Evaluation of ADHD Typology in Three Contrasting Samples: A Latent Class Approach

ROSALIND J. NEUMAN, PH.D., RICHARD D. TODD, PH.D., M.D., ANDREW C. HEATH, PH.D., WENDY REICH, PH.D., JAMES J. HUDZIAK, M.D., KATHLEEN K. BUCHOLZ, PH.D., PAMELA A.F. MADDEN, PH.D., HENRI BEGLEITER, M.D., BERNICE PORJESZ, PH.D., SAMUEL KUPERMAN, M.D., VICTOR HESSELBROCK, PH.D., AND THEODORE REICH, M.D.

ABSTRACT

Objective: To identify subtypes of attention-deficit/hyperactivity disorder (ADHD) and characterize them as either categorical or continuous; to investigate familial resemblance for ADHD among sibling pairs; and to test the robustness of all results by using contrasting data sets. **Method:** Latent class analysis was applied to the ADHD symptom profiles obtained from parents or best informant about their offspring in 3 samples: a population-based set of female adolescent twins (724 monozygotic pairs, 594 dizygotic pairs) and male ($N = 425$) and female ($N = 430$) child and adolescent offspring ascertained from high-risk alcoholic families. **Results:** Latent class analysis revealed 2 categories of clinically significant ADHD which were replicated in all 3 study groups: a subtype with high endorsements of ADHD inattention symptoms and a second combined type with high endorsements of both inattention and hyperactivity-impulsivity items. Both appeared to be continuous across all 3 data groups. The high-risk families contained a class in which members heavily endorsed the ADHD "fidget" item but not other ADHD items. A large proportion of the monozygotic sibs (80%) versus a smaller proportion of dizygotic sibs (52%) were assigned to the same latent class. Among the high-risk children and adolescents, 51% of the female and 41% of the male siblings were concordant for class membership. **Conclusions:** The pattern of latent classes suggested that ADHD consists of an inattentive and a combined subtype, within each of which lies a dimensional domain. These analyses further support that genetic factors are significant determinants of latent class membership. *J. Am. Acad. Child Adolesc. Psychiatry,* 1999, 38(1):25–33. **Key Words:** attention-deficit/hyperactivity disorder, latent class analysis, twin studies, offspring of alcoholics.

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder characterized by problems with inattention, impulsivity, and hyperactivity. Onset is in childhood and frequently persists into adulthood. Prevalence estimates vary considerably, with some studies estimating 6% to 9% of school-age children with the disorder (Milberger et al., 1995) and others more conservatively reporting 3% to 5% (American Psychiatric Association, 1994). Boys are 4 to 9 times more likely to obtain a positive diagnosis than girls (American Psychiatric Association, 1994). ADHD has also been shown to exhibit a high degree of comorbidity with conduct disorder, depression, and anxiety disorder in clinical (Eiraldi et al., 1997; Milberger et al., 1995) and community-based (August et al., 1996) studies, while coaggregation with bipolar disorder has been considered more controversial (Faraone et al., 1997).

Family, twin, and adoption studies have demonstrated that genetic factors may be a primary cause of susceptibility to ADHD in some families (Eaves et al., 1997; Faraone et al., 1994; Sherman et al., 1997a,b; Stevenson, 1992), with heritabilities for hyperactivity or inattention ranging from 40% to 90% (Hudziak, Heath, Madden et al., unpublished, 1998; Levy et al., 1997; van den Oord et al., 1994). However, no agreement has been

Accepted August 14, 1998.

Drs. Neuman, Todd, Heath, W. Reich, Bucholz, Madden, and T. Reich are with Washington University School of Medicine, St. Louis. Dr. Hudziak is with the University of Vermont, Burlington. Drs. Begleiter and Porjesz are with SUNY HSC at Brooklyn. Dr. Kuperman is with the University of Iowa, Iowa City. Dr. Hesselbrock is with the University of Connecticut Health Center, Farmington.

This work was supported by NIH grants MH52813, MH31302, AA10111, and AA07728. The Collaborative Study on the Genetics of Alcoholism (COGA) is supported by NIAAA USPHS grants U10AA08401, U10AA08402, and U10AA08403 (a list of study participants and sites appears at the end of the text). The Missouri Adolescent Female Twin Study (MOAFTS) is supported by NIAAA grant AA09022.

Correspondence to Dr. Neuman, Washington University Medical Center, Department of Psychiatry, 4940 Children's Place, St. Louis, MO 63110.

reached on its mode of inheritance. There is, nevertheless, general agreement that ADHD is not a simple mendelian trait, but rather it is genetically complex with incomplete penetrance, nongenetic phenocopies, and genetic heterogeneity and is further complicated by environmental effects (Hudziak and Todd, 1993).

