Is There an Increased Familial Prevalence of Psychopathology in Children With Nonverbal Learning Disorders?

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The cognitive and behavioral symptoms of nonverbal learning disabilities (NLD) have been described by previous investigators. Nevertheless, we know far less about the potential genetic contributions that may predispose a child to have NLD. An endophenotype model was investigated in 5 samples of children ages 9 to 15 years: NLD (n = 32); reading disorders (RD; n = 59); participants with a psychiatric diagnosis but without a learning disability (n = 55); typically developing controls (n = 31); and children with velocardiofacial syndrome (VCFS), a chromosomal deletion syndrome that has been proposed as being an exemplar of NLD (VCFS + NLD; n = 20). Based on a family genetic interview, the authors’ data suggest that children with NLD, RD, or a psychiatric diagnosis have a higher prevalence rate of attention-deficit/hyperactivity disorder (ADHD) and substance abuse/dependence. Psychiatric controls and children with NLD—but not children with RD—showed higher prevalence rates of familial bipolar disorder.

**Keywords:** nonverbal learning disabilities; genetics; prevalence rates; endophenotype

Learning disabilities (LD) occur in approximately 5% of school-age children (Lyon, 1996), and two major subtypes of LD have been described: children with reading disorders (RD) and children with nonverbal learning disabilities (NLD; Drummond, Ahmad, & Rourke, 2005). Compared to RD, far less research has focused on NLD. Thus, the incidence and prevalence rates of NLD are currently unclear partly due to the difficulty in formulating an inclusive set of classifications that characterizes NLD (Roman, 1998). Most extant research at this point has been descriptive, and the data on treatment outcomes and familial origins of NLD have been less forthcoming. Thus, we know relatively little about potential genetic contributions that may play a role in the development of NLD.

The first documented cases of NLD were elucidated in the 1970s, when researchers began studying children who had discrepancies between their Performance and Verbal IQs on the Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1991; see Semrud-Clikeman and Hynd, 1990, for a review of these early studies). The results from these early studies reported that learning disabilities were more heterogeneous than once thought and that various subtypes existed. From these early subtype studies, conceptual underpinnings for a theory of NLD were elucidated. Since this pioneering work, a specific cognitive and behavioral profile has been described in youth with NLD, whose areas of strength include reading, decoding, spelling, and general language skills, yet who have vulnerabilities in math and the visuospatial/perceptual domain that are central to the disorder (Rourke, Ahmad, Hayman-Abello, & Warriner, 2002). Other cognitive NLD symptoms include problems with tactile perception, complex psychomotor skills, and visual perception (Drummond et al., 2005; Johnson & Myklebust, 1971).

Behaviorally, children with NLD are often described as socially inept (Rourke, 1995; Tsatsas, Fuerst, & Rourke, 1997), and they have significant difficulties related to the processing of nonverbal social information (Badian & Ghiblikian, 1983; Loveland, Fletcher, & Bailey, 1990). Children with NLD may exhibit hyperactivity and are often characterized as being disruptive and unruly (Fuerst, Fisk & Rourke, 1990). As adolescents, individuals with NLD generally encounter progressive socioemotional problems, including difficulty adapting to social situations (Harnadek & Rourke, 1994; Loveland et al., 1990). Adolescents and young adults with NLD are often described as asocial and withdrawn (Rourke, 1995; Rourke, Young, & Leenaars, 1989). Though not specific to NLD, others have demonstrated that children with significantly greater WISC-R Verbal IQ relative to Performance IQ (thought to be a characteristic of NLD) have more aberrant personality characteristics, both disruptive and inhibited (Fuerst et al., 1990). Others (Ikebuchi, Nakagome,
Tugawa, & Asada, 1996; Wong & Cornell, 1999) have similarly proposed that lower Performance IQ scores, poor peer relationships, and internalizing symptoms often coexist, interact, and potentiate one another (Nangle, Erdley, Newman, Mason, & Carpenter, 2003).

Despite the literature on emotional and psychiatric functioning in individuals with NLD, there has been little work addressing how genetic variables may contribute to the increased prevalence of psychopathology in this population. This line of investigation may not only hold promise for identifying neuropsychological and behavioral characteristics of disorders that may frequently co-occur, but also be important in guiding a further understanding of the familial and genetic relationships that underlie these disorders. Moreover, integrating heritability with theoretical conceptions that emphasize neuropsychological vulnerabilities may help to advance our knowledge of NLD and, ultimately, enhance our ability to treat the psychopathology that often accompanies this learning disorder (Kibbey & Hynd, 2001).

