Chapter • 4

Dyslexia Subtypes Genetics, Behavior, and Brain Imaging

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The first purpose of the study is to define the chromosomal location of the several genes that produce autosomal dominantly inherited dyslexia. The second purpose is to define the effects that each of these different genes produces on the form and function of the brains of people with these variant genes, not only in respect to reading and writing, but on all aspects of brain function that we can study. If similar clinical problems are inherited in a polygenic, autosomal recessive, and x-linked fashion, then, by definition, multiple disorders and genes are involved. Moreover, if information from families with each of those different disorders is pooled, it is very difficult to interpret the resulting data. In this study, therefore, we chose to include only three-generation families with an autosomal dominant (AD) mode of inheritance in order to simplify the data analysis. This is probably the most frequent form of inheritance of dyslexia. Equal numbers of males and females are affected and half of offspring from a parent who has the gene are also affected. Even with the limitation to families showing AD inheritance, it is still likely that multiple genes are in-

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volved in the genesis of dyslexia and that subtle differences will be found between different AD genetic types.

This is a very different study from others presented in this volume and it is also a different study from any that have been carried out previously. Once we have identified the several genes for dyslexia, we can then utilize the data from the wide variety of test procedures used in the study to define the effects of the presumed several genes. We are not starting with a definition based upon a laboratory or behavioral test. Rather, we start with a gene and then define its clinical expression or phenotypes. It is a biologic approach to the definition of the various subtypes of dyslexia.

Background of the Present Study

Genetics is the study of individual variation. Each person has, roughly, a hundred thousand functional genes. This information is encoded in our DNA by more than three billion base pairs. A project to map this genome is in the planning stage now, and will be the largest biological study that has ever been done. The data generated from this study will actually exceed the capacity of the largest computers that are now used. Within ten years, significant data will come from it and in twenty perhaps, it will be completed. Ultimately, it will help this study immensely by providing new markers and new information about our genome.

The present study will require ten years to complete. It is an extremely complex undertaking for both investigators and the dedicated family members who participate in all aspects of the project. It requires over 20 hours of testing for each family member, over 4 or 5 days. Approximately 350 variables of all types are recorded, at least on those individuals who participate in all aspects of the study. If we are successful, our view of dyslexia will be quite changed.

The predecessor to this study began about 15 years ago, when Shelley Smith came to do her thesis in Denver with one of us (HL). As a clinical geneticist interested in the application of genetics to common problems, I suggested a study of a little-investigated disorder—namely dominantly inherited dyslexia. The broad goal of this first study was to provide additional support for the idea that there was a group of families with dyslexia due to autosomal dominant inheritance. Since we were starting with three-generation families with apparent autosomal dominant inheritance, such a study might be viewed as a self-fulfilling prophecy. We decided, in addition, to do a linkage study. The nature of the linkage study, which determines the frequency with which two genes are inherited together through a large family, has as its basis for accepting a linkage the fact that the results

are not likely due to chance. The likelihood of flipping a coin and having it come up heads ten times in a row is $1/2^{10}$ or 1/1024. That is essentially the same likelihood that two genes will be inherited together in 10 transmissions through a family by chance. The first step in detecting a linkage is to recognize co-transmission of genes that occurs a 1000 times more likely than chance alone. Thus there are few false positive results. The second step is to repeat the study to confirm the findings. Since we were unlikely to find a false positive result, we felt a positive study would confirm that there was at least one autosomal dominant gene leading to dyslexia. This was the basis of the initial study that Drs. Smith, Kimberling, and I undertook. Dr. Pennington later also became involved in extending the family data.

To understand linkage studies fully, however, the behavior of chromosomes in meiosis must be understood. Not only do homologous chromosomes pair (No. 1 with No. 2, etc.), but an average of two crossovers, or exchanges, occur in each of the 23 pairs of chromosomes. These recombinations occur randomly throughout each chromosome and result in greater biologic mixing; they also provide geneticists with a means of doing detailed linkage studies using normal variations in the genetic code, called restriction fragment length polymorphisms (or RFLPs). The likelihood with which any two variant genes will be inherited together depends on how close they are on the same chromosome. If they are extremely close, they will nearly always be transmitted together to one child, and another child of the same parents will almost always get both normal genes. If two genes are far apart on the chromosome or on different chromosomes, the inheritance of the two genes will be totally random. Thus, the closer together the genes are, the more likely we will be to find such linkage. The ideal study would utilize a series of markers equally distributed through the 23 chromosomes: about 200 RFLPs would yield a good probability of detecting a linkage to a disease gene. That is too expensive to do routinely, so we must take another approach, namely to pursue specific clues about possible localizations or linkages.

A few additional terms must be defined. The frequency of recombination is indicated by the symbol *theta* (θ); a 1% recombination rate was defined in classical genetics as one centimorgan. In molecular terms, one centimorgan, or a 1% recombination frequency, is equivalent to about one million base pairs. This is roughly the size of our largest known disease gene, the Duchenne muscular dystrophy gene. Results of linkage studies are given in terms of the *Log* of *Odds* of linkage, or the so-called LOD score. A LOD score of +3, for example, indicates that the odds are a thousand to one ($10^3/1$) in favor of linkage over a random occurrence of the same findings. A low score, less than −2.0 ($1/10^2$) indicates that the odds are 100/1 against linkage. These are the

usual levels for accepting or rejecting a linkage between two genes. Since the odds are expressed as base 10 logarithmic data, a score can be accumulated over a period of time from a number of families by summing these LOD scores. When Dr. Smith began the initial study in the early 1970s the distribution of the markers was limited. Many were genes for blood groups and are, including the Rh locus, now known to be on chromosome 1. There are five chromosomes—13, 14, 15, 21, and 22—with small, variable short arms; these variations were used as "chromosomal markers." Similarly, variations in protein were also used as markers in linkage studies. In the study reported by Smith et al. (1983), there were no markers on chromosomes 4 or 5 for example, and we could not have detected a linkage on either chromosome. Overall, only about 20% of the genome was studied. Current studies, including the more recent reports of Smith et al. (1990a, 1990b) and the present study are slightly more inclusive but still leave many gaps in the genome due to a lack of useful, inexpensive markers to detect.

The families included in this study had a number of family members with major problems in reading and spelling. Each person's intelligence was normal and no reason for the reading difficulty was known. This study group, however, was significantly different from prior study groups because now we required a three-generation family history with the same problem. These results were published (Smith et al. 1983) when the LOD score exceeded 3.0 between dyslexia and short arm variations on chromosome 15. These studies have continued and have been summarized (Smith et al. 1990b). The results of the current linkage analysis of dyslexia and chromosome 15 heteromorphisms is shown in table I (reprinted from Smith et al. 1990b). Fourteen new families were added and five of the eight families published in 1983 were extended.

Both inspection of the data in table I and a formal analysis for genetic heterogeneity lead to the conclusion that more than one locus for dyslexia exists (Smith et al. 1990a, 1990b). Family 432, which contributed most of the initial information leading to a total LOD score greater than 3.0 in the eight initial study families, was the subject of further study and now yielded an LOD score of 2.961. No crossovers were observed ($\theta = 0$) and it is quite likely that a gene exists near the centromere of 15 that results in a phenotype with dyslexia. Overall, 18% of the 20 families were found to fit the hypothesis of linkage to a gene on 15. Thus, both further studies of chromosome 15 using new markers adjacent to the centromere as well as a continued search for loci on other chromosomes is appropriate. The family data continued to be consistent with an autosomal dominant mode (AD) of inheritance both in the newly studied families and the extended studies of the original families. The latter observation, of course, is particularly important evi-

Table I. Linkage between SRD and Chromosome 15 Heteromorphisms

	Recombination Fraction				
Family	0.00	0.10	0.20	0.30	0.40
9007	$-\infty$	−0.384	−0.047	0.032	0.020
9008	$-\infty$	−0.264	−0.109	−0.049	−0.015
9102	$-\infty$	−0.957	−0.426	−0.168	−0.040
6372	$-\infty$	−0.350	0.614	0.276	0.201
6375	0.628	0.535	0.370	0.191	0.051
6432	2.907	2.401	1.877	1.323	0.712
6484	$-\infty$	−2.279	−0.750	−0.141	0.060
6491	$-\infty$	−1.332	−0.582	−0.228	−0.054
6576	0.523	0.334	0.180	0.071	0.015
8001	$-\infty$	−2.201	−1.114	−0.553	−0.215
8002	$-\infty$	−0.888	−0.297	−0.084	−0.014
8005	−1.703	−0.335	−0.122	−0.038	−0.006
8006	$-\infty$	0.159	0.232	0.182	0.093
8007	0.301	0.255	0.204	0.146	0.079
8008	0.903	0.725	0.541	0.356	0.175
8010	$-\infty$	−0.252	−0.092	−0.036	−0.010
6371	0.602	0.465	0.318	0.170	0.049
1000	0.292	0.208	0.129	0.062	0.016
1001	$-\infty$	−0.229	−0.060	−0.011	−0.001
1002	0.292	0.208	0.129	0.062	0.016
Total	$-\infty$	−4.181	0.995	1.563	1.132

LOD scores are given for each family at 5 values of θ; 0.00, 0.10, 0.20, 0.30, and 0.40. The symbol minus infinity ($-\infty$) at $\theta = 0.00$ indicates that a crossover event has taken place. By convention, a LOD score less than or equal to -2.0 excludes linkage at that value of θ, and a LOD score of at least 3.0 is evidence of linkage. SRD is standard reading disability.