Although sophisticated statistical methods have greatly improved our ability to detect major loci contributing to complex traits, a high degree of etiological homogeneity is required to be successful in finding susceptibility genes. It would then follow that the primary task prior to any genomic analysis should be to define phenotypes for study that most likely result from a common genetic background. To that end several approaches have been tried. One common strategy has been to define the phenotype based on comorbidity with disorders such as conduct, anxiety, mood, or oppositional defiant disorder, to name just a few (reviewed by Hudziak and Todd, 1993). It is thought that ADHD co-occurs with at least one of these disorders in up to two thirds of clinically referred children with ADHD (in more than 50% with oppositional defiant disorder, 30%–50% with conduct disorder, 15%–20% with mood disorders, and 20%–25% with anxiety disorders) (American Academy of Child and Adolescent Psychiatry, 1997; Biederman et al., 1991, 1996). The *DSM* provides guidelines for phenotypic definitions of ADHD based on a set of symptom items. *DSM-III* regarded the disorder as attention deficit disorder either with or without a hyperactive component, whereas *DSM-III-R* took a more unidimensional approach and did not differentiate between these two forms. The current *DSM-IV* classifies ADHD as either a predominantly inattentive type, predominantly hyperactive-impulsive type, or a combined type, i.e., meeting criteria for both inattentive and hyperactive-impulsive types.

Subtyping with respect to comorbid diagnoses or *DSM-IV* criteria assumes a categorical perspective for ADHD. An alternative view regards ADHD as a quantitative or dimensional phenotype in which susceptibility is a function of an underlying continuous latent trait. This model hypothesizes that the risk for ADHD increases as a function of a latent liability and a positive diagnosis occurs when a threshold of the continuum is crossed. Levy et al. (1997) used regression methods in a twin study to conclude that ADHD is best conceptualized as the extreme of a continuum rather than as a discrete disorder. Hudziak et al. (1998) applied latent class and factor analysis to show that ADHD could be represented as consisting of 2 common and 1 rare subtype, each of which was dimensional. Both of these theoretical perspectives hypothesize as a fundamental feature of ADHD an unmeasured or latent variable that is quantitative or continuous in the one case and categorical or discrete in the other.

To determine which model of ADHD is most plausible, we applied latent class analysis to the ADHD symptom profiles obtained from 3 disparate samples: (1) female adolescent twin pairs ascertained through a population-based twin registry, (2) child and adolescent males ascertained from high-risk alcoholic families, and (3) child and adolescent females ascertained from the same high-risk families as the males. Latent class analysis (Goodman, 1974) has been a popular statistical tool for resolving these two contrasting views of disease. In the psychiatric field, it has been used in twin and family studies for nicotine withdrawal (Madden et al., 1997), antisocial behavior (Silberg et al., 1996), depression (Kendler et al., 1996), conduct disorder (Biederman et al., 1987), alcoholism (Bucholz et al., 1995; Heath et al., 1994), and ADHD (Hudziak et al., 1998), to name just a few. Results of our analyses were evaluated across sample groups to determine the extent of their generality across gender, age differences, population versus high-risk families, and familial latent class concordance, i.e., how often siblings were assigned to the same latent class. Future work will address associations between latent class assignments and comorbid traits.

METHOD

Subjects

Missouri Adolescent Female Twin Pairs. Our sample of female twins (1,318 twin pairs), aged 13 to 21 years at interview, were identified from a computerized database of all births to Missouri-resident parents for the years 1968 through 1994, as part of an ongoing prospective study of alcohol problems in women. Telephone diagnostic interview data were collected from female adolescent twins and their parents by methods described elsewhere (Hudziak et al., 1998). Briefly, the parent telephone interview about the twins, adapted for telephone administration from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994), included questions to elicit *DSM-IV* diagnoses for ADHD, oppositional defiant disorder, conduct disorder, major depressive disorder, and separation anxiety in each twin. Diagnoses were made using a computer-generated algorithm. Zygosity determinations were based on a standard series of zygosity questions. In these analyses, the biological mother's report was used for 90.4% of the twins, the biological father's for 7.8% of the twins, and the remaining 1.7% of the reports were from a close nonparental relative or guardian of the twins.

Child and Adolescent Offspring of Families Ascertained Through an Alcoholic Proband. Data from children and adolescents, aged 7 through 17 years, were collected through families ascertained as part of the 6-center Collaborative Study on the Genetics of Alcoholism (COGA) research project (Begleiter et al., 1995). COGA's ascertainment protocol is divided into several stages. Probands were initially recruited from inpatient and outpatient alcohol treatment facilities if they met lifetime criteria for both *DSM-III-R* alcohol dependence and Feighner definite alcoholism (Feighner et al., 1972). For a family to progress into the more detailed phenotypic and genetic study, 3 or more first-degree adult relatives had to receive the COGA diagnosis of alcohol dependence. All probands, their spouses, and first-degree relatives were interviewed using the SSAGA (Bucholz et al., 1994). Interviews on psychopathology within child and adolescent offspring from the alcoholic families were conducted using the C-SSAGA, a modified version of the Diagnostic Interview for Children and Adolescents into which *DSM-III-R* diagnostic criteria have been incorporated. Personal interviews with the parents (or best informant) about their children's psychiatric status were conducted for approximately 87% of the offspring; telephone interviews were conducted with the remaining parents. In this study, we analyzed data obtained from the parents or best informant for 425 male and 430 female offspring. Approximately 80% of the interviews about offspring behavior were conducted with the biological mother of the offspring. The analyses reported here do not include any offspring from the COGA control families.

