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INTERHEMISPHERIC RELATIONSHIPS BETWEEN HOMOTOPICAL CORTICAL REGIONS: SEX AND HANDEDNESS DIFFERENCES IN HUMAN REGIONAL CEREBRAL BLOOD FLOW

By

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ABSTRACT

INTERHEMISPHERIC RELATIONSHIPS BETWEEN HOMOTOPICAL CORTICAL REGIONS: SEX AND HANDEDNESS DIFFERENCES IN HUMAN REGIONAL CEREBRAL BLOOD FLOW

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On the basis of behavioral data, it has been proposed that the cerebral hemispheres of males are more functionally asymmetric than those of females, and that the hemispheres of right-handers are more functionally asymmetric than those of left-handers. This study examined functional asymmetries using a physiological measure of brain function: regional cerebral blood flow (rCBF).

The subjects were 15 right-handed males, 14 right-handed females, 15 left-handed males, and 17 left-handed females. Each subject was studied with the 133-xenon inhalation technique. Measurements of rCBF were made at 8 pairs of homotopical loci during each of three cognitive conditions: resting, solving verbal analogies, and solving spatial problems. Right-left asymmetries in the absolute magnitude of blood flow indicated asymmetrical activity. Right-left partial correlations (controlling for total brain blood flow) between homotopical loci addressed the issue of functional interplay between the hemispheres, more positive correlations indicating a more symmetrical (excitatory) interaction.

A greater number of positive interhemispheric correlations and more strongly positive correlations were observed for females than males and for right-handers than left-handers. Regional asymmetries

were more frequent for males than for females and more frequent among right-handers than left-handers.

These sex and handedness differences were more evident during rest than during cognitive activity. The sex differences were most evident at the middle and superior precentral regions, and the handedness differences were most noticable in the superior precentral and superior postcentral regions. Differences were not found at all homotopical pairs of loci. In fact, at some loci group differences opposite to the general pattern were observed.

The results support the hypothesis that male brains are more functionally asymmetric than female brains with the following qualification: group differences in interhemispheric functioning are not ubiquitous but seem to have a regional and task specificity. Data relevant to the hypothesis of greater asymmetry in right-handers appear contradictory. The correlational results contradict the hypothesis, whereas the asymmetry data support it. The apparent contradiction may reflect the greater heterogeneity of brain organization among left-handers.

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INTRODUCTION

Knowledge of human brain function is primarily inferential. For many questions of interest technical and ethical considerations have made impossible the use of most methods that measure neurophysiology _in vivo_ for many questions of interest. The study of non-human brains, observations of presumptive behavioral indices of brain function, and natural "experiments" in neurology and neurosurgery have been the nearly exclusive sources of ideas on how the normal human brain works. These indirect approaches entail certain risks. Prominent among them is the necessity of making assumptions about the relationship between the indirect measure and the normal neurophysiology it purports to describe. These assumptions are inherently difficult to validate, since validation requires making the measure _in vivo_ that could not be obtained in the first place. A body of literature based upon these indirect measures inevitably contains few conclusions for which any consensus has been reached. The study of lateral asymmetries in the human brain is a case in point. The principle that in nearly all right-handers the left hemisphere plays the leading role in language functions, the right-hemisphere in non-verbal, visuospatial, and certain emotional functions is well-established (e.g., Dimond and Beaumont, 1974). What is less clear -- and the subject of some dispute at present -- is the extent to which this modal pattern may be correlated with the sex and handedness of the subject.

INDIRECT MEASURES

To illustrate some of the problems in using the indirect methods, an examination of the two most common techniques in neuropsychology follows. Broca's description of a lesion in the inferior frontal cortex of an aphasic patient (Broca, 1861) established the major paradigm of neuropsychology. Studies of behavioral abnormalities consequent to neural lesions, incurred either by accident or surgical necessity, have provided insight into cerebral localization not only of sensory-motor but also higher cognitive functions (e.g., Luria, 1966). The accuracy with which a brain lesion can be identified and localized solely on the basis of clinical interview and behavioral testing (Luria, 1966; Golden et al., 1980) is a testament to the validity of this paradigm. However, this predictive validity is not perfect (e.g., 74% correct localization for the Luria-Nebraska Neuropsychological Battery; Golden et al., 1981), and for much work such checks on the conclusions do not exist. The most notable modern example of this paradigm is the investigation of split-brain patients. The work of Sperry and his collaborators has demonstrated that verbal abilities are preferentially the domain of the left hemisphere and spatial abilities are preferentially right hemisphere functions (e.g., Gazzaniga, Bogen, & Sperry, 1965; Gazzaniga & Sperry, 1967; Sperry, 1974). However, the generalizability of conclusions reached from these studies is not clear, since the brains of commissurotomy patients are not normal to begin with. This surgery is performed on patients with a long history of uncontrollable epilepsy that is generalized or multifocal in origin. Profound intellectual deficits are often present in these patients.

The working physiological assumption of this lesion strategy is that any behavior that is changed following damage to the brain is a normal function of the tissue injured. Implicit in this assumption is that the neurophysiological effects of damage are restricted to the site of lesion; in the case of commissurotomy patients, the hemispheres are assumed to be functionally unchanged, merely disconnected. Due to the successful application of this technique and the lack of technical alternatives, this assumption has rarely been questioned, but it is undoubtedly wrong. Damaged neurons degenerate. This phenomenon is so well established that it not only can be found in neuroanatomical textbooks (e.g., Brodal, 1981) but has served as the basis for techniques to trace axonal connections between brain regions. Degeneration distal to an injured axon is inevitable, proximal to it likely, and transneuronal to it common. For example, Ebner and Myers (1965) demonstrated widespread bilateral degeneration in the neocortex following cutting of the corpus callosum and anterior commissure in cats and racoons, and Glickstein and Whitteridge (1976) observed degeneration of Layer III pyramidal cells in Area 18 of cats after the cutting of the corpus callosum or destruction of the homotopical cortex. Thus degeneration caused by neural damage is not restricted locally but is present at sites distant from the lesion site. Functional changes subsequent to neural damage are also expected. These include collateral sprouting from remaining input fibers to the denervated cells (e.g., Tripp and Wells, 1978), neurotransmitter receptor supersensitivity in denervated cells (e.g., Creese et al., 1977), and changes in the physiological response properties of the denervated cells (e.g., Millar et al., 1976). A lesioned brain is not a normal brain with one piece missing; it is abnormal away from the lesion site as well as within it.

A second paradigm to assess functional asymmetry involves normal subjects studied with instruments, such as the tachistoscope, that permit lateralized presentation of cognitive tasks. In tachistoscopic presentation, subjects are required to fix their gaze to the center of the visual field. Stimuli, such as a vertical arrangement of a three-letter nonsense syllable, are flashed to one side of the fixation point for a duration too brief to allow saccades. The procedure is repeated for a set of a given stimulus type, and the presentation varies randomly between right and left visual fields. If the subject correctly identifies a greater number of stimuli in one visual field than the other, the experimenter concludes that the cerebral hemisphere contralateral to that visual field (the initial hemisphere to receive the visual stimulus) excels in the processing of stimuli of the type presented. This conclusion is considered valid if callosal transmission occurs at the same speed from right to left as from left to right. The absence of a visual field bias would imply that the hemispheres are equipotential for the task or that a roughly equivalent bilateral involvement is necessary. The length of time the stimulus is exposed to the subject is critical. The longer the exposure time, the longer the opportunity for interhemispheric communication and, therefore, the less noticeable the effects of a truly lateralized function. The exposure time is either identical for each subject (e.g., Graves et al., 1981) or determined individually for each subject (e.g., Levy and Reid, 1976). It is usually a fixed amount added to the briefest exposure time at which the subject can correctly solve a simplified version of the task. Studying interindividual or intergroup differences tachistoscopically makes the further assumptions that the speed of callosal transmission and the number of synapses required for processing are constant from subject to subject. If, for example, callosal transmission were quicker in females than males, a tachistoscopic study using a constant exposure time criterion would show a smaller visual field bias in females even if their brains had identical functional asymmetry. This condition, in fact, may be the case. The corpus callosum of females has been shown to have a thicker splenium, that portion connecting visual and other posterior cortices, than that of males (Delacoste-Utamsing and Holloway, 1982a). If this size difference is due to the presence of thicker fibers, thicker myelination, or a greater proportion of thick or myelinated fibers, faster callosal transmission would be expected for females. The hypothesized sex difference in functional asymmetry, as induced from tachistoscopic studies, might be an artifact of a sex difference in the speed of callosal transmission.

Given the limitations of these indirect measures of neurophysiology, it is not surprising that a point would be reached in neuropsychology at which uniformity of opinion was noticeably missing.

SEX DIFFERENCES

Considerable evidence has accrued to support the hypothesis that male brains are more asymmetrically organized than female brains, yet many reject this interpretation (cf. McGlone, and Commentary, 1980). Evidence that verbal skills are characterized by a greater bilateral involvement in females includes observations that left hemisphere lesions are associated with more severe speech disturbances (McGlone, 1977) and a greater decrement in verbal relative to performance IQ (McGlone, 1978; Inglis and Lawson, 1982; Inglis et al., 1982) among males than females, stimulation of left inferior frontal cortex is followed by a greater incidence of naming errors in male versus female patients (Mateer et al., 1982), and alternate injection of sodium amytal into each hemisphere leads to a greater discrepancy for males in oral fluency (McGlone, 1982). Right hemisphere lesions are reported to cause less severe impairment of spatial functions in females (Hecaen et al., 1981), implying greater bilateral involvement in spatial functions. However, other studies (e.g., Lansdell, 1968; McGlone and Kertesz, 1973) found no significant interaction of sex and hemisphere in the cognitive disturbance subsequent to lesions. Such clinical studies have been criticized for the small sample sizes used, lack of control for the extent of lesion, and for other methodological problems (Kinsbourne, 1980; McGlone, 1980). The interpretation of greater female symmetry in verbal functions has also been challenged as possibly due to the females' premorbid superiority in verbal functions (Sherman, 1980).

Dichotic listening studies of normal subjects have been taken as support for the idea that males show a greater lateralization of verbal functions (Lake and Bryden, 1976; Springer and Searleman, 1978). These studies found a greater right ear advantage in males, indicating a greater left hemisphere bias. However, other studies have found a greater right ear advantage in females (Carter-Saltzman, 1979; McKeever and VanDeventer, 1977). Similarly, many tachistoscopic studies have indicated a greater right visual field (left hemisphere) advantage for males in the processing of verbally presented material (e.g., Levy and Reid, 1976; Bradshaw and Gates, 1978) and a greater left visual field (right hemisphere) advantage for males in the processing of non-verbally presented material (e.g., Kimura, 1969; Rizzolatti and Buchel, 1977). Many other studies, however, did not find these sex differences (e.g., Hanney and Boyer, 1978; McKeever and VanDeventer, 1977). Furthermore, the interpretations of experiments using tachistoscopic (Sergent, 1982) or dichotic listening (Teng, 1981) techniques have been called into question (see also McGlone, 1980).

Electroencephalographic (EEG) records have also been used to assess functional lateralization, but there are methodological problems in the interpretations of EEG cognitive asymmetries (Donchin et al., 1977; Gevins et al., 1979). It is therefore not surprising that some investigators find greater asymmetry in task related EEG for men (Ray et al., 1976; Tucker, 1976), others find a greater asymmetry for females (Davidson et al., 1976; Rebert and Mahoney, 1978), and still others find no sex difference (Galin et al., 1982).

Anatomical asymmetries have been described in frontal (Falzi et al., 1982; LeMay, 1977; Weinberger et al., 1982), temporal (Geschwind and Levitsky, 1968; Wada et al., 1975), occipital (Weinberger et al., 1982; LeMay, 1977), and parietal (LeMay and Culebras, 1977; DeLacoste-Utamsing and Holloway, 1982b) regions. Trends toward more anatomically asymmetrical brains in males have been noted (e.g., LeMay, 1977).

In summary, the hypothesis that female brains function more symmetrically than male brains is countered by opinions that the reports of sex differences in functional lateralization are, in general, unreliable (Annett, 1980), unconvincing (Fairweather, 1976; Fairweather, 1980; Kinsbourne, 1980), or inconclusive (Marshall, 1973; Bryden, 1978; Martin, 1980; Sherman, 1980).

HANDEDNESS DIFFERENCES

Similar types of data have been used in support of the hypothesis that left-handers as a group show less functional asymmetry than right-handers (see Herron, 1980 for reviews). In this case as well, the neurophysiological conclusions are rarely based on neurophysiological measures; however, handedness differences are generally reported in the hypothesized direction.

The study of cerebral blood flow may also address other questions of handedness differences. Harris (1980) has described early theories on the origin of handedness. The results of the present study can address one such theory that relates hand preference to cerebral blood supply. According to this theory a greater blood supply to one hemisphere causes contralateral handedness. Although this theory fell from popularity because its anatomical premises proved faulty, current techniques to directly blood supply to the brain allow a reassessment.

DIRECT MEASURES

Techniques to measure cerebral blood flow and metabolism make it possible to assess sex and handedness differences in functional asymmetries of the brain on a direct physiological basis. Since these techniques simultaneously measure activity in a number of relatively local regions, they provide the opportunity to localize functional asymmetries with an anatomical resolution much better than that of a cerebral hemisphere or cortical lobe, an impossibility with the indirect measures. Furthermore, these techniques permit analysis, beyond the scope of the present study, of interactions among many (potentially all) brain regions, and thus will eventually fulfill their promise to advance neuropsychology beyond the simple conceptions of functional localization and hemispheric asymmetry to which the field has been technologically limited. In the early stages of their use, however, these techniques must be put to the questions of asymmetry and localization, to test and refine the ideas generated from the indirect measures.

Prohovnik et al. (1980) examined regional cerebral blood flow (rCBF) during rest in a group of young, right-handed males. They calculated interhemispheric correlations between 16 pairs of homotopic regions and found positive correlations between all but one pair. These correlations were higher over primary sensory regions than over secondary or tertiary (association) regions. They also chose from their sample of 22 subjects the five subjects scoring highest and lowest with respect to right-handedness on a handedness questionnaire. They found that mean hemispheric flow was higher to the right hemisphere for the high right-handedness group relative to the low right-handedness group. This group difference was significant at three superior precentral regions; in two of the regions there was an apparent left asymmetry for the low right-handedness group, whereas in the other region there was an apparent right asymmetry for the high right-handedness group. The results suggest that rCBF asymmetries in superior precentral regions interact with the handedness, however, tests of significance for within group asymmetries were not reported.

Gur et al. (1982) studied rCBF during rest and cognitive activity in a group of 62 healthy, young adults composed of right-handed males, right-handed females, left-handed males, and left-handed females. They found that solving verbal analogies or line orientation problems resulted in increased blood flow in all groups relative to rest, and that overall flow was greater during the spatial task than during the verbal task. They reported a task by hemisphere interaction reflecting a greater left hemisphere flow during the verbal task and a greater right hemisphere flow during the spatial task. They also reported a sex by handedness by task by hemisphere interaction reflecting a greater asymmetrical change from task to task for females than for males and for right-handers than for left-handers. The question of sex and handedness differences in interhemispheric asymmetries or correlations at homotopical regions within each hemisphere was not directly addressed in the paper of Gur et al. (1982). The purpose of this study is to do so.