The endophenotype model (Gottesman & Gould, 2003) guided our research design. A shared predisposing vulnerability should be familial, and although not all relatives of children with NLD will have a particular psychiatric disorder (the vulnerability presumably combines with other factors only in some family members to cause the full disorder), we may observe an increased prevalence of certain psychiatric disorders in relatives of children with NLD. This basic premise has been relatively well validated for schizophrenia and ADHD, conditions that share neuropsychological vulnerabilities (i.e., prefrontal mechanisms; Asarnow et al., 2002).

Method

Participants

Participants in the current project represented consecutive referrals from (a) several large, ongoing prospective psychiatric longitudinal research studies; (b) a general outpatient child/adolescent psychiatric clinic; and (c) an outpatient learning disorders clinic at an urban academic medical center. Potential participants were classified into five samples based on the presence and type of learning disorder:

1. NLD sample (n = 32);
2. reading disorders (RD) sample (n = 59);
3. psychiatric control group of participants with a psychiatric diagnosis but without LD (n = 55);
4. comparison group composed of typically developing children (n = 31); and
5. a sample of children with velocardiofacial syndrome (VCFS)—a chromosomal deletion syndrome that has been proposed as being an exemplar of NLD (Rourke et al., 2002; Swillen et al., 1999)—who also met criteria for NLD (VCFS + NLD; n = 20).

Our rationale for including children with VCFS + NLD was to compare this sample to the sample of children with idiopathic NLD (i.e., NLD not associated with a medical disease) to further investigate the NLD endophenotype model.

As Table 1 shows, the study population ranged in age from 9 to 15 years (M = 11.4, SD = 1.8). The majority (90%) of our participants were Caucasian, and no differences emerged between the five groups with respect to the percentage of ethnic minority participants. Children whose histories included a neurological condition other than VCFS were excluded from our analyses. The sample included more boys (n = 118) than girls (n = 79), which was consistent with other clinic-referred samples of children with LD.

Nonverbal learning disability. The 32 children in our NLD sample met the criteria outlined by Rourke et al. (2002). To qualify for inclusion, participants needed to meet criteria for at least 8 of the 10 diagnostic criteria outlined by Rourke et al. (see Table 2). The diagnosis of NLD was made in a systematic fashion through psychological test results for six criteria:

1. bilateral deficits in tactile perception;
2. psychomotor coordination, usually more marked on the left side of the body;
3. notable impairments in nonverbal problem solving;
4. impaired visuospatial abilities;
5. well-developed rote verbal abilities (e.g., single word reading and spelling); and
6. substantial deficits in mechanical arithmetic and reading comprehension.

We relied on parent report on our social skills measure to assess the criterion of extreme deficits in social perception, judgment, and interaction. Similarly, the psychiatric interview helped to determine whether the child met the criterion of sense of time; this was probed during the ADHD module. Finally, given that two NLD criteria—substantial difficulty in dealing with novel or complex information or situations, and high verbosity that is rote and repetitive—are assessed in interpersonal situations, we computed kappa coefficients of agreement by having two licensed clinical child psychologists independently
<table>
<thead>
<tr>
<th>Variable</th>
<th>NLD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RD&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Group Psychiatric&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Control&lt;sup&gt;d&lt;/sup&gt;</th>
<th>VCFS + NLD&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Main effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Mean Age (years-months)</td>
<td>10-7</td>
<td>2-1</td>
<td>10-5</td>
<td>2-4</td>
<td>11-1</td>
<td>2-7</td>
</tr>
<tr>
<td>WISC-III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>94.9</td>
<td>17.1</td>
<td>92.4</td>
<td>14.5</td>
<td>95.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>99.8</td>
<td>14.4</td>
<td>90.1</td>
<td>15.9</td>
<td>95.6</td>
<td>12.4</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>87.7</td>
<td>16.5</td>
<td>96.2</td>
<td>15.0</td>
<td>94.8</td>
<td>16.1</td>
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<tr>
<td>WIAT-II</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Reading</td>
<td>100.4</td>
<td>14.4</td>
<td>82.0</td>
<td>13.3</td>
<td>94.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Math Composite</td>
<td>80.1</td>
<td>17.1</td>
<td>89.8</td>
<td>12.9</td>
<td>93.9</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Note: NLD = Nonverbal learning disabilities; RD = Reading disabilities; VCFS = Velocardiologic syndrome; WISC-III = Wechsler Intelligence Scale for Children, 3rd ed. (Wechsler, 1991); WIAT-II = Wechsler Individual Achievement Test, 2nd ed. (Wechsler, 2001).  
<sup>a</sup> n = 32.  
<sup>b</sup> n = 59.  
<sup>c</sup> n = 55.  
<sup>d</sup> n = 31.  
<sup>e</sup> n = 20.
Table 2
Diagnostic Criteria for Nonverbal Learning Disability (NLD), With Number of Participants Who Met Each Criterion

