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CANADIAN THESES ON MICROFICHE

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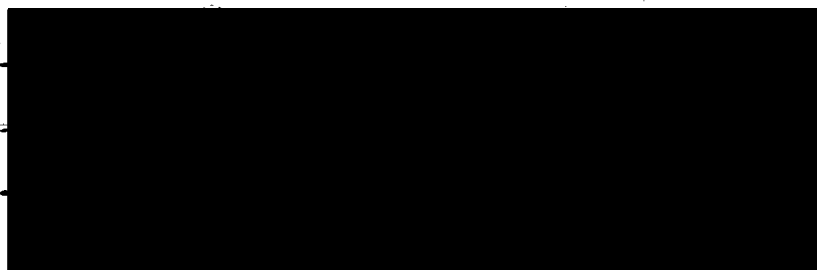
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SMOOTH PURSUIT EYE MOVEMENTS, CONJUGATE LATERAL EYE MOVEMENTS
AND THE MINNESOTA MULTIPHASIC PERSONALITY INVENTORY : CONVERGENCE
OF PUTATIVE VULNERABILITY MARKERS IN AN UNDERGRADUATE SAMPLE

by

Michael Patrick Kelley

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THE REQUIREMENTS FOR THE DEGREE OF

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of

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Smooth Pursuit Eye Movements, Conjugate Lateral Eye Movements
and the Minnesota Multiphasic Personality Inventory:
Convergence of Putative Vulnerability Markers in an
Undergraduate Sample

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ABSTRACT

Smooth pursuit eye movements (SPEM) were recorded using electro-oculography during visual tracking of .4 hertz and .8 hertz sinusoidal targets in 121 undergraduates, who were also administered the conjugate lateral eye movement (CLEM) test and the Minnesota Multiphasic Personality Inventory (MMPI). The digitized electrooculograph and target data were subjected to a Root Mean Square (RMS) analysis of tracking accuracy. Tracking was much poorer at the faster frequency. Leftmovers on the CLEM test had greater phase lag during SPEM than did rightmovers. Leftmovers also had higher RMS scores for averaged halfcycles, a measure of systematic tracking error. When median halfcycle RMS scores were examined (an accuracy measure more sensitive to transient tracking error) male leftmovers and female rightmovers had poorer tracking than male rightmovers and female leftmovers, respectively. Averaged across all subjects and both frequencies rightward tracking was superior to leftward tracking for the median halfcycle RMS measure. When individual SPEM asymmetry indices were examined an association was found between rightward tracking superiority and poorer overall tracking. Rightward SPEM superiority (or leftward SPEM impairment) and impaired overall SPEM were associated with high scores on a schizotypy scale of the MMPI. Leftward SPEM deficiency may indicate relative left hemisphere dysfunction, since neurological evidence implicates ipsilateral cortical mediation of SPEM. The findings are discussed in terms of the potential utility of SPEM and CLEM oculomotor lateralization indices as well as overall SPEM accuracy measures as markers of schizotypy or

vulnerability to schizophrenia spectrum psychopathology, which may be associated with a left hemisphere dysfunction. The sexes differ with respect to the characteristic direction of orienting or 'hemisphericity' associated with SPEM impairment and, by extension, vulnerability. Individual SPEM asymmetry deserves further study as a putative marker of schizotypy, with the longitudinal "biologically at risk" paradigm involving screening of normal populations as a recommended research strategy.

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TABLE OF CONTENTS

Approval..... ii

Abstract..... iii

Acknowledgements..... v

List of Tables..... ix

List of Figures..... x

I. Genetic and High Risk Studies of Schizophrenia..... 1

 Family Studies..... 1

 Twin Studies..... 8

 Adoption Studies..... 17

 Genetic Specificity and the Spectrum Concept..... 27

 Biological Heterogeneity..... 34

 Vulnerability..... 43

 Children of Schizophrenic Mothers..... 49

 Sampling Bias and Alternative High Risk Strategies..... 68

 The MMPI as a Vulnerability Marker..... 79

II. Lateralization of Function in Schizophrenia..... 85

 Language Disorder in Schizophrenia..... 91

 Neuropsychological Test Results of Schizophrenics..... 96

 Brain Damage..... 101

 Temporal Lobe Epilepsy..... 106

 Motoric Laterality..... 110

 Conjugate Lateral Eye Movements..... 124

 Torque - Clockwise Circling..... 131

 Anatomical Asymmetries..... 135

 Asymmetric Skin Conductance..... 140

Electroencephalographic Asymmetries	140
Evoked Potential Asymmetries	143
Cerebral Blood Flow Asymmetries	144
Corpus Callosum Dysfunction	145
Tactile Modality Asymmetries	145
Visual Modality Asymmetries - Tachistoscopic Studies	146
Auditory Modality Asymmetries	148
Interhemispheric Spillover	150
Summary and Conclusions	152
III. Smooth Pursuit Eye Movements in Schizophrenia	155
IV. The Neurophysiology of Eye Movement Control	181
Eye Movements	182
Frontal Eye Fields (FEF)	187
Visual Cortex	193
Posterior Parietal Cortex	195
Superior Colliculus	204
Cerebellum	209
Paramedian Pontine Reticular Formation	214
The Hemispheres and Eye Movement Control	222
The Neglect Syndrome, Attention and Hemispheric Activation	235
Neurophysiological Evidence Concerning CLEM	249
V. Introduction - Experimental Rationale	262
VI. Methods	267
Subjects	267

Apparatus	267
Procedure	269
Data Analysis	271
VII. Results	276
Frequency	276
Tracking Direction	280
Sex	281
CLEM	285
SEX x CLEM	287
Age	294
Individual SPEM Asymmetry	295
SPEM Accuracy and the MMPI	303
VIII. Discussion	308
Appendix I - CLEM Questions	337
Appendix II - ANOVA TABLES	339
Bibliography	374

LIST OF TABLES

Table I.	Morbidity risk estimates for parents and siblings of schizophrenic index cases.....	3
Table II.	Morbidity risk figures for schizophrenia compiled from the most important investigations of various authors.....	5
Table III.	Morbidity risk for schizophrenia when neither parent or at least one parent is schizophrenic.....	6
Table IV.	Psychopathology in the offspring of schizophrenic couples.....	7
Table V.	Concordance rates in twin studies of schizophrenia.....	9
Table VI.	The effect on MZ and DZ concordance rates of different diagnostic criteria for classifying cotwins.....	13
Table VII.	Pairwise and probandwise concordance rates for MZ and DZ twins.	14
Table VIII.	Schizophrenic illness in biologic paternal half sibs of index and control adoptees.....	22
Table IX.	Etiotypes and their potential markers.....	45
Table X.	Psychiatric disability and left sided lesions.....	102
Table XI.	Psychiatric disability, sensory motor and visual field defect.	103

LIST OF FIGURES

Figure 1 - Frequency and Tracking Direction277

Figure 2 - Phase Lag, Frequency, Sex and CLEM279

Figure 3 - .4 Hz. Median Halfcycle RMS, Tracking Direction,
Sex and CLEM282

Figure 4 - Frequency, Sex and CLEM289

Figure 5 - .8 Hz. Median Halfcycle RMS, Sex and CLEM291

Figure 6 - .8 Hz. Overall RMS, Sex and CLEM292

Figure 7 - Tracking Direction, Sex and CLEM293

I. Genetic and High Risk Studies of Schizophrenia

Family Studies

The first studies to examine the genetic contribution to schizophrenia utilized the family study method. If the occurrence of schizophrenia is influenced by genetic factors, then those individuals who are closely biologically related to schizophrenics should show an increased incidence of schizophrenia compared to the incidence in the general population, as relatives share a greater proportion of their genes than unrelated individuals. First degree relatives share about 50% of their genes, second degree relatives about 25%, etc., so the closer the biological relationship to a schizophrenic subject, the greater the incidence of schizophrenia should be if genetic factors are operative in the etiology of the disorder. To determine if this is the case information is needed concerning the incidence of schizophrenia in the general population and the incidence in relatives of different degree.

The incidence of schizophrenia in the general population may be determined by several methods. The different methods

yield different estimates of the 'morbidity-risk' for schizophrenia, that is, the probability that any individual in a population will develop the disorder if he or she lives to a certain age. The normal proband or genealogical random test method starts with a random sample of nonschizophrenic subjects and determines the morbidity-risk among their relatives. With the birth-register method a random sample or consecutive series of names is obtained from an old birth register and the incidence among these individuals in adulthood is assessed using interview or archival data. In the census method, all individuals in a specific geographical area are psychiatrically evaluated and the incidence of schizophrenia among them is determined. The rates of schizophrenia in various studies have ranged from .35 to 2.85 percent, with a mean and median value of around .85%. The variation in estimates across the various studies may be the result of methodological differences such as differences in the three sampling procedures used, differences in diagnostic procedures used to define schizophrenia, or differences in the age of risk used by the investigator. They may also be the result of cultural differences in psychosocial or environmental factors contributing to the development of a predisposition to schizophrenia. Finally, variations in the incidence of schizophrenia in different population studies may suggest that the frequency of the implicated genotype may vary in different population gene pools. Despite this variation, we

can be reasonably sure that if the incidence of schizophrenia in the families of schizophrenic subjects is greater than 3%, this represents an excess above the general population incidence.

A summary of fourteen studies utilizing the family method is provided in Table I. It can be seen that the rates of schizophrenia among parents and sibs of schizophrenics are higher than in the general population, the family rates varying from about 2 to 46 times the population rates.

TABLE I
Morbidity risk estimates for parents and siblings of schizophrenic index cases.

Study	Number of Probands	Estimated morbidity risk		
		Parents	Sibs	Sibs : Parents : General Population
Brugger (1928)'	85	4.3	10.3	2.4:1 1.53
M. Bleuler (1930)''	100	2.0	4.9	2.5:1
Schulz (1932)'	660	2.6	6.7	2.6:1 0.76
Luxemburger (1936)'	128	11.7	7.6	.65:1 0.85
Smith (1936)'	200	1.2	3.3	2.8:1
Galatschjan (1937)'	214	4.9	14.0	2.9:1
Stromgren (1938)''	195	0.7	6.7	9.6:1 0.48
Kallmann (1938)'''	1047	2.7	7.5	2.8:1 0.35
M. Bleuler (1941)'	100	5.6	10.4	1.9:1 1.53
Kallmann (1946)'''	691	9.2	14.3	1.6:1
Book (1953)''''	80	12.0	9.7	.81:1 2.85
Slater (1953)'	158	4.1	5.4	1.3:1
Hallgren & Sjogren (1959)''	247	0.2	5.7	28.5:1 0.83
Garrone (1962)'''''	227	7.0	8.6	1.2:1 2.40

Age of risk	' 15-40 yrs.	(from Rosenthal, 1971).
	'' 20-40 yrs.	
	''' 15-45 yrs.	
	'''' 15-50 yrs.	
	'''''' 15-70 yrs.	

There is a correlation between the reported incidence of schizophrenia in the general population and the incidence found among parents or sibs (rho correlations are .75 and .71 respectively), suggesting variations in the frequency of pathological genes in the various populations (Rosenthal, 1971). From the table it is apparent that, with the exception of the Luxenburger (1936) and Book (1953) studies, the rate of schizophrenia in sibs is consistently higher than that in parents. This may be a result of the fact that schizophrenics are less likely than normals to marry, and likely to have fewer children if they do marry. Thus, the parents of schizophrenics represent a select group, as many potential schizophrenic parents are weeded out and do not make it into the studies (Rosenthal, 1970).

Among the first degree relatives of schizophrenics, the average risk for the disorder is roughly between 8 and 10%. If genetic factors are operative, the incidence of the disorder among second degree relatives should be less than that for first

degree relatives, but greater than the general population incidence. A compilation of morbidity-risk figures for various relatives from several studies is presented in Table II (from Zerbin-Rudin, 1972). Clearly, the risk for schizophrenia increases dramatically with increasing genetic relationship. Thus, relatives who share fewer genes with an affected individual have a lower expectancy for schizophrenia than those who share more of their genes with a schizophrenic.

TABLE II

Morbidity risk figures for schizophrenia compiled from the most important investigations of various authors.

Relationship to a Schizophrenic	Morbidity Risk (corrected percentages)	
Parents	5 - 10%	(6.3 +/- 0.3)
Children	9 - 16	(13.7 +/- 1.0)
Siblings	8 - 14	(10.4 +/- 0.3)
Dizygotic twins	5 - 16	
Monozygotic twins	20 - 75	
Children of 2 affected people	40 - 68	
Half siblings	1 - 7	(3.5 +/- 1.7)
Stepsiblings	1 - 8	
Grandchildren	2 - 8	(3.5 +/- 0.7)
Cousins 2 - 6		(3.5 +/- 0.4)
Nieces and nephews	1 - 4	(2.6 +/- 0.3)
Uncles and aunts	2 - 7	(3.6 +/- 0.3)
Grandparents	1 - 2	(1.6 +/- 0.5)

(from Zerbin-Rudin, 1972)

Another type of evidence supporting the influence of genetic factors provided by family studies comes from different rates of schizophrenia among subjects with none, one, or both parents diagnosed as schizophrenic. If neither parent is schizophrenic the morbidity-risk for a sibling of an affected individual ranges from 5.5% to 12.2%, whereas if at least one parent is schizophrenic, the risk increases to 8.1% to 33.7%, as shown in Table III.

TABLE III

Morbidity risk for schizophrenia in sibs of schizophrenics when neither parent or at least one parent is schizophrenic

Study	Parental Schizophrenia Neither at least one Morbidity (percent)	Percent Increase
Schulz (1932)	6.6%	23
Luxenburger (1936)	6.7	82
Galatschjan (1937)	12.2	91
Kallmann (1938)	6.5	80
Book (1953)	9.0	41
Garrone (1962)	5.5	513

(from Rosenthal, 1971).

It is apparent that in every study, the risk for schizophrenia in siblings of affected individuals is greater if at least one parent is schizophrenic than if neither are. The rate of schizophrenia in children of two schizophrenics is higher still, averaging 24.7% across the five studies listed in Table IV.

TABLE IV
Psychopathology in the offspring of schizophrenic couples.

Study	Schiz.	Questionable Schiz.	Other Psychopath.	Normal	Total N
Kahn (1923)	7	2	5	3	17
Kallmann (1938)	13	3	16	3	35
Schulz (1940)	13	5	22	20	60
Elsasser (1952)	12	3	12	32	59
Lewis (1957)	4	0	3	20	27
Total	49	13	58	78	198

(from Rosenthal, 1967).

Another interesting finding apparent in Table IV is that the families of 2 schizophrenic parents contain not only more

schizophrenic children, but also more psychopathology in general. About 60% of the children of schizophrenic couples have some form of psychopathology. This suggests a lack of specificity of the schizophrenic genotype, in other words, the genotypic component of schizophrenia may give rise to a whole spectrum of psychopathology.

The family study method has certainly provided evidence consistent with the hypothesis of a genetic factor in schizophrenia, but this evidence is inconclusive. The studies cannot separate the influence of genes from the influence of familiarly mediated environmental factors, such as rearing by a schizophrenic parent(s).

Twin Studies

The strongest evidence for genetic factors in the etiology of schizophrenia comes from studies of twin pairs, at least one of whom is schizophrenic. This method is based on the fact that there are two types of twins: monozygotic or identical twins, who are formed from the same zygote and share identical genes, and dizygotic or fraternal twins, who are formed from different ova and sperm and so share only half of their genes in common, as many as regular siblings. If genetic factors are operative, the monozygotic (MZ) twin pairs should be concordant (both twins affected) for schizophrenia more often than dizygotic (DZ) twin

pairs.

TABLE V
Concordance rates in twin studies of schizophrenia.

Study	Sampling		MZ Twins		DZ Twins	
	Method	Location	N (pr)	%Con.	N (pr)	%Con.
Luxenburger (1928)	CA & RHP	Germ	17-27	33-77	48	2.1
Rosanoff (1934)	RHP	US&Can	41	61.0	101	10.0
Essen-Moller (1941)	CA	Sweden	7-11	14-71	24	8.3-17
Kallmann (1946)	RHP & CA	USA	174	69-86	517	10-14.5
Slater (1953)	RHP & Ca	Engl	37	65-74.7	115	11.3-14
Inouye (1961)	NSS	Japan	55	36-60	17	6-12
Tienari (1963, 1968)	TR	Finland	16	0-6	21	4.8
Gottesman & Shields (1966)	CA	England	24	41.7	33	9.1
Kringlen (1967, 1968)	TR	Norway	55	25-38	172	8-10
Fischer (1968)	TR	Denmark	16	19-56	34	6-15
Hoffer, et al (1969)	TR	US Vets	80	15.5	145	4.4
Fischer, Harvald & Hause (1969)	TR	Denmark	21	24-48	41	10-19
Pollin, et al (1969)	TR	USA	95	14-25	125	4-5
Tienari (1971)	TR	Finland	17	6-36	20	5-14
Gottesman & Shields (1972)	CA	England	22	40-50	33	9-10

CA = Consecutive admissions

RHP = Resident Hospital Population

TR = Twin Register

NSS = No Systematic Sampling

(from Rosenthal, 1971 and Gottesman & Shields, 1976).

In the many studies summarized in Table V, all but the Tienari

(1963, 1968) studies provide impressive evidence that MZ concordance for schizophrenia is significantly higher than DZ concordance rates, which approximate those for regular siblings. Overall, the earlier studies tended to produce generally higher concordance rates due to differences from later studies in sampling procedures, determination of zygosity, diagnostic procedures, the method of determining concordance rates, and the age of the sample. Each of these methodological considerations will be considered in turn, but even in later studies using more sophisticated methods, the consistent findings have been of significantly higher concordance rates in MZ compared to DZ twins pairs.

One source of sampling bias that may have produced inflated concordance rates in several of the earlier studies was the use of a resident hospital population as the starting point in the search for a sample of twins. For instance, Kallman (1946) started with the resident population of 20 hospitals and added subsequent admissions over 9 years. Since resident populations generally have a more severe form of schizophrenia, with a chronic deteriorating course, the use of a resident population biases the sample toward greater severity of illness.

Rosenthal (1959, 1961, 1962) in a reanalysis of Kallman's data, showed that the cotwins of more severely ill index twins had a higher morbidity rate for schizophrenia. This association between severity of illness and concordance rates produces a

high concordance rate in studies using more severely ill index twins, such as would be found in a resident hospital population. The use of consecutive admissions, such as in the studies of Essen-Moller (1940, 1971) and Gottesman and Shields (1966), produces lower concordance rates, since the samples include less severely ill schizophrenics. The twin register method produces still lower concordance rates since the starting point for the sample is not a psychopathological population (consecutive admissions or residents of a hospital) but rather a large group of twin pairs including normal twins. For instance, Pollin, et al (1969) identified all twin pairs born between 1917 and 1927 of whom both had been enlisted in the military. Since draftees were rejected because of schizophrenia, all those twin pairs in which one of the twins had early onset schizophrenia were eliminated from consideration, thus biasing the sample toward health rather than severe illness. Despite these sampling differences, the results of these studies consistently show higher concordance rates in MZ than DZ twins.

Another methodological flaw of the earlier studies was the use of inaccurate means of determining the zygosity of twin pairs. Most of the early studies used physical resemblance as the criterion for zygosity, and so some dizygotic twins bearing a close resemblance were misclassified as monozygotes. Although physical resemblance and a few questions about birth can yield accurate zygosity determination in over 90% of cases (Cohen, et

al, 1973; Nichols & Bilbro, 1966), the use of fingerprints and blood typing produces much greater accuracy. If twins are identical with respect to the 10 blood groupings commonly used (B, M_S, Rh, Pt, Le neg, K neg, Lu neg, Fy neg, Yt, and Do) there is a greater than 98% chance that they are monozygotes. If discordant MZ cases were incorrectly classified as DZ, MZ concordance rates would be inflated. It is possible that this sort of error occurred in some earlier studies, such as Luxenburger (1928) or Kallman (1946). Later studies using blood typing produced lower concordance rates. The bias due to zygosity determination inaccuracy, however, is probably not as great as bias resulting from sampling procedures.

Two sources of interstudy variation arise from differences in diagnostic procedure. First, all of the early studies failed to use blind diagnostic procedures when evaluating cotwins. Thus, estimates of concordance would be inflated since cotwins with questionable schizophrenia or character disorders might be diagnosed as schizophrenic by diagnosticians influenced by the knowledge of the index twin's schizophrenic diagnosis. Another source of variation across studies is the use of differing diagnostic criteria. For instance, Kallman (1946) used a broad 'Americanized' set of diagnostic criteria which undoubtedly included some borderline or psychoneurotic schizophrenics. When less strict diagnostic criteria are used, concordance rates are higher than with stricter criteria, as illustrated by the data

of Fischer, et al (1969), reproduced in Table VI.

TABLE VI
The effect on MZ and DZ concordance rates of different diagnostic criteria for classifying cotwins.

Grade	Probandwise Concordance	
	MZ	DZ
I. Definite Kraepelinian schizophrenia	36%	18%
II. Includes paranoid, atypical and schizophreniform psychoses	56%	26%
III. Includes any cotwin with noted psychiatric abnormality	64%	41%

(from Fischer, et al, 1969).

Varying methods of calculating concordance rates yield different estimates. Using the probandwise method one calculates the concordance rate in cotwins of an index sample of independently ascertained schizophrenics. If both members of a twin pair are independently ascertained, that pair will be represented twice in the concordance statistic, thus artificially inflating the value. In the pairwise method one calculates the proportion of all pairs in which both twins are schizophrenics, thus yielding a more conservative and accurate

estimate of concordance rates. The differences in the values obtained by these two methods is illustrated in Table VII. Even with the more conservative pairwise method, MZ concordance is higher than DZ in all of the studies.

TABLE VII
Pairwise and probandwise concordance rates for MZ and DZ twins.

Study	MZ Twins			DZ Twins		
	N (pr)	Pair-wise	Proband-wise	N	Pair-wise	Proband-wise
Kringlen (1968)	55	25-38%	45%	90	4-10%	15%
Fischer, et al (1969)	21	24-48	56	41	10-19	26
Pollin, et al (1969)	95	14-27	43	125	4-5	9
Tienari (1971)	17	6-36	35	20	5-14	13
Gottesman & Shields (1972)	22	40-50	58	33	9-10	12

(from Kessler, 1980).

Another source of variation is the age range of the sample. The age of risk for schizophrenia is generally considered to be 15-45 years old. If one uses a relatively young sample, many index twins and their cotwins will still be in the risk period. If a cotwin is not diagnosed as schizophrenic, the

pair is considered discordant, but the cotwin still has time to manifest clinical symptomatology and the pair may actually be concordant eventually. Thus, using a younger sample will lead to an inaccurately low concordance estimate. An age correction in which older subjects' data are weighted more heavily may be used, but this probably leads to an overcorrection since there is a significant correlation between the ages of onset within a twin pair (Hoffer & Pollin, 1970). One study (Fischer, et al, 1969) used a sample of advanced age, in which all twin pairs had passed the age of risk, thus eliminating the need for age correction. Their results still showed MZ concordance to be double the DZ rate.

Despite the methodological variations among the twin studies, the findings all impressively demonstrate that monozygotic twins are significantly more often concordant for schizophrenia than dizygotic pairs, thus providing strong support for genetic theories of schizophrenia. However, like the family studies, the twin studies fail to separate genetic effects from the influence of rearing by psychopathological parents. The fact that both of the twins are reared by their biological parents does not insure that environmental influences are held constant. MZ and DZ twins may differ not only in the number of genes shared, but may also be subjected to different environmental influences. Jackson (1960) argued that MZ twins were at special risk for psychopathology since they are more likely to have

problems with ego boundaries and identity as a result of being treated more similarly than DZ twins. However, since there is no excess of schizophrenia among MZ twins per se, and there is not an overrepresentation of MZ pairs among schizophrenic twin samples (Rosenthal, 1960) it seems that Jackson's criticism is not supported.

Although the twin studies have provided strong support for the genetic hypothesis, the fact that the concordance in MZ twins do not even approach 100%, but instead average only around 50%, confirms the presence of environmental influences in the development of schizophrenia. The study of discordant MZ twins may provide insights into the operation and nature of these environmental influences (Pollin & Stabneau, 1967). Trait similarities between MZ twins may provide information concerning the nature of the schizophrenic genotype as well (Wahl, 1976). Such studies demonstrate consistent early differences, in personality and parental treatment between discordant MZ twins, but the evidence from these studies concerning environmental etiological factors is thus far inconclusive. Fischer (1971, 1973) compared the incidence of schizophrenia in the children of MZ twins discordant for schizophrenia. She reasoned that if genetic factors are more important in the development of schizophrenia, the children of non-schizophrenic cotwins should manifest schizophrenia as often as the children of affected index twins, but if environmental factors were more salient, the children of

the affected twins should have higher morbidity risks than those of the unaffected cotwins. The rates of schizophrenia and schizophreniform psychoses were identical in the two groups of children, thus providing further support for the greater importance of genetic factors in the etiology of the disorder. A study of MZ twin pairs reared apart showed that 11/17 (65%) were concordant for schizophrenia, a rate higher than that reported for MZ twins reared together (Slater & Cowie, 1971). These findings suggest that the environmental factors that produce discordance in MZ twins have nothing to do with common rearing. This study is interesting methodologically in that it provides a means of contrasting differing environments while holding genetic factors constant.

Adoption Studies

The family and twin studies have provided evidence consistent with the genetic hypothesis, but this evidence is not conclusive since genetic influences cannot be separated from the effect of rearing by psychopathological parents. Although comparisons between MZ and DZ twins supposedly vary the genetic component while holding the environmental factors constant, there is still the possibility that there are differences in the degree of environmental similarity between MZ and DZ twins, and in most cases the twins are still reared by their biological

parents, thus confounding genetic and environmental factors. The study of MZ twins reared apart allows the separation of these factors by holding genetic influences constant (MZ twins have identical genes) and varying the rearing environment. An extension of this logic is utilized in studies of individuals who were adopted away at an early age and reared by foster parents, thus removing the effect of rearing by a psychopathological parent and allowing the assessment of the genetic influence independent of rearing environment.

The first adoption studies were those of Heston (1966) and Heston and Denny (1968), who studied a group of 47 children born to actively schizophrenic mothers who were hospitalized at the time of their babies' birth, and whose babies were placed either in foundling homes or in the care of members of the mothers' family shortly after birth. These children were compared to 50 children separated at birth from mothers without psychiatric problems, identified through the records of the same foundling homes, and matched with the index group for sex, age, type of eventual placement, and length of time in child care institutions. The children in both groups have had similar environments, being raised by normal adoptive parents, but the index children have a genetic loading for schizophrenia from their biological mothers. Five of the index and none of the control children were diagnosed schizophrenic as adults (mean age of the sample at follow-up was 36 years). The age-corrected

risk for schizophrenia in the index group was 16.6%, a value which corresponds closely to the risk estimates found in studies of the children of schizophrenics who were not separated from their parents. Heston's index group also had a greater incidence than the control group of criminality, sociopathy, and neurosis. Heston (1966) suggested a genetic link between schizophrenia and 'schizoid psychopathy'.

Another study using the adoptees study method (Rosenthal, et al, 1968, 1971) started with the names of about 5,500 persons given up for adoption from an Adoption Register of the Copenhagen area. The names of about 10,000 biological parents were then compared with the Danish National Psychiatric Register, and parents with a history of psychiatric hospitalization were identified. Blind independent diagnosis were made of the parents based on hospital records, and those with a full consensus diagnosis of schizophrenia or manic depressive illness were index parents; their children were index adoptees. Control adoptees whose parents had no psychiatric history were chosen from the remaining names, matched to the index adoptees for age, sex, age at transfer to the adopting family, and socio-economic status. Of the index group, 31.6% (of 76 cases) had a 'schizophrenia spectrum' diagnosis, compared to only 17.8% (of 67) of the control adoptees. The 'schizophrenia spectrum' was defined by Kety, et al (1968) as a genetically related group of disorders including chronic schizophrenia, latent or

borderline schizophrenia, acute schizophrenic reaction, uncertain schizophrenia, and schizoid and inadequate personality. The only three diagnoses of chronic schizophrenia were found in index adoptees. In a later study of the same data, the use of consensus diagnoses and at least one elevated clinical scale of the MMPI to define a schizophrenia spectrum disorder produced rates of 21.9% of the index and 6.3% of the control group (Haier, Rosenthal & Wender, 1978). The two studies using the adoptees study method have been consistent in the finding that children of schizophrenic parents have the same risk of psychopathology, or schizophrenia per se, whether they are reared by their psychopathological biological parents or by normal adopting parents.

Lidz, Blatt & Cook (1981) criticized the Danish American 'Adopted away offspring of schizophrenic parents' studies of Rosenthal, et al for including nonschizophrenic parents, manic-depressives, in the index parent group. Since the index group also contained parents with uncertain schizophrenia, it should not be called a study of offspring of schizophrenic parents. When the adopted away children of manic-depressives and the uncertain schizophrenics were excluded from the index group, the difference in spectrum disorder incidence from the controls was no longer significant. Also, since the incidence of spectrum disorders was as high as 17.9% in the control series, the spectrum diagnosis concept failed to significantly differentiate

the index and control series. It is possible that the high incidence of psychopathology in the control group is the result of an increased incidence in psychopathology in adoptees compared to the general population, and/or to a higher rate of undiagnosed psychiatric disorders in parents who give their children up for adoption than in parents in the general population (Horn, et al, 1975).

Using the adoptees family method, Kety, et al (1968,1971,1975) started with the Danish Adoption Register used by Rosenthal, et al (1968,1971) and identified those adoptees whose names were also on the psychiatric register. The hospital records of these individuals were reviewed and an index group of 33 adoptees with diagnoses of process, acute, or borderline schizophrenia were selected, and matched to 33 control adoptees for age, sex, age at transfer to adoptive parents, and SES of adoptive parents. The biological and adoptive families of the adoptees were identified and those with a psychiatric history were revealed by a search of the psychiatric register. Blind diagnoses of the hospital records of these relatives were made for schizophrenia spectrum disorders. There was a significantly greater number of spectrum diagnoses among the biological relatives of schizophrenic adoptees than among the relatives of normal adoptees, whereas among the adoptive relatives there was no difference between index and control groups. If deviant childrearing practices were more salient in the etiology of

schizophrenia spectrum disorders, the adoptive relatives would be expected to show more psychopathology than biological relatives of the index group, while if genetic factors were more salient the reverse pattern would occur. Thus, these results support the genetic hypothesis.

A smaller similar study in Iceland by Karlsson (1966) reported that among the relatives of 6 adult schizophrenics raised in foster homes, 6/29 biologic sibs and none of 28 foster sibs were schizophrenic, thus corroborating the finding of the finding of the Danish study.

TABLE VIII

Schizophrenic illness in biologic paternal half sibs of index and control adoptees.

Diagnosis of half-sibling	Schizophrenic Index Cases (N=63)		Normal Control Cases (N=64)	
	number	%	number	%
Definite schizophrenia	8	13%	1	1.6%
Definite or uncertain schizophrenia	14	22%	2	3.0%

Definite schizophrenia includes process, acute & borderline schizophrenia.

(from Kety, et al, 1974).

Kety, et al (1974,1975) pointed out that their study does not rule out the effect of environmental influences that occur in utero, since for prenatal environment biologic sibs would be more similar than foster sibs. Since paternal half-sibs share only paternal genes and do not share similar prenatal environment, the paternal half-sibs of index and control adoptees were examined. The results of this investigation are presented in Table 8.

Even among paternal half-sibs who do not share any common environmental influences, the occurrence of schizophrenia was greater in the sibs of index schizophrenics than normal controls, offering strong support for the genetic hypothesis, with the suggestion that maternal pre- and perinatal factors are not involved in the etiology of schizophrenia.

A variation on the adoptees extended family method relies on the comparison of biological and adoptive parents, termed the adoptive parents method. Wender, Rosenthal, & Kety (1968) started with a group of schizophrenics adopted by nonrelatives in the first year of life, matched to a control group of schizophrenics reared by their biological parents, for sex, age and severity of illness. The adoptive and biological parents of the index group were further matched for age, religion, and SES. The biological parents had significantly more severe psychopathology than the adoptive parents of schizophrenics, who in turn had a higher degree of psychopathology than a third

group of adoptive parents of normal children. These results again support the genetic hypothesis, but leave open the possibility that parental psychopathology also had a part in the development of schizophrenia. Wynne, Singer and Tooney (1976) examined the Rorschach protocols of parents in the Wender, et al (1968) study, and found that they could accurately differentiate the biological and adopting parents of schizophrenics from the adopting parents of normal individuals. In a further study using the same data, Wender et al (1977) showed that the biological mothers of schizophrenics showed more psychopathology on the Rorschach than the adopting mothers of schizophrenics or the biological or adopting parents of normals.

Another variation of the adoptees study method includes a group of adoptees born to normal parents and raised by a schizophrenic parent(s) in order to assess the effect of adoptive parental psychopathology. This 'crossfostering' method was used in a study by Wender, et al (1974) utilizing the same Danish adoption and psychiatric registers as previous studies. The psychopathology of the crossfostered group was not increased compared to that of the control adoptees, whereas the adoptees with schizophrenic biological parents but normal adoptive parents did have more psychopathology. These results suggest that the rearing practices of psychopathological parents do not have nearly as significant an effect on the development of schizophrenia as the genetic contribution from

psychopathological biological parents. In a further study of this sort, Rosenthal, et al (1975) included a group of nonadopted individuals, born to and raised by a schizophrenic parent. The quality of parent-child relationships and the degree of psychopathology were rated in all groups. The cross-fostered and nonadoptee groups (both groups with psychopathological rearing parents) had the worst parent-child relations, while the index and nonadopted group (both with psychopathological biological parents) had the worst psychopathology. The index and control adoptees showed no difference in the quality of parent-child relationships (both groups had normal rearing parents), yet the index group had more psychopathology. These findings again suggest that the amount of variance in psychopathology accounted for by rearing is low compared to that accounted for by genetics. The two groups without schizophrenic biological parents, the control and cross-fostered adoptees, had a higher cross-correlation between parent-child relationship quality and psychopathology than did the index and nonadoptee groups (both with schizophrenic biological parents). This suggests that whatever effect deviant parental rearing practices have on the development of psychopathology is greater in individuals without a genetic loading for schizophrenia than in those with such a genetic predisposition.

The variety of methods used in studies of the genetic influence on schizophrenic etiology have produced consistently

strong and compelling evidence that the development of schizophrenia is substantially influenced by genetically transmitted factors. Although each study may be criticized on methodological grounds, the convergence of findings from many studies using different methodologies is overwhelming. This weight of evidence prompted Rosenthal (1971) to state

In all the studies done so far... the evidence has turned up so consistently and so strongly in favor of the genetic hypothesis that this issue must now be considered closed. Genetic factors do contribute appreciably and beyond reasonable doubt to the development of schizophrenic illness. Any theory of schizophrenia must take this fact into account.

In a similar vein, Kety (1974) wrote, "If schizophrenia is a myth, it is a myth with a strong genetic component." All of these studies suggest that the presence of the genetic factor(s) is often a necessary but not sufficient condition for the development of a schizophrenic illness. That it is not sufficient is demonstrated by the fact that concordance rates for schizophrenia among MZ twins are considerably less than the 100% expected if the genetic loading were both necessary and sufficient.

Once the operation of a genetic factor is accepted, its mode of operation becomes a salient question. Is the genetic transmission dominant or recessive, and is it monogenic or polygenic? Evidence from various studies has been mustered in favor of each of these alternatives, and as yet there is no clear and definitive argument in favor of or against any of the

alternative genetic models. These arguments are beyond the scope of the present review, and the reader is referred to a series of papers in Kaplan (1972) eloquently arguing each of the alternative models.

Genetic Specificity and the Spectrum Concept

In genetics a distinction must be made between the genotype, the underlying genetic coding in the nuclear DNA, and the phenotype, the expression of the genetically influenced trait in the individual organism. The phenotype may be a biochemical or physiological trait, or a derivative behavioral/personality trait. It must always be remembered that one genotype may produce several different phenotypes, and conversely, several different genotypes may result in similar or indistinguishable phenotypes. This is because the phenotype is a function of the interaction of genotype with environmental factors influencing development. These considerations, when applied to the schizophrenia-genetics research, give rise to two related hypotheses. The first to be considered in this section is that the schizophrenic genotype may give rise to a variety of behavioral phenotypes. This hypothesis suggests that there are a broad group of disorders, the 'schizophrenia spectrum', that are genetically related. It also suggests the possibility that non-psychopathological phenotypes may be associated with the

schizophrenic genotype. The second hypothesis is that the schizophrenic phenotype may be related to a number of different genotypes, that is, that schizophrenia is characterized by biological heterogeneity. Each of these hypotheses will be considered in turn.

In a review of the spectrum concept, Reich (1976) defined it as:

...a theory which maintains that there exists a cluster or spectrum of psychopathological states, some characterized by psychosis and others not, which share a genetic etiology with schizophrenia---and which, therefore, constitute, together with classical schizophrenia itself, a 'spectrum of schizophrenic disorders'. This genetic spectrum concept adopts the traditional nosological forms but creates new groupings. It stands on a diathesis-stress theory, with the genetic diathesis being seen as requisite for the development of a spectrum-included illness. Any particular schizophrenia spectrum disorder is, therefore, seen as representing not a discrete state which is unrelated to the other disorders, but a point on a genetic continuum, with differences among the points reflecting differences in intensity or in some other clinically evident quality, which may be environmentally and/or genetically determined.

The major evidence for the validity of the spectrum concept has come from the adoption studies already reviewed. The prevalence of all spectrum disorders in the biological relatives of index probands with a spectrum diagnosis was twice that seen in the relatives of non-spectrum controls, thus providing evidence that the spectrum disorders are genetically associated. In another study, the adopted-away children of parents with a spectrum disorder had twice as many spectrum disorders as

adopted-away children of normal parents. The spectrum disorders may be grouped according to the degree of genetic relationship with classical schizophrenia. The 'hard-spectrum' disorders include process and borderline schizophrenia, questionable or definite, and these all have similar distributions among the biological relatives of schizophrenics. The 'soft-spectrum' disorders include questionable and definite acute schizophrenic episode, schizophrenic personality such as undifferentiated, inadequate and subparanoid disorders, and schizoid personalities. The schizoid personalities tend to cluster in the relatives of schizophrenic probands, but more weakly than the hardspectrum disorders, while the acute schizophrenic episodes show only a weak genetic association with chronic and borderline schizophrenia (Rosenthal, 1975).

Although Kety, et al (1975) report that the incidence of soft spectrum disorders was distributed equally among the biological relatives of schizophrenic and non-schizophrenic adoptees, and only the hard spectrum diagnoses were concentrated in the relatives of schizophrenics, Rosenthal (1975) has argued that the soft spectrum diagnoses are nonetheless related genetically to schizophrenia. To test this hypothesis, he studied both biologic parents of the index adoptees. He found that when the index parent is female, the co-parent was diagnosed as having a spectrum disorder or psychopathic disorder in 56% of the couples, the two disorders occurring about equally in the male

co-parents. When the index parent was male, 45% of the female co-parents had a spectrum diagnosis. These findings indicate that assortative mating, or matings in which both persons have a spectrum disorder, occurs at an appreciable rate. Furthermore, all of these assortative matings involved co-parents with a soft spectrum diagnosis. Rosenthal found that the frequency of spectrum disorders was three to five times greater among the offspring of assortative than non-assortative matings (a difference significant at the 0.006 level). Thus, when the co-parent had a soft spectrum diagnosis, the risk for a schizophrenia spectrum disorder was increased in adopted-away offspring. Rosenthal suggested that this increased risk was the result of the additive influence of schizophrenic genes from the hard spectrum index parent and the soft spectrum co-parent.

An independent analysis of the Danish-American adoption study data provides corroborative evidence for the inclusion of 'soft-spectrum' personality disorders in the schizophrenic genetic spectrum. Kendler, Gruenberg and Strauss (1981b) found a significantly higher incidence of schizotypal personality disorder, as defined by DSM III, among the biologic relatives of schizophrenic adoptees than in the biologic relatives of control adoptees, and the occurrence of SPD was low in the two groups of adoptive relatives.

Although the spectrum concept broadens the nosologic entity of schizophrenia to include etiologically related disorders, the

schizophrenic genotype has some specificity. The diathesis that is genetically transmitted is not a vulnerability for all forms of psychopathology, but rather a vulnerability for only those disorders included within the spectrum. Although some early studies suggested some genetic overlap between manic-depressive psychosis and schizophrenia, their findings are very likely the result of misdiagnosis of remitting schizophrenia as affective psychosis, due to the Kraepelinian diagnostic biases which by definition exclude periodic or remitting disorders from the category of schizophrenia (Palansky, 1972). A recent study of morbidity risks for schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions has provided evidence that schizophrenia and manic-depressive illness are indeed genetically distinct (Tsuang, 1975; Tsuang, Winokur, & Crowe, 1980). Kendler, Greenberg & Strauss (1981a, 1981c) also found that anxiety disorders and paranoid delusional disorders were likewise genetically distinct from schizophrenia spectrum disorders. Thus, the spectrum genotype has some genetic specificity.

The fact that one genotype may give rise to diverse phenotypes also leaves open the possibility that there are non-psychopathological manifestations of the schizophrenic genotype. Since schizophrenics and their unaffected siblings have a lower fertility rate than the rest of the population

(Buck, et al, 1975; MacSorley, 1964), and children of schizophrenics have a higher than average mortality rate at birth and in the first years of life (Garnezy, 1974; Garnezy and Steitman, 1974), the frequency of the schizophrenic genotype in the population gene pool should be decreasing, and with it, the incidence of schizophrenia should be dropping with time. The incidence rate for schizophrenia has, however, remained stable world-wide for at least 100 years (Sartorius and Jablensky, 1976). One way in which the findings of stable incidence rates, lowered fecundity and survival of the schizophrenic phenotype, and a genetic component in the etiology of the disorder can be reconciled is by supposing that schizophrenia is a 'balanced polymorphism'. This has been defined by Bodmer and Cavalli-Sforza (1976) as "A polymorphism that is stable (tends to remain unchanged over time) and is probably maintained by advantage of the heterozygote over both homozygotes". Heterozygotes as unaffected gene carriers may have favorable psychological characteristics conferred by the schizophrenic gene(s), and so may also have a reproductive advantage, thus maintaining the gene frequency. Heston (1966) reported that, in addition to an increased rate of schizophrenia and schizoid psychopathy in the children of schizophrenic mothers, there were also unaffected children who were described as more artistic, spontaneous and interesting than a control group. Karlsson (1966) also reported a higher than expected number of creative individuals in the pedigrees of

schizophrenics. These more creative than average relatives of schizophrenics have been termed 'superphrenics'. Five studies have reported that the rate of superphrenia in the first degree relatives of schizophrenics is from 5 to 45% (Anthony, 1970; Blau, 1977; Heston and Denny, 1968; Karlsson, 1968; McNeil, 1971), and Heston and Denny (1968) report that such creative individuals do not appear in the offspring or relatives of normal control groups. Superphrenics are described by Brodsky and Brodsky (1981) as "a group of people who are artistically or musically creative, intelligent and rational, and are functioning at an above average level in their lives." Brodsky and Brodsky (1981) also cite evidence that creative adults, adult schizophrenics, the children of schizophrenics, and the normal relatives of schizophrenics are similar on two dimensions: lower than average sensory thresholds and a reticulothalamocortical (RTC) brain system that is easy to arouse to high peaks of arousal (cortical hyperarousal).

Thus, the schizophrenogenic genotype may have several phenotypic expressions in the schizophrenia spectrum as well as non-pathological 'superphrenia'. Such phenotypic diversity can account for the stable incidence rates in the face of gene attrition due to lowered fecundity in pathologically affected individuals. The assumption of heterozygosity/homozygosity differences accounting for phenotypic diversity is unnecessary, since there may be polygenic or environmental determinants of

phenotypic expression. Rosenthal(1971) has criticized the 'sibling advantage hypothesis' on the grounds that no demonstration of elevated reproductivity in unaffected relatives of schizophrenics has been produced, and indeed the available evidence suggests that the fertility rate of unaffected siblings is lower than that of the rest of the population (Buck,et al,1975; MacSorely,1964). Further tests of the balanced polymorphism model, focussing on fertility rates in superphrenics, would be particularly interesting. Rosenthal's criticism would not apply if reproductive advantage were conferred on individuals with the schizophrenic/ creative genotype in unaffected families. Thus, the gene frequency would increase despite the fact that in families with pathologically affected individuals, the fertility rate is lowered.

Biological Heterogeneity

The concept of a schizophrenic spectrum of disorders, or a genetically related group of disorders, does not rule out the possibility that there might be several genetic continua producing the spectrum. It is possible that many genotypes are related to a spectrum of phenotypes, and even to a single narrowly defined clinical phenotype, schizophrenia. For every phenotype, there are a number of genotypes that can produce the phenotype, depending upon differences in environmental action.

Some 'phenocopies' may not have a genetic basis at all, and appear solely as the result of environmental factors. Strictly speaking, it is incorrect to consider the schizophrenic illness a 'phenotype' at all (Cancro, 1975a; 1975b; 1979). The only thing that can be transmitted directly by the genetic code in the DNA is a certain sequence of amino acids in peptide structures. Thus, direct phenotypes are relatively simple patterns of biochemical traits. Neurophysiological and psychological processes may be affected by these biochemical parameters, and so may be considered as having significant genetic determinants, but they are indirect results of the genetic information, and so are, at best, only derivative second or third order phenotypes, not direct phenotypes. Any indirect phenotype that is necessary for a vulnerability to schizophrenia may be produced by different genes acting through different biochemical pathways, and interacting with different environmental factors to produce schizophrenic behavior. Each of these different gene-environment pathways may define separate etiological subgroups of the disorder. This etiological or biological heterogeneity has important consequences for both research and treatment in schizophrenia. Before considering these implications, some evidence for the existence of genetic subgroups in schizophrenia will be considered.

There are very likely some schizophrenic psychoses precipitated by organic causes without a significant genetic

determination. These 'phenocopies' have been referred to as 'symptomatic' schizophrenia, while schizophrenia with no obvious organic cause, or psychogenic causation, is called 'true' or 'idiopathic' schizophrenia. Symptomatic schizophrenia may occur as a result of damage to various areas in the brain stem (Davison and Bagley, 1969); it may be associated with temporal lobe epilepsy (see review in Chapter 3), and rare endocrinological syndromes (Bleuler, 1948; Sachar, 1976), or in immunological disorders such as systemic lupus erythematosus (Rudin, 1980), as well as a variety of metabolic disorders. The symptomatic schizophrenias are probably not genetically related to idiopathic schizophrenia. Schultz (1932, 1934) found a significantly higher incidence of schizophrenia in the biological siblings of idiopathic schizophrenics (7.5%) than in the sibs of schizophrenics with detectable organic precipitating factors (3.7%). Similarly, Davison and Bagley (1969) found that symptomatic and idiopathic schizophrenics were significantly differentiated by family history, premorbid history, and clinical symptomatology. A family history of schizophrenia and premorbid schizoid personality were found four times as frequently among the idiopathic than among symptomatic schizophrenics.

The idiopathic schizophrenias may be further categorized, and the subgroups may be genetically different. The most popular subdivision of idiopathic schizophrenia is into typical and

atypical forms. Both types show characteristic schizophrenic features, but the typical form shows a continuous deterioration with chronic course, corresponding to the Kraepelinian definition, and is also referred to as process or poor-prognosis schizophrenia. The atypical form has a more episodic course with good-prognosis and is also called reactive or schizophreniform. Mitsuda (1972) found that 66/68 (97%) of families with a typical schizophrenic showed concordance of affected relatives for the typical form of the psychosis, while 41/48 (85%) of the families with an atypical schizophrenic showed concordance for the atypical form, suggesting genetic differentiation of the typical and atypical forms. Pedigrees were classified as to the apparent mode of genetic transmission, and typical schizophrenia was found to be associated with a recessive transmission in 75.5% of the families, and dominant transmission in only 8.2% of the families. Atypical schizophrenics, on the other hand, showed patterns of inheritance equally distributed between the dominant and recessive types. In a small twin study, Mitsuda (1972) found that seven MZ pairs were concordant for typical schizophrenia, one pair was concordant for atypical schizophrenia, and in no MZ twin pairs was there a combination of atypical and typical psychoses. In a blind study of the families of 28 good-prognosis (atypical) and 25 poor-prognosis (typical) schizophrenics, McCabe, et al (1971) found that the first degree relatives of good-prognosis cases had a high risk for affective disorder

(10.0%) and a lower risk for schizophrenia (3.3%), while the relatives of poor-prognosis cases had a high risk for schizophrenia (11.6%) and a low risk for affective disorders (1.5%). Similar findings have been reported by others (Weinberg and Lobstein, 1943; Vaillant, 1962).

Subtypes of typical schizophrenia are traditionally labelled simple, catatonic, hebephrenic and paranoid, and these symptomatic groupings may or may not have distinct etiologies. Kallman's (1938) family study reported a high degree of subtype concordance in the children of schizophrenics, since there was a significant tendency for the affected children of hebephrenics (60.7%) and catatonics (52.9%) to have the same subtype diagnosis as the parent. Slater (1947) found family concordance for Kraepelinian subtypes in a reanalysis of Zehnder's data. Kringlen (1967) reported that 13/14 (92.9%) schizophrenic MZ twin pairs showed subtype concordance. On the other hand, Luxemburger (1928), Essen-Moller (1941), and Slater (1953) all found significant intrapair variability among MZ twins.

Thus, Planansky (1972) concluded that the twin partner of a typical schizophrenic may develop practically any kind of schizophrenic psychoses, i.e., simple, hebephrenic, catatonic, or paranoid.

Tsuang (1975a, 1975b) has argued that differences in risk of schizophrenia in relatives between different subgroups of schizophrenics may imply genetic heterogeneity of these

subgroups. Several studies have found a higher risk of schizophrenia in the relatives of hebephrenics than the relatives of paranoid schizophrenics (Schultz, 1932; Hallgren and Sjogren, 1959; Kallman, 1938; Winokur, et al, 1974). Tsuang, et al (1974) failed to find any significant subtype concordance or risk differences in the families of paranoid and non-paranoid schizophrenics, calling into question previous findings.

Carpenter and Stevens (1979) have reviewed evidence suggesting that the usefulness and validity of the traditional subtypes are quite questionable. Guggenheim and Babigian (1974) reported very low diagnostic consistency for the traditional subtypes. Several studies have reported extensive overlap of symptoms and similarity in psychopathological manifestations across the subtypes (Hay and Forrest, 1972; WHO, 1973), and a broad range of symptoms failed to differentiate the four subgroups from each other (Carpenter, et al, 1976). Furthermore, symptomatology is not consistent over time, and patients manifesting symptoms characteristic of one subtype at one time may show symptoms associated with a different subtype at another time (Bleuler, 1978; Janzarik, 1968). Given this state of affairs, and the conflicting evidence on subtype concordance and risk differences across subtypes, it appears that the traditional subtypes are unlikely to be associated with distinct etiological-biological-genetic subgroups. If symptomatic subclassifications are of little utility, subclassification of

schizophrenia according to non-symptomatic biological and genetic criteria may prove more useful.

The potential utility of biological subclassification and the importance of the recognition of biological heterogeneity for schizophrenia research have been argued by Buchsbaum and Haier(1978). Traditionally, the researcher looking for biological etiological factors underlying schizophrenia has compared symptomatically defined schizophrenics and controls on some biological or psychophysiological test. Even when the symptomatic classification is rigorously defined and achieves considerable symptom homogeneity, the schizophrenic group is still biologically heterogenous, and so t-test comparisons between the schizophrenics and controls will fail to yield significant results if the proportion of schizophrenics with the biological abnormality in question is low or the sample size small. Consider, for example, the biologically heterogenous disorder, mental retardation, which in some cases is caused by phenylketonuria. Comparing blood levels of phenylalanine in a group of MR subjects and normals is unlikely to yield evidence for a role of phenylalanine metabolism in the etiology of MR, because those clinically indistinguished individuals for whom PKU is the determining factor are only a small proportion of the MR population. Buchsbaum and Rieder(1979) used a computer simulated Monte Carlo study to investigate the effects of biological heterogeneity on research of the traditional design.

The program simulated the efforts of 1,000 research teams doing studies with schizophrenic and control groups of equal size. Power curves were generated for differing sample sizes and varying proportions of the schizophrenic population characterized by the biological abnormality. They assumed the 'abnormality' took the form of differences more than two SDs away from the control mean on the measure under investigation. Their results indicated that if only 25% of schizophrenics are characterized by a particular biological abnormality, it would take sample sizes of at least $N=40$ for even half of the 1,000 studies to produce significant results, and an N of 125 subjects would be needed for 95% of the researchers to produce consistent results. Even if as much as 70% of the schizophrenic population had the abnormality under study, sample sizes of 20 would be needed to achieve 95% unanimity in the field. Typically, research into biological factors in schizophrenia uses small sample sizes. When this perspective is applied to reviews of biological research in schizophrenia, for example studies of platelet MAO abnormalities (Buchsbaum & Rieder, 1979) or abnormal endorphins (Buchsbaum, Davis & Van Kammen, 1980), it appears that inconsistent findings are very likely the result of biological heterogeneity, since studies using larger sample sizes have generally produced more significant positive and more consistent results.

Buchsbaum and Haier (1978) suggest that the traditional strategy of using symptom-based diagnosis as the independent variable and the biological factor as the dependent variable is doomed to failure. They instead propose that grouping or diagnosing individuals on biological variables instead of symptoms may be a better way to decrease heterogeneity, and they mention that such a reversal of the usual dependent and independent variables is not uncommon in epidemiology research. The call for the use of biological subclassification has been taken up by many other schizophrenia researchers recently (Henn, 1980; Galdi, et al, 1981; Wyatt, et al, 1981). Buchsbaum and Haier (1978) elucidated three advantages of this strategy. First, this strategy will be more useful for detecting biological etiological factors, since statistical results are not diluted by irrelevant cases included in the index sample because of symptomatic similarity. Second, the use of biological classification would enable the inclusion of less severe or atypical cases, excluded from studies using strict symptom-based diagnosis, but which are still members of the schizophrenia spectrum, and may share etiological determinants with more severe or typical psychoses. Third, the use of biological classification allows the study of nonhospitalized unmedicated persons before symptomatic breakdown confounds biological processes, thus avoiding artifacts of hospitalization and prior drug treatment, which plague traditional biological research in

schizophrenia. This strategy allows the screening of large populations on the biological variable(s) to identify individuals biologically 'at-risk' who can then be compared to matched controls who are not abnormal on the given measure for family incidence of psychopathology, a variety of psychological abnormalities, physiological or biochemical differences, and eventual development of psychopathology themselves. This research strategy was also recommended by Kidd and Mattyse (1978). The use of such a 'biologically at risk' strategy will be discussed more fully in a later section.

Vulnerability

Paul Meehl (1962) pointed out in his landmark paper that of course the schizophrenic illness as such cannot be inherited because it has behavioral and phenomenal contents which are learned. In recognition of the interaction of genotype with environmental influences to produce the direct phenotype, and the chain of causation from the biochemical phenotype through neurophysiological functions to psychological and behavioral processes, Meehl proposed that what is inherited is a vulnerability or predisposition to schizophrenia, which he termed 'schizotaxia'. His was the first explicit exposition of the 'vulnerability' concept.

Granting its initial vagueness as a constant, requiring

to be filled in by neurophysiological research, I believe we should take seriously the old European notion of an 'integrative neural defect' as the only direct phenotypic consequence produced by the genic mutation. This is an aberration in some parameter of single cell function, which may or may not be manifested in the functioning of more molar CNS systems, depending upon the organization of the mutual feedback controls, and upon the stochastic parameters of the reinforcement regime. This neural integrative defect, which I shall christen schizotaxia, is all that can properly be spoken of as inherited. The imposition of social learning history upon schizotaxic individuals results in a personality organization which I shall call, following Rado, the schizotype. The four core behavior traits (which Meehl identifies as cognitive slippage, interpersonal aversiveness, anhedonia, and ambivalence) are obviously not innate; but I postulate that they are universally learned by schizotaxic individuals, given any of the actually existing social reinforcement regimes, from the best to the worst. If the interpersonal regime is favorable, and the schizotaxic person also has the good fortune to inherit a low anxiety readiness, physical vigor, general resistance to stress and the like, he will remain a well-compensated 'normal' schizotype, never manifesting symptoms of mental disease. He will be like the goutprone male whose genes determine him to have an elevated blood uric acid titer, but who never develops clinical gout.

Only a subset of schizotypic personalities decompensate into clinical schizophrenia."

Meehl goes on to speculate that the most important causal influences pushing the schizotypic toward schizophrenic decompensation is the schizophrenogenic mother. He further postulates that schizotaxia is a necessary condition for the development of schizophrenia, and that a nonschizotaxic individual would at most develop a character disorder or a psychoneurosis, and would not become a schizotype or manifest its decompensated form, schizophrenia. This vulnerability theory suggests that the schizotype is characterized by a subtle

neurointegrative defect which may manifest in subtle abnormalities of psychophysiological, cognitive, affective or personality functioning. The vulnerability concept recognizes the interaction of gene and environment and was further developed under the name of the 'stress-diathesis' model (e.g. Rosenthal, 1971), the diathesis consisting of the inherited trait predisposing to schizophrenia.

TABLE IX
Etiotypes and their potential markers.