Data Analysis

Latent class analysis is a statistical methodology that can be used to investigate an observed association among a set of categorical manifest items or variables. The premise of the latent class model is that the observed variables are imperfect indicators of an underlying latent variable with a finite number of mutually exclusive levels or classes, such that when the latent variable is introduced into the model, the manifest variables will be mutually independent within each class. In this sense, latent class analysis may be understood as a categorical variant of factor analysis, since factor analysis assumes continuously distributed latent variables. The condition of mutual independence within classes is termed "local independence" in the latent class literature (Goodman, 1974).

The parameters to be estimated in a latent class model are the latent class probabilities p_j (i.e., p_j is the probability that an individual belongs to the *j*th class) and the class-specific item endorsement probabilities f_{jk} (i.e., f_{jk} is the conditional probability an individual in the *j*th class will endorse the *k*th item, where the *k*th item has only 2 possible responses in this case). The local independence assumption implies that the probability of an individual's response to any item is dependent only on latent class membership. It also implies the latent classes will become more homogeneous as the number of classes increases. Thus, the rationale for latent class analysis is that the observed association between the manifest variables is due to heterogeneity in the data and latent class analysis will "unmix" the data, producing homogeneous classes differing in their symptom endorsement profiles only because of random measurement error.

The relative patterns of within-class item response frequencies derived from latent class analysis will indicate whether the latent variable is best described as continuous (dimensional) or categorical. Evidence in favor of a continuous underlying trait would be apparent if the pattern of responses for all items increases across classes (i.e., $f_{1k} \leq f_{2k} \ldots$, for all k). A different pattern would occur if there are really qualitatively different subtypes (i.e., categorical diagnoses): some of the frequencies for the responses would be higher in class s than in class t and others would be more prevalent in class t than in class s. Hence, latent class analysis can help determine the underlying characterization of the disorder.

Latent class models were fitted to the 18 *DSM-IV* ADHD symptom response data (i.e., symptom profiles) for the twin data and the 14 *DSM-III-R* ADHD items for the male and female COGA data. A program written by one of us (R.J.N.), in which maximum likelihood methods are implemented via the EM algorithm (Dempster et al., 1977), was used to fit 1-class through 7-class solutions to the data. After determining the best-fitting model, individuals were assigned to class membership based on their most probable class given their symptom profile. To evaluate choice of latent class models, we compared an m-class solution to an $(m + 1)$-class solution using a likelihood ratio χ^2 test with degrees of freedom equal to $p + 1$ where p is the number of variables used in the model, choosing the most parsimonious model. When choosing the latent class model, one should also consider how reasonable the model is with respect to research questions being investigated, the generalizability of the model to other populations, and the sample sizes examined. An overall goodness-of-fit statistic is difficult to interpret in these data because there are a large number of symptom items producing sparse contingency tables in which the distribution of the goodness-of-fit statistics is unknown. Thus, we did not rely on global test statistics to determine the optimal number of classes. To determine whether classes could be considered familial, concordance for class membership was computed for the monozygotic (MZ) and dizygotic (DZ) twins and all COGA sib pairs.

RESULTS

The Missouri twin sample consisted of 724 and 594 pairs of MZ and DZ female twins, respectively, with an average age of 15.9 ± 2.5 years (Table 1). The COGA males (N = 425) and females (N = 430) were younger, with an average age of 11.7 ± 3.3 years. The COGA males consisted of 42.4% first-degree, 50.6% second-

TABLE 1
Characteristics of the Three Samples

	Missouri Twins		COGA	
	MZ	DZ	Females	Males
No (%)	1,448 (54.9)	1,188 (45.1)	430 (50.3)	425 (49.7)
Mean age (SD)	15.9 (2.3)	15.9 (2.9)	11.7 (3.3)	11.7 (3.2)
Age range	13 to 21	13 to 21	7 to 17	7 to 17
Race (% African-American)	11.2	14.3	21.2	22.6

Note: COGA = Collaborative Study on the Genetics of Alcoholism; MZ = monozygotic pairs; DZ = dizygotic pairs.

TABLE 2
Percentage Endorsed for Each ADHD Symptom

	Missouri Twin Females (N = 2,636)	COGA Females (N = 430)	COGA Males (N = 425)
Inattention items			
1. Lack of attention to detail	19.2		
2. Difficulty sustaining attention	$8.4^{a1,b1}$	$22.1^{a1,c1}$	$35.5^{b1,c1}$
3. Does not listen	$13.0^{a1,b1}$	$19.3^{a1,c1}$	$33.4^{b1,c1}$
4. Fails to finish tasks	$13.9^{a3,b1}$	$18.6^{a3,c1}$	$31.5^{b1,c1}$
5. Difficulty organizing tasks	16.5		
6. Difficulty concentrating	19.7		
7. Often loses things	18.6^{b1}	17.4^{c2}	$26.6^{b1,c2}$
8. Easily distracted	27.2^{b1}	24.9^{c1}	$40.7^{b1,c1}$
9. Often forgetful	19.8		
10. Shifts between activities		16.5^{c3}	23.5^{c3}
Hyperactivity-impulsivity items			
11. Fidgets	$11.5^{a1,b1}$	$18.4^{a1,c1}$	$32.7^{b1,c1}$
12. Leaves seat	9.7^{b1}	12.3^{c1}	$23.3^{b1,c1}$
13. Runs or climbs excessively	10.8		
14. Difficulty playing quietly	10.0	10.2	12.5
15. Always on the go	20.2		
16. Talks excessively	21.5	17.7	21.6
17. Blurts out	9.5^{b2}	10.5	14.4^{b2}
18. Difficulty waiting turn	9.5^{b1}	12.1^{c2}	$18.6^{b1,c2}$
19. Often interrupts	16.3^{a2}	$10.5^{a2,c2}$	17.2^{c2}
20. Engages in physically dangerous activities		5.6^{c1}	14.8^{c1}