INTERHEMISPHERIC CORRELATIONS AND ASYMMETRIES

Correlations between homotopical regions are believed to be indicative of interhemispheric communication. Two exceptions are the situations in which homotopical regions are functionally independent yet react to a stimulus condition in similar (positive correlation) or opposite (negative correlation) ways. Subcortical structures are poor candidates to be the direct substrate of correlations since structures known to have widespread bilateral cortical efferents, specifically the locus coeruleus and the raphe nuclei, are not known to affect the cortex with any regional specificity. The claustrum has been reported to have bilateral cortical efferents (Macchi et al., 1981), but the functional significance of these connections has not been established. On the other hand, the role of the corpus callosum in interhemispheric communication is well established (Steele-Russell et al., 1979), and there are abundant interhemispheric connections (e.g., Ebner and Myers, 1965). Given the anatomical facts, the possibility of the hemispheres being correlated in activity but functionally independent seems relatively unlikely. Therefore, a positive correlation, in the absence of an absolute asymmetry in flow, is to be interpreted as evidence of symmetrical (excitatory) communication between the hemispheres, and more positive correlations for one group as evidence of more symmetrical interplay between the hemispheres for that group.

Lateral asymmetry is a general term signifying that one hemisphere (or regions thereof) is different from the other. There are three, not necessarily exclusive, types of functional asymmetries. Hemispheric superiority is the condition in which one hemisphere participates in a function to a greater extent than the other. Hemispheric specialization is the condition in which one hemisphere has features that the other does not. Hemispheric dominance is the condition in which one hemisphere has a competitive advantage in contributing to a function that could have involved either hemisphere; this would include inhibition of a potentially interfering function. An asymmetry occurring with a positive correlation is consistent with superiority, an asymmetry occurring with a negative correlation is consistent with dominance, and an asymmetry that occurs with no correlation is consistent with specialization. Each of these possibilities could result in a right-left asymmetry in rCBF.

The laterality index and interhemispheric correlation to be calculated reflect different aspects of interhemispheric functional asymmetries. The laterality index is a measure of the percent of interhemispheric difference in the magnitude of rCBF. The interhemispheric correlation is not predictable _a priori_ from the laterality index, i.e., the two measures are conceptually independent. A positive correlation is interpreted as excitatory communication between the hemispheres (symmetrical interhemispheric interplay) and a negative correlation is interpreted as inhibitory interhemispheric communication (asymmetrical interhemispheric interplay). Thus, whereas the laterality index is a measure of asymmetry in the magnitude of activity, the correlation is a measure of asymmetry in the direction of activation.

METHOD

SUBJECTS

The sample of subjects was the sample of Gur et al. (1982). One right-handed female was excluded since data from all 8 homotopical pairs of regions were not available on her. The sample used in this study was comprised of 61 volunteers ranging in age from 18 to 26. Subjects were recruited from an advertisement in the University of Pennsylvania student newspaper. Most of the subjects were undergraduate students, but that status was not one of the selection criteria. Informed consent was obtained from the subjects, and participating females signed a declaration of non-pregnancy. The subjects received $15 for participation. As a monetary incentive the subjects were informed that they would receive 25 cents for each problem they correctly solved. Payment was disbursed to the subjects after their testing sessions were complete.

Subjects were grouped according to sex and handedness. The groups consisted of right-handed males (n=15), right-handed females (n=14), left-handed males (n=15), and left-handed females (n=17). Sex was determined by inspection. The criterion for handedness classification was the hand preferred for writing. The following personal data were recorded on each subject: age, handwriting posture, eye dominance, familial sinistrality, history of handedness change, and self-reported behavioral dominance for pointing, drawing, hammering, throwing a ball, dealing cards, using a screwdriver, and cutting with scissors. Although subtypes of left-handedness (reversed laterality, mixed laterality, pathological etiology) have been suggested, and left-handedness has been considered to be a continuum of non-dextrality (cf. Herron, 1980), this study will consider the group of left-handers in general. An initial step in understanding the interhemispheric relationships of cerebral blood flow that are characteristic of left-handers is to examine the matter in an undifferentiated group of left-handed subjects. Examination of regional cerebral blood flow in subtypes of left-handers will be the subject of future work.

PROCEDURE

All procedures and protocols have been approved by the Committee on Studies Involving Human beings and the Radioactive Drug Research Committee of the University of Pennsylvania and the University Committee on Research Involving Human Subjects of Michigan State University.

Regional cerebral blood flow was measured three separate times on each subject, once during each of three cognitive conditions: resting -- the subject was instructed to lie still, keep eyes open, and stay awake; verbal -- the subject solved verbal analogies taken from Miller's Analogies Test (Turner, 1973); spatial -- the subjects solved Benton's Line Orientation Test (Benton et al, 1975) adapted for slide presentation. Each cognitive condition lasted 15 minutes, and a break of 15-20 minutes separated the conditions. The order of the conditions was varied randomly across the subjects, and a significant effect of task order was not found. The cognitive problems were projected from slides onto a screen located above the supine subjects, who indicated their answers using a bimanually controlled flashlight arrow. The subjects' responses were recorded by the experimenter, who controlled the slide projector from the subject's left. The verbal and spatial tasks were chosen to exploit the functional biases of each hemisphere. Gur and Reivich (1980) showed that the analogies used do preferentially activate the left hemisphere in right-handed males. The Line Orientation Test was chosen on Benton's recommendation (personal communication) that it is the most sensitive test for detecting right hemisphere lesions. The validity of these choices of tasks was further substantiated by the analysis of Gur et al. (1982), which was repeated on the 61 subjects of this analysis: an ANOVA of rCBF data indicates a significant task by hemisphere interaction [$F(2,114)=13.45, p < .001$] that reflects a greater left than right hemisphere increase in flow for the verbal task and a greater right than left hemisphere increase in flow for the spatial task.

THE 133-XENON INHALATION TECHNIQUE

The rates of regional cerebral blood flow (rCBF) were measured in all subjects. The ideas behind this measurement are straightforward and a brief exposition of them follows. The technical details can be found in Obrist et al. (1975) and Obrist and Wilkinson (1980).

Cerebral blood flow is highly coupled to glucose metabolic rate in normal brains and is therefore postulated to be an index of neuronal activity (Reivich, 1974; Raichle et al., 1976). Regional variations in the distribution of blood in the brain are controlled primarily by the local chemical environment that reflects the state of metabolic need. Changes in the concentrations of the products and reactants of metabolic reactions cause local changes in the diameter of cerebral blood vessels. For example, glucose metabolism and oxidative phosphorylation result in an increased tissue concentration of carbon dioxide (CO_2) and a decreased tissue concentration of oxygen (O_2).

Vasodilation of cerebral arterioles is caused by decreased O_2 or incresed CO_2 concentration. As a result, more blood and therefore more nutrients are brought to the area in need.

In the experimental procedure the subjects lie comfortably on their back with a mask fitted over their mouth and nose. A mixture of room air and 133-xenon (approximate dose is 5mCi/liter of air) is inhaled continuously for approximately one minute, followed by 14 minutes breathing of normal room air. During these fifteen minutes the clearance of the radioactive xenon from the brain is recorded by 16 extracranial sodium-iodide crystal scintillation detectors 15 mm in surface diameter with lateral collimation 1.9 cm in diameter and 2.1 cm in length. The 133-xenon diffuses into the blood from the lungs and the tissue from the blood, but, being inert, it does not react with any of the tissue constituents. It leaves the tissue and is exhaled. The rate of rCBF is calculated from the rate of clearance of the isotope from the tissue under a particular detector.

The number of radioactive counts registered at each detector is recorded in six-second intervals and may be plotted versus time (Figure 1). From these data a clearance curve for the isotope is generated by a least squares curve-fitting algorithm. This curve fitting does not make use of data points that are collected during approximately the first minute and one-half of the study to avoid the problem of air passage artifact. Air passage artifact is the scattered radiation measured by extracerebral detectors due to the presence of 133-xenon in the mouth, throat, and nasopharynx. This problem disappears shortly after the isotope inhalation ceases. Curve fitting begins when the count rate in the exhaled air has decreased to 20% of its maximum.

Three tissue types (called compartments) contribute to the clearance curve: gray matter, white matter, and extracerebral tissue (see Figure 8 of Obrist et al., 1975). Gray matter flow can be readily separated from white matter flow, since its clearance rate is seven times that of white matter. In a two compartmental model that is commonly used, the gray matter compartment is mathematically separated from a compartment containing white matter and extracerebral tissue. The extracerebral compartment is relatively small with a relatively slow clearance rate and constitutes a minor portion of the slow perfusing compartment.

The data were collected on line by a PDP-11 computer, which is used for the clearance curve analysis. One commonly used measure of rCBF is f1, or fg, the rate of rCBF in the gray matter (first) compartment in terms of ml/100 gm tissue/minute. In pathological brains or brains with a low overall rate of flow, f1 is an unreliable measure because of the problem of slippage. Slippage is a violation of the basic assumption of the two compartmental model: the two compartments are not as greatly different and therefore contaminate one another. To get around the problem of slippage, flow parameters are also calculated from the entire clearance curve, using a so-called non-compartmental model.

Obrist's Initial Slope (IS) is a non-compartmental parameter that provides an index of gray matter flow but is virtually unaffected by slippage. It is defined as the tangent to the clearance curve at time zero of curve-fitting for an equivalent bolus injection of 133-xenon (Obrist and Wilkinson,1980). It is preferable to Risberg's Initial Slope (Risberg et al., 1975), since the latter, using a later portion of the clearance curve (minutes 2 to 3), is less purely a measure of gray matter. IS may be used for normal as well as pathological conditions. Since there are no precise criteria for defining a neurologically normal human being, normal is a default category including anyone with no known history of neurological or psychiatric problems. It is therefore possible that the normal subjects in this study include some people with undiagnosed abnormality. To minimize the potential effects of this possibility, i.e., to use a stable measure, Obrist's IS parameter was used.

The detectors were positioned over eight pair of homotopical regions. These detectors were attached to a helmet worn by the subjects and were oriented at angles normal to the curvature of the skull. The approximate detector positions, as illustrated in Figure 2, were determined by a neuroradiologist using an X-ray of one subject wearing the helmet. The locations of the detectors are 1: precentral, 2: inferior precentral, 3: middle precentral, 4: superior precentral, 5: superior posterior temporal, 6: inferior parietal, 7: superior postcentral, 8: posterior parietal-superior occipital. Due to individual variations in the size and shape of skulls and brains, the localization of the tissue seen by a detector is not precise, but it does yield a good approximation, probably within a few millimeters. A further imprecision in localization stems from the fact that the region of tissue potentially surveyed by a detector is conical with its apex near the detector. This is not considered to be a major problem, since most of the activity registered at a detector comes from a roughly cylindrical volume extending through neocortex and underlying white matter and, to a diminishing extent, deeper structures.

STATISTICAL ANALYSIS

Product-moment correlation coefficients were calculated for rCBF between homotopical regions for all groups for each of the three tasks. Therefore, for each grouping of subjects there were 24 correlation coefficients generated: one for each of the eight homotopical pairs and eight for each of the three tasks. The subject groupings were male (n=30), female (n=31), right-handers (n=29), left-handers (n=32), right-handed males (n=15), right-handed females (n=14), left-handed males (n=15), and left-handed females (n=17). Group differences between correlations were tested by comparing the Fisher z-transformations of the correlation coefficients. The formulas used were $(z1-z2)/[(1/n1-3)+(1/n2-3)]$ for the unpartialled correlations and $(z1-z2)/[(1/n1-4)+(1/n2-4)]$ for the partialled correlations. It was necessary to use partial correlations because intersubject differences between detector values are much greater than intrasubject differences. In other words, total brain blood flow is a greater determinant of the absolute values of rCBF than are region to region variations in blood flow. Thus, correlations between a pair of regions will not only reflect the correlation between those particular regions but also their mutual correlation with total brain flow. It is therefore important to statistically control for the effect of total brain flow on the interregional correlations. Total brain flow is the mean IS at the 16 detector locations. Partial correlations between homotopical pairs were calculated in which the effect of whole brain flow was partialled out. All statistical analyses were performed using programs of BMDP (UCLA Dept. of Biomathematics, 1979) at the Michigan State University Computer Laboratory. Correlations were calculated using program

BMDP6R.

An analysis of variance with repeated measures (using program BMDP2V) has been performed on the total sample of 61 subjects for all three tasks, using sex and handedness as between group variables, and task, hemisphere, and region the within group (repeated measures) variables (see Gur et al., 1982 for the analysis of the original 62 subjects). Significant interactions were found that justify the search for regional asymmetries and group differences in asymmetries. These interactions include hemisphere by region [$F(7,399)=4.24$, $p < .001$], hemisphere by sex [$F(1,57)=4.21$, $p < .05$], hemisphere by hand preference [$F(1,57)=5.14$, $p < .03$], and the four way interaction of task by hemisphere by sex by hand preference [$F(2,144)=5.96$, $p < .004$].

Within group asymmetries in regional flow were assessed by paired t-tests between homotopical regions. Group differences in regional asymmetry were assessed using a t-test comparison of the laterality index [(right-left)/(right+left)] X 100. Analyses were done using program BMDP3D.

RESULTS

SEX DIFFERENCES

<u>Resting:</u> <u>correlations</u>. The right-left correlations for the 30 male and 31 female subjects are illustrated in Figure 3 and listed in Table 1. All the correlation coefficients were very high, between .80 and .95, well beyond the .001 level of significance. In all 8 regions the correlation coefficients were higher for females than for males.

As noted above, these correlation coefficients not only reflect the interhemispheric covariance between homotopical regions but also reflect the subject to subject variability in total brain flow due to the high correlation of regional to total brain blood flow. To focus on purely regional correlations, the effects of total brain flow were controlled by computing the partial correlations of rCBF between homotopical regions, partialling out total brain blood flow.

All 8 of the partial correlation coefficients for females were positive (chi square=8.0, df=1, $p < .01$; Figure 4, Table 3). These correlations reached statistical significance at the middle precentral and superior postcentral regions. A significant negative correlation was found for males at the middle precentral region. The sexes differed significantly at the middle precentral region: the partial correlation coefficient was more positive for the females than for the males. The incidence of positive correlations was greater for females than for males (chi square=7.3, df=1, $p < .01$).

Among right-handed subjects, all 8 of the partial correlation coefficients for females were positive (chi square=8.0, df=1, $p < .01$;

Figure 5, Table 3). These correlations reached statistical significance at the inferior precentral, middle precentral, superior posterior temporal, and superior postcentral regions. A significant positive correlation was found for the males at the superior precentral region. The sexes differed at the inferior and middle precentral regions, where the partial correlation coefficients were more positive for females than for males, and at the superior precentral region, where the correlation was more positive for males. The incidence of positive correlations was greater for females than for males (chi square=5.3, df=1, $p < .05$).

Among left-handers, the partial correlation coefficients for females were positive at 7 of the 8 pairs of regions (chi square=4.5, df=1, $p < .05$; Figure 5, Table 3). None of these correlations reached statistical significance. There was a significant negative correlation for males at the middle precentral region. The sexes differed significantly at this region. Thus, the same sex difference in the correlation between the right and left middle precentral regions was found for left-handers as well as right-handers. The incidence of positive correlations was again greater for females than for males (chi square=4.3, df=1, $p < .05$), as was the case for the right-handers.

Resting asymmetries. The group of 30 males had significantly asymmetrical rCBF to the left hemisphere, i.e., greater left than right hemisphere rCBF, at the inferior precentral and superior precentral regions (Figure 6, Table 5). The 31 females had a significant mean right asymmetry at the superior precentral region. Significant sex differences in asymmetry were found at both inferior and superior precentral regions. At the superior precentral region, however, the sexes each had an asymmetry that was significant but in opposite directions. The magnitude (absolute value) of the asymmetry was greater for males than for females at 7 of the 8 loci (chi square=4.5, df=1, $p < .05$)

Among right-handers, males had significantly asymmetrical rCBF to the left hemisphere at the inferior precentral region, whereas females had no significant asymmetries (Table 6). A significant sex difference in asymmetry was found at the superior precentral region.