Model	Etiotype	Example of potential marker
Genetic	Genotype	Consanguinity
Internal Environment	Chemotype	Monoamine oxidase
Neurophysiological	Neurophysiotype	Evoked potentials
Ecological	Ecotype	Constricted social network
Developmental	Auxienotype (a)	Parental loss in early childhood
Learning Theory	Mathetotype (b)	Communication disorder
Vulnerability	Schizotrope (c)	Profile of etiotype markers

- (a) Suggested by E.I. Burdock from the Greek root for growth.
 (b) Suggested by K. Salzinger from the Greek root for learning.
 (c) Because Rado and Meehl have preempted the term schizotype a new term had to be provided for one prone to schizophrenia without exhibiting schizotypy.
 (from Zubin, 1980).

The vulnerability concept was extended and developed by Zubin and Spring (1977) and Zubin (1980), who suggested that there are numerous contributions to an individual's degree of vulnerability, ranging from genetic inheritance to acquired propensities. Their extension of the concept begins with the recognition of six different etiological models of schizophrenia: the genetic, internal environment, neurophysiological, ecological, developmental, and learning theory models. Just as the concept of genotype corresponds to the genetic model of etiology, each of the other models has a corresponding 'etiotype' as illustrated in Table 9. The vulnerable individual, or 'schizotrope' may be schizotaxic, that is, may bear the genotype for schizophrenia, or may bear any one of the other etiotypes, or any combination of etiotypes, as they overlap. Thus, this model does not require the assumption that the schizotaxic genotype is a necessary condition for schizotropy, which may also result from non-genetic etiological factors. The common denominator of all the etiological models and their corresponding etiotypes is the factor of vulnerability.

The extension of the vulnerability model as elucidated by Zubin and Spring (1977) and Zubin (1980) also distinguishes between vulnerability, which is a relatively enduring trait, and episodes of the schizophrenic disorder, which are seen as waxing and waning states. Zubin (1980) cites evidence for the episodic

nature of the schizophrenic illness. Hospital statistics reveal that the average duration of hospitalization has dropped in the last several decades, and most chronic cases probably reflect the iatrogenic effects of long-term hospitalization. Bleuler (1978) reported that 25% of the schizophrenics he studied eventually recovered fully without further relapse and without requiring maintenance medication, and only 10% remained permanently hospitalized. Bleuler (1978b) further reported that 5 or 10 years after onset, the proportions of recoveries (30%), mildly chronic (38%), moderately (17%) and severely (15%) chronic cases remained constant throughout the follow up period, but when individual cases were studied it was seen that probands constantly changed back and forth between different stages of recovery. Wing (1966) found that 75% of a group of first admission schizophrenics had a good outcome (mild or no disability) at the 5-year follow-up. Paul and Lentz (1977) found that 90% of their chronic schizophrenics were able to remain in the community, while only 5% required rehospitalization during a two year follow-up period. These findings suggest that the permanent factor in schizophrenia is not the episode, but the vulnerability to the disorder.

The vulnerability to schizophrenia, determined by multiple etiological factors, interacts with stressors, or challenging life events, to elicit homeostatic imbalances expressed as illness. The highly vulnerable person is one for whom many

situations encountered in daily living are stressful enough to elicit episodes of the disorder. Zubin and Spring (1977) state this relationship:

"As long as the stresses induced by the challenging life event stays below the threshold of vulnerability, the individual responds to the stressor in an elastic homeostatic way and remains well within the limits of normality. When the stress exceeds the threshold, the person is likely to develop a psychopathological episode of some sort. Further, we postulate that the episode is time limited. When the stress abates and sinks below the threshold, the episode ends and the patient returns to a state similar to his pre-episode level of adaptation."

Persons with very high vulnerability, such as chronic patients, may continuously pass in and out of closely spaced episodes with relatively slight provoking stress, while less vulnerable individuals may have few or only one episode in reaction to more stressful life events. The amount of stress generated by a challenging life event may depend on coping abilities which are not necessarily related to the vulnerability factor. Thus, some individuals with high vulnerability may raise their effective threshold for disorder through the development of coping skills that ameliorate the stressful effects of challenging life events. Thus, the development of illness can be seen as a function of both vulnerability and stress, the latter being a function of the magnitude of stressors and the coping ability of the individual.

The testability of the vulnerability model depends upon the identification of markers for vulnerability that will accurately

identify individuals 'at-risk' for the disorder. The type of marker chosen will be related to the particular model of etiology guiding an investigation. Any marker must be present in individuals who have already exhibited vulnerability by having had a schizophrenic episode, and it should be absent in matched controls. Furthermore the marker should be present in remitted schizophrenics and in preschizophrenic individuals to insure that the marker is not just an episode marker or an effect of the illness brought on by drugs, hospitalization, the anxiety evoked by psychotic experience, etc. One fruitful area for the search for vulnerability markers is the study of children who are at increased risk for schizophrenia by virtue of having a schizophrenic parent. From such studies, and comparisons of adult schizophrenics with normal controls, putative vulnerability markers may be identified and then used to screen populations for unidentified persons who are vulnerable or 'at-risk'. If follow-up investigation reveals the putative vulnerability marker to be predictive of actual psychopathology, the marker may be considered a useful index of vulnerability.

Children of Schizophrenic Mothers

Traditionally designed research into etiological factors in schizophrenia typically relies on the comparison of a group of adult schizophrenics with a matched group of normal controls.

This strategy is weakened by the heterogeneity of the schizophrenic group for the putative etiological factor, and any significant results that are found despite this heterogeneity may reflect not etiologically significant factors, but consequences of the schizophrenic illness. Drugs, iatrogenic effects of long-term incarceration, dietary factors, and the biological/psychological effects of the disorder all confound the interpretation of such results. One research strategy which circumvents this problem is the study of individuals before the onset of psychiatric disorder. This may be done in a number of ways. First, the clinical retrospective method which relies on the subjective retrospective reports of patients and their families may be used, but there are obvious methodological problems concerning the validity of such reports. In the follow-back study, records of adult schizophrenics are traced back to childhood and a profile of development is obtained. This second method is limited because the restricted range of information contained in school records may not include etiologically significant information. In the follow-up study of the child-at-risk as an adult, a group of deviant children seen in child guidance clinics are followed-up when adults. This method also suffers from the possible etiological irrelevance of information obtained through the child guidance clinics' records, the use of a biased sample, and the loss of information concerning etiologically relevant factors operative in the time

between child guidance clinic contact and adult follow-up investigation. The fourth and most powerful method, is the prospective longitudinal method. In this method, a group of children with an increased genetic vulnerability to schizophrenia due to schizophrenic parentage are compared to matched controls, several times over many years, on measures of hypothetical etiologic significance chosen by the experimenter. This method has clear advantages over the other three developmental approaches, since potentially important variables can be chosen at the outset of the study, a matched control sample and double blind ratings can be used, and repeated assessments allow the investigation of developmental patterns. These four methods encompass the study of 'children at risk for schizophrenia', and have been reviewed extensively by Garnezy (1974a,b) and Neale and Oltmanns (1980); as well as by Kestenbaum (1980). Because of the methodological weaknesses of the first three methods, and their limited applicability to the investigation of genetic and biological etiologic factors, I will focus now on high-risk studies using the prospective longitudinal method.

One of the first studies of children at risk due to schizophrenic parentage was begun in 1962 by Mednick and Shulsinger in Denmark (Mednick and Shulsinger, 1964, 1965a, 1965b, 1968, 1973, 1974; Mednick, 1962a, 1962b, 1966, 1967, 1970, 1976; Mednick and McNeil, 1968; Shulsinger, 1972, 1976; Mednick,

Shulsinger and Shulsinger, 1975; Mednick, et al, 1978). They selected as high-risk subjects 207 children of chronic schizophrenic mothers, and 104 control children without parental psychopathology, matched to the highrisk subjects for sex, age, years of education, father's occupation, residence (rural vs urban), and family structure (institutional vs familial). In 1967, when the mean age of the sample was 15.7 years, an investigation using many variables revealed a host of differences between the high risk and control groups (Mednick and Shulsinger, 1968). The high risk group showed higher amplitude and shorter latency of galvanic skin response (GSR) to stressful stimuli than the matched controls. They also showed less habituation to stressful stimuli (indexed by latency of responses) and greater responsivity to generalization stimuli. The recovery rate of electrodermal levels following stressful stimuli was also faster in the high risk children. These findings in high risk children are in accord with data from adult schizophrenics, who show marked overgeneralization (Mednick, 1955; Rodnick and Garnezy, 1957), and slower habituation, lower levels of basal resistance, and a higher level of responsiveness to stimuli (Zahn, 1964).

The high risk children also gave more idiosyncratic and fragmented responses and had longer response latencies on the Kent-Rosanoff Word Association test. The high risk group produced significantly more clang associates, chain associations

and repetitions of the response words on a Continuous Association Test, in which each subject continuously associated for one minute to each of thirty response words. On the WISC, the high risk group had significantly lower IQ's (100.7 mean) compared to the controls (mean= 104.3). Teachers rated the high risk children as more passive, quiet and detached, more nervous, shy and reserved, and as more often reacting to excitement by withdrawal. In addition, high risk males were rated by teachers as more aggressive and more often disruptive in class than controls. Psychiatric interview data indicated that the high risk children had a greater amount of conflict in their homes than controls. The high risk children rated their mothers as more weak, ineffectual, high strung, easily upset, intolerant and perfectionistic. They also had a more negative self-image and more difficulty making friends. Psychiatrists rated the high risk children as more tense, sensitive, reactive, schizoid and nervous, and as showing a vague train of associative thinking and a more unnatural manner in their interpersonal relations.

An association between the schizophrenic mother's absence in the first two years of the child's life and subsequent pathology of the child was revealed by the parental interview, the psychiatric interview of the subjects, and teacher's reports. Mednick and Shulsinger (1968, 1974; Mednick, 1970) found that by 1967 twenty high risk individuals had shown signs of severe psychiatric disorder, with twelve requiring

hospitalization, and the other eight receiving diagnoses of schizoid, delinquent or alcoholic. These twenty were designated the 'sick group' and were matched on the basis of initial level of adjustment, age, sex, and social class with twenty high risk subjects who had not shown any behavior disorder (the 'well group'). Comparisons of the sick and well high risk groups revealed that the sick group was distinguished by loss of the mother to psychiatric hospitalization early in life, teachers' reports of more disturbing, aggressive behavior in school, associative drift on the continuous word association test, higher amplitude GSR responses and faster latencies to stressful stimuli, slower habituation, faster extinction, increased generalization, and faster recovery rates of the GSR. The sick group also had a greater number of pregnancy and birth complications (70% of the sick group) compared to the well high risk subjects. A reanalysis of the data by Birgette Mednick (1973) revealed that the fathers of the sick group had more often been psychiatrically hospitalized, as well (7/18 or 39% compared to 0/19 of the well group).

A subsequent psychiatric interview of the subjects (Shulsinger, 1976) revealed 15 schizophrenics in the high risk group. Of the six schizophrenics in the Sick group identified in 1967, three committed suicide and the other three were included in the subsequent schizophrenic group. The new schizophrenic group contained 11/15 subjects who had not been included in the

previous group of 20 'sick' high-risk subjects. Although statistical analyses were not presented, Mednick, Shulsinger and Shulsinger (1975) reported that, compared to all other high risk subjects, the schizophrenics had mothers whose psychoses began earlier, they had more difficult births, and teachers rated them as more easily upset, slower to calm down, more aggressive teachers rated them as more easily upset, slower to calm down, more disturbing and inappropriate in class, and more aggressive and violent. A statistical analysis of prognostic maternal characteristics revealed that the mothers of children who became schizophrenic tended to have had psychosis precipitated by childbirth and they had exhibited more instability in their relations with men as well as antisocial behaviors (Talovic, Mednick, Shulsinger and Falloon, 1980). Mednick, et al (1978) used path analysis to investigate the relationship between the development of schizophrenia in the high risk child and several constructs: 1) mother's age of onset of illness, 2) parental separation in the five years of life, 3) pregnancy and birth complications, 4) autonomic nervous system responsivity and recovery rate, and 5) socioeconomic status. The results revealed different patterns of association among these variables for male and female schizophrenics. In males, the development of schizophrenia was significantly related to two factors: parental separation and autonomic nervous system abnormality. Parental separation was related to mothers age of onset and social class,

while autonomic nervous system factors were related to pregnancy and birth complication. Among the females, the development of schizophrenia was related only to mother's age of onset, which was in turn related to parental separation and social class. PBC'S and the ANS factor were related to each other, but not to the subsequent development of schizophrenia. These different patterns of results for males and females led Mednick, et al (1978) to the conclusion that some aspects of the etiology of schizophrenia are different in high-risk men and women.

The schizophrenics were also compared with other high risk subjects on the continuous association test, and although high risk subjects as a group had more deviant associations than low risk subjects, associative disturbance was not found to characterize those who later became schizophrenic (Griffith, Mednick, Shulsinger and Diderichsen, 1980), thus calling into question the proposal by previous investigators that associative disturbance is a central characteristic of schizophrenia. As the sample is still in the age of age of risk, further analyses of this Danish study are as yet incomplete and more reports should continue to appear in the literature from this group of investigators. Their results so far clearly indicate that children at genetic risk for schizophrenia differ from low risk controls on a variety of measures of psychophysiological function, cognitive function, social and educational function, as well as pre- and perinatal complications.

The first longitudinal prospective study of the children of schizophrenic mothers began with infants born 1952-1953, randomly sampled from the Bellevue hospital well-baby clinic, and 10 children born in 1959-1960 to hospitalized schizophrenic mothers (Fish 1957, 1959, 1960, 1961, 1963; Fish, et al., 1965, 1966, 1968; Fish, 1971 a, 1971 b, 1975 a, 1975 b, 1976, 1977; Fish and Hagin 1972, 1973; Fish and Dixon, 1978, 1979). The children were tested ten times between birth and 2 years of age on a battery of standard infant tests, and independent psychologic and psychiatric evaluations were conducted at ages 10 and 18 years. Among the well-baby clinic group, three infants were identified as having abnormally uneven development at 1 month, and were independently evaluated as pathological on psychological testing at 16 years of age. Nine of ten state hospital subjects (children of schizophrenic mothers) also had severely uneven motor development, and eight of these had severe to moderate emotional impairment at 10 years. The only two subjects with a diagnosis of childhood schizophrenia were both children of schizophrenic mothers, and of the other 10 children of schizophrenic mothers, 8 showed some psychiatric illness, while only 3/12 children of non-psychiatrically ill mothers showed any psychopathology. Fish (1975, 1977) stated:

"Analysis of the developmental curves points to an early biologic disorder in the two childhood schizophrenics. Both infants had a major disorganization of neurologic maturation, which involved postural-motor, visual-motor, and physical development as early as the first month of

life. There was no fixed neurologic defect, but rather a disorder of the timing and integration of neurologic maturation.

Several features distinguish this from the usual forms of retardation and precocity. First, there was an unusual fluctuation in the rate of development, with marked acceleration and marked retardation succeeding one another."

A large 'scatter' of scores on tests at a single time and across many testings found in several children was termed by Fish 'pandevopmental retardation', defined as an intermittent retardation or uneven development in physical growth posturalmotor, and visual-motor function. Pandevopmental retardation in infancy was significantly related to the appearance of severe to moderate psychiatric disorder at 10 years of age. The pandevopmental retardation was most severe in the two preschizophrenic infants. Children with milder and shorter pandevopmental retardation had psychiatric disturbances less severe than those of the schizophrenic children, and those without associated retardation of physical growth had still milder psychiatric disorders. Thus, the spectrum of mild to severe irregularity and retardation of visual-motor, postural-motor and physical development is related to subsequent mild to severe behavior disorders of the schizophrenia spectrum. Fish hypothesized that the poor integration of neurologic development in infancy was analogous to neurointegrative defects seen in adult schizophrenics, and suggested that pandevopmental retardation may serve as an

early 'marker' of the inherited neurointegrative defect in schizophrenia. Another sequel of pandevelopmental retardation was the later occurrence of specific reading disabilities, perceptual deficits reflected in poor performance on WISC block design, Koppitz and Bender Gestalt tests. These perceptual deficits occurred more often in children of schizophrenics, who also showed more pandevelopmental retardation.

Fish (1975) further maintained that the overt manifestations of the neurointegrative defect change with maturation. As the child with the inherited neurointegrative defect matures, gross retardation of visual-motor function is succeeded by abnormalities of form perception, and in adulthood, perhaps by such subtle neurointegrative disorder as abnormal smooth pursuit eye tracking. Of all the individual tests of visual-motor function administered in infancy, only one, a failure of 'hand to hand' integration at 9 months, was correlated with the presence of subsequent emotional impairment. As Fish (1975, 1977) describes :

This integrated functioning of one hand with the other at the midline normally begins with the mutual fingering of one hand by the other at 16 weeks, followed by the transferring of objects from one hand to the other at 28 weeks, and finally at 40 weeks to the simultaneous grasp of one object in each hand and approximating them. Failure in these specific bimanual skills occurred in all eight of the children rated as having severe to moderate psychiatric impairment at 10 years, but they were not failed by either of the two children rated as having mild to no impairment. There was also a significant relationship between the times when the midline bimanual skills were failed and when vestibular

response was reduced on one or both sides."

The midline coordination seems to involve an awareness of the proximity of two objects in the two hands. Fish attempted a psychoanalytic explanation of this finding by supposing that the mutual touching of the hands provides the infant with the early experience that touching oneself is different from touching anything else, thus allowing the differentiation of self from non-self, and the development of ego boundaries. Another explanation for the relationship between early failures in midline coordination and later psychopathology may be that such failures are a reflection of abnormality in the interhemispheric transfer of information. Such transfer deficits may be etiologically significant in the development of later schizophrenia spectrum disorders.

Other features of the neurointegrative disorder in infants at risk include an abnormally quiet state (found in 4 children of schizophrenic mothers) which is manifested in an unusual "ability to maintain an unbroken state of quiet visual alertness for up to one hour and 20 minutes as early as 18 hours of age." The abnormally quiet infants also had extreme underactivity, flaccidity, and overextensibility of joints, as well as hypotonia, decreased nystagmus and normal or increased visual fixation and following. The other feature of the neurointegrative defect described by Fish is decreased or absent nystagmus to caloric stimulation. These abnormalities of

arousal, nystagmus, visual attention, and bimanual coordination may appear in adults with neurointegrative defect as characteristic abnormalities of arousal and attention, oculomotor control, and lateralized functional processes. Furthermore, Fish concluded, on the basis that there was no excess of PBC's in children with pandedevelopmental retardation, that the neurointegrative defect was of genetic origin. In summary, Fish concluded that a dysregulation of the overall timing and patterning of neurologic maturation, affecting many systems under CNS control, including physical growth, gross motor, visual-motor, vestibular functioning and arousal may be an early marker for the inherited neurointegrative defect underlying vulnerability to schizophrenia.

Neurologic abnormalities have been found in offspring of schizophrenics by other investigators. Marcus (1970, 1974) reported significantly more neurological 'soft-signs' in the 7 to 10 year old offspring of schizophrenics, compared to controls matched for rearing environment. Half of the schizophrenic offspring showed poor overall neurologic function. The items significantly differentiating the schizophrenic offspring under age 11 from the controls were facial asymmetry, fine motor coordination, left-right orientation, visual perception and auditory-visual integration. After age 11 these functions matured and no longer differentiated the groups. Perhaps other more subtle disorders of lateralization, motor and perceptual

functions characterize older individuals 'at -risk'. Others reported more neurologic soft signs in psychiatrically disturbed adolescents than controls (Hertzog and Birch, 1968), and in schizophrenic adults with thought disorder (Tucker, Campion and Silberfarb, 1975) or premorbid asociality (Quitkin, Rifkin and Klein, 1976).

Marcus, Auerbach, Wilkinson and Burack (1981) studied children of psychiatrically disturbed parents (17 schizophrenic, 6 affective, 13 personality disorders and neuroses, and 17 with no mental illness) identified by screening pregnant mothers and their husbands in the municipality of Jerusalem for psychiatric disorder. Infants were tested at 3 and 14 days of age with the Neonatal Behavioral Assessment Scale (NBAS), and at 4, 8 and 12 months with the Bayley Scales of Infant Development (BSID). Multidimensional Scalogram Analysis was used to identify a subgroup of 13 infants born to schizophrenics who repeatedly performed poorly in motor and sensorimotor functioning in the first year of life. The deficits were concentrated in and specific to the subgroup of infants of schizophrenics. Seven of the infants in the subgroup had low to low-normal birthweights, but this could not be accounted for by pre-, peri-, and postnatal insults, suggesting a genetic etiology for the low birthweights. The infants of schizophrenics were, however, more sensitive to trauma when it occurred. These findings suggest that motor and sensorimotor deficits, increased with

vulnerability to PBCs, and low birthweights found in the children of schizophrenics are genetically determined.

Other investigators have also reported disrupted motor development in children of schizophrenics and in preschizophrenic children. Ragins, et al. (1975) found retarded maturation of reflexes in 4/10 children of schizophrenic mothers. Difficulty in walking was one of the developmental symptoms that significantly differentiated preschizophrenic children from controls (Robins, 1966; O'Neal and Robbins, 1958). Preschizophrenics were differentiated from classmate controls by the presence of severe organic handicaps, including 'neurologic disorders', i.e., soft signs (Watt, 1974). Slow motor development and other symptoms of neurologic impairment were found in 20% of preschizophrenics and 10% of controls (Ricks and Maneche, 1966), and these neurologic abnormalities were related to the chronicity of later schizophrenia (Ricks and Berry, 1970). Mednick, et al. (1971) found that retarded motor development at 5 days and 1 year of age significantly differentiated the offspring of schizophrenics from controls. A composite index of measures of poor skills, intraindividual variability on cognitive tests and schizoid behavior (apathy, withdrawal, emotional flatness and instability, irritability and negativism), significantly differentiated offspring of schizophrenics from controls (Hanson, Gottesman and Heston, 1976). All of these findings support the hypothesis that the

genetic diathesis underlying vulnerability to schizophrenia involves a 'neurointegrative defect' which manifests as neurologic soft signs and disrupted motor and sensorimotor function during infancy and childhood.

Several investigators have suggested that psychophysiological measures may provide a 'marker' for the neurointegrative defect in schizophrenia. Putative markers may be identified by finding differences between offspring of schizophrenics (or some subgroup thereof) and controls on measures that differentiate adult schizophrenics and controls. The GSR abnormalities found in offspring of schizophrenics by Mednick and Shulsinger (1968) have already been mentioned. Van Dyke (1972) failed to replicate these findings and Salzman and Klein (1978) replicated only the findings of larger amplitude skin-conductance responses to interpolated unreinforced presentations of conditioned stimulus, as well as the unconditioned stimulus, and greater responsivity to the US. Mednick (1973) has argued that these failures to replicate were the result of the fact that the GSR abnormalities were concentrated in offspring of schizophrenics from nonintact families, and the other studies used subjects from intact families; and the children were younger than in the Mednick and Shulsinger (1968) study. Venables (1977) reported that in offspring of schizophrenics in the Mauritian High Risk Study, there occurred a bimodal distribution of GSR, with marked

hyporesponsivity occurring in some subjects and hyperresponsivity occurring in others. The same bimodality of GSR responding has been reported in adult schizophrenics (Gruzelier and Venables, 1973, 1974, 1975).

Electroencephalographic characteristics may also provide vulnerability markers. Children of schizophrenic parents have been found to differ from normal controls (children of nonpsychiatrically ill parents) by the presence of more high frequency beta activity, fewer fast alpha waves, and more very slow low voltage delta activity, as well as shorter latencies in auditory evoked potentials (Itil, Hsu, Saletu, and Mednick, 1974). Similar differences have been found for adult schizophrenics (Itil, Saletu, Davis, 1972) and psychotic children (Itil, Saletu, Simeon, 1974) compared to matched controls. Interestingly, the most frequent significant differences between the high risk children and controls were found in the right temporal to parietal lead (T4-P4). Other psychophysiological vulnerability markers have been proposed, including abnormal pupillary responses (Steinhauer, Harkerem and Spring, 1979), and deviant autonomic nervous system responding (Zahn, Carpenter, and McGlashan, 1979). Two putative psychophysiological markers of vulnerability will be discussed more thoroughly in the next two chapters: abnormalities or characteristic patterns of hemisphere lateralization or 'hemisphericity', and smooth pursuit eye movements (SPEM).

Attentional deficits in adult schizophrenics have been documented by many investigators. A large body of literature has grown on schizophrenic reaction time deficits as a measure of attentional disorders (Neuchterlein, 1977), Marcus (1972) found that the children of schizophrenic mothers were slower than controls in a RT paradigm. The children of psychotic mothers made more nonlooking responses and errors on the Children's Embedded Figures Test, suggestive of attentional problems as well as more errors of omission on the Continuous Performance Test (CPT), a measure of sustained attention (Gamer, et al. 1977; Grunebaum, et al., 1974). The CPT deficits in high risk children have been confirmed by other investigators (Rutschmann, Cornblatt and Erlenmeyer-Kimling, 1977; Erlenmeyer-Kimling and Cornblatt, 1978). Children of schizophrenics demonstrated in studies of adult schizophrenics on the span-of-apprehension-task (Asarnow, et al. 1977, 1978), as well as other attentional tests such as the Spokes Test, Stroop Color/Word Test, CPT, Simple RT, Concept Attainment Task, Digit Symbol Substitution Test and Competing Voices. Half of the high risk sample had significant impairment on this battery of eight attention tasks as well as increased social isolation, difficulties in the student role, elevated total symptom scores on the Psychiatric Status Schedule, and elevated schizophrenia scale scores on the MMPI (MacCrimmon, et al., 1980).

Spring and Zubin (1978) have argued that attention tasks and information processing tests may serve as indicators of vulnerability to schizophrenic episodes. They recommend the following techniques as putative vulnerability markers, based on studies showing deficient performance of adult schizophrenics on these tasks:

1. Dichotic listening as a measure of the ability to maintain selective attention;
2. Simple reaction time to ipsimodal and cross modal stimulus sequences measuring the ability to shift attention;
3. Pupillary dilation to ipsimodal and cross modal stimulus sequences;
4. Evoked potential to ipsimodal and cross modal stimulus sequences;
5. Pupillary constriction to simple light stimuli;
6. Pursuit eye movements;
7. Visual threshold and visual temporal integration;
8. Auditory threshold and auditory reaction time facilitation by the addition of a masking stimulus;
9. Comprehensibility of verbal utterances as measured by the cloze procedure.

(Spring and Zubin, 1978, pp. 290)

They also recommended a set of methodological maxims to guide research concerned with the validation of putative vulnerability markers. An example of the application of these maxims to research on shift of attention as a marker, by Spring (1980), demonstrated that high cross-modal retardation to lights may be a marker of schizophrenic disorder rather than vulnerability. The use of 'high-risk' longitudinal prospective studies would be required to definitively validate attentional or any other

putative vulnerability markers.

The literature reviewed thus far suggests that the neurointegrative defect underlying the vulnerability to schizophrenia may be identified by a variety of markers: neurological, psychophysiological, attentional and information processing measures. Many of the reports of neurological abnormalities in children at risk have referred to abnormalities of lateral asymmetry or bilateral integration. These manifestations of the neurointegrative are very likely closely related to the attention deficits just discussed. Matthysse (1977) has argued that attentional control is intimately related to lateralization processes. The relationship between lateralization and attention will be discussed more fully later. Attentional deficits are also related to difficulties on the Smooth Pursuit Eye Movement (SPEM) test, as will also be elucidated further.

Sampling Bias and Alternative High Risk Strategies

Although the prospective longitudinal study of children or infants at genetic risk for schizophrenia may have many advantages for the study of the development of schizophrenia, there are some serious methodological limitations to the strategy (Garnezy, 1977; Shields, 1977). Bleuler (1978) has pointed out that while 10-15% of adult schizophrenics have a

schizophrenic parent, some 80-85% of adult schizophrenics do not have a schizophrenic parent. Since virtually all of the 'high-risk' studies have used as a 'high-risk' criterion having a schizophrenic mother, the high-risk sample is biased. The children in such samples who eventually become schizophrenic may not be representative of schizophrenics in general, but rather "may represent a subgroup of all schizophrenics who have atypically strong genetic and environmental diatheses" (Hanson, Gottesman and Meehl, 1977, p. 582). Thus, because the traditional high-risk samples are biased by higher parent-child concordance than found in schizophrenics in general, the results may be applicable only to a subgroup of all schizophrenics, the 10-15% with a schizophrenic parent. Further research is needed to determine the degree of similarity or differences between this select subgroup and the majority of schizophrenics without a schizophrenic parent(s) before the results obtained thus far can be considered generalizable to all schizophrenics.

Another sampling bias arising out of the currently popular risk criterion is the overrepresentation of females among index parents (Lewine, Watt and Grubb, 1981). Of the 25 high risk projects currently in progress, 14 (56%) have used only the children of schizophrenic mothers, while in the other 11, female index parents far outnumber male index parents (606 to 355). In light of the reported equivalent prevalence rates of schizophrenia in the sexes (Dohrenwend and Dohrenwend, 1976),

the overrepresentation of mothers among schizophrenic index parents clearly introduces another sampling bias. Systematic sex differences in schizophrenia could make this source of bias a serious problem for generalizability. There is good evidence that male schizophrenics are characterized by earlier onset, poor premorbid history, and typical negative symptoms, while female schizophrenics are characterized by late onset, good premorbid history, and atypical positive symptoms (Lewine, 1979, 1980 a; Lewine, Strauss, Gift, in press). As schizoaffective symptoms occur more often in female schizophrenics, overrepresentation of females among index parents may introduce diagnostic and etiological heterogeneity into the index sample. Lewine, Watt and Grubb (1981) summarize the implications of the sampling bias problem:

"To present a highly simplified example, our review of the sample characteristics of current high risk research suggests that we are ultimately studying a form of schizophrenia transmitted largely through the Mother (Lewine, 1979), accompanied by affective, atypical symptoms (Lewine, 1979, 1980 A), and yielding a 100 percent concordance rate between an affected child and its parent" (Hanson, Gottesman and Meehl, 1977).

Lewine, et al. (1981) suggest the use of behavioral risk indices such as teacher rating forms to assist in the identification of children and adolescents at behavioral risk for schizophrenia. The adolescents who eventually develop schizophrenia would not be characterized by the sampling biases of the samples of schizophrenic mothers' offspring. Use of a

full sibling or parental relationship to an identified schizophrenic as a risk criterion would also circumvent the sex bias problem but would still produce a sample of schizophrenic 100% of whom have a schizophrenic first degree relative. These strategies may provide useful complements to the current high-risk strategy defining risk in terms of parental (particularly maternal) schizophrenia.

Another potentially powerful method for studying vulnerability and the development of schizophrenia which overcomes the sampling bias problem is the use of a biological measure to define 'high risk'. The biologically at risk paradigm was first introduced by Buchsbaum, Coursey and Murphy (1976) as the 'biochemical high-risk paradigm'. These investigators screened 375 college students for platelet levels of monoamine oxidase (MAO), which has repeatedly been found to be reduced in patients with affective disorders and schizophrenia. The upper and lower deciles in MAO activity were further interviewed and the low platelet MAO probands reported more frequent psychiatric or psychological counselling and more problems with the law. More suicide and suicide attempts occurred in the families of low MAO probands, as well as more psychiatric hospitalization and problems with the law. These findings suggest that low platelet MAO may predict a vulnerability to psychiatric disorder.

Buchsbaum, Coursey and Murphy (1980) list three advantages of the use of a biological definition of high risk:

First, it tests explicit hypotheses about a biological variable and its psychological correlates, and also gives some indication of how potent that variable is in relationship to other vicissitudes of living. Second it avoids the problem of biological heterogeneity (Buchsbaum and Rieder, 1979) and lack of reliability of psychiatric diagnoses. Third, it requires the researcher to explore the hypothesized psychological expression of the biological variable in the normal as well as pathological range.'

In addition the biological high risk strategy shares with the usual high-risk strategy the freedom from the effects of hospitalization, labelling and treatment factors that confound other biological studies of psychopathology. And it is relatively free of sampling bias.

Further studies of this college sample have produced interesting results suggesting that elaborations of the original design may be useful. Because this research program is the first and most highly developed using the biological high-risk paradigm, these results will be reviewed in some detail.

Higher MMPI and Zuckerman sensation-seeking scale scores were found in male but not female non-psychiatric volunteers with low platelet MAO, with males exhibiting negative correlations between MAO and sensation seeking while females exhibited positive correlations (Murphy, et al., 1977). In the college sample a discriminant analysis of MMPI items was used to create MAO scales which discriminated low and high MAO subjects,

with 100% accuracy for females and 94% accuracy for males. Cross validation of the 2 scales on another part of the population of subjects yielded a combined 97% accurate discrimination (Donnelly et al., 1979). The female MAO scale contained items reflective of social contact-related behavior, including avoidance of activities done alone, items reflective of strong positive affect, self confidence and activity seeking or sensation seeking behaviors. The male MAO scale contained items reflective of social concern, especially tolerance of others, sociopathy, and a 'feel more intensely' item. These results offer support for a relationship between MAO levels and sensation seeking, and an association of sociability with low MAO levels. Interview data revealed that low MAO males and females were more socially active than high MAO subjects (Coursey, Buchsbaum and Murphy, 1979). Low MAO males also experimented more with illegal drugs, had elevated scores on the MMPI and were more often left-handed than high MAO males (Coursey, Buchsbaum and Murphy, 1979).

An extension of the biochemical high risk paradigm included the addition of a second biochemical parameter, levels of platelet dopamine beta carboxylase (DBH), the enzyme which converts dopamine to norepinephrine (Buchsbaum et al., 1978). Higher levels of DBH were associated with greater amplitude increases for the visual average evoked response (AER) in an attention condition (counting light pairs) over amplitude in the

unattending condition, particularly in the low MAO group. High DBH probands showed a significant difference in visual AER N140 amplitude between attending and nonattending conditions while the low DBH group did not. Subjects with low MAO and low DBH made significantly more errors of commission on the CPT vigilance task than low MAO, high DBH probands, whereas among the high MAO subjects, DBH levels were not significantly associated with CPT errors. These results demonstrate an association of low DBH and impaired selective attention, inferred from AER measures, and defective vigilance performance, measured by CPT, and this association is especially strong among low MAO subjects. Thus, the concurrent use of two biological markers may yield more interesting results than screening on just one biological variable.

In a similar extension of the biochemical high risk paradigm, subjects were characterized by both MAO levels and AER augmenting/reducing. Male low MAO subjects with a family history of suicide or suicide attempts were all AER augmenters, suggesting that the combination of low latelet MAO activity and AER augmenting may be associated with psychiatric vulnerability (Buchsbaum, Haier and Murphy, 1977). Low MAO augmenters also had higher MMPI schizophrenia scale scores as well as more suicides among their relatives than low MAO reducers or high MAO subjects (Coursey, Buchsbaum and Murphy, 1979). A later analysis showed that psychopathology revealed by the MMPI and/or Research

Diagnostic Criteria (RDC) evaluations, especially affective disorder, was more prevalent among both low MAO augmenters and high MAO reducers (Haier, et al., 1980). The authors explained these results in terms of an interactive model of sensation seeking and sensory inhibition. Low MAO subjects have sensation seeking, and if they are augmenters, a lack of sensory protection, the combination producing overarousal. High MAO subjects avoid sensation seeking behaviors, and if they are reducers, also have high levels of sensory inhibition, the combination leading to underarousal. The low MAO/reducing and high MAO augmenting groups, having balanced sensation seeking and sensory protection, have balanced arousal and so less psychopathology than the low MAO augmenters and high MAO reducers. During an 18-month follow-up period concluded by clinical interviews, higher incidences of major depression and hypomania characterized the low MAO augmenters and the high MAO reducers (Haier, Buchsbaum and Murphy, 1980). These findings suggest associations between low MAO, AER augmenting and high MAO, AER reducing with affective disorder. A battery of psychological tests including the MMPI, WAIS, Korschach, Zuckerman and Zung Scales, TSCS, Kent-Rosanoff Word Association test and others, was administered to the high and low MAO groups and the results were factor analysed. Low MAO males scored significantly higher on a general psychopathology factor, while high MAO females scored high on this factor (Coursey, Buchsbaum

and Murphy, 1980). The low MAO reducers, who are theoretically at risk for schizophrenia (schizophrenics have both low MAO and AER reducing), had significantly more remote word association than the high MAO augmenters.

Finally, when parents of the high and low MAO probands were examined, it was discovered that there were significant positive correlations between parents' and childrens' MAO levels. The parents of high MAO probands had more 'high MAO related' psychiatric disorders (major or minor depression), while parents of low MAO probands had significantly more 'low-MAO-related' disorders (schizophrenia, bipolar affective disorders I and II, including mania and hypomania; alcoholism, and antisocial personality) (Puchall, Coursey, Buchsbaum and Murphy, 1980).

These findings all support the utility of a strategy reversing the traditional dependent and independent variables, and defining the risk groups in terms of biological measures rather than diagnostic or symptomatic categories. Conceptually, many advantages of this 'biological high risk' strategy can be seen:

1. The problem of biological heterogeneity is solved because biologically homogenous subgroups are defined at the outset.
2. Iatrogenic effects of hospitalization, effects of labelling, and drug or other treatment effects upon the measures of biological and psychological function are eliminated since the sample consists of as yet undiagnosed 'preschizophrenics'

at risk. The interaction of biological, psychological and environmental factors may be examined before the onset of clinical disorder.

3. The sample need not be biased in favor of parent-child concordance for illness, sex prevalence of the probands or their parents, or biasing toward a particular type of psychopathology.
4. Explicit hypotheses concerning psychological correlates of the biological variable(s) can be tested.
5. The expression of the biological pattern can be examined along the entire spectrum of psychopathology to health.

Granting the potential strength of the strategy, the next most salient question becomes which biological or other measure to use for screening. The MAO research continues to produce promising, if ever more complicated results. Any other biological, psychophysiological, behavioral, and/or psychological variables which distinguish psychotic and remitted schizophrenics, relatives at risk and high risk children from healthy controls seems promising. Ideally, the variable(s) should be specific for schizophrenia or schizophrenia spectrum disorders, though more general vulnerability to psychosis markers would also be of use and interest. Practical considerations would lead to the choice of measures which are low in cost of time and high in yield of information. Biochemical assays seem more directly related to current

neurochemical etiological theories, but they are expensive, time-consuming and require highly trained technicians. Simple electrophysiological and behavioral tests may have even more utility, being more closely related than the biochemical measures (conceptually) to the 'symptomatic' behaviors of interest. Paper and pencil psychological tests are easy to administer and score and may reveal latent or emergent psychopathology.

This study will consider three putative markers for for 'schizotaxia'. The first is a behavioral measure of 'hemisphericity', characteristic or preferential asymmetric activation of the hemispheres, the Conjugate Lateral Eye Movement (CLEM) test. The evidence implicating lateralization and hemisphericity in schizophrenic psychopathology will be considered. The second measure involves the electrophysiological recording of eye movements during smooth pursuit tracking of a slow velocity target. Research relating disordered Smooth Pursuit Eye Movements (SPEM) to psychopathology and genetic vulnerability will be considered. Since both CLEM and SPEM are eye movement measures, neurophysiological mechanisms involved in the control of the dual saccadic/smooth-pursuit eye movement systems will be reviewed, and an argument for the construct validity of the CLEM measure will be offered, as well as hypotheses concerning asymmetric smooth pursuit. Theoretical relationships among eye movements, attentional processes and

lateralization of function will also be considered. The third measure which may provide the schizotaxia marker is the Minnesota Multiphasic Personality Inventory (MMPI). Many of studies already reviewed have made use of the MMPI, so a brief review of the rationale behind its use as a marker of vulnerability will be presented first.

The MMPI as a Vulnerability Marker

Golden and Meehl (1979) have argued that the Minnesota Multiphasic Personality Inventory (MMPI) may be useful in the detection of the 'schizoid taxon'. They began with 53 items which significantly discriminated between 96 diagnosed schizophrenics and a normal sample by a difference in class proportions of .20 or more. These items were then administered to a sample of 211 nonschizophrenic male inpatients who had diagnoses of neurosis personality disorder or transient situational disorders. A taxometric statistical procedure described by them was applied to the data and 7 items were chosen which significantly discriminated the schizoid from the nonschizoid patients with a combined accuracy rate of 85%. The seven items were:

1. (61) I have not lived the right kind of life (T).
2. (239) I have been disappointed in love (T).

3. (20) My sex life is satisfactory (F).
4. (317) I am more sensitive than most other people (T).
5. (284) I am sure I am being talked about (T).
6. (501) I usually work things out for myself rather than get someone to show me how (F).
7. (207) I enjoy many different kinds of play and recreation (F).

These items reflect disappointment in life and love (61,239, 20), interpersonal aversiveness (317,284) and restriction of interest perhaps suggesting anhedonia (501). Because florid schizophrenics are not identified by these 7 items, but rather schizoid individuals, the item content is not very 'crazy'.

Using these 7 indicators each individual whose probability of being a member of the schizoid taxon exceeded .5 was classified as a probable schizoid, the others being classified as probable nonschizoids. When the two subsamples were compared on the MMPI, the probable schizoid group had higher means on all 10 clinical scales, with significant differences (in descending order of magnitude) on Psychasthenia, Hysteria, Psychopathic Deviance, Masculinity-Femininity, Paranoia, Schizophrenia, Social Introversion, Depression and Hypomania. The mean MMPI profile for schizoid taxon members was identical to the 2-7-8 code type, even though only a small percentage of the individual profiles were of the 2-7-8 type. The mean MMPI profile of the schizoid taxon was very similar to that of a sample of preschizophrenics studied by Peterson (1963).

Factor analysis of the 13 standard MMPI scales in the total sample with a varimax rotation produced a factor accounting for 41% of the common variance which correlated highly with Psychasthenia (.69), Schizophrenia (.53), Depression (.61) and Social Introversion (.79). The 7-item scale correlated .56 with Psychasthenia, .53 with Schizophrenia, .41 with Social Introversion and .42 with the Depression Scale. Use of an indicator consisting of the sum of these four standard scales (D, Pt, Sc, Si) produced classification results and estimates of the schizoid taxon base rate in close agreement with the other taxonomic methods. This 'schizotypy' scale will be used in the present study as an MMPI index of schizotaxia.

The use of the MMPI in diagnosing schizophrenia has a long history, which is too involved to review here. The use of the schizophrenia scale alone is insufficient yielding many false positives. However a combination of scales may be more useful. For instance, Newmart, Gentry, Simpson and Jones (1978) found that a set of MMPI criteria detected 72% of a group of reliably diagnosed schizophrenics and only 5.5% of a group of nonschizophrenics. These criteria were: T score on Sc GE 80, LT 100, total raw score of SC consisted of no more than 35% K items, T score on P GT75, LT95, T score on P LT Sc. Although such findings require independent validation, they indicate at least that the MMPI may possibly successfully discriminate schizophrenics or schizotaxics from normals and other

nonschizophrenic or nonschizotaxia psychiatric subjects.

The use of the MMPI as a vulnerability marker is further supported by reports of scale deviations in the relatives of schizophrenics. Female relatives of schizophrenics had higher elevations of psychopathic deviance, schizophrenia, and social introversion scales than females from families with no history of psychosis; and male relatives of schizophrenics had elevations of F, Depression, Hypochondriasis, Psychopathic Deviance, Paranoia, Psychasthenia and Schizophrenia, compared to males from psychosis-free families (Rahn, Gfeller and Vaughn, 1977). The correlation of scale scores between subjects, particularly scale 8-schizophrenia, was related to the degree of consanguinity between family members (Rahn, 1977).

Some support for the utility of MMPI criteria in identifying the schizophrenic genome has come from MMPI results from the Danish-American Adoption Studies (Baier, Rosenthal and Wonder, 1978). Adopted offspring of schizophrenics did not differ on group mean single scale scores of the MMPI from matched controls. But the male index group had higher scores than controls on all nine clinical scales and masculinity / femininity. Based on these ten scales the overall elevation of the MMPI is significantly higher in index than control males. The same tendency occurred in females, though nonsignificantly. Univariate analysis of variance revealed significantly higher schizophrenia and masculinity/ femininity scales in the male

index group, and higher hysteria and psychopathic deviate scales in the female index group compared to controls. The use of 3 MMPI predictors for psychological disturbance (Cooke Index), psychosis (Peterson Signs), and schizophrenia (Eichman Schizophrenia Signs), all identified a greater proportion of high scores in the index than control groups, though only the difference on the Psychological Disturbance Index reached statistical significance. Of the 32% (21/64) of the index group given a consensus diagnosis of chronic (3), or borderline (10) schizophrenic, or schizophrenic personality (8), 66% (14/21) also had a divergent MMPI (i.e., one or more clinical scales with T GE 70). Only 4 of 16 (25%) of the control cases had a divergent MMPI. The combination of consensus diagnosis and a divergent MMPI identified 14/64 index/cases and 4/64 control cases. This difference of 22% of the index to 6% of the controls is statistically significant (Haier, Rosenthal and Wender, 1978). Interestingly the difference between index and control groups is found only in the men, since as a group the women diagnosed in the spectrum do not have elevated MMPI scales. These results offer tentative hope that the MMPI may be useful in identifying latent or covert psychopathology in those genetically at risk for schizophrenia.

The validity of the MMPI in detecting psychopathology in a previously undiagnosed population has been recently demonstrated in a study of 385 college males screened with the MMPI (Haier,

Rieder, Khouri and Buchsbaum, 1979). Of the 56 subjects with scores at least 3 SD above the mean on at least one MMPI scale, 82% met the Research Diagnostic Criteria (RDC) for at least one psychiatric diagnosis. Of the 27 with MMPI scores within normal limits (no scale scores over T=60) only 22% met the RDC for any diagnosis. Some correspondence between profile code types and RDC diagnoses was observed. These results suggest that the MMPI may be quite useful in identifying individuals in a nonhospital setting who manifest latent or overt psychopathology.

The findings of discriminative validity of MMPI indices for identifying members of the schizoid taxon or schizotypics, schizophrenics, and offspring and relatives of schizophrenics, along with evidence demonstrating convergence of MMPI indices with psychiatric consensus or RDC diagnosis strongly suggests that the MMPI may have utility in high risk studies. The MMPI may itself provide a 'personality vulnerability marker' or it may be used as a dependent variable to quantify psychopathological tendencies in groups defined on the basis of other putative marker variables.

II. Lateralization of Function in Schizophrenia

Since Sperry's pioneering experiments with commissurotomed or "split-brain" patients, a wide variety of research with normal subjects, brain-lesioned or commissurotomed subjects, epileptics, and other neuropsychiatric groups has unquestionably established the existence of lateral asymmetry of function in the human brain. The left hemisphere of most people is specialized for language functions, and exhibits superior performance on tasks requiring phonetic, grammatical, or semantic analyses, mathematical or logical reasoning, temporal discrimination, and writing. The mode of processing of the left hemisphere has been characterized as "symbolic, abstract, linear, rational, focal, conceptual, propositional, secondary process, digital, logical, active, and analytic." (Bakan, 1978). The right hemisphere is more specialized for visuospatial and gestalt functions. It has been described as "iconic, concrete, diffuse, perceptual, appositional, primary process, analogue, passive, and holistic" and, "the two modes are antagonistic and complementary suggesting that a unity and struggle between opposites is characteristic of mental functioning." (Bakan, 1978).

Several recent authors have proposed a theoretical

synthesis of Freudian psychoanalytic and Jungian depth psychological theories of psychodynamics with neurophysiological theories of cerebral lateralization. Galin (1974) was the first to propose the hypothesis that the psychic duality described by psychodynamic theorists is isomorphic with the duality of the brain described by recent neurophysiological research. He reviewed a large body of evidence supporting his argument that characteristics of right hemisphere processing bear a striking formal resemblance to the characteristics of primary process thought as it is described by psychoanalytically oriented writers. The left hemisphere mode of processing is isomorphic with secondary process thought. From this apparent structural isomorphism Galin postulated a dynamic process isomorphism in which psychodynamic processes would have their neural equivalents in interhemispheric inhibition or facilitation. He postulated that the maintenance of unilateral engrams, or isolated lateral information stores, producing a "functional commissurotomy", may serve as a neurophysiological mechanism for some instances of repression. He further suggested that the right hemisphere may be the neuroanatomical locus of unconscious mental contents.

McLaughlin (1978) has added further to this hypothesis of the lateralization of primary and secondary process thought to right and left hemispheres respectively. Considering primary process in developmental terms, he emphasized the idea that

"As the first organizing mode of infantile development, it shapes the primitive content of the dynamic unconscious. Thereafter, it can be viewed as coexistent and mingled with secondary process in dynamic tension, complementarity, and developing complexity....primary processes are not confined to archaic levels but are open to growth and developmental integration into the complete range of ego functions."

He cites Martindale (1975) who provided EEG evidence indicating that secondary process thinking occurs when cortical arousal is intermediate, while primary process thought occurs when the cortex is at low levels of arousal (slow alpha waves) or at high levels of arousal when anxiety or stress have strongly activated cortical function.

Further support for this psychodynamic neurophysiological synthesis is supplied by Hoppe (1976) who reported that "split brain" subjects remember few dreams, and those they do recall are marked by a paucity of vivid imagery, symbolization, or fantasy. The same absence of primary process components characterizes these patients' waking fantasy life as well. Hoppe interpreted this as due to

"an interruption of the preconscious stream between the two hemispheres, which causes a separation of word presentations from thing presentations, as well as to a predominance of a feedback free primary process in the right hemisphere."

Obsessive compulsives use repression and denial to a great degree, and are, like the split-brain patients, characterized by a lack of imagery, fantasy, or memory of their dreams. Thus, the obsessive-compulsive's repressive defenses may constitute a

state of "functional commissurotomy". Hoppe also postulates that severe psychosomatic disorders which also involve the use of repression may have similar neurophysiological mechanisms and processes at work. It is perhaps interesting in light of what is to come to note that Brill (1979) has argued that schizophrenia is a severe psychosomatic disorder.

This theoretical synthesis has been carried beyond the Freudian framework by Rossi (1977) and has been extended to the depth psychology of Jung. Rossi proposes that the transcendent function, the union or integration of unconscious and conscious contents, the interaction of ego and archetype, has its neurological concomitant in the interhemispheric integration of information from both hemispheres. Just as failure to remember dreams is the result of repression and functional separation of the two halves of the brain, the remembering of dreams, a result of the transcendent function, would involve the reverse process, an integration of the halves.

Keeping this theoretical synthesis in mind, let us examine some of the explanations of the schizophrenic process proposed by Carl Jung (1907, 1939, 1957, 1958). Jung believed that schizophrenia is a pathological aberration of the transcendent function, or a disordered integration of the two halves of psychic duality, the ego and the unconscious. In normal people the transcendent function is expressed in dreams, fantasy, creativity, and such religious and therapeutic activities as

meditation, yoga, or depth analysis. The process is controlled and to a large degree capable of conscious direction. In the schizophrenic, on the other hand, the process seems to have gotten out of control, and the schizophrenic's ego consciousness is overwhelmed by a flood of unconscious and archetypal contents. Thus, the schizophrenic is dominated by primary process. Jung wrote, "in a schizophrenic patient the connection between the ego and some of the complexes is more or less completely lost." (Jung, 1960, pp. 157). Possibly, this would indicate a deficiency of interhemispheric transfer. He also states that schizophrenia "lowers the threshold of consciousness, thereby allowing normally inhibited contents of the unconscious to enter consciousness in the form of autonomous invasions." (Jung, 1960, pp. 158). According to the proposed model this would probably involve a "spill-over" of right hemisphere information into the left hemisphere, implicating abnormally extensive interhemispheric transfer. These two postulates of overactive and underactive interhemispheric transfer are not necessarily contradictory or mutually exclusive. The corpus callosum is an enormous pathway with both excitatory and inhibitory tracts. It is quite possible that some of these are hyperactive at the same time others are hypoactive. There are also extensive interhemispheric connections through limbic and subcortical commissures. Jung also maintained that in schizophrenia consciousness (is) weak and unable to keep back

the onrush of unconscious material. Weak ego strength, a breakdown of ego boundaries and normal repressive mechanisms (a failure of inhibition of right hemisphere processing by the left via reciprocal inhibitory pathways of the callosum), are all consistent, given our synthetic model, with the hypothesis of a left hemisphere dysfunction in schizophrenics.

Jung described several cases of schizophrenia which he treated by a cultivation of rational analytic ego functions, and a diversion of attention away from overpowering "numinous" experiences of unconscious contents. He achieved some success with this therapeutic strategy, but in one patient after treatment, "only the left side of the body (was) still under the domination of the unconscious"; in another patient, "after about eight years the right half of her body was completely freed of voices, up to a line running down the middle of the body. The voices persisted only on the left side." (Jung, 1960, pp. 170, 188).

This may strengthen the argument for a psychodynamic-laterality theoretical synthesis, and the potential usefulness of such a model for understanding the psychological and neurophysiological abnormalities seen in these schizophrenics.

These considerations, along with the extensive body of literature to be reviewed here suggest several hypotheses concerning laterality disturbances in schizophrenia. These four hypotheses outlined below are not mutually exclusive, and one or

more of them might apply to a variety of etiological subgroups of schizophrenia. The hypotheses are that schizophrenia is characterized by :

1. Left hemisphere dysfunction;
2. A disturbance of interhemispheric communication : functional disconnection of the hemispheres, diminished or disordered callosal transfer, particularly a decrease of the usual reciprocal inhibition between the hemispheres;
3. Release of the right hemisphere from inhibition, increase of right hemisphere mentation, and possible subsequent "spillover" of right hemisphere mentation into the left hemisphere. This may involve an increase in the activity of excitatory callosal activity transferring information from the right to the left, at the same time a decrease in the activity of the inhibitory callosal transmission from left to right, thus disinhibiting the right.
4. As a compensatory response to right hemisphere predominance the left hemisphere is overactivated, but being dysfunctional, it fails to achieve an equilibrium.

Language Disorder In Schizophrenia

The left hemisphere is the language processing center of the brain, and many investigators have described language disorders in schizophrenia, implicating the involvement of a

left cerebral dysfunction in this psychosis. Flor-Henry has reviewed some of the literature on linguistic malfunction in schizophrenia (Flor-Henry, 1974, 1976, 1978) providing evidence that defects of schizophrenic language include paralogias, sensory aphasia, paroxysmal dysphasia, mishearing of words, failure to utilize syntactic redundancies, mutism, echolalia, palilalia, word salad, and other so-called 'non-aphasic' disorders of speech. The speech disorder of schizophrenia may bear some resemblances to the disordered speech of aphasic patients. Horsfall (1972) was unable to differentiate schizophrenics from aphasics on the Porch Index of Communicative Abilities. Chaika (1974, 1977) has argued that schizophrenic speech is quite similar to that of aphasics and represents "a true break in normal language competence". Gerson, Benson and Frazier (1977) noted language disorder similarities in schizophrenia and posterior aphasia that result in the frequent cross-diagnoses between the two. Verbal output in both is vague, loosely associated, and confused. They propose six differentiating characteristics founded on the theoretical position that the disordered verbal output of schizophrenics derives from a subcortical-cortical dysfunction, while aphasia results from a cortical-cortical disruption.

Taylor, Greenspan and Abrams (1979) and Abrams and Taylor (1979) reported that schizophrenics gave more abnormal responses on an aphasia screening test than normal controls or patients

with affective disorders, with more than three times as many schizophrenics as affectives making dominant temporal/ tempoparietal errors (anomia, neologisms, paraphasias, letter/ number agnosia).

Faber and Reichstein (1981) found that schizophrenics with formal thought disorder showed significant abnormalities compared to normal controls and affective disorder patients on the Boston Diagnostic Aphasia Examination, especially the repetition of phrases subtest, and on the Token Test, a reliable and sensitive test of auditory comprehension entailing identification and manipulation of round and square tokens of various colors according to increasingly complex instructions. These deficits are suggestive of language comprehension and repetition dysfunctions in a substantial subgroup of rigorously defined schizophrenics.

Based on a detailed analysis of language behavior in an interview situation of 45 schizophrenics and 32 manics, Andreason and Grove (1979) formulated the following generalizations concerning schizophrenic language. Most schizophrenics show a mild language disorder and about half will show derailments or associative loosening, while only 16% have incoherent speech. While schizophrenics and manics are syntactically competent, schizophrenics show many semantic errors such as errors of reference or inappropriate word choice, and both groups' speech is characterized by loose or random joining

of phrases and clauses. Both groups also show impairment in the pragmatic aspects of language, violating rules governing discourse and clear communication. For example, they often fail to answer questions or change the topic of conversation without warning, and they are apparently unaware of their errors. Finally, the schizophrenics with severe language disorder resemble aphasics, suggesting that they may have neurological dysfunctions, particularly of the left cerebral hemisphere. Wykes and Leff (1982) found that the speech of schizophrenics contained significantly fewer structural links to relate sentences than did the speech of manic patients.

One quantitative approach to language analysis uses the 'type-token ratio', a measure of flexibility or variability in lexicon usage, computed by dividing the total number of words (tokens) into the number of different words (types) in a sample of written or spoken language (usually 100 word segments). The type-token ratio has been found to be lower in spoken and written language samples produced by schizophrenics compared to those produced by normals (Mann, 1944). Manschreck, Maher and Ader (1981) found significantly lower type-token ratios in spoken language samples from thought disordered schizophrenics compared to non thought disordered schizophrenics, other psychiatric patients, and normal control subjects. This measure of language disorder was also strongly associated with elicited and spontaneous motor abnormalities. Manschreck, Maher, Rucklos

and Vreen (1982) reported disturbed voluntary motor activity in schizophrenics, such as clumsiness and awkwardness, stereotypic and manneristic movements, and motor blocking, as well as abnormal elicited performance on Luria and Ozeretski tests. These motor abnormalities were associated with features of formal thought disorder, affective blunting, and neurological soft signs (graphesthesia, or recognizing digits traced on the palm, and stereognosis, or recognizing common objects held in the hand). Thus, disorders of spoken thought or language, such as poor understandability, derailment, faulty logic, poverty of information conveyed, and neologisms, characteristic of schizophrenics are associated with motor disorders and neurological soft signs. Manschreck, Maher, Rucklos, Vreen, and Ader (1981) found that the clinical motor abnormalities observed were significantly related to disrupted synchronization of tapping with a predictable auditory stimulus. The deficient motor synchrony of schizophrenics occurred at intermediate rates of stimulus presentation (80 and 120 beats/minute) and not at slower or faster rates, suggesting that the difficulty of the task and a general schizophrenic performance deficit cannot account for the results. Reduced synchronization accuracy was significantly related to anomalous motor behavior, evidence of formal thought disorder, and lower mean sample type-token ratios. These results suggest a close association of abnormalities of language and motor function in schizophrenics,

with an inability to make use of redundant information occurring in both spheres.