Note: ADHD = attention-deficit/hyperactivity disorder; COGA = Collaborative Study on the Genetics of Alcoholism. a1, b1, c1: $p < .001$; a2, b2, c2: $p < .01$; a3, b3, c3: $p < .05$; a1–a3: comparisons between twins and COGA females; b1–b3: comparisons between twins and COGA males; c1–c3: comparisons between COGA females and males.

degree, and 7.1% more distant relatives of the alcoholic proband. The corresponding percentages for the COGA females were 40.2%, 53.3%, and 6.5%, respectively.

Proportions of the ADHD symptoms endorsed by parent (or best informant) for each sample group are displayed in Table 2. Five inattention and 7 hyperactivity-impulsivity ADHD items are the same in the *DSM-IV* and *DSM-III-R* diagnostic criteria (items 2, 3, 4, 7, 8, 11, 12, 14, and 16–19 in Table 2). Among these 12 items, the COGA males' endorsement proportions were, without exception, greater than those of either of the female groups. These differences were statistically significant for all 5 inattention items and 3 of the 7 hyperactivity-impulsivity items (items 11, 12, and 18). In general, the ADHD items for COGA females were endorsed at a higher frequency than those of the female twins. Overall, the sample reported to have the highest proportion endorsing more than 6 ADHD items was the COGA males, followed in order by the COGA females and the female twins (25.4%, 14.7%, 9.1%, respectively). The order for the data samples was reversed for endorsing zero or one item: 65.1%, 63.3%, and 48.0% for the twins, COGA females, and males, respectively. The average number of items endorsed (for the ADHD items in common) was 3.1 (±3.5) for the COGA males, followed by the COGA females and twins with 1.9 (±2.9) and 1.7 (±2.5), respectively. The percentage of twins, COGA females, and males meeting criteria for ADHD was 6%, 7.5%, and 15.1%, respectively.

Seven latent class models (1-class though 7-class) were fitted to the data. Significant improvements were made as the number of classes increased (details available upon request). However, changes in class prevalence rates when progressing from a 6- to 7-class solution did not produce additional meaningful classes. Consequently, for consistency across data sets and without loss of generality, we shall consider only the 6-class solutions. In the 6-class solutions, most offspring in all data sets were assigned to a class in which very few items were endorsed. The prevalence rates for these largest classes were 52.8%, 61.8%, and 46.2% for the twins, COGA females, and COGA males, respectively ("Few" in Figs. 1a, 2a, and 3a).

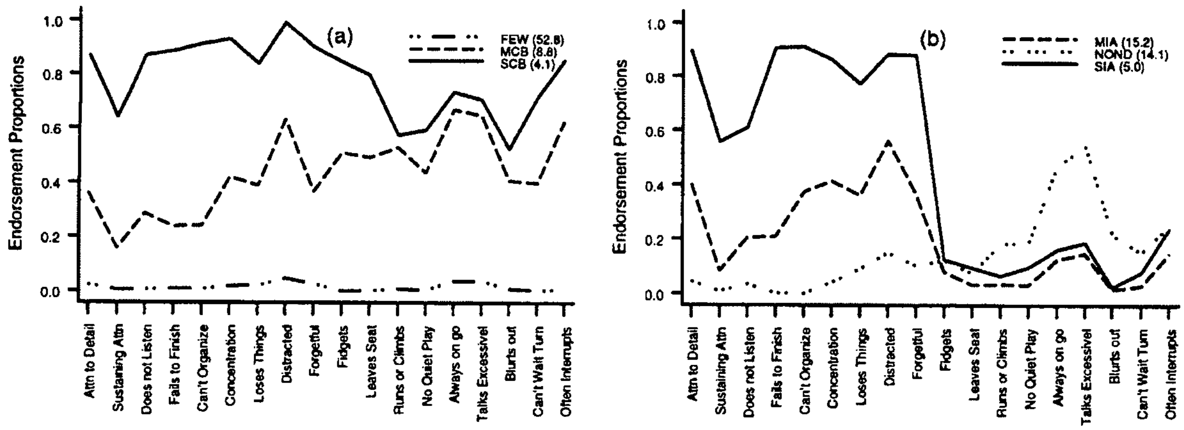

Fig. 1 Female Missouri twins (N = 2,636). Few = few or no symptoms; MCB = moderate-combined; SCB = severe-combined; MIA = moderately inattentive; NOND = nondescript; SIA = severely inattentive.