Among left-handers, males had a significant asymmetry to the left hemisphere at the superior precentral region (Table 6). Females had no significant asymmetries. A significant sex difference in asymmetry was found at the superior precentral region, as was the case for right-handers. For both handedness groups males had greater left hemisphere rCBF at this region and females had greater right hemisphere flow. However, the magnitude of the asymmetry was greater for females among right-handers, and greater for males among left-handers, although these magnitude differences were not statistically significant. The magnitude of the asymmetry was greater for males than for females at 7 of the 8 loci (chi square=4.5, df=1, $p < .05$), but the direction of the asymmetry differed between the sexes at 6 of the 8.

<u>Verbal task: correlations</u>. A significant positive correlation was found for females at the prefrontal and superior postcentral region (Figure 7, Table 3). A significant negative correlation occured for females at the middle precentral region, whereas during rest they had a positive correlation at this region. The correlations for males were negative at 5 of the 8 loci. No correlations were significant for males. The sexes differed significantly at two regions: the partial

correlation coefficient was more positive for the females than for the males at the prefrontal region, but it was more negative at the middle precentral region. The sex difference at the middle precentral region was opposite to that found during rest.

Among right-handed subjects, the partial correlation coefficients for females reached statistical significance at superior prefrontal and superior postcentral regions. At the middle precentral region the correlation for females was significantly negative. The correlations for males reached significance at no region. The sexes differed significantly at the prefrontal and superior postcentral regions, the partial correlation coefficients were more positive for the females than for the males.

Among left-handers, none of the partial correlation coefficients for males or females reached statistical significance. The sexes differed significantly at the middle precentral region; the correlation coefficient was more negative for females. The sex difference at this same region was opposite to that found among left-handers during rest.

<u>Verbal task: asymmetries</u>. The group of 30 males had significantly asymmetrical rCBF to the left hemisphere at 3 regions: inferior precentral, inferior parietal, and posterior parietal-superior occipital (Figure 8, Table 5). The 31 females had a significant mean left asymmetry, i.e., greater left than right rCBF, at the superior postcentral region. Significant sex differences in asymmetry were found at both the superior postcentral and posterior parietal-superior occipital.

Among right-handers, males had significantly asymmetrical rCBF to the left hemisphere at 4 regions: inferior precentral, superior precentral, inferior parietal, and posterior parietal-superior occipital (Table 6). Females had significant left asymmetries at the superior postcentral and posterior parietal-superior occipital regions. Although the magnitudes of the left asymmetries were even greater for females than males at the inferior frontal and inferior parietal regions, these did not reach significance due the higher standard errors. A significant sex difference in asymmetry was found at the superior postcentral region, where males had a non-significant right asymmetry and females had a significant left asymmetry.

Among left-handers, males had a significant asymmetry to the left hemisphere at the inferior precentral and posterior parietal-superior occipital regions. Females had no significant asymmetries. A significant sex difference in asymmetry was found at the posterior parietal-superior occipital region.

Spatial task: correlations. The partial correlation coefficients for females reached statistical significance at the posterior parietal-superior occipital region. A negative correlation for males reached significance at the superior precentral region. The sexes did not differ significantly at any region.

Among right-handed subjects, the females had a significant positive correlation at the superior posterior temporal region, whereas males had a significant negative correlation at superior postcentral region (Table 3). The sexes did not differ significantly at any region. At 6 of the 8 regions, however, the female correlations were more positive.

Among left-handers, none of the partial correlation coefficients for females were significant (Table 3). At the superior precentral region left-handed males had a significant negative correlation. The sexes differed significantly at this region.

__Spatial task: asymmetries__. The group of 30 males had one significant asymmetry in rCBF (Figure 8, Table 5). This asymmetry was at the posterior parietal-superior occipital region, and despite the fact that the cognitive task was spatial, the asymmetry was to the left hemisphere. At 6 of the other 8 regions the asymmetry was to the right hemisphere but not significant. The 31 females had no signicant asymmetry, but the mean asymmetry at the posterior parietal-superior occipital region was also to the left. There were no significant sex differences, and, with the exception of the inferior parietal region, the asymmetries for both sexes were nearly identical.

Among right-handers, males had significant asymmetrical rCBF to the left hemisphere at the posterior parietal-superior occiptal region (Table 6). Right-handed females also had a significant left asymmetry at this region and had a right asymmetry at the superior posterior temporal region. No significant sex difference was found. Among left-handers, males had a significant asymmetry to the right hemisphere at the middle precentral region. Left-handed females had no significant asymmetries. No significant sex difference was found for left-handers, as in the case for right-handers. Left-handers of both sexes also showed a mean left asymmetry at the posterior parietal-superior occipital but neither were significant.

__Summary of sex differences__. Sex differences in interhemispheric partial correlations were most evident during the resting condition.

Females had a greater number of positive correlations, and correlations that were more strongly positive. The differences were most evident precentrally and among right-handers. Females had a more positive correlation at the middle precentral region than males in both the right- and left-handedness groups. The pattern was similar during the cognitive tasks, but regional sex differences were less frequent. Sex differences among left-handers at the middle precentral region were reflected in more positive correlations for females during rest but more positive correlations for males during the verbal condition. Males had a greater number of significant regional asymmetries than females. This was especially so during the resting and verbal conditions and among the right-handed subjects. A sex difference was found at the superior precentral region; this difference was present for both handedness groups with males showing greater relative left-hemisphere flow. Left-handed females had no significant regional asymmetry during any of the three conditions.

HANDEDNESS DIFFERENCES

Resting: correlations. The right-left correlations for the 29 right-handed and 32 left-handed subjects are listed in Table 2. For the reason mentioned above only partial correlations will be examined in detail.

In 7 of the 8 regions the partial correlation coefficients for right-handers were positive (chi square=4.5, df=1, $p < .05$; Figure 9, Table 4). These correlations reached statistical significance at the superior posterior temporal and superior postcentral regions. The positive correlation for left-handers at posterior parietal-superior occipital region is significant. The handedness groups differed significantly at 4 regions: the inferior and middle precentral, superior posterior temporal, and posterior parietal-superior occipital, at which the correlations for right-handers were more positive than those for left-handers.

Among female subjects, all 8 of the partial correlation coefficients for right-handers were positive (chi square=8.0, df=1, $p < .01$; Figure 10, Table 4). These correlations reached statistical significance at the inferior precentral, middle precentral, and superior postcentral regions. The correlations for left-handers were positive at 6 of the 8 loci, with none reaching significance. The handedness groups differed significantly at the inferior and middle precentral regions, the partial correlation coefficients were more positive for the right-handers than for the left-handers.

Among males, a significant positive correlation occurred at the superior precentral region. None of the correlations for left-handers were significant. The handedness groups differed significantly at the superior precentral region.

<u>Resting: asymmetries</u>. The group of 32 left-handers had no significant asymmetrical rCBF (Figure 11, Table 7). The 29 right-handers had a significant mean left asymmetry at the inferior precentral region. No significant handedness differences in asymmetry were found.

Among females, there were no significant asymmetries for right-handers or left-handers and no significant handedness differences (Table 8). Mean asymmetries were to the right in 7 of 8 regions for left-handers and to the left in 5 of 8 for right-handers (chi square=4.3, df=1, $p < .05$).

Among males, left-handers had a significant asymmetry to the left hemisphere at the superior precentral region (Table 8). Right-handers had a significant asymmetry at the inferior precentral region. A significant handedness difference in asymmetry was found at the superior precentral region, the region at which significant sex differences were found for both handedness groups (see above).

<u>Verbal task: correlations</u>. The partial correlation coefficients for right-handers were positive at 6 pairs of regions (Figure 9, Table 4). The positive correlations reached statistical significance at region the prefrontal, and superior postcentral regions. A significant negative correlation occurred at the middle precentral region. No correlations were significant for left-handers. The handedness groups differed significantly at the prefrontal and superior postcentral regions: the partial correlation coefficient was more positive for the right-handers than for the left-handers at both regions.

Among female subjects, partial correlation coefficients for right-handers reached positive significance at the superior prefrontal and superior postcentral regions. At the middle precentral region, the correlation for right-handers was significantly negative. None of the correlations for left-handers were significant. The handedness groups differed significantly at the prefrontal and superior precentral regions the partial correlation coefficients were more positive for the right-handers than for the left-handers.

Among males, none of the partial correlation coefficients for either left-handers or right-handers reached statistical significance (Table 4).

Verbal task: asymmetries. The group of 32 left-handers had significant asymmetrical rCBF to the left hemisphere at the inferior precentral region (Figure 12, Table 7). The 29 right-handers had a significant mean left asymmetry at the inferior precentral, inferior parietal, and posterior parietal-superior occipital regions. No significant handedness differences in asymmetries were found during verbal stimulation.

Among males, right-handers had significantly asymmetrical rCBF to the left hemisphere at 4 regions: inferior precentral, superior precentral, inferior parietal, and posterior parietal-superior occipital. Left-handers had significant left asymmetries at the inferior precentral and posterior parietal-superior occipital regions. Although the magnitude of the left asymmetries was even greater for left-handers than right-handers at the inferior precentral and inferior parietal regions, these did not reach significance due the higher standard errors. No significant handedness difference was found for males.

Among females, right-handers had significant asymmetry to the left hemisphere at the superior postcentral and posterior parietal-superior occipital regions. Left-handers had no significant asymmetries. A significant handedness difference in asymmetry was found at the posterior parietal-superior occipital region. The magnitude of the asymmetry was greater for right-handers than for left-handers at 6 of the 8 loci.

Spatial task: correlations. The positive correlation coefficients for right-handers reached statistical significance at the prefrontal and the posterior parietal-superior occipital regions, and a negative correlation was significant at the superior precentral region (Figure 9, Table 4). None of the correlations for left-handers were significant. Two significant handedness differences were found: at the prefrontal region, the correlation for right-handers was more positive than for left-handers, whereas at the superior postcentral region, the correlation for right-handers was more negative. At 6 of the 8 regions right-handers had a more positive correlation than left-handers.

Among female subjects, the right-handers had significant positive correlations at the superior posterior temporal and posterior parietal-superior occipital regions, whereas left-handers had no significant correlation (Table 4). The handedness groups differed at the posterior superior temporal region where right-handers had a more positive correlation.

Among males,there was a significant negative correlation at the superior postcentral region for right-handers (Table 4). At the superior precentral region the left-handed males had a significant negative correlation. The handedness groups differed significantly at the prefrontal and superior postcentral regions; right-handers were more positive at the prefrontal and left-handers more positive at the superior postcentral region.

<u>Spatial task: asymmetries</u>. The group of 29 right-handers had one significant asymmetry in rCBF (Figure 12, Table 7). This asymmetry was at the posterior parietal-superior occipital region and despite the fact that the cognitive task was spatial the asymmetry was to the left hemisphere. At 6 of the other 8 regions the asymmetry was to the right hemisphere but not significant. The 32 left-handers had significant

asymmetries to the right at prefrontal and middle precentral regions. The mean asymmetry at the posterior parietal-superior occipital region was to the left as was the case for right-handers, but it was not significant.

Among right-handers, males had a significant asymmetry to the left hemisphere at the posterior parietal-superior occipital region (Table 8). Left-handed males had a non-significant left asymmetry at the posterior parietal-superior occipital region and had a right asymmetry at the middle precentral region. A significant handedness difference was found at this region. Among females, right-handers had a significant asymmetry to the right hemisphere at the superior posterior temporal region. Female left-handers had no significant asymmetries. No significant handedness difference was found for females. Females of both handedness groups show a mean left asymmetry at the posterior parietal-superior occipital region, but this was significant only for right-handers.

Summary of handedness differences. Handedness differences in interhemispheric partial correlations were also most evident during the resting condition. Right-handers had a greater number of positive correlations, and correlations that were more positive. The differences were present both precentrally and postcentrally and were more evident among right-handers. The pattern was similar during the cognitive tasks, but handedness differences were less frequent. Right-handers had a greater number of significant regional asymmetries than left-handers. This was especially so during the resting and verbal conditions and among the male subjects. Left-handed females had no significant regional asymmetry during any of the three conditions.

Figure 1. Example of 133-Xe clearance curve.

A graph of the radioactive counts at an extracranial detector (thousands of counts) along the ordinate versus time (minutes) along the abscissa. The points are the result of a six-second sampling interval. The curve-fitting was performed by a computerized least-squares algorithm after air passage artifact had become negligible. The data in this figure were taken from a young male who was not a subject in this study; they are used for illustrative purposes only.

FIGURE 1

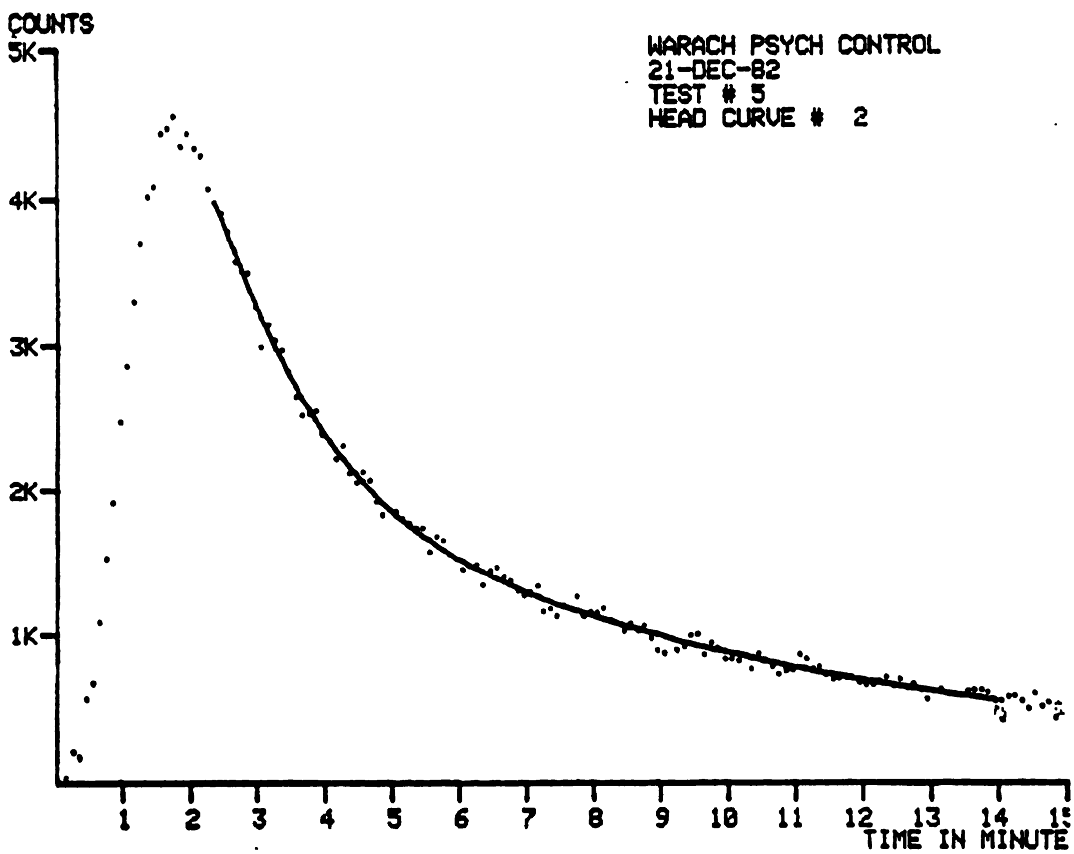
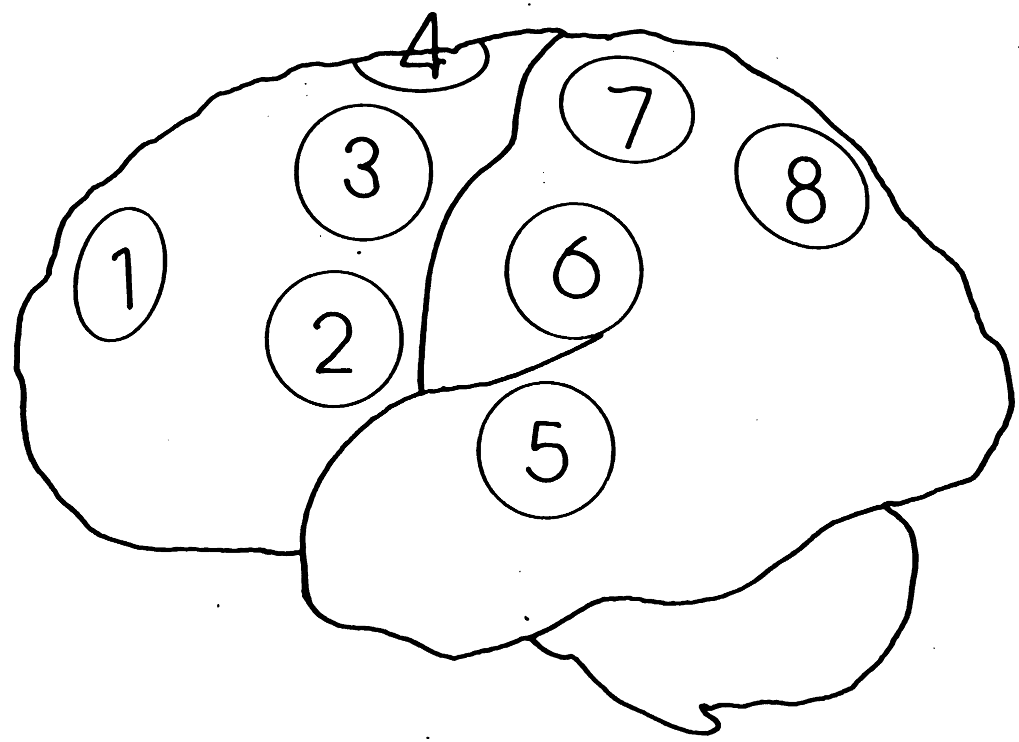

COUNTS
5K
4K
3K
2K
1K
WARACH PSYCH CONTROL
21-DEC-82
TEST # 5
HEAD CURVE # 2
1
2
3
4
5
6
7
8
9
10
11
12
13
14
TIME IN MINUTE

Figure 2. Location of detectors.