Neuropsychological Test Results of Schizophrenics

Neuropsychological tests have repeatedly provided evidence consistent with the hypothesis of left hemisphere dysfunction in schizophrenics. Flor-Henry, Yeudall, Stefanyk, and Howarth (1975), Flor-Henry (1976), and Flor-Henry and Yeudall (1979) reported a study of 54 schizophrenics and 60 affective psychoses patients tested on a battery of 'laterality' neuropsychological tests developed by Yeudall, including the Wechsler Adult Intelligence Scale (WAIS). Schizophrenics had significantly more impaired performance relative to affectives on the Wepman Aphasia Screening Test, the Seashore Speech Sounds test, Oral Word Fluency, Trail-Making B, and an ideomotor apraxia test. The schizophrenics had poorer fingertip writing and finger localization bilaterally, but especially for left hand responses. A multiple stepwise discriminant function analysis using the neuropsychological test results yielded an 85% correct classification for schizophrenics and a 94% correct classification for affective disorder patients. Schizophrenics also had lower mean verbal IQ scores on the WAIS than affectives, but did not differ in mean Performance IQ. Vocabulary and Digit Span subtests were significantly lower in

the schizophrenic group. These findings were interpreted by Flor-Henry (1976) as an indication of predominantly left frontotemporal dysfunction in schizophrenia and right frontotemporal dysfunction in affective patients.

Gruzelier and Hammond (1976) found that schizophrenics scored significantly worse on WAIS subtests reflecting left hemisphere verbal function (Comprehension, Similarities, and Vocabulary) than on those associated with right hemisphere spatial performance ability (Block Design and Picture Assembly). Previous studies had shown that the Similarities and Vocabulary subtests measure dominant hemisphere functions while Block Design and Object Assembly measure non-dominant hemisphere functions (Anderson, 1950; Reitan, 1955; Fitzhugh, Fitzhugh and Reitan, 1962; Matthews and Reitan, 1964; Parsons, Vega and Burn, 1969). Similarly, Klonoff, Fibiger and Hutton (1970) found lower Verbal IQ than Performance IQ on the Wechsler-Bellvue I of 66 chronic schizophrenics. Although Wechsler (1958) found higher Verbal than Performance scores on the WAIS in schizophrenics, he may have used anxious subjects, while Gruzelier and Hammond (1976) tested patients relatively free of anxiety, and anxiety may lower WAIS Performance IQ (Wechsler, 1958). Gruzelier and Hammond (1976) and Gruzelier, Mednick and Schulsinger (1979) reported that children of schizophrenic parents had lower Full Scale IQ and Verbal IQ on the WISC than children of parents with non-schizophrenic psychopathology and children of normal

parents, while no group differences occurred for Performance IQ scores. The children of schizophrenics had significantly lower scores than children in the other two comparison groups on the Vocabulary and Similarities subtests, paralleling the findings with adult schizophrenics. Krynicki and Mahas (1979) found that schizophrenic children had lower Vocabulary and Similarities WISC subtest scores compared to non-psychotic psychiatrically disturbed children.

Taylor, Redfield and Abrams (1981) studied 52 patients with affective disorders, 17 schizophrenics, and 8 patients with coarse brain disease using Smith's neuropsychological test battery. Schizophrenics were significantly worse than manics or depressives but did not differ from patients with coarse brain disease on tests measuring dominant hemisphere functioning: WAIS Verbal IQ, Peabody Picture Vocabulary, Benton Sentence Repetition, right-handed pegboard speed, and simultaneous stimulation. Using a discriminant function analysis, 86.5% of the affectively ill patients and 76.5% of the schizophrenics were correctly classified (84.1% overall hit rate), using a jackknifed classification procedure. Torrey (1980) found that among 84 inpatient schizophrenics, 8% of the acute/subacute group, and 49% of the subchronic/chronic group had abnormal performances on a test of graphesthesia (recognition of numbers traced on the open palm with eyes closed) and the face-hand test (localization of simultaneous touches on the hands and face).

The abnormalities seen in the schizophrenics were more pronounced on the right hand than on the left hand, suggesting left hemisphere dysfunction in the schizophrenics. Weller and Kugler (1979) and Dimond, Scammel, Pryce, Huys, and Gray (1979) found that schizophrenics made more left hand errors on stereognosis tasks, which they interpreted as indicative of a defect in interhemispheric communication.

Sarcone, Garavaglia and Cazzullo (1981) compared chronic undifferentiated schizophrenia inpatients with normals matched for age, sex, and handedness on the Short Aphasia Screening Test (SAST) (Taylor, et al, 1979) and the Quality Extinction Test (QET), which "quantifies the percentage of unilateral extinctions during bilateral stimulation of the two palms of the hands". Schizophrenics displayed abnormalities on the SAST indicative of left hemisphere dysfunction. On the QET schizophrenics showed more extinction on the left side compared to the controls, similar to the extinction seen in neurological patients with disease of the left frontal lobe (Schwartz, Marchok, Kreinick, and Flynn, 1979). These findings suggest that schizophrenics have a dominant hemisphere dysfunction, as well as a specific malfunctioning of the dominant side limbic system, as the frontal lobe receives the major neocortical projection of the limbic system (Nauta, 1971).

Walker and Green (1982) recently reported that 20 schizophrenics showed more soft signs of neurological

dysfunction than 20 psychiatric controls with affective disorder and 20 normal controls on tests of stereognosis, hand pronation-supination coordination, successive opposition coordination and speed. No significant effects of laterality were found, either within or between diagnostic groups, in contrast to the findings of Torrey (1980), Weller and Kugler (1979), and Dimond, et al (1979), although the stereognosis tasks used in all of these studies were similar. Thus, the literature on neurological soft signs in schizophrenia has reached no clear consensus on the question of lateralization of soft signs, although the greater number of studies suggest left hemisphere dysfunction. It is possible that these inconsistencies are the result of the use of small samples and the biological heterogeneity of the schizophrenic population with respect to the nature of lateralization abnormalities.

The pattern of asymmetrical dominant hemisphere dysfunction inferred from neuropsychological tests is not specific to schizophrenia. Yeudall and Fromm-Auch (1979) found neuropsychological test performance indicative of left hemisphere dysfunction in criminal psychopaths (72%), sexual offenders (70%), male violent criminals (72%), mentally retarded adults with behavior problems (85%), male adolescents with conduct disturbances (73%), male alcoholics with a personality disorder (66%), children with behavioral problems in school (77%), and learning disabled children in adaptation (82%) and

resource room (100%) remedial classes. They also found evidence of asymmetric non-dominant hemisphere dysfunction in patients with clinical depression (100%), personality disorders with affective features (65%), alcoholics with an affective disorder (71%), and female juvenile delinquents (70%).

Brain Damage

In brain damaged soldiers (Hilbom & Kaila, 1949; Hilbom, 1960; Lishman, 1966, 1968; Revitch & Zallanski, 1969), patients with closed head injuries (Davison & Bagley, 1969), and patients with cerebral tumors (Davison & Bagley, 1969; Bingley, 1958) an association has been found between severity of psychotic, particularly schizophrenic, symptomatology and left hemisphere involvement.

A number of investigators have found that left-sided brain injury or tumor is associated with a greater risk for psychiatric disorders, particularly schizophrenia. Hilbom and Kaila (1949) examined 1821 brain injured soldiers and found 81 cases of psychosis of which 20 were of the paranoid schizophrenia type. Of these 20, 17 had temporal lobe lesions of the left side. Hilbom (1960), in an expanded series of 3552 cases, found temporal localization and left sided localization associated with psychosis. In patients with no psychiatric disturbance there were equal numbers of right and left sided

lesions.

Penetrating wounds of the left side were also found to be associated with psychiatric disorder in a group of 670 soldiers by Lishman (1966,1968). The following table from his study indicates that in soldiers with no psychiatric disability left and right sided lesions are equally frequent, but as psychiatric disturbance becomes more severe the left sided lesions become predominant.

Table X
Psychiatric disability and left sided lesions.

	Psychiatric Disability		
	Mil	Mild	Severe
Total Cases	93	108	144
No. with unilateral lesions	71	92	108
No. & % with left-sided lesions	36 (51%)	51 (55%)	67 (62%)

These results were not statistically significant, but when sensorimotor deficits and right visual field defects are considered in lieu of left-hemisphere localization of the lesion, the association with severity of psychiatric disorder becomes significant, as shown in the following table.

Table XI

Psychiatric, disability, sensory motor and visual field defect.

	Psychiatric Disability		
	Mil	Mild	Severe

% of cases with sensory-motor defects			
Right and/or left	51.5	51.75	66
Right only	17.5	24.0	40
Left only	22.75	25.0	23.75

% of cases with visual field defect			
Right and/or left	28	37	43.75
Right only	9.75	21.25	30
Left only	17.25	14	11

The association of right sided visual and sensorimotor defects with psychiatric disability implicates a dysfunction of the left hemisphere. One possible explanation for the failure to obtain significance in the analysis involving lesion laterality, but significant differences when sensory and visual field defects are considered, is that right or bilateral lesions could cause a left hemisphere disorder through the absence of reciprocal inhibition.

There is also an association between the laterality of cerebral tumors and psychiatric disorder. Bingley (1958) noted that dominant temporal lobe gliomas were associated with a greater frequency of psychic symptoms than non-dominant tumors. Blunting of affect was especially associated with dominant side

tumors.

Davison and Bagley (1969) examined 77 cases of schizophrenia associated with cerebral tumors. Davison and Bagley (1969) found

"an association of left cerebral hemisphere and particularly temporal lobe lesions with primary delusions and catatonic symptoms, basal ganglia lesions with catatonic symptoms, diencephalic lesions (including basal ganglia) with auditory hallucinations, and brain stem lesions with thought disorder and Schneider's symptoms of the first rank." (Davison & Bagley, 1969, p.151).

In a group of 2335 psychotic veterans a significant excess of left sided cerebral pathology in both epileptics and non-epileptics was found by Revitch and Zallanski (1969).

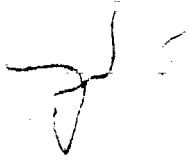
Walker and Jablon (1961) found that in soldiers with head wounds, there was an increased frequency of high Schizophrenia scale scores on the MMPI in those with aphasia compared to those without aphasia. This supports the notion of a language disorder association with schizophrenic personality tendencies.

Black (1975) examined penetrating missile wounds: the right lesioned group produced a composite profile with all scales within normal limits, whereas the left sided lesion group showed significant composite profile elevations on the Sc, D, and Hs scales, suggesting increased psychopathological responses in the left lesion group.

Louks, Calsyn, and Lindsay (1976) used a localization key applied to the Reitan Battery to designate 30 patients as left

or right hemisphere dysfunctional. The patients' MMPIs were then designated as "neurotic" or "psychotic" using the Goldberg Psychotic Index. Patients with left hemisphere deficits tend to score in the psychotic range, while right hemisphere deficit subjects scored in the neurotic range of the Goldberg Index. A 38% reduction in error of predicting neurotic or psychotic category was obtained by using the neuropsychological test laterality information. Gasparrini, et al (1978) found that the only clinical scale score that was significantly different between left and right hemisphere lesioned patients was the Depression scale. Seven out of sixteen left hemisphere, and zero out of eight right hemisphere dysfunctional patients had T scores greater than 70 on the MMPI-D scale.

Smirnov (1977) reported symptoms characteristic of schizophrenia in patients with both right and left cerebral tumors, though the symptoms were lateralized: left hemisphere damage associated with speech disorder, motor and sensory aphasia, twilight states and ambulatory automatisms, while right hemisphere involvement was associated with auditory, visual, and olfactory hallucinations, loss of reality, depersonalization, deja vu, and altered kinesthetic perception. This finding suggests an aberration of both hemispheres' function in schizophrenia.



Temporal Lobe Epilepsy

Temporal lobe epilepsy patients with schizophrenic symptoms had epileptic foci more often in the left hemisphere than the right (Flor-Henry, 1969; 1972a, 1972b, 1976a; Gregoriadis, et al, 1971; Sherwin, 1977). In a review of the records of 100 TLE patients, 50 with psychosis and 50 without, Flor-Henry (1969 a, 1969 b), found an association of dominant hemisphere foci with schizophreniform psychoses and nondominant hemisphere foci with affective disorders. Alpert and Martz (1977) argued that Flor-Henry's findings may have been due to an underrepresentation of patients with leftsided foci in Flor-Henry's non-psychotic control group, and their reanalysis of his data suggests an association of psychosis with bilateral foci (Slater, Beard and Glithero, 1963; Mignone, Donnelly and Sadowsky, 1970). The association of bilateral temporal lobe epilepsy with psychosis was also reported by Kristiansen and Sindrup (1978 a, 1978 b), in a controlled study of a large series of psychotic TLE patients. However, several other studies have also reported an association of left-hemisphere TLE and schizophrenic-like psychoses (Gregoriadis, et al., 1971; Sherwin, 1977, 1981; Taylor, 1975, 1977 a, 1977 b). Taylor (1975, 1977a, 1977b) found an excess of sinistrals among epileptics and reported that the most likely individual to become psychotic due to TLE was a left handed female with an

alien tissue lesion in the left hemisphere, whose seizures began after the age when language is organized. Still another study failed to find any association of laterality of epileptic focus with psychiatric diagnosis (Shukla and Katiyar, 1980).

It has also been reported that there was an inverse correlation between seizure activity and psychotic symptoms (Flor-Henry, 1969), termed "forced normalization" by Landolt (1953). Dopamine agonists block photically induced epilepsy and exacerbate schizophrenic symptoms, while dopamine antagonists diminish psychotic symptoms and enhance EEG spike and wave activity, increase seizure susceptibility, and induce seizures (Trimble, 1977). Dopamine activity is related to both schizophrenic and epileptic processes and has also been implicated in the biochemical control of lateralization by rat rotation studies (Perlman, 1976). Sherwin (1977) suggested that schizophrenic hallucinations are the result of 'spillover' of pent up REM activity into the waking state, and that epileptic seizures provide an alternate channel for the expression of pent up REM, thereby reducing psychotic expression. The observation that REM deprivation produces psychosis, and that REM deprivation effects in animals can be reversed by induced convulsions support this hypothesis.

TLE patients without psychosis have interictal behavior and personality traits that may be in the schizophrenic direction, and these symptoms exhibit a laterality effect. Bear (1977) and

Bear and Fedio (1977) found significant associations between the lateralization of TLE and 18 behavior/personality areas sampled with both self-report and observer ratings by 5 true-false questionnaire items for each area. Epileptic subjects in general self reported a profile of humorless sobriety, dependence, and obsessionism. Right temporal epileptic foci led to external emotive or behavioral manifestations, such as anger, sadness, elation, circumstantiality, viscosity and hypermoralism. Right temporals exhibited 'denial' de-emphasizing disapproved tendencies and greatly overemphasizing desirable qualities, a pattern of behavior described as 'polishing'. Left temporal lobe patients had more ruminative, intellectual tendencies such as increased concern with personal destiny, religiosity, philosophical interests, and intellectual and moral self-scrutiny. Left temporals overemphasized disapproved behaviors and de-emphasized desirable qualities, exhibiting a 'catastrophic' emotional reaction, described as 'tarnishing'. The emotive-ideative dimension very significantly differentiated the right and left groups, with no overlap: left temporals being ideational and right temporals emotional. The occurrence of flattened affect, increased religiosity and cosmological conceptualizing are often observed in schizophrenics, suggesting a parallel between certain aspects schizophrenic personality and left TLE interictal personality. Mungas (1982) found that none of the 18 traits measured by Bear and Fedio's questionnaire

discriminated temporal lobe epileptics with behavioral-psychiatric disorders from patients with concomitant neurological and behavioral-psychiatric disorders and a group of patients with psychiatric but no neurological illness, suggesting that Bear and Fedio's (1977) findings reflect differences between TLE patients and normals in the degree of nonspecific psychopathology and do not necessarily indicate the presence of a specific behavioral syndrome in TLE. Despite the lack of specificity for TLE, Bear and Fedio's (1977) findings certainly support the concept of differing psychopathological concomitants of right and left temporal lobe epilepsy.

Schenk and Bear (1981) subsequently reported an association of dissociative phenomenon with TLE. Of clinic patients with TLE, 33% exhibited some dissociative phenomenon. Three patients with multiple personalities showed altered speech patterns, personality, sense of personal identity and handedness and had amnesia for the dissociative episodes, while another 10 patients identified demons or alternate personalities as the motivators of ego-alien behavior. The switch in handedness during dissociative episodes was also reported by Hall, LeCann and Schoolar, 1978 and Taylor and Martin, (1944), and other alterations in laterality accompanying changes in personality were reported by Ischlondsky (1955), Condon, Ogston and Pacoe (1968) and Sutcliffe and Jones (1962). These findings suggest that a temporary change in cerebral lateralization processes may

accompany or underly psychopathological dissociative episodes accompanying TLE, as well as, perhaps, schizophrenia. 5

Motoric Laterality

Disturbances of lateralization in schizophrenics may manifest as changes in the cerebral organization of motor functions, with the normal superiority of the left hemisphere and right side of the body giving way to 'mixed dominance' or a shift toward left-sided (right-hemisphere) superiority for motor functions. Walker and Birch (1970) found that schizophrenic children had poorly developed lateral preference, with unstable or inconsistent hand usage occurring in significantly more cases compared to normal children. There were also a larger number of schizophrenic children who showed inconsistent hand and eye preference (crossed hand-eye dominance). A disproportionately large number of schizophrenic children had poorly developed lateral awareness, manifested as an inability to identify right or left on their bodies with perfect accuracy. Inconsistent or 'mixed' handedness, and to a lesser extent, crossed hand-eye dominance, were significantly associated with poorly developed lateral awareness. There was no clear evidence of improvement in these abilities with increasing age in schizophrenic boys. Krynicki and Mahas (1979) also found an increased incidence of crossed eye-hand dominance in schizophrenic children and

adolescents, with a significantly greater number of schizophrenics showing left-eye dominance. The schizophrenic group showed a lefthand superiority on a finger agnosia test, in contrast to the right hand superiority shown by normals, and among the schizophrenics finger agnosia scores were significantly related to left-right confusion. Among autistic children there is an unusually large proportion of left handed children (Boucher, 1977; Colby and Parkinson, 1977).

Oddy and Lobstein (1972) reported that although handedness and eye dominance considered separately showed no differences between schizophrenics and normals, schizophrenics showed significantly more crossed eye-hand dominance than normals. Mixed-handed schizophrenics were significantly younger than pure right or left handed groups, suggesting an association of mixed handedness with early breakdown. The finding of crossed hand-eye dominance in schizophrenic adults is consistent with the reports of increased crossed dominance in schizophrenic children and adolescents (Walker and Birch, 1970; Krynicki and Mahas, 1979). Chander (1934) had previously reported a higher incidence of crossed eye-hand dominance in schizophrenics compared to normal subjects. Clyma (1976) criticized Oddy and Lobstein (1972) on the grounds that they seem to assume that hand and eye dominance are related in a normal population, while several studies have shown that in the normal population hand and eye dominance are unrelated (Merrell, 1957; White, 1969; Gronwall and Sampson,

1971). Clyma (1976) and Gur (1977) presented evidence that eye dominance is highly related to visual acuity, and therefore is probably more determined by ocular than by cerebral factors. On the other hand, reports that crossed eye-hand dominance is related to poorer verbal learning skills (Swiercinsky, 1977) and an increase in bilateral representation of language, while uncrossed eye-hand dominance is associated with greater bilateral representation of spatial abilities (Kershner, 1974), suggest the influence of cerebral lateralization factors on ocular dominance. Abnormalities of lateralization may be present in schizophrenics at both cerebral and ocular levels. Maggio (1979) reported that almost half (47.3%) of 336 schizophrenics showed clear evidence of eye size discrepancy. Ninety-five had the right eye larger than the left and 64 others showed the reverse. Only 10 of 336 (2.9%) normal controls showed any eye size discrepancy. The eye that looked larger in the asymmetric cases actually protruded from the orbital cavity. Whatever the relationship between hand and eye dominance or cerebral lateralization for other non-motor functions and eye dominance, the increased incidence of crossed dominance reported by Oddy and Lobstein (1972) was not found in other groups of adult schizophrenics (Lishman and McMeekan, 1976; Gur, 1977).

Several studies have reported evidence for a shift toward sinistrality, or left-sidedness, in schizophrenics. Lishman and McMeekan (1976) found a small excess of left handed writers, an

excess of strong left handers and mixed handed subjects, and a dearth of strong righthanders in a group of 130 psychiatric patients compared to Annett's normal subjects. Psychotic patients showed this sinistral shift more clearly than neurotic or personality disordered subjects, and among psychotics the excess sinistrality was more prevalent in manic-depressive and schizoaffective patients than in purely schizophrenic patients. Left-handedness was strongly associated with delusion formation. The sinistral shift was more marked among younger patients, suggesting that "the abnormal distribution of handedness is in some way related to vulnerability to psychiatric disorder, rather than a purely chance finding." Male patients showed a much more marked excess of left handedness than female patients, perhaps indicating that males are more prone to abnormalities of cerebral dominance than are females. Finally, the psychotics had no excess of sinistral relatives, and lefthanded patients had a smaller proportion of sinistral first-degree relatives than did right handed patients, suggesting that the excess sinistrality among the psychotics is due not to genetic influences, but rather to an acquired abnormality of motor dominance in left-handed psychotics.

Dvirskii (1976) found an increased frequency of left handedness in schizophrenic men (n=660) and women (n=610) compared to normal controls, (n=4310, total) and this was attributable mainly to patients with the continuous (chronic

unremitting) type of schizophrenia rather than to patients with episodic and recurrent forms of schizophrenia. When subjects were asked to clasp their hands with the fingers interlocked it was found that the left type of finger clasping (left thumb on top) was significantly more frequent in schizophrenics than in normal controls. Schizophrenic men had significantly more left-eye dominance than controls, and in schizophrenic women there was a tendency for more left-eye dominance. The increase of left eye dominance and left finger clasping was more pronounced in schizophrenics with the continuous form than in those with the episodic and recurrent forms. There was also an increased incidence of the combination of left eye dominance and left type of finger clasping in schizophrenics with a continuous illness compared to controls. Male schizophrenics with continuous illness also had a higher digital ridge count on the left hand or the same count on both hands more often than controls.

In a study of 200 schizophrenics and 200 nonpsychiatric patients and hospital workers, Gur (1977) found significantly more leftward tendencies for handedness and footedness, and a tendency for more left eye dominance among schizophrenics. The handedness-footedness questionnaire used was validated against behavioral performances of the same tasks sampled by the questionnaire, on 60 patients, who were tested a week later. No increased incidence of crossed eye-hand dominance was found, and

while acuity and eye dominance were related, handedness and eye dominance were unrelated, suggesting that these measures tap independent aspects of laterality. A more recent investigation of 93 schizophrenics, 25 affective psychotics, 32 neurotics, and 150 normal controls using Annett's handedness questionnaire, found that schizophrenics were significantly more likely to be non-dextral than controls, while affective psychotics and neurotics were no different from controls (Chaugule and Master, 1981). Nasrallah, Keelor, Schroeder and Whitters (1981) found a significantly increased frequency of left-handedness and mixed handedness among 84 male schizophrenics compared to 82 hospital employees.

Not all studies have found increased sinistrality among schizophrenics or psychiatric patients in general. Wahl (1976) found no significant differences in the pattern of hand preference among 26 schizophrenics, 21 non-schizophrenic psychiatric patients, and 18 hospital staff controls, although there were (nonsignificantly) more left handers in the entire patient sample than in the normals, and more ambidextrals were found among the patients, especially the schizophrenics. The schizophrenics showed somewhat more confusion about hand preference, as indicated by discrepant self-report and behavioral performance of 10 manual tasks, perhaps indicating deficient lateral awareness or left-right confusion, such as that reported for schizophrenic children and adolescents (Walker

and Birch, 1970; Krynicki and Nahas, 1979).

Fleminger, Dalton, and Standage (1977) studied 800 psychiatric patients and 800 controls using Annett's 12-item handedness questionnaire and found no significant differences between these groups, although the patient group had a nonsignificant overrepresentation of full sinistrals. There was a significantly higher proportion of dextrals and a low proportion of mixed and left handed writers among patients with functional psychoses (schizophrenics and affective patients), especially among females, compared with neurotics and controls. A highly significant shift toward dextrality with increasing age was found in both psychiatric patients and controls. Also, there was a significantly higher proportion of left-handed writers among male than female psychotics, and this increase in male sinistrality relative to the female incidence was most notable for the schizophrenics, similar to the findings of Lishman and McMeekan (1976). Finally, Fleminger, Dalton and Standage (1977) found a smaller proportion of right and a much higher proportion of mixed handedness among females with personality disorders compared to controls. They suggest that this latter finding is consistent with a report by Palmer (1963) that undifferentiated or mixed handedness was associated with greater maladjustment, and strong lateralization of manual functions was related to 'greater ego strength' among undergraduates. In a further study, Taylor, Dalton and Fleminger (1980) found a significantly higher

frequency of full dextrality among 272 schizophrenics compared to 800 normal controls.

Thus, the shift to sinistrality reported by Lishman and McMeekan (1976), Dvirski (1976), Gur (1977), Chaugule and Master (1981), and Narrallah, et al. (1981), has not been replicated by Wahl (1976) or Fleming, Dalton and Standage (1977) and Taylor, Dalton and Fleming (1980). Wahl's (1976) study suffers several methodological flaws: he did not divide his sample according to sex, no diagnostic criteria were specified, the sample was small and 'unselected' or heterogenous, and the patient groups were older and had more restricted age range than controls. Fleming, Dalton and Standage (1980) used a large sample, analysed sexes separately and used ICD-8 diagnostic criteria. This one methodologically sound study yielding negative evidence on the sinistrality-schizophrenia link is in direct conflict with results produced by Chaugule and Master (1981) using the same handedness questionnaire, the same diagnostic criteria, and only nine fewer schizophrenics. The conflict may be a result of the way handedness was defined in each study. Fleming, Dalton and Standage (1976) defined right handers as those preferring the right hand for all 12 items of Annett's questionnaire, left handers preferred the left for writing, and mixed-handers had less than perfect consistency but preferred the right for writing. The dextral/non-dextral division used by Chaugule and Master (1981) combined the left and mixed categories used by

Fleminger, et al., (1976). There is some reason to believe that continuous measures of motoric laterality may be more sensitive in detecting sinistral shifts than are dichotomous or trichotomous categories. Clinical and biological heterogeneity in the populations studied may also contribute to inconsistent findings.

Another finding relating unusual motoric laterality to psychiatric disorders has come from investigations of the ability of each thumb to oppose itself to its own fifth digit, with the thumb more able to rotate being defined as dominant. Normal subjects were evenly divided between 'pure dominance', where the dominant thumb is on the dominant hand, and 'crossed dominance', where the dominant thumb is on the non-dominant hand. Schizophrenics and bipolar affective disorder patients were significantly more likely than normals to be pure dominant, while unipolar depressives were more likely to be cross-dominant compared to normals (Ast, Rosenberg and Metzlig, 1976; Metzlig, Rosenberg and Ast, 1975; Metzlig, Rosenberg, Ast and Krashen, 1976).

Boklage (1977) found a significantly greater incidence of non-right handedness (NRH) in monozygotic twins, one or both of whom were schizophrenic, compared to similar dizygotic twin pairs, and this MZ-DZ difference was greater than in normal twin pairs. The excess of NRH was concentrated in twins discordant for schizophrenia, and the left handed twin more often received

the schizophrenic diagnosis. Discordance for left handedness was higher in 72% of MZ twins discordant for schizophrenia but only 20% in normal MZ twins or MZ twins concordant for schizophrenia. The left handed schizophrenics also tended to have a less severe form of schizophrenia than schizophrenics from concordant right handed pairs. These results were replicated by Luchins, Pollin, and Wyatt (1980) and Luchins, Weinberger, and Wyatt (1979), who also confirmed the association of a milder form of schizophrenia with anomalous lateralization in non-twin schizophrenics. They found that schizophrenics from twinships with one or both members left-handed had a less severe illness than the concordant dextral schizophrenic twins, and that left handedness in individual twins was associated with a schizophrenic diagnosis. These findings, along with absence of an excess of sinistrality in the relatives of schizophrenics (Lishman & McMeekan, 1976), suggest the existence of a subgroup of schizophrenics with a milder disorder whose etiology involves anomalous lateralization due to prenatal or natal hypoxia-inducing trauma. In discordant twin pairs the schizophrenic twin tended to have a lower birth weight and was second-born more often (Stabenau & Pollin, 1967), and schizophrenia has been related to pregnancy and birth complications (Mura, 1969, review), as has left handedness (Bakan, 1971, 1977, 1978; Bakan, Dibb & Reed, 1973).

Boklage (1977) interpreted his findings as evidence that at least some schizophrenia is associated with anomalous motoric laterality related to abnormalities of embryonic symmetry development which are reflected in the twinning process itself. Boklage (1977) and Boklage, Elston and Potter (1979) reviewed literature on embryonic development and the twinning process to support his theory of a relationship between twinning, abnormal symmetry development, and subsequent anomalous lateralization related to schizophrenic etiology. Boklage cites evidence that monozygotic twinning occurs before amniogenesis, eight or nine days after conception, during the time span in which the inner cell mass is rearranging itself to form the bilaminar disk. This coincides closely with the timing of the cellular definition of basic bilateral organization, since the appearance 14 days post-conception of the prochordal plate and primitive streak, defining the dorso ventral axis, and thus an antero-posterior gradient, marks the point at which the first signs of right and left differentiation become visible. Boklage, et al. (1979) believes:

"it is reasonable to consider monozygotic twinning as an anomaly of embryonic asymmetry development, representing the formation of two gross body symmetry organizations from cells which yield one such organization in 99.7% of viable human embryos, and further that this is likely to occur at or near the normal appropriate developmental time for such determinations" (i.e., determinations of bilateral symmetry organization).

To examine some of these hypotheses Boklage, Elston and Potter (1979) examined dentition patterns in DZ and MZ twins. Dentition patterns are the result of genetic influences as well as embryonic developmental processes, and the tooth buds develop from cells almost immediately adjacent to the end of the neural plate near the developing forebrain. Fifty-six variables of tooth development were measured and the pattern of 1540 MZ-DZ bivariate correlation differences was analysed. Many significant MZ-DZ differences in bivariate correlations were observed, the differences were greater in males, differences were stronger and more symmetrically patterned in males, and the pattern of differences were visibly different between the sexes. These results were interpreted as evidence that the development of this integrated system, arising from cells near the embryonic forebrain, is less well organized, and less coherent in relationships among the parts of this developing system, in MZ than in DZ twins. In addition the MZ dental patterns were more asymmetric than those of the DZ twins, and individual bilateral asymmetry was an important component of the effective discrimination of MZ from DZ twins. MZ rightsides and leftsides differed significantly, while DZ rightsides and leftsides were indistinguishable. The generalized variances among left or right half jaws and side to side differences was twice as large in the MZ as in the DZ twins. These results support Boklage's hypothesis that twinning in MZ pairs is associated with abnormal

embryonic development of lateral symmetry patterns. They conclude:

"the early cellular development of the (at least MZ) twin population is anomalous, for reasons which bear no demonstrable relationship to identifiable obstetric misfortune. Brain function development, through its special and newly-evolved complexity and its dependence on balanced side-to-side integration, may be expected to be especially vulnerable. Mimicry of 'environmental' effects, pleiotropic involvement of a broad assortment of features, and the production of various more specific anomalies may be expected features. The excess of nonrighthandedness and the excess of atypical schizophrenia in MZ's may be examples."

Another morphological characteristic laid down early in life is the pattern of dermatoglyphic ridges on the skin of the hands. Gengerelli and Trasher (1979) reported a non-significant trend toward a longer palmar main line A on the left hand of schizophrenics compared to nonpsychotic chronically hospitalized patients and normal subjects. These findings, if supported by further investigation, may indicate that schizophrenia involves lateral asymmetry and abnormality of embryonic development of lateral asymmetry, even in non-twin schizophrenics.

In a review of lateralization abnormalities in schizophrenia, Flor-Henry (1979) maintained that a common thread running through all of the literature indicates that in the psychoses there are abnormalities of the mechanisms determining cerebral lateralization, involving altered transcallosal neural inhibition, altered hemispheric balance, and abnormal activation with resultant lateralized disorganization. He summarized his

impressions of the sinistrality schizophrenia association in the following paragraph:

"The situation is complex. On the other hand there appears to be a group within the schizophrenic syndrome where sinistrality is under-represented, where the illness is the more severe as the subject is dextral and as speech is lateralized more to the dominant hemisphere. Here gender is not a related variable. This category exemplified by monozygotic twins, is established before the neuro-humoral gender-determined hemispheric specialization of the male and female brain has taken place in the second to third months of intra-uterine life. On the other hand there is another variety of schizophrenia, where chronicity and severity are linked to sinistrality, and here there is a clear male preponderance. There is a third variety of schizophrenia occurring in sinistral monozygotic twins and in the general population where the sinistrality is associated with a benign (or schizo-affective) type of schizophrenia." (pp. 15-16)

Flor-Henry (1979) suggested that the second type of schizophrenia involves dominant hemisphere pathology which is likely acquired, giving rise to both sinistrality and schizophrenic brain organization. The dominant hemisphere pathology, resulting in sinistrality whether a result of abnormalities of embryonic development such as twinning or of cerebral insult pre- or perinatally, is a long standing condition predating the development of the schizophrenic disorder, and as such may have utility as a risk indicator or prognostic sign. If so, left handers or individuals with other anomalies of motoric lateralization may comprise populations containing an overrepresentation of individuals who are vulnerable to schizophrenia.

Conjugate Lateral Eye Movements (CLEM)

Another aspect of motoric laterality which has received attention is the asymmetry of the direction of conjugate lateral eye movements (CLEM's) made in response to reflective questions. CLEM's appear to be a component of a contralateral orienting response, involving selective activation of the hemisphere contralateral to the direction of the eye movement (Bakan, 1969, 1971; Kinsbourne, 1972). Neurophysiological evidence supporting this interpretation of the CLEM phenomenon will be detailed in a later chapter. Gur (1978, 1979) was the first to report that schizophrenics made more rightward CLEM's than normal controls regardless of question type, and she interpreted this as evidence that schizophrenics overactivate their dysfunctional left hemispheres. Interestingly, male schizophrenics showed a pattern of eye movement directionality in response to 4 types of questions (verbal and spatial, emotional and nonemotional) which was similar to the pattern shown by female controls, and female schizophrenics were similar to male controls, although schizophrenics of both sexes moved their eyes to the right more often than controls. Schizophrenics also had a significantly higher proportion of stares than did controls. The rightward CLEM preponderance of schizophrenics was also found by Schweitzer, Becker and Welsh (1978), who reported that

schizophrenics inappropriately activated the left hemisphere (made right CLEM's) especially during spatial/ emotional questions, more often than normal controls. They concur with Gur in their interpretation of this finding as an indication of left hemisphere overactivation in schizophrenia. They suggested that

"the appearance of greater left hemisphere activity in the patient group may thus actually reflect a lack of right hemisphere reciprocal inhibition and/or modulation of incoming information" (Schweitzer, Becker and Welsh, 1978, p. 984).

Schweitzer, et al. (1978) used a patient sample containing significantly more males than their control group. Schweitzer, Becker and Welsh (1978) and Schweitzer and Chako (1980) also reported that females produced more rightward CLEM's than males, regardless of diagnosis. Although the main effects of sex and diagnosis were significant, no significant interaction between these factors was observed. Schweitzer (1979) replicated his findings of increased right CLEM and excessive left hemisphere processing of spatial and emotional material in schizophrenics in a new sample. A group of psychotic depressives included in this study showed more leftward CLEM's than controls or schizophrenics, suggesting a right hemisphere overactivation in these patients. Tomer, Mintz, Levi and Myslobodsky (1979) and Myslobodsky, Mintz and Tomer (1979) also reported that schizophrenics showed a preponderance of rightward CLEM's as well as a greater number of stares and a higher rate of blinking than normal subjects, in response to visual, emotional and

verbal-neutral questions. The normal control group in this study showed a preponderance of leftward CLEM's, but unfortunately these investigators used only female control subjects. Thus, their results may not be generalizable to male schizophrenics, since Gur (1978, 1979) reported a significant sex by diagnosis by question type interaction in her CLEM study.

In contrast to the previously mentioned reports, Sandel and Alcorn (1980) found that right hemisphericity, as indicated by a preponderance of leftward CLEM's, was associated with nonparanoid schizophrenia, depression, and alcoholism, while bilaterality of CLEM's was associated with manic-depression, schizo-affective disorder and antisocial personality. Only males were used in this study, and no normal control group was used for comparison. Further studies of CLEM directionality associated with schizophrenia or other psychopathology should use large samples consisting of both males and females, and sex should be taken into account in all data analyses. The finding of Gur, Sackeim and Gur (1975) that right hemisphericity is associated with greater psychopathology in males, while left hemisphericity is associated with greater psychopathology in females indicates that significant interactions of sex and CLEM occur in relation to psychopathology. Perhaps such interactions coupled with sex-biased sampling can explain the discrepant results obtained by Sandel and Alcorn (1980), and Schwietzer, et al. (1978), Tomer, et al. (1979) and Myslobodsky, et al. (1979).

However, Gur (1978, 1979) used equal numbers of males and females and found a rightward CLEM preponderance in schizophrenics, regardless of sex, and Schwietzer, et al. (1978) compared each schizophrenic to a sex matched control, again finding a rightward CLEM preponderance in the schizophrenics. Further studies are needed to clarify the issue.

Among normal subjects, left movers have many personality and behavioral correlates of CLEM in the 'schizophrenic direction' compared to right movers. Some schizophrenics are thought to exhibit a preponderance of parasympathetic activity (Gellhorn & Kiely, 1973), and left movers show greater parasympathetic reactivity (Bliss, 1971). Slower alpha frequency is found in schizophrenics (Giannitrapani & Kayton, 1974; Giannitrapani, 1979) and left movers (Day, 1967a). Both schizophrenics and left movers are field dependent (Bakan & Shotland, 1969), and both are prone to alcohol abuse (Mendels, 1976; Bakan, 1978, 1971). Leftmovers make more somatic complaints, daydream and fantasize more, are preoccupied with religious themes or describe themselves as religious, have vivid imagery and are more inner attentive (Meskin & Singer, 1974; Singer, 1974; Bakan, 1971, 1978; Gur & Gur, 1975), and these characteristics also occur in many schizophrenics. Males with right hemisphericity (left movers) report more psychopathology than right movers, while females with left hemisphericity report more psychopathology than left movers (Gur, Sackheim & Gur,

1976). In college students left CLEMs were significantly correlated with MMPI Schizophrenia scale scores and more torque, considered by Blau (1977) to be an indicator of schizophrenic vulnerability (Winterbotham, 1979; Laing, 1979). It could be that individuals with a vulnerability to schizophrenia or personality characteristics in the schizophrenic direction are right hemisphericity types (left movers). Under stress this more primitive right hemisphere cognitive style may prove inadequate to environmental demands, leading to a switch to left hemisphericity, which results in left hemisphere overactivation and right CLEMs. This switching of hemisphericity is supported by clinical observations made by Day (1964) indicating a reversal of characteristic CLEM direction during acute or active phases of schizophrenia. It may be that left CLEM's are a marker of preschizophrenic or 'high risk' personality types, while active schizophrenia is associated with right CLEMs.

The suggestion by Winterbotham (1979) that left movers are a population at risk has not been supported by studies of smooth pursuit eye movements (SPEM) in normals and schizophrenics. SPEM disorder has been associated with schizophrenic psychopathology, an area to be reviewed later. If CLEM is associated with schizophrenic vulnerability one would expect one CLEM group to show more signs of vulnerability, i.e., disordered behavior characteristic of schizophrenics and children at genetic risk for the disorder. SPEM is just such a vulnerability marker, so

one would expect the CLEM group with more disordered SPEN during the tracking of a slowly moving target to be at greater risk for schizophrenia, by virtue of their similarity to schizophrenics.

Two studies have appeared in the literature recently reporting differences between CLEM left-movers and right-movers on eye tracking tasks (Tomer and Mintz, 1980; Tomer, Mintz, Levy and Myslobodsky, 1981). Tomer and Mintz (1980) had 34 women track a slowly moving (5 /sec) constant velocity target with a maximal target excursion of 35 degrees of visual angle to each side. Tracking was performed without distraction and while listening to and answering syllogistic questions. While tracking without questions, right movers had a greater number of saccades than left movers. The left movers also answered more syllogisms correctly and did so more quickly than right movers. There were no differences in either group between the number of saccades to left and the number of saccades to the right. In another experiment of similar design, Tomer, Mintz, Levy and Myslobodsky (1981) tested 20 hospitalized schizophrenic patients (11 males and 9 females) and 25 normal controls (5 males and 20 females). The velocity had the same constant velocity target (5 /sec) as in the previous experiment but a target excursion of only 18 degrees of visual angle in either direction was used. The CLEM test consisted of 12 verbal and 12 spatial-emotional questions presented binaurally over headphones while the subject sat semi-reclined in a semi-darkened room. Overall schizophrenics

had very poor tracking with more intervening saccades. Left movers made fewer saccades during tracking than right movers and fewer than schizophrenics, while right movers did not differ significantly from schizophrenics. Tracking performance deteriorated considerably during the cognitive task (syllogisms) for schizophrenics and right movers, but left movers continued to show smooth tracking during the cognitive task. Arrests in tracking were made less often by leftmovers than rightmovers and schizophrenics, while the latter two groups did not differ. During the cognitive task schizophrenics and rightmovers had poor tracking, with more saccades and arrests during leftward tracking than rightward tracking. The duration of arrests was longer when they occurred during the leftward tracking compared to rightward tracking. No such asymmetry in tracking was displayed by leftmovers. These authors suggested that leftward tracking is particularly disrupted by the cognitive task because tracking is ipsilaterally mediated, and the left hemisphere is overloaded by concurrent tracking and cognitive tasks. They also concluded that, because of the similarity in tracking performance between schizophrenics and right movers, normal right movers may represent a high risk population from which schizophrenics are recruited. It should be noted that these results may apply only to females, since the normal sample was strongly biased by an overrepresentation of females (20 to 5 males). The association of psychopathological tendencies with

CLEM rightmoving in females and left moving in males was reported by Gur, Sackheim and Gur (1975). Thus, the finding of worse tracking by right movers than left movers in a largely female sample is consistent with Gur, et. al.'s (1975) results for females only. The failure to perform separate analyses for males and females is a crucial flaw in this study and much CLEM research, since sex differences in lateralization and sex x CLEM direction interactions have been found in many studies. The relationship between CLEM and other vulnerability indices in the normal population warrants more thorough investigation.

Torque - Clockwise Circling

The drawing of circles in a clockwise as opposed to counterclockwise direction, termed 'torque', has been suggested as a motoric index of cerebral lateralization related to schizophrenic vulnerability (Blau, 1977 b). Among children seen for psychological evaluation at a private clinic, those who showed torque at age 9 had a much higher incidence of diagnosed schizophrenia at age 21 (11/52) than did children who showed no torque (1/54). Torque children also showed subsequent poor-to-bad adjustment ratings compared to no-torque children who had more good-to-fair adjustment ratings. Sinistrality and torque are also significantly related (Blau, 1977 a). These findings, in conjunction with evidence suggesting links between

sinistrality and unadjustive behavior (particularly schizophrenia), and between handedness, risk for schizophrenia, and genetics, led Blau (1977 b) to propose that:

"mixed cerebral dominance, sinistrality, torque, and the predisposition to schizophrenia may share similar genetic antecedents. The hereditary link may involve a defect in the corpus callosum and/or its function. As a result of the dysfunction of the corpus callosum...a developmental lag occurs, manifested by neural integrative deficiencies...The etiology of clinical schizophrenia may arise out of the effects of the neural integrative deficiency." (Blau, 1977 b, p. 1003)

He further suggested that torque is a manifestation of this neural integrative defect.

Winterbotham (1979) found that CLEM left movers have a higher incidence of torque than rightmovers, and conversely, subjects with torque had a higher incidence of leftmoving than those without torque, in a sample of 97 elementary school children. In a sample of 56 university undergraduates, he found a similar though non-significant association of left CLEM and torque. A discriminant function analysis of MMPI scores correctly classified 87% of the subjects as to the presence or absence of torque. Torque was significantly related to MMPI Schizophrenia (SC) Scale Scores, and although the ANOVA main effect for CLEM was nonsignificant, left movers with torque had the highest MMPI SC Scores compared to other groups. A chi square revealed that left movers with torque had a significantly higher incidence of subjects with SC T scores greater than 70, compared to other torque by CLEM groups. Winterbotham (1979)

interpreted his results as an indication that left moving and torque may be related to vulnerability to psychopathology, particularly schizophrenia, although the pathological significance of the SC scale or its relation to vulnerability are unclear. Winterbotham's results and conclusions are rendered somewhat questionable by the more recent report of Woods and Oppenheimer (1980) that individuals with torque showed a greater tendency toward right looking across all questions than did non-torque subjects. One possible explanation for this discrepancy may be the noncomparability of questions used to elicit CLEM.

Although Blau's (1977 b) findings suggest that torque in childhood may predict schizophrenia a decade later, several investigators have reported that adult schizophrenics do not have an increased incidence of torque. Tolor (1981) found that schizophrenics did not show torque significantly more often than other comparison groups: elderly individuals, general medical patients, adults functioning well in the community, graduate students and undergraduate students. He found that elderly individuals showed significantly more torque (47%) than undergraduate students (26%), but the occurrence of this one significant result in a series of 15 comparisons could have been due to chance. He also found, like Blau (1977 a), that left handers showed more torque (55%) than right handers (36%).

Wyatt, et al. (1981), found no differences between schizophrenics and a normal population in the frequency of sinistrality, a family history of sinistrality, or torque. However, schizophrenics with torque were less frequently chronic, tended to have fewer years of hospitalization, and spent a smaller percentage of their illness hospitalized than patients without torque (Wyatt, et al., 1981; Luchins, Weinberger and Wyatt, 1979). The results for torque parallel their results for left handedness, and suggest the association of anomalous lateralization with a milder form of schizophrenia. Like Blau (1977 c) and Tolor (1981), Wyatt, et al. (1981) found an association of left handedness and torque, as well as a relationship between torque and familial sinistrality. However, torque, sinistrality and familial sinistrality, while related to each other, were unrelated to CT scan evidence of abnormal cerebral asymmetry.

Demarest and Demarest (1980) have questioned the use of torque as a measure of cerebral lateralization. Based on their findings of no relationship of torque to lateralization of language as indicated by a dichotic listening test, and an association of torque and left handedness, they suggested that torque is more related to the muscle mechanics of the hand than to cerebral dominance. Although the validity of the dichotic listening procedure as a test of cerebral dominance is itself questionable, their results do suggest that, at least, torque

may measure aspects of lateralization independent of the lateralization of language processes.

The failure of adult schizophrenics to show an increased incidence of torque seriously undermines the utility of torque as a vulnerability marker. However, it may be that signs of the neurointegrative defect underlying vulnerability which appear at one age may mature, and thus at later ages may not differentiate vulnerables from those at low-risk. The work of Barbara Fish certainly suggests that the manifestations of the neurointegrative defect change with age. Further work on the torque test is needed not only to clarify its relationship to vulnerability, but also to illuminate its relationship to cerebral lateralization factors.

Anatomical Asymmetries

In normal righthanders CT scans show wider right frontal and left occipital lobes, while right handed schizophrenics had an increased frequency of both frontal and occipital reversals (Luchins, Weinberger, Wyatt, 1979). When divided on the basis of CT evidence suggestive of cerebral atrophy (Weinberger, Torrey, Neophytides & Wyatt, 1979a, 1979b) the structural reversals were found to be confined to those schizophrenics without cerebral atrophy, who also had a milder form of illness. Wyatt, Potkin, Kleinman, Weinberger, Luchins and Veste (1981) subsequently

reported that in 24 patients for whom WAIS scores were available, none of the 16 schizophrenics without reversals had lower verbal than performance WAIS IQ's, while 3/4 with occipital reversals and 3/6 with frontal reversals had significantly lower verbal than performance IQ's. Naeser, et al (1981) have confirmed the CT scan evidence of an increased incidence of equal or reversed occipital width in right-handed schizophrenics. They also report that asymmetric hemisphere widths are associated with good recovery, while equal widths, especially occipital, are associated with poor recovery.

Luchins, Torrey, Weinberger, et al. (1980) found an increased incidence of human leukocyte antigen (HLA), A2, in 92 black schizophrenics without CT scan evidence of cerebral atrophy compared to 563 black controls, but black schizophrenics with evidence of atrophy did not have an increased incidence of HLA-A2. The results for white schizophrenics and controls were in the same direction but nonsignificant. Luchins, Weinberger, Kleinman, et al., (1980) found that in drug free chronic schizophrenics, those with HLA-A2 are less symptomatic than those without A2, a difference that is obscured by neuroleptic treatment. Luchins, Weinberger and Torrey, et al. (1981) further reported that black schizophrenics with reversed asymmetry had a significantly greater incidence of HLA-A2 (100%) than did black schizophrenics with normal asymmetry (36% HLA-A2), or black controls (30% HLA-A2). Again, among whites, differences were not

significant but were in the right direction, and the white sample was small (N = 22 schizophrenics). Luchins, et al. (1981) concluded that HLA-A2 genes and genes controlling brain asymmetry are in linkage disequilibrium or that "a schizophrenic population tends to be overrepresented by individuals with both HLA-A2 and reversed asymmetry and that conjunction of these two factors predisposes to schizophrenia." (Luchins, et al., 1981, p. 242). These results may provide the foundation for a new biological classification of schizophrenia, as HLA antigens have been shown to be under strong genetic control, and have been suggested as possible markers of heterogeneity in schizophrenia (Ivanyi, Zemek and Ivany, 1978). HLA antigens and lateral asymmetry abnormalities may provide interrelated markers of schizophrenic vulnerability.

Reversed cerebral asymmetry may be related to other variables putatively linked to schizophrenic etiology and may, with these, serve as biological tools for subclassification of the schizophrenic syndrome (Wyatt, Potkin, Kleinman, et al., 1981; Jeste, Kleinman, Potkin, Luchins, and Weinberger, 1982). The abnormal asymmetry group of schizophrenics had significantly lower platelet MAO activity than the normal asymmetry group (Jeste, et al., 1982). In a stepwise discriminant function analysis the most discriminating variable was the presence of HLA-A2, followed by gender, with an excess of females in the abnormal asymmetry group. Together, HLA-A2 and gender correctly

classified 74% of the cases, with or without the jack-knifed technique. Curiously, reversals of cerebral asymmetry were unrelated to left-handedness, familial sinistrality, or the presence of torque, although these last three measures were all related (Wyatt, Potkin, Kleinman, et al., 1981).

In another CT scan investigation, Golden, Graber, Coffman, Berg, Melvlin and Block (1981) found that five out of six measurements of anterior left-hemisphere density showed lower density in schizophrenics' brains compared to normal brains. Two of six differences for measures of left posterior density were significant, and only one of 12 measures of right hemisphere density showed any significant difference. Among the normal controls all 12 measures of different levels of the brains showed greater density in the left than in the right hemisphere, while in schizophrenics, only 4 of 12 measures showed significant differences, indicating that the normal asymmetry in cerebral density was less pronounced in schizophrenics, especially anteriorly.

Another recent study has failed to confirm the CT scan asymmetry reversals just reviewed. Andreasen, Dennert, Olsen and Damasio (1982) found that there were no significant differences between 43 right handed schizophrenics and 40 right handed controls on measures of frontal and occipital petalia and width. However, the control group used was not composed of normal individuals but of epileptics, personality or neurotic disorder

patients, and patients with dizziness or syncope, facial pain and amebic colitis. There is a possibility that these patients may also have characteristic abnormalities of cerebral asymmetry which may not be specific for schizophrenia. Also, if such abnormalities were characteristic of only a subgroup of schizophrenia, sampling error due to the use of a small sample size, and the problem of schizophrenic heterogeneity could have contributed to the washing out of real differences between the subgroup and the control group. Andreasen, et al. (1982) did, however, report that their 8 left handed schizophrenic patients had higher ventricular brain ratios, indicative of cortical atrophy, compared to the right handed patients.

Left handed normal children had a greater percentage of frontal reversals or absence of asymmetry than right handed (Geschwind, 1979), and reversals of normal occipital asymmetry on CT scans is more frequent in children with disorders of higher cortical function, such as autism (Hier, Lemay, Rosenberger, 1978), delayed speech onset (Rosenberger, Hier, Epstein, 1978), developmental dyslexia (Hier, Lemay, Rosenberger, 1978), and poorer verbal WISC (Rosenberger & Hier, 1979).

Asymmetric Skin Conductance

Asymmetric skin conductance has been found in schizophrenic patients, some of whom exhibited unilateral non-responding of the left hand, slowly habituating and large amplitude right hand responses, as well as other abnormalities of the laterality of skin conductance responses (Gruzelier and Venables, 1973, 1974). The abnormalities of skin conductance laterality are normalized by chlorpromazine (Gruzelier & Hammond, 1978).

Electroencephalographic Asymmetries

A variety of EEG findings in schizophrenics implicate left hemisphere dysfunction or an abnormality of interhemispheric communication. Compared to normals, schizophrenics have hypovariability of the mean integrated amplitude of the EEG from a left occipital lead (Goldstein et al, 1965). The preponderance of in-phase synchronization over the dominant hemisphere seen in normals is reduced or reversed in schizophrenics (Monakhov, et al, 1971). The asymmetry of EEG (9c/sec) activity in parietal, lateral and temporal areas seen in normals, with left side activity greater than right, is absent in schizophrenics, who typically show more right side activity (Giannitrapani & Kayton, 1974). Changes in alpha associated with lateralized tasks were in schizophrenics reversed from normal (Giannitrapani & Kayton,

1974), or weaker than normal (Flor-Henry, 1976b; Alpert & Martz, 1977), suggesting that schizophrenics are less polarized than normals in their alpha shifting patterns in response to lateralized tasks. Deviations of right/left energy ratios, indicating shifts of relative hemispheric activation, were of greater magnitude and longer duration in schizophrenics than normals, and such sluggish lateral energy shifts suggest a defect of interhemispheric integration (Flor-Henry, 1976b). Schizophrenics failed to specifically inhibit left temporal alpha energy during verbal tasks, but like normals, inhibited right temporal alpha during visuo-spatial tasks. The abnormal energy densities in the fast beta band in the temporal lobe in schizophrenics are correlated with psychotic symptoms, disappearing with clinical improvement, whether spontaneous, induced by chemotherapy or induced seizures (Flor-Henry, 1978). Clinical improvement or drug treatment induced a gain in EEG voltage over the left hemisphere in schizophrenics (Serafetinides, 1972, 1973). Normal subjects show more EEG alpha activity in the right temporal lobe than in the left, while psychotics show the reverse, and the laterality disturbance follows the clinical course (Urstad, 1979). Abnormalities of the EEG record such as slowing, spikes or sharp waves, slow bursts, suppression, asymmetry, sharp-slow bursts, and abnormal fast activity were more frequently seen from the left temporal lobes than in other brain areas in schizophrenics, while affective

patients had fewer abnormalities than schizophrenics, more parieto-occipital abnormalities, and reversed lateralization, i.e., more right-sided abnormalities (Abrams & Taylor, 1979). Left sided EEG abnormalities are most prominent in schizophrenics with no family history of schizophrenia, suggesting left hemisphere perinatal damage as an etiological factor in a subgroup of non-familial schizophrenics (Hays, 1977). Variance of the EEG amplitude was greater in the left than the right hemisphere in paranoid (mostly schizophrenic) adolescents, while in normal adolescents the two hemispheres were similar, and amplitude variances in adolescents with depressive symptoms were greater in the right than left hemisphere (Rochford, Weunapple & Goldstein, 1981).

Giannitrapani (1979) measured phase angle, the average degree of synchrony of a given frequency component in two EEG leads, and found significant left leading in the temporal lobes (T3-T4, T5-T6) for most frequencies in normals, while in schizophrenics activity in the temporal lobes was more bilaterally symmetrical. Temporal lobe amplitude was greater in left than right in right handed subjects, and greater in right than left in left handed subjects, while schizophrenics showed no consistent pattern. Coherence, the degree of correlation between two signals regardless of average phase angle, was greater bilaterally in schizophrenics than in normals. The greater homogeneity of the two hemispheres in schizophrenics

indicates a lower degree of lateralization of functions, and a lack of diverse utilization of brain areas in schizophrenics.