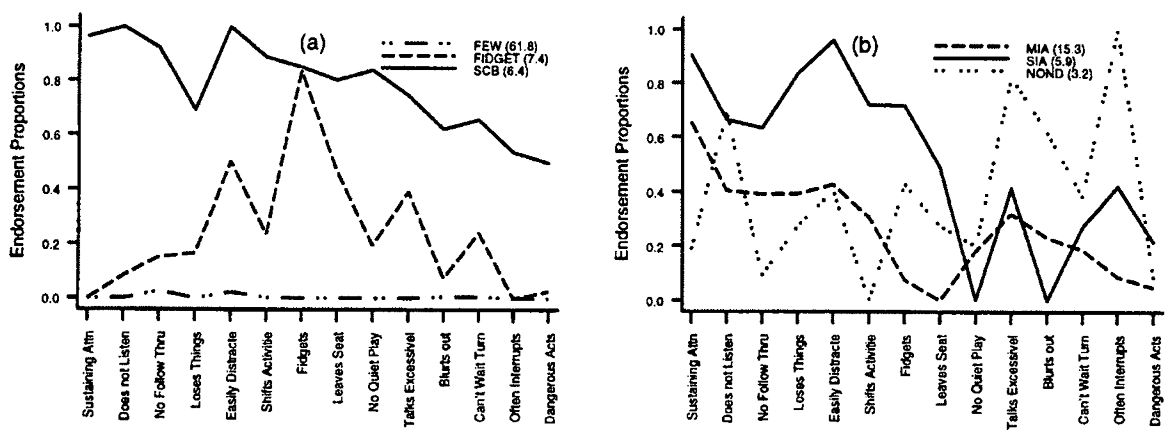

Fig. 2 Collaborative Study on the Genetics of Alcoholism females (N = 430). Few = few or no symptoms; SCB = severe-combined; MIA = moderately inattentive; SIA = severely inattentive; NOND = nondescript.

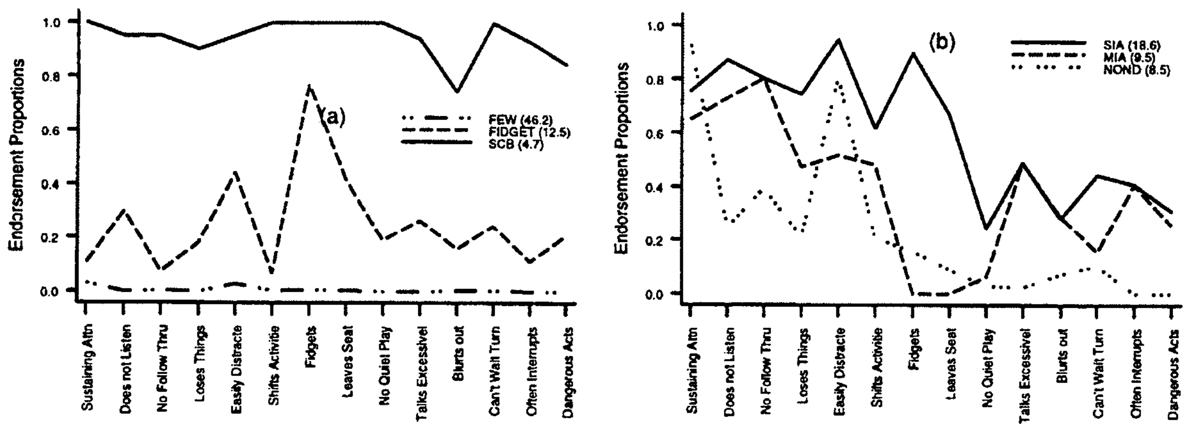

Fig. 3 Collaborative Study on the Genetics of Alcoholism males (N = 425). Few = few or no symptoms; SCB = severe-combined; SIA = severely inattentive; MIA = moderately inattentive; NOND = nondescript.

There were remarkable similarities among 3 clinically relevant classes in the 3 samples (Figs. 1, 2, and 3). The first was a class in which almost every ADHD symptom was endorsed in each data set ("severe-combined class" [SCB] in Figs. 1a, 2a, and 3a). Parents of individuals in this class endorsed, on average, 7.9 (female twins), 5.5 (COGA females), and 5.8 (COGA males) inattention items. For the hyperactivity-impulsivity items the corresponding averages were 6.4, 5.7, and 7.5. We note that the maximum possible number of items that could be endorsed was 9 inattention, 9 hyperactivity-impulsivity using *DSM-IV* criteria, and 6 inattention, 8 hyperactivity-impulsivity items for *DSM-III-R*. Hence, both female samples for this class endorsed essentially the same percentage of possible symptoms for inattention (87.8% versus 91.7%, respectively) and hyperactivity-impulsivity (71.1% versus 71.3%, respectively). Overall, the average percentage of positive responses for the twins in the severe-combined class was 78.8%. Likewise, a large proportion of the COGA females and males in this class endorsed all 14 *DSM-III-R* items. The average percentages of items endorsed among the COGA females and males in this class were 78.7% and 94.4%, respectively. Prevalence rates of the severe-combined class for the female twins, COGA females, and males were approximately the same: 4.1%, 6.4%, and 4.7%, respectively.

