Butler, 1984, p.447).

There are two additional points which should be made regarding the gender difference found in healthy controls on SP1 and SP2. The first point is that the gender difference is strictly a group effect. There is considerable overlap of individual performances between males and females. Some males perform in a plastic manner, and some females are stable. This is what has typically been found in studies of gender differences in cerebral asymmetry (see McGlone, 1980 and Springer and Deutsch, 1989). Springer and Deutsch stated that the gender difference found in dichotic listening and tachistoscopic studies is only about a quarter of a standard deviation. Secondly, evidence was previously presented indicating that the stage of the menstrual cycle greatly affected cognitive functioning. In this study the phase of

the female's menstrual cycle (both healthy control and lesion subjects) was not taken into account. Although possible, it was unlikely that a systematic bias was present, which produced a confounding effect on how females performed on SP1 and SP2. However, this will be taken into account with subsequent female subjects.

The effect of left and right prefrontal lesions on SP1 and SP2

Males. Left and right PFC lesions in males had opposite effects. A left PFC lesion caused a more plastic (higher) score, while a right PFC lesion yielded a more stable (lower) score, relative to MHC. This suggested that the left PFC had a stability bias, and the right PFC, a plasticity bias.

This confirmed the hypothesis originally set forth that the left PFC was important in the maintenance of an internalized set of rules or strategies, and the right PFC was important in switching between cognitive sets or attending to, and interacting with, perceptual novelty. The lesion effect on SP1 and SP2 became exceptionally evident when comparing LFM with RFM. While the two groups did not differ in age, education, Full Scale IQ, Verbal IQ, Performance IQ, or Raven's Standard Progressive Matrices, their performance on SP1 and SP2 were dramatically different.

Another interesting finding in the lesion groups was their extremely low group variance. This was particularly

striking because typically patient populations are characterized by large group variances. The fact that LFM and RFM group variances were so small relative to MHC, supported the notion that the left and right PFC lesions lead to extreme biases, whereas normal performance was an interactive balance between the two.

Females. Regardless of the side of lesion LFf and RFf had stable (low) scores on both SP1 and SP2, relative to MHC. In comparison to each other, the RFf score was somewhat lower than the LFf group, but not significantly so.

It appeared then, that there was a large gender difference in the effect left and right PFC lesions had on SP1 and SP2. The males' right and left PFC were complementary in function. Females' left and right PFC, on the other hand, appeared to be additive and more like a healthy male's right PFC.

This can be explained by reviewing the effects of the gonadal hormones on the developmental organization of the brain, and the difference in hemispheric specialization between males and females. Testosterone was an important factor in producing left/right cortical asymmetry in males, especially in the prefrontal cortex (see above), but not in females. This explained why the male lesion groups' performances were opposite, while the female groups' were similar and almost symmetrical. However, it does not explain why the lateralized PFC lesions in females produced a bias

towards stability. Perhaps, this may be answered by studying females with lateralized, posterior lesions.

The concept of a more symmetrical hemispheric organization in women is common (see McGlone, 1980). The idea that the females' PFC is more like the male's right PFC is consistent with the findings that females: 1) are more sensitive to sensory stimuli (see Gandelman, 1982), 2) are better at interhemispheric transfer tasks (Potter and Graves, 1988), and that 3) female rats have higher levels of NE (Vaccari et. al., 1977), which, is critical in the processing of novel environmental stimuli.

The finding that females are more verbal than males (see McGlone, 1980, Kimura, 1987, and Springer and Deutsch, 1989) appears to conflict with the present interpretation. If females are more verbal than males, why is there no difference between left and right PFC lesions in females, and why is the females' performance similar to that of a male's right, rather than left, PFC? Possibly, the greater verbality of females is a function of the posterior cortex. The present study is limited to prefrontal functions, and therefore may not reflect the greater verbality of females.