<table>
<thead>
<tr>
<th>Criterion</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>Bilateral deficits in tactile perception, usually more marked on the left side of the body</td>
<td>17</td>
</tr>
<tr>
<td>Bilateral deficits in psychomotor coordination, usually more marked on the left side of the body</td>
<td>18</td>
</tr>
<tr>
<td>Extremely impaired visual–spatial organizational abilities, generally worsening compared to peers</td>
<td>32</td>
</tr>
<tr>
<td>Substantial difficulty in dealing with novel or complex information or situations. A strong tendency to rely on rote, memorized reactions, approaches, and responses (often inappropriate to the situation), and failure to learn or adjust responses according to feedback</td>
<td>32</td>
</tr>
<tr>
<td>Notable impairments in nonverbal problem solving</td>
<td>32</td>
</tr>
<tr>
<td>Distorted sense of time. Estimating elapsed time over an interval and estimating time of day are both notably impaired</td>
<td>30</td>
</tr>
<tr>
<td>Well-developed rote verbal abilities (e.g., single word reading and spelling), frequently superior to age norms, in the context of notably poor reading comprehension abilities</td>
<td>32</td>
</tr>
<tr>
<td>High verbosity that is rote and repetitive, with content disorders of language and deficits in functional/pragmatic aspects of language</td>
<td>32</td>
</tr>
<tr>
<td>Substantial deficits in mechanical arithmetic and reading comprehension relative to strengths in single word reading and spelling</td>
<td>32</td>
</tr>
<tr>
<td>Extreme deficits in social perception, judgment, and interaction, often leading to eventual social isolation and withdrawal. Easily overwhelmed in novel situations, with a marked tendency toward extreme anxiety, even panic, in such situations</td>
<td>29</td>
</tr>
</tbody>
</table>

Note: N = 32. Diagnostic criteria for NLD from Rourke et al. (2002).

assess participants from videotaped interviews of the child and examiner during two 15-min scheduled breaks during the neuropsychological battery. To ensure consistency across participants, three similar discussion themes (i.e., college basketball; Pokemon;™ relations with siblings) were used in all videotaped interviews. Based on 32 interviews, the median kappa was .94.

**Reading disorders.** The 59 participants in our RD group met the criteria for a reading disorder as specified in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994).* We used the regression method advocated by Yule et al. (1974) to identify children with RD, and our selection criteria were as follows:

1. Full Scale IQ (FSIQ) on the third edition of the *Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991)* at or above 80,

2. performance on the second edition of the *Wechsler Individual Achievement Test (WIAT-II; Wechsler, 2001)* Reading composite at least 1.5 standard errors of the mean below what FSIQ would predict, and

3. enrollment in school at the time of assessment.

We chose an IQ of 80 so as to parallel as closely as possible the selection criteria used by Shaywitz et al. (1990).

**Psychiatric controls.** The 55 participants in our psychiatric control group consisted of children with a psychiatric diagnosis but without a learning disability. The diagnoses of these psychiatric control participants were ADHD (n = 19), oppositional defiant disorder (n = 21), conduct disorder (n = 5), major depressive disorder (n = 12), generalized anxiety disorder (n = 15), obsessive–compulsive disorder (n = 3) and tic disorder (n = 2). Comorbidity was the rule, not the exception, and the average number of diagnoses in our psychiatric control group was 2.1 (SD = 0.8). These participants represented consecutive referrals during a 9-month time period. Referred children with a comorbid identified learning disability (n = 11) or a history of a neurological condition (i.e., traumatic brain injury; n = 3) were excluded.

**Typical controls.** Typically developing children were also included as control participants. Our 31 control participants were recruited from the same schools as the LD clinic-referred sample and were selected through a stratified random sampling procedure so as to be demographically proportional to the participants with LD. No significant age or gender differences existed between the control participants and the other four samples (see Table 1).

