Psychobiological Heterogeneity of Familial and Sporadic Schizophrenia

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Background: *Although schizophrenia is presumed to be heterogeneous, there has been limited success distinguishing familial from sporadic cases. We used psychobiological measures to examine heterogeneity, as they may be closer to neurobiology than symptoms. Smooth pursuit eye movement quality (SPEM) and dichotic listening (DL) tests to tones and words were used to assess hemispheric laterality asymmetry.*

Methods: *Forty-six research unit patients participated in assessments of family history (FH) and physiological measures. FH was categorized by three exclusive groups: FH-1 patients had a chronic schizophrenia-related psychosis in a first-degree relative, FH-2 had it in second-degree relative, and FH-3 had no family member with a reoccurrence.*

Results: *Analysis of variance showed a significant group difference for SPEM and DL tones. SPEM was significantly worse in all three schizophrenia groups than for the normal comparison subjects. Among the schizophrenia groups, the nonfamilial group (FH-3) had the worst SPEM quality, FH-2 had intermediate quality, and FH-1 had the best quality. Conversely, only the nonfamilials (FH-3) had normal right hemispheric lateralization for tones, whereas familials did not, and FH-2 again had intermediate values. The lateralization quotient for DL words did not significantly differ among the groups.*

Conclusions: *SPEM was affected most in sporadic, not familial schizophrenia, whereas dichotic listening was most affected in familial schizophrenia. This double dissociation supports the utility of the familial/sporadic distinction and suggests that etiological factors in different forms of schizophrenia may impact principally on distinct neurobiological substrates, despite similar patient phenomenology.* Biol Psychiatry 1998;43: 489–496 © *1998 Society of Biological Psychiatry*

Key Words: Familial, sporadic, schizophrenia, heterogeneity, dichotic listening, eye movements

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Introduction

The etiology of schizophrenia is assumed to be heterogeneous, with both genetic and environmental factors causing illness. If genes and environment act principally on distinct neural regions, then their primary neuropathology may differ. Although major genes for schizophrenia are not yet identified, patients can be categorized based on the presence or absence of schizophrenia in their family members. Nonetheless, few studies using a familial–sporadic approach have found measures that differentiate subgroups based on family history. This method may lack power and sensitivity to detect such changes. Kendler (1987) indicates that low specificity is a particular problem for this approach in schizophrenia. Family history positive cases are likely to be genetic, but those lacking family history may still have genetic vulnerability, as families can vary in size and age structure and/or have incompletely penetrant or nondominant disease genes. It is still considered, however, that sporadic schizophrenia may be a phenocopy of genetic schizophrenia that has resulted from perinatal events impacting on neurodevelopment.

Likewise, studies may have compared measures that are common to both groups, possibly reflecting secondary changes, rather than primary neuropathology. Symptomatic overlap is common for many neuropsychiatric abnormalities; for example, hemiplegia can result from cortical, subcortical, brain stem, or spinal cord lesions.

We considered that psychobiological variables may be more proximate indicators of regional brain function and adopted the direction suggested by several authors (Venables 1991; Gruzelier 1994; Andreasen et al 1989) to use biological, rather than symptom measures to examine schizophrenia heterogeneity. We chose smooth pursuit eye movement quality (SPEM) and dichotic listening (DL) to tones and words. SPEM is disrupted in patients with schizophrenia and in many of their relatives (reviewed by Levy et al 1994; Pogue-Geile and Keshavan 1991). There is also some preliminary evidence that SPEM may be linked to chromosome 6 (Arolt et al 1996). SPEM deficits

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have been associated with prefrontal function (Fukushima et al 1994; MacAvoy and Bruce 1995), and decreased frontal activation on positron-emission tomography (PET) (Ross et al 1995). Its performance is dependent on a distributed neural network, as it depends upon coupled parallel processing of sensory input with motor output, involving cortico-cortical and cortico-subcortical pathways (Tusa and Ungerleider 1988). There may be many potential causes of abnormal SPEM in schizophrenia, but the consensus favors brain networks including frontal cortices as relevant to SPEM dysfunction in schizophrenia.