The approximate location of the tissue seen by the extracranial detectors. The detectors were attached to a helmet worn by the subjects and oriented at angles normal to the curvature of the skull. For ease of illustration only one hemisphere is depicted, but the locations were over homotopical regions of each hemisphere. The locations of the detectors were 1: prefrontal, 2: inferior precentral, 3: middle precentral, 4: superior precentral, 5: posterior superior temporal, 6: inferior parietal, 7: superior postcentral, 8: posterior parietal-superior occipital.

FIGURE 2



LOCATION OF DETECTORS

Figure 3. Sex differences in correlations during rest.

The right-left correlations for the 30 male and 31 female subjects are illustrated. All the correlation coefficients were very high, between .80 and .95, well beyond the .001 level of significance. In all 8 regions the correlation coefficients were higher for females than for males (chi square=8, df=1, $p < .01$).

FIGURE 3

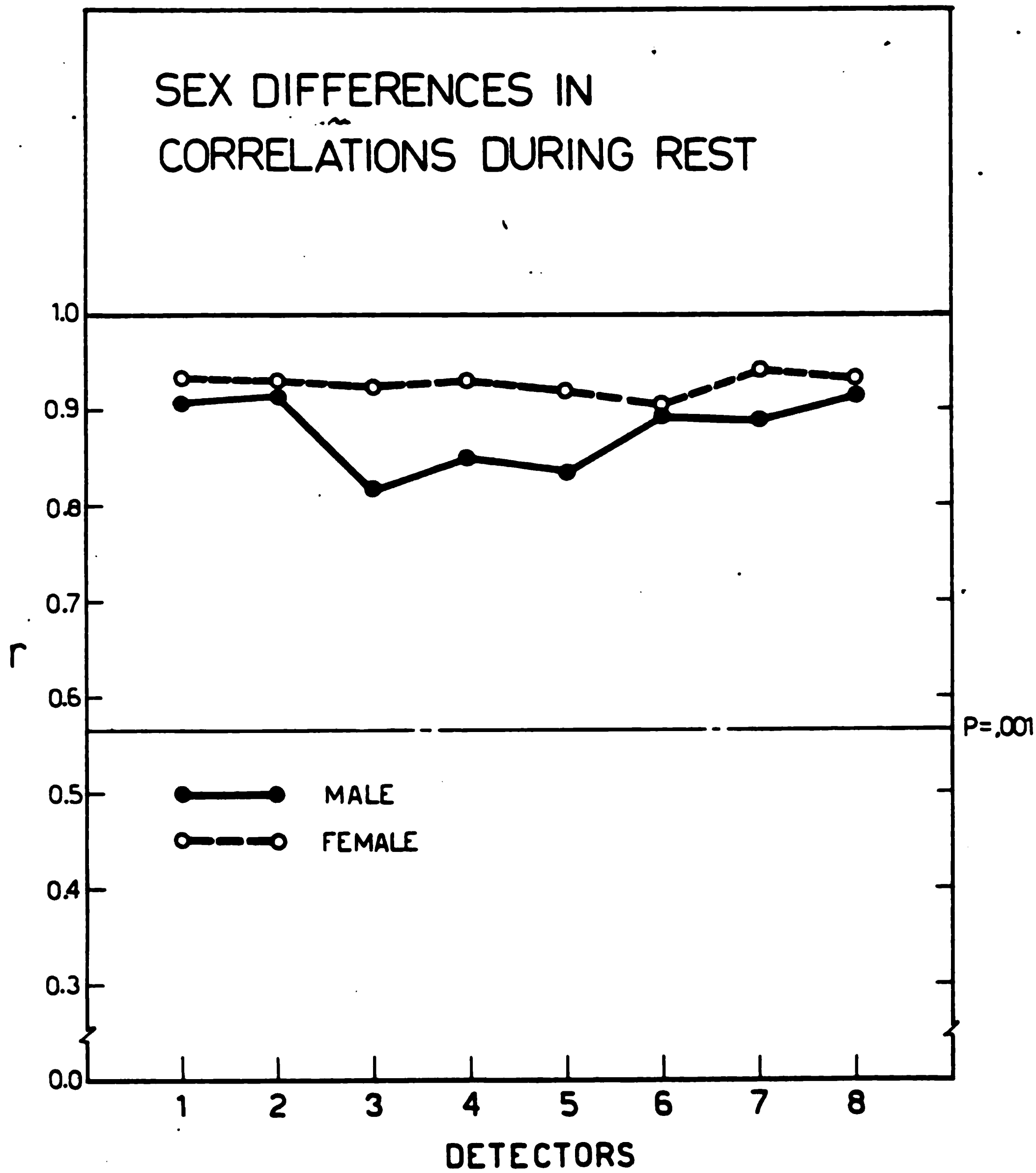

SEX DIFFERENCES IN
CORRELATIONS DURING REST
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.0
r
P=.001
MALE
FEMALE
1
2
3
4
5
6
7
8
DETECTORS

Figure 4. Sex differences in partial correlations during rest.

All 8 of the partial correlation coefficients for females were positive (chi square=8.0, df=1, $p < .01$). These correlations reached statistical significance at detectors 3, middle precentral region, and 7, superior postcentral region. The correlations for males were negative at 5 of the 8 loci, reaching significance at detector 3, the middle precentral region. The sexes differed significantly at detector 3: the partial correlation coefficient was more positive for the females than for the males. At 5 of the remaining 7 regions, the sexes differed in the same direction. The incidence of positive correlations was greater for females than for males (chi square=7.3, df=1, $p < .01$).

FIGURE 4

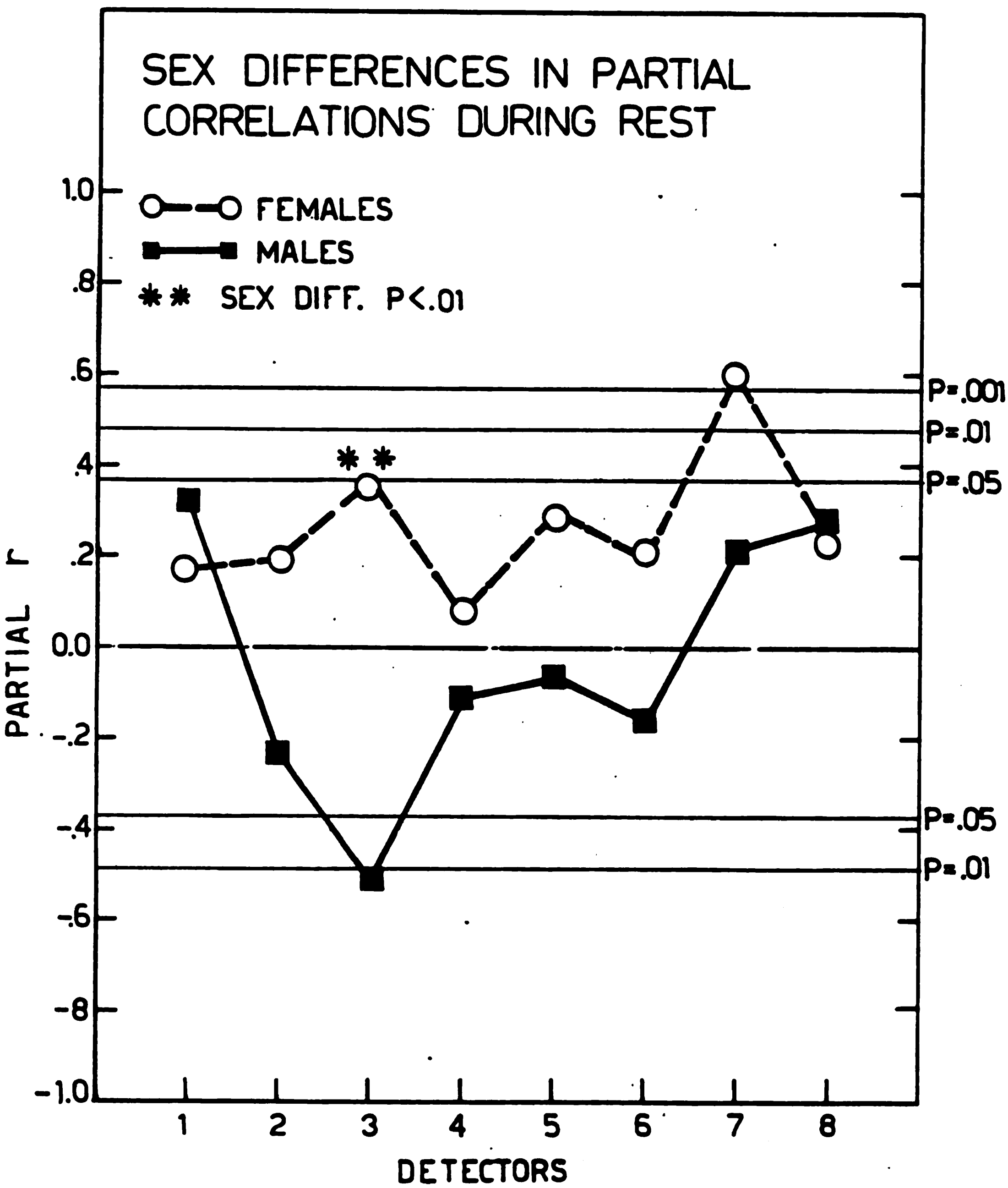

SEX DIFFERENCES IN PARTIAL CORRELATIONS DURING REST
FEMALES
MALES
** SEX DIFF. P<.01
1.0
.8
.6
.4
.2
0.0
-.2
-.4
-.6
-8
-1.0
PARTIAL r
P=.001
P=.01
P=.05
P=.05
P=.01
1
2
3
4
5
6
7
8
DETECTORS

Figure 5. Sex differences in partial correlations during rest: handedness groups.

Among right-handed subjects, all 8 of the partial correlation coefficients for females were positive (chi square=8.0, df=1, $p < .01$). These correlations reached statistical significance at detectors 2, inferior precentral, 3, middle precentral, 5, superior posterior temporal, and 7, superior postcentral. The correlations for males were negative at 4 of the 8 loci, and positive at 4 of the 8; reaching significance at detector 4 where a positive correlation was found. The sexes differed significantly at detectors 2 and 3, where partial correlation coefficients are more positive for the females than for the males, and at detector 4, where the correlation was more positive for males. At all of the 5 remaining regions, the female correlations were more positive. The incidence of positive correlations was greater for females than for males (chi square=5.3, df=1, $p < .05$).

Among left-handers, the partial correlation coefficients for females were positive at 7 of the 8 pairs of regions (chi square=4.5, df=1, $p < .05$). None of these correlations reached statistical significance. The correlations for males were negative at 5 of the 8 loci, reaching significance at detector 3, the middle precentral region. The sexes differed significantly at detector 3. Thus, the same sex difference in the correlation between the right and left middle precentral regions was found for left-handers as well as right-handers. At 5 of the remaining 7 regions, the sexes differed in a similar manner. The incidence of positive correlations was again greater for females than for males (chi square=4.3, df=1, $p < .05$), as was the case for the right-handers.

FIGURE 5

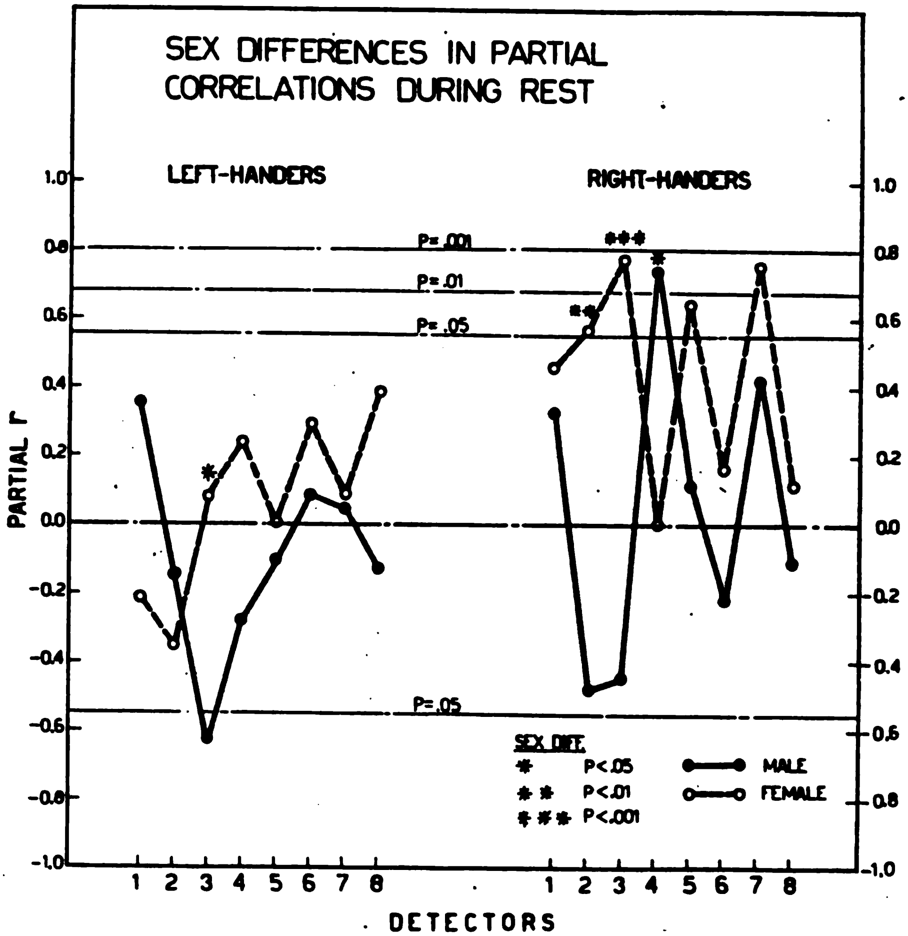

SEX DIFFERENCES IN PARTIAL CORRELATIONS DURING REST
LEFT-HANDERS
RIGHT-HANDERS
PARTIAL r
P=.001
P=.01
P=.05
P=.05
SEX DIFF.
* P<.05
** P<.01
*** P<.001
MALE
FEMALE
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
DETECTORS

Figure 6. Sex differences in asymmetry during rest.