(Taken from Smith, Pennington, Kimberling, and Ing 1990)

dence in favor of the hypothesis of AD inheritance and against multifactorial or a non-genetic origin of the newly ascertained cases.

THE PRESENT STUDY

Criteria for Entry into the Study

Families with a three-generation history of relatively pure dyslexia are candidates for admission into the study. Generally, at least ten potentially informative matings are required for each family. As in prior studies, dyslexia is initially defined as a significant difficulty in reading and spelling in persons with no medical or neurological disorders, a normal intelligence, and adequate educational opportunity. Only primary En-

glish speaking families are considered. A questionnaire relating to medical, educational, and behavioral history is given to each person (Lubs et al. in press). The majority of family members reside in south Florida so that many of the special studies, which require special equipment, can be carried out. An IQ test and a variety of reading, vision, speech, and neuropsychological studies are administered to as many affected and normal family members as possible. Magnetic resonance imaging (MRI) and positron-emission tomography (PET) studies are carried out in a smaller number of family members. In figure 1 each person is given a unique number (shown above the circles or squares in the pedigrees).

The diagnostic screening battery includes a standard intelligence test and tests for reading and spelling skills. These are divided into four classes of subtests, as shown in figure 1: those that measure oral reading, comprehension, decoding, or spelling. Criteria for diagnosis of dyslexia changes with the age or grade of the child. In the first year of school, a score only half a standard deviation below their expected score (based on IQ) is required in at least one of the four categories (see figure 1). This increases to one standard deviation for the age group 9–14 years, on two of the four categories, and to 1.5 standard deviations on two of the four categories for those age 15 or over. The Nonsense Passages, initially described by Finucci et al. (1976) have been particularly helpful. This test removes guessing as an effective strategy. Dyslexics generally have shown either a need for increased time to read the passages correctly or an increased number of errors (Gross-Glenn et al. 1985, 1990).

Results of Family Studies

To date, of 14 families initially entered in the study, 10 have proven appropriate and sufficiently motivated to participate. Sufficient data to warrant presentation at this time are available from five families. Pedigrees of three families are shown in figure 2, as are the explanations for the pedigree symbols. Pedigrees of the remaining two families are presented in the section on neuropsychological studies. Two individuals (Families 3015-253 and 258) were dyslexic by history but psychometric test results did not meet the criteria for a diagnosis of dyslexia. Rarely, a person such as 3015-237 will be negative by history and by testing but will transmit the presumed gene. Such an individual represents an example of decreased penetrance. This occurred in only one individual of 53 who were clearly affected, had a history of dyslexia, or clearly transmitted the gene. Such decreased penetrance occurs frequently with dominant inheritance of all types and a penetrance rate of about 90% should not be considered in any way unusual or to weaken

Diagnostic Reading/Spelling Battery and Criteria for Diagnosis of Dyslexia

1.	Spelling	Wide-Range Achievement Test-Revised: Spelling subtest
2.	Oral Reading	Gray-Oral Reading Test-Revised Woodcock-Johnson Psycho-Educational Battery Letter-Word Identification subtest
3.	Comprehension	Woodcock-Johnson Psycho-Educational Battery Passage Comprehension subtest
4.	Decoding	Woodcock-Johnson Psycho-Educational Battery Word-Attack Scale subtest Nonsense Passages (ages 16+)

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IQ Discrepancy (in comparison to IQ score)	Grade	Age-graded cutoffs
≥ 0.5 standard deviation on 1 out of 4 reading and spelling tests	< 3	≤ 8 years
≥ 1.0 standard deviation on 2 out of 4 reading and spelling tests	3 - 8	9-14 years
≥ 1.5 standard deviations on 2 out of 4 reading and spelling tests	> 8	≥ 15 years

Figure 1. Age-graded cutoffs.

the concept of a single gene of dyslexia. Because of the large three-generation families and the transmission to an equal number of offspring of both sexes of the normal and dyslexic genes, the current families provide strong additional support for AD inheritance in a significant portion of cases of dyslexia. The exact proportion of cases of similarly "pure" dyslexia (having problems primarily with reading and spelling) remains unknown, but probably represents a significant proportion of all cases.

It is often stated that there is a 3:1 or 4:1 ratio of diagnosed males to females with dyslexia. Three of the four people who showed no currently detectable effects of the gene(s) but transmitted it in these five

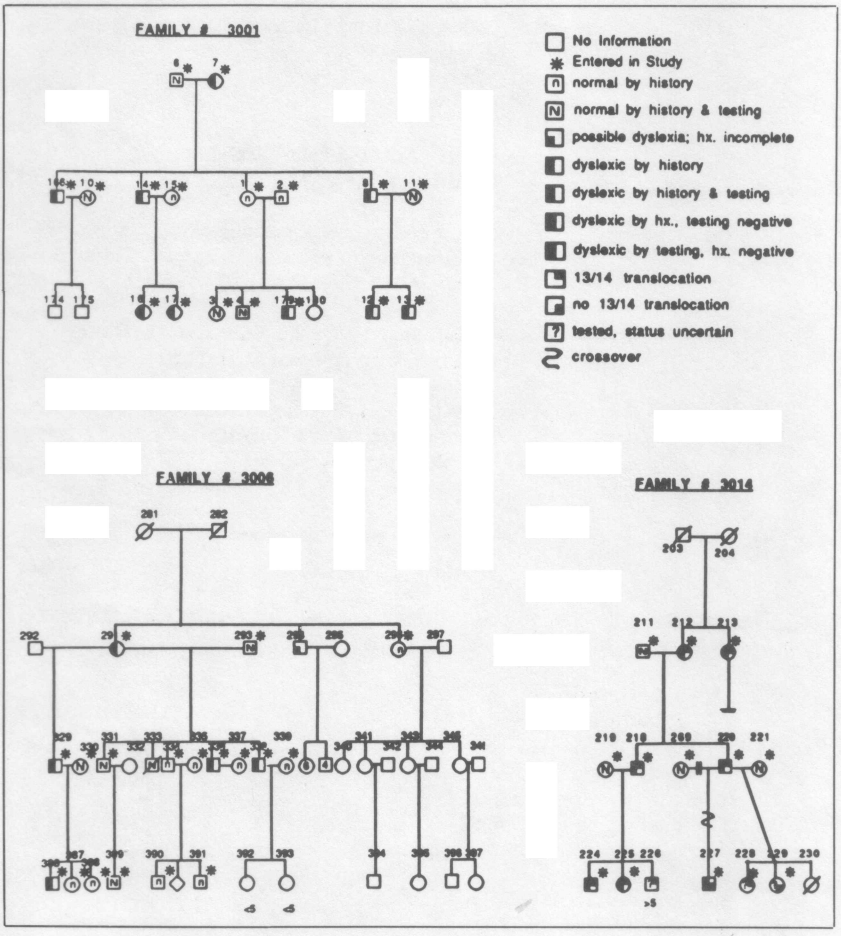

Figure 2. Pedigrees of families, 3001, 3006, and 3014.

pedigrees were females. We have suspected for some time that in general the females in the families are less severely affected. Our current data support this concept. The sex ratio is equal within these families and those of Smith et al. (1983). It appears, therefore, that the higher rate of diagnosis in males results from a greater severity in males, i.e., a threshold effect; perhaps, also, the more active behavior of males in classrooms results in more frequent attention and diagnosis. We are, of course, examining the results of the test battery carefully to determine whether individuals #237 and #241, and others with similar histories and test results, show any evidence of being unusual or abnormal. This approach may lead to a test that would detect all individuals with a gene for dyslexia and would greatly simplify the study of dyslexia.

Family #3015 is an example of an excellent family for the study.

There are 23 potentially informative matings. This family alone, if there were no crossovers, could give significant evidence for a linkage. The chance of co-inheritance of dyslexia and a marker without linkage is only $1/2^{23}$.

We are looking for possible linkages with conventional approaches to avoid carrying out the approximately 200 DNA tests on every person and every family that are otherwise required. One study family (3014) has a Robertsonian translocation with a centrometric fusion of chromosomes 13 and 14, and dyslexia. Individuals with this translocation are perfectly normal although they have only 45 chromosomes. Initially it was reported that everyone with this translocation also had dyslexia, and they were included in our study. With more detailed studies, only 6 of the 7 family members have both the translocation and dyslexia (see Family 3014, figure 2). The two children (228 and 229) still are being evaluated for dyslexia. The "wiggle" above patient 227 indicates there is a clear separation of the translocation and dyslexia, and would be an example of a crossover if the gene were close to the centromere. This family, at least, represents a possible clue that there might be another gene for dyslexia on chromosome 13 or 14.

The second approach to the detection of possible linkage involves the use of the "classical" blood group and protein markers. These are relatively inexpensive and can be run on each family. As in the initial study 15 years ago with these markers, and also by the current slightly larger batteries, less than 25% of the genome is screened. The distribution and frequency of these and other markers are shown in figure 3 and table II.

Our initial laboratory effort, using normal DNA variants (RFLPs), has been directed at developing appropriately located and informative probes in the region of the long arm of chromosome 15 (15q), so that the reports of Smith et al. (1983, 1990a, 1990b) can be confirmed. Because there were few available informative probes in this region, much of the preliminary work has involved probe development. Details of these studies have been given elsewhere (Lubs et al. 1990). Cell lines are established on all family members who participate in the linkage study. To date, no data suggestive of linkage to chromosome 15 have been found in our families. The two probes reported by Smith (1990a, 1990b) were located quite distally on 15q and the absence of evidence for significant linkage was, therefore, to be expected. Similarly, the small negative study of five two-generation Danish families (Bisgaard et al. 1987), using chromosomal heteromorphisms, does not negate the findings in Family 432 and is difficult to interpret since diagnosis was by history alone. Restudy of Family 432 will be critical in confirming or refuting the chromosome 15 linkage, and in determining the direction of linkage studies in the future.