A second severe class identified in all data sets consisted of individuals who responded positively to almost every inattention item contrasted with few endorsements of most or any of the hyperactivity-impulsivity items ("severely inattentive" class [SIA] in Figs. 1b, 2b, and 3b). Class prevalence for the COGA males (18.6%) was significantly higher than in the female groups (5.0% and 5.9% in the twins and COGA females, respectively). All 9 inattention items for the twins and 6 inattention items for the COGA data consistently had high (more than 50%) symptom endorsements, with few endorsing the hyperactivity-impulsivity symptoms (Figs. 1b, 2b, and 3b). Individuals in this class endorsed, on average, 7.4 (female twins), 4.9 (COGA females), and 4.7 (COGA males) inattention items, contrasted with, respectively, 1.1, 2.6, and 3.8 hyperactivity-impulsivity items. Two hyperactivity-impulsivity symptoms were endorsed by more than 50% of the COGA males: "often fidgets" (89.8%) and "often leaves seat" (67.0%). As for the severe-combined class, the percentages of possible inattention symptoms endorsed for the female twins and COGA females in this class were essentially the same.

A moderately inattentive class (MIA in Figs. 1b, 2b, and 3b) was also present in all 3 samples. All inattention items were endorsed by a moderate proportion of the individuals assigned to this class versus few endorsements for the hyperactivity-impulsivity items (approximately one fifth to one third the average endorsement of inattention items). The female twins in this class had a mean endorsement frequency of 33.0% for the 9 *DSM-IV* inattention symptoms and 7.2% for the 9 hyperactivity-impulsivity items. The average endorsement for the 6 *DSM-III-R* inattention items in the COGA females was 42.8% versus 14.2% for the 8 hyperactivity-impulsivity items. Comparable figures for the COGA males were 60.9% and 20.1%. Class prevalence rates were about the same for both groups of females (15.2% and 15.3%) and lower for the COGA males (9.5%).

In the COGA samples only, a class was identified in which the ADHD symptom "fidgets" was endorsed by approximately 80% of those assigned to this class ("Fidget" in Figs. 2a and 3a). All other symptoms received fewer endorsements. The prevalence rates of this class were 7.4% in the COGA females and 12.5% in the males. Latent class analysis also produced a class in the twins not replicated in the COGA sample in which positive responses for the 18 *DSM-IV* ADHD symptoms ranged between 15.6% and 66.6% (the "moderate-combined" class, MCB in Fig. 1a). Finally, a class was produced in each data group that could not be distinguished as either mainly inattentive or hyperactive-impulsive ("nondescript" [NOND] in Figs. 1b, 2b, and 3b) and which could not be compared across data sets.

In the COGA samples more than 90% of those assigned to the severe-combined classes met criteria for *DSM-III-R* ADHD (Table 3). *DSM-IV* ADHD had been diagnosed in approximately 69% of the female twins in this class. When *DSM-III-R* criteria were applied to the twin data, 87.6% of this severe-combined class met criteria for ADHD. The severely inattentive class contained the next highest proportion of subjects with diagnosed ADHD for all 3 data sets. It was not surprising that no one in the COGA fidget classes was given the ADHD diagnosis, as the average number of symptoms endorsed was too low to meet criteria (Table 3).

A substantial proportion of the MZ twins, 80.4%, was assigned to the same latent class versus 51.7% of the DZ twins, consistent with a genetic hypothesis for latent class membership. Similar to the rate for DZ twins, 51.3% of the female and 40.6% of the male sibling pairs

TABLE 3
Percentage of Within-Class ADHD Diagnoses

Class	Female Twins (N = 2,636) 6.0% ADHD[a]	COGA Females (N = 430) 7.5% ADHD[b]	COGA Males (N = 425) 15.1% ADHD[b]
Few or none	0.0	0.0	0.0
Moderately inattentive	0.5	0.0	5.0
Severely inattentive	45.8	22.2	55.8
Moderate-combined	9.6	—	—
Severe-combined	68.6	92.3	95.0
Fidget	—	0.0	0.0
Nondescript	0.0	14.3	0.0

Note: ADHD = attention-deficit/hyperactivity disorder; COGA = Collaborative Study on the Genetics of Alcoholism.
[a] *DSM-IV* criteria.
[b] *DSM-III-R* criteria.

from alcoholic families were concordant for latent class membership. We next looked at sibling class membership by type of class: few or none, inattentive type (moderate or severe), and combined type (moderate or severe). Among the female twins a larger percentage of the MZ siblings than DZ siblings were assigned to the moderately or severely inattentive classes (12.2% and 8.4%, respectively). Likewise, more MZ pairs than DZ pairs were assigned to the ADHD moderate- or severe-combined type classes (8.3% versus 5.9%). We also considered sibling pairs assigned to extremely different types of classes: few or none versus either of the inattentive classes (moderate or severe), and few or none versus the combined classes. Again, consistent with a genetic basis for class membership, *fewer* MZ siblings than DZ pairs were separated and placed in extremely different classes: 6.8% of MZ twin pairs were divided such that one twin was placed in the few or no symptom class and the other assigned to one of the inattentive classes, contrasted with 16.2% of DZ siblings. Furthermore, 7% of the DZ pairs had 1 twin assigned to the few or no symptom class and her twin assigned to one of the combined type class, compared with 0.7% of the MZ pairs. We note that genetic analysis of inattention and hyperactivity-impulsivity symptom counts conducted by Hudziak, Heath, Madden et al. (unpublished, 1998) in the adolescent female twin sample produced heritabilities of 94% and 93%, respectively.