It is also possible that males and females differ in their axis of cognitive asymmetry, such that males are specialized left to right, and females are specialized along the anterior/posterior axis (Kimura 1987, 1983; Kimura and Harshman, 1984). It is also possible that there is a sex by

axis interaction, such that males are more asymmetric in PFC functions, and females are more asymmetric for posterior functions. The latter possibility is consistent with the finding that male rats show significantly greater prefrontal development, while female rats show greater posterior cortical growth during early postnatal development (Diamond, 1987). It is also compatible with the finding that consistent right-handed (CRH) males have significantly less callosal area than non-consistent right-handed males (NCRH), especially in the anterior subregions. In females, there is no difference in callosal area (for any subregion) between CRH and NCRH subjects (Habib, Gayraud, Oliva, Regis, Salamon, and Khalil, 1991). Non-right handed subjects are less lateralized in cognitive functioning (see, Springer and Deutsch, 1989) and have a larger corpus callosum (CC) (Habib et. al., 1991; Witelson, 1985, 1989). Therefore, a smaller CC indicates greater degree of lateralization. A difference between CRH and NCRH males' CC size suggests that males are lateralized along the left/right axis (Witelson and Nowakowski, 1991). Since CRH and NCRH females show no difference in callosal size, they may not be specialized along the left/right axis.

Conclusion

Methodological Considerations

There are a few methodological considerations which should be discussed. The first is lesion etiology. Although

never verified or empirically determined, a common assertion is that lesion etiology can differentially affect performance. In the present study three types of etiologies were used: CVA, neoplasm excisions, and post-traumatic excisions (see Table 1). It does not appear that lesion etiology had a differential effect. Both the LFM and RFM groups had multiple etiologies. The LFM had both tumor and post-traumatic excisions, while the RFM had all three etiologies represented. If the lesion etiology differentially effected performance, then one would not expect to have extremely similar scores (very low group variance) within each group. Both the LFM and RFM had extremely low group variance, suggesting that lesion etiology did not differentially affect performance.

It is much harder to determine if lesion etiology is a factor for the lesioned female subjects. Lesion etiology was not evenly distributed across LFf and RFf. The LFf group has four CVAs and one tumor excision. The RFf has four tumor excisions and one post-traumatic excision. Unless there is a lesion etiology by hemisphere interaction, lesion etiology does not appear to have a differential effect on performance. As more lesion subjects with different etiologies are tested, a direct comparison for lesion etiology will be made.

Another factor which must be considered when studying lateralized lesions is the size of the lesion, especially if it is a tumor or post-traumatic excision. The tendency might

be to remove larger areas of brain from the right hemisphere because of left hemisphere language representation. Unfortunately, it was not possible to do exact lesion analysis for size. However, simple viewing of the lesions using the Damasio and Damasio templates (see table 2) revealed that, between males and females, in both left and right frontal lesions, there was no consistent difference in lesion size (i.e., the number and extent of Brodmann regions involved). Also, location within prefrontal area (dorsolateral and orbito-frontal) did not appear to differ. As more subjects are tested the relationship between extent of lesion and critical PFC areas involved will be studied.

One other methodological consideration is the difference between SP1 and SP2. SP1 and SP2 have different methods of administration because they were designed to tap into the same fundamental principle in somewhat different ways. It was hypothesized that the difference in administration would have produced different effects in subjects. The "interlocking" of trials (making trial i+1 dependent upon the subject's response in trial i), was hypothesized to make the subject more sensitive to, or dependent upon, their own response strategy. Thus, possibly leading to greater stability. This did not appear to be the case.

The difference in the counter-balancing of SP1 and SP2 might explain why there was no differential effect between SP1 and SP2. SP1 was completely counter-balanced with respect

to the frequency of occurrence for all possible pairwise differences, and the occurrence of each dimensional property. SP2, because of its method of administration, could only be counter-balanced in a mirror-image, step-wise fashion. The frequency of occurrence for the dimensional difference of 5 was equal to that of 0. Both occur equally more than the dimensional differences of 4 and 1, which occurred equally more than the dimensional differences of 2 and 3. The frequency of occurrence of each dimensional property was counter-balanced in the same mirror-image, step-wise fashion. This might explain why SP1 tended to show greater differences between groups.

Possible extensions of the study

By extending the study to include posterior subjects it becomes possible to determine: 1) if the SP tasks are specific to prefrontal functions, and 2) the interaction between sex and axis of lateralization. It also allows one to determine if a gender difference is present in the posterior lesion subjects, and if so, whether it is consistent with the pattern found in anterior lesion subjects. This is presently underway and the preliminary data suggests that the female brain is differentiated along the anterior/posterior axis, and that the SP tasks are specific to prefrontal functions in males.