Three additional clues have emerged from the studies with classi-

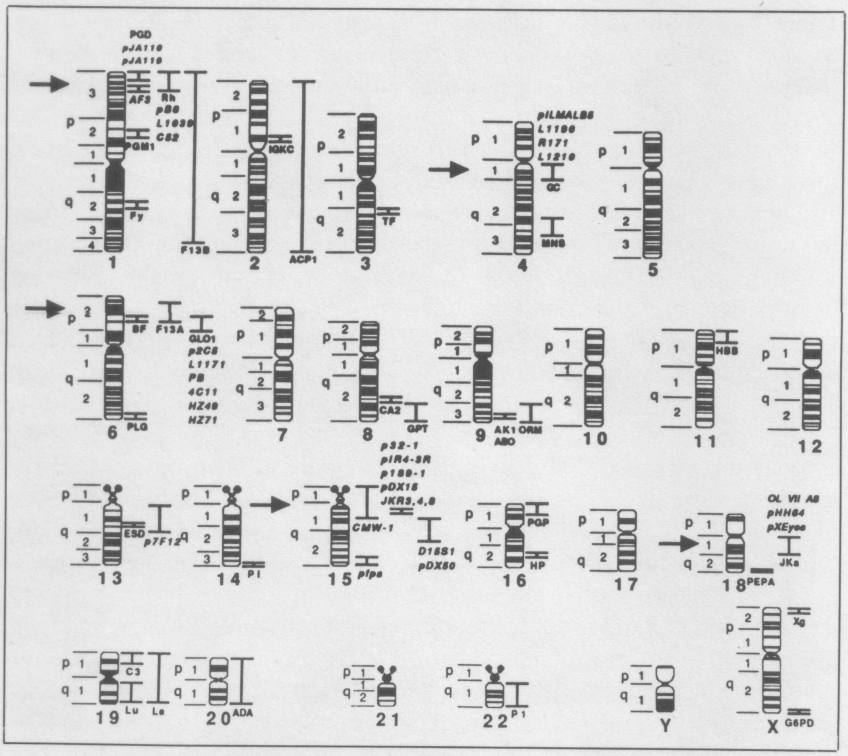

Figure 3. Chromosomal distribution of polymorphic protein markers (solid text) and DNA markers (outline text) used in the study of Smith et al. 1983 and the current University of Miami linkage studies. Subchromosomal localization of respective probes is indicated. The DNA markers are listed in table III.

cal markers. In two of our families (3001, 3015) there were positive LOD scores with GLO (glyoxylase), a marker for a locus on 6p (a total LOD score of 1.3, with no crossovers). Since Smith et al. (personal communication) also have noted slightly positive LOD scores with GLO, this appears to be the most interesting new possible linkage. These and other positive LOD scores are summarized in table III and figure 4. Both the Rh blood group (1p) and GC (4q) have slightly positive LOD scores in two families. We are currently pursuing these clues using RFLPs in these regions.

In summary, there are several possible, but no confirmed linkages. Large numbers of families and several years of study will be required to detect and confirm the linkage with the several (presumed) genes leading to AD inherited dyslexia.

Immunologic Studies. We are attempting to characterize all possible pertinent aspects of individuals with genetic dyslexia. For this

Table II. Polymorphic Protein Markers

System	Symbol	Chromosome Locus	No. Alleles
α 1-Antitrypsin	PI	14q32.1	5
ABO Blood Group+	ABO	9q34.1-q34.2	4
Acid Phosphatase+	ACP1	2	2
Adenosine Deaminase+	ADA	20	2
Adenylate kinase	AK1	9q34.1-q34.2	2
Carbonic Anhydrase*	CA2	9q22	2
Coagulation Factor 13A	F13A	6p24-p21.3	3
Coagulation Factor 13B	F13B	1	3
Complement (Third Component)	C3	1p13.3-p13.2	2
Complement (Fourth Component)	C4	6p21.3	28
Duffy Blood Group+	FY1	q22-q23	3
Esterase D+	ESD	13q14.1-q14.2	2
Glucose-6-Phosphaste Dehydrogenase*+	G6PD	Xq28	3
Glutamic Pyruvic Transaminase	GPT	8q23-qter	2
Glyoxylase	GLO1	6p21.3-p21.1	3
Group Specific Component+	GC	4q12-q13	2
Haptoglobin+	HP	16q22	2
Hemoglobin*	HBB	11p15.5	2
Immunoglobulin Gm+	IGHG	14q32,3	3
Immunoglobulin Km	IGKC	2p12	2
Kidd Blood Group+	Jk	18q11-q12	2
Lewis Blood Group	Le	19	2
Lutheran Blood Group	Lu	19q12-q13	2
MNS Blood Group+	MNS	4q28-q31	4
Orosomucoid	ORM	9q31-qter	2
P Blood Group	P1	22q11.2-qter	2
Peptidase A*	PEPA	18q23	3
Phosphoglucomutase+	PGM1	1p22.1	4
Phosphogluconate Dehydrogenase	PGD	1p36.2-p36.13	2
Phosphoglycolate Phosphatase	PGP	16p13	3
Plasminogen	PLG	6q26-q27	3
Properdin Factor B	BF	6p21.3	2
Rhesus Blood Group+	Rh	1p36.2-p34	5
Transferrin+	TF	3q21	3
Xg Blood Group	Xg	Xp22.3	2

*Blacks only
+Smith et al. 1983a

reason, we are pursuing the suggestion of Geschwind and Galaburda (1985) that there might be a relationship between immunologic abnormalities, left-handedness, and dyslexia. There has, however, not been an increased frequency of non-righthandedness in our study sample

Table III. Maximal LOD Scores for Polymorphic Markers in Miami Families (θ = 0.0)

Chromosome	Marker	Family 3001	3006	3014	3015	3017
1p36.2-p36.13	PGD	0.00	0.00	0.003	$-\infty$	0.00
1p36.2-p34	Rh	$-\infty$	$-\infty$	0.98	$-\infty$	0.54
1p22.1	PGM1	$-\infty$	0.00	0.27	$-\infty$	0.00
1p13.3-p13.2	C3	0.00	−0.02	$-\infty$	$-\infty$	0.055
1q22-q23	Fy	0.00	0.29	0.18	0.10	$-\infty$
1	F13B	0.00	0.00	0.057	0.08	0.00
2	ACP1	0.00	0.00	0.09	$-\infty$	0.00
3q21	TF	0.00	0.00	0.002	0.0003	0.002
4q12-q13	GC	$-\infty$	0.90	0.06	$-\infty$	0.45
4q28-q31	MNS	$-\infty$	$-\infty$	$-\infty$	$-\infty$	$-\infty$
6p24-p21.3	F13A	0.00	0.00	0.06	0.08	0.00
6p21.3-p21.1	GLO1	0.60	$-\infty$	$-\infty$	0.70	$-\infty$
6p21.3	BF	0.00	0.00	−2.07	−0.27	0.046
8q23	GPT	−2.3	$-\infty$	−0.32	$-\infty$	0.00
9q31-qter	ORM	0.29	0.00	0.35	−1.9	0.00
9q34.1-q34.2	ABO	$-\infty$	0.00	$-\infty$	$-\infty$	0.076
9q34.1-q34.2	AK1	0.00	0.00	0.008	−2.06	0.00
11p15.5	HBB*					
13q14.1-q14.2	ESD	$-\infty$	0.00	0.025	0.039	0.00
14q32.1	PI	0.00	0.30	−2.5	$-\infty$	0.29
15q11	p189-1*					
15q11	pIR4-3	$-\infty$	0.00	0.00	$-\infty$	0.00
15q11	pDX15	0.00	0.00	0.00	−0.29	*
15q14-q22	pDX50*					
16p13	PGP					
16q22	HP	$-\infty$	0.00	0.10	0.31	0.00
18q11-q12	Jk	−0.62	0.02	−0.43	0.70	−2.20
19q12-q13	Lu	0.00	$-\infty$	0.007	$-\infty$	0.007
19	Le	0.04	0.004	0.0185	0.117	−0.002
20	ADA	0.00	0.00	0.01	−0.42	0.00
22q11.2-qter	P1	0.18	0.029	0.013	0.12	−0.25
	KELL	0.00	0.00	0.011	$-\infty$	0.11

*Not polymorphic

(7.4%). Neither have we seen an increased frequency of autoimmune disease in these families (only one instance has been recorded in 26 affected and none in 13 unaffected relatives). The presence of atopic disorders (asthma, atopic dermatitis, hay fever) are also not different; 21/47 (45%) in dyslexic and 17/33 (52%) in non-dyslexic relatives. An initial battery of screening tests for autoimmune disease including antinuclear antibody (ANA) have not yielded positive results and have