DISCUSSION

Our results are consistent with the existence of 2 ADHD subtypes, a combined inattentive and hyperactive-impulsive type and a primarily inattentive subtype, each of which can be characterized as a continuous trait. Evidence for these findings came from applying latent class analysis to the ADHD symptom endorsement profiles in each of 3 disparate data sets. The first data set consisted of a population sample of Missouri adolescent female twin pairs. The remaining two contained female and male children and adolescents from the COGA high-risk alcoholic families. These data sets differed, not only with respect to gender, but with respect to age (the average age in the female twins was significantly older than in the COGA data), ascertainment criteria (the female twins were ascertained as a population-based sample contrasted with the COGA samples originating from alcohol treatment units), type of interview (telephone versus personal interview), and diagnostic criteria (*DSM-IV* versus *DSM-III-R*).

Our findings, that not only do primarily inattentive and combined inattentive and hyperactive-impulsive phenotypes exist within each of the data groups, but that each of these subtypes may also be part of separate continua, are supported by the existence of a moderately inattentive class in each data set in which each inattention item was endorsed by fewer individuals in this class than those in the severely inattentive class. Within the twin sample, a moderate-combined class was identified, giving weight to a continuum within the combined dimension also. Furthermore, the average number of inattention and hyperactivity-impulsivity items endorsed within each of these classes scales as a continuum. (Data available upon request.) It should be noted that in this study our continuum of severity is based on the ADHD item response probabilities. The question of continuity versus discontinuity arises at many different levels—the phenotypic continuity that we report here may in fact conceal etiological discontinuity or discontinuity of associated impairments. Unique to the COGA data was a class in which only the "fidget" item received a large proportion of positive responses; all other ADHD symptoms had many fewer endorsements.

These analyses also indicate that latent class membership is familial and furthermore, that genetic factors may influence latent class membership. More than 50% of the COGA female siblings and female DZ twin pairs were assigned to the same latent class out of 6 possible classes. In the COGA male sample, 40.6% of sibling pairs had the same class membership. Finally, MZ concordance for class membership was greater than 80%, compared with about 50% of DZ pairs. This pattern of class membership assignments is the expected pattern for a genetically influenced and highly heritable disorder. The similarity of nontwin sibling and DZ twin concordance rates also argues that the high ADHD heritabilities reported for twin studies are not an artifact of the twin process per se.

Our latent class analysis was based on 6-class solutions that could be easily compared and interpreted among all 3 samples. Our ability to consider more classes was limited by the sample size of the COGA adolescents in which solutions of 7 or more classes produced additional sporadic classes with very low prevalence rates while maintaining the structure and approximate prevalence rates of the classes reported for the 6-class solution. This would imply that the prevalence of a possible hyperactive-impulsive class is extremely low because it could not be detected in our high-risk sample even when increasing the number of latent classes. Fitting more classes to the twin data does produce a severe, primarily hyperactive-impulsive class but with a prevalence of less than 1%. We note that the twin sample did not include young children.

In spite of the consistent results across the different samples, this study has several potential limitations. One possible limitation is that the latent class analysis of the Missouri female twin pairs was based on data obtained from a parental telephone interview, whereas approximately 87% of the COGA data were based on personal interviews with parents. This potential limitation seems unlikely because of the similarity of results across samples irrespective of method of interview, suggesting that telephone reports by parents are a reliable and sensitive method for gathering information. A second limitation may be that the data in all samples consisted of mainly retrospective maternal reports. To examine the reliability of maternal telephone reports, we conducted a pilot study in a clinical sample comparing maternal telephone reports with clinician diagnosis. Kappa values of 0.89 for ADHD were generated, indicating excellent agreement between the clinician's assessment and the diagnosis based on the maternal telephone interviews (Todd, W. Reich, and Heath, unpublished, 1997). Furthermore, Faraone et al. (1995) examined the long-term reliability and diagnostic accuracy of maternal reports for their children's psychopathology in a cohort of ADHD and control children and found both to be excellent for ADHD, conduct disorder, and several other psychiatric diagnoses. Another potential limitation of this study is the use of a questionnaire to assign zygosity in twins. Numerous authors (for example, Eisen et al., 1989) have shown that determining zygosity on the basis of responses to a series of standard questions, such as those used in this study, results in misclassification rates of less than 5%. Finally, it must be acknowledged that twin pairs experience greater perinatal complications than is the case for singleton births. In the absence of data from an unselected sample of singletons assessed in the same way as the twins, we cannot yet state whether rates of ADHD symptomatology found in the twin sample would generalize to the general population.

In summary, this study indicates the existence of ADHD subtypes and suggests that each of these subtypes may be represented as part of a continuum of severity. These findings were able to be generalized to data sets that significantly differed from one another with respect to sex, age, method of ascertainment and data collection, and diagnostic criteria.