Since the degree of handedness and familial handedness appear to play an important role in hemispheric

specialization, it would be important to add these variables when testing healthy controls and lesion subjects. Another possible extension of the present study would be to determine the critical PFC region (i.e., dorso-lateral vs orbito-frontal) involved in SP1 and SP2, and the relationship between the scores on SP1 and SP2 and lesion size.

Implications

The results of the present study have several implications. First, they suggest that a different approach must be taken in studying hemispheric specialization. The findings suggest that cerebral lateralization is not limited to a language/non-language distinction. Rather, more fundamental processes are at play, of which language and non-language are specific exemplars.

The present findings suggest that differences in hemispheric specialization may not be based upon absolute ability, but instead on the hemisphere's preferential bias towards a particular strategy. If so, this has potentially significant implications for cognitive remediation. To make remediation more efficient different strategies might have to be used depending upon the side of lesion and sex of the client.

Also, the study has shown that gender is an important factor in hemispheric specialization. It appears that healthy males and females preferentially apply different cognitive strategies, and that they are differentially effected by

lateralized lesions - the full extent of which we do not yet know. This has important implications for studying normal brain-behavior relationships, and in cognitive remedial strategies.

Finally, and probably the most far reaching and important implication, at least theoretically, is the potential for studying the evolutionary continuity of cerebral lateralization. The present tasks can be modified for studying lateralization in non-human models. This would be one of the first, if not the first, attempt at directly looking at phylogenetic continuities in hemispheric specialization using the same paradigm.

Appendix 1

The handedness questionnaire used in the present study consists of the one developed by Briggs and Nebes (1975) plus additional questions regarding first degree familial handedness. The Briggs and Nebes Handedness Questionnaire is a modification of Annett's (1967) questionnaire. For the present study the original scoring system was modified. Each of the 12 items are scored on a five point system (0 to 4). The range of scores is from 0 completely left-handed on all 12 questions to 48 - completely right-handed on all 12 items. All scores above 40 are considered completely right-handed.

To determine if there was any first degree familial handedness subjects were asked if either parent was left-handed, or even a retrained left-hander. They were also asked how many siblings they had, and how many of their siblings were left-handed, or a retrained left hander. If either parent was left-handed the subject was not included. If the subject had any left-handed siblings or retrained left-handed siblings they were dropped from the study. The reason for the exclusion of subjects because of familial left-handedness is based upon a study conducted by Bryden (1987) which indicated that strongly left-handed parents are more likely to have offs-springs with less well lateralized functions even though they may be right-handed. Since it was not feasible to give potential subjects' parents and siblings handedness

questionnaires the subjects were asked if their first degree relatives were left-handed. See the following page for a sample copy (reduced in size) of The Briggs and Nebes Handedness Questionnaire.

Name_____ Sex_____ Age_____

Indicate hand preference:	Always left	Usually left	No preference	Usually right	Alway right
1. To write a letter legibly					
2. To throw a ball to hit a target					
3. To play a game requiring the use of a racquet					
4. At the top of a broom to sweep dust from the floor					
5. At the top of a shovel to move sand					
6. To hold a match when striking it					
7. To hold scissors to cut paper					
8. To hold thread to guide through the eye of a needle					
9. To deal playing cards					
10. To hammer a nail into wood					
11. To hold a toothbrush while cleaning teeth					
12. To unscrew the lid of a jar					

Are either of your parents left-handed? Mother_____ Father_____

How many brothers and sisters do you have? Brothers_____ Sisters_____

How many of your brothers and sisters are left-handed? Brothers____ Sister____

Appendix 2

There were two forms of The Stability/Plasticity Test: SP1 and SP2. SP1 and SP2 were drawn (centered) on 3" X 3" cards, and administered manually.

SP1 had a total of 60 trials (four blocks of 15 trials each). Each block was counter-balanced so that every possible combination of pairs of dimensional differences (15) were represented. The order of these pairs was randomly assigned for two blocks, A and B. Blocks C and D were the mirror inverse of blocks A and B, respectively. For example if trial 1 in block A has a dimensional difference pair of 2,5, then the fifteenth trial of block C has a dimensional difference pair of 5,2. Throughout the entire 60 trials each binary dimension was equally represented. On each trial a subject was presented with three new cards: A target card and two vertically aligned choice cards below it. The range of scores was from 80 to 220, with 150 being the midpoint.