**VCFS + NLD.** Children with VCFS + NLD were recruited from the Center for the Diagnosis, Treatment, and Study of VCFS at the State University of New York Upstate Medical University. Only children with a fluorescence in situ hybridization (FISH)—confirmed deletion of 22q11.2 were included in the sample. These 20 children were enrolled in a longitudinal study of risk factors for schizophrenia and represented approximately 20% of the total sample for this study. Exclusionary criteria for the ongoing VCFS study included a history of anoxia/hypoxia, seizures, or other neurological anomalies. Parents of potential participants were asked during a telephone-screening interview about these neurological conditions. The prevalence of NLD in our VCFS sample is somewhat lower than other research groups have reported (Moss et al., 1995; Swillen et al., 1999), which may be due to our strict adherence to requiring 8 of 10 symptoms from the Rourke et al. (2002) diagnostic criteria.

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Measures

The WISC-III (Wechsler, 1991) is composed of 13 subtests, 12 of which combine to form four factor scores: Verbal Comprehension (VC), Perceptual Organization (PO), Freedom from Distractibility (FD), and Processing Speed (PS). Moreover, the 10 subtests can be combined to yield Verbal IQ (VIQ) and Performance IQ (PIQ) scores, as well as a general measure of intellectual functioning, the Full Scale IQ (FSIQ). When analyzing the WISC-III results, the FSIQ, VIQ, and PIQ indices served as our primary outcome measures to compare verbal and nonverbal abilities.

The WJAT-II (Wechsler, 1991) is an individually administered test of academic achievement that has been standardized with 4,252 children in Grades K through 12. This test contains nine subtests, which are aggregated into four composite scores: Reading, Mathematics, Language, and Writing. Both the WISC-III and WJAT-II scores were converted to standard scores \( M = 100, SD = 15 \) using published norms.

Family Interview for Genetic Studies. The Family Interview for Genetic Studies (FIGS; Nurnberger et al., 1994) is a semistructured interview designed for psychiatric genetic studies. It screens for diagnostic information about the relatives of study probands. The interview probes for the history and presence of depression, bipolar disorder, substance abuse, schizophrenia, and personality disorders in first- and second-degree relatives. The interview is relatively open-ended, allowing the interviewer to probe for additional disorders such as anxiety and ADHD as well. Assessment personnel were blind to child diagnosis and ascertainment site (psychiatric or school). Although it is recommended that multiple family members provide information for this screen, respondents for this study were limited to the parents (and grandparents, if present) who brought the child for the assessments.

Semistructured psychiatric interview. To determine DSM-IV psychiatric diagnoses, either the Schedule for Affective Disorders and Schizophrenia in School-Aged Children (K-SADS; Kaufman et al., 1997) or the Diagnostic Interview Schedule for Children (DISC; Shaffer et al., 1996) was administered by a trained doctoral-level clinician (either a clinical psychologist or a child psychiatrist). Based on 25 randomly chosen interviews, the kappa coefficient was .90, signifying adequate interrater reliability.

Procedure

Informed consent/assent was obtained from parents and children under protocols approved by the institutional review board. Each child enrolled in the study completed a psychoeducational battery covering intelligence and academic achievement. An experienced doctoral-level examiner conducted the tests in a quiet room in the clinic. A licensed psychologist or a trained assistant familiar with the measures double-scored all protocols. While the children were being assessed, parents completed behavior rating scales and background information questionnaires. On completion of the psychological assessment, the family genetic interview and semistructured psychiatric interviews were administered.

Planned Analyses

Preliminary chi-square analyses were used to compare our five groups on categorical data, and a multivariate analysis of variance (MANOVA) was used to compare the groups on continuous data. Post hoc analyses of univariate ANOVAs were conducted using the Tukey HSD. To assess our a priori hypothesis, a logistic regression was computed. Familial diagnoses (yes/no) across seven broad categories of DSM-IV Axis I and II conditions (depression, bipolar disorder, schizophrenia/psychosis, substance abuse/dependence, anxiety disorders, ADHD, and personality disorders) were used as the dependent variables, and the participant group was used as our predictor. The results are shown as odds ratios with 95% confidence intervals (see Table 3). The fit of the model was judged by the Hosmer-Lemeshow test and by residual analysis.