The group of 30 males had significantly asymmetrical rCBF to the left hemisphere at regions 2, inferior precentral, and 4, superior precentral. The 31 females had a significant mean <u>right</u> asymmetry at region 4. Significant sex differences in asymmetry were found at both detectors 2 and 4. At detector 4 the sexes each have a significant asymmetry, but in opposite directions. The magnitude (absolute value) of the asymmetry was greater for males than for females at 7 of the 8 loci (chi square=4.5, df=1, $p < .05$). The direction of the asymmetry differed between the sexes at 5 of the 8 regions.

See Table 3 for sex differences among handedness groups during the cognitive tasks.

FIGURE 6

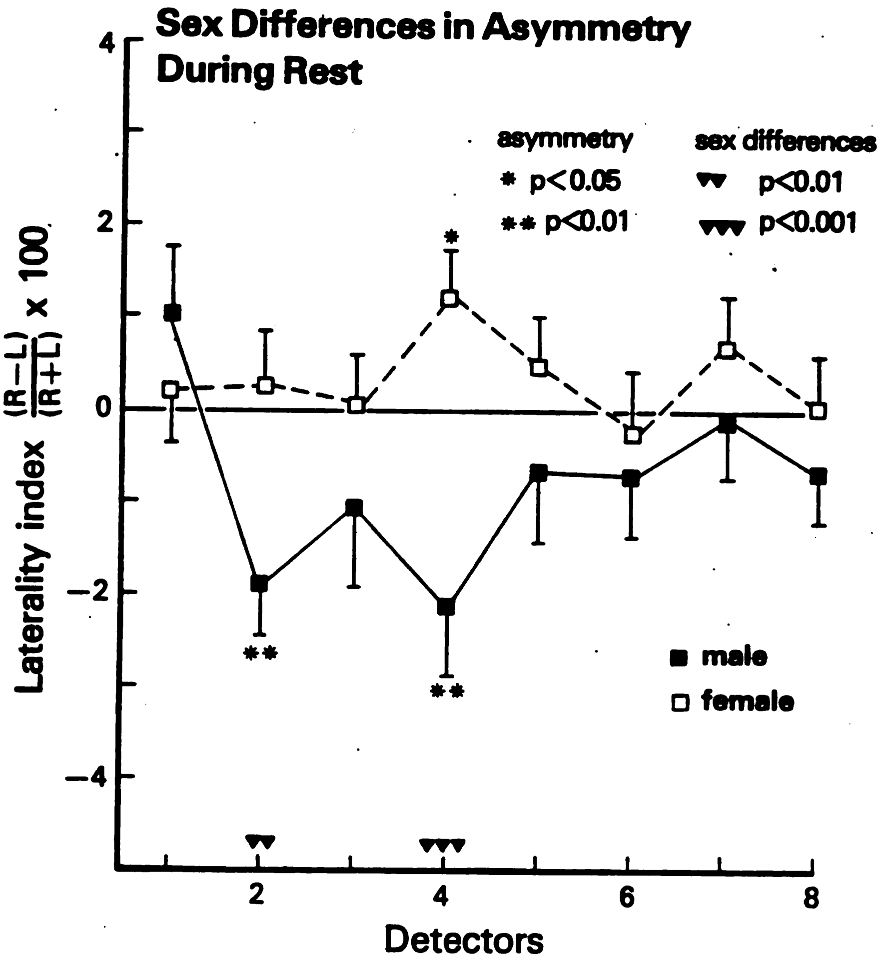
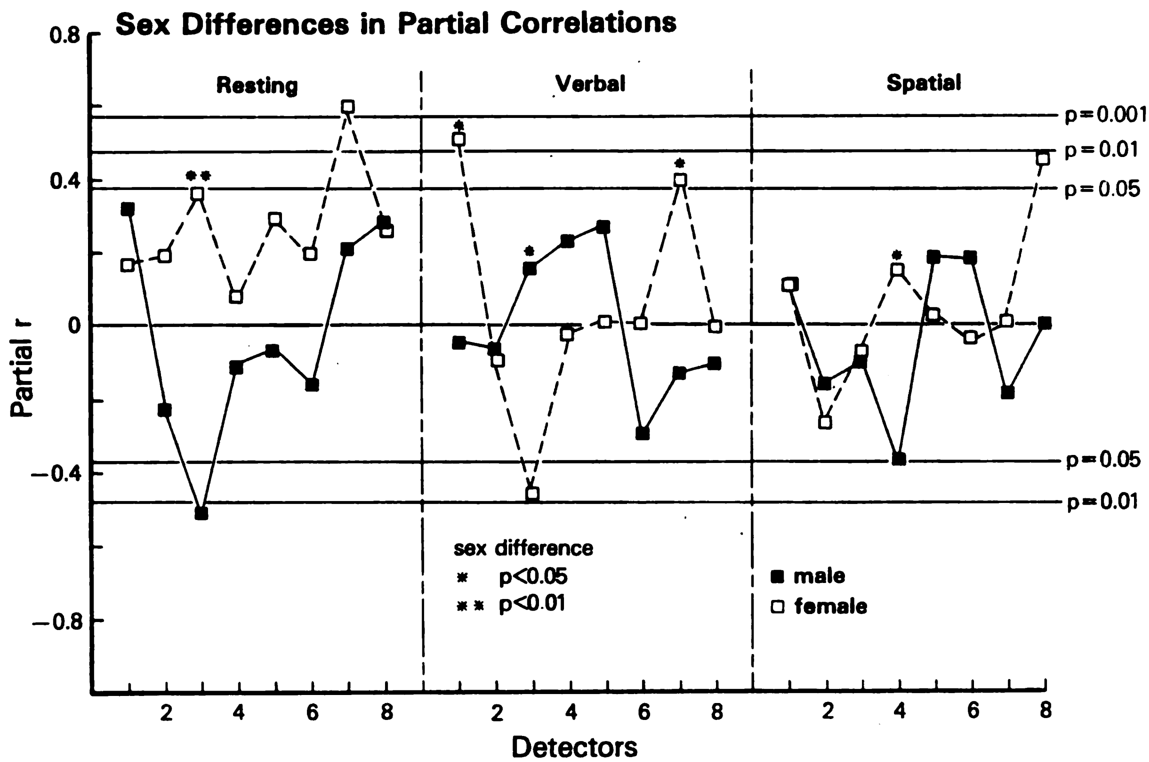

Sex Differences in Asymmetry
During Rest
asymmetry
* p<0.05
** p<0.01
sex differences
▼▼ p<0.01
▼▼▼ p<0.001
Laterality index (R−L)/(R+L) x 100
4
2
0
−2
−4
**
**
*
■ male
□ female
2
4
6
8
Detectors

Figure 7. Sex differences in partial correlations.

Resting: The results are as in Figure 4. Verbal: The partial correlation coefficients for females were positive at 4 pairs of regions and negative at 4 pairs. The positive correlations reached statistical significance at detector 1, the prefrontal region. A significant negative correlation occurred at detector 3, the middle precentral region, whereas during rest the females had a positive correlation at this region. The correlations for males were negative at 5 of the 8 loci; no correlations were significant for males. The sexes differed significantly at detectors 1 and 3: the partial correlation coefficient was more positive for the females than for the males at the prefrontal region, whereas it was more negative at the middle precentral region. The sex difference at the middle precentral region was opposite to that found during rest. At half of the remaining 6 regions, the females had more positive correlations than males; the opposite was true for the other three regions. Spatial: The partial correlation coefficients for females were positive at 5 of the 8 pairs of regions. These correlations reached statistical significance at detector 8, the posterior parietal-superior occipital region. The correlations for males, however, were negative at 5 of the 8 loci, reaching significance at detector 4, the superior precentral region. The sexes did not differ significantly at any detector. At 5 of the 8 regions, however, females had a mo

FIGURE 7



Sex Differences in Partial Correlations
0.8
0.4
0
-0.4
-0.8
Partial r
Resting
Verbal
Spatial
p=0.001
p=0.01
p=0.05
p=0.05
p=0.01
sex difference
* p<0.05
** p<0.01
■ male
□ female
2
4
6
8
Detectors

Figure 8. Sex differences in asymmetries.

Resting: The results are as in Figure 6. Verbal: The group of 30 males had significantly asymmetrical rCBF to the left hemisphere at 3 regions: 2, inferior precentral, 6, inferior parietal, and 8, posterior parietal-superior occipital. The 31 females had a significant mean left asymmetry at region 7, superior postcentral. Significant sex differences in asymmetry were found at both detectors 7 and 8. The magnitude of the asymmetry was greater for males than for females at 5 of the 8 loci, and the direction of the asymmetry differed between the sexes at 2 of the 8. Spatial: The group of 30 males had one significant asymmetry in rCBF. This asymmetry was at detector 8, posterior parietal-superior occipital, and despite the fact that the cognitive task was spatial the asymmetry was to the left hemisphere. At 6 of the other 8 detectors the asymmetry was to the right hemisphere but not significant. The 31 females had no significant asymmetry, but the mean asymmetry at detector 8 was also to the left. There were no significant sex differences, and except at detector 6 the asymmetries for both sexes were nearly identical.

FIGURE 8

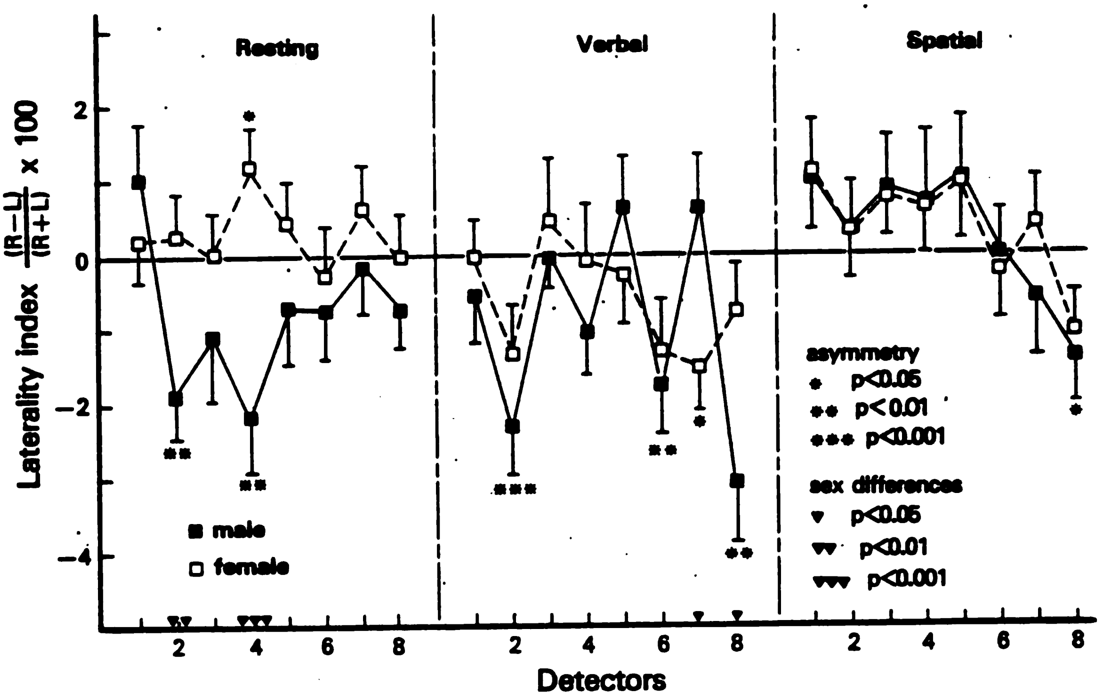

Resting
Verbal
Spatial
Laterality index $\frac{(R-L)}{(R+L)} \times 100$
2
0
−2
−4
male
female
asymmetry
* p<0.05
** p< 0.01
*** p<0.001
sex differences
▼ p<0.05
▼▼ p<0.01
▼▼▼ p<0.001
2
4
6
8
Detectors

Figure 9. Handedness differences in partial correlations.

Resting: In 7 of the 8 regions the partial correlation coefficients for right-handers were positive (chi square=4.5, df=1, $p < .05$). These correlations reached statistical significance at detectors 5, superior posterior temporal region, and 7, superior postcentral region. The correlations for left-handers were negative at 4 of the 8 loci. The positive correlation for left-handers at detector 8, posterior parietal-superior occipital, was significant. The handedness groups differed significantly at 4 detectors: 2, 3, 5, and 8, at which the correlation for right-handers were more positive than those for left-handers. Verbal: The partial correlation coefficients for right-handers were positive at 6 pairs of regions. The positive correlations reached statistical significance at detector 1, prefrontal, and 7, superior postcentral. A significant negative correlation occurred at detector 3, the middle precentral region. The correlations for left-handers were negative at 4 of the 8 loci; no correlations were significant for left-handers. The handedness groups differed significantly at detectors 1 and 7: the partial correlation coefficient was more positive for the right-handers than for the left-handers at both regions. At half of the remaining 6 regions, the right-handers had more positive correlations than left-handers; the opposite was true for the other three regions. Spatial: The partial correlation coefficients for right-handers were positive at 4 of the 8 pairs of regions. The positive correlations reached statistical significance at detectors 1 and 8, and a negative correlation was significant at detector 7. The correlations for left-handers were positive at 4 of the 8 loci also, but none were significant. Two significant handedness differences were found: at detector 1, prefrontal, the correlation for right-handers was more positive than left-handers, whereas at detector 7, superior postcentral, the correlation for right-handers was more negative. At 6 of the 8 regions right-handers had a more positive correlation than left-handers.