SP2 had a total of 64 trials (two sets of 32 trials). Since SP2 used a markovian design, each trial had two possible pairs of choice cards (k,l and m,n). These stimulus pairs for SP2 were counter-balanced using the following latin square design:

k,l and m,n

l,k and m,n

k,l and n,m

l,k and n,m

This counter-balanced "block" ensured an even distribution of the distances characterizing all possible consecutive choices between the top and bottom choice. The order in which each set of pairs occurred throughout the test was randomly distributed. Two pairs of possible choices from the same block never appeared in consecutive trials.

Also, the distances of different lengths (of dimensional differences) were evenly distributed across the top and bottom choices throughout the test (e.g. avoiding the situation where greater dimensional distances were concentrated in the top set of choices in the beginning of the sequence and in the bottom set of choices in the end of the sequence or vice versa).

The second set of trials were the top/bottom reverse of the first set. The frequencies of the dimensional differences were not completely counter-balanced. They were, however, countered-balanced in a step-wise mirrored fashion. Such that the frequency that dimensional difference of 0 occurred is equal to the frequency that the dimensional difference of 5 occurred. This also applied for dimensional differences of 1 compared to 4 (both of which occur equally less then 0 and 5), and 2 to compared to 3 (both of which occur equally less than 1 and 4). The range of scores was from 99 to 228 with 163.5 being the midpoint.

Appendix 3

Geschwind (Geschwind, 1984; Geschwind and Galaburda, 1985, 1987) was one of the first to hypothesize that sex hormones were an important factor in the development of sexual differentiation of the human brain. Geschwind theorized that during intrauterine and/or early postnatal periods, testosterone differentially suppressed or delayed the maturation of the left cerebral hemisphere, especially the neocortex. It was this differential selectivity of testosterone that accounted for neuroanatomical asymmetries between males and females, and an increased prevalence of left-handedness, dyslexia, and possibly auto-immune diseases in males. Since Geschwind first proposed the role of testosterone in the development of the brain, a substantial body of evidence in humans and non-humans has accumulated reinforcing the importance of gonadal hormones (especially testosterone) in CNS development and sexual differentiation. This has been referred to as the "Central Hypothesis" (McEwen, 1991).

A general point about the activity of hormones on the brain should be mentioned before discussing the role of sex hormones in the development of the brain. Gonadal hormones have an organizational and/or activational effect on the brain (Arnold and Breedlove, 1985; McEwen, 1983, 1991).[9] The

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[9]Arnold and Breedlove (1985) argue that while this is a valid, general concept present data does not fit a strict organizational/ activational model.

organizational effect is developmental. The gonadal steroids act for a short period of time during late prenatal and early postnatal development exerting effects on structures mediating behavior. These structural effects occur during a critical developmental period inducing permanent changes in neuronal organization. Conversely, activational effects are transient effects on already established neural systems in the adult. They involve temporary changes in chemical properties of neural tissue.

This difference between organizational and activational effects of gonadal hormones becomes important when discussing male/female differences in the brain. The same hormone (e.g., estrogen) can have different, sometimes even opposite effects, depending upon the stage of development and the sex of the organism.

Organizational effects

There are two views on the initial "sex" of the brain. One view suggests that the genetic brain is female, and exposure to testosterone during late uterine and/or early postnatal development masculinizes the brain (Geschwind and Galaburda, 1985, 1987; Toran-Allerand, 1978).[10] Another,

[10]In the brain, testosterone is aromatized into estradiol (an estrogenic compound). It is estradiol that exerts its effect on brain organization, at least in the rat. In primates, there is evidence that testosterone is aromatized into estradiol, but can also have a direct androgenic effect too.

highly consistent view, is that the brain is initially unisex. The level of estradiol determines whether the brain will be female or male. There is a continuum of sexual differentiation of the brain such that low levels of estradiol produces a female brain, while higher levels induce the development of a male brain (Dohler, Hancke, Srivastava, Hofman, Shryne, and Gorski, 1984). Both theories suggest that the masculinization of the brain is directly dependent upon the presence of testosterone during development (Goy and McEwen, 1980).