Results

Preliminary Analyses

Our groups did not differ on gender ratios, \( \chi^2(4, N = 197) = 2.12, p = .273 \). A MANOVA on age and all the psychological test data demonstrated significant differences between test scores as a function of group membership, Wilks’s \( \lambda = 0.15, F(10, 403) = 64.45, p < .001, \eta^2 = .40 \). Follow-up univariate analyses were nonsignificant for age, yet were significant for all psychological test scores. As shown in Table 1, children with VCFS + NLD generally performed lower on the psychological tests than other groups. Moreover, children with LD performed lower on the measures sensitive to their disabilities; children with RD performed lower than others on WJAT-II Reading, and children with NLD performed lower than others on WISC-III Performance IQ and WJAT-II Math. These results are consistent with the volumes of literature that document cognitive and academic difficulties of children with LD relative to controls.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>NLD</th>
<th>RD</th>
<th>Psychiatric</th>
<th>Control</th>
<th>VCFS + NLD</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>MADHD</td>
<td>2.14</td>
<td>1.45–2.70</td>
<td>2.03</td>
<td>1.31–2.66</td>
<td>2.87</td>
<td>1.92–3.42</td>
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<td></td>
<td></td>
<td></td>
<td>1.41</td>
<td>0.83–1.97</td>
<td>1.52</td>
<td>0.91–2.33</td>
</tr>
<tr>
<td>Substance abuse/dependence</td>
<td>2.16</td>
<td>1.43–2.88</td>
<td>2.39</td>
<td>1.87–3.03</td>
<td>3.44</td>
<td>2.59–4.03</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>1.68</td>
<td>1.09–2.79</td>
<td>1.74</td>
<td>1.11–2.42</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>2.89</td>
<td>1.76–0.91</td>
<td>1.13</td>
<td>0.79–1.82</td>
<td>3.12</td>
<td>1.42–5.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.05</td>
<td>0.68–1.55</td>
<td>1.19</td>
<td>0.99–3.01</td>
</tr>
</tbody>
</table>

Note: Data based on interviews with the *Family Interview for Genetic Studies* (FIGS; Nurnberger et al., 1994). OR = odds ratio; CI = confidence interval; NLD = Nonverbal learning disabilities; RD = Reading disabilities; VCFS = Velocardiofacial syndrome; ADHD = Attention-deficit/hyperactivity disorder.
Hypothesis Testing

In the omnibus analyses (all five samples included), diagnostic category was not associated with familial depression, $\chi^2(df = 4, N = 197) = 2.43, p = .441$; familial anxiety disorder, $\chi^2(df = 4, N = 197) = 3.69, p = .376$; familial schizophrenia/psychosis, $\chi^2(df = 4, N = 197) = 2.15, p = .503$; or familial personality disorder, $\chi^2(df = 4, N = 197) = 4.16, p = .329$. Diagnostic category was associated with familial substance abuse, $\chi^2(df = 4, N = 197) = 9.92, p = .048$; familial ADHD, $\chi^2(df = 4, N = 197) = 13.14, p = .011$; and familial bipolar disorder diagnoses, $\chi^2(df = 4, N = 197) = 14.80, p = .008$. When diagnostic categories were examined separately, it was evident that the clinical samples (both LD and psychiatric) were associated with an increased risk of ADHD, substance abuse/dependence, and familial bipolar disorder; the NLD and psychiatric control groups, but not the RD group, were associated with increased risk of familial bipolar disorder. Figure 1 shows familial prevalence rates of bipolar disorder in our five groups.

Discussion

Psychopathology results from interactions between genetics and the environment (Rutter & Silberg, 2002); although our study did not assess environmental factors, our results are consistent with a vast volume of psychiatric literature (see Kendler, 2005, for a review) suggesting the heritability of psychiatric disorders. Familial ADHD and substance abuse/dependence were more likely in our three clinically referred samples (NLD, RD, psychiatric controls) than in our control and VCFS + NLD samples. Familial bipolar disorder was more common in our psychiatric and NLD groups, yet not in our RD, VCFS + NLD, or control samples. A large percentage of our psychiatric controls were diagnosed with ADHD; bipolar disorder and ADHD have significant syndromatic and symptomatic overlap (Biederman et al., 2005; Faraone, Glatt, & Tsuang, 2003). Thus, it is not surprising that we found an increased prevalence rate of bipolar disorder in extended family members of our psychiatric control participants. The elevated rate of bipolar disorder in children with NLD, yet not RD, was more surprising, especially given that children with VCFS + NLD were not at increased risk of having a family member diagnosed with bipolar disorder. A de novo deletion, VCFS + NLD may therefore not have the same familial underpinnings as idiopathic NLD.