Disturbed structural and functional brain laterality in schizophrenia is widely described. Recent studies suggest that abnormal brain laterality may be associated with genetic vulnerability. Magnetic resonance imaging (MRI) scans have identified reversed brain asymmetries in familial, but not sporadic, schizophrenia patients, with asymmetries also found in well relatives presumed to be transmitting genes in multiplex pedigrees, known as obligate gene carriers (Sharma et al 1996). DL can be used to test perceptual asymmetry, a neurobehavioral indicator of functional brain laterality. In dichotic tests different stimuli (words or tones) are simultaneously presented to the two ears, and the difference in performance between the two ears provides the measure of perceptual asymmetry. Words are asymmetrically processed in the left hemisphere, and tones are asymmetrically processed in the right hemisphere. Dichotic listening laterality quotients, which are presumed to reflect temporal–parietal lobe function, show great variability in schizophrenia samples (Wexler et al 1991), consistent with heterogeneity.

We categorized schizophrenia patients into three family history (FH) subgroups to examine heterogeneity. We reasoned that patients with a first-degree relative with chronic schizophrenia-related psychosis most likely had familial illness; that patients with only an affected second- or third-degree relative would be mainly familial but more heterogeneous than the first group; and that patients without reported familial illness would be the least familial. Some misclassification with respect to genetic vulnerability would be expected, but the demonstration of within-group homogeneity and between-group heterogeneity on the measures would suggest differences among the groups.

Methods and Materials

Samples

The 46 patients in this study were recruited from an inpatient schizophrenia research unit. The controls for SPEM and DL did not overlap and were independently recruited. All patient, family, and control participants gave written informed consent for the research, which was approved by the institutional review board. All patients were physically healthy, as indicated by recent physical examinations, laboratory evaluation of serum chemistry (SMAC), complete blood count, urinalysis, and thyroid function tests. Structured clinical interviews with the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al 1994) or the Comprehensive Assessment of Symptoms and History (Andreasen et al 1992) were conducted by one of three clinicians (two with Masters degrees, one with a PhD in clinical psychology), who had completed initial calibration checks showing high interrater reliability (i.e., kappa $\geq$ .8 for individual symptom ratings and 95% agreement on diagnosis). DSM-III-R diagnoses were made from structured interviews, past records, and family informant data. Data on the patients including age, gender, patient education, Hollingshead social status (Hollingshead 1975), ages of onset of positive symptoms, and first hospitalization were assessed. All patients studied were on neuroleptic medications. Separate groups of comparison control subjects also had dichotic listening and SPEM. Controls for both tasks were volunteers recruited from the hospital community and screened with a modified Schedule for Affective Disorders and Schizophrenia–Lifetime version (Spitzer and Endicott 1975) to exclude any current or past Axis I psychopathology. Thirty-two patients had SPEM measured, 31 patients had the dichotic listening tone task, and 37 patients had the dichotic listening words task. Seventeen patients had both SPEM and dichotic words assessed, and 17 patients also participated in both the SPEM and dichotic tone studies. Concerning possible biases in using hospitalized patients, patients were not admitted to the unit or tested with regard to family history, nor was participation and nonparticipation in the various protocols related to family history. We rigorously assessed family history and studied all patients in the same research unit environment. All assessments were performed independently without knowledge of other data or the aims of this analysis.

Family History

A doctoral student with advanced diagnostic training, blind to all patient information, conducted structured interviews using the Family Interview for Genetic Studies (FIGS) (NIMH-Molecular Genetics Initiative 1991). At least one family informant provided information about all first- and second-degree family members, after which diagnoses were made by FHRDC criteria (Andreasen et al 1977). Family history data for four families was obtained by highly trained research social workers through semistructured interviews with at least one family informant. Only schizophrenia-related chronic psychosis (schizophrenia, schizoaffective, and psychosis not otherwise specified) defined the affectation status of the relatives in this study, because these diagnoses can be reliably obtained from family history informants. Presumably the use of spectrum personality disordered relatives for defining family history would have enhanced the divisions among the three groups. Probands were exclusively assigned to one of three FH groups based only on their Axis I diagnoses: FH-1 had at least one affected first-degree relative, the FH-2 group had such reoccurrence in at least one second-degree relative, and FH-3 had no family reoccurrences through the second-degree relatives.