There are several lines of evidence indicating testosterone's crucial role in producing organizational changes in the brain, specifically in the cerebral cortex. There is a significant surge in plasma testosterone up to day 18 - 21 post conception in the rat (Weisz and Ward, 1980). Consistent with this are the findings that cortical estrogen receptors are greatest soon after birth. There is a rapid proliferation of estrogen receptors from embryonic day 15 through postnatal day 18 in mice (Friedman, McEwen, Toran-Allerand, and Gerlach, 1983; Gerlach, McEwen, Toran-Allerand, and Friedman, 1983) and rats (Sandu, Cook, and Diamond, 1986). In the non-human primate, estrogen receptor concentration is greatest at postnatal day 70 (Sholl and Kim, 1989). Also, aromatase complex, which is responsible for converting testosterone into estradiol, is prevalent in all association cortices (particularly the prefrontal cortex) in both male and

female non-human primates immediately after birth (Clark, MacLusky and Goldman-Rakic, 1986, 1988; MacLusky, Naftolin, and Goldman-Rakic, 1986; Sholl, Goy, and Kim, 1989), and the frontal cortex of rats and human fetuses (Ryan, Naftolin, Reddy, Flores, and Petro, 1972).

The estrogen receptor findings support the role of testosterone's organizational effect because testosterone is aromatized into estradiol in the brain, and estradiol binds to the estrogen receptors (see Goy and McEwen, 1980; Toran-Allerand, 1978). The combination of an increase in plasma testosterone and estrogen receptors, with the presence of aromatase activity in the cortex during late intrauterine and early postnatal development, suggests that testosterone plays a significant role in the organizational development of the cerebral cortex.

Sex Differences In The Effects of Gonadal Hormones. Males and females are differentially effected by testosterone. Sandu et. al., (1986) found, in both male and female rats, that the greatest concentration of cortical estrogen receptors exist soon after birth (days 2 - 3). Males, regardless of age, always have a significantly higher concentration of estrogen receptors in their left cortex. This lateralized difference is greatest at days 2 - 3. Females, on the other hand, do not have a lateralized concentration of estrogen receptors at day 2 - 3. Females do, however, show an

inconsistent asymmetrical rate of loss of estrogen receptors. At first, the decline is greater in the right hemisphere. It then switches, and is greater in the left. It appears, that the males' left hemisphere is preferentially effected by testosterone (after it is aromatized into estradiol), while females do not show any systematic, lateralized effect to estrogen.

Given that testosterone was: 1) greater in males, 2) aromatized into estradiol, 3) considered to retard growth and development, and that 4) males had a greater concentration of estrogen receptors in the left hemisphere, there should be some indication that males, but not females, had asymmetric growth and development of the cerebral cortex. Male rats, until a very old age, had a significantly thinner left cerebral cortex compared to their right. Females had no significant left/right differences in cortical thickness (Diamond, Dowling, and Johnson, 1981; Diamond, Johnson, and Ingham, 1975; Diamond, Johnson, Young, and Sing, 1983). This finding even applied to the new born pup (Diamond, 1985). To show that estradiol was the factor producing the asymmetrical thickness, Papas, Diamond, and Johnson (1979) administered estradiol (in the form of ethinylestradiol) to ovariectomized female pups. Papas et. al., found that after the injection the rats had a significantly thinner cortex relative to sham operated controls. There was no left/right asymmetries, which was consistent with the previous finding that female rats did

not show an overall lateralized concentration of estrogen receptors (Sandu et. al., 1986).

Testosterone may not be the only hormone involved in the development of the cortex. Progesterone (considered to be "anti-estrogenic" and a neuronal cell growth enhancer), when injected into ovariectomized female rats, produced a thickening of the cortex (Papas et al., 1979). Also, adult female rats had a significantly higher concentration of progesterone receptors in the frontal cortex compared to males. The males, in fact, had their lowest concentration of cortical progesterone receptors in the frontal region. When gonadectomized females were masculinized (treated with testosterone propionate) immediately after birth, their distribution of frontal progesterone receptors was equivalent to normal males (Maggi and Zucchi, 1987).