Evoked Potential Asymmetries

Evoked potential (EP) recordings have also revealed lateralization abnormalities in schizophrenics. Visual and auditory evoked potential wave form stability was lower in the left hemisphere of schizophrenics than in nonpatients, nonpsychotic patients, and psychotic depressives. The VEP and AEP stability differed more between the hemispheres in latent schizophrenics as well (Roemer, et al, 1978, 1979). Medication led to a decrease of the EP hemispheric asymmetry by decreasing stability of the EP in the right hemisphere more than the left. The normal right hemisphere amplitude superiority for VEP's is absent in schizophrenics (Perris, 1974; Shagass et al, 1977; Roemer, et al, 1978). Lateralization of attentional processes has been suggested by several investigators (Matsumiya, et al, 1972; Buchsbaum & Drago, 1977; Kinsbourne, 1970) and selective attention is a psychological correlate of certain EP components. The negative component at 120 msec (N120) showed the greatest increase in amplitude with an attention task for left tempoparietal recording and right visual hemifield presentation (Buchsbaum & Drago, 1977). Buchsbaum, et al (in press) found that VEP's N120 component increased in amplitude in an attention

task, but both schizophrenics and left temporal lobectomy patients had unusually small indirect pathway EP's (RVF-RH, LVF-LH) under this condition and an inattention condition, compared to normal controls and affective patients, suggesting a defect of interhemispheric communication. The left hemisphere - right hemiretina (left visual field) pathway had especially low EP amplitude in the attention condition in schizophrenics and left temporal lobectomy patients, consistent with both the left hemisphere deficit hypothesis, and a difficulty transferrring information into the left hemisphere. Buchsbaum, et al, cite the diminished ability for sustained attention in commissurotomy patients (Zangwill, 1974) and attentional deficit in schizophrenics (Garnezy, 1978) in support of a synthesis of the concepts of attentional deficit, left hemisphere dysfunction, and hemispheric transfer abnormalities. Buchsbaum states that "the schizophrenic's problem is not a general lack of attention, but a specific disability in attending to stimuli from the left visual field with the left hemisphere" (Buchsbaum, 1980).

Cerebral Blood Flow Asymmetries

The dominant EEG frequency is correlated with cerebral oxygen uptake and cerebral blood flow (Ingvar, Sjolund, Ardo, 1976). Compared to normals schizophrenics have deficient CBF in the frontal regions (Franzen & Ingvar, 1975a), especially

in the left frontal lobe (Franzen & Ingvar, 1975b), as well as hypercirculation in tempo-parietal regions related to somato-sensation, vision, and audition (Franzen & Ingvar, 1975a; Ingvar, 1976).

Corpus Callosum Dysfunction

Several studies have demonstrated anatomical and functional abnormalities of the corpus callosum in schizophrenics, reflected in defects of interhemispheric communication. The corpus callosum of schizophrenics is 18% thicker than normals' while there were no significant differences in other brain areas examined (Rosenthal & Bigelow, 1972). High frequency electrical stimulation or surgical lesions of the genu of the corpus callosum diminished symptoms of anxiety and tension, and in one case hallucinations, in psychiatric patients, indicating a possible hyperactivity of interhemispheric transcalsal cingulostriate pathways associated with those symptoms (Laitinen, 1972).

Tactile Modality Asymmetries

Chronic schizophrenics had twice as many left hand errors as right when naming objects held in either hand, and left hand anomia is a classic sign of split brain conditions, suggesting a lack of transfer of right hemisphere kinesthetic and tactual

information to left hemisphere speech areas in schizophrenics (Diamond, et al, 1979). On a manual shape discrimination task schizophrenics but not controls had defective intermanual transfer, a pattern resembling the performance of split-brain monkeys on similar tasks, indicating an incomplete transfer of stereognostic shape information between the hemispheres (Green, 1978). Carr (1980) replicated Green's (1978) findings only for non-meaningful or random shapes, and found that intermanual transfer occurred in schizophrenics holding meaningful shapes, i.e., everyday familiar items. On a task requiring the subject to 'post' a shape into the correct hole using right and left hands (Kugler & Henley, 1979), and another involving identification of digits inscribed on the right or left palm (Weller & Kugler, 1979) schizophrenics' performance was consistent with the hypothesis of left hemisphere dysfunction and poor interhemispheric integration.

Visual Modality Asymmetries - Tachistoscopic Studies

Schizophrenics perform more poorly than normals and psychiatric controls when required to match two stimuli tachistoscopically presented, one to either visual field, yet perform adequately if both stimuli are presented to a single visual field, suggesting a deficiency of the callosal transfer of visual information (Beaumont and Diamond, 1973).

The normal superiority of the left hemisphere - right visual field in the recognition of dichoptically presented letters (simultaneously, different letters presented in right and left visual fields) was absent in schizophrenics, whose thresholds of recognition were more than twice those in healthy subjects (Kostandov, 1978). A series of experiments in healthy subjects involving visual perception of verbal material showed that when information was presented to both hemispheres performance was more efficient than with presentation to either hemisphere alone, indicating mutually complementary collaboration between hemispheres in perception of visual stimuli, and the necessity for perfect performance of the interaction between the hemispheres. In light of this, the findings with schizophrenics can be interpreted as consistent with both left hemisphere dysfunction and interhemispheric transfer deficit. Tachistoscopic presentation of letters to be named revealed a left hemisphere - right visual field deficit in paranoid and nonparanoid schizophrenics compared to non-psychotic psychiatric patients and normals, but these group differences disappeared when education was controlled for (Pic'1, Magaro & Wada, 1979). All but the nonparanoids did better with right hemisphere presentation than left. The right hemisphere maintains an iconic image while the left hemisphere does a serial phonetic analysis; thus, good performance requires bilateral integration with right hemisphere left visual field

presentation. Schizophrenics, especially nonparanoids, had poorer performance than controls with left hemisphere presentation because of inappropriate processing strategy (use of the right hemisphere) or transfer problems. Other studies have reported schizophrenics' difficulty with tasks requiring interhemispheric integration (Magaro, 1979; Magaro, et al, 1976,

Unlike normals, schizophrenics showed a right hemisphere superiority on both verbal and spatial tasks involving tachistoscopic presentation, indicating left hemisphere dysfunction in the initial processing of verbal material (Gur, 1978). Gur (1978) compared schizophrenics and normals on a task involving detection of the differences between pairs of pictures presented simultaneously or successively, measuring reaction time and response quality. Like right hemisphere lesion patients, the schizophrenics reacted faster in the successive condition while normals reacted equally fast in both conditions, implicating a left hemisphere overactivation in schizophrenia.

Auditory Modality Asymmetries

Schizophrenics' detection of short tone signals is more impaired in the right ear than the left (Bazhin et al, 1975), and two-click threshold is lower in the left ear (Venables, 1969; Murphy & Venables, 1970). Absolute auditory thresholds and auditory discrimination of temporal duration show abnormalities

of laterality in schizophrenics, which are normalized by administration of chlorpromazine (Gruzelier & Hammond, 1976, 1979). These findings all implicate a left temporal-limbic dysfunction involving a dopaminergic system.

Recovered male schizophrenics or manic-depressive patients showed larger ear differences than normals on a dichotic listening test involving monosyllabic words in groups of three (Lishman, et al, 1978). Auditory hallucinators had larger laterality quotients than nonhallucinators, those without family history of psychosis had larger quotients than those with, and females had larger quotients than males. Complete recovery was associated with a laterality quotient in the normal range. Nachshon (1980) reported a right ear superiority for identifying digits in a dichotic listening paradigm, which was greater for schizophrenics, and greater for paranoids than nonparanoids. He interpreted this as evidence for left hemisphere overactivation in schizophrenics. Gruzelier & Hammond (1980) found that the larger than normal ear difference due to less efficient recall of left ear material occurred only in high arousal patients identified by the presence of electrodermal orienting responses to nonsignal tones. In some cases, chlorpromazine produced performance worse than that seen on placebo, indicating that phenothiazines increase left hemisphere arousal more than right, and if augmented by high intensity sensory input, could produce overactivation of the left hemisphere. Wexler & Heninger (1979)

found that higher laterality scores on a dichotic listening test given to psychotic patients were associated with lower rating of psychotic thought and behavior. These findings may differ from the previously mentioned reports due to presentation of single rather than series stimuli, and the requirement of single rather than multiple responses.

Interhemispheric Spillover

Several authors have suggested a lateralization - psychoanalytic theoretical synthesis in which primary process thought or the 'unconscious' is related to right hemisphere processing while secondary process or rational ego consciousness is related to left hemisphere processing (Galín, 1974, 1978; McLaughlin, 1978; Hoppe, 1976; Rossi, 1976; Stone, 1977). According to this scheme repression has a neurophysiological analog in the functional disconnection of the hemispheres (Galín, 1974), while interhemispheric integration is the neurophysiological analog of the individuation process, specifically the transcendent function involving the union of ego and archetype or conscious and unconscious contents (Rossi, 1976). Jung (1907, 1939, 1957, 1958) proposed that schizophrenia is a pathological aberration of the transcendent function (abnormal interhemispheric integration), in which "the connection between the ego and some of the complexes is more or

less completely lost" (deficiency of interhemispheric transfer), and due to weakness of the ego consciousness (left hemisphere deficit), normally inhibited contents of the unconscious enter consciousness. This last aspect of schizophrenic psychodynamics may involve a 'spillover' of unconscious or primary process contents into waking consciousness, having a neurophysiological analog in excessive interhemispheric communication or spillover of right hemisphere mentation into the left hemisphere. Jung (1968) regarded the schizophrenic as a waking dreamer. There is extensive evidence that dreaming and REM sleep involve a relative dominance of the right hemisphere (Bakan, 1978b). It has been hypothesized that schizophrenia involves the abnormal spillover of dream-like fantasy usually confined to REM periods into the waking state (Dement, et al, 1969; Bakan, 1976, 1978b). Inability to confine dreaming to REM is manifest in a less clear differentiation of REM and NREM periods in schizophrenics (Hartman, 1967; Koresko, Snyder & Feinberg, 1963; Lairy, et al, 1965; De Barros-Ferreira, Goldsteinas & Lairy, 1973; Kupfer & Foster, 1975). Also, normals in whom dream-like material spills over to NREM periods are less likely to show REM rebound after REM deprivation (Cartwright, 1972; Cartwright, Monroe and Palmer, 1967; Zimmerman, 1970), a characteristic of schizophrenics (Zarcone, et al., 1969). In addition there is an association between dream material occurring in NREM periods and higher scores on the Schizophrenia scale of the MMPI (Cartwright

& Ratzel, 1972; Foultes, 1967). 1976; McDowell, et al, 1975).

Randall (1980) has hypothesized that schizophrenic symptoms occur as a result of increased callosal transmission due to the presence of myelinated interhemispheric fibers linking functional areas not connected in normals, leading to an interference of normal left hemispheric function and apparent left hemisphere deficits and disconnection phenomenon. It may be that the anatomical connections exist in normals but are nonfunctional or dormant, perhaps because unmyelinated. Abnormal fibers in schizophrenics may be dormant until released by a number of factors such as age, stress, or changes in the abnormality of input. Finally, extra callosal fibers could provide a greater range and complexity of cortical function. In adopted children of schizophrenics half had schizophrenia or other psychiatric abnormalities, while half had unusual eminence, perhaps indicating some selective value for a 'schizotaxic'

Summary and Conclusions

Evidence for abnormal cerebral lateralization in schizophrenia has been reviewed. The diverse findings reported in this literature may be interpreted as supporting four interrelated hypotheses:

1. Schizophrenics have dysfunctional left hemispheres.

2. There is in schizophrenics an abnormality of interhemispheric transfer leading to symptoms of hemispheric disconnection or 'functional commissurotomy'.
3. There may also be excessive interhemispheric transfer or 'spillover', during which right hemisphere information is abnormally transmitted to the left hemisphere. The 'deconnection' and 'spillover' may happen simultaneously if different callosal or commissural tracts are involved, and it is possible that deconnection symptoms are themselves the result of abnormal or excessive callosal transfer.
4. In acute stages of schizophrenia the dysfunctional left hemisphere is overactivated.

These four hypotheses are not mutually exclusive alternatives, and the relationships among them deserve further investigation. Although there are some inconsistencies in this literature, the convergence of a large number of studies utilizing diverse methodologies certainly warrants the conclusion that hemispheric lateralization is abnormal in schizophrenics. It must be remembered that schizophrenia is an etiologically heterogeneous disorder and any biological abnormality is likely to characterize only a subgroup of patients with the diagnosis. This is as true of lateralization patterns as of biochemical abnormalities. Future investigation of lateralization in schizophrenics would benefit by the utilization of research strategies and experimental designs which take the biological

heterogeneity of the schizophrenic syndrome into account.

III. Smooth Pursuit Eye Movements in Schizophrenia

Using photography of the corneal reflection of light, Diefendorf and Dodge in 1908 documented an impairment of smooth pursuit eye movements (SPEM) in schizophrenics visually tracking a swinging pendulum. In 1934 Couch and Fox repeated this experiment on a more diverse sample and found that other severely ill psychiatric patients as well as schizophrenics showed an impairment of SPEM. These studies did not receive much attention, and in 1973 Holzman, Proctor and Hughes rediscovered the schizophrenic SPEM disorder using electrooculographic recording of eye movement during tracking of a swinging pendulum. Schizophrenic patients showed significantly more SPEM deviation than normals and nonschizophrenic psychiatric patients on both a qualitative scoring of tracking records and a quantitative measure, the number of velocity arrests made during tracking. Holzman, Levy, Yasillo, Meltzer and Hurt (1974a) extended this finding to first degree relatives of schizophrenics, suggesting that the SPEM dysfunction may represent a genetic marker useful for studying vulnerability to schizophrenia. Holzman, et al (1974) reported that 86% of the chronic schizophrenics, 52% of recent schizophrenics and schizoaffectives, 44% of the relatives of schizophrenics, 22% of

manic-depressives, 21% of nonpsychotic psychiatric patients, and only 8% of the normal controls studied had qualitatively disordered SPEM records. The use of psychological test diagnoses improved the relationship between schizophrenia and impaired SPEM. Since the reports of Holzman, et al (1973, 1974a, 1974b) the finding of impaired SPEM in schizophrenics has been replicated many times using a variety of targets, recording and scoring techniques.

Long before the introduction of phenothiazines, Diefendorf and Dodge (1908) and Couch and Fox (1934) found deficient smooth pursuit eye tracking in schizophrenics. Pendular eye-tracking has been shown to be unaffected by neuroleptic medications (Holzman, et al, 1975; Shagass, Amadeo & Overton, 1974) so disordered smooth pursuit eye movements (SPEM) is not related to antipsychotic drug treatment. The deficit may be related to a disorder of attention, pathology of extraocular muscles or retina, or a dysfunction of neural mechanisms controlling saccadic and smooth pursuit eye movements (Holzman, et al, 1974). These etiological factors are not mutually exclusive, and there is evidence supporting all three hypotheses.

Deviant SPEM is not diagnostically specific for schizophrenia. SPEM is more disordered in nonschizophrenic functionally psychotic patients than in nonpsychotic patients or normal controls (Shagass, Amadeo, Overton, 1974; Holzman & Levy, 1977). Klein, et al (1976) found velocity arrest scores in

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schizoaffective patients comparable to those reported by Holzman and Shagass. Salzman, Klein and Strauss (1978) found that diagnoses was not related to deviant pendular eyetracking in remitted psychiatric patients. Global measures of current functioning were not related to SPEN disorder but ratings of the degree of psychosis at the time of the patients' last hospitalization were. These findings suggest that abnormal eye-tracking is associated with functional psychosis in general, and not schizophrenia specifically. However, disordered SPEN may still be much more frequent among schizophrenics than other psychotics. Holzman (1975) reported that SPEN impairment characterized 75% of the schizophrenics, 17% of the nonschizophrenic psychotics, and 5% of nonpsychotic psychiatric patients. Thus, although SPEN impairment is not specific to schizophrenia, a much greater proportion of schizophrenics than other patients show this oculomotor disorder.

When subjects are required to read numbers on the target while tracking, performance is improved, perhaps because extra feedback cues facilitate attention, and schizophrenics' performance is improved more than that of normal subjects, although differences between patients and nonpatients remained even in the number reading condition (Shagass, Roemer, Amadeo, 1974; Holzman, Levy & Proctor, 1976). Holzman, Levy and Proctor (1976) distinguished between two types of tracking disorder. Pursuit movements are interrupted by large saccades in

Type I, and in Type II the smooth tracking has small amplitude aberrations superimposed on an otherwise normal curve, giving it a spiky appearance. Type I involves a failure to activate the pursuit system, which when engaged functions properly. This could be due to lack of motivation, inattentiveness, or some neurophysiological disorder such as bradykinesia. Type II involves a disruption of smooth pursuit once it is engaged. Of the schizophrenics with deviant SPEN, 80% have the Type II disorder. The number reading task totally eliminates the Type I disorder, but only reduces the Type II disorder slightly. The Type II disorder can only be produced once the subject is attending to the pendulum, and 30 second realerting does not improve the deviant tracking. Holzman and his colleagues have hypothesized that the deviant SPEN is due to a disorder of nonvoluntary attention (Holzman, Levy & Proctor, 1976; Holzman, Levy & Proctor, 1978).

Iacono and Lykken (1979a) measured eye movements using both EOG and infrared reflectance techniques and discovered that the two types of tracking deficit are not mutually exclusive, but are positively correlated within individuals ($r = .53$). They also found high retest reliability for both types of tracking deficit (Type I, $r = .67$; Type II, $r = .80$). Iacono and Lykken (1979c) also found that the two recording techniques did not show good correspondence for individuals with Type II tracking deficit, indicating that the 8-10 Hz spiky pattern appearing in the EOG's

of Type II trackers does not reflect any movements of the eyeball. It is not simply a recording artifact either, because a recording artifact would not show high retest stability or concordance among twins. This spiky pattern appeared even when subjects closed their eyes or fixated on stationary targets. The degree of EOG spiking was correlated ($r=.53$) with the number of tracking cycles distorted by large saccades. This finding indicates that individuals who show the Type II spiky pattern produce large saccades and have poor tracking, so it may not be only unwanted noise, but rather a signal that is related to oculomotor function even though unrelated to movement of the eyeball per se.

Iacono and Lykken (1981) recorded EEG and EOG concurrently during SPEN from 20 subjects with and without the spiky tracking. Spectral analyses revealed close correspondance of EEG and EOG spectra in the alpha frequency range for the spiky trackers only. They suggested that this oscillation may be EEG kappa, an anteriorly recorded activity in the same frequency range as alpha, which increases with mental activity. They postulated the presence of kappa in the EOG of spiky trackers indicates the occurrence of mental activity directed away from the tracking task. Iacono and Lykken (1979b) also found that monitor tracking decreased spikiness ratings, suggesting that the attention enhancing task involving more mental activity directed to the tracking task and less away from it, reduced

kappa and improved tracking. On the other hand the 8-10 hz. spikiness could represent EEG alpha, indicative of decreased cortical alertness. The monitor tracking might boost cortical arousal and diminish alpha activity, thus explaining the diminished spikiness during monitor tracking. This latter explanation is consistent with previous reports that alpha was absent from EEG records during accurate SPEM but was present during saccadic interruption of SPEM (Pollen and Trachtenberg, 1972; Mulholland and Peper, 1971).

Brezinova and Kendell (1977) challenged the hypothesis of Holzman that abnormal SPEM reflects a deficit of involuntary attention, reporting that distraction or declining arousal and attention in normal subjects produced abnormal tracking movements indistinguishable from those of schizophrenics. They concluded that tracking abnormality is due to impaired voluntary attention or distractibility in schizophrenics. Acker and Toone (1978) reported that the impairment of eye-tracking in schizophrenics was related to the occurrence of behavior which, a priori, was thought to preclude optimum attention to the tracking task. They also found that in normal controls competing tasks of increasing levels of difficulty resulted in increasing degrees of SPEM impairment, suggesting that tracking performance is sensitive to superficial inattention. Lipton et al (1980), using the same distraction task as Brezinova and Kendell (1977), found clear quantitative and qualitative differences in the SPEM

records of schizophrenics and distracted normals. The distracted normals' SPEN was characterized by slow deviations or intermittent interruptions with periods of intact tracking cycles, while schizophrenics' SPEN records showed few intact cycles and more pursuit arrests. Pass, et al (1978) found that dichotic listening as a distraction condition impaired the SPEN of both normals and schizophrenics, but that of the latter subjects to a greater degree. Auditory-visual distraction did not impair either group's performance, so attentiveness alone does not account for the tracking impairment in schizophrenics. They argue that the schizophrenics are more susceptible to disruption by distraction because of a generalized attention deficit.

Pivik (1979) also included a signal detection task in the tracking tests and found that the presence of the signal slightly improved the tracking of normal control subjects, produced little change in the tracking of psychiatric outpatients, and significantly impaired the tracking of psychiatric inpatients. This is similar to the findings of Shagass, et al (1976) that reading numbers on the pendulum aloud caused a decrement in the tracking of patients and improvement in controls. The effectiveness of the signal detection task in engaging attention was shown by the low incidence of failures to detect the signal, and reductions in blinking and positive saccades, both indicative of increased attention (Ponder &

Kennedy, 1928; Holzman, et al, 1973). The signal detection task provides feedback cues like the number reading task, but unlike number reading the information is discontinuous. The impairment of the tracking performance of inpatients by the signal detection task may have been due to stress resulting from stimulus unpredictability. The results may also have been related to increased distractibility and information overload in the inpatient group. The requirement of responding to signal interruptions and the information processing requirement of detecting signal interruptions while tracking may have led to information overload or distraction from the tracking task. The distractibility explanation is further supported by the finding that during realerting instructions there was an increase in tracking errors in inpatients (Pivik, 1979). Both increased distractibility and information overload have been suggested as explanations of the attentional dysfunction in schizophrenia (Blum, et al, 1969; Bush, 1977; Hemsley & Zawada, 1976)..

Cegalis and Sweeney (1979) have produced further evidence that attentional dysfunction is related to disordered SPEN in schizophrenic patients. They found that the frequency of saccades and the magnitude of temporal and spatial errors was greater in schizophrenics than control subjects for linear and nonlinear stimulus patterns with constant or variable velocity. The frequency of nontracked cycles was greater among the schizophrenics. They propose that this measure is related to

voluntary sustained attention to the tracking task, which is more difficult for the patients. Eye blink frequency, which is related to effortful attention, was also greater for schizophrenics than controls. Cegalis and Sweeney (1979) interpret these findings as an indication that the schizophrenics may expend a great deal of effort paying attention to the task, but they are unable to sustain this attention for the duration of the task.

The notion of an attention disorder in schizophrenia has received much attention, and is supported by the finding of deficient filtering of sensory information (Chapman & McGhie, 1962; Kornetsky & Mirsky, 1966; Silverman, 1964, 1967) and impaired performance on a test of sustained attention during distraction (Wohlberg & Kornetsky, 1973). Cegalis, Leen and Solomon (1977) found abnormalities of attention to stimuli presented in the periphery of the visual field in schizophrenics: acute schizophrenics discriminated peripheral signals more accurately than normals who were more accurate than chronic schizophrenics. Matthysse (1978) has proposed that nonvoluntary shifts of attention involve the smooth pursuit system, while voluntary shifts are saccadic. He has hypothesized, on the basis of disordered SPEN and attentional disorders in patients with Parkinson's disease and other basal ganglia diseases, that the control of attention is partly regulated by dopaminergic systems. A disorder of dopaminergic

function has also been implicated in the etiology of schizophrenia (Meltzer & Stahl, 1976).

The performance of tracking tasks may also be related to a subject's level of arousal. When subjects were required to monitor the appearance of a hole in the center of the oscillating target, a task similar to number reading, performance improved, and those whose baseline tracking was poorest improved most with the addition of the monitoring task (Iacono & Lykken, 1979a, b). In a post-monitor condition performance was not as good as in the monitor condition, but did not fall as low as the pre-monitor baseline condition. If feedback cues facilitating attention were to account for the improved tracking, one would expect the post-monitor performance to be no higher than the pre-monitor baseline. Increased arousal could improve performance during the monitor task and during the post-monitor condition arousal would fall off somewhat, but wouldn't return to baseline levels immediately. Iacono and Lykken (1979b) also report that in certain subjects who were tired and/or bored tracking was poor. Their suggestion that the subject's arousal level and the extent to which the subject finds the task arousing accounts for the tracking improvement with the monitor task may be valid when considering within subject effects but may not account for differences between groups in tracking performance. Pivik (1979) did not find any relationship between physiological indexes of arousal (GSR, EEG

alpha index during tracking, and reaction time to signal interruption) and group differences in tracking behavior.

Disordered SPEN is also found in a large percentage (44%) of the first degree relatives of schizophrenics (Holzman, et al, 1974). In a group of 228 psychiatric patients, their relatives, and normal control subjects, schizophrenics and their relatives accounted for 82% of all deviant SPEN. Holzman, et al (1977, 1978) found that 71% (5/7 pairs) of a group of monozygotic twins discordant for schizophrenia were concordant for deviant eye-tracking, while only 54% (7/13 pairs) of the dizygotic twins discordant for schizophrenia were concordant for deviant SPEN. Velocity arrest scores were correlated ($r=.77$) in the MZ twin pairs more highly than in the DZ pairs ($r=.40$). They found the tracking deviations in twins concordant for SPEN to be remarkably similar. From these findings Holzman, et al (1977, 1978) concluded that additive genetic effects are more important than nonadditive genetic or random environmental effects in determining deviant SPEN. Since SPEN integrity declines with age (Kuechenmeister, et al, 1977) and 10% of the variance in eye tracking is accounted for by age, Holzman, et al (1980) replicated the earlier twin study with a younger group of schizophrenics. They found similar concordance rates to the previous study when results were adjusted for age by partial correlation. Using an improved quantitative measure of eyetracking quality, the natural logarithm of the signal to

noise ratio, they found correlations of .77 between MZ twins and .40 between DZ twins. The involvement of a genetic factor in smooth pursuit tracking performance may be related to an inherited vulnerability to functional psychoses.

Iacono and Lykken (1979a,b) found high product moment correlations for retest stability and high intraclass correlations of twin concordance for several tracking tasks, scored using a root mean square deviation of tracking pattern from target pattern. This indicates that performance on tracking tasks represents a stable trait influenced by a genetic factor. Iacono and Lykken (1979a,b) had judges attempt to match EOG tracings across sessions. An EOG plot for each person was compared to four other plots: another plot from the same person, a plot of the person's identical twin, and two plots chosen randomly from among other subjects' plots. An individual was ranked as most similar to himself 41.5% of the time, and most similar to his twin 38.5% of the time, both significantly different from chance (25%). On second testing a person's tracking resembled his own performance on an earlier trial about as closely as his twin did. These findings indicate a qualitative constancy in EOG tracing quality within twin pairs and over time. The quantitative similarity in twins' performance was boosted by the monitor task. These authors found that 25% of a group of 64 normal subjects had disordered SPEN, a base rate for deviant eye tracking in normals significantly higher than

that reported by Holzman's group.

Salzman, Klein, and Strauss (1978) found that psychiatric patients in a state of remission had deviant eye tracking and that there was a relationship between past levels of psychotic functioning and current pendulum tracking performance. These authors conclude that pendulum tracking performance reflects an attentional dysfunction which is a stable trait characteristic. Individuals possessing such a trait would, if they develop psychiatric disorders, tend to manifest cognitive and perceptual disorders characteristic of psychoses. Thus, deficits in pendular eye tracking performance may be regarded as a marker variable for vulnerability to psychotic disturbance. Unfortunately, Salzman and Klein (1978) did not compare their patients to a control group. Salzman, Klein and Strauss' (1978) finding of impaired eye tracking in remitted schizophrenics was replicated and extended by Iacono, Tuason and Johnson (1981), who compared thirty patients to 21 normal healthy controls. The remitted schizophrenics derived little residual benefit from exposure to a monitor tracking task, while the post-monitor tracking of the normals was superior to their pre-monitor tracking performance, perhaps suggesting an abnormality of arousal mechanisms in the remitted patients. The remitted schizophrenics' tracking disorder was of a generalized nature: impaired SPEN was seen for all tracking frequencies examined (.2 to 1.2 Hz.), for both sinusoidal and triangular wave target-

motions, and impaired tracking also occurred for psychomotor manual analogues of SPEM tracking tasks. Furthermore, they reported that schizophrenic performance on a saccadic tracking task involving rectangular wave target motion did not differ from that of normal controls, suggesting that the SPEM impairment is not reflective of a generalized oculomotor deficit. The dissociation of saccadic and SPEM tracking performance was also interpreted as evidence against the proposition that tracking deficits reflect inattentiveness or insufficient effort, since both saccadic and SPEM tracking require cooperation and sustained attention.

The findings of high retest stability, higher MZ than DZ twin concordance for tracking impairment, disordered tracking in the first degree relatives of schizophrenics and in remitted schizophrenics, and the demonstration that disordered tracking is not related to antipsychotic medication all support the suggestion that SPEM disruption may serve as a marker for the vulnerability to schizophrenia (Holzman, 1979). Holzman (1979) further cautioned that confidence in SPEM as a vulnerability indicator is weakened by the lack of diagnostic specificity, the smallness of the sample size of the twin group examined thus far, the undetermined base rate in a large sample from the general population, the lack of information concerning the ontogenesis of SPEM, and the need of improvement in the quantification of SPEM. Still, SPEM impairment deserves further

investigation as a putative vulnerability marker. The SPEM disorder may not be the only ocular abnormality associated with schizophrenic vulnerability. Kinney (1979) found that 16/31 adopted schizophrenics from the Danish Adoptees Study (Kety, et al, 1975) had a visual handicap of a congenital nature, while only 3/23 control probands had a congenital visual handicap. Severe handicaps such as near blindness in one eye and nystagmus were seen only in the schizophrenic adoptees, schizophrenia and ophthalmologic defects were associated in the relatives of schizophrenics, and severity of schizophrenic symptoms was related to the incidence of visual defects in this sample. Also, the incidence of ophthalmologic defects in this sample was specifically related to schizophrenia since nonschizophrenic psychiatric patients showed no increased incidence relative to controls.

SPEM is disrupted by administration of barbituates, tranquilizers and anticonvulsants (Rashbass & Russell, 1967; Rashbass, 1961; Daroff, 1970; Gentles & Llewellyn-Thomas, 1971; Holzman, et al, 1975). Smooth pursuit tracking is also disrupted by alcohol consumption (Wilkinson, Kime & Purnell, 1974; Flom, et al, 1976). Levy, Lipton and Holzman (1981) found that the extent and duration of ethanol induced SPEM disruption was dose dependent. Levy, et al (1981) also found moderate SPEM impairment after injection of 1500 mg. of chloral hydrate. Number reading improved tracking disrupted by either alcohol or

chloral hydrate, suggesting that the number reading effect occurs not only in conditions of mere inattentiveness, but also during SPEM disrupted by CNS depressants. Since CPZ produced no SPEM impairment yet did produce as much sedative effect as these CNS depressants, the SPEM disruption induced by the latter is not simply a result of the sedative effects of these drugs.

SPEM has also been shown to be disrupted by methadone, which reduced the gain, or ratio of stimulus amplitude to eye movement amplitude, of tracking at a number of frequencies (Rothenberg, Schottenfeld, Selkoe, and Gross, 1980). Methadone also alters saccadic function in humans (Rothenberg, Schottenfeld, Gross and Selkoe, 1980). These findings suggest a role for endorphinergic mechanisms involved in the control of eye movements, and possible abnormalities of the endorphin system in schizophrenia have recently received widespread attention. Although Holzman, et al (1975) found little effect of diazepam on SPEM velocity arrest scores, Rothenberg and Selkoe (1981) found a dose dependent reduction in the gain of SPEM at a variety of target frequencies, and visual inspection of the tracking records revealed reduced peak to peak amplitude of eye tracking as well as replacement of SPEM with saccadic tracking, especially after administration of the 10 mg. dose. Bittencourt, Gresty and Richens (1980) found that anticonvulsant medications such as phenytoin and phenobarbitone were partly responsible for an impairment of SPEM observed in epileptic patients. Drug

status should be assessed in investigations of SPEM.

Another subject variable affecting SPEM which should be taken into account in future studies is age. Several investigators have reported that smooth pursuit tracking accuracy decreases with age (Shagass, et al, 1974; Kuechenmeister, et al, 1977; Sharpe & Sylvester, 1978; Spooner, Sakala, Baloh, 1980; Iacono, Tuason and Johnson, 1981). Although one study reported that males track more accurately than females (Kuechenmeister, et al, 1977) several others have found no effect of gender on eye-tracking (Shagass, et al, 1974; Holzman, et al, 1974; Pivik, 1979).

Stimulus variables affecting pursuit tracking include velocity and trial duration. May (1979) found less accurate pursuit tracking at higher target velocities and shorter trial durations. Iacono and Lykken (1979a,b) found the greatest error in tracking occurring at the higher target velocities. Within a given target cycle errors were greatest at the point of maximum target velocity and least when the target velocity was zero, that is, at the eccentric points where the target changes direction. The addition of the monitor task modified the relationship between error probability and target velocity by making it easier to track the target during the high velocity portion of the cycle, that is, at the center of a swing (also Miallet and Pichot, 1981). Faster frequencies of target oscillation entailing faster target velocities also cause more

SPEM impairment (Levin, Lipton and Holzman, 1981; Lisberger, Evinger, Johanson and Fuchs, 1981; Rothenberg, et al, 1980; Rothenberg and Selkoe, 1981; Iacono, Tuason and Johnson, 1981).

The original studies on eye-tracking and most subsequent studies have used a simple pendulum as the tracking target. Pendulum targets have a diminishing target excursion over the course of a trial and so diminishing target velocity.

Shagass, Amadeo and Overton (1974) improved on the pendulum by using as a target a spot of light moving on a cathode ray tube, whose pattern of movement was controlled by a computer. Several other investigators have employed the more sophisticated computer or wave generator driven CRO targets (Cegalis and Sweeney, 1978; Iacono and Lykken, 1979a, 1979b; Iacono, Tuason and Johnson, 1981). Levin, Lipton and Holzman (1981) found that schizophrenic SPEM disorder was apparent using either a simple pendulum or a rear projection target driven by a sine wave generator, and frequency analysis signal/noise ratios for tracking of the two targets was highly correlated.

Cegalis and Sweeney (1979) found a tracking deficit in schizophrenics using horizontal, vertical, diagonal, and pendulum tracking targets with constant or variable velocity, shown on a cathode ray oscilloscope. Thus, the previous findings of disordered SPEM in schizophrenic patients can be generalized from pendular tracking to a variety of target motion patterns. Iacono, Tuason and Johnson (1981) also found that remitted

schizophrenics showed impairment in tracking targets with triangular wave motion, confirming the general nature of the schizophrenic tracking deficit.

Recording and analysis techniques for assessing SPEM have also varied across investigations. Cegalis and Sweeney (1979) used an infrared reflectance recording technique, while most other investigations have utilized EOG recordings. Lindsey, Holzman, Haberman and Yasillo (1978) recorded SPEM with EOG and infrared reflectance techniques. The records were then scored using two quantitative measures: velocity arrests and the natural logarithm of the signal to noise ratio obtained from the harmonic regression of digitized and standardized eye movement data. The velocity arrest score was not well correlated between the two recording methods, while the $\ln(S/N)$ score was highly correlated across the two methods and was generally free of artifacts. ($r=.96$, $p<.01$). Thus, the latter measure is a more reliable and valid measure of tracking ability. Levin, et al (1981) found that the log signal to noise ratio of Lindsey, et al (1978) was highly correlated with qualitative assessment of tracking. Iacono and Lykken (1979c) found that the correspondance between IR and EOG recording techniques was not high for individuals whose EOG contained the 8 to 10 hz. spikiness of Type II tracking disorder, suggesting that this spikiness is not produced by movement of the eye per se. They argued that the spikiness was not just a recording artifact

either, since high retest reliability, high MZ twin concordance, and the high correlation between the degree of EOG spikiness and the number of tracking cycles interrupted by large saccades all suggest that the spikiness is a stable trait which may be related to oculomotor function in a meaningful way.

Iacono and Lykken (1979a,b) used a root mean square deviation of performance from target cycles, conceptually representing a measure of the degree to which the tracking record can be superimposed upon the target record. The RMS measure is readily computed and is less susceptible to recording artifacts than the velocity arrest index. It also enables computation and adjustment of phase relationships between target and EOG, production of an average EOG revealing systematic distortions, and determination of the degree to which tracking errors are concentrated in one part of the cycle. Iacono and Lykken (1981) found high within session, one week and two year retest reliabilities for RMS scores. High correlations were also found between RMS scores based on ECG records and RMS values based on IR recording, indicating the superiority of RMS scores over velocity arrests as a quantitative measure of SPEN accuracy. Lykken, Iacono and Lykken (1981) have argued that the RMS calculation is mathematically interchangeable with Lindsey, et al's (1978) $L_n(S/N)$ measure ($S/N = 1/(RMS)^2$). However, Lindsey, et al (1978) use too wide a filter for the signal quantification, thus including some noise in this value.

Cegalis and Sweeney (1979) measured saccade frequency, target overshoot, undershoot, and latency of responses to target reversal, as well as frequency of half cycles of target movement in which the subject failed to continue tracking, and frequency of eye blinks. They found that schizophrenics had a higher frequency of saccadic interruption of SPEM, as well as a greater magnitude of spatial error, i.e., overshoot and undershoot. The saccadic bursts were not limited to target reversal points and did not appear to be corrective saccades, since they were not initiated in response to tracking error. An increased frequency of saccades during SPEM tracking has also been reported by Miallet and Pichot (1981) and Tomer, Mintz and Myslobodsky (1981). These improvements in the analysis of eye movement records, along with developments in target presentation and eye movement recording techniques will enable more precise investigation of the relationship of eye tracking patterns to psychopathology and vulnerability or high risk.

Other disturbances of ocular movement have been reported in schizophrenics. In 45 schizophrenic patients off medications Stevens (1978) found abnormalities of eye contact, blink rate, lateral eye movements, and ocular pursuit. Patients would stare into the examiner's eyes or at a point in space, or would avoid eye contact. Blink rate decreased in some patients and increased in others, and some patients exhibited episodic paroxysms of rapid rhythmical blinking. Many patients had abnormal glabellar

blink reflexes. Abnormalities of lateral eye movements included rapid irregular searching movements, spontaneous rhythmic horizontal saccades, and single sustained lateral glances. Irregular ocular pursuit was noticed when patients were asked to follow a moving object (finger, flashlight, etc.) with their eyes. Stevens (1974) mentions that all of these extraocular disturbances were reported in the older literature concerning schizophrenia. Stimulation of the mesolimbic dopamine system in experimental animals and temporal lobe seizures in man produce very similar ocular disturbances, and drugs altering central dopamine function modulate these signs. Stevens (1979) has suggested that these ocular disturbances are signs of dysfunction of the mesolimbic dopamine system. In another paper reporting abnormal telemetered EEG and EOG activity in schizophrenia, Stevens, et al (1979) propose that the ocular signs and bizarre somatic symptoms in schizophrenics are related to abnormal excitation in paramedial diencephalic and mesencephalic areas, with localized cortical desynchronization in hallucinations, and inappropriate desynchrony in left or right temporal lobes in blocking and cognitive disorders. Karson (1979) also reported a higher incidence of staring, poor eye contact, pursuit breaks, searching glances, and blinking rates elevated in schizophrenics currently medicated or never medicated. Increased blink rates in schizophrenics have also been reported by Cancro, Gelder and Glazer (1979).

Eye movement control is related to feedback from the vestibular system, and disorders of the vestibular system are often detected by measuring ocular nystagmus responses. Levy, Holzman, and Proctor (1978) have reviewed the literature on abnormal vestibular system function in schizophrenia, and in an experimental study of vestibular responses to caloric stimulation discovered significantly greater dysrhythmic responses in chronic schizophrenics and recent schizophrenics compared to other psychiatric patients and normal controls. Citing evidence that improvements in the clinical condition of schizophrenic patients with or without drugs are accompanied by improved vestibular function, these authors argue that these vestibular abnormalities are a state related phenomenon associated with the severity of the psychosis. Fish and Dixon (1978) found vestibular hyporeactivity (diminished nystagmus responses) in infants at risk for schizophrenia. Abbreviation of nystagmus is seen in normal infants who are drowsy (Pendleton & Paine, 1961), and in normal adults during times of decreased mental alertness (Collins, 1963). Such vestibular disorder may be a result of a central dysfunction of attention and arousal systems. It is also possible that a peripheral disorder is responsible, as Dix and Hood (1970) found an association between peripheral vestibular disease and psychiatric symptoms. Latham, Holzman, Manschreck and Tole (1981) found that, in addition to impaired SPEN, schizophrenics showed irregular dysrhythmic

partial field optokinetic nystagmus (OKN), but normal full field OKN. They suggested that the oculomotor functions of the peripheral vestibular apparatus, the vestibular nuclei and the frontal cortex are intact in schizophrenia, while the parietal association cortex involved in smooth pursuit may be dysfunctional. The suggestion of nonspecific cortical dysfunction, particularly of the parietal lobe, is also consistent with the report of a dissociation of saccadic and SPEN tracking performance in schizophrenics (Iacono, Tuason and Johnson, 1981), and of frontal representation of saccades and parietal-occipital representation of SPEN. Disordered eye-tracking is seen in a variety of neurological conditions including brainstem and cerebellar disease or lesions (Benitez & Bouchard, 1974; Dichgans & Jung, 1975; Daroff & Hoyt, 1971; Jongkees & Oosterveld, 1973; Corvera, et al, 1973), basal ganglia disease (Hoyt & Daroff, 1971), Parkinson's disease (Slatt, Loeffler & Hoyt, 1966), anoxia related brain damage, cerebral vascular disease, and presenile dementia (Rodin, 1964), and cortical hemispheric lesions (Mayuzumi & Tsutsui, 1974) or hemispherectomy (Sharpe, Lo & Rabinovitch, 1979; Estanol, et al, 1980). Although the subcortical structures seem to represent both eye movement systems, at the cortical level there is some degree of divergence. Saccades are represented in the frontal lobes, while slow movements are represented primarily in the occipital lobes (Bach-y-Rita, 1971; Hoyt & Frisen, 1975).

Schizophrenia has been related to disorders of the basal ganglia (Davison & Bagley, 1969; Lidsky, Weinhold, Levine, 1979; Francis, 1979), the cerebellum (Snider & Snider, 1979; Weinberger, et al, 1980), brainstem reticular formation (Bowman & Lewis, 1980), and the mesolimbic dopamine system (Stevens, 1973; Stevens, 1978; Stevens, et al, 1979). The involvement of the vestibular system has already been mentioned and the evidence implicating a disorder of lateralization and function of the cerebral hemispheres has been reviewed. A similarity of schizophrenia with parietal lobe damage has been suggested on the grounds that both involve deficits of proprioception and disturbances in body image experience (Erwin and Rosenbaum, 1979). The emotional denial and inability to discriminate emotions in others seen in right parietal damaged patients may be seen as similar to the blunted affect and poor emotional discrimination seen in schizophrenics. The disorders of attention seen in schizophrenics and right parietal lobe damaged patients are also quite similar (Mesulam and Geschwind, 1978; Venables, 1980). The brain areas involved in disordered eye movements are also those implicated in neurophysiological studies of schizophrenia. These systems are diffuse and involve several transmitter systems, not just the dopamine system. These same diffuse centrencephalic integrative systems regulate lateralization, arousal, and attentional processes, which are also disturbed in schizophrenia. These neurophysiological

mechanisms will be described in the next chapter.

IV. The Neurophysiology of Eye Movement Control

Bakan (1969) was the first to suggest that conjugate lateral eye movements are indicative of contralateral hemispheric activation, and this hypothesis has been reiterated by other investigators (Kinsbourne, 1972; Gur, 1975). In much of the literature on CLEM the validity of this assertion has simply been assumed, and investigators have drawn conclusions about trait or state related asymmetric hemispheric activation and 'hemisphericity' on the basis of eye movement directionality. The hemispheric activation model of CLEM has not gone unchallenged, however, as Erlichman and Weinberger (1978) have stated that the CLEM construct is not well grounded in neurophysiology. The purpose of the following sections is to provide a synthetic review of neurophysiological investigations of oculomotor control, attention and orienting responses, and hemispheric activation and arousal in order to establish the neurophysiological plausibility of Bakan's hypothesis. Following the presentation of this evidence, several studies which bear directly on the question of the neurophysiological construct validity of the CLEM measure will be discussed.

Eye Movements

Eye movements may be roughly categorized as fast, or saccadic eye movements, which are involved in foveation of stimuli and scanning of the visual field, and slow, or smooth pursuit eye movements, involved in tracking slowly moving targets. A third type, nystagmus, consists of both fast and slow components, and is involved in stabilizing the visual field during motion of the body and head. Saccades are rapid, with velocities up to 600 degrees of visual angle per second. During saccades, meaningful sensory reception seems to be suppressed (Volkmann, 1962; Zuber and Stark, 1966). Saccades are thought to be under 'voluntary' control (Stark, 1971). Smooth pursuit eye movements (SPEM) occur with velocities up to 30 degrees per second, and meaningful sensory reception does occur during slow eye movements. SPEM is not, strictly speaking, a voluntary movement, since the signals generating SPEM are strongly affected by target velocity and position on the retina (Young, 1971). Dell'Osso and Daroff (1974) claim that SPEM is involuntary except under unusual circumstances, while saccades are volitionally controlled and self-paced. The saccadic and smooth pursuit systems work together during visual following of a moving object. Saccades enable the moving target to be initially centered on the fovea, and the SPEM system maintains it there by matching ocular velocity to the velocity of the

target. Correction saccades refoveate the target after blinks or following errors such as nonlinearities in the SPEN system. Effective horizontal SPEN involves the inhibition of saccadic eye movements (Heywood and Churcher, 1971), suggesting a reciprocal inhibitory relationship between fast and slow eye movement systems. At very high target velocities saccades intervene upon and then completely replace smooth pursuit, such that high velocity tracking is accomplished by a series of rapid saccades.

Nystagmus is a pattern of eye movement characterized by 'beats' consisting of a quick phase, a rapid eye movement opposite the direction of visual field rotation (in the same direction as the animal or person's rotation), and a slow phase involving pursuit-like movements in the same direction as visual field rotation (opposite the direction of the animal or person's rotation). Latham, Holzman, Manschreck and Tole (1981) distinguish between two types of optokinetic nystagmus (OKN: nystagmus evoked by visual and proprioceptive input): full field OKN and partial field OKN. Full field OKN stabilizes the visual surround on the retina when the animal is in motion, and so depends on full field stimulation; and it is suppressed or inhibited by stationary contours in the visual field (TerBraak, 1936; Dichgans, 1977). Full field OKN is always accompanied by circularvection, the sensation of rotation (Zee, Yee and Robinson, 1976; Robinson, 1977) suggesting that the brain

interprets motion of the entire visual surround as evidence of self motion. Full Field OKN is elicited in the laboratory by rotating the subject in chair or by rotating a brightly colored cloth drum in which the subject sits. If the lights are turned off and no deceleration is detected by the labyrinths, circularvection and optokinetic afternystagmus persist for 7 to 15 seconds.

Partial field OKN stabilizes moving objects on the retina rather than the entire visual surround. It is not inhibited by stationary contours, is not accompanied by circularvection, and is not followed by optokinetic afternystagmus. Partial field OKN is impaired by cortical lesions but not by labyrinthectomy, while full field optokinetic afternystagmus is abolished by labyrinthectomy and full field OKN is not interfered with by cortical lesions (TerBraak, 1936). Partial field OKN is controlled by the same pathways as saccadic eye movements and SPEN (Raphan and Cohen, 1978; Glaser, 1978). Indeed, Robinson (1977) has suggested that partial field OKN is simply smooth pursuit with refixation saccades. Partial field OKN is elicited by placing a subject inside a rotating cloth drum with vertical stripes.

Latham, et al. (1981) found that full field OKN is intact in both schizophrenics and normals, while the slow phase of partial field OKN is disrupted in schizophrenic patients, suggesting that there are indeed two separate systems mediating

two types of optokinetic nystagmus. Robinson (1981) has also argued that there are two or even possibly three different types of visual following reflexes in foveate animals: a smooth pursuit system used to track small moving objects, a full field optokinetic system used to supplement vestibular nystagmus, and perhaps a separate full-field stabilization system used to null unwanted ocular drift during attempted fixation. Although the full field optokinetic and smooth pursuit systems may involve different neurophysiological pathways at some levels, they do share some common neural mechanisms, and the slow phase of nystagmus is very similar to smooth pursuit.

In addition to optokinetic stimuli nystagmus can be elicited by vestibular inputs such as those evoked by caloric stimulation (cold water in the ear). Vestibular nystagmus involves the same pathways as full field OKN, and the quick and slow phases of vestibular nystagmus may, like the components of partial field OKN, resemble saccades and smooth pursuit, respectively. Guitton and Mandal (1980) found that the time courses of horizontal saccades and the quick phases of vestibular nystagmus in the cat are identical. There is no linear addition between oppositely directed slow and quick phases during vestibular nystagmus in the light or dark. During the quick phase there is a pause in the signal responsible for generating the slow phase, suggesting separate and reciprocally related saccadic and smooth pursuit systems interacting during

nystagmus. Identical time courses for the quick phases of nystagmus and saccades have also been found for man and monkey (Ron, Robinson, and Skavenski, 1972; Jürgens, Becker and Rieger, 1977). Thus, although there may be at least two different optokinetic systems (full field and partial field), all nystagmus seems to involve an alternation of saccadic and smooth pursuit-like eye movements. So, at a fundamental level there are two basic types of eye movements: fast or saccadic, and slow or smooth pursuit. The dissociation of saccadic and smooth pursuit tracking performance in schizophrenia (impaired SPEM but not saccadic eye movement) found by Iacono, Tuason and Johnson (1981) suggests divergent neural representation of saccades and SPEM. Although the subcortical substructures seem to represent both eye movement systems, at the cortical level there is some divergence, with saccades represented primarily in the frontal lobes, while slow movements are represented primarily in the occipital and parietal lobes (Bach-y-Rita, 1971; Hoyt and Frisen, 1975; Raphan and Cohen, 1978).

In the following sections neurophysiological evidence concerning the mechanisms controlling saccadic, smooth pursuit, and optokinetic nystagmus eye movements will be reviewed. The evidence arises primarily from three types of studies: studies of the effects of experimental lesions and ablations in animals and the clinical effects of lesions in humans, studies of single unit recording via implanted electrodes and studies employing

electrical stimulation of discrete brain areas via implanted or surface electrodes. The review will begin with cortical areas involved in eye movement control and will work down through subcortical areas to the oculomotor neurons innervating the eye muscles. Anatomical pathways involved in oculomotor control will be described in order to illustrate functional convergence in several areas of eye movement control, attention, orienting response, and hemispheric activation and arousal mechanisms.

Frontal Eye Fields (FEF)

Over the last century repeated investigations have firmly established the fact that electrical stimulation of the frontal eye fields in monkeys evokes contralateral saccadic eye movements (Ferrier, 1874; Beevor and Horsley, 1888; Horsley and Schaffer, 1888; Mott and Schaffer, 1890; Sherrington, 1893; Russell, 1894; Jolly and Simpson, 1907; Vogt and Vogt, 1907, 1919; Levinsohn, 1936; Smith, 1936, 1940; Crosby, Yoss and Henderson, 1952; Robinson and Fuchs, 1969; Schiller, 1977; Marrocco, 1978). Ablation of the frontal eye fields produces short-lived perceptual and motor defects. With unilateral ablations, monkeys show acutely a gross ipsilateral eye deviation and unwillingness to make contralateral eye movements, but this recovers with a few days (Brucher, 1966, Latto and Cowey, 1971 a, 1971 b; Ferrier and Yeo, 1884). FEF ablation also

6

produces neglect of of the contralateral visual hemifield (Latto and Cowey, 1971 a; Welch and Stuteville, 1958), difficulty with perimetry tasks (Latto and Cowey, 1971 b), and difficulty with visual search (Latto, 1978 a, 1978 b). Lesions which are restricted to the arcuate cortex produce circling movements of the head and eyes toward the side of the lesion as well as an apparent contralateral homonymous hemianopia (Kennard and Ectors, 1938; Kennard, 1939). In humans with frontal tumors seizures begin with contraversive eye movements and patients with frontal lesions tend not to make movements contralateral to the lesion (Holmes, 1938). Ablation of either the FEF or superior colliculus alone produces subtle or transient eye movement defects, but when both the superior colliculus and the FEF are lesioned, the combined lesion produces a severe and lasting loss of saccadic eye movement control as well as disrupted smooth pursuit and optokinetic nystagmus elicited by moving objects and gratings (Schiller, True and Conway, 1979, 1980). The superior colliculus ablation abolishes saccadic responses to stimulation of the striate cortex, but FEF stimulation continues to produce eye movements at thresholds comparable to those in intact animals (Schiller, 1977).

Single unit recording studies have found neurons in the monkey FEF related to spontaneous saccades, which discharge during and after, but not before the saccades (Bizzi, 1968; Bizzi and Schiller, 1970). Other FEF neurons have been found

with visual receptive fields which are usually contralateral and mostly large (Mohler, Goldberg and Wurtz, 1973; Kubota, Tonoike and Mikami, 1980; Pigarev, Rizzolatti and Scandolara, 1979; Wurtz and Mohler, 1976 a). Many of these cells respond more briskly to small spots of light than to larger spots with their receptive field. In half of these visually responsive cells there is an enhancement of the response to stimuli in the receptive field (Wurtz and Mohler, 1976 a; Bushnell and Goldberg, 1979; Goldberg and Bushnell, 1981 a, 1981 b). It has been argued that in order to be a pre-eye movement signal, the enhancement must be exclusively related to eye movements (Bushnell and Goldberg, 1979; Bushnell, Goldberg and Robinson, 1981 a; Goldberg and Bushnell, 1981 a; Robinson, Bushnell and Goldberg, 1981; Wurtz and Mohler, 1976 b). Goldberg and Bushnell (1981 b) found that the enhancement of response to visual stimuli of the neurons in the posterior part of the prearcuate gyrus (PEF) when the animal uses the stimulus in the visual receptive field as a target for an eye movement does not occur when the monkey performs a task that requires it to attend to the stimulus without making an eye movement toward it. There is no enhanced response when the animal reaches out and touches the stimulus but is not allowed to make a concurrent eye movement. Thus, the enhancement of response of these cells is exclusively related to eye movements. The burst of activity preceding eye movements to a target in the receptive field does not occur

before similar eye movements when there is no stimulus present (Goldberg and Bushnell, 1981 b). Goldberg and Bushnell (1981 b) concluded,

"These results suggest that the visually responsive cells in frontal eye fields may provide a retinal error signal to the brain stem gaze-shift centers, and the presaccade enhancement of these visual responses may be a cortical component of the neural events preceding purposeful, visually guided saccades."

Robinson, Goldberg and Stanton (1978) suggested that enhancement occurring only before an eye movement may be a mechanism by which visual information implicit in the neuron's discharge can be efficiently transmitted to the oculomotor system.

The afferent connections to the FEF which may be involved in its role in oculomotor control are varied. The FEF has reciprocal connections with the medial Pulvinar (Bender and Shanzer, 1964; Trojanowski and Jacobsen, 1974), a visually active area (Glickstein, et al., 1980; Keys and Robinson, 1979), which contains cells showing presaccadic enhancement of visual responsiveness (Keys and Robinson, 1977). The FEF also has reciprocal connections with visual cortical areas: prestriate, inferior temporal, and posterior parietal cortical areas (Chavis and Pandya, 1976). The FEF receives non-specific input from the cingulate gyrus, the nucleus of the diagonal band of Broca, the the claustrum, and the substantia inominata (Kievit and Kuypers, 1977; Pandya and Kuypers, 1969), and these areas contain cells whose reponses are motivationally related, but are not related

to specific movements (Niki and Watanabe, 1979; Rolls, Sanghera and Roper-Hall, 1979). The FEF receives a projection from the dorsal medial nucleus (pars multiformis) of the thalamus (Kievit and Kuypers, 1977), which in turn receives projections from the superior colliculus (Benevento and Fallon, 1975). The pars multiformis in the posterior thalamus may be critical for eye movements (Albano and Wurtz, 1981; Maldonado, Joseph and Schlag, 1979), and it contains single neurons whose activity is associated with eye movements (Schlag-Rey and Schlag, 1980).

Important efferent projections of the prearcuate cortex include a connection to the movement cell layers of the superior colliculus (Astruc, 1971; Leichnetz, 1980) although the FEF exerts an influence on the oculomotor system in the absence of the superior colliculus (Schiller, 1977; Schiller, True and Conway, 1979, 1980). Pathways which may mediate the effect of FEF stimulation on eye movements in the absence of the superior colliculus include projections to the basis pontis, cerebellum, medial dorsal thalamus, and mesencephalic reticular formation (Kunzle and Akert, 1977) as well as an FEF projection directly to the oculomotor nucleus (Leichnetz, 1980). Neurons with oculomotor properties have been found in these areas: medial dorsal thalamus (Albano and Wurtz, 1981), the mesencephalic reticular formation (King and Fuchs, 1979; Waitzman and Cohen, 1979), and the cerebellum (Noda and Suzuki, 1979). Robinson (1973) proposed the theory that the brain stem requires a

retinal error signal that gives a retinal position for a saccadic target, and Goldberg and Bushnell (1981) suggested that it is the FEF which supplies this retinal error signal.