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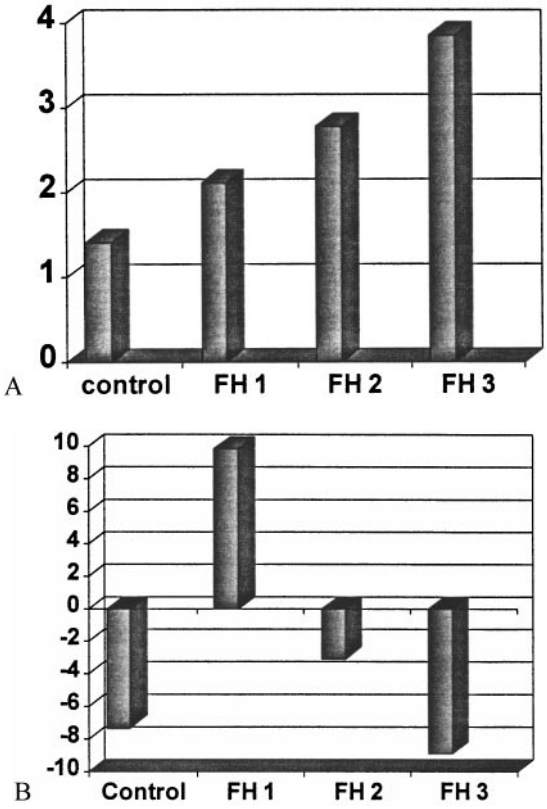

Figure 1. Mean SPEM quality **(A)** and DL tones laterality quotient **(B)** in comparison subjects and in schizophrenia subjects grouped by family history.

Psychobiological Measures

Electro-oculographic (EOG) recordings of eye movement quality were made on a Grass Model 7-D polygraph, using an AC coupler with a 3-sec time constant. SPEM was recorded with the subject positioned with chin and head support, 57 cm from a cathode ray tube monitor. Electrode impedances were kept below 10 kΩ, sensitivity was set at 15 mV/mm, and the band pass was 1.2–90 Hz with a 60-Hz notch filter. Miniature (9 mm) Ag/AgCl electrodes were placed bilaterally at the outer canthi to record horizontal movement (forehead ground). Electrodes placed above and below the left eye recorded eye blinks. Paper recordings were made of horizontal eye movements and blinks. Stimuli were presented on an Amdek 310A CRT. The target subtended 1.5° of visual arc, traversed a 20° horizontal visual angle, and had a period of 2.5 sec (0.4 Hz) and a maximum velocity of 27.78°/sec. Three trials of 30 sec each were recorded, and the best tracing was used for the analysis. SPEM quality was assessed by visual matching of the paper polygraph tracings (with blinks subtracted) to a nine-point scale, modified from Shagass et al (1974), and ranging from 1 to 5 in 0.5 intervals. The ratings were made by two experienced raters blind to subject diagnosis and identifying information, with intraclass correlation coefficients of .90. SPEM was measured while patients were being treated with typical neuroleptic medications.