FIGURE 9

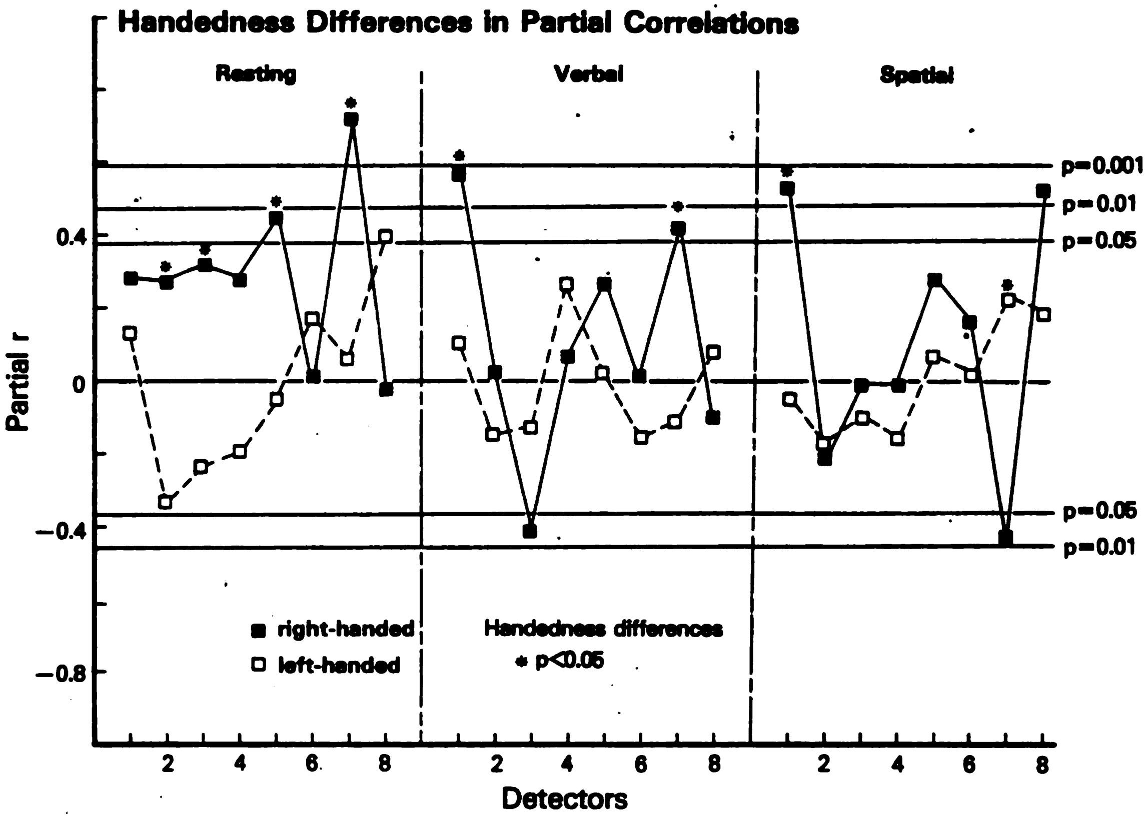

Handedness Differences in Partial Correlations
Resting
Verbal
Spatial
p=0.001
p=0.01
p=0.05
p=0.05
p=0.01
0.4
0
−0.4
−0.8
Partial r
right-handed
left-handed
Handedness differences
* p<0.05
2
4
6
8
Detectors

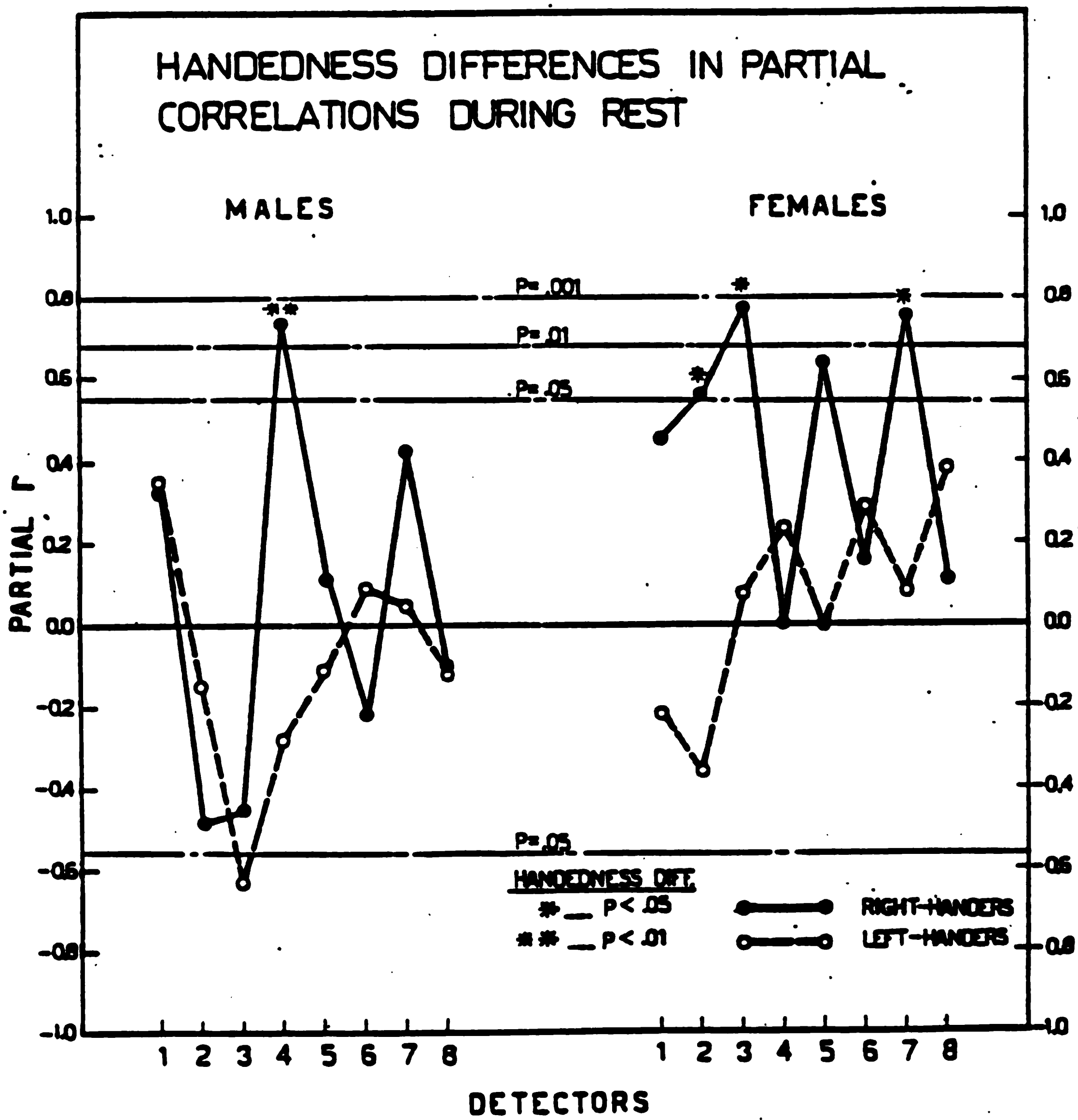
Figure 10. Handedness differences in partial correlations during rest: sex groups.

Among female subjects, all 8 of the partial correlation coefficients for right-handers were positive (chi square=8.0, df=1, $p < .01$). These correlations reached statistical significance at detectors 2, inferior precentral, 3, middle precentral, and 7, superior postcentral. The correlations for left-handers were positive at 6 of the 8 loci, none reaching significance. The handedness groups differed significantly at detectors 2 and 3, the partial correlation coefficients were more positive for the right-handers than for the left-handers. At 3 of the 6 remaining regions, the right-hander correlations were more positive.

Among males, the partial correlation coefficients for right-handers were positive at 4 of the 8 pairs of regions. A significant positive correlation occured at detector 4, the superior precentral region. The correlations for left-handers were negative at 5 of the 8 loci, none reaching significance. The handedness groups differed significantly at detector 4. At 4 of the remaining 7 regions, the handedness groups differed in the same direction.

See Table 4 for handedness differences among sex groups during the cognitive tasks.

FIGURE 10



HANDEDNESS DIFFERENCES IN PARTIAL CORRELATIONS DURING REST
MALES
FEMALES
PARTIAL r
P=.001
P=.01
P=.05
P=.05
HANDEDNESS DIFF.
* __ P<.05
** __ P<.01
RIGHT-HANDERS
LEFT-HANDERS
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
DETECTORS

Figure 11. Handedness differences in asymmetry during rest.

The group of 32 left-handers had no significant asymmetrical rCBF. The 29 right-handers had a significant mean left asymmetry at region 2. No significant handedness differences in asymmetry were found. The magnitude of the asymmetry was greater for right-handers than for left-handers at 5 of the 8 loci, and the direction of the asymmetry differed between the handedness groups at 3 of the 8.

FIGURE 11

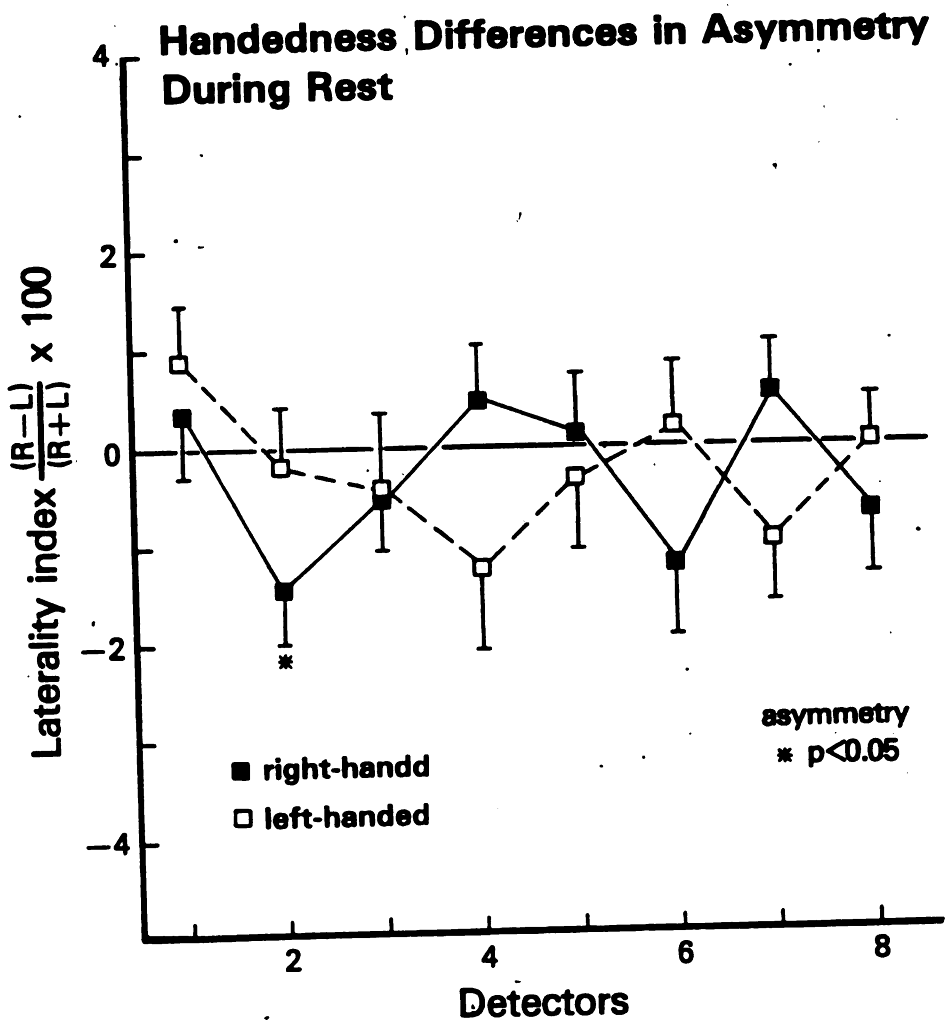

Handedness Differences in Asymmetry
During Rest
Laterality index (R−L)/(R+L) x 100
4
2
0
−2
−4
2
4
6
8
Detectors
*
asymmetry
* p<0.05
right-handd
left-handed

Figure 12. Handedness differences in asymmetries.

Resting: The results are as in Figure 11. Verbal: The group of 32 left-handers had significant asymmetrical rCBF to the left hemisphere at detector 2, inferior precentral region. The 29 right-handers had a significant mean left asymmetry at regions 2, 6, and 8. No significant handedness differences in asymmetries were found during verbal stimulation. The magnitude of the asymmetry was greater for right-handers than for left-handers at 5 of the 8 loci, and the direction of the asymmetry differed between the handedness groups at 3 of the 8. Spatial: The group of 29 right-handers had one significant asymmetry in rCBF. This asymmetry was at detector 8, posterior parietal-superior occipital, and, despite the fact that the cognitive task was spatial, the asymmetry was to the left hemisphere. At 6 of the other 8 detectors the asymmetry was to the right hemisphere but not significant. The 32 left-handers had significant asymmetries to the right at detectors 1 and 3. The mean asymmetry at detector 8 was to the left as was the case for right-handers, but it was not significant.

FIGURE 12

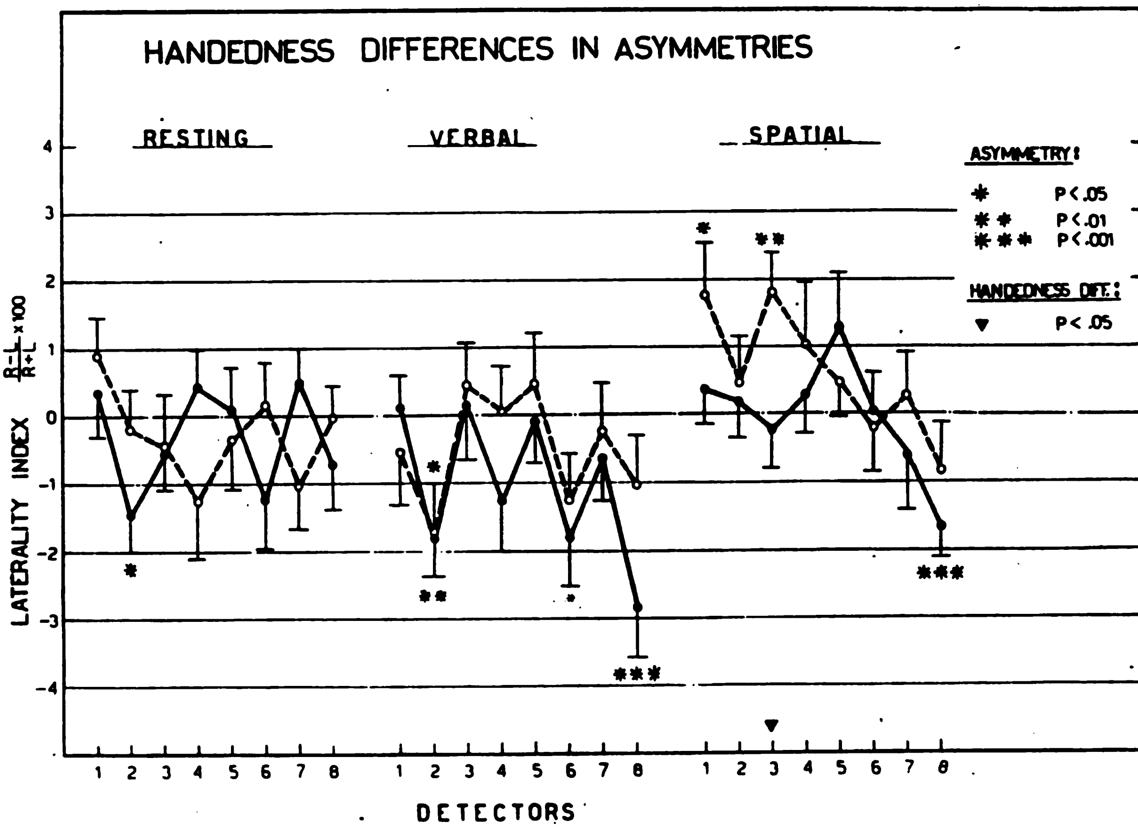

HANDEDNESS DIFFERENCES IN ASYMMETRIES
RESTING
VERBAL
SPATIAL
ASYMMETRY:
* P<.05
** P<.01
*** P<.001
HANDEDNESS DIFF.:
▼ P<.05
LATERALITY INDEX $\frac{R-L}{R+L} \times 100$
DETECTORS