Maggi and Zucchi (1987) did not analyze their data for lateralized effects. If it is assumed that there are no lateralized difference in frontal progesterone receptors in females, it suggests that females are predisposed to have symmetrically thick frontal cortex, while males are predisposed to have an asymmetrically thick frontal cortex.

The effect of testosterone on the frontal lobes. There is evidence indicating a gender difference for gonadal hormone receptors and activity, specifically testosterone, within the frontal cortex of rats and non-human primates. Studies in the

rhesus monkey reveal a gender difference in the prefrontal distribution of androgen receptors. Male rhesus monkeys have a greater concentration of androgen receptors in their right prefrontal region at gestational day 70 (rhesus monkeys require a 166 day gestational period) (Sholl and Kim, 1990). There is no consistent left/right asymmetry in females.

Initially, this might appear to contradict previous findings regarding testosterone's inhibitory effect on the left hemisphere. Testosterone (a specific type of androgen) is more prevalent in, and differentially suppresses the growth of, the left hemisphere in rats. In non-human primates, unlike rats, testosterone masculinizes the brain in two fashions. When converted into estradiol testosterone inhibits growth. Testosterone also has a direct androgenic effect without being converted. In non-human primates, but not rats, testosterone can directly masculinize the brain promoting neuritic growth and development, the opposite of estradiol (see Sholl and Kim, 1989 and Arnold and Breedlove, 1985). Therefore, the greater concentration of right prefrontal androgen receptors found in non-human primates (Sholl and Kim, 1990), suggests that the growth of the right PFC is enhanced by testosterone.

The prefrontal cortex of rhesus monkeys (both males and females) has estrogen receptors and high aromatization activity, especially in the orbito-frontal region (MacLusky et. al., 1986). The aromatase activity is significantly

greater in the males' frontal cortex (dorso-lateral aspect) compared to females (Roselli and Resko, 1986). This aromatase activity appears to be greatest during the later stages of gestation (days 119-124 of the 170 day gestational period). Aromatase activity has also been reported in the frontal cortex of rats and human fetuses in small amounts (Ryan et. al., 1972).

Although not confirmed, if estradiol's effects in retarding the growth of the left hemisphere applies to non-human primates (as it does in rats), then testosterone may have opposite effects in the development of the left and right prefrontal cortex of males - suppression in the left and enhancement in the right. Since androgen receptors are lateralized only in males, and males have greater aromatase activity, this suggests that gender specific left/right cerebral asymmetry exists in the prefrontal cortex of rhesus monkeys. This is consistent with the findings of the present study.

Diamond and her co-workers (see Diamond, 1987) have shown that the rate of development in the frontal cortex is gender specific in the rat. While there is rapid growth in all cortical areas until day 41, it is especially prevalent in the males' frontal cortex. Females show more posterior, than frontal, cortical growth. This might imply anterior/posterior difference between males and females. This finding is

consistent with the human cognitive studies performed by Kimura (see below).

Evidence has shown testosterone's direct effect on the asymmetrical cortical development and function of the frontal cortex in rats and non-human primates. Testosterone directly retards the growth of the frontal cortex in male rats. After male rats were gonadectomized at birth, a reversal of the left/right asymmetry in cortical thickness was found in the frontal lobes - the left frontal lobe became thicker than the right (Diamond, 1985). Thus, testosterone was important in the development of the male frontal cortex. The administration of testosterone to male and female rats, with left or right frontal lesions, produced hyperactivity only in the males with right frontal lesions. There was no asymmetrical effect in females (Starkstein, Ginsberg, Shnayder, Bowersox, Mersey, Robinson, and Moran, 1989).

In non-human primates the frontal lobe becomes functional sooner in males than in females, and is directly related to testosterone. Males become functional sooner than females on a task (object discrimination reversal) known to be dependent upon orbito-frontal functioning. Normal males performed the task better than normal females, and orbito- frontal lesions impaired males, but not females (Clark and Goldman-Rakic, 1989; Goldman and Brown 1975). This gender difference is seen up to 15 - 18 months of age (Goldman, Crawford, Stokes, and Rosvold, 1974).

The direct involvement of testosterone was found when Clark and Goldman-Rakic (1989) administered testosterone propionate to female rhesus monkeys from birth through day 46. The masculinized females performed as well as normal males, and significantly better than normal females. Furthermore, when the treated females were lesioned, their performance was the same as lesioned males, and they were significantly more impaired than normal females.