Dichotic listening tasks were performed as we have previously described (Malaspina et al 1997). Dichotic listening tasks were also performed by the patients while they were receiving antipsychotic medication, as we have not found a difference in dichotic listening laterality for patients tested when on or off their antipsychotic medications (Bruder et al 1995). Patients were excluded if they had a hearing loss greater than 30 dB in either ear or an ear difference greater than 10 dB at 500, 1000, and 2000 Hz. The Fused–Rhymed Words Test was used to provide an index of hemispheric dominance for language (Wexler and Hawles 1983). It yields a mean right ear (left hemisphere) advantage in normal adults. Single syllable word pairs differing only in the initial consonant were presented simultaneously to the right and left ear (e.g., coat, goat) via a matched pair of TDH-49 headphones at a comfortable level of 75 dB SPL. The words fuse into a single precept, and the subjects used a multiple choice answer sheet to indicate the word they heard. Four 30-item blocks yielded a total of 120 trials. The Complex Tone Test was used to measure cerebral dominance for pitch discrimination; it yields a mean left ear (right hemisphere) advantage in normal adults (Sidtis 1981). Different complex tones were presented to the two ears, followed by a binaurally presented probe tone that was the same as one member of the dichotic pair or different than both. Subjects pointed to a response card labeled yes or no to indicate whether or not the probe tone matched either member of the dichotic pair. The tones consisted of square waves with different fundamental responses. Subjects were tested for four blocks of 28 trials. Dichotic listening laterality scores were computed from the number of right or left ear words/tones correctly reported, as $100 \cdot (R-L)/(R+L)$. Positive scores are indicative of a right ear (left hemisphere) advantage, whereas negative scores are indicative of a left ear (right hemisphere) advantage.

Data Analysis

Initial statistical analysis compared patient groups (all DSM-III-R schizophrenia or schizoaffective) differing in the family history parameter. Demographic profiles were generated from statistical comparisons of age, education, age of onset, and age of first treatment performed using an analysis of variance (ANOVA). Sex and DSM-III-R diagnoses distributions were assessed using the Pearson chi-square statistic. Comparisons of the SPEM and the DL data were performed between the schizophrenic patients (grouped by FH categorization) and two separate control groups, one with SPEM data and the other with DL data (Figure 1). A one-way ANOVA (four group) was used for the SPEM comparison (individual sex data were not available on the control group). For the DL variable, a four group by two gender analysis of covariance (ANCOVA) was performed with education level as the covariate. Where there was a significant group F statistic, follow-up pair-wise comparisons were performed using the protected t test procedure (Welkowitz et al 1982) to protect for the multiple pair-wise comparisons.

Results

The entire patient sample consisted of 46 patients (18 female, 28 male). Family history group categorization was

Table 1. Demographics of Family History Subgroups

	Familial 1st degree (n = 11) MN (SD)	Familial 2nd degree (n = 13) MN (SD)	Sporadic (n = 22) MN (SD)	Test statistic
Male:female	6:5	9:4	13:9	$\chi^2 = 0.60$, ns
Age (years)	34.0 (10)	30.5 (6.5)	33.7 (8.0)	$F = 0.64(2,43)$, ns
Social Status[a]	32.2 (9.6)	26.2 (7.9)	33.1 (12.9)	$F = 1.56,(2,34)$, ns
Education (years)	12.5 (2.3)	12.4 (1.0)	13.0 (1.8)	$F = 0.60$ (2/42), ns
Age at onset (years)	18.9 (7.5)	17.8 (3.9)	19.2 (5.5)	$F = 0.23(2/42)$, ns
Age at 1st treatment (years)	23.3 (10.3)	17.2 (5.1)	20.1 (5.5)	$F = 2.30(2/42)$, $p = .11$
Number of relatives				
1st degree	24.0 (10.3)	32.6 (6.2)	26.7 (13.4)	
2nd degree	13.8 (5.1)	13.4 (5.5)	16.0 (5.8)	

[a]Social status = education (years) + highest occupation.

made for each patient to one of the three groups: 11 of the patients had a first-degree relative with psychosis and were assigned to the FH-1 group, 13 patients had an ill second-degree (but no first-degree) relative and were assigned to group FH-2, and 22 patients had no family history of psychosis through second-degree relatives and were assigned to the FH-3 group. Ratios of DSM-III-R schizophrenia and schizoaffective diagnoses (schizoaffective depressed, bipolar, and mixed) did not differ by FH group: in FH-1, 10 out of 11 had schizophrenia, the remaining patient had schizoaffective disorder; in FH-2, 9 out of 11 had schizophrenia; and in FH-3, 20 of 22 patients had schizophrenia. The total number of relatives assessed (and the number of first- plus second-degree relatives assessed) did not differ among the three groups (Table 1).