Endophenotypes may be particularly useful for understanding the etiology of complex disorders in which several genes and environmental factors influence the phenotype. Because it is conceptualized as an expression of the genetic liability for a disorder (yet not necessarily disorder expression), the endophenotype should appear in individuals who carry genes for a condition but do not express the disorder itself. If endophenotypes appear in relatives of affected individuals, this may provide a window into neurobiological risk mechanisms. In this regard, endophenotypes may help clarify the pathophysiological underpinnings of a condition and help to isolate genes that contribute to the disorder expression (Gottesman & Gould, 2003).
The increased prevalence of bipolar disorder in the extended family members of children with idiopathic NLD suggests the possibility for an endophenotype between bipolar disorder and NLD. Although some (Rourke et al., 2002) have argued for right-hemispheric processes as being central to NLD, the increased prevalence of familial bipolar disorder in our psychiatric control group (none of whom had NLD) suggests that proposing a right-hemispheric endophenotype model is ill justified. In fact, other psychiatric and neurological conditions are associated with right-hemispheric dysfunction, including ADHD (Sandson, Bacha & Morin, 2000) and schizophrenia (Dollfus et al., 2005).

Just as the right-hemispheric endophenotype may be nonspecific and applied to various domains of psychopathology, the probable etiologic heterogeneity of NLD (Rourke et al., 2002) also suggests that it is unlikely that any endophenotype will be present in all individuals with NLD. Thus, although our participants with NLD demonstrated increased familial bipolar disorder, not all participants with NLD had family members with bipolar disorder. In other words, we still do not know if the dysfunction seen in NLD is a consequence of the disorder or is etiologically relevant and thus might serve as biobehavioral marker of a genetic vulnerability to bipolar disorder.

Others have similarly investigated the overlap between bipolar disorder and NLD, though in the opposite direction. McDonough-Ryan et al. (2002) compared 28 children of bipolar I disorder parents to 24 control participants on a cognitive evaluation specifically selected to diagnose NLD. Although there were features of NLD (e.g., VIQ > PIQ) in the children of parents who had bipolar disorder, only 1 child in the bipolar offspring group met full NLD criteria and 9 children met subthreshold criteria. Participants in this study were high functioning (FSIQ M = 104.9) and had solid academic achievement, especially in math (Mean WRAT-3 Math = 102.6), leading these investigators to conclude that the NLD model in children of bipolar parents had limited utility. Although our data suggest that children with NLD have increased familial prevalence of bipolar disorder, this evidence suggests that the inverse of this may not be true.

An exhaustive review by Bearden et al. (2001) also argued against a right-hemispheric endophenotype model. Bearden et al. concluded that the previous literature failed to demonstrate a cohesive right-hemispheric pathology model. Rather, Bearden et al. suggested that executive function deficits (frontal mechanisms) were the most reliable neuropsychological abnormality documented in the extant bipolar literature. Thus, in light of the evidence, although proposing a right-hemispheric endophenotype may be appealing, our data together with the work of others suggest that a right-hemispheric endophenotype does not presently appear to be empirically justified in NLD.

Although our preliminary data are interesting, future research should consider the heritability of NLD, and familial transmission data should be followed up with twin or adoption studies to disentangle genetic and shared environmental influences. In addition to this more rigorous line of genetics research, the present data must also be viewed in the light of several methodological limitations. First, there is the distinct possibility of bias from self-report data. We did not conduct structured DSM-IV diagnostic interviews with the relatives who met the FIGS bipolar disorder criteria. It would have been more accurate to have taken a subsample of the positive reports and actually interviewed the affected family members to gain some sense of the validity of the self-report data. This is a significant methodological weakness, and our data should therefore be considered preliminary until other groups can replicate them. For example, our data suggest that our psychiatric controls came from families in which multiple psychopathologies (e.g., ADHD, antisocial personality disorder) probably exist, many of which may share nonspecific symptoms (e.g., irritability) consistent with bipolar disorder.

Moreover, our research was conducted in a behavioral science department and, thus, our participants may be biased toward more familial psychopathology. This suggests that our familial prevalence data should be considered with great caution and may not be readily generalizable to the broader NLD or bipolar disorder population.

Despite these methodological limitations, the clinical implications of our data are twofold: First, bipolar disorder is heritable and if the extended family members of children with NLD have higher prevalence rates of bipolar disorder, clinicians working with children with NLD should be cognizant of this during both diagnosis and treatment. Second, clinicians should also bear in mind that if a child has NLD, the risk for bipolar disorder may be elevated in the extended family. This may have more direct consequences for those clinicians who work with the entire family (e.g., family therapy, parent guidance).

References


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