The efferent projections of the FEF have been studied using techniques for staining degenerated neurons after lesions, and these projections are numerous. A study by Astruc (1971) revealed the following projections (also found by other authors): in the striatum and claustrum - caudate nucleus, dorsolateral putamen, and claustrum (Nauta, 1964); in the thalamus - ventralis anterior parvocellularis (Hassler, 1959), nucleus reticularis thalami (Chow, 1952), nucleus paracentralis, centralis lateralis, nucleus parafascicularis (Petra, 1964, 1965), and nucleus medialis dorsalis (Freeman and Watts, 1947; Scollo-Larizzari and Akert, 1962); subthalamus - zona incerta, and field H of Forel (Nauta, 1964); mesencephalic tegmental areas - superior colliculus, pretectal regions area praetectalis propria and praetectalis pars subcommissuralis, the interstitial nucleus of Cajal, the midbrain tegmentum mesencephalic central gray, and pontine nuclei medial pontine gray matter; basilar pons - processus griseus pontis supralemniscalis (Astruc, 1964; Hirasawa and Kato, 1935; Levin, 1936). As previously mentioned, several of these areas contain neurons with oculomotor properties, and many others are connected with other brain centers crucially involved in oculomotor control, such as the paramedian pontine reticular

formation.

Visual Cortex

Stimulation of occipital cortex elicits contralateral conjugate eye movements, just as stimulation of the frontal eye fields does (Crosby, 1953; Crosby and Henderson, 1948; Wagman, Krieger and Bender, 1958). Impairment of eye movements has been observed in the visual field contralateral to the occipital and occipitoparietal lesions of patients with homonymous hemianopia or neglect of the contralateral field (Karpov, Korchajinskaya, Popova and Yarbus, 1968; Bobrova, 1972; Chedru, LeBlanc and Lhermitte, 1973). Occipital lobectomy patients have jerky eye movements when their eyes were turned towards the side of the cerebral lesion or followed the motion of a pendulum (German and Fox, 1934; David and Hecaen, 1954). The fact that tracking toward the side of the lesion was impaired implies that smooth pursuit is ipsilaterally mediated. Karpov, Meerson and Tonkonojii (1979) noticed marked disturbances of visual fixation and tracking in two of five patients with unilateral or bilateral occipital lobe softenings. These disturbances included: increased latency of gaze shift toward a new point of fixation and increased latency of eye movements in following a spontaneously moving and stopping target, decreased duration of fixation of a stationary target and transitory blocking of

fixation, difficulties in gaze stabilization during visual fixations, and eye movements toward a new position of a luminous dot or pursuit of a moving target were performed jerkily and unevenly by a series of saccades. These findings support the notion of the importance of the occipital lobes in the control of SPEM. Interestingly, both cases with SPEM impairment had right-sided occipital lesions. Although it is unsafe to generalize from a sample of 5 subjects, these results may possibly point to an asymmetric hemispheric involvement in SPEM control.

Single unit recording studies have found presaccadic enhancement of visual responses in neurons in the striate cortex or Area 17 (Wurtz and Mohler, 1976 b), the peristriate cortex or Area 18 (Robinson, Baizer and Dow, 1980), and in the prelunate cortex or Area 19, which is located in the gyrus between the lunate sulcus and the superior temporal sulcus (Fischer and Boch, 1980, 1981 a, 1981 b). Cells in the prelunate cortex of rhesus monkeys are activated shortly before and during saccades to a continuously visible stimulus (Fisher and Boch, 1981 a), and in this respect are similar to cells found in the PEF. The enhancement seen in prelunate cells is spatially selective and doesn't occur when the animal makes an eye movement away from the stimulus. Thus, the prelunate cortex is the 'earliest' cortical stage along the visual pathway showing a spatially selective enhancement. Fisher and Boch (1981 b) concluded that

the prelunate cortex has access to an extraretinal signal which is activated in association with events preceding visually guided eye movements.

Many cells in Area 19 are driven easily by small visual stimuli, and the stimulus requirements are rather simple compared to cells in the striate cortex. This suggests that the prelunate cortex receives visual input which bypasses the geniculostriate pathway. This input may come from the inferior pulvinar, which receives its input from the retinocollicular pathway (Benevento and Rezak, 1976).

Posterior Parietal Cortex

Transcortical stimulation of the posterior parietal cortex, Area 7, induces contralateral eye movements (Fleming and Crosby, 1955; Wagnan, Krieger and Bender, 1958). A variety of oculomotor impairments follow experimental lesions of the parietal association cortex in monkeys (Lynch and McLaren, 1979 b; McLaren and Lynch, 1979). Optokinetic nystagmus is disrupted, with a reduction in the mean slow phase velocity when the OKN stimuli move from the hemifield contralateral to the lesion toward the ipsilateral hemifield. There are also impairments in saccadic and smooth pursuit eye movements following posterior parietal lesions (Lynch and McLaren, 1979 a). There is an increase in saccadic latency following 2-stage bilateral

posterior parietal lesions. Following unilateral lesions 2 monkeys had latency increases only for saccades into the contralateral visual field, and two had bidirectional latency increases. There was normal or near normal pursuit following unilateral posterior parietal lesions, but severe long lasting deficits in horizontal or vertical tracking following bilateral lesions (Lynch and McLaren, 1979 a).

Clinical evidence from humans with brain damage as a result of disease or trauma to the posterior parietal cortex reveals disorders of attention, affect, sensation, motor control and spatial perception (Lynch, 1980). Disorders of oculomotor control in these patients will be focussed on here. Patients with posterior parietal damage have an inability to direct their gaze toward an object in their peripheral visual field contralateral to the lesion, despite the absence of any oculomotor paralysis. A full range of eye movements is seen when the patient is not attempting to fixate any particular target. Although many patients are able to execute commands such as 'look to your left', when asked to look at a particular object in their peripheral visual field they are able to achieve fixation only after a series of apparently random gaze shifts or head movements (Allison, Hurwitz, White and Wilmot, 1969; Cogan, 1965; Cogan and Adams, 1953; Godwin-Austin, 1965; Hecean and DeAjuriaguerra, 1954; Holmes, 1918 a, 1918 b; Keiner and Keiner, 1958; Patterson and Zangwill, 1944; Sundquist, 1979; Tyler,

1968). OKN is often disrupted in patients with posterior parietal damage (Cogan and Loeb, 1949; Carmichael, Dix and Hallpike, 1954; Smith and Cogan, 1959; Smith, 1963), although several exceptions to this OKN effect have been reported (Davidoff; Atkin, Anderson and Bender, 1966; Feldman and Bender, 1969). In parietal lobe patients there is an inability to visually track a slowly moving target both in patients unable to hold a visual fixation of a stationary object (Holmes, 1918 a, 18 b), and in those able to maintain fixation (Godwin-Austin, 1965; Hecean and DeAjuriaguerra, 1954). During the SPEN of posterior parietal lobe damage patients a 'cog-wheel' pattern of eye movement disrupts the tracking of a slowly moving target (Cogan, 1965; Cogan and Adams, 1953). A similar cogwheel pattern is seen in the Type II tracking disorder with 10 Hz. spikiness seen in schizophrenics.

Single unit recording in the parietal lobe has demonstrated the existence of neurons whose activity is associated with eye movements (Hyvarinen and Poranen, 1974; Lynch, Mountcastle, Talbot and Yin, 1977; Mountcastle, Lynch, Georgopoulos, Sakata and Acuna, 1975) and especially with the fixation and pursuit of interesting visual targets (Lynch, Sakata, Georgopoulos and Mountcastle, 1973 a, 1973 b; Mountcastle, et al., 1975; Lynch, Yin, Talbot and Mountcastle, 1975; Yin, Lynch, Talbot and Mountcastle, 1975; Lynch, et al., 1977; Yin and Mountcastle, 1977, 1978). This suggests that the inferior parietal lobule (in

the posterior parietal lobe, Area-7) mediates the process of visual attention by directing eye movements. Yarbus (1967) argued that the process of attention is intertwined with gaze shift since the primate retina can best analyse visual stimuli in the fovea. Lynch (1980) has summarized the single unit recording studies of posterior parietal lobe indicating that there are four distinct types of cell located there: visual fixation neurons, visual tracking cells, saccade cells and light sensitive cells. The saccade cells emit intense high frequency bursts just before the initiation of a visually evoked saccade. The activity level of these cells did not rise above background levels during spontaneous saccades during light or darkness, suggesting a dependence upon attentional or motivational factors. Almost half (44%) of the saccade cells were active before saccades in only a single direction, while 20% were equally active before saccades in any direction. Thirty of 35 saccadic cells that were active with saccades in the horizontal plane were more active (or even exclusively active) before saccades into the contralateral visual hemifield than to the ipsilateral VF. The visual tracking cells discharged tonically at a high frequency while the animal accurately pursued a slowly moving visual target. Most of the tracking cells were directionally specific, with a five to twenty fold increase over background discharge levels during a visual pursuit in one direction, with no increase over the background level during tracking in other

directions. The investigators did not specify the numbers of ipsilaterally vs contralaterally sensitive tracking cells, presumably because each parietal lobe contains both. The activity of many tracking cells was suppressed before or during saccades made to follow the target if it suddenly jumped to a different part of the screen in the course of a smooth movement. The tracking cell activity then resumed before the re-initiation of SPEM. These results are consistent with the notion of a reciprocally inhibitory interaction between saccadic and smooth pursuit systems. Both the saccadic and the tracking neurons showed a dependence on attentional or motivational factors.

Another group of investigators using similar single unit recording techniques have also demonstrated that Area 7 of the posterior parietal cortex plays a role in visual attention and eye movement. Although many cells in Area 7 respond to visual stimuli independent of any behavior, the discharge to a stimulus may be enhanced when the animal makes an eye movement to the stimulus (Bushnell, Robinson and Goldberg, 1978; Bushnell, Goldberg and Robinson, 1981; Goldberg and Robinson, 1977 a, 1977 b; Robinson, Bushnell and Goldberg, 1981; Robinson, Goldberg and Stanton, 1978; Wurtz, Goldberg and Robinson, 1980; Yin and Mountcastle, 1977). Half the cells studied gave an enhanced response during a peripheral attention task in which the animal had to signal the occurrence of a peripheral stimulus without making an eye movement to it. Enhancement also occurred when the

animal reached out and touched the stimulus while refraining from making an eye movement to it. Bushnell, Goldberg and Robinson (1981) concluded:

"The behavioral enhancement of a visual response is independent of the specific movement used to respond to the stimulus. The physiological mechanisms of enhancement which is movement-independent and spatially selective, resembles the psychological phenomenon of selective spatial attention." (Bushnell, Goldberg and Robinson, 1981)

This close association of the parietal lobe with both eye movements and attentional processes will be developed more fully in a later section on the 'neglect syndrome' resulting from parietal lesions in humans.

The reciprocal connections supplying input for the posterior parietal lobe include: the frontal eye fields (Kunzle and Akert, 1977; Stanton, Cruce, Goldberg and Robinson, 1977 a, 1977 b), other areas of the frontal lobes (Jones and Powell, 1970; Mesulam, Van Hoesen, Pandya and Geschwind, 1977; Geschwind, 1977; Pandya and Kuypers, 1969), pretraite cortex (Divac, LaVail, Rakic and Winston, 1977; Kuypers, Szwarchart, Miskin and Rosvold, 1965; Pandya and Seltzer, 1980), the preoccipital gyrus to the lower bank of the intraparietal sulcus (Pandya and Seltzer, 1980), the temporal lobes (Jones and Powell, 1970; Mesulam, et al., 1977; Seltzer and Pandya, 1976, 1978), limbic areas including the substantia innominata, claustrum and cingulate gyrus; Mesulam, et al., 1977; Stanton, et al., 1977 a, 1977 b; Pandya, et al., 1979) and primary

somatosensory cortex of the postcentral gyrus via the medial surface of the superior parietal lobule and the adjacent lower anterior bank of the intraparietal sulcus (Pandya and Seltzer, 1980). The posterior parietal lobe also receives afferents from the medial and oral pulvinar and the lateral posterior nucleus of the thalamus (Bailey and Mauguier, 1977; Benevento and Rezak, 1976; Divac, et al., 1977; Kasdon and Jacobsen, 1978; Mesulam, et al., 1977; Stanton, et al., 1977 a, 1977 b).

Efferent pathways from the posterior parietal lobe include the frontal eye fields and the deep layers of the superior colliculus (Kuypers and Lawrence, 1967), the premotor cortex (Petras, 1971), prefrontal areas involved with integration of complicated behaviors such as delayed response (Chavis and Pandya, 1976), and the subcortical basis pontis (Glickstein, Cohen, Dixon, Gibson, Hollins, Labossiere and Robinson, 1980).

Lynch (1980) has cited a large body of literature (which will not be cited fully here) which demonstrates a rich diversity of afferent and efferent connections with the posterior parietal lobe, to and from many cortical, thalamic, and other subcortical regions. The cortical connections include the already mentioned primary somatosensory cortex, lateral prefrontal cortex, the depths of the superior temporal gyrus, prestriate visual cortex, motor and premotor cortex, the cingulate gyrus and the parahippocampal gyrus. The thalamic connections involve the nucleus lateralis dorsalis, lateralis

posterior, pulvinar ventralis anterior, medialis dorsalis, anterior-midline and intralaminar nuclei, the posterior group, the zona incerta and Fields H2 and H of Forel. Other subcortical connections involve the caudate nucleus, the dorsal two thirds of the putamen, the superior colliculus, pontine nuclei, claustrum, raphe nuclei, locus coeruleus and the pyramidal tract. The numerous references establishing these pathways are provided by Lynch, (1980).

Mesulam (1980) suggested that these heterogeneous connections may be classified as sensory association, limbic, reticular and motor pathways. He hypothesized that the ability of neurons in the posterior parietal lobe to attribute motivational significance to sensory stimuli is a result of the convergence of limbic and sensory inputs. The reticular input acts to regulate regional levels of cortical arousal and the motor output subserves exploratory and orienting activities for scanning the environment. Mesulam (1980) relates the anatomical connections of the posterior parietal lobe to three distinct cortical processes related to attention. First, afferent integration of input from polymodal association cortex provides area PG with the ability to construct an elaborate neural representation of sensory space and the major function of this area is the regulation of attention in extrapersonal space. Second, the limbic integration of inputs from the cingulate gyrus and basal forebrain enables PG to maintain a neural

representation of motivational space constructed according to past experience and present needs. The third process is efferent integration relating the sensory/motivational attention processes to initiation or inhibition of motor acts involved in exploratory or attentive behavior, via the PEF, motor and pre-motor cortex, and pretectal regions. The reticular input from the locus coeruleus, reticular formation, raphe nuclei, and intralaminar thalamic nuclei, which are all implicated in cortical activation, the recruiting response and sleep, may modulate posterior parietal activity according to general level of arousal, perhaps thus providing a neural anatomical explanation of the close link between arousal and the effectiveness of attention. This involvement of a single area, the posterior parietal lobe, in the control of eye movements, the orientation of attention, and involvement in processes of cortical arousal and activation provides the empirical basis of a general neurophysiological model relating conjugate lateral eye movements to hemispheric activation and arousal and orienting and attentional processes. This same functional convergence of oculomotor control, attention and orienting mechanisms, and cerebral activation and arousal processes will be seen for several of the subcortical regions also implicated in eye movement control.

Superior Colliculus

Another area concerned with eye and head movements involved in orienting behaviors is the superior colliculus (Gordon, 1975). Electrical stimulation of the superior colliculus, or tectum, causes conjugate deviation of the eyes to the contralateral side, with some vertical component present in the movement (Ferrier, 1886; Apter, 1946; Hyde and Eliasson, 1957; Monnier, 1946; Hess, Burgi and Bucher, 1946). Contraversive turning of not only the eyes but also the head and forequarters is observed after stimulation of the middle and deep layers of the superior colliculus and the dorsal part of the central gray (Hess, Burgi and Bucher, 1957; Monnier, 1946; Skultety, 1962; Harris, 1980). Other investigators have reported that stimulation of either the FEF or the superior colliculus elicits contralateral saccades whose sizes and directions depend on the specific site of electrical stimulation (Robinson, 1972; Robinson and Fuchs, 1969; Schiller and Stryker, 1972). Bilateral ablation of either the FEF or the superior colliculus alone produces only transient and subtle disturbances of oculomotor function (Latto and Cowey, 1971; Anderson and Symmes, 1969; Keating, 1974; Pasik, Pasik and Bender, 1966; Kurtz and Butter, 1976; Wurtz and Goldberg, 1972; MacKinnon, Gross and Bender, 1976). Ablation of both areas result in permanent and severe oculomotor control deficits (see FEF section for references).

Crosby and Henderson (1948) argued that the superior colliculus is a neural center for complex sensorimotor integration, particularly related to visually guided behavior.

Unilateral lesions in the superior colliculus of cats and monkeys produces contralateral neglect and a motor deficit (Sgobbo, 1900; Sprague, Chambers and Stellar, 1961; Denny and Brown, 1962; Meikle and Sprague, 1962; Sprague, Levitt, Robson, Liu, Stellar and Chambers, 1963; Sprague and Meikle, 1965; Sprague, Berlucchi and Berardino, 1970). The homonymous contralateral field defect with neglect of visual stimuli is seen particularly in extinction of the contralateral response when rival stimuli are simultaneously presented, suggesting that the visual deficit in attention-perception seen after collicular lesions involves a 'perceptual rivalry' process (Bender and Furlow, 1945; Denny-Brown, Meyer and Horenstein, 1952). Lesions of the brachium of the superior colliculus and parts of the tectothalamic system give rise to the visual neglect symptoms without the motor deficit. The motor deficit involves an absence of orienting movements to the side contralateral to the lesion and forced ipsiversive circling and a heightened compulsive ipsiversive turning of eyes, head, and body to orient to ipsilateral stimuli. Lesions of the tectospinal tract can induce the motor deficit without visual neglect. Closely associated with the motor and visual attention deficits are abnormal responses to acoustic, tactile, and sometimes nociceptive

stimuli appearing as inappropriate localization of stimuli rather than as changes in sensory threshold." (Sprague and Meikle, 1965). Sprague and Meikle (1965) concluded on the basis of their collicular lesion studies, that:

"the functions of the superior colliculus include that of visual attention and perception as well as classically accepted control of the movements of head and eyes" (i.e., visually guided behavior)

Single unit recording in the upper layers of the monkey superior colliculus has revealed the presence there of cells that respond selectively to visual stimuli. In the deeper layers more cells are found that discharge before saccadic eye movements, and selectivity for the spatial location of visual stimuli and for the amplitude and direction of saccades is arranged topographically (Schiller and Koerner, 1971; Sparks, Holland and Guthrie, 1976; Wurtz and Goldberg, 1972). The first demonstration of presaccadic enhancement of visual responses was found in cells of the superior colliculus (Goldberg and Wurtz, 1972 a, 1972 b). The cells which show presaccadic enhancement do not give an enhanced response in a task requiring the animal to respond to a peripheral stimulus without making an eye movement to it (Wurtz and Mohler, 1976 b). Thus, like the presaccadic enhancement seen in PEP cells, and in contrast to that observed in parietal, pre-striate, and striate cells, the enhancement of responses to visual stimuli seen before saccades in the superior colliculus is a specific oculomotor enhancement occurring only

before eye-movements.

Another single-unit recording study of the superior colliculus in cats showed that with the eyes straight ahead, visual and auditory receptive fields in the colliculus are well aligned and usually of about the same horizontal extent. When a saccade is initiated the eyes start near the center of the orbit so that the coordinates of visual and auditory space are aligned and complex neural compensation of auditory and visual inputs does not occur (Harris, Blackmore and Donaghy, 1980). The investigators reporting this study concluded that the cat's superior colliculus may be

"responsible for functional integration of visual and auditory space, triggering orienting movements towards peripheral objects whether identified by their visual appearance or by the noise they make." (Harris, Blackmore and Donaghy, 1980)

Afferent projections to the superior colliculus involve spinotectal, retinotectal and corticotectal (Sprague, 1963), as well as reticulotectal (Anderson and Berry, 1959; Nauta and Kuypers, 1958), and inferior colliculus-superior colliculus pathways (Moore and Goldberg, 1963). The efferent pathways of the superior colliculus include very important ascending tectothalamic paths (Burger and Bucher, 1960; Altman and Carpenter, 1961; Pearce, 1958). Some of the tectothalamic fibers terminate in the pretectum, which receives direct retinal input, implicated in visually guided behavior (Thompson, Lesse and Rich, 1963; Thompson and Rich, 1963). The pretectum also

receives afferent corticofugal fibers from the striate cortex) Other tectothalamic fibers terminate in the pulvinar and lateral posterior and dorsomedial nuclei, which all receive projections from the lateral geniculate (Altman, 1962) and project to the suprasylvian gyrus (Akimoto, Negishi and Yamada, 1956; Walker and Barris, 1937). This thalamocortical system receiving tectal inputs is responsible for mediating photoically driven activity in the suprasylvian gyrus. The superior colliculus also projects fibers to the subthalamus (zona incerta and H1), where lesions induce transient contralateral visual neglect and deficits in visual discrimination. Other thalamic areas receiving projections from the superior colliculus are the caudal part of the thalamus, the lateral geniculate and pars ventralis, the center median-parafascicular nuclei, which are involved in cortical activation and arousal, the suprageniculate and thalamic reticular nuclei. Sprague and Meikle (1965) report that fiber stains of the midbrain after colliculotomy show marked loss of fibers in the underlying tegmentum. The subcollicular tegmentum has been implicated in visual fuction (Hernandez-Peon, Guzman-Flores, Alcaraz and Fernandez-Guardiola, 1957; Hotta and Kameda, 1964; Ogawa, 1963; Pearce, 1960; Suzuki and Tiara, 1961), and in visually guided behavior (Porter and McKrioch, 1962; Sprague, et al., 1961, 1963). A large afferent tract from the superior colliculus to the midbrain reticular formation has also been demononstrated (Altman and Carpenter, 1961; Pearce,

1958; Rasmussen, 19). These anatomical studies demonstrate that the superior colliculus, is richly interconnected with areas involved in cerebral activation and arousal, as well as being itself involved in attention and orienting behaviors, particularly eye and head movements.

Probably the most important efferent pathways mediating the effect of the superior colliculus on eye movements are those terminating in the pontine reticular formation. Pathways from the superior colliculus have been demonstrated with fibers ending in the dorsolateral pontine nucleus (Graham, 1977; Harting, 1977; Hashikawa and Kawamura, 1977; Hokombe and Hall, 1979; Kawamura and Brodal, 1973; Mower, Gibson and Glickstein, 1979), the nucleus reticularis tegmenti pontis (Graham, 1977; Harting, 1977; Kawamura, Brodal and Hoddevik, 1974), the paramedian and lateral reticular nuclei (Kawamura, et al., 1974), and the inferior olive (Frankfurter, Weber, Royce, Strominger and Harting, 1976; Graham, 1977; Harting, 1977, Weber and Harting, 1978; Weber, Partlow and Harting, 1978).

Cerebellum

Stimulation of the cerebellar hemispheres evoked conjugate movements of the eyes (Cohen, Goto, Shanzer and Weiss, 1965; Ron and Robinson, 1973). Total cerebellectomy in monkeys created enduring deficits in optokinetic nystagmus, SPEN, and the

holding of eccentric gaze positions (Westheimer and Blair, 1973; 1974; Burde, Stroud, Roper-Hall, Wirth and O'Leary, 1975). The same oculomotor disturbances in OKN, SPEM and eccentric gaze are seen in human patients with cerebellar disease or lesions (Avanzini, Girotti, Crenna Negri, 1979; Baloh, Konrad and Honrubia, 1975; Estanol, Romero and Corvera, 1979; Larmande, Delplace and Autret, 1980; Nemet and Ron, 1977; Zee, 1981; Zee, Yee, Cogan, Robinson and Engel, 1976; Selhorst, Stark, Ochs and Hoyt, 1976). Ablation of the cerebellar flocculus interferes with the brain's ability to make long and short term adjustment of vestibulo-ocular reflex to distortions of visual input induced by prisms and magnifying lenses (Ito, Shiida, Yagi, and Yamamoto, 1974; Optican, Zee, Miles and Lisberger, 1980; Robinson, 1976; Takemori and Cohen, 1974). Ablation of the flocculi and paraflocculi in monkeys produced disruptions of nystagmus, SPEM and saccades (Zee, Yamazaki, Butler and Gucer, 1981). These lesions produced disruptions of the vestibulo-ocular reflex, impairment of the visual suppression of inappropriate vestibular nystagmus, persistent postoperative OKN, with a 50% decrease in slow phase velocity and a doubling of rise time to steady state response to constant velocity stimuli, impaired response to high velocity OKN stimuli, and horizontal gaze-paretic nystagmus (inability to hold eccentric gaze) with exponentially decaying centripetal drift. Saccadic velocity and accuracy was normal but there was brief, approximately

exponential postsaccadic drift with amplitudes up to 15% of the size of the saccade. This postsaccadic drift in flocculectomized monkeys may reflect a mismatch between phasic (pulse) and tonic (step) innervational changes, creating saccades. In addition, flocculectomized monkeys showed impaired smooth tracking of small moving targets with the head still (SPEM) or moving (cancellation of VOR by fixation of a target rotating with the head). Zee, et al. (1981) concluded from these findings that,

"the flocculus and possibly paraflocculus participate in the control of oculomotor reflexes that insure the best visual acuity by preventing retinal slip. The flocculus serves both the specific needs of the fovea (pursuit saccades and gaze holding) as well as the phylogenetically older requisite stabilization of images on the retina during head rotation (VOR and OKN)."

Furthermore, lesions in the dorsal cerebellar vermis and underlying fastigial nuclei produce saccadic dysmetria (Optican and Robinson, 1980; Ritchie, 1976).

Single unit recording in the cerebellum has revealed that purkinje cells in the flocculus discharge in relation to saccadic and smooth pursuit eye movements as well as position of the eye during visual fixation (Lisberger and Fuchs, 1978; Miles, Fuller, Braitman and Dow, 1980; Noda and Suzuki, 1979 a, 1979 b). Lisberger and Fuchs, (1978) suggested that the flocculus purkinje cells may provide a positive feedback signal encoding gaze velocity that increases the gain of and sustains SPEN.

The cerebellum receives important projections from the superior colliculus via the pontine nuclei. Single unit recording in the granule cell layer of the cerebellum revealed cerebellar responses to superior colliculus stimulation (Kassel, 1980). The short latency of the response (2.2-2.5 msec. for the early potential and 2.5-3.5 msec. for the multiple unit response) indicates that there is only one synapse in the pathway, and this is probably in the dorsolateral pontine gray. Since the SC evoked responses were recorded in the GC layer, they are most likely relayed by mossy fibers.

The cerebellum receives projections from several pontine areas receiving inputs from the superior colliculus. The dorsolateral pontine nucleus projects to the contralateral cerebellar hemisphere (Brodal, 1979; Brune, Eriksson, Saint-Cyr and Woodward, 1978; Hodderick and Walberg, 1979). The cerebellar vermis receives a heavy projection from the nucleus reticularis tegmenti pontis (Brodal, 1980; Hodderik, 1978). The paramedian and lateral reticular nuclei project to the cerebellar hemispheres (Brodal, 1957; Brodak and Torvik, 1954; Dietrichs and Walberg, 1979; Martin, Andrezik, Crutcher, Linauts and Panneton, 1977; Somana and Walberg, 1978). The superior colliculus-pontine-cerebellar projections are relayed by mossy fibers terminating in the cerebellar hemispheres and the vermis (Brodal, 1954; Brodal and Hodderik, 1978; Brodal and Torvik, 1954; Eisenman and Noback, 1980; other studies cited above).

Projections relayed by climbing fibers have been found only for the posterior vermis (Frankfurter, Weber and Harting, 1977; Weber and Harting, 1978; Weber, Partlow and Harting, 1978).

Other afferent connections to the cerebellar flocculus, in addition to those cited from the pontine reticular formation (dorsolateral pontine nuclei, nucleus reticularis tegmenti pontis, and paramedian and lateral reticular nuclei), include projections from the inferior olive, vestibular nuclei, the perihypoglossal complex, the abducens nucleus, and the accessory optic system (Langer, Fuchs, Chubb and Scudder, 1980; Winfield, Hendrickson and Kim, 1978). These structures may relay information to the cerebellum about target motion (Glickstein, et al., 1980; Hodderik, 1978; Kellar and Crandall, 1980; Miyashita, Ito Jasteboff, Maekawa and Nagao, 1980) and about eye and head motion (Kellar and Crandall, 1980; Lopez-Barnes, Darlot and Berthoz, 1979; Nakao, Curthoys and Markham, 1980; Waespe, Buttner and Henn, 1981). A convergence of information about target movement and eye and head movement is necessary for accurate SPEM.

The afferent connections by which the flocculus affects eye movements are the dentate nucleus and more especially the perihypoglossal complex and vestibular nuclei. The perihypoglossal nuclei are reciprocally connected to the cerebellum as well as to other oculomotor structures (McCrea, Baker and Delgado-Garcia, 1979), and probably mediate the

flocculus' effect on brain stem neural integrators controlling eye movements. Gaze paretic nystagmus is induced by perihypoglossal lesions (Vemura and Cohen, 1973) and single unit recording has demonstrated the presence of neurons there that discharge in relation to eye position (Lopez-Barnes, et al., 1979). The gaze paretic nystagmus is also produced by lesions of the medullary reticular formation adjacent to the perihypoglossal complex (Vemura and Cohen, 1973).

Paramedian Pontine Reticular Formation

The paramedian pontine reticular formation is generally considered to be the final supranuclear neural integrator responsible for generating all lateral eye movements. Signals arising from the PPRF drive motoneurons in the abducens and oculomotor nuclei, producing ipsilateral saccades, the quick and slow phases of vestibular nystagmus, and ipsilateral smooth pursuit eye movements (Henriksen and Nilsson, 1975; Luschei and Fuchs, 1972; Ron, Robinson and Skavensk, 1972; Robinson, 1975). Electrical stimulation of the PPRF induces all kinds of slow and fast ipsilateral eye movements, and stereotaxic lesions in the PPRF cause ipsilateral gaze palsies, abolishing all horizontal eye movements toward the side of the lesions (Teng, Shanzer and Bender, 1956; Bender and Shanzer, 1964; Cohen, Komatsuzaki, Bender and Cohen, 1971; Cohen and Komatsuzaki, 1972; Luschei and

Fuchs, 1972). In human patients with neurological lesions of the pontine reticular formation, disorders of nystagmus, saccades, SPEM, and visual fixation are observed (Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979; Pierrot-Deseilligny, Chain, Serdau, Gray and Lhermitte, 1981).

Single unit recording from the ocular motoneurons in the abducens and oculomotor complex in cats and monkeys showed that they discharge in a 'pulse-step' firing pattern in association with rapid changes of eye position. The burst or pulse of high frequency activity drives the eye muscles at high velocity, producing a saccade, while the 'step' of maintained firing rate holds the eye at the new position (Fuchs and Luschei, 1970; 1971; Graybiel, 1977; Manni, Casey and Dow, 1965; Matsunami, 1972; Robinson, 1970; Schiller, 1970). Since lesions of the PPRF produce gaze paresis, the burst activity producing horizontal saccades probably originates in the medial pontine reticular formation (Goebel, 1971).

Single unit recording in the PPRF has revealed several classes of neurons related to eye movements (Henn and Cohen, 1976; Kellar, 1974; Luschei and Fuchs, 1972). These neurons may be grouped into two major types: phasic cells or 'burst neurons' that are active during saccades (voluntary saccades and quick phases of nystagmus--i.e., all rapid eye movements), and tonic cells that are active during fixation and SPEM, as well as during the slow phases of nystagmus (Sparks and Travis, 1971;

Luschei and Fuchs, 1972; Kellar, 1973; Kubo, Matsunaga and Hayashi, 1978). The burst neurons show a firing pattern similar to what would be expected of neurons producing the pattern of activity seen in the ocular motoneurons, and they discharge just before the motoneurons (Luschei and Fuchs, 1972). Quantitative analyses of the firing patterns of PPRF burst neurons indicate that they might be responsible for generating saccadic eye movements (Buttner, Buttner-Ennever and Henn, 1977; Buttner, Hepp and Henn, 1977; Henn and Cohen, 1976; King and Fuchs, 1979). Several electrophysiological studies have demonstrated that the PPRF burst neurons do in fact drive the ocular motoneurons (Highstein, Maekawa, Steinacker and Cohen, 1976; Hikosaka and Kawakami, 1976, 1977; Hikosaka, Igusa, Nakao and Shimazu, 1978; Hikosaka, Maeda, Nakao, Shimazu and Shinoda, 1977; Horcholle-Bossavit and Tyc-Dumont, 1969; Igusa, Sasaki and Shimazu, 1980; Kaneko, Evinger and Fuchs, 1977; Kaneko, Steinacker, Cohen, Maciewicz and Highstein, 1975; Van Gisbergen, Robinson and Gielen, 1981). The burst neurons are located rostral and ventral to the abducens nucleus in the nucleus reticularis tegmenti pontis, the nucleus reticularis pontis caudalis and the nucleus reticularis pontis oralis. They discharge with a high frequency burst just prior to and during saccades and quick phases of OKN, but not during SPEN. All horizontal burst neurons had an ipsilateral on direction, but some also discharged less vigorously for saccades in other

directions. The size of the saccade and the number of action potentials produced were correlated. These findings suggest that the PPRF burst neurons are direct excitatory premotor neurons responsible for generating saccadic eye movements (Kaneko, Evinger and Fuchs, 1981).

Electrical stimulation of the PPRF produces monosynaptic excitatory post-synaptic potentials (EPSP's) in the motoneurons of the ipsilateral abducens nucleus (Grantyn and Grantyn, 1976; Highstein, et al., 1976). There are also burst neurons caudal to the abducens that inhibit the motoneurons of the contralateral abducens (Hikosaka and Kawakami, 1976, 1977; Hikosaka, et al., 1977, 1978). These inhibitory burst neurons are activated by electrical stimulation of the superior colliculus (Hikosaka and Kawakami, 1977). Stimulation of the superior colliculus also evoked activity in the excitatory burst neurons (Grantyn and Grantyn, 1976). Henn and Cohen (1976) presented evidence that there are three types of burst neurons: One related to direction and two related to amplitude.

Single unit activity has been found in the region inferior to the abducens in which the instantaneous impulse rate (IR) increases dramatically during ipsilateral smooth pursuit eye movements, and decreases to nil during SPEM in the contralateral direction. SPEM velocity was highly positively correlated with IR in these neurons (Eckmiller and Mackeben, 1980). Electrical stimulation of the same area can elicit SPEM (Cohen and

Komatsuzaki, 1972). These electrophysiological studies demonstrate the importance of the PPRF as the final premotor neural integrating mechanism responsible for generating SPEM and saccadic eye movements, as well as the fast and slow phases of nystagmus.

The paramedial pontine reticular formation receives afferents from the frontal eye fields, posterior parietal cortex, superior colliculus, and cerebellum have already been described. Other afferents from thalamic nuclei and mesencephalic tegmentum, areas which like the above are also involved in eye movement control, attention, orienting, and cortical activation and arousal, have been described by Carpenter (1976). Nearly all the cortical and subcortical areas where eye movement related neurons have been found have efferent projections to the pontine reticular formation.

The efferent projections through which the pontine reticular formation affects eye movements include important excitatory connections to the ipsilateral abducens nucleus (Buttner-Ennever and Henn, 1976; Highstein, Maekawa, Steinacker and Cohen, 1976) which seem to involve a relay close to the abducens nucleus itself (Maciewicz, Eagen, Kameko and Highstein, 1977; Gacek, 1979; Igusa, Sasaki and Shimazu, 1980). There is also evidence for an inhibitory pathway from the pontine reticular formation running through the gigantocellular tegmental field, caudal and close to the ipsilateral abducens,

and terminating in the contralateral abducens (Hikosaka and Kawakami, 1976, 1977; Graybiel, 1977; Maciewicz, et al., 1977; Gacek, 1979). This pathway has been found to be important in the generation of saccadic eye movements (Hikosaka and Kawakami, 1977; Hikosaka, et. al., 1980; Yoshida, McCrea, Berthoz and Vidal, 1980). The PPRF is also the primary relay for SPEM (Cohen, et al., 1968; Goebel, et al., 1971; Cohen and Komatsuzaki, 1972; Keller, 1974; Kubo, et al., 1978; Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979; Eckmiller and Mackeben, 1980). Pierrot-Deseilligny, et al. (1979) showed that the occipito-parieto pontine pathway involved in horizontal SPEM and terminating in the PPRF decussates at least once in the lower brain stem. These authors present clinical evidence in support of this showing that a unilateral lesion in the pontine reticular formation abolishes both ipsilateral smooth pursuit by damage of this area, and contralateral smooth pursuit by damage of the adjoining occipito-parieto-pontine pathway above its lower decussation. Pierrot-Deseilligny, Chain, Serdaru, Gray and Lhermitte (1981) presented further cases in support of this hypothesis, as well as further clinical evidence that horizontal SPEM may be controlled in a manner analogous to saccades by the pontine reticular formation. The excitatory pathway from the PRF projects to the ipsilateral abducens nucleus and an inhibitory pathway projects contralaterally to the other abducens nucleus

(via a relay near the ipsilateral abducens).

Three type of afferent input contribute to the production of optokinetic nystagmus and other oculocephalic reflexes: visual input related to fixation, proprioceptive input from muscular and and vertebral structures of the neck related to head movement and position, and vestibular input related to acceleration and movements of the head. Not only the vestibular, but also the visual and proprioceptive inputs involved pass through the vestibular nuclei (Frederickson, Schwarz and Kornhuber, 1965), although the vestibular input is functionally the most important of the three (Takemori and Duzuki, 1971; Dichgans, Bizzi, Morasso and Tagliasco, 1974). There is experimental evidence that the vestibular nuclei may be an integral part of neural mechanisms generating the slow phase of optokinetic nystagmus (Henn, Young and Finley, 1974; Azzena, Azzena and Marini, 1974; Waespe and Henn, 1977, 1979; Robinson, 1977; Raphan and Cohen, 1978). The vestibular nuclei project excitatory fibers to the oculomotor nuclei controlling contralateral movements as well as inhibitory fibers to the oculomotor nuclei controlling ipsilateral eye movements (Carpenter, 1971; Cohen, 1971; Precht, 1977). There are three distinct pathways, evidence for which has been described by Pierrot-Deseilligny, et al. (1981).

The abducens and oculomotor nuclei contain the motoneurons innervating the eye muscles. The abducens contains the

motoneurons of the lateral rectus muscle as well as excitatory internuclear neurons that decussate at the level of the nucleus and ascend in the contralateral medial longitudinal fasciculus (MLF) to terminate in the medial rectus area of the oculomotor nucleus (Graybiel and Hartweg, 1974; Baker and Highstein, 1975; Buttner-Ennever and Henn, 1976; Graybiel, 1977; Delgado-Garcia, Baker and Highstein, 1977; Highstein and Baker, 1978; Steiger and Buttner-Ennever, 1978, 1979; Bienfang, 1975; Carpenter and Batton, 1980). Lesions of the abducens produce an ipsilateral gaze palsy for all lateral eye movements (Carpenter, McMasters and Hanna, 1963). The necessity of the abducens-oculomotor pathway through the MLF has been demonstrated by studies showing gaze palsies following lesions of the MLF (Schiller, 1924; Bender and Weinstein, 1944; Cogan, Kubik and Smith, 1950; Carpenter and McMasters, 1963; Harrington, Hollenhorst and Sayre, 1966; Cambier, Masson, Lechevalier, 1972; Evinger, Fuchs and Baker, 1977). Axons of excitatory internuclear neurons mediating burst and tonic signals involved in all slow and fast conjugate lateral eye movements have been found in the MLF (King, Lisberger and Fuchs, 1976; Pola and Robinson, 1978).

The oculomotor complex contains the motoneurons supplying all of the ocular muscles (Carpenter, 1976). The lateral dorsal cell column or nucleus innervates the inferior rectus, the intermediate cell column innervates the inferior oblique muscle, and the ventral cell column innervates the medial rectus. A

medial cell column projects crossed fibers innervating the superior rectus muscle. The central caudal nucleus supplies fibers, both crossed and uncrossed, to the levator palpebrae muscle. Other areas of the oculomotor complex, such as the Edinger-Westphal nucleus, are involved in control of the ciliary body modulating accommodation of the lens, as well as the iris sphincter muscle controlling pupillary responses.

The Hemispheres and Eye Movement Control

Thus far evidence has been reviewed demonstrating that eye movements of all types, fast and slow, are controlled by a diffuse circuit including the frontal eye fields, the posterior parietal cortex, striate and prestriate visual cortex, various thalamic nuclei including the pulvinar and dorsomedial nucleus, the superior colliculus and the subcollicular tegmentum, the mesencephalic reticular formation, the cerebellum, the pontine reticular formation, and the vestibular, abducens and oculomotor nuclei. At subcortical levels there is a convergence of mechanisms controlling saccadic, SPEM and nystagmus eye movements. At the cortical level there is a differentiation of SPEM and saccadic systems along the anterior-posterior axis, with saccades represented frontally and SPEM represented in the parietal-occipital areas (Bach-y-Rita, 1971; Hoyt and Frisen, 1975; Raphan and Cohen, 1978). There may also be interactions

between eye movement systems involving differentiation along the left-right lateral dimension. At the brainstem pontine level excitatory mechanisms for both saccades and SPEM are ipsilaterally organized (i.e., neurons on the left side generate eye movements toward the left visual field.) There is evidence that at the cortical level the two systems diverge laterally, with saccades being organized contralaterally while SPEM is organized ipsilaterally. Studies of eye movements in hemispheric lesion patients, and lateral asymmetries in saccadic, OKN, and SPEM systems may reveal an involvement of lateralization processes in oculomotor control, orienting and attention processes.

The relationship between laterality processes and eye movements may be further elucidated by examining more closely the effect of hemispherectomy on eye movements. Sharpe, Lo, and Rabinovitch (1979) studied five patients with hemidecortication and found slower saccades in both directions, especially saccades to the side contralateral to the lesion. They also found subnormal pursuit velocities during pursuit tracking, especially tracking toward the lesioned side. Daroff and Hoyt (1971) noted directional impairment of SPEM after hemispherectomy, in the form of saccadic tracking to the lesioned side. The ipsilateral SPEM disorder after hemispherectomy is persistent (Gassel & Williams, 1963; Troost, et al, 1972a, 1972b). Sharpe, Lo, and Rabinovitch (1979) also

reported abnormally high SPEM velocity when tracking toward the side of the hemianopia, i.e., away from the lesion. Compensatory saccades were unidirectional, toward the lesioned side. Daroff and Hoyt's (1971) observation of disordered ipsilateral pursuit after unilateral posterior hemispheric damage seems to imply ipsilateral control of smooth pursuit movements. But the discovery of neurons in both occipital lobes which are responsive to the velocity of retinal stimuli in either direction (Dow, 1974), and equal numbers of parietal neurons active during ipsilateral and contralateral pursuit (Lynch, et al, 1977) indicates that each hemisphere receives the retinal information needed for pursuit in both directions. Sharpe and his colleagues propose that

"either unilateral involvement of the occipito-parietal prestriate cortex or intrahemispheric disconnection of the extrastriate cortex from visual input from both hemifields are pathological correlates of such pursuit asymmetry".

Estanol, et al (1980) examined a patient with a left hemispherectomy and found an inability of the patient to hold left eccentric gaze, resulting in gaze evoked nystagmus to that side. There was defective SPEM to the left, inaccurate saccades to the right with overshooting of more than 90%, and decreased gain of the visuo-vestibular-ocular reflexes when rotating in either direction, though more so during rotation to the right. The contralateral defect in saccadic movements and ipsilateral defect in smooth pursuit after unilateral cortical lesions may

indicate that these complementary eye movement systems are represented asymmetrically at the cortical level. Effective horizontal pursuit movements may involve the inhibition of saccadic movements (Heywood & Churcher, 1971). A disorder of interhemispheric communication leading to a release of the normal reciprocal inhibition of the hemispheres may lead to a failure of pursuit systems in one hemisphere to inhibit saccadic systems in the other. Thus, abnormalities of lateralization and SPEN may be neurophysiologically related, with a failure of interhemispheric communication leading to saccadic intervention during smooth pursuit movements of the eyes. If patients with schizophrenia and individuals at risk for the disorder have some form of left hemisphere dysfunction one might expect asymmetries in the abnormalities of SPEN and saccadic eye movements. Specifically, these individuals should show more irregularity of smooth pursuit eye movements to the left than to the right, since SPEN is ipsilaterally controlled. Conversely, these individuals would be expected to have inaccurate or slow saccades to the right. The hypothesis that saccades are contralaterally controlled is supported by the finding that electrical stimulation of the frontal eye fields in monkeys evoked contralateral saccadic eye movements (Robinson & Fuchs, 1969).

Lateral asymmetries in the saccadic system have been described by several investigators. Normal subjects have been

found to have shorter oculomotor reaction times for rightward saccades than for leftward saccades (Rayner, 1978; Pirozzolo, 1979). Pirozzolo and Rayner (1980) found this to be so in righthanded subjects but not in left handers. Some lefthanded subjects showed shorter latencies for saccades to the left, some shorter latencies for saccades to the right, and some showed no asymmetry at all. All of the dextrals, however, had shorter latencies for stimuli presented to the right of fixation, while the sinistrals as a group showed no asymmetry. Iacono and Lykken (1979a) found no difference in mean latencies of saccadic eye movements to the right and left when subjects tracked square wave targets, but these authors did not take report the subjects' handedness.

Krauklis and Janson (1980) found a relationship between eye movement reaction time and EEG alpha asymmetry. In one group of subjects (n=24) eye movement latencies were shorter to the right than to the left. In the other group (n=6) the reaction time was shorter for leftward movements. The asymmetry in eye movement reaction time was diminished in both groups after intense mental exertion. Before the exertion task the first group (faster rightward RT) had higher EEG alpha amplitude in right hemisphere leads, while the second group (faster leftward RT) had higher alpha amplitude in left hemisphere leads. As the alpha rhythm purportedly indicates the level of activation in the cortical hemispheres (higher alpha amplitude indicating lower activation

or less information processing), the group with shorter leftward saccadic latencies had more activated right hemispheres and those with shorter rightward latencies had more activated left hemispheres. These findings suggest the intriguing possibility that 'hemisphericity' may be reflected in asymmetries of saccadic reaction time. If this is so one might expect saccadic latency asymmetry to correlate with CLEM.

Another indication of asymmetry in the saccadic system in normal subjects is provided by a study of saccadic velocity and conjugation of gaze recorded when the head of the subject is turned voluntarily to the left or right. Gresey (1977) reported that 20% to 30% of healthy subjects tested showed derangements of ocular motility when their head was turned to the left or the right, and these 'latent' disorders of eye movement were interpreted as subclinical evidence of pathological lesions of the nervous system, since the disorders would occur when the head was turned to one side but not when the head was turned in the opposite direction. Unfortunately, Gresey (1977) did not report any data on the direction of head turning producing abnormalities and its relationship to the subjects' handedness. It is possible that these asymmetric ocular disturbances in 'normals' are an indication of a neurointegrative defect involving lateralized dysfunctions of ocular control which are perhaps related to both 'risk' and hemisphericity.

Recent studies by Rosenberg (1980, 1981) have revealed task related asymmetries of optokinetic nystagmus, elicited by having subjects watch a projection of vertical stripes moving in a lateral direction (partial field OKN). Across subjects and tasks there were no differences in frequency of OKN when stripes moved from right to left and from left to right, but there was a significant task main effect resulting from higher OKN frequency during the verbal-analytic tasks than the visual-spatial activities. Interestingly, the highest OKN frequency during verbal-analytic activities occurred when the stripes were moving from left to right, while the highest OKN frequency during the visuo-spatial activities was seen when the stripes moved toward the left (Rosenberg, 1980). The observation that OKN frequency was higher when the stripes were moving in the direction contralateral to the involved hemisphere is interesting in light of the hypothesis that partial field OKN consists of alternating SPEM (slow phase in the direction of stripe movements) and saccades (fast phase in the direction opposite to stripe movements). Since SPEM, or OKN slow phases, are ipsilaterally mediated, these results seem to suggest an interference between cognitively evoked hemispheric activation and OKN slow phases mediated by the same hemisphere. In other words, when a hemisphere was cognitively activated the OKN slow phases directed ipsilaterally and regulated by the same hemisphere were depressed, while OKN slow phases directed contralaterally and

controlled by the noninvolved hemisphere were enhanced. These results bear a resemblance to those of Kinsbourne and Cook (1971) who demonstrated interference between verbalization, a left hemisphere process, and right hand dowel balancing, also a left hemisphere process. It seems that each hemisphere has a limited capacity and it is difficult for such a limited capacity processor to handle more than one complex processing task at a time. Thus, OKN slow phases controlled by the right hemisphere (stripes moving rightward) are interfered with by visual-spatial (right hemisphere) activities, and left hemisphere mediated OKN slow phases (stripes moving leftward) are interfered with by verbal-analytic (left hemisphere) activities. When simple effects were examined it was found that the effect of type of mental activity was highly significant when the stripes were moving toward the right, while the mental activity effect was not significant during leftward stripe motion, suggesting an asymmetric representation of basic OKN mechanisms.

Rosenberg (1980) invoked the processing interference-inhibition argument to explain the main effect (across both directions) of a lower frequency of OKN for visuo-spatial activities than for verbal analytic activities, suggesting that OKN in either direction is more associated with right hemisphere processing than left. The finding of lower OKN frequency for both visuo-spatial activities and combination (visuo-spatial and verbal analytic components) activities than

for verbal-analytic activities confirms that there is a negative relationship between the frequency of OKN and the total amount of imagery, a right hemisphere function, involved in internal processing. A similar finding was also reported by Singer, Greenberg and Antrobus (1971), who found lower OKN frequency during daydreaming than a mind blank condition. Rosenberg (1980) further found that the OKN frequency during a song task was lower than for a lyrics task, suggesting that the interference between OKN and cognitive activity is not restricted to activities involving visual imagery, there is a general negative relationship between OKN frequency and the total amount of right hemisphere internal processing. Borderline statistical significance was found for greater OKN frequency during combination activities than visual-spatial activities, suggesting a positive relationship between OKN frequency and the amount of left hemisphere processing. Rosenberg applied the interference-inhibition argument of Kinsbourne and Cook (1971) to her results suggesting a predominantly right hemisphere mediation of OKN:

"The lowering of OKN rate by right-hemisphere activity can be interpreted as reflecting 'interference' within the right hemisphere: the nonsignificant trend toward facilitation of OKN by left hemisphere activity can be seen as reflecting 'disinhibition' of OKN during left-hemisphere activity." (Rosenberg, 1980, p. 469).

Another interesting finding of Rosenberg (1980) was that the OKN of right-movers on the CLEM test was more affected by

changes in mental activity than the OKN of CLEM leftmovers. Right moving during the 12 CLEM evoking questions used was positively associated with adjustments of OKN frequency during cognitive activity in the predicted direction, while left moving was negatively associated with adjustments in the predicted direction. However, CLEM directionality was not related to OKN frequency in the rightward and leftward directions, averaged across all mental activities, nor was CLEM related to the difference between leftward and rightward mean OKN frequencies. When the absolute value of the difference between leftward and rightward mean OKN frequency for each subject was examined, it was found to be negatively correlated with right moving and positively related to left moving. This suggests that left movers have a greater degree of OKN lateral asymmetry, across all tasks, than do rightmovers on the CLEM test. Because the sample size was small ($n=22$), no results were reported concerning possible relationships between CLEM directionality and task-related asymmetries of OKN frequency; only asymmetries of OKN averaged across all tasks for each subject were analysed. The results may also be applicable to only males, since no females were studied. In summary, Rosenberg (1980) found that CLEM rightmovers' OKN frequency was more strongly affected by cognitive task activity than was the OKN of leftmovers, while leftmovers had more asymmetric OKN across all tasks than did rightmovers. These results indicate that lateralization processes

affecting saccadic (CLEM) eye movement systems are related to lateralization processes affecting optokinetic nystagmus, which consists of both saccadic and smooth pursuit components.

Rosenberg (1981) has subsequently reported significant relationships between performance on the Rod-and-Frame Test and asymmetries of OKN. Subjects who had little asymmetry of OKN (either high or low frequency in both directions), or 'balanced' OKN had more accurate judgements of the vertical (i.e., were more field independent) than those whose OKN frequency was more asymmetric (high in one direction and low in the other). The asymmetric OKN subjects erred more to the left when the frame was tilted left, and more to the right when the frame was tilted right. Furthermore, subjects who had a higher frequency of OKN for rightward than for leftward stripe movement during verbal-analytic tasks, had more left deviations than right deviations on the Rod and Frame task; while subjects whose OKN frequency was higher for leftward than rightward slow phases during the left hemisphere verbal-analytic task had more deviation to the right than to the left on the Rod and Frame Test. These findings of an association of OKN asymmetry during verbal-analytic tasks and asymmetries in Rod and Frame Test performance were interpreted in the light of other studies suggesting a relationship between field dependence/ independence (FD/I) and lateralization processes. The large body of literature relating FD/I to lateralization of function contains

many inconsistent findings and conflicting hypotheses, consideration of which is beyond the scope of the present argument. If however, the general notion of a relationship between PD/I and hemispheric lateralization is assumed, Rosenberg's (1981) results suggest that these same lateralization processes affect asymmetries of oculomotor control during OKN.

Since OKN slow phases are identical to SPEM, one might expect asymmetries of SPEM to occur, or perhaps relationships between hemispheric asymmetries and overall SPEM accuracy. It has already been suggested that in schizophrenics and vulnerable subjects, lateralization abnormalities may be related to SPEM disruptions. The disorder of SPEM observed in schizophrenic patients has been reviewed in the last chapter. This relationship may take two forms. First, a failure of interhemispheric communication could lead to disruption or disorganization of interaction between asymmetrically represented saccadic and SPEM systems, leading to inappropriate saccadic intervention during SPEM, due to a loss of normal reciprocal inhibition, with the consequent disturbance of overall SPEM accuracy in both directions. Second, if schizophrenics and subjects at risk have a left hemisphere dysfunction, leftward SPEM may be more disrupted than rightward SPEM since SPEM is ipsilaterally organized. Unfortunately, most studies of SPEM have analysed only full cycles of tracking, with the beginning and end of a cycle, being defined by midpoint crossings. Using

this analytic procedure, leftward and rightward tracking cannot be compared.

One group of investigators has recently reported two studies in which analysis of SPEM was based on half-cycles of tracking, defined by maximum excursions of the target, allowing the comparison of leftward and rightward SPEM. The measure of tracking accuracy used was a count of the number of saccades occurring during SPEM tracking of a slowly moving target: the more saccades the poorer the tracking. During a cognitive task (answering syllogisms) with concurrent tracking, schizophrenics and CLEM right movers had not only poorer overall tracking, but also more saccades and pursuit arrests during leftward tracking than rightward tracking (Tomer and Mintz, 1980; Tomer, Mintz, Levy and Myslobodsky, 1981). Since SPEM is ipsilaterally mediated, these results suggest that both schizophrenics and normal right movers show more left hemispheric disorganization. Both of these groups also show a preponderance of rightward spontaneous saccadic CLEM's when asked reflective questions, perhaps indicating greater left than right hemispheric activation. This suggests a link between left hemispheric overactivation, left hemisphere disorganization, rightward orienting and poor performance of attention tasks, e.g. SPEM tracking. Perhaps because the right hemisphere is dominant for attention, those who tend more to activate the left hemisphere manifest more attentional problems, with consequent disruption

of oculomotor tracking, especially toward the left side.

The Neglect Syndrome, Attention and Hemispheric Activation

Lesions of the posterior parietal lobe in humans produce behavioral and cognitive deficits in motor control, attention, affect sensation and perception of spatial relations (Lynch, 1980). The disruption of oculomotor control in these patients has already been discussed. The most notable symptoms which is observed in these patients, especially if the lesion is in the right hemisphere, is a profound inattention or neglect to all sensory stimuli from the side contralateral to the lesion, termed heminattention or hemineglect. This neglect is polymodal: visual stimuli in the contralateral visual field, auditory stimuli in the contralateral ear and tactile stimuli on the contralateral side of the body may all be ignored. Even awareness of the contralateral half of the body may be disrupted, as these patients may groom and dress only the side of the body ipsilateral to the lesion (controlled by the intact hemisphere) and may even deny, during repeated questioning, that their contralateral limbs belong to them. They fail to notice or react to objects or people in the side of extrapersonal space contralateral to the lesion (Heilman, 1979, (review); Heilman and Valenstein, 1979; Weinstein and Friedland, 1977 (review); Heilman and Watson, 1977; Brain, 1941; Critchley, 1953;

Denny-Brown and Chambers, 1958; Denny-Brown, Meyer and Horenstein, 1952; Hecean, Penfield, Bertrand and Malm, 1956; Joynt and Goldstein, 1975; Paterson and Zangwill, 1944). These patients typically draw only the ipsilateral side of a clock-face or daisy, leaving out the contralateral features when they are asked to draw these objects (Heilman, 1979; Mountcastle, 1975; Jung, 1974; Critchley, 1953; Goody and Reinhold, 1952). Imperception or neglect of contralateral features occurs not only for real objects in extrapersonal space, but also for internal mental images (Bisiach and Luzzatti, 1978; Bisiach, Luzzatti and Perani, 1979).

The characteristics of the neglect syndrome change over time. As the patient recovers from contralateral neglect, there is commonly a phase during which they orient to contralateral stimuli as if they had occurred on the ipsilateral side (termed allesthesia). This is followed by a period during which they react appropriately to a single contralaterally presented stimulus, but when two stimuli are presented simultaneously and bilaterally, only the ipsilateral stimulus is noticed. This phenomenon has been referred to as 'extinction' and is obviously similar to the 'perceptual rivalry' process seen in cats with superior colliculus lesions (Heilman, 1979; Heilman and Watson, 1977; Schwartz, Marchok and Flynn, 1977; Critchley, 1953; Denny-Brown, Meyer and Horenstein, 1952).