Patient group demographic data are presented in Table 1, and, as seen, age, sex, age of onset, age of first treatment, and socioeconomic status (SES) did not differ among the groups. Education level, age, and SES did not differ among the schizophrenia groups. Normal control samples for SPEM and DL tasks were all without current or lifetime history of psychiatric disorder. For SPEM, the 20 normal controls were 50% female, had a mean age of 28.9 ± 5.6 years, and had a mean education of 16.4 ± 2.6 years. The 82 DL controls were 41.5% female, had a mean age of 34.6 ± 10.2 years, and had a mean education of 15.9 ± 2.2 years.

Differences in SPEM and the two DL tasks were examined among the three family history groups and the comparison group (results are presented in Table 2). SPEM quality significantly differed among the groups ($F = 30.3$, df = 3,48, $p < .0001$). Also for SPEM, all follow-up pair-wise comparisons differed at the $p < .05$ level, except for the comparison of FH-1 versus FH-2,

Table 2. Psychobiological Measures

Measure	Familial 1st degree MN (SD) (95% CI)	Familial 2nd degree MN (SD) (95% CI)	Sporadics MN (SD) (95% CI)	Controls MN (SD) (95% CI)	ANOVA results (df)	Pair-wise[a]
SPEM quality[b]	2.11 (0.42) (1.8–2.4) (n = 9)	2.78 (1.09) (1.9–3.6) (n = 9)	3.86 (0.95) (3.3–4.4) (n = 14)	1.41 (0.48) (1.2–1.6) (n = 20)	Group: $F = 30.27$ (3/48), $p < .0001$; sex not included	1 > 4 2 > 4 3 > 4 1 < 3 2 < 3 1 < 2 t
Dichotic listening (tones)[c]	9.84 (16.4) (−2.8–22.4) (n = 9)	−4.88 (20.5) (−20.6–10.9) (n = 9)	−8.1 (10.4) (−14.3–−1.8) (n = 13)	−7.3 (10.8) (−12.3–−2.3) (n = 20)	Group: $F = 4.07$ (3/43), $p < .012$; sex: $F = 5.85$ (1/43), $p < .020$[d]	1 > 2 1 > 3 1 > 4 m > f
Dichotic listening (words)[c]	10.81 (11.3) (2.7–18.9) (n = 10)	6.96 (9.8) (0.38–13.5) (n = 11)	6.50 (8.7) (1.9–11.1) (n = 16)	9.73 (15.2) (5.9–13.6) (n = 62)	Group: $F = 0.55$ (3/91), p = ns; sex: $F = 1.61$ (1/91), p = ns[e]	

CI, confidence interval; MN, mean.
[a]Protected t test at the $p < 0.05$ level (1 = FH-1, 2 = FH-2, 3 = FH-3 sporadics, 4 = controls) (t = trend).
[b]Neither sex nor education were included here as factor or covariate.
[c]Sex was included as a factor and education as a covariate, and means are unadjusted.
[d]No significant group by sex interaction.
[e]Marginal group by sex interaction ($F = 2.32$, $p < .081$)—m > f except in 1st-degree family history group.

which were different only at a trend level ($p < .07$). The poorest SPEM was in the patients without a family history. There were no age or sex effects for SPEM within the schizophrenia groups, nor did they interact with the family history group. There were also no significant correlations of education with SPEM, examined overall and within each of the FH groups.