TABLE 1. SEX DIFFERENCES IN RIGHT-LEFT CORRELATIONS

		MALE	FEMALE	RIGHT-HANDED MALE	RIGHT-HANDED FEMALE	LEFT-HANDED MALE	LEFT-HANDED FEMALE
N		30	31	15	14	15	17
DETECTORS							
RESTING	1	.907	.934	.918	.953	.893	.912
	2	.915	.931	.943	.954	.879	.914
	3	.817	.925	.894	.973	**.726	.895
	4	.848	.930	.983	.939	.763	.936
	5	.832	.919	.935	.957	**.716	.898
	6	.889	.905	.919	.906	.896	.922
	7	.887	.941	.938	.962	.824	.936
	8	.917	.936	.914	.930	.927	.953
VERBAL	1	.897	.938	.939	.971	.856	.911
	2	.878	.904	.945	.908	.796	.897
	3	.922	.791	.929	.692**	.940	.849
	4	.908	.837	.917	.864	.914	.862
	5	.899	.897	.957	.918	.881	.893
	6	.886	.865	.970 !	.789	.786	.929
	7	.880	.904	.928	.940	.857	.888
	8	.870	.891	.870	.908	.867	.923
SPATIAL	1	.866	.860	.958	.955	**.747	.798
	2	.864	.872	.934	.913	**.757	.844
	3	.833	.896	.899	.926	.865	.890
	4	.675 !	.888	.913	.901	+.259 !!	.877
	5	.791	.804	.809	.946	.855	.662**
	6	.914	.854	.946	.928	.883	.781
	7	.812	.847	.826	.819	.835	.863
	8	.877	.890	.939	.871	.765	.823

+ NOT SIGNIFICANT
** P < .01
ALL OTHER CORRELATION COEFFICIENTS SIGNIFICANT AT P < .001

SEX DIFFERENCE: ! P < .05
!! P < .01

TABLE 2. HANDEDNESS DIFFERENCES IN RIGHT-LEFT CORRELATIONS

				MALE		FEMALE	
		RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT
N		29	32	15	15	14	17
DETECTORS							
RESTING	1	.944	.921	.918	.893	.953	.912
	2	.953	.908	.943	.879	.954	.914
	3	.950	.865	.894	.726**	.973	.895
	4	.962 !	.858	.983!!!	.763	.939	.936
	5	.943 !	.837	.935	.716**	.957	.898
	6	.921	.920	.919	.896	.906	.922
	7	.963	.917	.938	.824	.962	.936
	8	.929	.953	.914	.927	.930	.953
VERBAL	1	.962	.897	.939	.856	.971	.911
	2	.932	.895	.945	.796	.908	.897
	3	.834	.899	.929	.940	**.692	.849
	4	.882	.914	.917	.914	.864	.862
	5	.936	.882	.957	.881	.918	.893
	6	.885	.900	.970 !	.786	.789	.929
	7	.914	.880	.928	.857	.940	.888
	8	.903	.908	.870	.867	.908	.923
SPATIAL	1	.960!!	.805	.958 !	.747**	.955 !	.798
	2	.927	.849	.934	.757**	.913	.844
	3	.917	.897	.899	.865	.926	.890
	4	.911 !	.751	.913!!	.259+	.901	.877
	5	.843	.767	.809	.855	.946 !	.662
	6	.939	.868	.946	.883	.928	.781
	7	.842	.889	.826	.835	.819	.863
	8	.951	.861	.939	.765	.871	.823

+ NOT SIGNIFICANT

** P < .01

ALL OTHER CORRELATION COEFFICIENTS SIGNIFICANT AT P < .001

HANDEDNESS DIFFERENCE: ! P < .05
!! P < .01
!!! P < .001

TABLE 3. SEX DIFFERENCES IN RIGHT-LEFT PARTIAL CORRELATIONS

				RIGHT-HANDED		LEFT-HANDED	
		MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
N		30	31	15	14	15	17
DETECTORS							
RESTING	1	.322	.172	.328	.454	.361	.216
	2	-.228	.194	-.478!!	.552*	-.149	-.352
	3	*-.509!!!	.362*	-.447!!!	.774**	*-.623 !	.080
	4	-.111	.076	** .742 !	.001	-.280	.240
	5	-.069	.292	.113	.638*	-.106	.004
	6	-.161	.193	-.221	.161	.091	.297
	7	.211	.600*	.428	.754**	.048	.076
	8	.286	.261	-.111	.121	-.127	.390
VERBAL	1	-.044 !	.510*	-.050!!	.794**	-.156	.145
	2	-.063	-.097	-.182	-.172	-.235	-.238
	3	.151 !	-.466*	-.031	-.554*	.406 !	-.433
	4	.232	-.026	.414	.379	-.203	.178
	5	.265	.006	.220	.335	.317	-.267
	6	-.290	.004	.137	-.052	-.485	.191
	7	-.132	.396*	.005 !	.759**	-.190	.064
	8	-.112	-.009	-.521	.208	.058	.044
SPATIAL	1	.103	.126	.529	.530	-.294	-.025
	2	-.167	-.269	-.066	-.438	-.233	-.124
	3	-.108	-.074	-.033	.073	.135	-.156
	4	*-.373	.145	.032	-.026	*-.532 !	.255
	5	.182	.022	.137	.567*	.453	-.259
	6	.175	-.046	.055	.226	.421	-.235
	7	-.190	.019	*-.587	-.478	.269	.185
	8	-.031	.442*	.170	.746	-.154	.276

SIGNIFICANT CORRELATION: * P < .05
** P < .01

SEX DIFFERENCE: ! P < .05
!! P < .01
!!! P < .001

TABLE 4. HANDEDNESS DIFFERENCES IN RIGHT-LEFT PARTIAL CORRELATIONS

				MALE		FEMALE	
		RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT
N		29	32	15	15	14	17
DETECTORS							
RESTING	1	.282	.132	.328	.361	.451	-.216
	2	.270 !	-.329	-.478	-.149	* .552 !	-.352
	3	.320 !	-.236	-.447	-.623	** .774!!	.080
	4	.278	-.198	** .742!!	-.280	.001	.240
	5	* .449 !	-.049	.113	-.106	.638	.004
	6	.010	.176	-.221	.091	.161	.297
	7	*** .717 !	.070	.428	.048	** .754	.076
	8	-.025	.396*	-.111	-.127	.121	.390
VERBAL	1	* .566 !	.104	-.050	-.156	** .794 !	.145
	2	.024	-.150	-.182	-.235	-.172	-.238
	3	*-.410	-.133	-.031	.406	*-.554	-.433
	4	.069	.272	.414	-.203	-.379	.178
	5	.273	.020	.220	.317	.335	-.267
	6	.011	-.155	.137	-.485	-.052	.191
	7	* .421 !	-.116	.005	-.190	** .759 !	.064
	8	-.103	.082	-.521	.058	.208	.044
SPATIAL	1	* .524 !	-.054	.529 !	-.294	.530	-.025
	2	-.213	-.170	-.066	-.233	-.438	-.124
	3	-.016	-.100	-.033	.135	.073	-.156
	4	-.015	-.160	.032	-.532*	-.026	.255
	5	.278	.073	.137	.453	* .567 !	-.259
	6	.160	.017	.055	.421	.226	-.235
	7	*-.429 !	.222	*-.587 !	.269	-.478	.185
	8	* .522	.187	.170	-.154	** .746	.276

SIGNIFICANT CORRELATION: * $P < .05$
** $P < .01$

HANDEDNESS DIFFERENCE: ! $P < .05$
!! $P < .01$
!!! $P < .001$

TABLE 5. SEX DIFFERENCES IN RIGHT-LEFT ASYMMETRIES.

MEAN (STANDARD ERROR OF MEAN) LATERALITY INDEX:
((RIGHT-LEFT)/(RIGHT+LEFT)) X 100

		MALE		FEMALE
N		30		31
DETECTORS				
RESTING	1	1.048 (.628)		.190 (.542)
	2	**-1.879 (.564)	!!	.262 (.561)
	3	-1.096 (.842)		.061 (.518)
	4	**-2.169 (.742)	!!!	1.197 (.519)*
	5	- .685 (.764)		.431 (.558)
	6	- .703 (.648)		- .313 (.688)
	7	- .169 (.601)		.635 (.579)
	8	- .699 (.533)		- .033 (.557)
VERBAL	1	- .509 (.635)		- .065 (.551)
	2	**-2.288 (.643)		-1.299 (.647)
	3	.102 (.515)		.471 (.834)
	4	- .105 (.547)		- .111 (.782)
	5	.638 (.697)		- .260 (.635)
	6	**-1.737 (.613)		-1.309 (.713)
	7	.653 (.710)	!	-1.481 (.591)*
	8	***-3.065 (.771)	!	- .761 (.664)
SPATIAL	1	1.025 (.682)		1.168 (.644)
	2	.336 (.643)		.319 (.617)
	3	.906 (.711)		.770 (.538)
	4	.694 (.959)		.685 (.640)
	5	1.015 (.843)		.953 (.748)
	6	.043 (.579)		- .217 (.639)
	7	- .643 (.724)		.398 (.660)
	8	*-1.370 (.605)		-1.078 (.552)

SIGNIFICANT ASYMMETRY: * P < .05
** P < .01

SEX DIFFERENCE: ! P < .05
!! P < .01
!!! P < .001

TABLE 6. SEX DIFFERENCES IN RIGHT-LEFT ASYMMETRIES FOR HANDEDNESS GROUPS.

MEAN (STANDARD ERROR OF MEAN) LATERALITY INDEX: ((RIGHT-LEFT)/(RIGHT+LEFT)) X 100

		RIGHT-HANDER		LEFT-HANDER	
		MALE	FEMALE	MALE	FEMALE
N		15	14	15	17
DETECTORS					
RESTING	1	.835(.937)	- .241(.764)	.262(.865)	.546(.771)
	2	**-2.414(.726)	- .395(.729)	-1.344(.868)	.803(.825)
	3	- .558(1.020)	- .546(.505)	-1.635(1.363)	.560(.843)
	4	- .665(.495)	! 1.638(.815)	*-3.672(1.300)	! .834(.677)
	5	- .721(.721)	1.108(.740)	- .649(1.377)	- .126(.809)
	6	- .923(.893)	-1.580(1.155)	- .482(.967)	.731(.757)
	7	.565(.698)	.389(.845)	- .902(.964)	.837(.814)
	8	-1.250(.782)	- .155(1.033)	- .147(.722)	.068(.586)
VERBAL	1	.012(.732)	.229(.567)	-1.030(1.047)	- .307(.903)
	2	*-1.800(.662)	-1.835(.882)	*-2.775(1.114)	- .858(.941)
	3	.072(.737)	.203(1.421)	.133(.746)	.691(1.011)
	4	*-1.773(.792)	- .685(1.254)	- .324(.733)	.362(1.003)
	5	.618(.609)	- .873(.873)	.659(1.281)	.244(.910)
	6	*-1.418(.530)	-2.259(1.264)	-2.056(1.123)	- .526(.763)
	7	1.120(.772)	!!-2.541(.719)**	.187(1.209)	- .607(.861)
	8	*-3.282(1.125)	-2.365(.860)*	*-2.848(1.092)	! .559(.879)
SPATIAL	1	.039(.683)	.711(.688)	2.010(1.150)	1.544(1.040)
	2	- .079(.726)	.449(.763)	.751(1.079)	.211(.953)
	3	- .838(.902)	.433(.696)	* 2.650(.921)	1.047(.810)
	4	.740(.831)	- .131(.879)	.648(1.765)	1.357(.905)
	5	.532(1.415)	2.045(.704)*	1.499(.952)	.054(1.214)
	6	.043(.937)	.000(.695)	.042(.714)	- .396(1.034)
	7	-1.958(1.146)	.839(1.013)	.672(.781)	.035(.886)
	8	*-2.009(.684)	-1.313(.510)*	- .730(.996)	- .885(.904)

SIGNIFICANT ASYMMETRY: * P < .05
** P < .01

SEX DIFFERENCE: ! P < .05
!! P < .01

TABLE 7. HANDEDNESS DIFFERENCES IN RIGHT-LEFT ASYMMETRIES

MEAN (STANDARD ERROR OF MEAN) LATERALITY INDEX:
((RIGHT-LEFT)/(RIGHT+LEFT)) X 100

DETECTORS		RIGHT-HANDER		LEFT-HANDER
N		29		32
RESTING	1	.316 (.607)		.881 (.571)
	2	*-1.439 (.540)		- .204 (.618)
	3	- .552 (.571)		- .469 (.792)
	4	.446 (.510)		-1.278 (.806)
	5	.162 (.536)		- .371 (.764)
	6	-1.240 (.714)		.162 (.606)
	7	.480 (.535)		.022 (.635)
	8	- .722 (.639)		- .033 (.452)
VERBAL	1	.116 (.460)		- .646 (.678)
	2	**-1.817 (.536)		-1.756 (.732)*
	3	.135 (.770)		.430 (.633)
	4	-1.248 (.725)		.041 (.627)
	5	- .102 (.537)		.438 (.758)
	6	*-1.824 (.661)		-1.243 (.667)
	7	- .647 (.624)		- .235 (.720)
	8	***-2.839 (.708)		-1.038 (.747)
SPATIAL	1	.364 (.480)		1.763 (.760)*
	2	.176 (.519)		.464 (.706)
	3	- .224 (.577)	!	1.798 (.616)**
	4	.319 (.599)		1.025 (.942)
	5	1.262 (.806)		.731 (.783)
	6	.023 (.579)		- .191 (.635)
	7	- .608 (.800)		.334 (.590)
	8	***-1.673 (.445)		- .812 (.659)

SIGNIFICANT ASYMMETRY: * P < .05

TABLE 8. HANDEDNESS DIFFERENCES IN RIGHT-LEFT ASYMMETRIES FOR SEX GROUPS

MEAN (STANDARD ERROR OF MEAN) LATERALITY INDEX: ((RIGHT-LEFT)/(RIGHT+LEFT)) X 100

		MALE		FEMALE	
		RIGHT-HANDER	LEFT-HANDER	RIGHT-HANDER	LEFT-HANDER
N		15	14	15	17
DETECTORS					
RESTING	1	.835(.937)	1.262(.865)	- .241(.764)	.546(.771)
	2	**-2.414(.726)	-1.344(.866)	- .394(.729)	.803(.825)
	3	- .558(1.020)	-1.635(1.363)	- .546(.505)	.560(.843)
	4	- .665(.495)	!-3.672(1.305)*	1.638(.815)	.834(.677)
	5	- .721(.721)	- .649(1.377)	1.108(.740)	- .126(.809)
	6	- .923(.893)	- .482(.967)	-1.580(1.155)	.731(.757)
	7	.565(.698)	- .902(.964)	.389(.845)	.837(.814)
	8	-1.250(.782)	- .147(.722)	- .155(1.033)	.068(.586)
VERBAL	1	.012(.732)	-1.030(1.047)	.229(.567)	- .307(.903)
	2	*-1.800(.662)	-2.775(1.114)*	-1.835(.882)	- .858(.941)
	3	.072(.737)	.133(.746)	.203(1.421)	.691(1.011)
	4	*-1.773(.792)	- .324(.733)	- .685(1.254)	.362(1.003)
	5	.618(.609)	.659(1.281)	- .873(.878)	.244(.910)
	6	*-1.418(.530)	-2.056(1.123)	-2.259(1.264)	- .526(.763)
	7	1.120(.772)	.187(1.209)	**-2.541(.719)	- .607(.861)
	8	*-3.281(1.125)	-2.848(1.092)*	*-2.365(.860) !	.559(.879)
SPATIAL	1	.039(.683)	2.010(1.150)	.711(.688)	1.544(1.040)
	2	- .079(.726)	.751(1.079)	.449(.763)	.211(.953)
	3	- .838(.902) !	2.650(.921)*	.433(.696)	1.047(.810)
	4	.740(.831)	.648(1.765)	- .131(.879)	1.357(.905)
	5	.532(1.415)	1.499(.952)	* 2.045(.704)	.054(1.214)
	6	.043(.937)	.042(.714)	- .396(1.034)	.000(.695)
	7	-1.958(1.146)	.672(.781)	.839(1.013)	.035(.886)
	8	*-2.004(.684)	- .730(.996)	*-1.313(.510)	- .885(.904)

SIGNIFICANT ASYMMETRY: * P < .05
** P < .01

HANDEDNESS DIFFERENCE ! P < .05

DISCUSSION

Sex and handedness differences have been found in interhemispheric correlations and in asymmetries in rCBF to homotopical regions.