Discrete lesions of the caudal portion of the inferior parietal lobule and both banks of the caudal part of the superior temporal gyrus in monkeys has produced a pattern of inattention to contralateral visual, auditory and somesthetic stimuli, very similar to the hemineglect seen in humans.

The 'eye shift' phenomenon observed in neglect patients is particularly interesting. The persistent gaze aversion has been described by Friedland and Weinstein (1977):

"When the examiner presents a hand or some other object simultaneously in each visual field, the patient, without prior instructions to fixate, is asked to say what he sees. There is a marked conjugate deviation to the unaffected side, i.e., side of lesion, which is so consistent on repetition that Cohn emphasizes its magnetic quality. The eye-shift is observed in almost all cases of visual hemi-inattention and persists even after it is called to the patient's notice." (Friedland and Weinstein, 1977, p. 6).

The conjugate lateral eye movements in these patients occur in the direction contralateral to the intact, and presumably more activated, hemisphere. Although this extreme CLEM phenomenon seen in patients with neurological lesions of the parietal lobe may not bear directly on the question of the interpretation of CLEM directionality in normals, this evidence does suggest that CLEM may be a valid indicator of greater contralateral than ipsilateral (to the direction of eye movement) hemispheric activation. In these patients the asymmetric eye deviation is extreme and exaggerated, perhaps because the imbalance in hemispheric activation due to the presence of a unilateral

lesion is also extreme. The studies of the neglect syndrome illustrated the close interrelationship of eye-movements, orienting responses and attentional mechanisms.

Right hemisphere posterior parietal lesions induce a more profound attentional disorder than do left hemisphere parietal lesions. Right hemisphere lesions induce the neglect syndrome significantly more often than do left-hemisphere lesions and significantly more severely as well (Costa, Vaughn and Horowitz, et, al., 1969; Gainotti, Messerli and Tissot, 1972). When only very severe neglect is considered, the ratio of neglect-producing unilateral lesions is 8 right to every left-sided lesion (Hecean, 1962; Weinstein and Cole, 1963). Heilman, Watson, Valenstein and Bowers (1980) explained this asymmetric effect of parietal lesions by hypothesizing that,

"the right hemisphere of humans may be dominant for attention. By right hemisphere dominance we mean that the left hemisphere attends mainly to contralateral stimuli. A lesion of the left parietal lobe therefore does not produce severe contralateral inattention, because the right parietal lobe continues to attend to ipsilateral (right-sided) stimuli. Lesions of the right parietal lobe are likely to produce more profound inattention because the left parietal lobe cannot attend to ipsilateral stimuli."

The right hemisphere dominance for attention was tested in 12 normals using tachistoscopically lateralized visual stimuli and EEG recording (Heilman and Van Den Abell, 1980). The desynchronization or activation of each hemisphere was determined by comparing alpha power one second prior to and one

second after each lateralized stimulus presentation. The left parietal lobe desynchronized to the greatest extent after right sided stimuli, while the right parietal lobe desynchronized equally after left or right-sided stimuli, suggesting that the right hemisphere is dominant for attention by virtue of attending both ipsi- and contralaterally, while the left hemisphere attends only contralaterally. Heilman and Van Den Abell (1980) proposed that alpha desynchronization is a valid psychophysiological correlate of attention arousal.

The right hemisphere dominance for attention has been supported by several other studies. Diamond and Beaumont (1973) studied vigilance performance in 22 undergraduates, using a 200 msec long brightening of one of 4 red lights as the task detection signal. False positives occurred more frequently in the right hemisphere group, for whom signals were presented in the left visual field. The left hemisphere-RVF group showed superior performance initially, with a continuing decrement over the course of the vigilance task. The right hemisphere group, on the other hand, showed no decrement, though they had initially poorer performance. Diamond and Beaumont (1973) concluded that vigilance performance has two components: primary vigilance with high initial performance and exhaustibility is associated with left hemisphere processes and secondary vigilance with lower levels of performance, but without decrement, is associated with right hemisphere performance.

Dimond (1979) used a battery of visual, tactual and auditory vigilance tasks to test the vigilance performance of commissurotomy patients. In every case the right hemisphere displayed superior vigilance performance, with a higher percentage of signals detected and fewer numbers of repeated signals necessary to prompt the hemisphere into action, compared to the left hemisphere. The left hemisphere had more ~~gaps~~ or lapses of attention extending over many seconds, since there were more cases in which 10 signals in a row were presented without eliciting a response in the left hemisphere than in the right. These results demonstrated that the left hemisphere shows a failure of sustained attention, which is more effectively maintained by the right hemisphere. Previous reports had indicated a loss or depletion of sustained attention in commissurotomy patients (Sperry, 1974; Zangwill, 1974; Dimond, 1976), suggesting that vigilance performance requires the interaction and co-operation of the right hemisphere sustaining processes with the decremental primary vigilance processes of the left hemisphere.

In another study using normal subjects, Warm, Schumsky and Hawley (1976) investigated the effect of the density of presentation of signals on accuracy in detecting occasional increments in the duration of white noise pulses throughout an hour long vigil. When the rate of signal presentation was increased from 29 to 96 signals per hour there was a

corresponding decrease of 124 msec in the reaction time (RT) to left ear signals, whereas detection RT to right ear signals decreased by only 54 msec. These results were interpreted as an indication that in a sustained attention task the right hemisphere may dominate in the processing of the temporal properties of signals.

In a further study using the same critical signal (increments of white noise bursts) Warm, Richter, Sprague, Porter and Schumsky (1980) had 36 normal right handers engage in an 80 minute vigil with either monaural or binaural presentation and either regular or irregular interstimulus intervals (ISI). Although the ear of input did not have a significant overall effect on the speed of signal detections, the RT's in each ear have different courses over time. There was a similarity in the time course of performance when subjects listened binaurally and with the left ear only, with identical initial RT's and similar increases of RT in a negatively accelerated manner over time. The right ear signal detection RT's were initially sluggish but remained stable as time progressed. Warm, et al. (1980) concluded that the right hemisphere is predominantly involved in controlling the course of sustained attention. They suggested that the two hemispheres may be jointly involved in organizing behavior during a vigilance task and the final outcome is the result of a weighted average of input from the two hemispheres. It is interesting to note that the asymmetries of performance

decrement found by Warm, et al. (1980) and Diamond and Beaumont (1973) are in the opposite direction, with the left hemisphere remaining stable in the latter study. Although these differences may be due to methodological differences in the vigilance tasks used, the issue is somewhat clouded by the fact that opposite patterns of results led different investigators to the same conclusion of a right hemisphere predominance for sustained attention. This example illustrates the theoretical looseness or flexibility of the 'laterlization' and 'attention' constructs: the same data can lead to different interpretations and different data can lead to the same interpretations.

If the right hemisphere dominance for attention (or at least 'sustained attention') is validated, one would predict that individuals who preferentially utilize the right hemisphere may perform better on tasks involving (sustained) attentional processes compared to individuals who prefer the use of the left hemisphere. SPEN is thought to involve involuntary attentional/oculomotor processes. Tower, Mintz and Myslobodsky (1981) found that left movers on the CLEM test have more accurate SPEN (fewer saccades during SPEN) than right movers, whose tracking behavior closely resembled the tracking disorder seen in schizophrenics. They interpreted this finding as consistent with the hypothesis of a right hemisphere dominance for attention resulting in a right hemisphericity association with superior performance on an attention task. An alternate

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explanation in terms of a possible sex by CLEM interaction and sex bias in their sample has been presented. The notion of a right hemisphere dominance for attention leads not only to individual differences hypotheses but also to the hypothesis that rightward SPEN will be more accurate than leftward SPEN, at least for most individuals or averaged across many individuals. Since the slow phase of nystagmus is identical to SPEN, the finding of Rosenberg (1980) of a right hemisphere predominance for OKN, is consistent with the hypothesis of a right hemisphere dominance for attention as it is manifested in slow eye movements.

Not only does the right hemisphere dominate in attentional processes, there is evidence that it also dominates cerebral activation as measured by physiologic readiness to respond or reaction time (RT). Heilman and Van Den Abell (1979) studied 24 normal subjects given laterlized warning stimuli (WS) followed by central reaction time (RT) stimuli. WS to the right hemisphere (LVP) reduced the RT of the right hand more than WS to the left hemisphere (RVF) reduced the RT of the left hand. Also, WS to the right hemisphere (LVP) reduced RT of the right hand even more than warning stimuli presented directly to the left hemisphere (RVF). Thus, the right hemisphere has a bilateral effect on RT, suggesting a right hemisphere dominance for 'intention' to make a motor response. Right hemisphere lesion patients have slower simple reaction times than do patients with

left hemisphere lesions, using the hand ipsilateral to the lesion (Howes and Boller, 1975; DeRenzi and Faglioni, 1965). Boller, Howes and Patten (1970) found a significant correlation between visual and auditory RT's and the size of lesion in 20 patients with right unilateral lesions, while in patients with left hemisphere lesions, no such correlation was found. Heilman (1979) concluded that right hemisphere lesion patients have a defect of intention for movements of the contralateral extremities and also for movements of the ipsilateral extremities. Heilman and Van Den Abell (1979) argue that the right hemisphere is dominant for both attention arousal and intention. Pribram and McGuinness (1975) proposed that attention arousal (concerned with stimulus reception) and intention (physiologic readiness to respond, measured by RT) are independent but closely related processes involved in the control of attention. Further support for the right hemisphere dominance for intention or readiness to respond has come from studies of simple RT to lateralized RT stimuli showing that LVF stimuli (projected to right hemisphere) evoke faster RTs than do RVF (left hemisphere) stimuli (Anzola, et al., 1977; Jeeves and Dixon, 1970). Processing speed is increased by cortical activation (as measured by EEG desynchronization) (Lansing, et al., 1959), thus, activation asymmetries may produce the visual field asymmetries in simple RT (Heilman and Van Den Abell, 1979), and RT is a behavioral measure of arousal (Surwillo,

1969). These findings indicate that the right hemisphere dominates cerebral activation and arousal.

Heilman, Schwartz and Watson (1978) found that right hemisphere lesion patients with the neglect syndrome and emotional indifference had smaller galvanic skin responses (GSR) (recorded from the fingers with stimulation of the forearm) on the side ipsilateral to the lesion, when compared to normal control subjects, while left hemisphere lesioned aphasic patients had higher GSR amplitudes than controls. This indicates an association of neglect and right hemisphere damage with a bilateral disorder of arousal. The GSR is a peripheral measure of phasic sympathetic activity which correlates with central, i.e., EEG, measures of arousal (Lindsley, 1960). The neglect patients also had a significantly higher baseline skin resistance than aphasics or controls, and since baseline resistance is an index of tonic arousal levels (Raskin, 1973), patients with neglect have a defect in both phasic and tonic arousal mechanisms.

In summary, it seems that while each hemisphere can mediate its own activation, the right hemisphere is better at activating the contralateral hemisphere than is the left hemisphere. For this reason left hemisphere lesions do not produce as severe or frequent neglect as right hemisphere lesions because the right hemisphere is capable of activating both itself and the left hemisphere. A right hemisphere lesion would produce a bilateral

but asymmetrical defect because the left hemisphere cannot activate the right hemisphere, and left hemisphere activation (arousal) would be diminished by the right hemisphere lesion (Heilman, Schwartz and Watson, 1978; Heilman and Valenstein, 1979).

The neglect syndrome can be produced by lesions in areas of the brain other than the posterior parietal lobe. Neglect has been produced by lesions of the dorsolateral frontal lobes (Heilman and Valenstein, 1972; Welch and Stuteville, 1958), the cingulate gyrus and the supplementary motor cortex (Heilman and Valenstein, 1972; Watson, Heilman, Cauthien and King, 1973), thalamic and mesencephalic reticular formations (Watson and Heilman, 1979; Watson, Heilman, Miller and King, 1974; Reeves and Hagamen, 1971; Watson, Miller and Heilman, 1978), and the superior colliculus (Sprague and Meikle, 1968). The very same areas are involved in the control of eye movements, suggesting functional convergence of mechanisms controlling arousal, attention, cerebral activation, orienting and eye movements.

It has been suggested that hemineglect is an 'attention-arousal' defect induced by lesions interrupting a cortico-limbic-reticular activating loop (Heilman and Valenstein, 1972; Watson, Heilman and Cauthien, 1973). In this loop lies the basis of a two stage attention-arousal process similar to that described by Solokov (1963). The first stage depends on cortical (e.g. inferior parietal lobule) processing

of stimulus characteristics such as novelty or significance for the individual, while the second stage involves the mediation of arousal by the reticular formation (mesencephalic RF and intralaminar thalamic nuclei). Solokov (1963) suggested that the activation of the cortical neurons involved in the comparative first stage gives rise to EEG desynchronization. Attention to or orienting toward a stimulus causes EEG desynchronization (reduced alpha) in humans (Berger, 1930; Barry and Beh, 1972; Adrian and Matthews, 1934), and in cats (Rheinberger and Jasper, 1937).

High frequency unilateral electrical stimulation of the mesencephalic reticular formation evokes behavioral arousal and EEG desynchronization, and although the arousal is bilateral, the ipsilateral hemisphere shows more arousal than the contralateral hemisphere (Moruzzi and Magoun, 1949; Segundo, 1969). Lesions of the mesencephalic reticular formation produce multimodal unilateral neglect as well as EEG asymmetry (Reeves and Hagamen, 1971). Stimulation of the intralaminar nuclei, nucleus reticularis and nucleus ventralis anterior, induces an arousal response and EEG desynchronization (Moruzzi and Magoun, 1949; Weinberger, Velasco and Linsley, 1965). Multimodal neglect has been produced in primates by intralaminar lesions (Watson, Miller and Heilman, 1978). Unilateral intralaminar thalamic lesions in cats also produce visual neglect, defects in visual orientation, increased blinking to visual threat and the placing

of visual objects on the contralateral side. The frequency and duration of OKN is also altered by these lesions (Orem, Schlag-Rey and Schlag, 1973). Thus, the same areas of subcortex which when stimulated produce bilateral activation as measured by EEG desynchronization and behavioral arousal, are the same areas whose ablation results in neglect. These findings are supported by reports that right hemisphere EEG slowing occurs in case of thalamic lesion induced neglect (Watson and Heilman, 1979). Discrete lesions of the cortex and subcortical white matter can induce EEG slowing (Watson, Andriola and Heilman, 1977), thus a local activation defect may underly the behavioral defect in thalamic neglect.

In conclusion, it seems that the subcortical structures involved in cortical activation are also involved in attention and orienting responses. Activation on one side produces EEG desynchronization on the ipsilateral side and contralateral behavioral orienting, i.e., conjugate lateral eye movements and head deviations to the opposite side. Unilateral lesions in these laterally organized systems produce disruptions of attention and orienting to the contralateral side. Thus, CLEM's, OR's, lateral attention and arousal are subserved by the same areas involved in cortical activation. These considerations support the hypothesis that CLEM is related to hemispheric activation of the half brain contralateral to the direction of eye movement.

Neurophysiological Evidence Concerning CLEM

The saccadic nature of CLEM's elicited by reflective questions has been demonstrated using concurrent EOG recording (Tomer, Mintz, Levi and Myslobodsky, 1979; Myslobodsky, Mintz and Tomer, 1979). Two types of saccades were observed: a primary short latency (200-500 ms) saccade, related to the auditory stimulus and thought to be associated with orienting response mechanisms unaffected by question content, followed by a secondary longer latency saccade occurring toward the end of the question or within 10 seconds. The secondary saccade was thought to be related to decision making or formulating hemispheric activity-dependent response strategy (Tomer, et al., 1979, p. 115). The longer latency saccade tended significantly to deviate in the same direction as the immediately preceding short latency saccade. Since saccades are, at the cortical level, mediated primarily by contralateral mechanisms, it is reasonable to suppose that CLEM's in response to reflective questions, having the temporal characteristics of saccades, are also contralaterally mediated: activation of saccadic centers in one hemisphere giving rise to rapid eye movements toward the opposite side. Neurophysiological validation of the CLEM construct as an index of relative hemispheric activation may be provided by demonstrating differences between CLEM leftmovers

and rightovers on other physiological measures of relative hemispheric activation (individual differences or trait approach), or by demonstrating a relationship within individuals between eye movement direction and other physiological measures of relative hemispheric activation (state approach) recorded concurrently with eye movements. Of course, traditional clinical studies on the effects on CLEM of unilateral lesions may also be useful. The CLEM exaggeration in neglect syndrome patients for example, may provide some support for the contralateral hemispheric activation interpretation of CLEM.

Paradowski, Brucker, Zaretsky and Alba (1978) found that left hemisphere damaged patients had a preponderance of leftward CLEM's in response to both visuospatial and verbal questions, while right hemisphere damaged patients showed no directional asymmetry of eye movement. A control group of non-brain-damaged, chronically hospitalized patients showed a high incidence of left-moving, like the left damaged patients. No question type effects occurred in any group but individuals showed highly consistent directional asymmetries of CLEM in response to both question types. Although the left-moving seen in the left-hemisphere damaged group is consistent with the contralateral hemispheric activation model of CLEM, the failure of the right hemisphere damaged group to show a rightward CLEM preponderance is not consistent with the simple version of the model. The extent and locations of lesions were not reported so

it is difficult to compare right and left hemisphere lesions in these patients, and the absence of a rightward CLEM preponderance in the right damaged group could reflect a lesser severity or smaller extent of lesions in this group, or the fact that the lesions may not have been located in the eye-movement related areas as frequently as in the left damaged cases. The failure of the CLEM measure to differentiate the left damaged patients from controls may indicate that there is an overrepresentation of left movers among patients with polio-myelitis and other diseases represented in this control group. Thus, this study of CLEM's in patients with unilateral lesions provided some limited support for the contralateral hemispheric activation model but the methodological weaknesses of the study render questionable the evidence it provides both for and against the model.

More adequate tests of the hypothesis that CLEM's in normal or psychiatric subjects (i.e., those without overt lesions of the brain) are a reflection of or are associated with relatively greater activation of the contralateral hemisphere may be provided by testing these subject populations using CLEM and neurophysiological indices putatively reflecting hemispheric activation such as ongoing EEG activity, evoked potentials, cerebral blood flow measurements and skin conductance levels or responses. Meyer (1977) reported that a laterality index, $(R-L)/(R+L)$, based on EEG alpha power measures differed between

left movers and right movers (at the parietal leads), indicating that left movers activate the right hemisphere more than right movers. Signals from parietal leads also yielded significant effects of question type, with spatial-synthetic questions eliciting more right hemisphere activity (more negative laterality indices) than verbal analytic questions. The questions used to determine CLEM type in a preliminary session were different but similar to those used during EEG recording, and eye movements during the EEG session were not concurrently recorded.

Warren and Haueter (1981) recorded occipital and parietal EEG alpha and EOG concurrently, while asking subjects 20 questions in alternating blocks of 5 verbal and mathematical questions and 5 visual and spatial questions. They found a significant effect of question type on eye movement direction, with verbal and mathematical questions eliciting more rightward CLEM's and spatial and visual questions eliciting more CLEM's to the left. They also found a significant effect of question type on an EEG alpha asymmetry index ($\text{Right/Right} + \text{Left} \% \text{ time alpha}$), with a higher ratio indicative of more left hemisphere activation during verbal than spatial questions. This alpha asymmetry related to question type preceded eye movements and occurred during both pre and post eye movement intervals, regardless of the direction of eye movement, suggesting that the alpha asymmetry-question type relation may be independent of eye

movements. When they analysed changes in alpha asymmetry from pre- to post-eye movement intervals they found a significant interaction with eye movement directionality such that:

"Alpha asymmetry increased following right eye movements and decreased following left eye movements, indicating a relative increase in activation in the hemisphere contralateral to eye movement direction."

These results offer strong support for the contralateral hemispheric activation model of CLEM, provided the assumption is made that hemispheric EEG alpha ratios are a valid indicator of relative hemispheric activation. Warren and Haueter (1981) also reported that the effects of rightward CLEM's on EEG alpha asymmetry were considerably greater than the effects of left CLEM's, that is, the increase in the right to left hemisphere alpha ratio following right CLEM's was larger than the decrease in this ratio following left CLEM's. A three way ANOVA with question type, CLEM direction, and pre and post intervals as the factors revealed only a marginally significant main effect for question type on alpha asymmetry, implying that the "effect of question type on alpha asymmetry may depend in large part on the co-occurrence of task related lateral eye movements." Despite the equivocal evidence presented for and against independence of CLEM and question type related alpha asymmetry, the relationships between CLEM direction and both question type and pre-post interval changes in alpha asymmetries are entirely consistent with the contention that CLEM's are associated with

greater activation of the hemisphere contralateral to the direction of eye movement. Unfortunately, these investigators concentrated only on question type effects across all subjects and did not consider possible individual differences in hemisphericity, nor did they take into account the sex of their subjects.

In a study of event related potentials (ERP's) in response to a checkerboard stimulus, Sherrin, Smokler and Kooi (1980) found that left movers had a greater amplitude on the right than on the left of a positive going occipital ERP component occurring at 90 msec poststimulus. The occipital P90 ERP was larger on the left than on the right in right movers. These results suggest that left movers respond more with the right hemisphere while right movers respond more with the left hemisphere, consistent with the contralateral hemispheric activation model of CLEM. No significant sex difference or interaction of sex with eye movements was found. These investigators did not examine eye movements and electrophysiological responses concurrently, though they did demonstrate ERP asymmetry related to characteristic eye movement asymmetry.

Perhaps an even better measure of hemispheric 'activation' than the EEG is the measurement of the rate of cerebral blood flow (rCBF) by scintillation detectors placed around the scalp to detect radiation emitted by a radiosotope, Xenon 133, introduced into the cerebral bloodstream by carotid injection or

inhalation as a gas. This technique has provided support for the popular interpretations of EEG activity with the finding of high correlations between local blood flow and increased mean scalp EEG frequency ($r=0.73$) Ingvar, 1976), and association both of these with a measure of cerebral oxygen uptake, demonstrating close links between rCBF, cerebral energy metabolism and local changes in neural electrical activity.

Using carotid injection of Xenon 133, Melamed and Larsen (1977) demonstrated that contralateral 'voluntary' conjugate eye movement was associated with a 12% increase in mean hemispheric rCBF and localized increases of 25% in the temporo-occipital visual association cortex (Area 19), 25% in the periorlandic motor eye field, as well as 20% in the adjacent supplementary motor area, corresponding to Area 8, the frontal eye fields. Although these findings support the contralateral hemispheric activation interpretation of conjugate eye movements, their finding of similar local increases during ipsilateral and vertical eye movements is not consistent with the hypothesis in its simple form. In this study only one hemisphere's rCBF was measured at a time, due to limitations of the injection method, thus relative hemispheric activation could not be assessed. Although each hemisphere may contain neurons activating in association with both ipsilateral and contralateral eye movements, it is possible that concurrent measurement of both hemisphere's rCBF would reveal relatively greater contralateral activation during eye

movement laterally. Melamed and Larsen (1977) reported no statistical comparisons of the magnitude of rCBF changes during ipsilateral and contralateral eye movements. The nature of elicitation of conjugate eye movements in this study differed from CLEM studies of spontaneous saccades occurring in association with cognitive activity following questions, in that Melamed and Larsen (1977) had subjects "follow a grey object which was rapidly moved from side to side from the midline." This task may have engaged smooth eye pursuit movement systems which are somewhat different in their neural representation from saccadic eye movement systems generating spontaneous saccades (such as CLEM's evoked by questions) in the absence of visual target. The ipsilateral representation of SPEM may account for their finding of local increased CBF during ipsilateral conjugate eye movements. If the target was moved sufficiently rapidly saccadic mechanisms represented contralaterally would also have been engaged, as their findings suggest.

In an important recent study Gur and Reivich (1980) used the Xe133 inhalation technique, allowing concurrent measurement of rCBF over both hemispheres, to demonstrate both state and trait influences on rCBF asymmetries. They observed a significant increase in left relative to right rCBF during the performance of a verbal task, taken from the Miller Analogies Test, while no significant increase in right relative to left hemispheric blood flow was seen during the performance of a

spatial task, the Gestalt Completion Test. However, greater increase in rCBF to the right hemisphere was associated with better performance on the task, suggesting that although the spatial task could be solved by either hemisphere, those subjects who activated the more task appropriate right hemisphere did better on the task. The same spatial task was performed significantly better by CLEM left movers than by right movers, while left and right movers did not differ on the verbal task (Packer and Gur, cited in Gur and Reivich, 1980). These results suggest that the verbal task is more 'hardwired' to the left hemisphere, causing greater left than right hemisphere rCBF increases in most subjects and failing to differentiate left and right movers. When hemispheric flow was averaged across the three conditions (verbal task, spatial task, relaxed baseline condition), it was found that left movers had relatively more blood flow in the right compared to the left hemisphere while right movers showed a tendency to have more blood flow in the left than the right hemisphere. This finding strongly supports the contralateral hemispheric activation hypothesis of CLEM; although concurrent recording of bilateral rCBF and CLEM's would offer the most convincing demonstration of this, Gur and Reivich (1980) determined CLEM directionality only after the rCBF measurements were taken.

Other investigators have also reported task-related asymmetries of rCBF. Risberg, Halsey, Blauenstein, Wilson and

Wills (1975) reported that although bilateral increases in rCBF were observed during problem solving, verbal problems were associated with greater increases in the left hemisphere while spatial problems were associated with greater right hemisphere increases. Reading has been observed to induce an increase in left hemisphere blood flow (Ingvar and Schwartz, 1974), while a spatial perception test induced increased blood flow in the right hemisphere (Jacquy, Paroux, Jocquet, Lhoas and Noel, 1977). Dobbs (1980) used an indirect measure of cerebral blood flow to demonstrate trait-related asymmetries. He presumed that following a drink of ice water, the circulation of the blood would carry the cooling to the head, and changes in the temperature of the external auditory canal would reflect cooling proportional to the blood flow on that side. He found that English majors showed more cooling and hence greater blood flow on the left, while architecture students showed greater cooling on the right. Although the relationship of college major to hemisphericity is tentative at best, these results do indicate characteristic or trait-related asymmetries of cerebral blood flow, in addition to the task or state-related asymmetries demonstrated by others. Thus for cerebral blood flow, as for EEG alpha asymmetry and conjugate lateral eye movements, both state and trait factors have been demonstrated to be operative, depending on the experimental conditions and data analysis strategies. In the Gur and Reivich (1980) study, both of these

effects were demonstrated in the same study for blood flow asymmetries.

Another putative measure of hemispheric activation is the galvanic skin conductance response (SCR) or skin conductance levels (SCL). Two studies have measured CLEM direction in response to questions and bilateral SCR and SCL, concurrently (Erwin, McClanahan and Kleinman, 1980; O'Gorman and Siddle, 1981). While both studies demonstrated significant effects of question type on CLEM directionality, neither found any relationship between eye movements and skin conductance measures. Erwin, et al. (1980) showed that some subjects had consistent SCR and amplitude asymmetries irrespective of the question type, suggesting trait-related or characterological skin conductance asymmetries, but a trait factor approach to the CLEM data was not attempted. This study failed to find question-type or task-related asymmetries of SCL or SCR, in contrast to the findings of Myslobodsky and Rattok (1978), Lacroix and Comper (1979), Ketterer and Smith (1977) or Smith, Ketterer and Concannon (1981), who all showed task-related asymmetries of SCL or SCR. O'Gorman and Siddle (1981) found a significant main effect for hands on SCR, with the right hand having higher mean SCR than the left hand, as well as a main effect of question type, with larger SCR's following verbal than spatial questions. The hand by question type interaction effect on SCR seen in the previously mentioned studies was however not

found by O'Gorman and Siddle (1981). The conflicting findings with respect to task-related or trait-related asymmetries of SCR and SCL throws doubt on the interpretation of these measures as reliable indices of relative hemispheric activation, so their failures to correlate with CLEM directionality is hardly strong evidence against the hemispheric activation model of CLEM.

Further studies using experimental methods and analytic procedures designed to examine both trait and state factors in skin conductance parameters and CLEM's concurrently are needed to resolve some of the conflicts apparent in the available literature.

In summary, studies of normals relating CLEM's to contralateral hemispheric activity via EEG alpha power asymmetries, evoked potential asymmetries and cerebral blood flow asymmetries have provided convergent support for the contention of Bakan (1969), Kinsbourne (1972) and Gur (1975) that CLEM's are associated with relatively greater contralateral hemispheric activation. Some studies have focussed on CLEM directionality related to question type (Warren and Haueter, 1981; Erwin, et al., 1980; O'Gorman and Siddle, 1981), while others have focussed on individually consistent or trait-related CLEM directionality (Meyer, 1977; Shevrin, Smokler and Kooi, 1980; Gur and Reivich, 1980). Gur and Reivich (1980) argued that both question type and trait factors influence CLEM directionality, but some experimental designs and analytic

strategies may focus on only one or the other. Some studies have measured neurophysiological processes concurrently with eye movement recording (Warren and Haueter, 1981; Melamed and Larson, 1977; Erwin, et al., 1980; O'Gorman and Siddle, 1981), while others have measured neurophysiological differences between subjects previously or subsequently identified as left or right movers (Meyer, 1977; Shevrin, Smokler and Kooi, 1980; Gur and Reivich, 1980). Although the evidence seems to support the contralateral hemispheric activation model, stronger support would require a study in which eye movements, EEG, SCR and SCL, and rCBF were all measured concurrently during questions (verbal and spatial) designed to elicit hemispheric specific cognitive activity, as well as 'neutral' questions which maximize trait variance.

V. Introduction - Experimental Rationale

Genetic contribution to the etiology of schizophrenia has been compellingly demonstrated by a variety of methods. The genetically inherited diathesis has been hypothesized to be a subtle neurointegrative defect which may manifest as personality, cognitive, perceptual-motor, psychophysiological, and biochemical traits. These traits may provide vulnerability markers for the identification of individuals 'biologically at risk' for psychopathology. Characteristic abnormalities of the lateralized function of the brain have been demonstrated by many methodologies to be associated with schizophrenia and other psychopathology. It has been suggested that characteristic patterns of lateralization as measured by the Conjugate Lateral Eye Movement (CLEM) test are associated with the schizophrenic vulnerability. Smooth pursuit eye movements (SPEM) have also been demonstrated to be impaired in psychotic schizophrenics, remitted schizophrenics, and many relatives of schizophrenics. SPEM accuracy has been shown to be a stable trait which is strongly influenced by genetic factors, and has been suggested as a psychophysiological vulnerability marker. Research using the MMPI also suggests that certain aspects of performance on this test are related to schizotaxia or vulnerability.

One previous study using CLEM and the MMPI found higher Schizophrenia scale scores as well as more torque among leftmovers than rightmovers (Winterbotham, 1979; Laing, 1979). These results were interpreted as indicative of greater vulnerability to psychopathology, particularly schizophrenic spectrum psychopathology, among leftmovers compared to rightmovers. Another 2 studies using CLEM and SPEM measures found that rightmovers had more impaired SPEM than did leftmovers, suggesting that the former group had more vulnerability (Tomer and Mintz, 1980; Tomer, et al, 1981). In an attempt to resolve this apparent conflict normal subjects were assessed on all three measures : CLEM, SPEM and the MMPI.

The work of Gur, et al (1976) suggested that left hemisphericity (rightmoving) females and right hemisphericity (leftmoving) males manifest more psychopathology than do right hemisphericity females and left hemisphericity males, respectively. Since the Tomer and Mintz (1980) and Tomer, et al (1981) studies were biased by an overrepresentation of females, their finding of a rightmover SPEM impairment is consistent with the findings of Gur, et al (1976) for females only. It was hypothesized that a sex by CLEM interaction would occur, such that rightmoving females and leftmoving males would show more disordered SPEM.

A review of the literature on lateralization in schizophrenia suggested that schizophrenics and schizotaxics

would be characterized by a leftward SPEM impairment, or rightward SPEM superiority, since a left hemisphere deficit has been associated with schizophrenia, and SPEM is thought to be ipsilaterally controlled. A review of neurophysiological literature on eye movement control mechanisms suggested that CLEM, a saccadic eye movement, and SPEM, a smooth slow eye movement, are related. Specifically, it was hypothesized that leftmovers, with greater right hemisphere activation, would show more accurate rightward than leftward SPEM, while the reverse would be the case for rightmovers. There is some evidence that the right hemisphere is dominant for attention and that SPEM is a task involving attentional processes, suggesting that for most subjects or averaged across subjects rightward SPEM would be superior to leftward SPEM. In the present study SPEM leftward and rightward halfcycles were examined to assess possible laterality effects in SPEM.

As the MMPI has been suggested for use as a personality vulnerability marker, it was hypothesized that psychopathology apparent in the MMPI, as defined by Golden and Meehl's schizotypy scale, would be associated with overall SPEM impairment as well as a specific impairment of leftward tracking resulting in rightward SPEM superiority. It was also hypothesized that leftmoving males and rightmoving females would have higher schizotypy scores than their counterparts.

Since the study was conceived originally as a 'biological high risk' paradigm study, a normal population was sampled. Although a true high risk study is necessarily longitudinal in design, practical considerations prevented a longitudinal followup. It was thought that a cross sectional study of the convergence of several putative vulnerability markers would serve as an interesting and useful pilot study for a larger 'biological high risk' study involving subsequent followup investigation.

VI. Methods

Subjects

One hundred and twenty-one subjects were recruited from undergraduate psychology and mathematics courses at Simon Fraser University in Burnaby, British Columbia, during the summer and fall semesters of 1981. There were 62 males and 59 females in the sample. Fifteen subjects wrote with their left hand, while the other 106 were right-handed writers. The racial composition of the sample was as follows: 105 Caucasians, 10 Orientals, 5 East Indian/ Pakistanis and 1 Negro. The age range of the sample was 17 to 47, with a mean age of 23.6 years. There was no selection of subjects on the basis of handedness, race, CLEM direction or any other variable used in the study.

Apparatus

The smooth pursuit eye tracking task utilized a smoothly moving target spot of light generated by a Wavetek 5 MHz Lin/Log Sweep Generator Model 185 and displayed on a Hewlett Packard 1317A X-Y Display oscilloscope. The target motion was

sinusoidal (pendulum-like), presented at .4 hz and .8 hz frequencies, for 16 full cycles of tracking at each frequency. The subjects sat with head stabilized in a chin-head rest, with their eyes 24 inches from the oscilloscope screen. The target spot had an excursion 13 inches wide on the screen, thus subtending 30° of visual angle. Custom control hardware regulated target presentation, cycle counting and data collection sequences.

Eye movements were recorded using electroculography, with two Grass silver-silver chloride electrodes attached to the outer canthi of each eye with Beckman electrolyte paste and adhesive collars. For the 51st through 121st subjects, blinks were also recorded using a vertical electrode placement above and below the midline of the left eye. EOG signals and the target signal were fed through a selection panel to Penn State design amplifiers and then Bell and Howell 1-182 filter/amps, with the filters on both devices set to the 'out' position. The gain on the two amplifiers was set individually so that the eye movement and target curves had approximately the same size on a display oscilloscope. In addition, a marker channel was recorded which consisted of a square wave with steps at target midline crossings. From the amplifiers, the EOG, marker and target signals were fed to a NOVA-3D computer which digitized the data and stored it on magnetic tape. The sampling rate for data collection was 50 hz, and each .4 hz trial lasted 42 seconds,

thus giving 2100 data points spaced 20 msec apart for the .4 hz trials, and 1050 data points spaced 20 msec apart for the .8 hz trials, which were of 21 second duration.

Procedure

Subjects were first told that this was an investigation of the relationship between eye-tracking and personality. Each measure was briefly described and the subject read and signed an informed consent statement. Confidentiality of individual results was assured. The experimenter then asked the subjects' age and recorded observations of sex, race, eyecolor, haircolor and writing hand.

Each subject was then given the Conjugate Lateral Eye Movement (CLEM) test (Bakan, 1977). Twenty 'neutral' reflective questions (Appendix I) chosen to maximize trait variance and minimize 'question-type' effects (Bakan, Coupland, Glackman and Putnam, 1974), were asked by the experimenter, who sat 4 feet away facing the subject, directly across a small table. The visual background behind the experimenter was a uniform symmetric wall of burlap material. The first and second detectable eye movements were scored using a scheme in which an imaginary clockface is superimposed on the subject's face (vertical eye movements are scored 12, leftward eye movements without any vertical component are scored 3, similar rightward

eye movements scored 9, downward eye movements are scored 6). Eye movements without a lateral component (12 and 6), stares and eye closures were considered unscorable responses. If 70% of the scorable first lateral eye movements were in one direction the subject was designated as a leftmover or a rightmover, while those falling short of the 70% consistency criterion were designated as bidirectionals.

The subjects then sat in front of the display oscilloscope and the skin at the outer canthi, the center of the forehead and above and below the midline of the left eye was cleaned with isopropyl alcohol. EOG electrodes were attached at these sites while the experimenter explained the function of, and hazard-free nature of, the electrodes. Subjects then placed their heads in the chin-forehead restraint, those with corrected vision fitting their glasses through the device. The lights were turned off and the subjects dark adapted for three minutes. They were told to fixate on the target dot in the middle of the oscilloscope screen and to follow the dot as closely as they could with their eyes once it began moving. Four trials were presented: a practice .4 hz sinusoidal trial during which gain calibrations were made (no data collected), a .4 hz sinusoidal trial (during which data was collected), a .8 hz sinusoidal trial, and a .4 hz square wave tracking trial. Before each trial the following instructions were given.

"Stare at the dot. When the dot begins to move, follow

it as closely as you can with your eyes. Try very hard not to blink, and don't stop smoothly tracking the dot until it stops moving. Just before the dot begins to move I'll warn you by saying 'get ready, go.' Again, don't blink, and keep your eyes right on the dot."

The experimenter then went into the adjoining room where the amplifiers and control equipment were located and before each of the trials, which were initiated by a button press, yelled "Get ready, go." After completion of the four eye tracking trials, the lights were turned on and the electrodes were removed.

Subjects were then escorted to an empty classroom, where they completed Form R of the Minnesota Multiphasic Personality Inventory (MMPI). They also completed a questionnaire consisting of multiple choice questions concerning motoric laterality, pregnancy and birth complications, medical and psychiatric history of self and relatives and other miscellaneous items. The data from this questionnaire were exploratory, as were eyecolor and haircolor observations, and they will not be considered in this thesis. Upon completion of the MMPI and questionnaire, subjects returned the completed materials to the laboratory. The entire procedure lasted approximately 1-1/2 hours.

Data Analysis

The digitized eye tracking data were subjected to an analysis designed to provide information concerning the accuracy of SPEN tracking. First, the marker channel was examined to find

the beginning and end of the data. Then, the digitized target channel data was filtered, using a 'Brickwall' low pass digital filter, and was adjusted about a baseline. The adjusted target data was examined to find the sinewave peaks and the average number of data points between peaks. The first and last quarter cycles of tracking data were discarded (the target began and ended at the midline) and an additional halfcycle of data was deleted from the beginning of the tracking record, in order to avoid start-up artifacts. This left 15 full cycles of tracking data within the 'outer bounds' of the analysis.

The raw target and subject EOG data curves were then adjusted about a baseline and corrected for amplitude differences by multiplying the EOG data points by a scalar so that their standard deviation was equal to that of the target data points. Then an RMS or root mean square calculation was performed on the adjusted target and EOG data within inner bounds defined by deleting the first and last full cycles within the outer bounds. These inner bounds were used to facilitate the phase correction described later. The RMS calculation was performed by taking the point by point differences between the EOG and target data, squaring these differences, taking their mean and then taking the square root of this value. First, RMS scores were calculated for each halfcycle of tracking within the inner bounds, giving 13 leftward halfcycle and 13 rightward halfcycle RMS values. Then, an overall RMS was calculated for

the entire 13 cycles of tracking within the inner bounds, with no divisions made between halfcycles. Next, a 'constructed average halfcycle' was constructed for each tracking direction by averaging the first data points in each of 13 EOG halfcycles in one direction, then the second data points, and so on, in the same manner that averaged evoked responses are constructed. Following this averaging of homologous data points an RMS calculation was performed on the leftward and rightward constructed average halfcycles.

Next the tracking EOG and target curves were corrected for phase differences. This was done by shifting the EOG curve relative to the target curve, one data point at a time, and calculating the overall RMS value for each shift. The EOG curve was shifted up to 15 points to the right and 20 points to the left, relative to the target curve; the shift which produced the minimum overall RMS value was chosen as the optimal phase correction. Visual inspection of plotted data for phase corrected and uncorrected data confirmed that this strategy did indeed select the optimal shift for phase correction. After shifting the 13 left and 13 right halfcycle RMS scores and left and right constructed average halfcycle RMS scores were calculated, just as for the phase uncorrected data. The number of points and direction of phase shift were also noted. The use of an 'inner bound' for these RMS calculations and an 'outer bound' for standardization of the curves assured that the same

standardization scalar applied to both phase-uncorrected and phase corrected analyses.

Medians for each of the sets of 13 halfcycle RMS scores were then calculated. Thus, for each subject, median halfcycle RMS scores were obtained for leftward and rightward half cycles of tracking, for phase-uncorrected and phase-corrected data, at .4 hz and .8 hz target frequencies. For each left-right pair, two laterality indices were calculated: a simple lateral difference score consisting of the leftward halfcycle RMS score subtracted from the rightward halfcycle RMS score, and a laterality quotient providing an index of asymmetry corrected for overall tracking accuracy, $(R-L) \times 100 / (R+L)$. Both of these laterality indices were negative when rightward tracking was superior to leftward tracking, and were positive when leftward tracking was superior to rightward tracking.



VII. Results

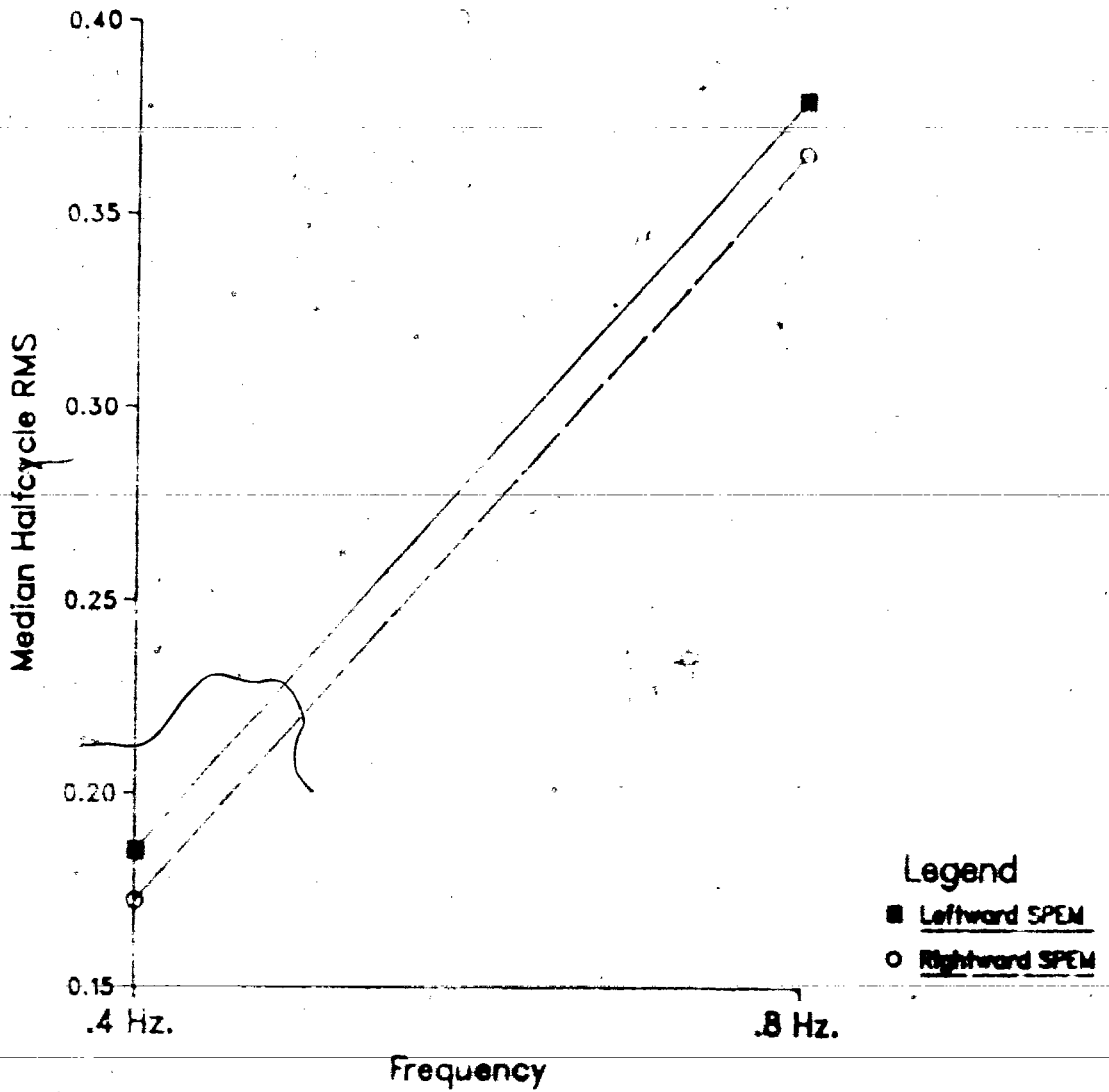
Frequency

The medians of four sets of 13 halfcycle RMS scores, two each of leftward and rightward halfcycles at .4 hz and .8 hz target frequencies, for tracking curves corrected for phase lag, were subjected to an analysis of variance with Sex and CLEM as between subjects factors, and frequency and tracking direction as repeated measures (Table 1). By far the most significant main effect, was for Frequency ($F(1,113 \text{ df}) = 184.25 \text{ } p < .00001$). RMS scores were significantly higher for the faster .8 hz frequency across all sex and CLEM groups, and for both tracking directions, indicating that tracking was worse for the faster target (see Figure 1).

The 4 RMS values of the constructed average half cycles, rightward and leftward, .4 hz and .8 hz, were subjected to similar SEX x CLEM x FREQUENCY x DIRECTION ANOVA. Again, the main effects for frequency were strikingly significant. The constructed average half cycle RMS scores (Table 2) produced for the Frequency main effect an $F(1,113 \text{ df}) = 29,236$ with $p < .00001$. Examination of the means revealed significantly higher

Figure 1

Frequency and Tracking Direction



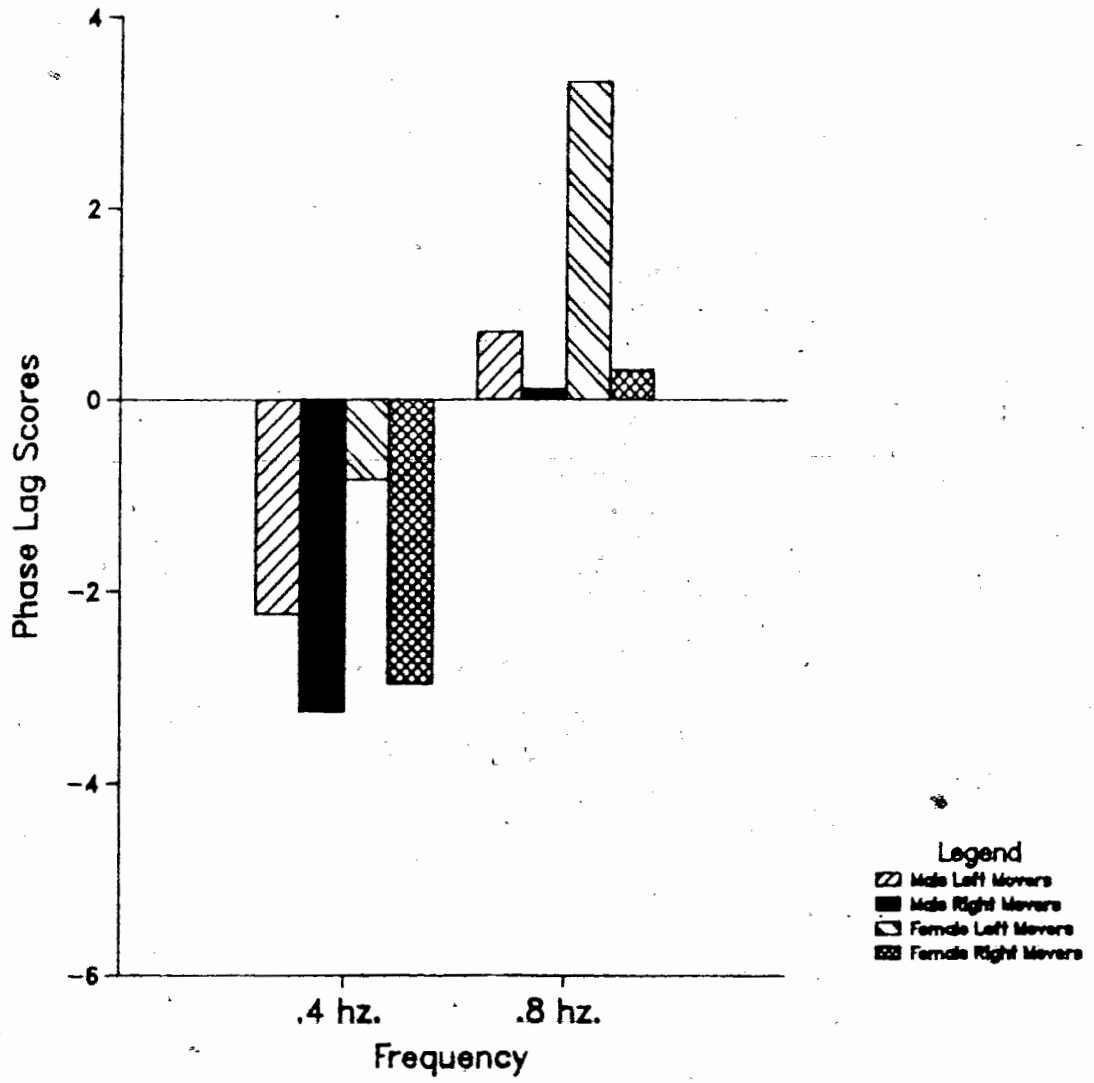
RMS values for the faster .8 hz frequency, across all sex and CLEM groups and for both tracking directions.

The RMS scores for the entire 13 cycles at .4 hz and .8 hz were examined, with the RMS calculation done for all points in the range, not divided into half cycles. An ANOVA with SEX and CLEM as between subject factors and frequency repeated (Table 3) produced a Frequency main effect with $F(1,113 \text{ df}) = 189.92$, $p < .00001$. The 'overall RMS scores', showed that overall tracking accuracy was significantly worse at the faster target frequency for all sex and CLEM groups.

The amount and direction of phase lag also differed across the two frequencies when lag scores (the number of points the EOG curve must be shifted relative to the target curve to produce the minimum overall RMS) were analysed. A SEX x CLEM x FREQUENCY ANOVA on lag scores for .4 hz and .8 hz tracking (Table 4) revealed a significant for Frequency ($F(1,113 \text{ df}) = 295.85$, $p < .00001$) (see Figure 2). An examination of the mean lag scores revealed that at the slower .4 hz frequency mean phase shifts were actually negative, indicating that the EOG curve had to be shifted rightward relative to the target curve to achieve the minimum RMS, suggesting that the eyes of most subjects actually led the target slightly. The negative phase shifts at .4 hz. are probably the result of a systematic error in phase relationships between the EOG and the target due to data collection circuitry. At the faster frequency the mean lag

Figure 2

Phase Lag, Frequency, Sex and CLEM



scores become more positive for all groups, and were greater than zero for all but the male bidirectionals. Positive phase shifts indicate that the EOG was shifted leftward relative to the target curve, suggesting that the eyes followed slightly behind the target for most subjects at the faster frequency.

Tracking Direction

To examine the effect of tracking direction on tracking accuracy the medians of the sets of 13 leftward and 13 rightward halfcycle RMS scores were subjected to ANOVAS with SEX and CLEM as between-subject factors and frequency and tracking direction as repeated measures. For the median halfcycle RMS scores of phase uncorrected curves (Table 1), the main effect for tracking direction was significant ($F(1,113 \text{ df}) = 6.68, p < .011$). Examination of the means revealed that leftward half cycles had higher RMS scores than rightward half cycles, indicating that rightward tracking was more accurate, averaged across all subjects, and both frequencies (see Figure 1).

ANOVAS with SEX and CLEM as between subject factors and frequency and laterality as repeated measures were performed on the RMS scores for constructed average halfcycles of tracking (Table 2). The main effect for laterality marginally approached significance ($F(1,113 \text{ df}) = 2.76, p < .0994$). Cell means revealed that rightward SPEN had higher RMS and thus more impaired

tracking than leftward SPEN.

Sex

The phase-corrected .4 hz. constructed average halfcycle RMS scores (Tables 9 and 10) showed significant main sex effects for both leftward ($F(1,113 \text{ df}) = 4.25, p < .0415$) and rightward tracking ($F(1,113 \text{ df}) = 4.34, p < .0394$). In both of these analyses mean RMS values were higher for females than for males.

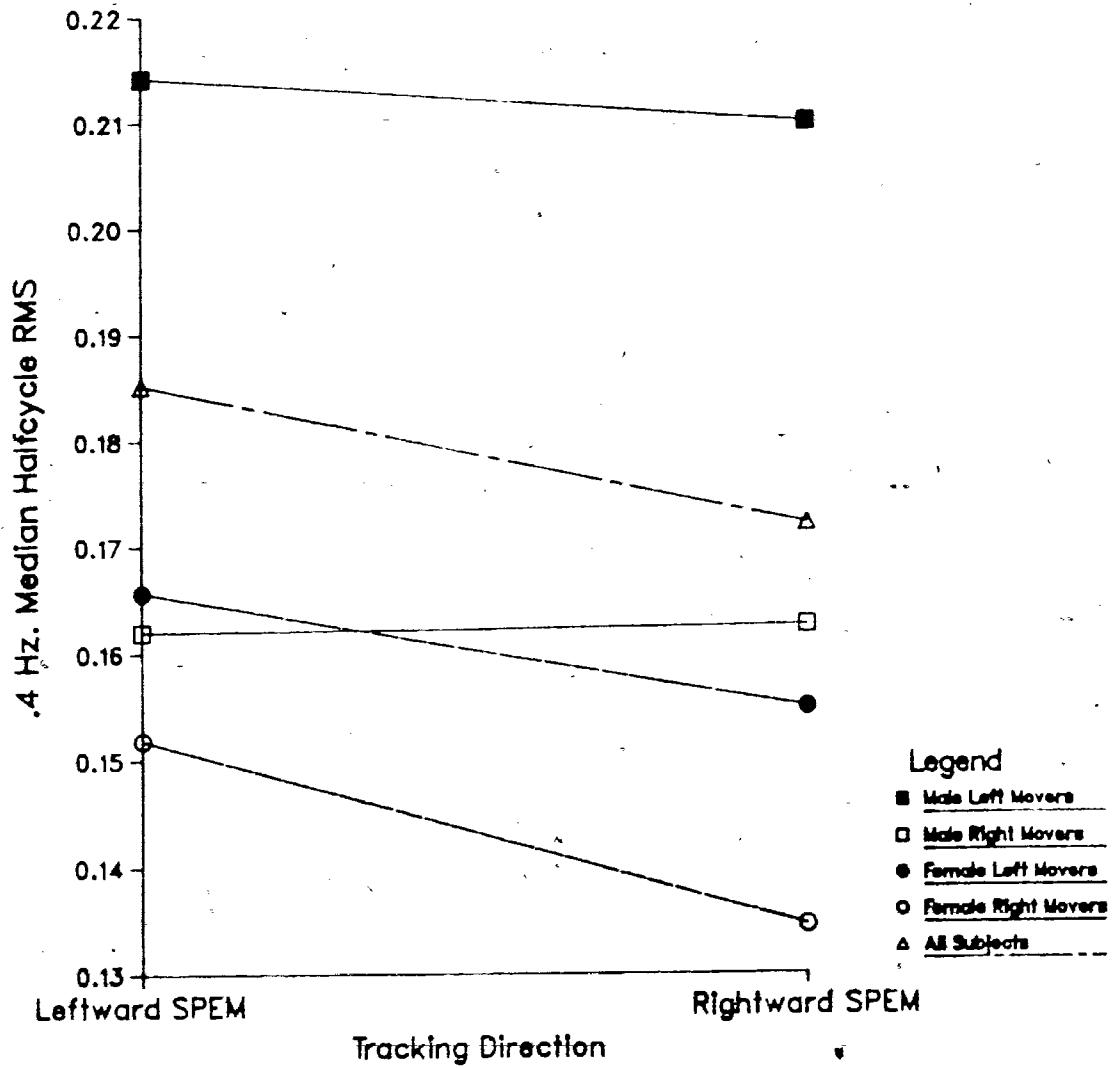
The constructed average halfcycle RMS scores were subjected to SEX x CLEM x FREQUENCY x DIRECTION ANOVAS. The SEX x FREQUENCY interaction effect was significant for phase-corrected data (Table 2) ($F(1,113 \text{ df}) = 6.94, p < .0096$). This finding was the result of a greater change across the frequencies in the females than in the males.

Sex differences were further investigated by performing SEX x CLEM two-way ANOVAS, without repeated measures, on individual variables comprised of the various combinations of .4 hz or .8 hz frequencies and rightward or leftward direction of tracking. The only main effect for sex approaching significance was for phase corrected .4 hz rightward median halfcycle RMS scores ($F(1,113 \text{ df}) = 3.74, p < .0588$). For phase corrected .4 hz rightward median halfcycle RMS scores, higher scores for males than females were observed (see Figure 3).