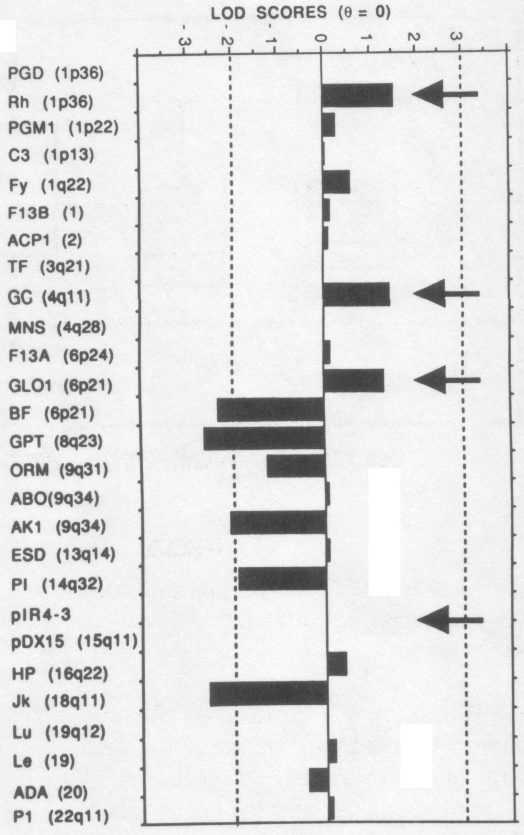

Figure 4. Graph of total LOD scores for protein and DNA markers. Data treatment is described in the text. Arrows indicate genomic loci targeted for further study.

been discontinued. An analysis of T-cell subsets, however, was also carried out and some of the results were unexpected. Cells that carry the monoclonal surface marker T4 are named *helper cells*, because they induce B-cells to make antibodies. Cells that carry the surface marker T8 are *suppressor cells*, which suppress, or turn off B-cell function. The majority of females with the gene for dyslexia in these families have an elevated T4/T8 lymphocyte ratio (figure 5). The clinical significance of this finding is unclear. These females may be more immunologically reactive although they were all clinically normal at the time of the study. The elevated T4/T8 ratios tended to cluster in two families and be unremarkable in others (figure 6). In Family 3015, two females warrant comment. The ratio was high in 3015-237, who was an unaffected obligate carrier. There remains the possibility that 3015-246, an apparently unaffected female with an elevated ratio, is actually a similarly unaf-

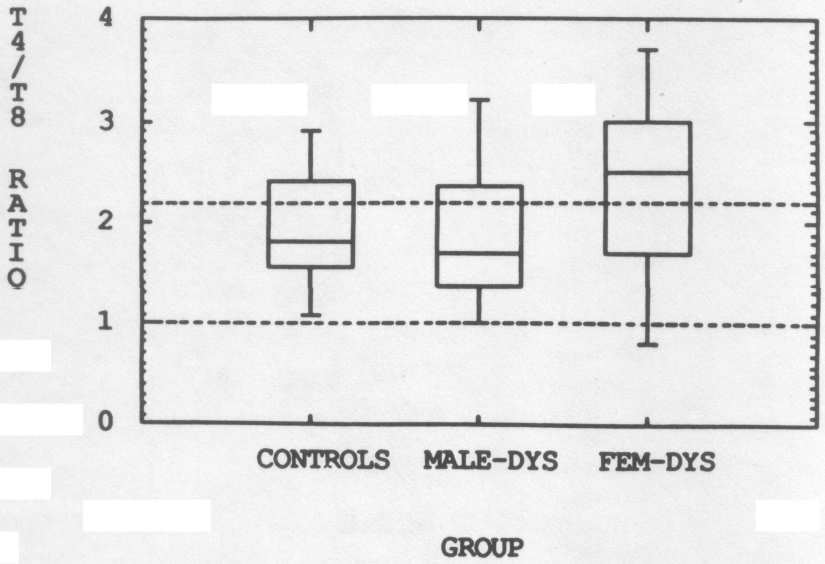

Figure 5. Dotted lines indicate usual normal limits. Mean values are indicated by lines in boxes; boxes indicate one standard deviation. Female dyslexics have significantly higher values.

fected carrier and that the T4/T8 ratio was the only current indicator of her carrier status. More data are needed.

The general observation that the elevated T4/T8 ratio was found predominantly in affected females in certain families is of uncertain biological significance. Both the brain asymmetry in dyslexic females (to be discussed below) and these findings might result from early hormonal differences, as suggested by Geschwind and Galaburda (1985).

Vision and Auditory Studies. Because reading involves both vision and language, we have undertaken studies of both processes using psychophysical methods that are sensitive enough to detect subtle abnormalities. Because dyslexics have clinically normal sensory function in both modalities, the problem is likely to be one that is more centrally located and involves a later stage of information processing in the brain. To study these "higher order" processes, it is of course necessary to rule out more peripheral sensory problems. We have accomplished this by providing visual and auditory screening exams that establish sensory function normality prior to participation in the psychophysical studies. We will discuss here the results of the visual studies only.

The vision-oculomotor screening examination in general yielded no differences between dyslexics and normal readers on most of the tests conducted. However, results of the visual psychophysical studies

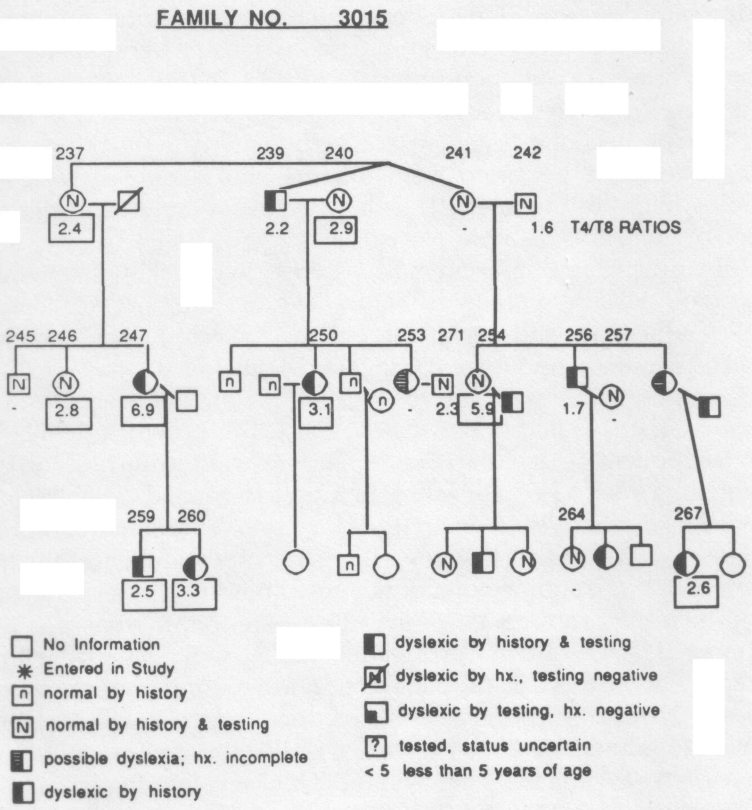

Figure 6. T4/T8 ratios in Family 3015 with many high values (≥ 2.4). High values are shown in box under circle or squares.

differentiated visual performance of dyslexics and normal-reading adults. These studies are based on the concept of a two-channel visual system: a sustained, or pattern-detecting system, and the transient system, which is specialized for motion detection. These systems, roughly speaking, have their anatomical analogues in the parvocellular and magnocellular divisions of the visual system (Livingstone and Hubel 1987; Zeki and Shipp 1988). The sustained system is focal, and sensitive to patterns with high spatial resolution, i.e., small fine-grained objects such as letters. This system also has a slow temporal response, i.e., perception is not immediate. The transient system, which is designed to detect moving objects, often using peripheral vision, recognizes large objects having low spatial resolution. This system, although poor in spatial resolution, has fast temporal responses. The interaction between these two systems is probably critical in reading.

As one reads, the eye moves across the page in a series of sac-

cades, interspersed with periods of visual fixation. During saccadic eye movements, vision is briefly suppressed, which prevents spatial overlapping of text information from one fixation to the next (Breitmeyer and Ganz 1976). This process may be thought of as a sort of beneficial masking of sustained system responses by activity in the transient system. However, if the period over which masking takes place is too long, reading might be impaired. This may be part of the problem encountered by some dyslexics.

To investigate a transient masking effect in the laboratory, we used a forward-masking paradigm. Figure 7 shows the time relationships between the mask and target. Targets to be detected were high or low spatial-frequency sine-wave gratings, presented on a video screen under computer control. Subjectively these patterns appeared as fuzzy horizontal stripes across the screen, the width of which defined the spatial frequency (high, narrow stripes; low, wide stripes). Contrast of the grating was varied according to a predetermined psychophysical procedure to assess the sensitivity of the observer under different conditions. We also varied how long the pattern remained on the screen (target duration) and whether or not it was preceded by a visual mask.