DL scores for tones and words are also given in Table 2. Pair-wise comparison of the mean education levels indicated that the controls were significantly higher than each of our patient groups. We were able to covary education with the dichotic listening data and found that while education differed significantly between the groups (mean (MN) 95% confidence interval: 15.4–16.5) (overall comparison $F = 18.68$, df = 3/93, $p < .0001$), significant group effects were still present when the data were covaried for education. The laterality quotients from the dichotic listening tones task showed main effects for family history and sex, and there was no significant two-way interaction of family history and sex. The dichotic tone task, which was expected to show a left ear/right hemisphere advantage, differentiated the family history and comparison groups ($F = 4.07$, df = 3,43, $p < .012$). The FH-2, the FH-3 sporadics, and normal subjects all showed the expected right hemispheric advantage for tones, but the FH-1 familials had the opposite asymmetry for tones (right ear/left hemisphere advantage). The FH-1 familial group differed pair-wise from each of the other groups, including the FH-2 group. The DL words laterality quotients did not reveal main effects for family history grouping or for sex, but there was a marginal two-way interaction of family history and sex.

The laterality scores for DL words showed the expected right ear/left hemisphere advantages in all groups, with no significant differences among the groups.

SPEM and DL tone scores were unrelated to right or nonright reported handedness ($t = 0.10$, df = 5.5 and $t = -0.27$, df = 5.61, respectively). DL word scores, which did not discriminate among the family history subgroups, were related to handedness with laterality quotient = 9.0 ± 10.45 for right and 3.2 ± 4.35 for nonright handers ($t = 2.27$, df = 24.3, $p = .032$).

The analysis of demographic factors for the subgroups participating in the SPEM and dichotic listening tests showed no differences in age, education, socioeconomic status, or onset or treatment ages among the groups or compared to the full group. Associations of SPEM and dichotic scores were examined in patients having both measures. SPEM and DL words were correlated by Spearman's $r = -.59$, df = 16, $p = .017$, and SPEM and dichotic tones were $r = -.44$, df = 17, $p = .078$. Both DL measures suggest that having worse SPEM was associated with greater right hemisphere advantage.

Discussion

Although familial–sporadic distinctions are generally regarded as having low power in schizophrenia, we were able to distinguish among the groups by examining biobehavioral variables that may be more proximate to brain function than symptoms and some other biological measures. We found group differences in SPEM quality and dichotic tone laterality scores among schizophrenia patients who were categorized by family history. Familial groups had better SPEM than sporadics; however, first-degree familials did not have the expected right hemisphere advantage for dichotic tone discrimination, as did the second-degree familials, sporadics, and comparison subjects.

Although all schizophrenia groups had worse SPEM quality than the normal comparison group, patients with a positive family history had better SPEM than those without family reoccurrences. Other authors have also reported better SPEM quality in schizophrenia patients with a family history of psychiatric illness (Schwartz et al 1995; Ebmeier et al 1990). Relatives of patients with schizophrenia also have impaired SPEM (Levy et al 1994), but the specificity of SPEM quality for more or less genetic forms of schizophrenia has just recently been examined and is not yet established (Roy and Crowe 1994). Disturbances at multiple neural nodes may disrupt SPEM quality. The SPEM abnormality in familial schizophrenia could be associated with the right-sided tempoparietal abnormality we saw in familial patients, as right-sided tempoparietal brain mechanisms are proposed to be responsible for the attentional components of normal saccadic latency (Evans and Schwartz 1997). Additional or distinct abnormalities may underlie the poorer SPEM quality in sporadics. The presence and heritability of poor SPEM in our patients' families is unknown, because we studied only a few of our patients' relatives. We only assessed SPEM quality and thus could not assess quantitative eye movement indices, which may have shown a different pattern among the family history groups.