Sex and laterality or direction of tracking interacted in several analyses. The SEX x CLEM x FREQUENCY x DIRECTION ANOVA

Figure 3

.4 Hz. Median Halfcycle RMS, Tracking Direction, Sex and CLEM



on median halfcycle RMS scores for the phase corrected data (Table 1) yielded a significant SEX x DIRECTION interaction effect ($F(1,113 \text{ df}) = 7.11, p < .0088$) and examination of the cell means revealed that differences between leftward and rightward tracking were greater for females than for males (see Figure 7).

Individual or within-subject laterality effects were also examined using the two laterality indices: lateral differences, $(R-L)$ and laterality quotients $(R-L \times 100 / (R+L))$. The lateral difference scores based on median right and median leftward 1/2 cycles RMS scores for phase corrected data, were subjected to an ANOVA with sex and CLEM as between subject factors and frequency as a repeated measure (Table 5). The main effect for sex was significant ($F(1,113 \text{ df}) = 7.11, p < .0088$) and examination of the cell means showed that, averaged across CLEM groups and frequencies, the females had more negative lateral difference scores than did the males. Negative lateral difference scores are the result of higher leftward than rightward RMS values and thus, better rightward than leftward tracking accuracy. These results show that the superiority of rightward tracking was more pronounced in females than males, at least for median halfcycle RMS scores for phase corrected data.

When laterality quotients (corrected for overall tracking accuracy) were examined, a similar pattern of results emerged. Laterality quotients based on median halfcycle RMS scores for

phase corrected data (Table 6) showed a significant main effect for sex ($F(1,113 \text{ df}) = 6.88, p < .0099$) in an ANOVA with SEX x CLEM x FREQUENCY as the factors. For this analysis cell means showed more negative laterality quotients for females than males, averaged over CLEM groups and frequencies. This indicates that even with an asymmetry index corrected for overall task difficulty, females show a stronger rightward SPEN superiority compared to males.

Two-way ANOVAS with SEX x CLEM as between subjects factors and no repeated measures were performed on laterality indices for the two frequencies separately. Lateral difference scores based on median halfcycle RMS values for the .4 hz phase-corrected data (Table 16) revealed a significant main effect for sex ($F(1,113 \text{ df}) = 8.10, p < .0052$). A similar pattern emerged for laterality quotients. The phase-corrected .4 hz laterality quotients based on median halfcycle RMS scores (Table 17) produced a significant sex main effect ($F(1,113 \text{ df}) = 6.99, p < .0094$). These results indicate that the significant main effects of sex on laterality indices occur only for the slower, .4 hz, tracking frequency.

CLEM

Analysis of phase-corrected halfcycle RMS medians of right and left tracking at both frequencies produced no significant CLEM effects. A 4-way ANOVA (S x C x F x L) on the RMS values for constructed average halfcycles, based on phase-corrected curves (Table 4) produced a significant main effect for CLEM ($F(2,113 \text{ df}) = 3.16, p < .0463$), with leftmovers having higher RMS scores than rightmovers across both frequencies and sexes.

There was also a significant main effect for CLEM in the 3-way ANOVA (S x C x F) on lag scores (Table 4) ($F(2,113 \text{ df}) = 3.20, p < .0445$) (see Figure 2). Cell means revealed more positive lag scores for left movers than right movers across both frequencies. Two-way (SEX x CLEM) ANOVAS on lag scores for the two frequencies separately revealed very nearly significant main effects of CLEM for both .4 hz (Table 13) ($F(2,113 \text{ df}) = 2.97, p < .0551$) and .8 hz tracking (Table 14) ($F(2,113 \text{ df}) = 3.07, p < .0502$). At the slower frequency all groups led the target (i.e., had negative lag scores, indicating that the EOG curve was shifted rightward relative to the target to attain the minimum overall RMS), but the rightmovers led more than the leftmovers, for both sexes (i.e., had more negative lag scores). At the faster frequency all groups (except male bidirectionals) followed rather than led the target, and left movers followed further behind (had more positive lag scores) than did right

movers.

A 4-way ANOVA on phase-corrected median halfcycle RMS scores (Table 1) revealed a significant FREQUENCY x DIRECTION x CLEM interaction effect ($F(2,113 \text{ df}) = 4.43, p < .0140$). In this analysis cell means revealed that the difference between leftward and rightward tracking deterioration over the frequencies was greater in rightmovers than leftmovers.

Another approach to CLEM effects on tracking asymmetry utilized the individual laterality indices. A 3-way ANOVA (SEX x CLEM x FREQUENCY) on lateral difference (R-L) scores based on median halfcycle RMS values for phase-corrected data (Table 5) revealed a significant FREQUENCY x CLEM interaction ($F(2,113 \text{ df}) = 4.43, p < .0140$). Cell means revealed that the difference between .4 hz and .8 hz mean lateral difference scores was greater in rightmovers than leftmover, averaged across sexes. A three-way ANOVA (S x C x F) on laterality quotient scores, $(R-L) \times 100 / (R + L)$, based on median halfcycle RMS values for phase-corrected data (Table 6) produced a significant FREQUENCY x CLEM interaction effect ($F(2,113 \text{ df}) = 3.26, p < .0420$), again with rightmovers showing greater change in mean laterality quotients over frequencies than leftmovers.

Two-way SEX x CLEM ANOVAS performed on laterality indices separately for the two frequencies revealed significant CLEM main effects for .4 hz tracking and not for .8 hz tracking. Lateral difference scores based on median halfcycle RMS scores

for .4 hz phase-corrected data produced a significant CLEM main effect when subjected to a 2-way ANOVA (Table 16) ($F(2, 113 \text{ df}) = 3.30, p < .0405$). The laterality quotient scores based on medians for .4 hz phase corrected data (Table 17) also produced a nearly significant main CLEM effect in a 2-way ANOVA ($F(2, 113 \text{ df}) = 2.88, p < .0603$). The absence of any significant CLEM main effects for the .8 hz tracking data laterality indices is a reflection of the significant CLEM x FREQUENCY interactions seen in the 3-way ANOVAS on laterality indices.

SEX x CLEM

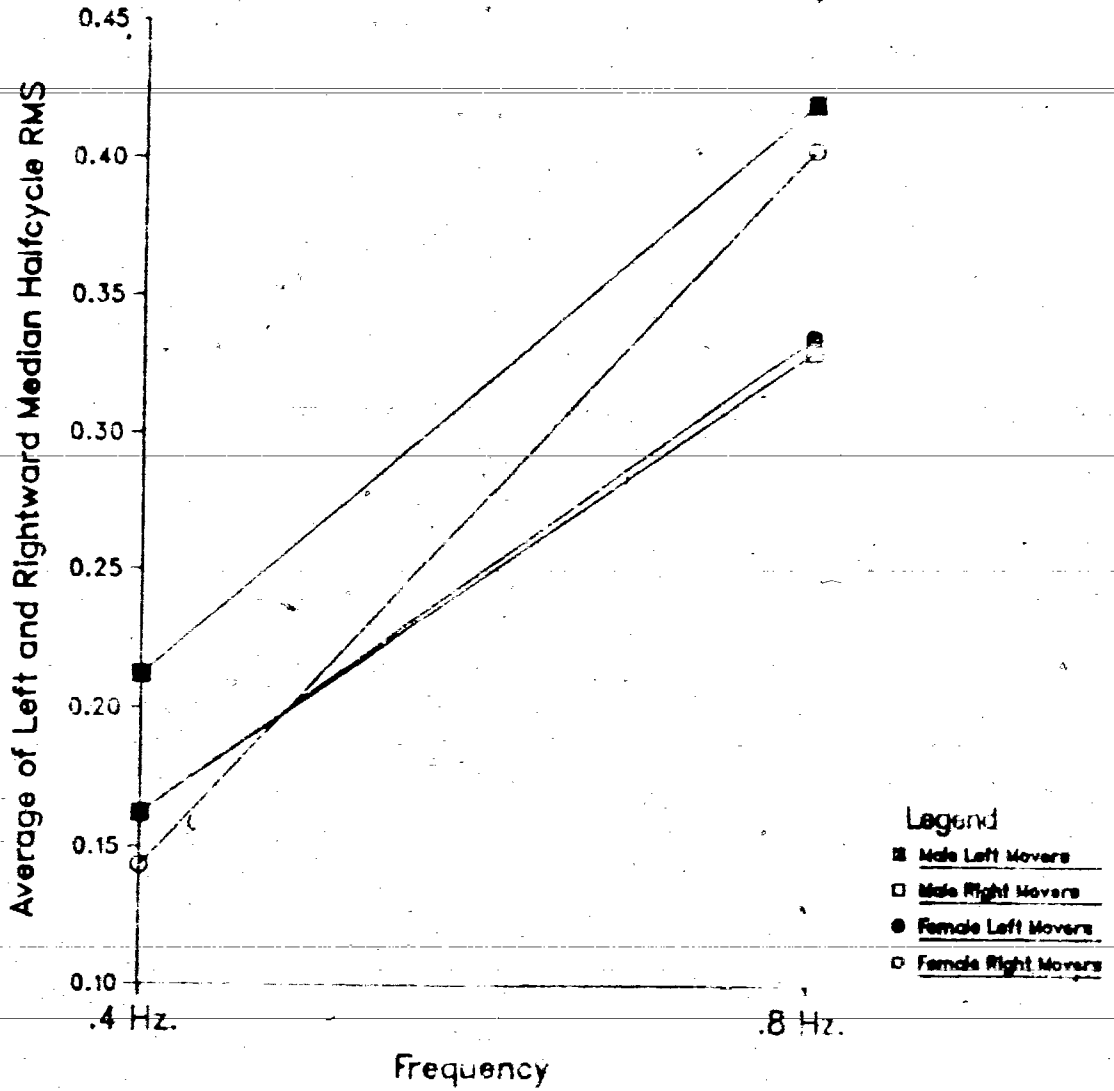
While phase-uncorrected data yielded many significant main effects for SEX and CLEM, when the curves were corrected for phase lag or lead, these main effects disappeared and significant SEX x CLEM interaction effects replaced them. The SEX x CLEM interaction effects were also seen primarily for the .8 hz tracking data, giving rise to FREQUENCY x SEX x CLEM interactions in the repeated measures analyses.

When median halfcycle RMS scores for phase-corrected data were subjected to a 4-way ANOVA (S x C x F x L) (Table 1), a nearly significant 3-way interaction effect occurred for FREQUENCY x SEX x CLEM ($F(2, 113 \text{ df}) = 2.73, p < .0698$). Cell means showed that male leftovers and female rightovers showed a greater change of RMS over the two frequencies than did male

rightmovers and female leftmovers, respectively (see Figure 4). Interestingly, among males bidirectionals showed the greatest change while among females they showed the least change across frequencies. The constructed average 1/2 cycle RMS scores for phase corrected curves (Table 2) also showed a significant FREQUENCY x SEX x CLEM interaction in a 4-way ANOVA ($F(2,113 \text{ df}) = 5.56, p < .0050$). Again, cell means showed greater change over the frequencies for male leftmovers and female rightmovers. Two-way ANOVAS of phase-corrected .8 hz median halfcycle RMS scores produced a marginally significant SEX x CLEM interaction effect for leftward tracking (Table 7) ($F(2,113 \text{ df}) = 2.95, p < .0566$) but not for rightward tracking (Table 8) ($F(2,113 \text{ df}) = 2.32, p < .1302$) (see Figure 5). The averages of leftward and rightward median halfcycle RMS scores for phase-corrected .8 hz data (Table 15) produced a SEX x CLEM interaction effect for the 2-way ANOVA, which approached significance ($F(2,113 \text{ df}) = 2.62, p < .0772$). A two-way ANOVA on the overall RMS scores taken over the entire 13 cycles for phase-corrected .8 hz data (Table 12) yielded a significant SEX x CLEM interaction effect ($F(2,113 \text{ df}) = 3.72, p < .0273$) (see Figure 6). In all of these analyses, examination of group means showed that among males leftmovers had higher RMS scores and thus poorer tracking than rightmovers, while among females, the rightmovers had more disrupted SPEN than the leftmovers. The corresponding analyses of .4 hz tracking data revealed no significant SEX by CLEM interactions,

Figure 4

Frequency, Sex and CLEM



reflecting the significant FREQUENCY x SEX x CLEM interaction effects seen in 4-way and 3-way analyses.

The three-way ANOVA (S x C x F) on overall RMS scores for the entire 13 cycles for phase corrected data (Table 3), produced a nearly significant SEX x CLEM interaction effect ($F(2,113 \text{ df}) = 2.62, p < .0775$), again with male leftmovers and female rightmovers having more impaired SPEN than male rightmovers and female leftmovers, respectively, averaged across frequencies and tracking directions.

The fact that the 2-way ANOVAS on phase-corrected .8 hz halfcycle RMS scores yielded significant SEX x CLEM interactions only for leftward tracking suggests that there are also interactions of SEX, CLEM and DIRECTION effects. The 4-way ANOVA (S x C x F x L) on median halfcycle RMS score for phase corrected data (Table 1) produced a nearly significant DIRECTION x SEX x CLEM interaction effect ($F(2,113 \text{ df}) = 3.03, p < .0522$) (see Figure 7). Examination of the cell means revealed that for female rightmovers, the overall rightward tracking superiority is much more pronounced than for other SEX by CLEM groups.

The 3-way ANOVA on lateral difference scores based on medians for phase-corrected data (Table 5) showed a nearly significant SEX x CLEM interaction effect ($F(2,113 \text{ df}) = 3.03, p < .0522$). When two-way ANOVAS were done separately for the 2 frequencies, the .4 hz phase-corrected median lateral difference scores (Table 16) produced a significant SEX x CLEM interaction

Figure 5

.8 Hz. Median Halfcycle RMS, Sex and CLEM

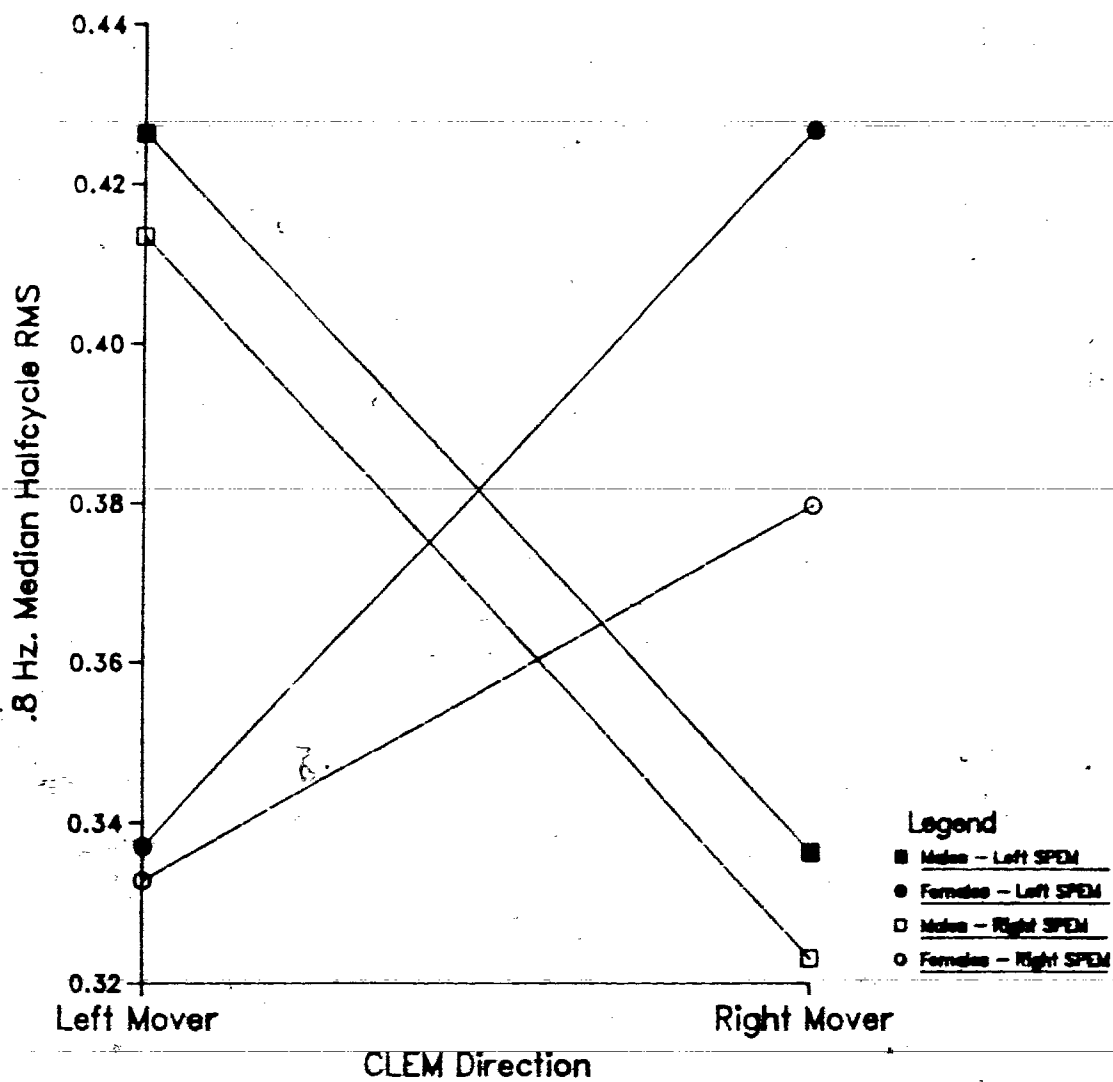


Figure 6

.8 Hz. Overall RMS, Sex and CLEM

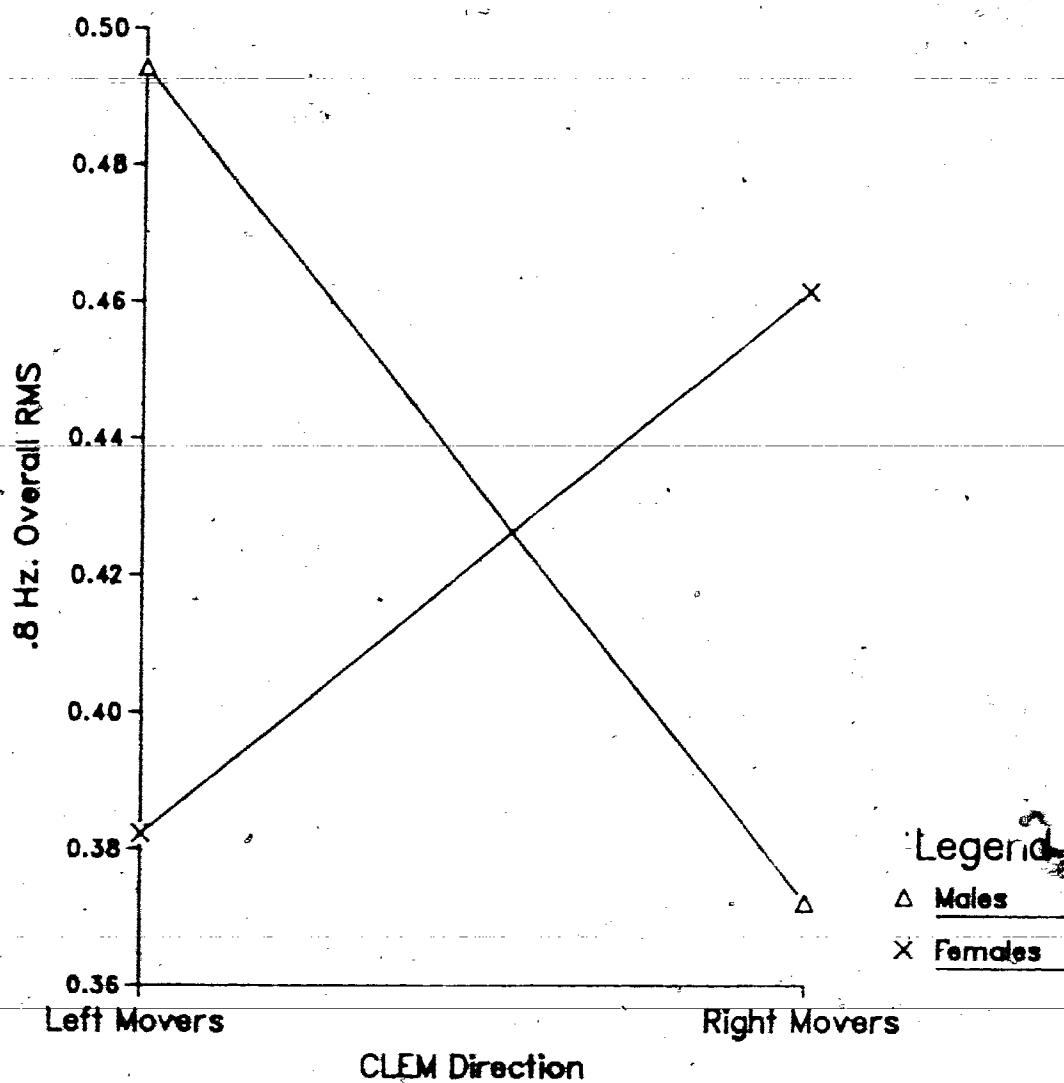
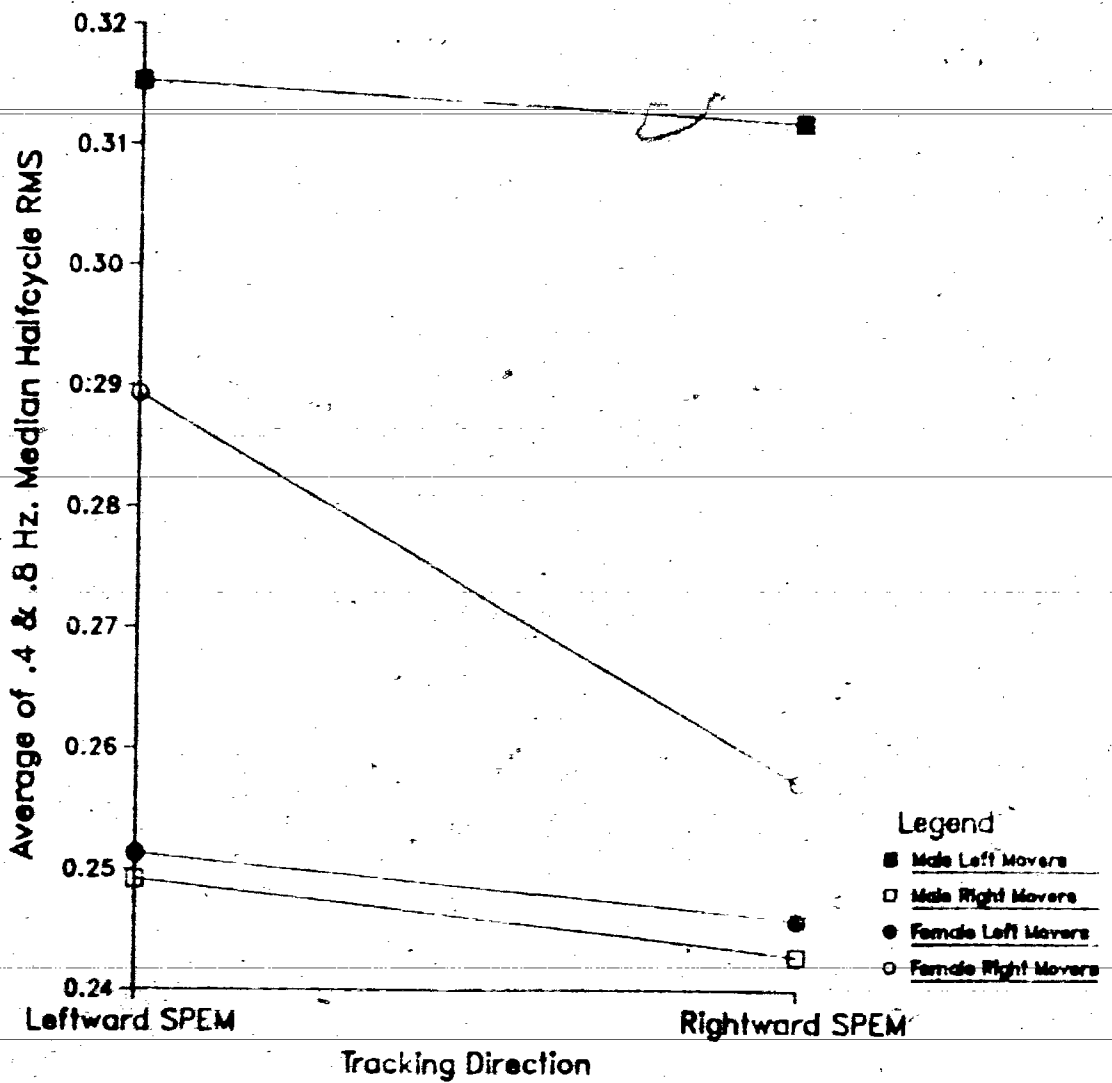


Figure 7

Tracking Direction, Sex and CLEM



effect ($F(2, 113 \text{ df}) = 3.30, p < .0404$). In both of these analyses the cell means showed that the rightward SPEN superiority was greater in male leftmovers and female rightmovers compared to male rightmovers and female leftmovers, respectively.

Laterality quotient scores based on medians for phase-corrected data subjected to a 3-way ANOVA ($S \times C \times F$) (Table 6), yielded a nearly significant interaction effect for $SEX \times CLEM$ ($F(2, 113 \text{ df}) = 2.90, p < .0590$). When laterality quotient scores were analysed separately for the 2 frequencies by 2-way ANOVAS, the .4 hz phasecorrected median laterality quotient scores (Table 17) showed a nearly significant interaction effect for $SEX \times CLEM$ ($F(2, 113 \text{ df}) = 2.67, p < .0739$). The cell means revealed the same pattern as for lateral difference scores. Thus, even for asymmetry indices corrected for overall tracking accuracy, male leftmovers and female rightmovers had greater rightward SPEN superiority than did male rightmovers and female leftmovers, respectively.

Age

To investigate the effect of age on the accuracy of SPEN, subjects were grouped into age categories with five year intervals (less than 20 years, 20 to 24, 25 to 29, etc.), and this age grouping was used as the independent variable in a series of one way ANOVAS with SPEN variables as dependent.

Significant effects for age were seen for phase corrected data at both frequencies, and for both tracking directions (Tables 18 - 23). The relationship between age and tracking performance was not linear. A wider range of age groups and larger samples of subjects over 30 years old would be required for any trustworthy conclusions about the association of SPEM with age. When SEX X CLEM 2-way ANOVAS on SPEM variables were redone with age as a covariate, no remarkable changes in the pattern or significance of results occurred, compared to the initial SEX X CLEM ANOVAS without the covariate.

Individual SPEM Asymmetry

Although the four way ANOVAS on phase corrected and uncorrected median halfcycle RMS scores showed significant main effects for laterality, reflecting a superiority of rightward tracking, averaged across all subjects and both frequencies, this rightward SPEM superiority did not hold for all subjects individually. A small majority of subjects did show rightward SPEM superiority at the .4 hz. frequency (67/119 or 56.3%, vs. 52/119 or 43.7% with a leftward SPEM superiority), and at the .8 hz. frequency (62/119 or 52.1%, vs. 57/119 or 47.9% with left SPEM superiority) for phase corrected median indices of individual SPEM laterality.

One possible reason that a rightward SPEM superiority emerged when data were averaged over all subjects is that the small majority of subjects with a rightward SPEM superiority (henceforth referred to as the RSPEM group) had a greater absolute value of asymmetry than did the subjects with leftward SPEM superiority (LSPEMers). This possibility was investigated by splitting subjects into LSPEM and RSPEM groups using zero cutpoints on the lateral difference (R-L) of median halfcycle RMS scores based on phase corrected .4 hz. data. With this as the independent grouping factor, a one way ANOVA was performed with the absolute values of the .4 hz. median lateral difference scores as the dependent variable. A nearly significant effect for the LSPEM - RSPEM grouping was observed ($F(1,113 \text{ df})=3.24$, $p<.0744$); with the RSPEM group having greater absolute values of the .4 hz. median lateral difference scores (mean=.04473, SD=.05972) than the LSPEM group (mean=.02789, SD=.03551). When subjects were classified as LSPEM or RSPEM on the basis of the .8 hz. phase corrected median lateral difference scores (0 split), a one way ANOVA on the absolute values of the .8 hz phase corrected median lateral difference revealed a significant effect of the grouping variable ($F(1,113 \text{ df})=4.29$, $p<.0406$). Again the RSPEMers had a greater average magnitude of asymmetry (mean=.07359, SD=.06923) than did the LSPEMers (mean=.05113, SD=.04562), though there was considerable overlap between the groups. Thus, the RSPEM group were not only somewhat more

numerous but also had a greater magnitude of asymmetry than did the LSPEMers, leading to a RSPEM superiority averaged across all subjects.

The possibility that individual lateral asymmetry in SPEM accuracy was related to overall SPEM accuracy was investigated next. Subjects were divided into four groups defined as quartiles of the phase corrected .4 hz. median halfcycle RMS lateral difference scores. With this grouping factor as the independent variable a series of one way ANOVAS was performed on several SPEM variables reflecting tracking accuracy. Significant effects for the quartile .4 hz. median lateral difference grouping factor were seen when the dependent variable was the overall 13 cycle RMS score for .4 hz. phase corrected data (Table 24) ($F(3,115 \text{ df})=7.19, p<.0002$). Significant effects were also seen for the overall 13 cycle RMS scores for .8 hz. tracking data, both phase corrected (Table 25) ($F(3,115 \text{ df})=11.14, p<.00001$).

Individual lateral asymmetry of .4 hz. phase corrected median halfcycle RMS scores was also non-significantly related to RMS scores for the constructed average halfcycles at the .8 hz. frequency. The phase corrected constructed average halfcycles did not yield significant results, but the effect on leftward 1/2 cycle RMS (Table 26) approached significance ($F(3,115 \text{ df})=2.45, p<.0672$) while the effect on rightward halfcycle RMS scores was much smaller (Table 27) ($F(3,115$

df)=1.84, $p < .1432$).

Median halfcycle RMS scores for both leftward and rightward tracking at both frequencies yielded significant effects as dependent variables in one way ANOVAS with the quartile grouping on corrected .4 hz. median lateral difference scores as the independent variable. For .4 hz. tracking phase corrected leftward median halfcycle RMS scores (Table 28) the effect of the grouping factor was highly significant ($F(3,115 \text{ df})=13.40$, $p < .00001$), as it was for corrected .4 hz. rightward median scores (Table 29) ($F(3,115 \text{ df})=7.11$, $p < .0002$). For phase corrected .8 hz. leftward median scores (Table 30) the SPEM asymmetry grouping effect was significant ($F(3,115 \text{ DF})=12.16$, $P < .00001$), as it was for .8 hz. corrected rightward median scores (Table 31) ($F(3,115 \text{ df})=11.39$, $p < .00001$). Examination of group means for all of these analyses showed that the group with the greatest RSPeM superiority (the lowest quartile on the grouping variable) had the highest RMS scores, followed by the group with the greatest RSPeM superiority (the highest quartile), while the groups with smaller SPEM asymmetry (quartiles 2 and 3) had the lowest RMS scores. This pattern suggests two hypotheses : that RSPeMers have poorer tracking than LSPeMers, and that subjects with larger SPEM asymmetries (whether LSPeM or RSPeM) have more impaired tracking than subjects with smaller SPEM asymmetries. To investigate the first hypothesis further analyses were performed using as independent

variables grouping into RSPEN and LSPEN groups using zero cutpoints on the median lateral difference scores. The second hypothesis was investigated by grouping subjects on the basis of the absolute values of the median lateral difference scores.

A series of one way ANOVAS was performed with SPEN variables as the dependent variables and the RSPEN - LSPEN dichotomy based on phase corrected .4 hz. median lateral difference scores as the independent between subjects variable. Significant effects of individual tracking asymmetry direction were found for overall 13 cycle RMS scores (Table 32) ($F(2,113 \text{ df})=6.22, p<.0141$). Phase corrected constructed average halfcycle RMS scores showed a significant effect for leftward tracking ($F(2,113 \text{ df})=5.20, p<.0244$), but that for rightward tracking only approached significance ($F(2,113 \text{ df})=3.38, p<.0684$) (Tables 33 & 34).

When median halfcycle RMS scores were examined for .4 hz. tracking significant effects of tracking asymmetry direction were seen only for leftward tracking ($F(2,113 \text{ df})=7.65, p<.0066$) (Table 35). For .8 hz. tracking both tracking directions showed significant effects, but the effect was greater for leftward tracking. For phase corrected .8 hz. data the SPEN asymmetry had a significant effect on both leftward tracking ($F(2,113 \text{ df})=7.09, p<.0089$) and rightward tracking ($F(2,113 \text{ df})=5.50, p<.0207$) (Tables 36 & 37). Examination of group means in all of these analyses revealed that in each case the RSPEN group had

higher RMS values and so more disordered pursuit tracking than LSPEMers. The disordered tracking of the RSPEN group was especially noticable for leftward tracking, but also appeared for overall tracking measures, suggesting an association of leftward tracking deficit and overall tracking disruption, while LSPEM superiority was not associated with an overall tracking deficit.

To examine the effect of the magnitude of tracking asymmetry on overall tracking performance, subjects were divided into four groups defined as the quartiles of the absolute values of phase corrected .4 hz. median lateral difference scores. This grouping factor was used as the independent variable in a series of one way ANOVAS on SPEN variables. Significant effects of the grouping factor were seen for three of four of the overall 13 cycle RMS scores: (Tables 38 & 39) phase corrected .4 hz. ($F(3,115 \text{ df})=9.71, p<.00001$), and phase corrected .8 hz. ($F(3,115 \text{ df})=9.11, p<.00001$). When median halfcycle RMS values were used as the dependent variables, many significant effects of tracking asymmetry magnitude were observed. For .4 hz. tracking significant effects occurred for phase corrected leftward median scores ($F(3,115 \text{ df})=16.84, p<.00001$), phase corrected rightward median values ($F(3,115 \text{ df})=10.34, p<.00001$) (Tables 40 & 41). For phase corrected .8 hz. tracking significant effects of asymmetry magnitude were seen for both leftward ($F(3,115 \text{ df})=7.83, p<.0001$) and rightward median halfcycle RMS scores

($F(3,115 \text{ df})=10.25, p<.00001$) (Tables 42 & 43). Examination of group means revealed that in each of these analyses the 4th quartile, the group with the largest absolute values of lateral difference scores, had the highest RMS scores, indicating an association between greater tracking asymmetry magnitude and disordered SPEN in both directions.

Another interesting finding occurred when the absolute values of .4 hz. phase corrected median lateral difference scores quartile grouping was used as the independent variable and the MMPI scale scores were used as dependent variables. The SPEN asymmetry magnitude measure was significantly related to Schizophrenia scale scores ($F(3,115 \text{ df})=2.94; p<.0362$), (Table 44) and the group with the largest asymmetries had the highest average Sc scores.

In all of the foregoing analyses LSPEN and RSPEN groups were defined by zero cutpoints on the phase corrected .4 hz. median lateral difference scores. Similar analyses were conducted using .8 hz. phase corrected median lateral difference scores to define LSPEN and RSPEN groups, with a zero cutpoint. One way ANOVAS were performed on SPEN and MMPI variables. Among the SPEN variables, the only one to show a significant effect of .8 hz. tracking asymmetry was .8 hz phase corrected leftward median halfcycle RMS scores (Table 45) ($F(1,113 \text{ df})=7.01, p<.0092$), with RSPENers showing higher .8 hz. leftward RMS scores than LSPENers. Several MMPI scales showed significant

effects of the .8 hz. asymmetry. The Depression scale (Table 46) showed a significant effect ($F(1,113 \text{ df})=5.60, p<.0196$) with RSPeMers having higher D scores than LSPeMers. The Social Introversion scale (Table 47) showed a significant effect in the same direction, i.e., RSPeMers higher than LSPeMers ($F(1,113 \text{ df})=5.62, p<.0194$). A significant effect also occurred for Hypomania (Ma) (Table 48) ($F(1,113 \text{ df})=4.88, p<.0291$), and LSPeMers had higher Ma scale scores, on the average, than RSPeMers. Finally, a significant effect of .8 hz. SPeM asymmetry was observed for scores on Golden and Meehl's schizotypy measure, the sum of D, PT, Sc and Si scale scores (Table 49). ($F(1,113 \text{ df})=4.13, p<.0334$). Cell means showed that subjects with RSPeM superiority at .8 hz. had higher schizotypy scores than subjects with LSPeM superiority (RSPeM mean=237.9, SD=37.9, LSPeM mean=223.9, SD=32.7).

The absolute value of the lateral difference for .8 hz. phase corrected halfcycle RMS scores was examined by grouping subjects into quartiles on this measure and using this grouping as the independent variable in a series of one way ANOVAS. No significant effects were seen for MMPI scale scores, but there were several significant effects on SPeM variables. Overall 13 cycle RMS scores for phase corrected .8 hz. data showed a significant effect ($F(3,115 \text{ df})=10.69, p<.00001$). Phase corrected .8 hz. median 1/2 cycle RMS scores showed significant effects of .8 hz. tracking asymmetry magnitude for both leftward

($F(3,115 \text{ df})=12.81$, $p<.00001$) and rightward ($F(3,115 \text{ df})=7.77$, $p<.0001$) tracking directions. In all of these analyses the group with the largest asymmetry magnitude had the highest RMS scores.

SPEM Accuracy and the MMPI

Impaired SPEM has been suggested as a putative high risk or vulnerability marker, as has elevation on the schizotypy scale of the MMPI. Some convergence of these measures was noted for .4 hz. phase corrected median halfcycle RMS scores. Subjects who obtained scores in the upper quartile on the average of leftward and rightward median halfcycle RMS measures, a measure of overall tracking ability, were designated as poor trackers. Subjects in the lowest quartile, i.e., with the smallest RMS values, were designated as good trackers. MMPI scale scores and the schizotypy scale were compared for good and poor trackers by T test. Poor trackers had significantly higher schizotypy scores than good trackers (poor trk. mean=241.9, SD=40.8, good trk. mean=222.9, SD=30.2, $T(\text{pooled})=-2.03$, $p<.047$). Poor trackers also had significantly higher Social Introversion scale scores compared to good trackers (poor trk. mean=57.2, SD=40.8, good trk. mean 51.1, SD=9.7, $T(\text{pooled})=-2.26$, $p<.028$), as well as nonsignificantly higher schizophrenia scale scores (poor trk. mean=65.0, SD=11.2, good trk. mean=60.4, SD=9.0, $T(\text{pooled})=-1.46$, $p<.152$) and psychasthenia scale scores (poor

trk. mean=61.5, SD=11.2, good trk. mean= 57.1, SD=9.5, T(pooled)=-1.62, p<.111). Poor trackers also had significantly lower scores on the K scale than good trackers (poor trk. mean=49.9, SD=7.9, good trk. mean=54.7, SD=10.1, T(pooled)=2.03, p<.046).

When subjects were defined as good or poor trackers by virtue of being in the lowest and highest quantiles, respectively, for leftward .4 hz. phase corrected median halfcycle RMS scores, similar results were obtained. Poor leftward trackers had significantly higher schizotypy scores than good leftward trackers (poor trk. mean=243.2, SD=40.7, good trk. mean=222.9, SD=30.2, T(pooled)=-2.16, p<.037) as well as significantly higher Social Introversion scores (poor trk. mean=57.4, SD=10.7, good trk. mean=51.2, SD=9.8, T(pooled)=-2.31, p<.025). Poor leftward trackers also had nearly significantly higher Psychasthenia scale scores than good trackers (poor trk. mean=61.7, SD=11.2, good trk. mean=56.6, SD=9.5, T(pooled)=-1.89, p<.065).

When rightward .4 hz. phase corrected median 1/2 cycle RMS scores were used to define good and poor trackers, the latter group was again found to have significantly higher schizotypy scores (poor trk. mean= 241.1, SD=40.6, good trk. mean=220.9, SD=27.3, T(pooled)=-2.26, p<.028). Poor rightward trackers also had significantly higher Depression scale scores than good rightward trackers (poor trk. mean=58.2, SD=11.2, good trk.

mean=53.1, SD=8.0, $T(\text{pooled})=-2.04$, $p<.046$), as well as nonsignificantly higher scores on Hysteria (poor trk mean=54.6, SD=10.3, good trk. mean=50.7, SD=6.4, $T(\text{pooled})=-1.73$, $p<.089$), Psychasthenia (poor trk. mean= 62.1, SD=11.8, good trk mean=56.8, SD=9.5, $T(\text{pooled})=-1.92$, $p<.06$), Schizophrenia (poor trk. mean=65.0, SD=14.5, good trk. mean=59.8, SD=8.0, $T(\text{pooled})=-1.72$, $p<.091$), and Social Introversion (poor trk. mean=55.7, SD=11.2, good trk. mean=51.2, SD=9.9, $T(\text{pooled})=-1.66$, $p<.102$). Thus, elevation of an MMPI index of schizotypy provided by the sum of D, Pt, Sc and Si scale scores was significantly associated with impaired leftward, rightward, or the average of left and rightward or overall tracking. If the significance values for each set of comparisons is multiplied by 13, the number of comparisons in each set, none of the MMPI differences between good and poor trackers remains significant. Thus, these relationships must be considered cautiously as pilot results in need of replication.

Another strategy for investigating the relationship between SPEN and the MMPI was to reverse their roles as independent and dependent variables. Subjects were defined as having MMPI psychopathology by the criteria of Haier, et al (1979). Subjects who had at least one T-score of the ten clinical scales elevated 4 SD above the mean (T greater than or equal to 90) or four or more scales elevated 2 SD above the mean (T greater than or equal to 70) were designated as the MMPI index group (n=17).

Using these same criteria Haier, et al (1979) found that 82% of the index group from a university sample met the RDC for some psychopathology. A comparison group of subjects without MMPI evidence of psychopathology was comprised of 25 students of whom none had any clinical scale scores greater than or equal to 1-1/2 SD above the mean ($T = 65$).

Using this index/control grouping factor as the independent variable, one way ANOVAS were performed on SPEN variables. Significant differences between index and control subjects were found for RMS scores of constructed average halfcycles of tracking : phase corrected .4 hz. leftward ($F(1,40 \text{ df})=5.7876$, $p<.0209$) and rightward ($F(1,40 \text{ df})=6.0709$, $p<.0181$), phase corrected .8 hz. rightward tracking ($F(1,40 \text{ df})= 4.5429$, $p<.0393$), and a nearly significant difference for phase corrected .8 hz. leftward tracking ($F(1,40 \text{ df})= 3.2413$, $p<.0793$). The difference between index and control subjects on phase corrected .4 hz. overall 13 cycle RMS approached significance ($F(1,40 \text{ df})=3.0838$, $p<.0867$). In all of these analyses the index group of subjects with pathological MMPIs had higher RMS scores and so more disordered SPEN than the control subjects with 'normal' MMPIs.

VIII. Discussion

The use of the EOG limits the conclusions that can be made about movements of the eye per se, as the EOG can be contaminated by the EEG. Iacono and Lykken (1981) demonstrated that the 10 hz. spikiness of the Type II tracking disorder seen in many schizophrenics is correlated with EEG signals, and infrared reflectance recording of eye movements do not show the spikiness. The use of the IR technique allows the most precise quantification of actual movements of the eyeballs. While certain measures of the EOG such as the RMS measure used here show high correlations with the same measures based on IR records, the EOG is still influenced by EEG activity, although the later may be related meaningfully to oculomotor function.

The EOG can be analysed in a number of ways each method giving somewhat different information. Counting the number of saccades in the EOG record is one method, but the only errors in SPEM which the method is sensitive to are saccades. Counting velocity arrests is another, but its relationship to IR measures is low and inconsistent, and its validity is questionable. The use of an RMS measure or Ln S/N ratio, which are mathematically interchangeable, is more sensitive to a variety of SPEM errors. In addition to saccades and tracking arrests, these measures can

be affected by relatively slow non-saccadic nonlinearities of the SPEN system. The RMS may be calculated for either phase corrected or uncorrected data. In the present study phase lag at .4 hz. was significantly correlated with the phase corrected overall 13-cycle RMS for .4 hz. ($r = -.283$, $p < .002$), and the same was true for .8 hz. data ($r = -.4291$, $p < .0001$). Since phase lag is significantly negatively correlated with the phase corrected measures of tracking accuracy indicating that more phase lag is associated with better tracking, the phase uncorrected measures are confounded, and separate phase lag and phase corrected RMS measures are preferable. The RMS value can be calculated for the entire trial of tracking, or for full, half, and quarter cycles of tracking, each providing a more molecular measure than the previous. The RMS values for a given segment of tracking can be averaged point by point with similar segments, producing a constructed average segment, analogous to an AER. Finally, if RMS values for individual segments are used, each trial will produce a large set of individual segments. Either average or median measures of central tendency can be used to summarize such data. Also, one can either delete or include epochs during which blinks occur. Iacono, Tuason and Johnson (1981) did not delete epochs of tracking contaminated by blinks, as they found that removing cycles containing blinks did not affect the median RMS score. The number of blinks did not differ between groups in their study, and subjects were asked repeatedly to refrain from

blinking. In this study subjects were asked twice before each trial to refrain from blinking, cycles containing blinks were not deleted, and median RMS measures resistant to the effects of blinks were analysed. The average RMS values may provide a more global measure of tracking ability influenced by a diversity of oculomotor events while the median values would be less susceptible to blinks. In this study more significant results were obtained using medians than averages, particularly for laterality effects.

The finding of higher RMS scores indicative of more disrupted SPEN at the faster .8 hz. tracking frequency was expected, and replicates several earlier reports of more impaired or inaccurate tracking at faster target velocities and higher frequencies of oscillation (Iacono and Lykken, 1976a, 1979b; Iacono, Tuason and Johnson, 1981; Levin, Lipton and Holzman, 1981; Lisburger, Evinger, Johanson and Fuchs, 1981; May, 1979; Miallet and Pichot, 1981; Rothenberg, Schottenfeld, Selkoe and Gross, 1980; Rothenberg and Selkoe, 1981).

Many studies have found an association of impaired SPEN with increasing age (Shagass, Amadeo and Overton, 1974; Holzman, Levy and Proctor, 1976; Kuechmeister, Linton, Meuller and White, 1977; Sharpe and Sylvester, 1978; Spooner, Sakala and Baloh, 1980; Iacono, Tuason and Johnson, 1981). Significant effects for age were not found by Holzman, et al (1974) for their entire sample, although they later reported that for the 72 normal

subjects there was a significant correlation ($r=.36$) between age and the number of velocity arrests during tracking (Holzman, et al, 1976). Pivik (1979) also failed to find significant effects of age on velocity arrest scores across or within groups of normals, psychiatric inpatients or outpatients, but the size of his groups was rather small and the velocity arrest score has been criticized on methodological grounds. In the present study, for subjects over 20 years of age there was a tendency to increasing tracking impairment with increasing age. The subjects aged 17 to 19 years had as a group tracking almost as poor as that of the three subjects over 40 years old. The impaired tracking of this younger group may be due to a higher representation among the younger group of schizotypes with an early onset form of psychopathology. Such subjects may make it into a university in the premorbid stage, but the end of the highest risk period for the typical, early onset 'male' form of schizophrenia is at about age 20, so such subjects would be found far less frequently among older university populations, having instead found their way into psychiatric populations. The limited range of age groups sampled and the small number of subjects over 30 years of age in this sample warrants caution in interpreting these data. Further analyses are required to rule out the possibility that sex and CLEM group differences in age related SPEM disruption. The covariance analyses performed do not rule out this possibility since the age - SPEM relationship

was nonmonotonic.

The male superiority for SPEM found in this study (for constructed average halfcycle data) replicates the findings of Kuechmeister, Linton, Mueller and White (1977), but not those of other investigators reporting the absence of significant sex differences in SPEM (Shagass, Amadeo and Overton, 1974; Pivik, 1979; Mialet and Pichot, 1981). The sex difference found by Kuechmeister, et al (1977) were more pronounced at the faster tracking velocity (20 degrees/second) than at the slower velocity (5 degrees/second). The three studies reporting negative findings with respect to sex differences in SPEM all used slower target frequencies corresponding to the .4 hz. tracking frequency used in the present study. Significant sex effects were found for .4 hz. but not .8 hz. constructed average halfcycles. The interaction of sex and frequency was significant for the 4-way ANOVA (SxCxFxD) involving constructed average halfcycle RMS scores for phase uncorrected data, with the difference between RMS scores at the two frequencies being greater for females. Further investigation of the relationship between sex and tracking accuracy should make use of a variety of target oscillation frequencies and target velocities.

The finding of an overall rightward SPEM superiority, averaged across subjects and frequencies and for both phase corrected and uncorrected data is unprecedented. Mialet and Pichot (1981) and Tomer, Mintz, Levy and Myslobodsky (1981) both

reported that tracking direction did not affect the number of saccades intervening during SPEM. Other SPEM studies have analysed full cycles of tracking defined by every other midline crossing, and so have not even considered the possibility of SPEM asymmetry. Tomer, et al (1981) did find, however, that leftward SPEM was more disrupted by saccadic intervention or pursuit arrests than rightward SPEM, during tracking while answering syllogisms, in schizophrenics and normal CLEM rightmovers. Both Mialet and Pichot (1981) and Tomer, et al (1981) studies assessed SPEM by counting saccades, while the present study utilized an RMS measure which may be sensitive to other errors of SPEM in addition to saccadic intervention. It is possible that the non-saccadic rather than saccadic sources of tracking error show lateralized effects. Tomer, et al (1981) used such a slowly moving target (5 degrees/second constant velocity), that their results may not be at all comparable to those of the present study, in which the slowest target frequency used, .4 hz., had an average target velocity of 24 degrees per second. Though the Mialet and Pichot (1981) study utilized a .4 hz. tracking frequency like the present study, the maximum and average target velocities in their study were slower because the target excursion was 20 degrees, while in this study it was 30 degrees.

The rightward SPEM superiority is consistent with the hypothesis of a right hemisphere dominance for "attention" and

the dependence of accurate SPEM on attentional processes. The rightward SPEM superiority is also consistent with the findings of Rosenberg (1980) that OKN is more strongly associated with right than left hemisphere activity, since OKN consists of alternating saccades and SPEM. The right hemisphere dominance for attention model cannot easily accommodate the finding that rightward SPEM superiority is associated with poorer overall tracking, as the opposite pattern of results would be expected on the basis of this model.

For median halfcycle and overall 13-cycle measures rightward SPEM RMS scores are lower than leftward SPEM. For constructed average halfcycles leftward SPEM RMS scores were lower than rightward RMS scores. Although the rightward halfcycles were on the whole better than leftward halfcycles, using a measure of central tendency to compare tracking directions, the SPEM errors during rightward tracking may have been consistently concentrated in certain parts of the halfcycle, producing larger RMS scores upon averaging, while leftward SPEM errors may have been more randomly distributed throughout the halfcycles, washing out larger deviations upon averaging. This suggests that, since SPEM is ipsilaterally mediated, the left hemisphere is more susceptible to transient non-systematic errors in SPEM, while the right hemisphere suffers more from systematically recurring errors, such as saccadic intervention at the point of maximum target velocity.

The constructed average halfcycle data have yet to be analysed point by point in the manner of Iacono and Lykken (1979a,b), to confirm that rightward SPEM is particularly disrupted (relative to leftward SPEM) at the target midline crossing. This pattern of results suggests that the right hemisphere's tracking ability is consistent but 'mediocre', while the left hemisphere has spurts of good tracking interspersed with more or less randomly occurring breakdowns of tracking performance. This may be seen as consistent with the literature reviewed on the relationship between hemispheric functional asymmetry and attention, in which it is suggested that the right hemisphere is dominant for 'sustained attention' and 'attention-activation' while the left hemisphere is dominant for 'selective attention'. When focussed on the task at hand the left hemisphere excels, but it may suffer more from distractibility or fatigue. The right hemisphere is, on the other hand 'stronger' or more consistent, but does not perform as well as the left can on tasks requiring 'focussed' or 'selective' attention. If this explanation of the present findings is tenable, one might expect monitor tracking or number reading, presumably enhancing selective attention, to have a greater effect on transient errors, improving leftward more than rightward SPEM.

The CLEM rightovers SPEM superiority relative to the leftovers for constructed average halfcycles is in direct conflict with the reports of Tomer and Mintz (1980) and Tomer,

et al (1981) that rightmovers show more impaired SPEM than leftmovers. A number of methodological differences between the studies could be related to this discrepancy. Tomer, et al (1981), Tomer and Mintz (1980) and Tomer, et al (1979) utilized a very different CLEM procedure. They asked 12 verbal and 12 spatial - emotional questions based on examples given by Schwartz, et al (1975), and designed to elicit CLEM lateralization related to question type variance. The questions used in this study were selected from a larger pool of questions using a statistical procedure designed to choose questions maximizing trait variance and neutralizing or minimizing question type effects (Bakan, et. al., 1974). Gur and Revich (1980) have argued that both question type and trait effects on CLEM exist, and different experimental procedures or analytic strategies may enhance or focus on one or the other. Tomer, et al (1981) also had subjects sit in the dark, in a semi-reclined position with a head rest, and with the CLEM questions presented through ear phones. In the present study subjects sat upright in a well lighted room, across a table from an experimenter asking them the CLEM questions face to face. Gur (1975) reported that trait effects were most salient when CLEM questions were asked in an experimenter facing condition, while question type effects emerged more clearly in an experimenter behind subject condition. Further research is needed to assess the comparability of various CLEM question lists and procedures

since interstudy differences could be the result of differences in the manner in which leftmovers and rightmovers are defined.

Tomer, et al (1981) and Tomer and Mintz (1980) also used a much slower target velocity than was used in the present study. It is possible that frequency or velocity of the tracking target may interact with CLEM effects, and perhaps leftmovers may be impaired relative to rightmovers in tracking high velocity targets, but are superior at tracking very slow targets such as that used by Tomer, et al (1981).

The association of leftward CLEM with vulnerability to psychopathology has been suggested by several investigators. Sandel and Alcorn (1980) found a preponderance of left CLEMs among patients with nonparanoid schizophrenia, depression and alcoholism. Winterbotham (1979) and Laing (1979) reported that leftmovers showed more torque and had higher scores on the Sc scale of the MMPI than rightmovers, although the validity of both torque and single scale MMPI Sc elevations as vulnerability markers for schizophrenia are questionable. Cole (1982) has found higher scores for leftmovers than rightmovers on an 'alexithymia' questionnaire, again with the suggestion of a left CLEM link with psychopathology. Alexithymia, the inability to express emotion verbally, may be seen as similar to the flattened affect of schizophrenics. If accuracy of SPEN is validated as a vulnerability marker by longitudinal studies, the results of the present study could be interpreted as at least

consistent with the hypothesis of an association of a preponderance of leftward CLEMS with vulnerability to psychopathology.

Iacono, et al (1981) found that schizophrenics show more phase lag than do normal subjects, and that while phase lag and tracking accuracy were inversely related in schizophrenics, the relationship was in the opposite direction in normal subjects. In the present study leftmovers showed more phase lag than rightmovers, and for the entire sample phase lag was positively and significantly related to tracking accuracy, replicating the previous report. Thus although leftmovers show more phase lag, they cannot be considered as poor trackers since they do not differ from the rightmovers on phase corrected RMS measures.

When phase corrected data were analysed, the main effects seen for sex and CLEM with phase uncorrected data disappeared, and significant sex by CLEM interaction effects emerged. For phase corrected .8 hz. overall 13 cycle RMS scores and leftward average halfcycle RMS scores, male leftmovers and female rightmovers had higher RMS values than male rightmovers and female leftmovers, respectively. For corrected .8 hz. rightward average halfcycle RMS scores the interaction barely approached significance, and thus was not nearly as strong as for leftward tracking. For phase corrected .8 hz. median rather than average halfcycle RMS scores neither tracking direction showed a significant effect of the sex by CLEM interaction, but the

effect was nearly significant for leftward tracking and only barely approached significance for rightward SPEM. Thus, although male leftmovers and female rightmovers showed more impaired SPEM overall than did male rightmovers and female leftmovers, respectively, this SPEM impairment was much more pronounced for leftward tracking than for rightward tracking.

The significant sex by CLEM interactions occurred only for the .8 hz. tracking frequency, suggesting a three way interaction of sex, CLEM and frequency. This three way interaction was significant for constructed average halfcycle RMS values in a four way ANOVA (SxCxFxL). It was also nearly significant in the four way ANOVA on phase corrected median halfcycle RMS scores. In all of these analyses cell means revealed that the greatest difference between the two frequencies was observed in male leftmovers and female rightmovers, while the smallest change over the frequencies was observed for male rightmovers and female leftmovers. The overall poorer tracking at the faster frequency may be interpreted in terms of increasing task difficulty with increasing target velocity. A greater difference in performance between the two frequencies may then be an indication of greater susceptibility to the performance decrement effects of increasing task difficulty. Just this sort of generalized performance decrement for difficult tasks has been well documented in schizophrenics. The greater SPEM impairment, especially at the higher

frequency, suggests that male leftmovers and female rightmovers may be populations with an overrepresentation of individuals 'at risk' or vulnerable to psychopathology.