The results showed a very specific difference in visual sensitivity between dyslexic and normal-reader adults. Only when the to-be-detected target was a high spatial-frequency grating of brief exposure did the dyslexics show a significant reduction in contrast sensitivity, relative to normal readers. This was observed both with and without the mask. Using the two-channel model of visual information processing, we suspect that this finding indicates a slowness in responding of

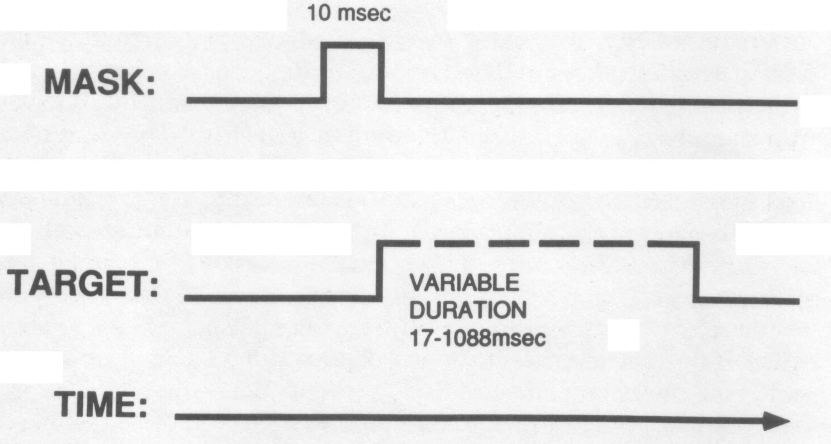

Figure 7. Time relationships between presentation of masking stimulus and a to-be-detected target, a sine-wave grating pattern of varying duration and spatial frequency.

the sustained visual channel. If it takes dyslexics longer to perceive detailed visual information (such as letters in a word), this might also make them more vulnerable to the sensory effects of masking by saccadic suppression. Studies are in progress to explore this hypothesis further.

In sum, our study adds support to the notion that some dyslexics have a temporal visual information processing deficit. As this is a rather specific disorder, it is not easily demonstrated except by sensitive laboratory procedures in which stimulus parameters are well-controlled. Similar differences have been observed when other psychophysical methods have been used to compare visual information processing in dyslexics and normal readers (see Gross and Rothenberg 1979 for a review of these studies).

The idea of a decrease in efficiency for perception of detailed visual information has a parallel in the auditory system, as some dyslexics have been shown to have difficulty in processing rapidly changing speech (Tallal 1980), as well as non-speech auditory information (McCrosky and Kidder 1980). Our multiple measurements of both visual and speech discrimination in the same individuals will indicate whether or not this temporal deficit is modality specific. Preliminary data on a small sample of dyslexic adults suggest that it may not be, at least for some individuals. More conclusive data will be provided by studies that are currently underway.

Neuropsychological Studies. These studies have been organized to test a wide range of cognitive abilities related to the reading and writing process (figure 8). Two approaches have been taken in the interpretation of these data. The first uses conventional statistics and compares the findings of dyslexic and non-dyslexic groups. The second approach involves inspection of the data by pedigree. These findings are summarized in table IV.

Since the number of children studied is still small, table IV includes only the adult comparisons. This approach allows for the detection of statistically significant differences, and allows the geneticist to determine whether positive results are due to random variation or whether certain families are unremarkable while most of the positive tests occurred in other families. Both approaches are valid, but have different strengths and limitations.

The results of several tests can be presented in this fashion. The FAS test measures verbal fluency by requiring the subjects to name as many words as possible beginning with the letter F, A, and S. The number of words are individually recorded and summed. Overall, 33 words were given by unaffected adults compared to 45 for dyslexics ($p = .01$). This was an unexpected result, not observed in prior developmental studies. Similarly, the Menyuk Syntactic Comprehension

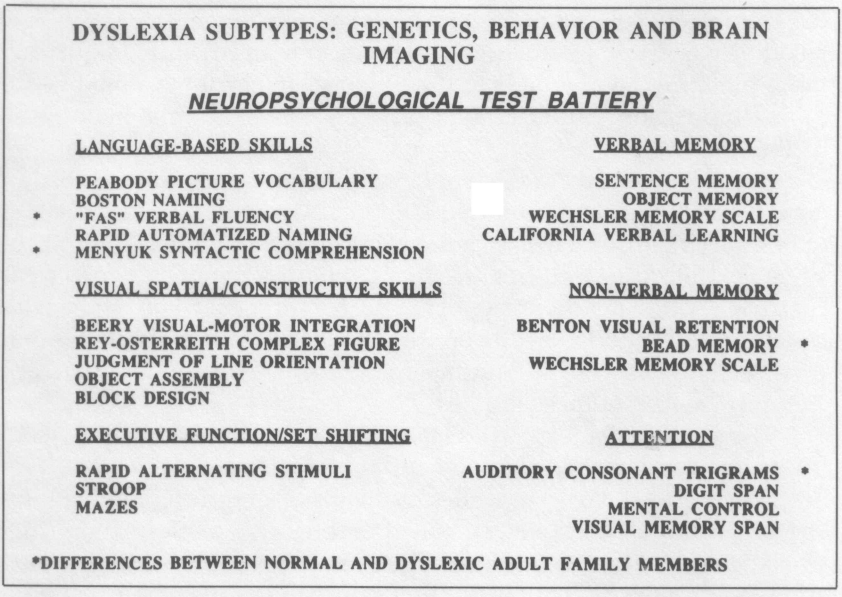

Figure 8. The various neuropsychological tests are noted according to the cognitive domain tested.

Test, also given verbally, yielded unexpected results. A simple statement is given, such as: "The lion that the tiger bit, jumped over the giraffe." The subject is asked "Who jumped over the giraffe?" Answer: "The lion." On this task, dyslexics did less well than normals ($p = .001$), a finding suggesting difficulty handling embedded syntactic markers. The Auditory Consonant Trigrams test also yielded unexpected and possibly very significant results. Three-letter meaningless trigrams (words with no vowels) are presented (example: LDX) and the subjects are asked to either recite the trigram immediately or to count backwards for 3, 9, then 18 seconds before repeating the three letters. This task becomes difficult at 9 seconds and, by 18 seconds, it is quite hard. At 9 seconds and at 18 seconds, and for the total scores, the scores were significantly different between the 18 normals and 16 dyslexics ($p < .03$). This suggests that dyslexics may have difficulty ignoring competing stimuli that interfere with immediate recall.

The second approach, which involved inspection of the data by pedigree, also gave quite interesting results. This review was greatly facilitated by developing a system for storing more than 400 variables on each family member in a MacIntosh computer system programmed to select up to 4 variables to be printed out below each appropriate circle or square (figures 9 and 10). The person's pedigree number is above the circle or square (413, 411, 418, etc. in figure 10). The totals for the

Table IV. Summary of Significant T-Test Results on Adult (>18 Yrs.) Family Members

			Language Based Skills	ΣN	
				D	N
(Verbal Fluency FAS Test)			Dyslexics (D) Normal Readers (N)		
	F	$p = .027$	$16 \pm 6 > 12 \pm 4$	16	18
	A	$p = .019$	$13 \pm 6 > 9 \pm 3$	16	18
	S	$p = .001$	$17 \pm 5 > 11 \pm 4$	16	18
	Total	$p = .010$	$45 \pm 16 > 33 \pm 11$	16	18
			Visual-Spatial/Constructive Skills		
(Beery Visual Motor-Integration)		$p = .036$	Dyslexics Normal Readers $21 \pm 2 < 22 \pm 2$	16	18
(Rey Osterreith Complex Diagram)		$p = .046$	$34.6 \pm 1.5 < 35.5 \pm 9$	15	17
			Verbal Memory Skills		
(Menyuk Syntactic Comprehension)		$p = .001$	Dyslexics Normal Readers $12 \pm 2 < 15 \pm 2$	16	18
			Dyslexics Normal Readers		
(Auditory Consonant Trigrams)	9 secs.	$p = .038$	$2 \pm 1 < 3 \pm 2$	16	18
	18 secs.	$p = .003$	$.8 \pm 1 < 2 \pm 1$	16	18
	Total	$p = .029$	$12 \pm 3 < 15 \pm 4$	16	18

dyslexics in this pedigree are shown with a box around them (63, 68, etc.). The two normals scored 38 and 27 words respectively, which was comparable to other normals. The average for the dyslexics, however, was 58. The data from this family account for all of the difference shown in table IV. Clearly, in this family the dyslexics have remarkably good verbal fluency. This is especially interesting since many people with dyslexia do extremely well in real life, particularly in business. Increased verbal fluency may be part of the explanation for this observation, at least in a subgroup of families, and more data are needed to validate this observation.

When pedigree data were inspected, similar results occurred in two other tests: the Menyuk Test and Auditory Consonant Trigrams. Two families (3001 and 3015) did poorly with Auditory Consonant Trigrams. Menyuk Test results are shown for one family in figure 9. Other families were unremarkable. Together these results provide important preliminary evidence of behavioral differences between families and indirectly for genetic heterogeneity, with several different genes producing important and previously unrecognized differences in the phenotype(s) associated with dyslexia in adults.

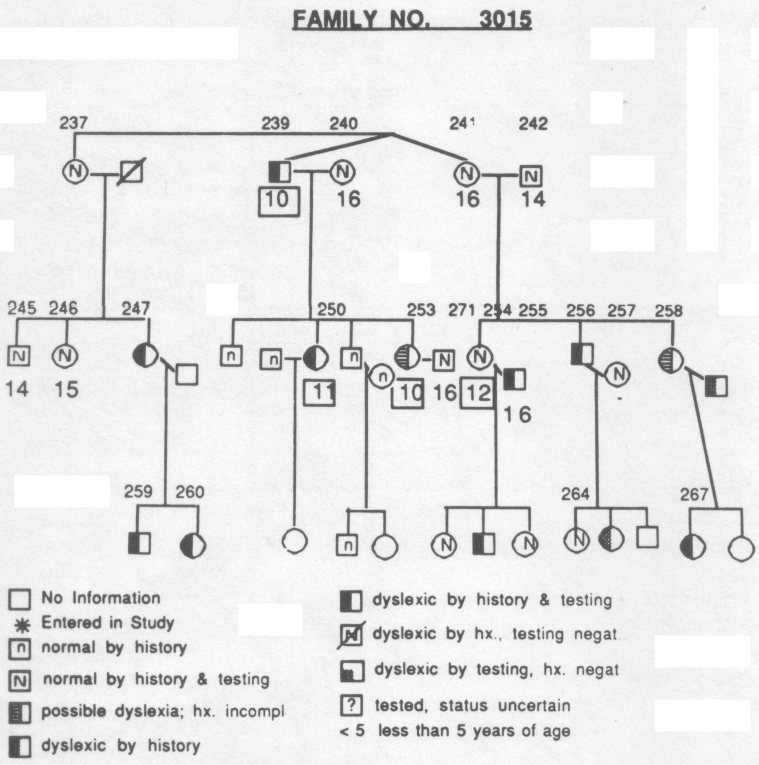

Figure 9. Pedigree 3015. Most affected members scored below the overall mean dyslexic performance on the Menyuk Syntactic Comprehensive Test, as well as below unaffected family members. The low scores for the Menyuk Syntactic Comprehension Test are shown in the boxes under the circles and squares.