These findings suggest that the development of frontal lobe functions are facilitated by testosterone. In the non-human primate testosterone can directly act on the cortex and enhance neuronal growth (Sholl and Kim, 1990).

Finally, there was some evidence indicating a sex difference in the development of the human fetal prefrontal cortex. In studying 21 fetal brains (from the Yakovlev series) de Lacoste, Horvath, and Woodward (1991) performed volumetric analysis of several different cortical regions. The results indicated males were more likely to have larger right, than left, prefrontal regions (frontal pole to genu of corpus callosum), while females tended to have more symmetrical prefrontal regions, or slightly larger left, than right, prefrontal regions. The authors suggested that their findings were due, at least in part, to the effect of testosterone on fetal brain development.

In summary, the gonadal hormones, particularly testosterone, play an important role in the development of

the cerebral cortex. This effect is quite evident in the frontal lobes. Testosterone, when aromatized into estradiol, retards cortical growth in the rat, especially in the left frontal lobe. The males' frontal cortex also develops faster than the females'. There are other hormones, e.g., progesterone, which appear to be differentially distributed in the frontal lobes depending upon gender (the exact role of progesterone is unknown). Androgen receptors are lateralized in the male rhesus monkeys' prefrontal cortex, and the males' orbito-frontal region becomes functional before the females', because of testosterone.

Appendix 4

In studying the groups' whose scores were relatively higher (LFM and healthy females), it was not possible to determine if their score represented a true cognitive bias, or an inability to consistently use the same internalized strategy. Therefore, two additional experimental conditions (which I will refer to as the explicit conditions) were given to a subset of subjects to determine if their performance on SP1 and SP2 represented a cognitive bias rather than an inability to consistently employ a particular strategy.

After SP1 and SP2 were administered a five minute break was given. Then, SP1 was re-administered twice more - the difference being in the instructions given to the subject. Instead of being asked to choose the one they liked the best, subjects were told to choose the choice card which was **more similar** to the target card, or **more different** from the target card. The order of administration was counter-balanced between subjects. Below is a table showing the mean scores and standard deviations for all of the groups used in the study. Please note that since this condition was added later in the study cell sizes are different.

For the more similar condition a score of 80 was obtained if on every trial the subject choose the more similar choice. Conversely, a score of 220 on the more different condition indicated that on every trial the subject choose the more

different choice. Since cell sizes were so small no direct parametric analyses were performed.

Table 8

Mean and Standard Deviation Scores On SP1 Using The Explicit (more similar or more different choice) Conditions For Left and Right Frontal Lesion and Healthy Male and Female Groups.

Group	n	More Similar Mean(S.D.)	More Different Mean(S.D.)
		Males	
Left Frontal	3	87.0(4.0)	209.3(8.3)
Right Frontal	1	85.0(0.0)	215.0(0.0)
Healthy Controls	8	86.7(5.5)	214.0(3.3)
		Females	
Left Frontal	3	90.0(10.2)	203.0(9.9)
Right Frontal	3	86.7(2.9)	216.0(1.0)
Healthy Controls	6	83.2(2.5)	216.2(3.1)

Table 8 indicates that while not perfect, all of the groups were able to consistently choose the more similar or more different choice over successive trials. Although healthy controls performed slightly better than the lesion groups, it does not appear that the lesion groups' performances were noticeably different than those of the healthy control groups. This indicates that the performance

on SP1 and SP2 (when told to "choice the one you like the best") represents a bias rather an inability Because when explicitly told to follow a specific strategy all of the groups were able to internalize it and consistently follow it over successive trials.

The two critical groups to study are the LFM and healthy control females. It is these two groups which obtained relatively higher scores. It was hypothesized that higher scores are due to a bias towards cognitive plasticity - not consistently following an internalized strategy. The question arises whether the higher score represents a bias towards cognitive plasticity or an inability to consistently follow an internalized strategy. By showing that the LFM and healthy control females where capable of consistently following the same strategy when instructed, it indicates that performance during the "like the best" condition represents a bias towards cognitive plasticity, rather than an inability to follow a consistent strategy.

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