Gur, Sackheim and Gur (1976) found that males with right hemisphericity showed more psychopathology than left hemisphericity males on the Manifest Symptom Questionnaire, while among females the reverse pattern occurred, with left hemisphericity being more closely associated with psychopathology than right hemisphericity. Their index of hemisphericity in this study was classroom seating position, which had previously been found to be significantly related to CLEM directionality (Gur, Gur and Marshalek, 1975). Moretti (1982) found that male leftmovers and female rightmovers had lower Verbal and Full Scale Wais IQ scores than male rightmovers and female leftmovers, respectively. Lower WAIS Verbal and Full Scale IQs have also been reported for schizophrenics (Gruzelier and Hammond, 1976) and children of schizophrenics (Gruzelier, Mednick and Schulsinger, 1979) compared to controls. Assuming that impaired SPEM is a psychophysiological correlate of psychopathology, the same pattern of results was observed in the present study. Male leftmovers and female rightmovers had more impaired SPEM and a greater deterioration of SPEM at the faster frequency than did male rightmovers or female leftmovers. Gur, et al (1976) interpreted their results in terms of a possible association of left hemisphericity with a masculine personality

and cognitive style and right hemisphericity with a feminine style. Presumably individuals whose hemisphericity related personality and cognitive style traits run counter to the culturally prescribed or preferred sex role stereotype will be more deviant and so will manifest a greater degree of psychopathology. The left moving males would have a right-brained feminine style and right moving females would have a left-brained masculine style, and the stress generated by trying to adjust to the sociocultural environment will be greater for these two groups than for the two groups whose hemisphericity related cognitive style is congruent with the sex role stereotypes.

Another possible explanation for the interaction of sex and CLEM in relation to psychopathology or risk is that there are sex differences in lateralization of function, lateralization processes are related to etiological factors in psychopathology, and the specific relationships between abnormal lateralization and psychopathological etiology differ between the sexes. Numerous sex differences in the lateralization of brain function have been reported (McGlone, 1980, review), suggesting that the male brain is more asymmetrically organized than the female brain, for both verbal and nonverbal functions. The role of abnormal lateralization in the etiology of psychopathology has been reviewed for schizophrenia, and abnormal lateralization has also been implicated in a variety of other psychopathologies

(Wexler, 1980; Marin and Tucker, 1981). The interaction of sex and hemispheric specialization in the etiology of psychopathology have been reviewed by Flor-Henry (1979b), who suggests that gender differences in hemispheric organization lead to unequal vulnerability to disturbances of cerebral function related to psychopathology. Given this perspective, it is reasonable to speculate that different characteristic patterns of lateralization will be found in male and female schizotaxics and schizophrenics. Flor-Henry (1979b) also suggested that female late onset schizophrenia is a different disorder from male early onset schizophrenia. If male and female schizotaxia are biologically different it is possible that each is associated with different patterns of hemisphericity, as is suggested by the results of this study.

The finding of this study that among normal female subjects rightmovers show more impaired SPEM than leftmovers (for phase corrected .8 hz. data) is consistent with the reports of Tomer and Mintz (1980) that rightmovers make more saccades during pursuit tracking than leftmovers, since they investigated only female subjects. It is also consistent with the leftmover SPEM superiority reported by Tomer, et al (1981) since the sample of normals in that investigation was heavily biased by an overrepresentation of females (20/25). Thus, the suggestion of Tomer, et al (1981) that rightward CLEM is associated with vulnerability to schizophrenia may apply only to females. A

crucial flaw in their studies was the failure to account for sex. Since many studies have demonstrated sex and CLEM interaction effects, and sex differences in lateralization processes have been well documented, all further studies of the relationship of lateralization or hemisphericity to psychopathology or vulnerability should use both male and female subjects, and should analyse data separately for the sexes as well as pooled across sexes.

The fact that male leftmovers and female rightmovers showed SPEM impairment more for leftward than rightward tracking suggests a threeway interaction of sex, CLEM and tracking laterality. This three way interaction was nearly significant in the four way ANOVAS on phase corrected and uncorrected median 1/2 cycle RMS scores. Female rightmovers showed the greatest RSPEM superiority, followed by male leftmovers while female leftmovers and male rightmovers showed smaller asymmetries, averaged across the two frequencies and across subjects within the sex by CLEM groups. A significant sex by CLEM interaction effect was also seen in the two way ANOVA on .4 hz. phase corrected median lateral difference score, indicating an interaction of sex and CLEM with SPEM asymmetry for individual SPEM laterality indices as well as for laterality effects averaged across individuals within a group. Male leftmovers and female rightmovers had more negative lateral difference scores than male rightmovers and female leftmovers, respectively,

indicating a greater rightward SPEM superiority in the former two groups. These two groups also showed greater overall SPEM impairment, and especially an impairment of leftward tracking. These results suggest that 'RSPeM superiority' is a superiority by default, that is, it is really more of a LSPeM deficit. The groups with more impairment of overall tracking differed from those with better overall tracking more for leftward than for rightward tracking. This suggests that a leftward SPEM deficit, reflected in more negative lateral difference scores, is associated with impaired overall tracking and perhaps is also associated with vulnerability or high risk for psychopathology.

Thus, the findings with sex and CLEM as grouping factors and lateral difference scores as the dependent variable suggested an association of RSPeM superiority or LSPeM deficit with an impairment of overall tracking performance. This was further investigated using lateral difference scores as the grouping factor (RSPeM vs. LSPeM) and other SPEM variables as the dependent variables. RSPeM subjects (defined using .4 hz. corrected medians) had significantly higher RMS scores than LSPeMers for the overall RMS, constructed average halfcycle RMS, .4 hz. leftward median halfcycle RMS, as well as for .8 hz. median halfcycle RMS scores in both directions. The disrupted tracking of the RSPeM group was seen especially for leftward tracking, while the LSPeM group did not show a corresponding impairment of rightward tracking relative to the RSPeM group.

These results confirm the suggested association of a leftward SPEM deficit or rightward SPEM superiority (by default) with impaired overall tracking ability.

Individual SPEM asymmetry at the .4 hz. frequency was associated with many indices of SPEM accuracy, while at the .8 hz frequency SPEM asymmetry was associated only with .8 hz. leftward median halfcycle RMS scores. Thus, .8 hz. RSPEM superiority is associated not with an overall SPEM impairment but rather with a specific .8 hz. leftward tracking deficit. The .8 hz. SPEM asymmetry is also related to an MMPI indicator of schizotypy, with RSPEMers having higher scores on this index than LSPEMers. The RSPEM group also had higher single scale scores on the Depression and Social Introversion scales, as well as lower scores on the Hypomania scale compared to the LSPEM group. Although MMPI associations occurred only for .8 hz asymmetry, and overall SPEM associations occurred only for .4 hz. asymmetry, the phase corrected median lateral difference scores for the two frequencies were significantly correlated ($r=.2194$, $p<.016$). The findings of impaired overall SPEM, a leftward tracking deficit, and high personality test scores on a schizotypy scale for subjects with rightward SPEM superiority suggest that RSPEM superiority or rather leftward SPEM impairment, is associated with vulnerability to schizophrenia spectrum psychopathology. This is consistent with the large body of evidence revealed earlier for a left hemisphere dysfunction

involved in the etiology of at least some types of schizophrenia. Normal individuals who manifest subtle left hemisphere performance deficits expressed as impaired leftward SPEM show personality test results indicative of schizotypy as well as overall SPEM deficits, a putative psychophysiological vulnerability marker. These findings within a normal population, in which manifest psychopathology is relatively infrequent and not severe, suggest that SPEM asymmetries, particularly impaired leftward SPEM, deserve further study in clinical populations. It is hypothesized that actively psychotic schizophrenics, schizophrenics in remission, and the first degree relatives of schizophrenics will all show greater leftward than rightward SPEM impairment, and the magnitude of this asymmetry will be greater than in normal control subjects.

Asymmetry of SPEM was influenced not only by a sex by CLEM interaction, but also by sex main effects. A significant sex by laterality interaction occurred for the four way ANOVA on phase corrected median halfcycle RMS scores, such that the difference between rightward and leftward RMS values was greater for females than for males, averaged across the two frequencies and across subjects within each sex. Sex effects were also seen for the individual laterality indices. Significant main effects for sex were seen in three way ANOVAS performed on phase corrected median laterality quotient scores, and a nearly significant sex effect was observed for phase corrected median lateral

difference scores. In all of these analyses females had more negative laterality indices than males, averaged across the two frequencies and across CLEM groups. This indicates that the RSPEN superiority was greater among females. Females also performed more poorly than males on overall SPEN measures. These results suggest a convergence of RSPEN superiority and impaired overall tracking. This is again consistent with the hypothesis of an association of RSPEN superiority or leftward SPEN deficit with vulnerability to psychopathology.

These results also suggest that females in this sample are characterized by greater vulnerability than are the males, provided of course that the SPEN markers of vulnerability receive further validation. Many sex differences have been reported in the schizophrenia literature. Of particular interest here are the findings that in men schizophrenia is characterized by poor premorbid social competence, early onset, and 'typical' schizophrenic clinical course, while in women schizophrenia has a later onset, good premorbid social competence, and an atypical course (Lewine, 1979, 1981, review). In the present investigation the use of a university population would act to select out schizotaxic males, since attendance at university would require at least moderately good social competence and so more schizotaxic females would find their way into such a sample. The average age of this sample was 23.6 years. Since the age of highest risk in males is 20 years and in females is

almost a decade later, the present sample would very likely contain more schizotaxic females, the males having never made it into the sample by virtue of early onset disease preventing their enrollment in university. If the sample was biased to include more schizotaxic females than schizotaxic males (by virtue of the social competence and age selection), then it would also be expected that the schizotaxia occurring in this sample would also involve vulnerability to a more atypical and benign form of the disorder, characteristic of female schizophrenics. Interestingly, Jeste, et al (1982) found an excess of females in their group of schizophrenics with abnormal CT scan asymmetries. Abnormal asymmetries were also found to be associated with a milder or atypical form of schizophrenia (Luchins, et al, 1979; Wyatt, et al, 1981). Thus, the abnormal asymmetry of SPEN association with poor overall tracking and related to female gender in this study may be a vulnerability marker for the less severe, good premorbid, atypical, later onset schizophrenia characteristic of female schizophrenics (although such atypical forms can occur in males as well). Of course these speculations require further experimental confirmation. It is also possible that the SPEN irregularity is a marker for all sorts of schizotaxia, but the sample characteristics of this study were such that the 'female' or atypical variety was overrepresented. If the former speculation is borne out by further study, the SPEN impairment, particularly

for leftward tracking, could be a useful tool for the biological subclassification of schizophrenia: useful for achieving biological homogeneity of schizophrenic samples for research, and potentially useful for diagnosis, prognosis, and treatment implications.

Evidence was reviewed that implicates ipsilateral mediation for SPEM and contralateral mediation for saccades or CLEM, at the cortical level. CLEM has been suggested as an index of hemisphericity, i.e., characteristic or preferential hemispheric activation. If smooth pursuit were performed more accurately by the preferred or more activated hemisphere, one would expect leftmovers to show a rightward SPEM superiority and rightmovers a leftward SPEM superiority. The data presented by Tomer, et al (1981) shows this pattern for undistracted tracking, using the number of saccades as the measure of tracking impairment. In their study rightmovers made more saccades during rightward than leftward tracking, while leftmovers made more saccades during leftward than rightward tracking, although these investigators did not report statistical tests of these relationships apparent in their table. For tracking while answering syllogisms these asymmetries were reversed. In the present study the leftmover RSPEN superiority and rightmover LSPEN superiority were found only among males, while the opposite pattern was found for females, among whom rightmoving was associated with RSPEN superiority. The reason for this sex difference in the

relationship between CLEM and SPEM asymmetries is not clear.

When the SPEM asymmetry - CLEM relationship is considered for both sexes together, there appears to be an independence of these measures of oculomotor asymmetry. This independence of CLEM and SPEM asymmetries might be the result of the fact that neural representation of these ocular movements are divergent not only along the lateral axis but also along the posterior anterior gradient. Saccades or CLEM are thought to involve predominantly the frontal lobes while SPEM involves primarily the posterior parietal and occipital areas. Lateralization of posterior ocular control mechanisms governing slow eye movements could be independent of the lateralization of more anterior ocular control mechanisms governing rapid eye movements. The dissociation of saccadic and SPEM tracking ability observed by Iacono, et al (1981) in schizophrenics suggests that this is indeed the case. This explanation runs into difficulty however when one considers that these oculomotor asymmetries are related significantly in each sex but in opposite directions. It is possible that the hemispheric representation of SPEM and or CLEM differs between the sexes. The neurological literature suggesting ipsilateral cortical mediation of SPEM is based predominantly on male neurological patients. Larger numbers of subjects of both sexes with unilateral brain damage are needed to test the hypothesis that asymmetric representation of SPEM or saccadic eye movement systems differs between males and females.

It may be that there are sex differences in the lateralization of oculomotor control. If males had primarily ipsilateral control of SPEM but females had a greater contralateral contribution to SPEM control the results obtained might be expected. Each hemisphere contains cells that are active during SPEM in either direction, so each hemisphere has the potential to control SPEM in either direction. Perhaps the proportions of ipsilateral versus contralateral smooth pursuit cells differs between the sexes.

Impaired leftward SPEM, rightward SPEM and the average of leftward and rightward SPEM for .4 hz. tracking was related to Golden and Meehl's MMPI schizotypy scale. This index is a putative personality test marker for detecting the schizoid taxon, or schizotaxic individuals who are vulnerable to schizophrenic spectrum psychopathology. This association of overall SPEM accuracy with an MMPI schizotaxic indicator lends support to the previous suggestions that SPEM disorder may provide a useful marker of vulnerability to schizophrenia (Holzman, 1979).

The empirical basis for the use of impaired SPEM performance as a vulnerability marker has been reviewed and includes demonstrations of higher MZ than DZ twin concordance for impaired tracking, disordered SPEM in half of the first degree relatives of schizophrenics, many of whom show no obvious psychiatric disorder, disordered SPEM in remitted

schizophrenics, and high retest reliability indicating trait stability. If the SPEM asymmetries investigated in this study are to be pursued as putative vulnerability markers these same demonstrations of trait stability and genetic influence would be required. Evidence supporting the validity of these putative vulnerability markers would also be provided by longitudinal predictive studies of the 'biologically at risk' paradigm. Indeed, the ability to predict later psychopathology is the most clinically relevant fact of vulnerability marker validation. In the absence of retest data for this sample, or longitudinal followup involving psychiatric evaluation, no definitive statements about SPEM asymmetries as vulnerability markers can be made. As a cross sectional study only promising leads and interesting speculations can be offered in this direction by this investigation. Nevertheless, the convergence of MMPI, sex and CLEM, and SPEM indices of susceptibility to psychopathology offers some convergent support for the validity of each, since this convergence was predicted on the basis of previous investigations and theoretical considerations of the relationships between lateralization of function, oculomotor control systems and psychopathology.

The present study had several factors working against finding the predicted relationships. First, the sample size of 121 was quite small as high risk studies go. The first 'biologically at risk' study of Buchsbaum, Coursey and Murphy

(1976) started with a sample of 375 students. The MMPI screening study of Haier, et al (1979) started with a sample of 385 students. In the latter study 49 subjects with at least one scale T score greater than or equal to 90 (4 SD above the mean) were found. Subjects with such elevations were shown to have a high incidence of RDC diagnoses, indicative of previously undiagnosed psychopathology. Only one of their subjects received a schizophrenic diagnosis. SPEN studies have reported base rates of impaired SPEN in the normal population ranging from 7% to 25%. Although such base rate determinations should be made for much larger populations, it is likely that 25% represents an upper limit. Of course what is defined as 'impaired' is arbitrarily determined. SPEN measures produce a range of individual values and cutoff points in most studies have been quite arbitrary. Buchsbaum, et al (1976) compared upper and lower deciles of MAO blood levels. At any rate, it seems likely that in the normal population the incidence of individuals with a strong genetic diathesis is not high. The average base rate for diagnosed schizophrenia is about .85%, although the base rate for vulnerability or schizotaxia must be higher, since not all susceptible individuals will become schizophrenic. Even if the vulnerability base rate were 10% in the normal population, very large samples would be required to find enough vulnerable individuals to consistently produce significant results. The power of the marker variable may also be enhanced by comparing

only extreme groups, such as upper and lower deciles. To achieve even moderate sized comparison groups hundreds of subjects must be screened on the marker variable. This study used a relatively small sample and the relationships among variables were examined, for the most part, along the entire range, not just for extreme groups.

In conjunction with the small sample size, another factor working against finding significant results related to psychopathology or vulnerability in this study was the use of a university population. It is likely that high intelligence protects against psychopathology, and a university population is preselected for higher than average intelligence. Thus, the expected base rate in a university population would be lower than in lower SES unemployed, for instance. The variance in pathological indices would be lower and means biased toward the 'healthy' end of the continuum in a university sample, thus making it more difficult to demonstrate relationships among putative vulnerability markers.

Despite the small sample and healthy university population, the present investigation found the predicted convergence of MMPI schizotypy, impaired SPEN, and a sex by CLEM interaction. The results are only of a suggestive or pilot study nature, but they provide promising leads for further, larger, longitudinal 'biological high risk' studies. If normal individuals identified as 'at risk' by the SPEN and CLEM tests were to subsequently

manifest a higher incidence of psychopathology than controls designated as 'low risk' by the oculomotor measures, these variables could be used as tools for large scale screening of populations for individuals at risk. Both measures are quickly and easily administered and involve relatively simple procedures.

The SPEN analysis would not necessarily require the expensive computer equipment used in the present study, as the analytic programming could be implemented on new inexpensive microcomputers. Also, measures highly correlated with pursuit tracking ability and of the same nature could be used. Kennedy, Bittner and Jones (1981) found a high correlation ($r=.78$) between performance on Atari's Air Combat Maneuvering video game and conventional compensatory tracking, in which the subject keeps a moving circle centered in a horizontal track by making left-right movements of a control stick. This sort of psychomotor tracking task was found to differentiate schizophrenics from normals just as SPEN RMS scores did (Iacono, Tuason and Johnson, 1981). Kennedy, et al (1981) concluded:

"The implication is that the video game, a pursuit tracking task, measures the same thing as compensatory tracking, only more reliably. It appears that this particular video game may have a future as a portable, low cost substitute for traditional computer driven laboratory tracking tasks. This future, moreover, may include predictive testing and training as well as evaluation of performance."

The cost effectiveness and ease of such a tracking task measure

of vulnerability could make large scale high risk screening and preventive intervention programs a more viable prospect. The video game could easily be modified to yield scores for both leftward and rightward tracking ability. Asymmetries of SPEN may, if validated as genetically influenced stable traits related to schizophrenic vulnerability, provide one of the least expensive, quickest, and most efficient means of screening populations for individuals 'biologically at risk' for psychopathology involving abnormal lateralization of brain function. It may also provide an inexpensive means for the biological subclassification of schizophrenics into groups which are biologically homogenous with respect to certain characteristics of lateralization.

Appendix I - CLEM Questions

1. What is the meaning of the proverb: A watched pot never boils.
2. What is the meaning of the proverb: It is an ill wind that blows no one good fortune.
3. Make up a sentence using two forms of the same verb.
4. Tell me two verbs beginning with "N".
5. What is the meaning of the proverb: A poor worker blames his tools.
6. Spell therapeutic.
7. What is the meaning of the proverb: More than enough is too much.
8. List two adverbs.
9. What is the meaning of the proverb: Lend your money and lose your friends.
10. What is the meaning of the proverb: Call no man happy till he's dead.
11. List two prepositions.
12. What is the meaning of the proverb: Words should be weighed not counted.
13. What is the meaning of the proverb: He is rich who has few wants.
14. Define inflation.
15. What is the meaning of the proverb: A rolling stone gathers no moss.
16. Make up a sentence using two adverbs.
17. Tell me two verbs beginning with "R".

18. What is the meaning of the proverb: The hardest work is to go idle.
19. What is the meaning of the proverb: What saddens a wise man gladdens a fool.
20. Define the word economics.

Appendix II - ANOVA TABLES

TABLE 1a

CELL MEANS FOR CORRECTED MEDIAN HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4LMED	0.21414	0.21203	0.16195	0.16560	0.24093	0.15183
C4RMED	0.20997	0.20899	0.16254	0.15885	0.15757	0.13454
C8LMED	0.42637	0.34874	0.33641	0.33705	0.35516	0.42680
C8RMED	0.41344	0.38433	0.32312	0.33277	0.33547	0.37976
MARGIN	0.31598	0.28852	0.24601	0.24857	0.27228	0.27323
N	30	11	20	25	10	23

STANDARD DEVIATIONS FOR CORRECTED MEDIAN HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4LMED	0.15866	0.11571	0.09567	0.13488	0.17732	0.10404
C4RMED	0.14875	0.11526	0.10324	0.10229	0.08792	0.09041
C8LMED	0.19806	0.14240	0.13253	0.17727	0.20434	0.20585
C8RMED	0.17873	0.17903	0.12527	0.17085	0.20739	0.15665

TABLE 1b

ANALYSIS OF VARIANCE - SEX x CLEM x FREQUENCY x DIRECTION
 DEPENDENT VARIABLE - CORRECTED MEDIAN HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	30.24355	1	30.24355	445.99	0.0000
SEX	0.03560	1	0.03560	0.52	0.4702
CLEM	0.05373	2	0.02687	0.40	0.6738
SC	0.21635	2	0.10817	1.60	0.2074
ERROR	7.66270	113	0.06781		
FREQ	3.44577	1	3.44577	184.25	0.0000
FS	0.00629	1	0.00629	0.34	0.5631
FC	0.05565	2	0.02783	1.49	0.2302
FSC	0.10196	2	0.05098	2.73	0.0698
ERROR	2.11327	113	0.01870		
LR	0.02156	1	0.02156	6.68	0.0110
LS	0.02294	1	0.02294	7.11	0.0088
LC	0.00405	2	0.00203	0.63	0.5355
LSC	0.01957	2	0.00978	3.03	0.0522
ERROR	0.36465	113	0.00323		
FL	0.00192	1	0.00192	0.90	0.3455
FLS	0.00029	1	0.00029	0.14	0.7125
FLC	0.01893	2	0.00946	4.43	0.0140
FLSC	0.00181	2	0.00091	0.42	0.6553
ERROR	0.24136	113	0.00214		

TABLE 2a

CELL MEANS FOR CORRECTED CONSTRUCTED AVERAGE HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIREC	FEMALE RIGHTMVR
C4LRMS	1.05203	1.05114	1.05189	1.05589	1.07567	1.05149
C4RRMS	1.05241	1.05174	1.05187	1.05616	1.07661	1.05166
C8LRMS	1.47825	1.48097	1.47430	1.47948	1.47338	1.47749
C8RRMS	1.47763	1.50698	1.47457	1.47802	1.47352	1.47759
MARGIN	1.26508	1.27271	1.26316	1.26739	1.27480	1.26456
N	30	11	20	25	10	23

STANDARD DEVIATIONS FOR CORRECTED CONSTRUCTED AVERAGE HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIREC	FEMALE RIGHTMVR
C4LRMS	0.00280	0.00359	0.00374	0.01844	0.07392	0.00364
C4RRMS	0.00260	0.00352	0.00460	0.01847	0.07416	0.00360
C8LRMS	0.01020	0.01113	0.00836	0.01547	0.00875	0.00863
C8RRMS	0.01003	0.09505	0.00883	0.01495	0.00848	0.00804

TABLE 2b

ANALYSIS OF VARIANCE - SEX x CLEM x FREQUENCY x DIRECTION
 DEPENDENT VARIABLE -CORRECTED CONSTRUCTED AVERAGE HALFCYCLE

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	647.17349	1	647.17349	30292.00	0.0000
SEX	0.00038	1	0.00038	0.42	0.5162
CLEM	0.00560	2	0.00280	3.16	0.0463
SC	0.00002	2	0.00001	0.01	0.9886
ERROR	0.10014	113	0.00089		
FREQ	17.99002	1	17.99002	22236.06	0.0000
FS	0.00561	1	0.00561	6.94	0.0096
FC	0.00032	2	0.00016	0.20	0.8202
FSC	0.00899	2	0.00450	5.56	0.0050
ERROR	0.09142	113	0.00081		
LR	0.00050	1	0.00050	2.76	0.0994
LS	0.00049	1	0.00049	2.70	0.1034
LC	0.00087	2	0.00043	2.39	0.0966
LSC	0.00068	2	0.00034	1.86	0.1607
ERROR	0.02054	113	0.00018		
FL	0.00034	1	0.00034	1.87	0.1746
FLS	0.00052	1	0.00052	2.85	0.0944
FLC	0.00074	2	0.00037	2.04	0.1354
FLSC	0.00071	2	0.00035	1.94	0.1490
ERROR	0.02067	113	0.00018		

TABLE 3

CELL MEANS FOR CORRECTED OVERALL 13-CYCLE RMS

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4RMS	0.27698	0.27595	0.19490	0.19352	0.23179	0.18452
C8RMS	0.49424	0.41958	0.37213	0.38222	0.39677	0.46136
MARGINO.	0.38561	0.34776	0.28352	0.28787	0.31428	0.32294
N	30	11	20	25	10	23

STANDARD DEVIATIONS FOR CORRECTED OVERALL 13-CYCLE RMS

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4RMS	0.19453	0.12565	0.12698	0.11567	0.13452	0.11179
C8RMS	0.19638	0.14682	0.12285	0.18171	0.23998	0.18544

ANALYSIS OF VARIANCE FOR SEX x CLEM x FREQUENCY
DEPENDENT VARIABLE - CORRECTED OVERALL 13-CYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	21.08515	1	21.08515	488.97	0.0000
SEX	0.04711	1	0.04711	1.09	0.2981
CLEM	0.05666	2	0.02833	0.66	0.5204
SC	0.22568	2	0.11284	2.62	0.0775
ERROR	4.87272	113	0.04312		
FREQ	1.90896	1	1.90896	189.92	0.0000
FS	0.01193	1	0.01193	1.19	0.2782
FC	0.03720	2	0.01860	1.85	0.1619
FSC	0.04933	2	0.02466	2.45	0.0905
ERROR	1.13582	113	0.01005		

TABLE 4

CELL MEANS FOR PHASE LAG

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
LAG4	-2.23333	-4.45455	-3.25000	-0.84000	-3.10000	-2.95652
LAG8	0.70000	-0.45455	0.10000	3.32000	0.50000	0.30435
MARGIN	-0.76667	-2.45455	-1.57500	1.24000	-1.30000	-1.32609
N	30	11	20	25	10	23

STANDARD DEVIATIONS FOR PHASE LAG

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
LAG4	3.72950	3.90803	1.58529	5.69854	4.62961	3.87859
LAG8	4.08656	2.38175	1.83246	5.28930	4.79004	4.31103

ANALYSIS OF VARIANCE FOR SEX x CLEM x FREQUENCY
DEPENDENT VARIABLE - PHASE LAG SCORES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	213.69087	1	213.69087	6.79	0.0104
SEX	65.01695	1	65.01695	2.07	0.1534
CLEM	201.45062	2	100.72531	3.20	0.0445
SC	37.09848	2	18.54924	0.59	0.5564
ERROR	3556.39157	113	31.47249		
FREQ	634.39029	1	634.39209	295.85	0.0000
FS	0.76031	1	0.76031	0.35	0.5527
FC	1.81110	2	0.90555	0.42	0.6566
FSC	7.55744	2	3.77872	1.76	0.1763
ERROR	242.30572	113	2.14430		

TABLE 5

CELL MEANS FOR CORRECTED MEDIAN LATERAL DIFFERENCE

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4MLD	-0.00417	-0.00304	0.00060	-0.00675	-0.08336	-0.01730
C8MLD	-0.01293	0.03559	-0.01329	-0.00428	-0.01969	-0.04704
MARG	-0.00855	0.01628	-0.00635	-0.00552	-0.05152	-0.03217
N	30	11	20	25	10	23

STANDARD DEVIATIONS FOR CORRECTED MEDIAN LATERAL DIFFERENCE

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4MLD	0.05953	0.06485	0.05029	0.05895	0.10375	0.03225
C8MLD	0.08533	0.07486	0.05345	0.08242	0.10642	0.10214

ANALYSIS OF VARIANCE - SEX x CLEM x FREQUENCY
DEPENDENT VARIABLE - CORRECTED MEDIAN LATERAL DIFFERENCE

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	0.04313	1	0.04313	6.68	0.0110
SEX	0.04588	1	0.04588	7.11	0.0088
CLEM	0.00811	2	0.00405	0.63	0.5355
SC	0.03913	2	0.01957	3.03	0.0522
ERROR	0.72931	113	0.00645		
FREQ	0.00383	1	0.00383	0.90	0.3455
FS	0.00058	1	0.00058	0.14	0.7125
FC	0.03786	2	0.01893	4.43	0.0140
FSC	0.00362	2	0.00181	0.42	0.6553
ERROR	0.48271	113	0.00427		

TABLE 6

CELL MEANS FOR CORRECTED MEDIAN LATERAL QUOTIENT

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4MLQ	-0.35711	-0.65750	-0.26395	-0.25373	-14.54472	-5.23865
C8MLQ	-0.85172	4.40816	-2.03068	-0.48732	-2.84849	-3.85065
MARG	-0.60442	1.87533	-1.14731	-0.37052	-8.69660	-4.54465
N	30	11	20	25	10	2

STANDARD DEVIATIONS FOR CORRECTED MEDIAN LATERAL QUOTIENT

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4MLQ	9.98760	12.94410	14.20951	11.66358	14.36626	10.39256
C8MLQ	10.49293	7.38632	8.73112	11.96485	12.10270	11.07383

ANALYSIS OF VARIANCE - SEX x CLEM x FREQUENCY
DEPENDENT VARIABLE - CORRECTED MEDIAN LATERAL QUOTIENT

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	1017.16720	1	1017.16720	6.64	0.0113
SEX	1054.79257	1	1054.79257	6.88	0.0099
CLEM	389.46705	2	194.73353	1.27	0.2845
SC	889.23892	2	444.61946	2.90	0.0590
ERROR	17312.69394	113	153.20968		
FREQ	342.55399	1	342.55399	3.45	0.0660
FS	141.07133	1	141.07133	1.42	0.2360
FC	648.09832	2	324.04916	3.26	0.0420
FSC	81.09762	2	40.54881	0.41	0.6659
ERROR	11229.32844	113	99.37459		

TABLE 7

CELL MEANS and SD FOR CORRECTED .8 HZ. LEFTWARD MEDIAN HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C8LMED	0.42637	0.34874	0.33641	0.33705	0.35516	0.42680
N	30	11	20	25	10	23
SD	0.19806	0.14240	0.13253	0.17727	0.20434	0.20585

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .8 HZ. LEFTWARD MEDIAN HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARES	F	TAIL PROBABILITY
MEAN	13.90827	1	13.9082	420.63	0.0000
SEX	0.00016	1	0.00016	0.00	0.9453
CLEM	0.01523	2	0.00761	0.23	0.7947
SC	0.19482	2	0.09741	2.95	0.0566
ERROR	3.73637	113	0.03307		

TABLE 8

CELL MEANS and SD FOR CORRECTED .8 HZ. RIGHTWARD MEDIAN HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
CORMED	0.41344	0.38433	0.32312	0.33277	0.33547	0.37976
N	30	11	20	25	10	23
SD	0.17873	0.17903	0.12527	0.17085	0.20739	0.15665

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .8 HZ. RIGHTWARD MEDIAN HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	13.15015	1	13.15015	468.39	0.0000
SEX	0.01485	1	0.01485	0.53	0.4685
CLEM	0.01149	2	0.00574	0.20	0.8153
SC	0.11655	2	0.05827	2.08	0.1302
ERROR	3.17253	113	0.02808		

TABLE 9

CELL MEANS and SD FOR CORRECTED .4 HZ. LEFTWARD
CONSTRUCTED AVERAGE HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4LRMS	1.05203	1.05114	1.05189	1.05589	1.07567	1.05149
N	30	11	20	25	10	23
SD	0.00280	0.00359	0.00374	0.01844	0.07392	0.00364

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .4 HZ. LEFTWARD
CONSTRUCTED AVERAGE HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	112.29869	1	112.29869	217806.38	0.0
SEX	0.00219	1	0.00219	4.25	0.0415
CLEM	0.00200	2	0.00100	1.94	0.1480
SC	0.00230	2	0.00115	2.23	0.1122
ERROR	0.05826	113	0.00052		

TABLE 10

CELL MEANS and SD FOR CORRECTED .4 HZ. RIGHTWARD
CONSTRUCTED AVERAGE HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4RRMS	1.05241	1.05174	1.05187	1.05616	1.07661	1.05166
N	30	11	20	25	10	23
SD	0.00260	0.00352	0.00460	0.01847	0.07416	0.00360

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .4 HZ. RIGHTWARD
CONSTRUCTED AVERAGE HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	112.38190	1	112.38190	216412.31	0.0000
SEX	0.00226	1	0.00226	4.34	0.0394
CLEM	0.00224	2	0.0011	2.15	0.1207
SC	0.00235	2	0.00117	2.26	0.1092
ERROR	0.05868	113	0.00052		

TABLE 11

CELL MEANS and SD FOR CORRECTED .8 HZ RIGHTWARD CONSTRUCTED AVERAGE HALFCYCLES

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C8RRMS	1.47763	1.50698	1.47457	1.47802	1.47352	1.47759
N	30	11	20	25	10	23
SD	0.01003	0.09505	0.00883	0.01495	0.00848	0.00804

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .8 HZ. RIGHTWARD
CONSTRUCTED AVERAGE HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	220.84854	1	220.84854	244222.75	0.0000
SEX	0.00252	1	0.00252	2.79	0.0975
CLEM	0.00308	2	0.00154	1.70	0.1872
SC	0.00532	2	0.00266	2.94	0.0567
ERROR	0.10218	113	0.00090		

TABLE 12

CELL MEANS and SD FOR CORRECTED .8 HZ. OVERALL 13-CYCLE RMS

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
CBRMS	0.49424	0.41958	0.37213	0.38222	0.39677	0.46136
N	30	11	20	25	10	23
SD	0.19638	0.14682	0.12285	0.18171	0.23998	0.18544

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .8 HZ. OVERALL 13-CYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	17.84139	1	17.84139	546.66	0.0000
SEX	0.00581	1	0.00581	0.18	0.6738
CLEM	0.01839	2	0.00920	0.28	0.7550
SC	0.24277	2	0.12139	3.72	0.0273
ERROR	3.68797	113	0.03264		

TABLE 13

CELL MEANS AND SD FOR .4 HZ. PHASE LAG

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIREC	FEMALE RIGHTMVR
LAG4	-2.23333	-4.45455	-3.25000	-0.84000	-3.1000	-2.95652
N	30	11	20	25	10	23
SD	3.72950	3.90803	1.58529	5.69854	4.62961	3.87859

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - .4 HZ. PHASE LAG

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	792.22995	1	792.2299	46.94	0.0000
SEX	25.85775	1	25.85775	1.53	0.2184
CLEM	100.37358	2	50.18679	2.97	0.0551
SC	8.10428	2	4.05214	0.24	0.7869
ERROR	1907.06046	113	16.87664		

TABLE 14

CELL MEANS and SD FOR .8 HZ. PHASE LAG

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
LAG8	0.70000	-0.45455	0.10000	3.32000	0.50000	0.30435
N	30	11	20	25	10	23
SD	4.08656	2.38175	1.83246	5.28930	4.79004	4.31103

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - .8 HZ. PHASE LAG

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	55.85121	1	55.85121	3.34	0.0704
SEX	39.91951	1	39.91951	2.38	0.1253
CLEM	102.88814	2	51.44407	3.07	0.0502
SC	36.55164	2	18.27582	1.09	0.3391
ERROR	1891.63684	113	16.74015		

TABLE 15

CELL MEANS and SD FOR CORRECTED .8 HZ. AVERAGE OF
LEFTWARD AND RIGHTWARD MEDIAN HALFCYCLE RMS

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
CBAMED	0.41991	0.36653	0.32977	0.33491	0.34531	0.40328
N	30	11	20	25	10	23
SD	0.18375	0.15736	0.12615	0.16914	0.19888	0.17564

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .8 HZ. AVERAGE OF
LEFTWARD AND RIGHTWARD MEDIAN HALFCYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	13.52655	1	13.52655	470.24	0.0000
SEX	0.00299	1	0.00299	0.10	0.7477
CLEM	0.00765	2	0.00382	0.13	0.8756
SC	0.15078	2	0.07539	2.62	0.0772
ERROR	3.25046	113	0.02877		

TABLE 16

CELL MEANS and SD FOR CORRECTED .4 HZ. MEDIAN LATERAL DIFFERENCE

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4MLATD	-0.00417	-0.00304	0.00060	-0.00675	-0.08336	-0.01730
N	30	11	20	25	10	23
SD	0.05953	0.06485	0.05029	0.05895	0.10375	0.03225

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .4 HZ. MEDIAN LATERAL DIFFERENCE

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	0.03634	1	0.03634	10.37	0.0017
SEX	0.02840	1	0.02840	8.10	0.0052
CLEM	0.02313	2	0.01156	3.30	0.0405
SC	0.02314	2	0.01157	3.30	0.0404
ERROR	0.39607	113	0.00351		

TABLE 17

CELL MEANS and SD FOR CORRECTED .4 HZ. MEDIAN LATERAL QUOTIENT

	MALE LEFTMVR	MALE BIDIRECT	MALE RIGHTMVR	FEMALE LEFTMVR	FEMALE BIDIRECT	FEMALE RIGHTMVR
C4MLQ	-0.35711	-0.65750	-0.26395	-0.25373	-14.54472	-5.23865
N	30	11	20	25	10	23
SD	9.98760	12.94410	14.20951	11.66358	14.36626	10.39256

ANALYSIS OF VARIANCE FOR SEX x CLEM
DEPENDENT VARIABLE - CORRECTED .4 HZ. MEDIAN LATERAL QUOTIENT

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	1270.14416	1	1270.14416	9.03	0.0033
SEX	983.67926	1	983.67926	6.99	0.0094

CLEM	810.57531	2	405.28765	2.88	0.0603
SC	750.50431	2	375.25215	2.67	0.0739
ERROR	15903.16463	113	140.73597		

TABLE 18

CELL MEANS and SDs FOR CORRECTED .4 HZ. LEFTWARD MEDIAN HALFCYCLES

AGE	LE20	LE25	LE30	LE35	LE40	GT40
C4LMED	0.22205	0.13565	0.22027	0.13927	0.1663	0.24787
N	44	42	19	7	4	3
SD	0.15036	0.08671	0.16213	0.08965	0.11898	0.15358

ANALYSIS OF VARIANCE FOR AGE
DEPENDENT VARIABLE - CORRECTED .4 HZ. LEFTWARD HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	1.55118	1	1.55118	92.67	0.0000
AGE	0.21421	5	0.04284	2.56	0.0311
ERROR	1.89147	113	0.01674		

TABLE 19

CELL MEANS and SDs FOR CORRECTED .4 HZ. RIGHTWARD MEDIAN HALFCYCLES

AGE	LE20	LE25	LE30	LE35	LE40	GT40
C4RMED	0.21520	0.11986	0.18087	0.15263	0.19263	0.23730
N	44	42	19	7	4	3
SD	0.13913	0.06345	0.10418	0.10924	0.13641	0.14356

ANALYSIS OF VARIANCE FOR AGE
DEPENDENT VARIABLE - CORRECTED .4 HZ. RIGHTWARD MEDIAN HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	1.46200	1	1.46200	121.35	0.0000
AGE	0.21491	5	0.04298	3.57	0.0049
ERROR	1.36137	113	0.01205		

TABLE 20

CELL MEANS and SDS FOR CORRECTED .8 HZ. LEFTWARD MEDIAN HALFCYCLES

AGE	LE20	LE25	LE30	LE35	LE40	GT40
CBLMED	0.41711	0.32898	0.39524	0.25553	0.48070	0.58627
N	44	42	19	7	4	3
SD	0.17071	0.18753	0.15987	0.04562	0.33257	0.03091

ANALYSIS OF VARIANCE FOR AGE
DEPENDENT VARIABLE - CORRECTED .8 HZ. LEFTWARD MEDIAN HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	7.35489	1	7.35489	237.37	0.0000
AGE	0.45092	5	0.09018	2.91	0.0165
ERROR	3.50134	113	0.03099		

TABLE 21

CELL MEANS and SDS FOR CORRECTED .8 HZ. RIGHTWARD MEDIAN HALFCYCLES

AGE	LE20	LE25	LE30	LE35	LE40	GT40
CBRMED	0.41372	0.30648	0.37277	0.27054	0.41527	0.59600
N	44	42	19	7	4	3
SD	0.16103	0.16305	0.15031	0.09395	0.23811	0.05041

ANALYSIS OF VARIANCE FOR AGE
DEPENDENT VARIABLE - CORRECTED .8 HZ. RIGHTWARD MEDIAN HALFCYCLES

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	6.83298	1	6.83298	271.90	0.0000
AGE	0.48203	5	0.09641	3.84	0.0030
ERROR	2.83976	113	0.02513		

TABLE 22

CELL MEANS and SDs FOR CORRECTED .4 HZ OVERALL 13-CYCLE RMS

AGE	LE20	LE25	LE30	LE35	LE40	GT40
C4RMS	0.28123	0.16077	0.23865	0.17403	0.23100	0.27987
N	44	42	19	7	4	3
SD	0.18030	0.08545	0.13159	0.11869	0.10618	0.14264

ANALYSIS OF VARIANCE FOR AGE
DEPENDENT VARIABLE - CORRECTED .4 HZ. OVERALL 13-CYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	2.25928	1	2.25928	117.76	0.0000
AGE	0.34317	5	0.06863	3.58	0.0049
ERROR	2.16790	113	0.01918		

TABLE 23

CELL MEANS and SDs FOR CORRECTED .8 HZ. OVERALL 13-CYCLE RMS

AGE	LE20	LE25	LE30	LE35	LE40	GT40
C8RMS	0.48344	0.36169	0.45103	0.31419	0.49350	0.60490
N	44	42	19	7	4	3
SD	0.17705	0.16794	0.17849	0.07660	0.32801	0.04046

ANALYSIS OF VARIANCE FOR AGE
DEPENDENT VARIABLE - CORRECTED .8 HZ. OVERALL 13-CYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	8.88980	1	8.88980	292.12	0.0000
AGE	0.53161	5	0.10632	3.49	0.0057
ERROR	3.43885	113	0.03043		

TABLE 24

CELL MEANS and SDs FOR CORRECTED .4 HZ. OVERALL 13-CYCLE RMS

C4MLATD	Q1	Q2	Q3	Q4	
C4RMS	0.29230	0.19602	0.14052	0.26246	0.22389
N	30	33	27	29	119
SD	0.13355	0.16354	0.08096	0.14277	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED .4 HZ. OVERALL 13-CYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	5.87761	1	5.87761	319.70	0.0000
C4MLATD	0.39682	3	0.13227	7.19	0.0002
ERROR	2.11425	115	0.01838		

TABLE 25

CELL MEANS and SDs FOR CORRECTED .8 HZ. OVERALL 13-CYCLE RMS

C4MLATD	Q1	Q2	Q3	Q4	
C8RMS	0.54677	0.40117	0.30251	0.45552	0.42874
N	30	33	27	29	119
SD	0.16988	0.16799	0.12500	0.18227	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED 4. HZ. OVERALL 13-CYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	21.53331	1	21.53331	804.95	0.0000
C4MLATD	0.89407	3	0.29802	11.14	0.0000
ERROR	8.07638	115	0.02675		

TABLE 26

CELL MEANS and SDs FOR CORRECTED .8 HZ. LEFTWARD
CONSTRUCTED AVERAGE HALFCYCLE RMS

C4HLATD	Q1	Q2	Q3	Q4	
C8LRMS	1.47894	1.48091	1.47453	1.47505	1.47754
N	30	33	27	29	119
SD	0.01064	0.01221	0.00978	0.01013	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN
LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED .8 HZ. LEFTWARD
CONSTRUCTED AVERAGE HALFCYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	258.37842	1	258.37842	2214754.00	0.0
C4HLATD	0.00086	3	0.00029	2.45	0.0672
ERROR	0.01342	115	0.00012		

TABLE 27

CELL MEANS and SDs FOR CORRECTED .8 HZ. RIGHTWARD
CONSTRUCTED AVERAGE HALFCYCLE RMS

C4HLATD	Q1	Q2	Q3	Q4	
C8RRMS	1.47984	1.48934	1.47356	1.47372	1.47956
N	30	33	27	29	119
SD	0.01045	0.05545	0.00934	0.00972	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN
LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED .8 HZ. RIGHTWARD
CONSTRUCTED AVERAGE HALFCYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	258.99271	1	258.99271	279762.19	0.0000
C4HLATD	0.00512	3	0.00171	1.84	0.1432
ERROR	0.10646	115	0.00093		

TABLE 28

CELL MEANS and SDs FOR CORRECTED .4 HZ. LEFTWARD MEDIAN
HALFCYCLE RMS

C4MLATD	Q1	Q2	Q3	Q4	
C4LMED	0.29338	0.15237	0.10863	0.18188	0.18518
N	30	33	27	29	119
C4LMED	0.15505	0.11690	0.06108	0.10839	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN
LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED .4 HZ. LEFTWARD MEDIAN
HALFCYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	4.01071	1	4.01071	295.59	0.0000
C4MLATD	0.54532	3	0.18177	13.40	0.0000
ERROR	1.56036	115	0.01357		

TABLE 29

CELL MEANS and SDs FOR CORRECTED .4 HZ. RIGHTWARD MEDIAN
HALFCYCLE RMS

C4MLATD	Q1	Q2	Q3	Q4	
C4RMED	0.20495	0.14209	0.11286	0.22778	0.17219
N	30	33	27	29	119
SD	0.11384	0.11592	0.06077	0.12359	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN
LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED .4 HZ. RIGHTWARD MEDIAN
HALFCYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	3.49894	1	3.49894	302.65	0.0000
C4MLATD	0.24675	3	0.08225	7.11	0.0002
ERROR	1.32952	115	0.01156		

TABLE 30

CELL MEANS and SDs FOR CORRECTED .8 HZ. LEFTWARD MEDIAN
HALFCYCLE RMS

C4MLATD	Q1	Q2	Q3	Q4	
C8LMED	0.50914	0.34414	0.25833	0.39807	0.37941
N	30	33	27	29	119
SD	0.15837	0.15044	0.13615	0.19520	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN
LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED .8 HZ. LEFTWARD MEDIAN
HALFCYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	16.86301	1	16.86301	646.32	0.0000
C4MLATD	0.95183	3	0.31728	12.16	0.0000
ERROR	3.00042	115	0.02609		

TABLE 31

CELL MEANS and SDs FOR CORRECTED .8 HZ. RIGHTWARD MEDIAN
HALFCYCLE RMS

C4MLATD	Q1	Q2	Q3	Q4	
C8RMED	0.47246	0.33760	0.24905	0.39527	0.36556
N	30	33	27	29	119
SD	0.15121	0.17224	0.11342	0.14810	

ANALYSIS OF VARIANCE WITH CORRECTED .4 HZ. MEDIAN
LATERAL DIFFERENCE QUANTILES AS GROUPING FACTOR
DEPENDENT VARIABLE - CORRECTED .8 HZ. RIGHTWARD MEDIAN
HALFCYCLE RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	15.65014	1	15.65014	702.74	0.0000
C4MLATD	0.76073	3	0.25358	11.39	0.0000
ERROR	2.56106	115	0.02227		

TABLE 32

CELL MEANS and SDs FOR CORRECTED .8 HZ.
OVERALL 13-CYCLE RMS

C4MLATD	RSPEN	LSPEN	
C8RMS	0.46488	0.38217	0.42874
N	67	52	119
SD	0.18024	0.17856	

ANALYSIS OF VARIANCE- RSPEN/LSPEN (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	21.00628	1	21.00628	651.89	0.0000
C4MLATD	0.20029	1	0.20029	6.22	0.0141
ERROR	3.77017	117	0.03222		

TABLE 33

CELL MEANS and SDs FOR CORRECTED .8 HZ.
LEFTWARD CONSTRUCTED AVERAGE HALFCYCLE RMS

C4MLATD	RSPEN	LSPEN	
C8LRMS	1.47953	1.47498	1.47754
N	67	52	119
SD	0.01139	0.01001	

ANALYSIS OF VARIANCE- RSPEN/LSPEN (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8LRMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	255.56446	1	255.56446	2187967.00	0.0000
C4MLATD	0.00061	1	0.00061	5.20	0.0244
ERROR	0.01367	117	0.00012		

TABLE 34

CELL MEANS and SDs FOR CORRECTED .8 HZ.
RIGHTWARD CONSTRUCTED AVERAGE HALFCYCLE RMS

C4MLATD	RSPEN	LSPEN	
C8RRMS	1.48408	1.47373	1.47956
N	67	52	119
SD	0.03966	0.00953	

ANALYSIS OF VARIANCE- RSPEN/LSPEN (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8RRMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	256.13668	1	256.13668	276339.44	0.0
C4MLATD	0.00314	1	0.00314	3.38	0.0684
ERROR	0.10845	117	0.00093		

TABLE 35

CELL MEANS and SDs FOR CORRECTED .4 HZ.
LEFTWARD MEDIAN HALFCYCLE RMS

C4MLATD	RSPEN	LSPEN	
C4LMED	0.21422	0.14778	0.18518
N	67	52	119
SD	0.15057	0.09703	

ANALYSIS OF VARIANCE- RSPEN/LSPEN (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C4LMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	3.83651	1	3.83651	227.11	0.0000
C4MLATD	0.12924	1	0.12924	7.65	0.0066
ERROR	1.97644	117	0.01689		

TABLE 36

CELL MEANS and SDs FOR CORRECTED .4 HZ.
LEFTWARD MEDIAN HALFCYCLE RMS

C4MLATD	RSPEN	LSPEN	
C8LMED	0.41778	0.32997	0.37941
N	67	52	119
SD	0.17268	0.18568	

ANALYSIS OF VARIANCE- RSPEN/LSPEN (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8LMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	16.36990	1	16.36990	513.96	0.0000
C4MLATD	0.22574	1	0.22574	7.09	0.0089
ERROR	3.72651	117	0.03185		

TABLE 37

CELL MEANS and SDs FOR CORRECTED .8 HZ.
RIGHTWARD MEDIAN HALFCYCLE RMS

C4MLATD	RSPEN	LSPEN	
C8RMED	0.39674	0.32539	0.36556
N	67	52	119
SD	0.17243	0.15406	

ANALYSIS OF VARIANCE- RSPEN/LSPEN (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8RMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	15.26719	1	15.26719	563.00	0.0000
C4MLATD	0.14903	1	0.14903	5.50	0.0207
ERROR	3.17276	117	0.02712		
MEAN	34.80727	1	34.80727	411.10	0.0000
C4MLATD	0.30163	1	0.30163	3.56	0.0616
ERROR	9.90632	117	0.08467		

TABLE 38

CELL MEANS and SDs FOR CORRECTED .4 HZ. OVERALL 13-CYCLE RMS

ABC4MLD	Q1	Q2	Q3	Q4	
C4RMS	0.17106	0.16860	0.22696	0.32903	0.22389
N	30	30	29	30	119
SD	0.12099	0.13826	0.14281	0.12509	

ANALYSIS OF VARIANCE- ABS (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C4RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	5.96507	1	5.96507	342.35	0.0000
ABC4MLD	0.50734	3	0.16911	9.71	0.0000
ERROR	2.00374	115	0.01742		

TABLE 39

CELL MEANS and SDs FOR CORRECTED .8 HZ. OVERALL 13-CYCLE RMS

ABC4MLD	Q1	Q2	Q3	Q4	
C8RMS	0.35072	0.38518	0.41833	0.56038	0.42874
N	30	30	29	30	119
SD	0.14446	0.17260	0.18455	0.16454	

ANALYSIS OF VARIANCE- ABS (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8RMS

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	21.86055	1	21.86055	783.67	0.0000
ABC4MLD	0.76252	3	0.25417	9.11	0.0000
ERROR	3.20794	115	0.02790		

TABLE 40

CELL MEANS and SDs FOR CORRECTED .4 HZ. LEFTWARD MEDIAN
HALFCYCLE RMS

ABC4MLD	Q1	Q2	Q3	Q4	
C4LMED	0.12129	0.13439	0.17833	0.30650	0.18518
N	30	30	29	30	119
SD	0.06299	0.11115	0.10866	0.15074	

ANALYSIS OF VARIANCE- ABS(C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C4LMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	4.07752	1	4.07752	320.53	0.0000
ABC4MLD	0.64274	3	0.21425	16.84	0.0000
ERROR	1.46294	115	0.01272		

TABLE 41

CELL MEANS and SDs FOR CORRECTED .4 HZ. RIGHTWARD MEDIAN
HALFCYCLE RMS

ABC4MLD	Q1	Q2	Q3	Q4	
C4RMED	0.12081	0.13402	0.17807	0.25605	0.17219
N	30	30	29	30	119
SD	0.06254	0.10767	0.11596	0.11967	

ANALYSIS OF VARIANCE- ABS(C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C4RMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	3.52942	1	3.52942	326.95	0.0000
ABC4MLD	0.33486	3	0.11162	10.34	0.0000
ERROR	1.24141	115	0.01079		

TABLE 42

CELL MEANS and SDs FOR CORRECTED .8 HZ. LEFTWARD MEDIAN
HALFCYCLE RMS

ABC4MLD	Q1	Q2	Q3	Q4	
C8LMED	0.30836	0.32729	0.38197	0.50010	0.37941
N	30	30	29	30	119
SD	0.14433	0.17128	0.19814	0.15844	

ANALYSIS OF VARIANCE - ABS (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8LMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	17.12853	1	17.12853	600.15	0.0000
ABC4MLD	0.67013	3	0.22338	7.83	0.0001
ERROR	3.28212	115	0.02854		

TABLE 43

CELL MEANS and SDs FOR CORRECTED .8 HZ. RIGHTWARD MEDIAN
HALFCYCLE RMS

ABC4MLD	Q1	Q2	Q3	Q4	
C8RMED	0.29265	0.31242	0.36833	0.48894	0.36556
N	30	30	29	30	119
SD	0.15366	0.14537	0.16197	0.14247	

ANALYSIS OF VARIANCE (- ABS (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - C8RMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	15.90108	1	15.90108	697.75	0.0000
ABC4MLD	0.70106	3	0.23369	10.25	0.0000
ERROR	2.62073	115	0.02279		

TABLE 44

CELL MEANS and SDs MMPI SCHIZOPHRENIA SCALE

ABC4MLD	Q1	Q2	Q3	Q4	
SC	60.63333	58.8000	64.13793	67.33333	62.71429
N	30	30	29	30	119
SD	10.49625	8.65189	11.74650	16.15727	

ANALYSIS OF VARIANCE - ABS (C4MLATD) GROUPING FACTOR
DEPENDENT VARIABLE - SC

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	468112.92238	1	468112.9223	3204.37	0.0000
ABC4MLD	1288.40411	3	429.46804	2.94	0.0362
ERROR	16799.88161	115	146.08593		

TABLE 45

CELL MEANS and SDs FOR CORRECTED .8 HZ. LEFTWARD
MEDIAN HALFCYCLE RMS

C8MLATD	RSPEN	LSPEN	
C8LMED	0.41867	0.33318	0.37769
N	63	58	121
SD	0.20033	0.14895	

ANALYSIS OF VARIANCE FOR RSPEN/LSPEN .8 HZ. GROUPING FACTOR
DEPENDENT VARIABLE - C8LMED

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	17.07050	1	17.07050	541.30	0.0000
C8MLATD	0.22075	1	0.22075	7.00	0.0093
ERROR	3.75277	119	0.03154		

TABLE 46

CELL MEANS and SDs FOR MMPI DEPRESSION

CBMLATD	RSPEN	LSPEN	
D	58.09524	53.63793	55.95868
N	63	58	121
SD	11.04056	9.93964	

ANALYSIS OF VARIANCE FOR RSPEN/LSPEN GROUPING FACTOR
DEPENDENT VARIABLE - D

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	377005.25752	1	377005.25752	3401.64	0.0000
CBMLATD	599.96827	1	599.96827	5.41	0.0217
ERROR	13188.82512	119	110.83046		

TABLE 47

CELL MEANS and SDs FOR MMPI HYPOMANIA

CBMLATD	RSPEN	LSPEN	
MA	61.41270	65.48276	63.36364
N	63	58	121
SD	8.84205	11.62912	

ANALYSIS OF VARIANCE FOR RSPEN/LSPEN GROUPING FACTOR
DEPENDENT VARIABLE - MA

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	486267.58624	1	486267.58624	4608.71	0.0000
CBMLATD	500.24740	1	500.24740	4.74	0.0314
ERROR	12555.75260	119	105.51053		

TABLE 48

CELL MEANS and SDs FOR MMPI SOCIAL INTROVERSION

CBMLATD	RSPEN	LSPEN	
SI	55.19048	51.22414	53.28926
N	63	58	121
SD	9.86499	10.29230	

ANALYSIS OF VARIANCE FOR RSPEN/LSPEN GROUPING FACTOR
DEPENDENT VARIABLE - SI

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	341968.19951	1	341968.19951	3371.01	0.0000
CBMLATD	475.07554	1	475.07554	4.68	0.0325
ERROR	12071.80049	119	101.44370		

TABLE 49

CELL MEANS and SDs FOR MMPI SCHIZOTYPY

CBMLATD	RSPEN	LSPEN	
SCHZTYP	236.93651	223.67241	230.57851
N	63	58	121
SD	38.46484	32.49636	

ANALYSIS OF VARIANCE FOR RSPEN/LSPEN GROUPING FACTOR
DEPENDENT VARIABLE - SCHZTYP

SOURCE	SUM OF SQUARES	DEGREES FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
MEAN	6406898.80042	1	6406898.80042	5018.42	0.0000
CBMLATD	5312.98224	1	5312.98224	4.16	0.0436
ERROR	151924.52189	119	1276.67665		

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