Magnetic Resonance Imaging (MRI) Studies. We have used positron-emission tomography (PET) (Gross-Glenn et al. 1986) and magnetic resonance imaging (MRI) to study localization of the putative neural substrate for dyslexia. Following Galaburda's post-mortem studies of dyslexic brains (Galaburda et al. 1985), others (using MRI) have noted symmetry of the planum temporale in dyslexics, rather than the usual L > R asymmetry for this region (Hynd et al. in press; Larsen et al. in press). As we have found this region difficult to measure reliably, we have taken an approach that involves measuring clearly specified brain areas on a cross-sectional plane that transects many of the regions thought to be important for reading. Since behavioral studies have suggested possible deficits for dyslexics in interhemispheric transmission of neural signals, we have also measured the cross-sectional area of the corpus callosum (Gross-Glenn et al. 1989).

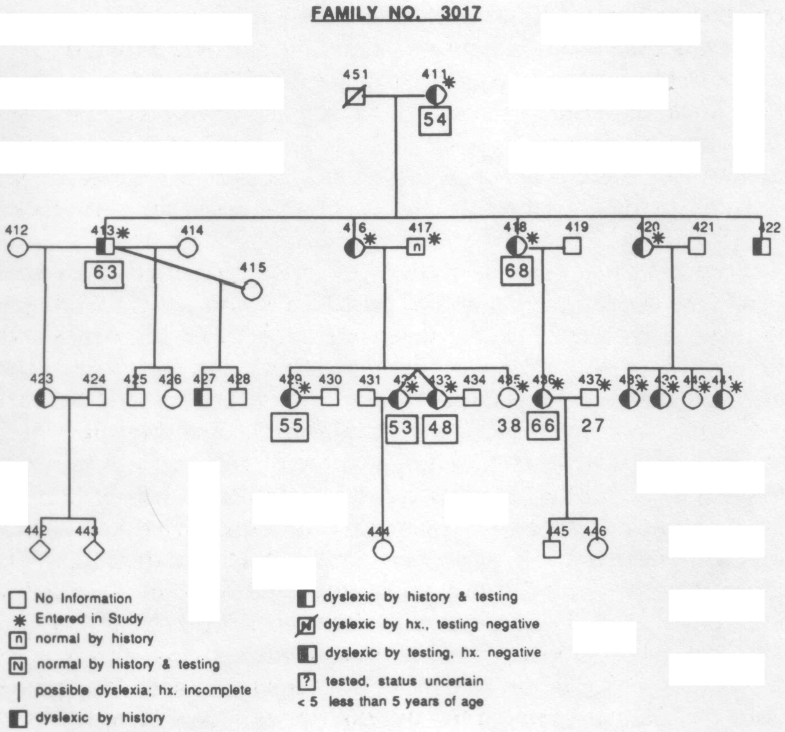

Figure 10. Pedigree 3017. Affected members scored higher on the FAS Verbal Fluency Test compared to overall unaffected members across all families. The high scores for the FAS Verbal Fluency Test are shown in the boxes under the circles and squares.

Twenty-one dyslexic and thirty non-dyslexic right-handed adults were studied by MRIs. Approximately 15% were members of families in the present studies, and the remaining were ascertained according to similar criteria. IQ was verified, and there existed both a childhood and a family history of reading and spelling difficulties in at least two generations. A diagnosis of developmental dyslexia in adults was made if there was a 1.5 standard deviation discrepancy between full scale IQ and performance on reading and spelling tests.

MRI studies were carried out with a Siemens Magnetom scanner (1.0 or 1.5 Tesla) at a slice thickness of 7.0 mm with 3.0 mm interslice intervals. Sagittal T1-weighted spin echo sequences (TR 500ms, TE 17ms) and transverse T2-weighted spin echo sequences (TR 2500ms, TE 25ms and 90ms) were used.

Planimetric area measurements (in cm^2) were derived from hand tracings of MRI scans. Horizontal areas were measured from transverse MRI scans at the level of the Foramen of Monro, containing the

plane transecting the basal ganglia and the four tips of the lateral ventricle horns. As shown in figure 11, a midline axis was drawn from the anterior to the posterior aspect of the interhemispheric fissure. Based on the linear extension of this midline axis, the cross-sectional area of this plane was divided into six regions: anterior and posterior 10%, plus four 20% regions between these poles. A laterality index (LI) was calculated using the absolute cross-sectional areas for each region: $LI = (R - L) \times 200/(R + L)$ (R = right area, L = left area).

Corpus callosum cross-section area was measured from scans taken in the midsagittal plane. The corpus callosum was traced directly and divided linearly from anterior to posterior (figure 12). Areas of the anterior fifth (genu), posterior fifth (splenium), and middle 3/5 section were normalized to the midsagittal brain area to control for differences in brain size. Two-way ANOVAs were performed on mean values of the areas measured, with sex and diagnosis being the constant factors.

Results of the MRI studies can be summarized briefly here. As shown in figure 11, there was a general progression from R > L asymmetry anteriorly to L > R asymmetry posteriorly in both groups. This pattern is consistent with previously reported cerebral asymmetries (Weinberger et al. 1982; Chui and Damasio 1980; LeMay and Kido 1978). The only region in which cerebral asymmetry for dyslexics and normals differed was the mid-posterior region, an area that encompasses the angular gyrus of the inferior parietal lobe. Here, dyslexics showed a R > L hemispheric asymmetry in contrast to the L > R pat-

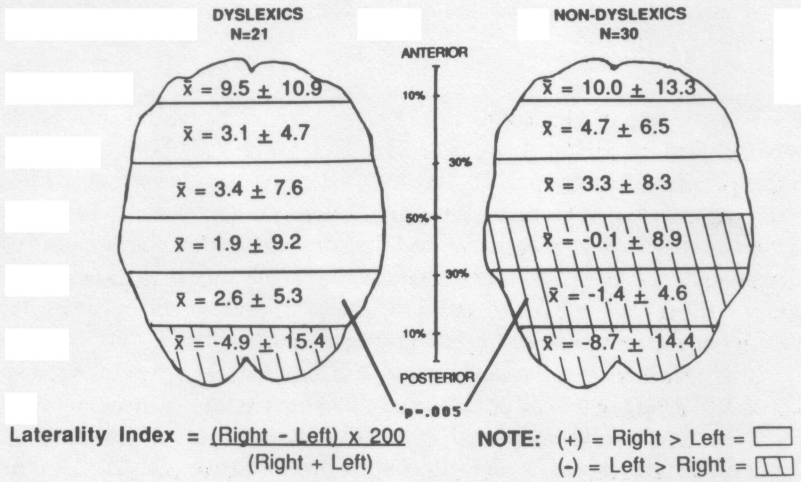

Figure 11. Laterality indices of transverse brain areas obtained from MRI scans at the level of the Foramen of Monro. Right > left asymmetry of the mid-posterior region for dyslexics was significantly different from the left right pattern of asymmetry observed here for normal readers.

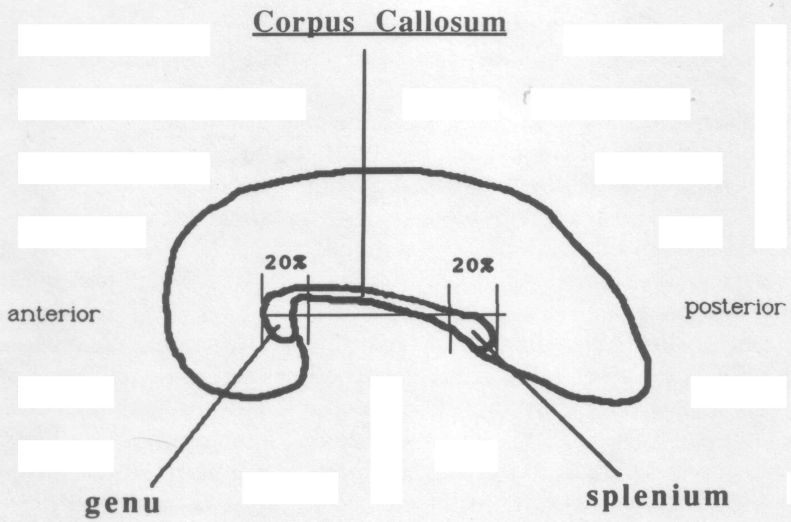

Figure 12. Sagittal area tracing of the corpus callosum, and midsagittal brain area to illustrate measurements taken from MRI scans. Areas of callosal regions were normalized to individual's midsagittal brain area.

tern observed in normal readers in the midposterior region ($F = 8.7$, $p = .005$). Group differences were also noted in the callosal area with dyslexics showing a relatively larger splenium than normal readers ($F = 8.9$, $p = .005$) (see table V). Much of this difference was due to female dyslexics, who also showed a significantly larger genu and total corpus callosum area than the other groups.