SEX DIFFERENCES

The results of this study support the proposition that female brains are more functionally symmetric than male brains. During rest females had a greater frequency of positive correlations than males. The interhemispheric correlation of the female group was significantly more positive than for males at the middle precentral region for both right-handers and left-handers and more positive at the inferior precentral region for right-handers. Furthermore, males had a greater magnitude of right-left asymmetry at 7 of the 8 pairs of regions, 2 significant asymmetries to 1 for females, and the only significant asymmetry in each of the two handedness groups. During the verbal task right-handed females had significantly more positive correlations at 2 regions. Right-handed males had 4 significant asymmetries, and females had 2. During the spatial task, the total sample of males had one significant negative correlation and one significant asymmetry, whereas females had one significant positive correlation and no significant asymmetries. Thus, the general pattern of significant sex differences is that males show relatively negative interhemispheric correlations and more asymmetrical rCBF. According to the argument put forth in the introduction, the sexes would most generally differ in functional asymmetry along the dimension of hemispheric dominance.

<u>Inferior Precentral</u>. The regions that best differentiate the sexes are precentral. The inferior precentral detector measures rCBF in the vicinity of Broca's area and its right hemisphere counterpart. This homotopical pair is believed to be involved in complementary language functions: the left hemisphere is concerned with the propositional aspect of speech production, and the right hemisphere is concerned with the prosodic aspect of speech production (cf. Ross, 1981). Although no speech was produced during the resting condition, sex differences were found that may reflect sex-specific predispositions in speech production. Right-handed females showed a positive correlation and no asymmetry, suggesting interhemispheric symmetry of function. Right-handed males, however, showed a significantly more negative correlation that was marginally significant by itself ($p < .10$; the total group of males did have a significant negative correlation in this region), and a significant left asymmetry, suggesting a greater left hemisphere dominance for speech in right-handed males than females. This finding is therefore in agreement with the clinical data that have demonstrated a greater incidence of aphasia (McGlone, 1977) and a greater decrement in verbal relative to performance IQ (McGlone, 1978; Inglis and Lawson, 1982; Inglis et al., 1982) following left hemisphere stroke among males than females, a greater incidence of naming errors in male versus female patients following stimulation of left inferior frontal cortex (Mateer et al., 1982), and a greater discrepancy for males in oral fluency following alternate injection of sodium amytal into each hemisphere (McGlone, 1982). Although presented as a preliminary report, the latter data of McGlone are exactly what would have been predicted on

the basis of the present rCBF results. A left hemisphere asymmetry in rCBF to Broca's area in males coupled with a negative interhemispheric correlation, presumably interhemispheric inhibition, leads to the prediction that 1) when the right hemisphere is anesthetized its inhibition of the left hemisphere would be removed and the verbal fluency produced by the left hemisphere would increase, and 2) when the left hemisphere is anesthetized the predominant brain region for verbal production would be inactivated and, although the right hemisphere would be disinhibited, verbal fluency would decrease. That is what McGlone found. In the 6 right-handed males she studied, verbal fluency increased to 139.1% of baseline following right hemisphere injection and decreased to 33.2% of baseline following left hemisphere injection ($p < .02$). The positive correlation (symmetrical function) and slight, non-significant asymmetry for females in rCBF would lead to the following prediction for the McGlone study: verbal fluency would decrease after either hemisphere is injected, but slightly more following left hemisphere injection. This is exactly what McGlone found for her 7 right-handed female patients (McGlone, 1982).

Another implication of this more positive correlation for females in the inferior precentral region is that female speech is more prosodic than males speech. Such a hypothesis could be readily tested by comparing the sexes on moment-to-moment variability in frequency, amplitude, and speed of spontaneous speech.

Middle Precentral. The sexes differed at the middle precentral detector, which presumably measures rCBF to the vicinity of the hand area of motor cortex, the frontal eye fields, and surrounding tissue of premotor cortex. During rest, males had a negative correlation at this region and females had a positive correlation. During the verbal condition females had the more negative correlation. These sex differences held for either handedness group, with a greater difference for right-handers during rest and a greater difference for left-handers during verbal stimulation. The results thus suggest an interaction (not tested) of sex by handedness by task in the vicinity of the frontal eye fields. Such an interaction is reminiscent of the three way interaction of sex by handedness and writing posture by problem type that was found by Gur and Gur (1980) in their study of lateral eye movements. Gur and Gur (1980) also found that rightward eye movements of either handedness group were more positively correlated with hypnotic susceptibilty than those of their male counterparts. The relationship between those data and these is not entirely clear, but it does suggest that the sex differences observed in this study are a function of the activity of the frontal eye fields and surrounding tissue involved in orientation (cf. Mesulam, 1981).

Superior Precentral. During rest, males had a more postive correlation at the superior precentral region than females, and females had a relatively greater right asymmetry. This region probably includes tissue in the arm and trunk area of the motor cortex as well as premotor and supplementary motor cortex. Clinical studies have implicated supplementary motor cortex along the medial surface of the brain as a speech area (e.g., Masdeu et al., 1978), and a recent study in normal right-handed male subjects discovered a left metabolic asymmetry in this region related to the perception of a verbal discourse (R.B. Schwartz, personal communication, April, 1983). The sex difference in this region may be related to the language functions of this region, however, the direction of the sex difference in the superior precentral region is opposite to that found in the inferior precentral region, another region important in language.

HANDEDNESS DIFFERENCES

An assessment of the handedness hypothesis in light of the present data yields contradictory results. The correlational analysis seems to indicate a greater functional symmetry for right-handers. During rest, right-handers had more positive correlations than left-handers. The interhemispheric correlation was significantly more positive at four pairs of regions. During the verbal task the correlation was significantly more positive for right-handers at two regions, and during the spatial task the difference was more positive at one locus and more negative at another. The handedness difference was most evident among females. Right-handed females relative to left-handed females had a significantly more positive correlation at 2 regions during rest, 2 during verbal stimulation, and 1 during spatial; left-handed females had none. Furthermore, right-handed females had a significant positive correlation at 3 regions during rest, 2 during verbal, and 2 during spatial; left-handed females had no significant correlations at all. Thus, it would seem that right-handed females display a greater functional symmetry (positive interhemispheric correlations) than their left-handed counterparts. However, right-handed females show a greater asymmetrical rCBF than left-handers during cognitive tasks: they had a significant asymmetry at two homotopical pairs of regions during both verbal and spatial tasks;

left-handed females had no significant asymmetries. The apparent discrepancy could be explained by an argument that the asymmetry of a negative correlation between right and left hemispheric activity is independent of the asymmetry in the magnitude of right-left difference in activity. The data of the right-handed females at region 7 during the verbal task and region 5 during the spatial task would seem to support this argument: they show a significant positive correlation and a significant asymmetry. A positive correlation may reflect interhemispheric excitation, and this could be consistent with a greater activity in one hemisphere. However, a different explanation may also account for this apparent contradiction. The category of left-handers is considered to be heterogeneous with respect to brain laterality (e.g., Milner et al., 1964; Levy and Reid, 1976). It would be difficult to find a statistically significant effect in a heterogeneous group. A heterogeneous group would tend to show correlations near zero (i.e., non-significant) and small, non-significant mean lateral asymmetries. The data in this study are consistent with this explanation. Further analysis of these data to take degree of handedness, incidence of familial left-handedness, and eye dominance into consideration may determine the extent to which the present results are determined by left-hander heterogeneity.

Theories of Handedness. In the sample used in this study, there was a significant interaction of hemisphere by handedness [$F(1,57)=5.14$, $p=.027$]: a greater left hemisphere blood flow was observed in right-handers, and a greater right hemisphere blood flow was observed in left-handers. This result is not inconsistent with the theory considered by Harris (1980) that an asymmetrical blood supply causes manual asymmetry. Additional support for this theory are to be found in the results of Brooks et al. (1975), who found a greater right hemisphere asymmetry in CBF of left-handers (n=5) than right-handers (n=5). If the theory is correct one might expect the contralateral asymmetry to be greatest in brain regions concerned with motor functions of the arm and hand, viz., the middle and superior precentral regions of this study. Among males, there was, in fact, a greater right asymmetry for left-handers at the middle precentral region during the spatial task. However, during rest left-handers showed a greater left asymmetry at the superior precentral region. The latter finding of left-hemisphere asymmetry among left-handed males was consistent with the study of Prohovnik et al. (1980) who found that weakly right-handed males had a greater left-hemisphere flow to this region during rest than strongly right-handed males. They also found a greater overall left hemisphere asymmetry in the weakly right-handed group. Carmen et al. (1972) studied the question of handedness differences in cerebral blood supply. They report a greater blood volume to the frontal right hemisphere in right-handers and to the frontal left hemisphere in non-right-handers. Thus, although blood flow data open up an old theory for reconsideration, they do not as yet present a consistent enough picture to complete the reassessment, and the results could also be interpreted with equal ease as compatible with a converse theory that handedness causes asymmetrical cerebral blood supply.

GENERAL DISCUSSION

Relation to Anatomical Asymmetries. Could the observed sex and handedness differences be due to differences in anatomical asymmetries? Anatomical asymmetries have been described in frontal (Falzi et al., 1982; LeMay, 1977; Weinberger et al., 1982), temporal (Geschwind and Levitsky, 1968; Wada et al., 1975), occipital (Weinberger et al., 1982; LeMay, 1977), and parietal (LeMay and Culebras, 1977; DeLacoste-Utamsing and Holloway, 1982b) regions. Although trends toward sex and handedness differences have been noted (e.g., LeMay, 1977) the magnitudes of these differences have not been reported, so it is difficult to comment on the extent, if any, to which sex and handedness differences in anatomical asymmetries can account for group differences in rCBF. Anatomical asymmetries could not account for the fact that group differences in asymmetries and correlations are task dependent. For example, during all three tasks there was a significant handedness difference at the superior postcentral region. Right-handers had the more positive correlation during rest and the verbal task (for the females alone as well as for the total sample) and left-handers had the more positive correlation during the spatial task (for the males alone as well as for the total sample). Furthermore, Warach et al. (1983) found that the pattern of interhemispheric correlations in rCBF (the correlations reported in this study) can be distinguished from the pattern of interhemispheric correlations in the percent of grey matter (blood flow weight W1) measured simultaneously in the same sample of subjects. For example, the reverse pattern of sex differences is observed: males had a greater number of positive interhemispheric correlations and more strongly postive correlations of

W1 than females.

Critics may argue that the statements of anatomical localization in this study are questionable; however, the anatomical localization of the detectors seems to be valid. Two groups of right-handed males were studied by Gur et al. (in press) under the same cognitive conditions used in this study: one group received the verbal task and the other group received the spatial task. Local cerebral glucose metabolism was measured using positron emission tomography, a technique that permits three-dimensional anatomical localization. The spatial group had a significantly more rightward asymmetry than the verbal group in the inferior frontal and inferior parietal regions. The same task difference was obtained in this study for the entire sample: a more rightward asymmetry occurred during the spatial task compared to the verbal task at detector 2, the inferior precentral ($t(60)=3.69$, $p < .001$), and detector 6, the inferior parietal ($t(60)=2.34$, $p=.023$). Given the accuracy of the detectors at these regions it is very likely that the other detectors are of comparable accuracy.

<u>Regional Specificity</u>. The group differences that have been identified suggest some degree of regional specificity. Not only were there many regions for which there were no significant correlations, but at some regions during some tasks the group difference was opposite to the general pattern. For example, left-handed males were more asymmetrical than right-handed males during rest at the superior precentral region, and right-handed females were more asymmetrical than right-handed males at the same region. Thus, group differences in laterality are not a ubiquitous feature of the cerebral hemispheres, and regional neurophysiological studies such as these may help define

the parts of the brain most responsible for group differences in functional lateralities.

<u>Comparison with a Previous Study</u>. The results of this study may be compared to those of Prohovnik et al. (1980). The pattern of interhemispheric correlations found by Prohovnik et al. for right-handed males is different from the one found in this study. They found significant positive interhemispheric correlations at 15 of 16 pairs of homotopical regions in resting, young right-handed males. The only non-significant correlation coefficient was .014. The present study found significant positive correlations at only 1 of 8 pairs of regions and the direction of non-significant correlations was negative in 4 of 8 regions. There are some methodological differences between these two studies: 1) Different flow parameters were used in the two studies. The present study used Obrist's Initial Slope Index, whereas Prohovnik et al. used Risberg's Initial Slope Index. Although this difference, as discussed in the method section above, would bias the present data toward grey matter flow, there is no reason to expect such a dramatic difference in the results. 2) The current study examined regional values after partialling out the average flow to all regions and Prohovnik et al. expressed each regional value as a percent of hemispheric mean, an approximation of a statistical partialling precedure. Interhemispheric correlations were computed on the fifteen right-handed males of the present study after expressing regional values as the percent of hemispheric mean. These correlation coefficients show only small deviations from those obtained from the initial partialling procedure: the only significant positive correlation was still at the superior precentral region, although the

deviations for 6 of the 8 regions were in the positive direction. Thus, the difference in the partialling procedure can not account for the differences in results between the two studies. 3) Prohovnik et al. used a blood flow measuring system of 32 detectors at 16 homotopical loci oriented perpendicular to the sides of the head, not normal to the curvature of the skull, the method used in the present study study. Since Prohovnik et al. surveyed more regions (i.e., only a subset of the regions they studied were examined in the present study), it is unlikely that this methodological difference accounts for the difference in results. 4) Their subjects were blindfolded, those studied herein rested with their eyes open. One may speculate that absence of visual input induces positive interhemispheric correlations in rCBF. 5) The two studies differed in the method of statistical analysis. Prohovnik et al. used the procedure of computing their correlations on 99 measurements taken from only 22 subjects. Each subject was studied 4 to 8 times. Considering these repeated measures as independent for the purpose of analysis very likely inflated the value of the correlation coefficients and/or the likelihood of a correlation reaching statistical significance, thus accounting for the different results between the studies.

Resting measures and Task Initiation. In light of previous clinical and behavioral research it is somewhat surprising that the sex and handedness groups are most different in rCBF during rest rather than during cognitive stimulation. This could be explained by hypothesizing that the important difference between the groups is in the degree to which hemispheres have roles in initiating task specific cognition. In such a case, clinical studies would show the group differences that have been reported due to the destruction of tissue that is the primary initiator of a task. Functional asymmetries observed in normal subjects may be due to hemispheric differences in task initiation. Tachistoscopic and dichotic listening tests are speed tests, presenting stimuli for brief durations, and therefore evaluate performance in the initial processing of cognitively meaningful material. A hemisphere better at initiating a task would show a contralateral receptive field bias to brief stimuli, although a bias would not necessarily be seen if healthy subjects, having intact interhemispheric communication, were exposed to a stimulus for a longer period of time. If group differences in asymmetry are primarily due to asymmetry in task initiation, then a difference in activity summed over 10 to 15 minutes would be diminished from differences seen at the initial stages of processing. The resting state may be a state of preparedness in which neural initiators are active to an extent that allows easy activation of functionally specific regions. Accordingly, the resting state in this study would reflect group differences in cognitive style (neural readiness), whereas rCBF during cognitive stimulation would be the relatively common result of differing neuropsychological styles. The neuropsychological style of females, as suggested by this study, is one of interhemispheric cooperation; of males, hemispheric dominance. It should also be noted that rCBF in all 16 regions for all groups is greater during cognitive stimulation than during rest, i.e., although there are task specific regional asymmetries, <u>all</u> regions are activated by continuous cognitive activity. Lateral asymmetries, on the other hand, are not found at each region during the cognitive tasks. One is led to entertain the heretical thought that, in understanding the neuropsychology of cognition, functional asymmetries may be of relatively minor importance in comparison to complex interactions among all brain regions.

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