In contrast to their better SPEM, the first-degree familials failed to show the expected right hemisphere advantage for dichotic tone discrimination that was seen in the sporadics and comparison subjects from this and other studies (Sidtis 1981; Tenke et al 1993). Such a dysfunction may be associated with core findings in schizophrenia patients. The neural circuits including right parietal and frontal areas participate in higher cognitive functions, with right-sided temporal and parietal regions being particularly associated with alertness and sustained selective attention (Posner 1995; Mesulam and Geschwind 1978). For example, right cortical regions have been linked to attention in the visual and auditory continuous perfor-

mance test (CPT) (Buchsbaum et al 1990). Attentional abnormalities are reported to precede schizophrenia onset in high-risk subjects and have been theorized to underlie the genetic diathesis (Cornblatt et al 1985). The right hemisphere is also dominant for autonomic function (Mesulam 1981; Lane and Jennings 1995). Abnormal asymmetry on the dichotic tone discrimination task has been associated with reduced right hemisphere electrophysiological amplitudes (Tenke et al 1993). We previously found this same right hemisphere disadvantage in schizophrenia patients with abnormal autonomic nervous system function assessed by measuring cardiac vagal tone with beat-to-beat heart rate variability (Malaspina et al 1997). This pattern of reversed dichotic tone asymmetry is also described in patients with melancholic depression (Bruder et al 1989). Since schizophrenia and schizoaffective diagnoses were not differentiated by family history in this study, it is unlikely that affective syndromes in our familial schizophrenia patients account for this finding.

Structural brain imaging studies have shown familial schizophrenia to be associated with lateral and medial temporal abnormalities, greater ventricular asymmetries, and reversed laterality (Honer et al 1994; Roy et al 1994; Sharma et al 1996). Crow (1989) has hypothesized that the gene for schizophrenia may be the same gene that controls the cerebral lateralization of language. Because we used only the DL words task to index verbal hemispheric advantage, it would be premature to speculate that familial patients do not have impaired language lateralization. Perhaps laterality is more broadly disrupted in familial schizophrenia, language being just one example of a normally asymmetric brain capacity. The large variations in brain asymmetry described in schizophrenia patients across studies preclude a consensus about which hemisphere (versus both or neither) functions abnormally, although left hemispheric overactivation/dysfunction is often hypothesized (Flor-Henry 1976; Walker and McGuire 1982; McCarley et al 1991). Altered asymmetries in our dichotic word test, which is expected to show a left hemisphere advantage, did not differ among the family history groups, so the left hemisphere differences in schizophrenia patients may be unrelated to family history. The present study does suggest that family history (as indexed by chronic schizophrenia-related psychoses in family members) may significantly contribute to the variability in DL tone asymmetry. It is not clear why brain laterality would differ between the family history groups, although subject heterogeneity in dichotic laterality quotients is well described (Wexler et al 1991). The etiology of impaired asymmetry could result from intrinsic temporal–parietal dysfunction, neurochemical abnormalities, aberrant neural connectivity, or aberrant interhemispheric balance. Differences in the developmental sequence among neural systems may render them more, or less, likely to be affected by pre- or perinatal environmental events.

The dissociation of the right hemisphere activation and SPEM quality were further supported by the negative correlations of the dichotic laterality quotients and SPEM quality; the subjects with better SPEM quality had less right hemisphere advantage. Inverse correlations between abnormal SPEM and MRI measures of medical temporal lobe abnormalities and ventricular enlargement (Levy et al 1992; Smeraldi et al 1987) in schizophrenia patients have been reported. Eye tracking deficits and CPT attentional measures appear to be independent factors in schizophrenia patients (Keefe et al 1997). SPEM was also unrelated to CPT impairments in nonpatients, but it was associated with social introversion and paranoia (Siever et al 1982).

Only schizophrenia-related chronic psychosis (schizophrenia, schizoaffective, and psychosis not otherwise specified) defined the affectation status of the relatives in this study, because these diagnoses can be reliably obtained from family history informants. Presumably the use of spectrum personality disordered relatives for defining family history would have enhanced the divisions among the three groups.

If replicated, these data could indicate that nonfamilial factors act on neural regions that further worsen eye tracking quality, and that inherited factors could act upon brain systems that underlie the right-sided tempoparietal brain advantage for pitch discrimination. Further research may be useful in developing criteria to define more homogeneous forms of schizophrenia for study. Family studies of the heritability of hemispheric asymmetries for dichotic tone could examine its utility as a candidate endophenotype for genetic research.

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