Positron-Emission Tomographic Studies. PET-scan studies were carried out on 25 right-handed adult male volunteers. The subject was

Table V. Normalized Mean Corpus Callosum Cross-Section Area Measurements 20 Dyslexics (D) Versus 30 Non-Dyslexics (N)

genu

	♀	♂	$\bar{X}$
D	.024	.019	.021
N	.020	.020	.020
$\bar{X}$	.021	.020	

Interaction Diagnosis x Sex ($F = 6.4$, $p = .015$)

splenium

	♀	♂	$\bar{X}$
D	.022	.018	.020
N	.018	.017	.017
$\bar{X}$	.020	.017	

Diagnosis ($F = 8.9$, $p = .005$)
Sex ($F = 7.9$, $p = .007$)
Interaction Diagnosis x Sex ($F = 3.1$, $p = .085$)

total

	♀	♂	$\bar{X}$
D	.075	.064	.069
N	.065	.066	.066
$\bar{X}$	.069	.065	

Interaction Diagnosis x Sex ($F = 5.8$, $p = .020$)

given an injection of a glucose analog, 2-deoxyglucose, which is labeled with a very short-lived isotope of fluorine (F-18). The brain initially utilizes this substance (FDG) as though it were glucose and it becomes concentrated in areas of the brain that are metabolically active over a 30-minute period. During this time, the subject read aloud a list of simple words. Following this activation period, the subject was scanned to reveal brain regions of varying metabolic activity, based on the PET camera's detection of the regional uptake of FDG.

PET studies have been carried out in a relatively small number of study families as well as a sample of other familial dyslexics and normal readers. Dyslexia was diagnosed according to the same criteria as for the MRI studies (see above). Similar to other studies during reading (Petersen et al. 1988), we found that a simple reading task produced wide-spread variations in metabolic activity in many brain regions. Significant differences in normalized metabolic activity between dyslexics and normal readers were localized to prefontal and inferior visual (lingual) regions (Duara et al. 1989; Gross-Glenn et al. in press).

Compared with normal readers, dyslexics showed a reversal of the $L > R$ pattern of metabolic asymmetry in the lingual region. This region is part of the occipito-temporal pathway that has been shown in monkeys to be important for identification of complex visual patterns (Mishkin, Ungerleider, and Macko 1983; Ungerleider and Mishkin 1982). In the prefrontal region, dyslexics showed more symmetry than the $R > L$ asymmetry observed in normal readers. Evidence from both animal and human studies suggests that prefrontal cortex plays an important role in temporal and cross-modal integration of behavior (Fuster 1985; Pandya and Yeterian 1985).

In order to determine whether metabolic and anatomic asymmetries in these regions correspond in the same individuals, we measured prefrontal and lingual areas from multi-slice horizontal MRI scans on 16 subjects having both types of scans. For normal readers, direction of asymmetry matched; for dyslexics, however, a significant number of subjects showed a "mismatch" between PET and MRI in the lingual region ($\chi^2 = 5.69$, $p < .02$) (figure 13). Prefrontal cortex showed a similar, but nonsignificant ($p = .08$) trend (figure 14). Usually the mismatch resulted from aberrant PET (rather than MRI) findings. This suggests that metabolic differences related to reading in dyslexics are not simply related to differences in gross structural anatomy. Despite this result, reversed anatomic asymmetry ($R > L$) for these dyslexics was observed more dorsally in the inferior parietal lobe as was found in the MRI studies on a larger group of subjects (see above).

Twenty-six of the subjects who underwent the visual psychophysical studies also participated in the MRI studies. To study the relationship between cerebral asymmetry and visual performance we correlated laterality indices derived from MRI measurements with performance on

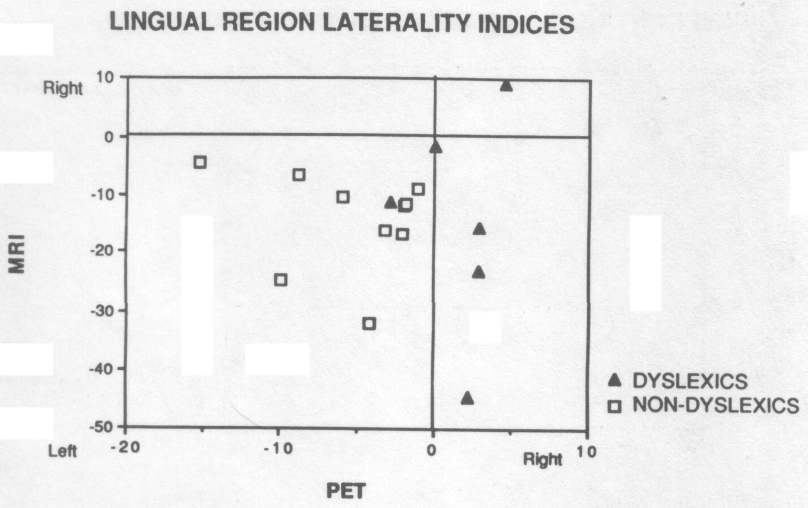

Figure 13. Plot of PET and MRI laterality indices for lingual regions showing clustering of normals to left on both measurements. In dyslexics left > right MRI asymmetry was not usually matched by direction of metabolic asymmetry on PET-scans.

the visual psychophysical study described above. The most significant finding in this vision study was dyslexics' elevated thresholds for detection of short duration high spatial frequency information, especially when targets were preceded by a mask.

To characterize each subject's masking vulnerability in this condition, we calculated a duration at which visual sensitivity was decreased by a factor of two. Long durations indicate less sensitivity as the target required more time for perception. In figure 15 this aspect of performance has been plotted on the x-axis. On the y-axis is plotted each subject's MRI laterality index for mid-posterior regions in which the two groups were found to differ. With one exception among dyslexics, those with the poorest visual performance also showed R > L asymmetry in this region (see upper right quadrant). The two measures were positively correlated in the combined group ($r = .41$, $p = .02$). Taken together, PET, MRI, and visual psychophysical studies suggest a difference in visual-system functioning for dyslexics, perhaps localized to extra-striate regions adjacent to temporal and inferior parietal cortex.

DISCUSSION

One likely outcome of these studies should be the development of both genetic and functional tests for each of the (presumed) types of dyslexia. There is now no single functional test for dyslexia and this has

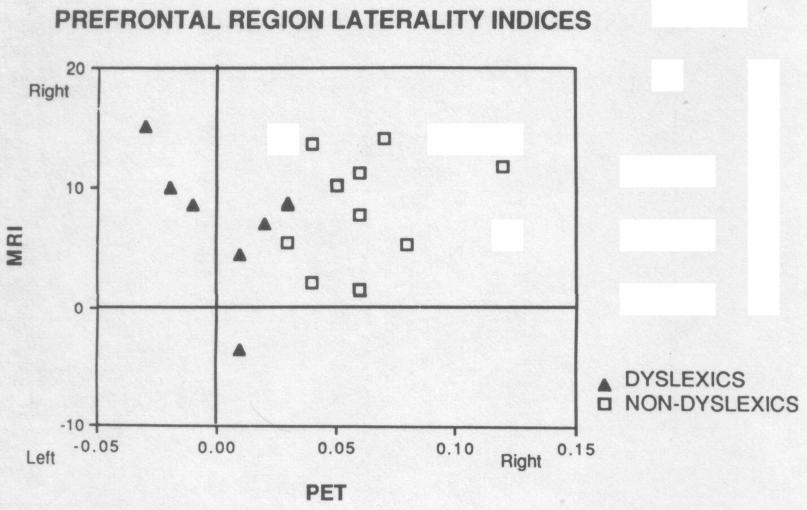

Figure 14. Plot of PET and MRI laterality indices for prefrontal region, showing a clustering of normals and some dyslexics with right > left asymmetry on both measures. Several dyslexics however failed to show this correspondence between measurements.

been a significant impediment to research. The lack of such a test has undoubtedly led to the selection of widely different study samples (all called "dyslexia"), but whose results then cannot really be compared. Several stages of genetic studies can be predicted. With a series of link-

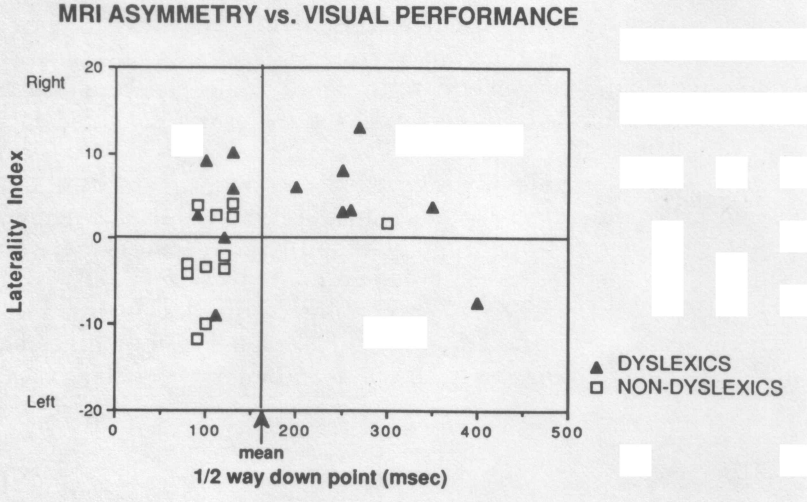

Figure 15. Individual subjects' laterality indices obtained from MRI measurements of midposterior region (figure 11) are plotted against each subjects' susceptibility to visual masking of high spatial-frequency patterns. Longer durations on the x-axis indicate a stronger masking effect and reduced sensitivity.

age studies resulting in more closely linked markers, we ultimately should be able to localize and isolate the gene(s), just as has been done for Duchenne muscular dystrophy and cystic fibrosis. Then we will have a simple, direct test for each type that will not require family studies, and that can be done at birth, or even before birth. This will provide an opportunity for both observing and introducing alternative forms of remediation early in life or different approaches to school. In a few years, it should be possible either to avoid many of the emotional and school problems that these children have or to alleviate them. The family history, in the interval, is critical, and asking about a history of dyslexia should be part of the school admission process. Recognition of the fact that a child should be specifically evaluated for dyslexia when there is a family history of dyslexia, should lead to early testing and make a major difference to many children. Eventually it is likely that different remediation strategies will be appropriate for different types of familial dyslexia.

SUMMARY AND CONCLUSION

There is a significant subgroup of children and adults with autosomal dominant inheritance of dyslexia, and the pedigrees and other data in this study provide additional evidence in support of this observation. Penetrance is greater than 90%, a value consistent with other autosomal dominantly inherited disorders. The frequency remains unknown, because we do not yet have a specific test, but is probably high. Clearly, it is not rare. There is also, now, significant evidence for genetic heterogeneity both from the genetic studies and the observation of phenotypic differences between families in the present study. These variant genes must have been present 10,000 years ago, long before reading and writing began. There may well have been advantages or disadvantage to these genes, having nothing to do with reading both then and now, and the present study has shown at least one possible advantage in verbal fluency.

The male-female differences remain challenging. The present evidence suggests that the reported excess of males is not biologically correct since the sex ratio is not different from 1.0 in these families; rather, females are less severely affected and less often recognized. There is likely an interaction between the gene(s) for dyslexia, sex hormones, and possibly even concomitantly caused immunologic responses in the development of brains in dyslexia, that requires much more data and study before a clear picture emerges. The linkage studies, however, have not as yet yielded a clearly confirmed linkage, but there is good evidence that several genes are involved; the most promising linkage studies suggest that there are genes leading to dyslexia on chromo-

somes 15 and 6. The PET, MRI, vision, speech perception, and neuropsychological studies are all extremely promising and have given highly suggestive evidence of "clinical" heterogeneity. They may result in the identification of parameters by which the (presumed) several genes may be measured functionally. Methods are available for resolution of the overall problem, but because of its complexity many more families need to be studied. A very different view of the mechanisms resulting in the phenotype(s) of dyslexia and what we might do about them should evolve from this and related studies over the next five to ten years.

REFERENCES

Bisgaard, M. L., Eiberg, H., Moller, N., Niebuhr, E., and Mohr, J. 1987. Dyslexia and chromosome 15 heteromorphism: Negative lod score in a Danish material. *Clinical Genetics* 32:118–119.

Breitmeyer, B. G., and Ganz, L. 1976. Implications of sustained and transient channels for theories of visual pattern masking, saccadic suppression, and information processing. *Psychological Review* 83:1–36.

Chui, H. C., and Damasio, A. R. 1980. Human cerebral asymmetries evaluated by computed tomography. *Journal of Neurology, Neurosurgery and Psychiatry* 43:873–78.

Duara, R., Gross-Glenn, K., Barker, W., Loewenstein, D., Chang, J. Y., Apicella, A., Yoshii, F., Pascal, S., and Lubs, H. A. 1989. PET studies during reading in dyslexics and controls. *Neurology* 39(suppl. 1):165.

Finucci, J. M., Guthrie, J. T., Childs, A. L., Abbey, H., and Childs, B. 1976. The genetics of specific reading disability. *Annals of Human Genetics* 40:1–23.

Fuster, J. M. 1985. The prefrontal cortex and temporal integration. In *Cerebral Cortex, Association and Auditory Cortices*, eds. A. Peters and E. G. Jones. New York: Plenum Press.

Galaburda, A. M., Sherman, G. F., Rosen, G. D., Aboitiz, F., and Geschwind, N. 1985. Developmental dyslexia: Four consecutive patients with cortical anomalies. *Annals of Neurology* 18:222–33.

Geschwind, N., and Galaburda, A. M. 1985. Cerebral lateralization—Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. *Archives of Neurology* 45:521–52.

Gross, K., and Rothenberg, S. 1979. An examination of methods used to test the visual perceptual deficit hypothesis of dyslexia. *Journal of Learning Disabilities* 12(9):670–77.

Gross-Glenn, K., Coleman-Lewis, D., Smith, S. D., and Lubs, H. A. 1985. Phenotype of adult familial dyslexia: Reading of visually transformed texts and nonsense passages. *International Journal of Neuroscience* 28:49–59.

Gross-Glenn, K., Duara, R., Barker, W., Loewenstein, D., Chang, J.-Y., Yoshii, F., Apicella, A., Pascal, S., Boothe, T., Sevush, S., Jallad, B., Novoa, L., and Lubs, H. in press. Positron emission tomographic studies during serial word-reading by normal and dyslexic adults. *Journal of Clinical Experimental Neuropsychology.*

Gross-Glenn, K., Duara, R., Yoshii, F., Barker, W., Chen, Y., Apicella, A., Boothe, T., and Lubs, H. 1986. PET-scan studies during reading in dyslexia and non-dyslexic adults. *Society for Neuroscience, Abstracts* 12(part 2):1364.

Gross-Glenn, K., Duara, R., Kushch, A., Pascal, S., Barker, W., Jallad, B., and Lubs, H. A. 1989. MRI and visual psychophysical studies of inherited dyslexia. *Society for Neuroscience Abstracts* 15(1):482.

Gross-Glenn, K., Jallad, B., Novoa, L., Helgren-Lempesis, V., and Lubs, H. A. 1990. Nonsense Passage reading as an aid to the diagnosis of familial dyslexia in adults. *Reading and Writing: An Interdisciplinary Journal* 2:149–61.

Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., Novey, E. S., and Eliopulos, D. (in press). Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. *Archives of Neurology.*

Larsen, J. P., Hoien, T., Lundberg, I., and Odegaard, H. in press. MRI Evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia. *Brain and Language.*

LeMay, M., and Kido, D. K. 1978. Asymmetries of the cerebral hemispheres on computed tomograms. *Journal of Computer Assisted Tomography* 2:471–76.

Livingstone, M., and Hubel, D. 1987. Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *Journal of Neuroscience* 7(11):3416–68.

Lubs, H. A., Rabin, M., Carland-Saucier, K., Wen, X. L., Gross-Glenn, K., Duara, R., Levin, B., and Lubs, M. L. 1990. Genetic bases of developmental dyslexia: Molecular studies. In *Neuropsychological Foundations of Learning Disabilities: A Handbook of Issues, Methods and Practice,* eds. J. Obrzut and G. Hynd. Orlando, FL: Academic Press, Inc.

McCroskey, R., and Kidder, H. 1980. Auditory fusion among learning disabled, reading disabled and normal children. *Journal of Learning Disabilities* 13(2):18–25.

Mishkin, M., Ungerleider, L. G., and Macko, K. A. 1983. Object vision and spatial vision: Two cortical pathways. *Trends in Neuroscience* 6:414–17.

Pandya, D. N., and Yeterian, E. 1985. Architecture and connections of cortical association areas. In *Cerebral Cortex Association and Auditory Cortices,* eds. A. Peters and E. G. Jones 4:3–61. New York: Plenum Press.

Petersen, S. E., Fox, P. T., Posner, M. I., Minton, M., and Raichle, M. E. 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331:585–589.

Smith, S. D., Kimberling, W. J., Pennington, B. F., and Lubs, H. A. 1983. Specific reading disability: Identification of an inherited form through linkage analysis. *Science* 219:1345–47.

Smith, S. D., Pennington, B. F., Kimberling, W. J., and Ing, P. S. 1990a. Familial dyslexia: Use of genetic linkage data to define subtypes. *American Academy of Child and Adolescent Psychiatry* 29(2):204–13.

Smith, S. D., Pennington, B. F., Kimberling, W. J., and Ing, P. S. 1990b. Genetic linkage analysis with specific dyslexia: Use of multiple markers to include and exclude possible loci. In *Perspectives on Dyslexia,* Vol. 1, ed. G. Th. Pavlidis. New York: John Wiley & Sons Ltd.

Tallal, P. 1980. Auditory temporal perception phonics and reading disabilities in children. *Brain and Language* 9(2):182–98.

Ungerlieder, L. G., Mishkin, M. 1982. Two cortical visual systems. In *Analysis of Visual Behavior,* eds. D. J. Ingle, M. A. Goodale, and R. J. W. Mansfield. Cambridge, MA: The MIT Press.

Weinberger, D. R., Luchins, D. J., Morihisa, J., and Wyatt, R. J. 1982. Asymmetrical volumes of the right and left frontal and occipital regions of the human brain. *Annals of Neurology* 11:97–100.

Zeki, S., and Shipp, S. 1988. The functional logic of cortical connections. *Nature* 335:311–17.