Clinical Implications

There are several important clinical implications resulting from this study. First, the current nosology for ADHD as defined by *DSM-IV* has been partially confirmed (latent class analysis identified 2 of the 3 subtypes defined in *DSM-IV*), indicating that it better represents ADHD in the general population than previous diagnostic criteria. This was found to be true, not only for the male sample, but also for the female samples, for which there are few ADHD studies. However, given that these latent class–derived subtypes represent the extreme ends of continuous liability distributions, the current *DSM-IV* diagnostic criteria represent arbitrary cutoffs for determining who is affected. A diagnosis of ADHD should be considered much the same as a diagnosis of hypertension, hypercholesterolemia, or diabetes mellitus in that the level of severity, not just the categorical diagnosis, must be taken into account. In particular, who receives treatment (behavioral or pharmacological) must be dictated by other factors in addition to *DSM-IV* diagnostic criteria. As we have demonstrated elsewhere (Hudziak et al., 1998), the intermediate latent classes are also associated with significant academic, social, and family dysfunction. A second clinical implication of the present findings is the clustering of subtypes within families. This is particularly important for clinicians when determining ADHD diagnosis in siblings of an ADHD patient. Whether genetic or not, the phenomenology of ADHD is familial. A third important clinical finding is the existence of a class of children and adolescents in the male and female COGA samples in which the ADHD symptom of fidgeting was the only symptom endorsed by most of the individuals assigned to this class. This class occurred only in the offspring of the alcoholic families, not in the general population sample. The etiology of this observation is currently unknown and requires further study.

The Collaborative Study on the Genetics of Alcoholism (COGA) (H. Begleiter, SUNY HSCB, Principal Investigator; T. Reich, Washington University, Co-Principal Investigator) includes 6 different centers where data collection takes place. The 6 sites and principal investigator and co-investigators are as follows: Indiana University (J. Nurnberger, Jr., T.-K. Li, P.M. Conneally, H. Edenberg); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego and Scripps Institute (M. Schuckit, F. Bloom); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (B. Porjesz, H. Begleiter); Washington University in St. Louis (T. Reich, C.R. Cloninger, J. Rice).

REFERENCES

American Academy of Child and Adolescent Psychiatry (1997), Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 36(suppl):85S–121S

American Psychiatric Association (1994), *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*. Washington, DC: American Psychiatric Association

August GJ, Realmuto GM, MacDonald AW III, Nugent SM, Crosby R (1996), Prevalence of ADHD and comorbid disorders among elementary school children screened for disruptive behavior. *J Abnorm Child Psychol* 24:571–595

Begleiter H, Reich T, Hesselbrock V et al. (1995), The Collaborative Study on the Genetics of Alcoholism. *Alcohol Health Res World* 19:228–236

Biederman J, Faraone S, Mick E, Moore P, Lelon E (1996), Child Behavior Checklist findings further support comorbidity between ADHD and major depression in a referred sample. *J Am Acad Child Adolesc Psychiatry* 35:734–742

Biederman J, Munir K, Knee D (1987), Conduct and oppositional disorder in clinically referred children with attention deficit disorder: a controlled family study. *J Am Acad Child Adolesc Psychiatry* 26:724–727

Biederman J, Newcorn J, Sprich S (1991), Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *Am J Psychiatry* 148:564–577

Bucholz KK, Cloninger CR, Dinwiddie SH et al. (1994), A new, semi-structured psychiatric interview for use in genetic linkage studies: a report of the reliability of the SSAGA. *J Stud Alcohol* 55:149–158

Bucholz KK, Heath AC, Reich T et al. (1995), Can we subtype alcoholism? A latent class analysis of data from relatives of alcoholics in a multicenter family study of alcoholism. *Alcoholism Clin Exp Res* 20:1462–1471

Dempster AP, Laird NM, Rubin DM (1977), Maximum likelihood from incomplete data via the EM algorithm. *J R Stat Soc* B 39:1–38

Eaves LJ, Silberg JL, Meyer J et al. (1997), Genetics and developmental psychopathology, 2: the main effects of genes and environment on behavioral problems in the Virginia Twin Study of adolescent behavioral development. *J Child Psychol Psychiatry* 38:965–980

Eiraldi RB, Power TJ, Nezu CM (1997), Patterns of comorbidity associated with subtypes of attention-deficit/hyperactivity disorder among 6- to 12-year-old children. *J Am Acad Child Adolesc Psychiatry* 36:503–514

Eisen S, Neuman R, Goldberg J, Rice J, True W (1989), Determining zygosity in the Vietnam Era Twin Registry: an approach using questionnaires. *Clin Genet* 35:423–432

Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T (1997), Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry* 36:1378–1390

Faraone SV, Biederman J, Milberger S (1994), An exploratory study of ADHD among second-degree relatives of ADHD children. *Biol Psychiatry* 35:398–402

Faraone SV, Biederman J, Milberger S (1995), How reliable are maternal reports of their children's psychopathology? One-year recall of psychiatric diagnoses of ADHD children. *J Am Acad Child Adolesc Psychiatry* 34:1001–1008

Feighner JP, Robins E, Guze SB, Woodruff AR, Winokur G, Munoz R (1972), Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry* 26:57–63

Goodman LA (1974), Exploratory latent structure analysis using both identifiable and unidentifiable models. *Biometrika* 61:215–231

Heath AC, Bucholz KK, Slutske WS et al. (1994), The assessment of alcoholism in surveys of the general community: what are we measuring? Some insights from the Australian twin panel interview survey. *Int Rev Psychiatry* 6:295–307

Hudziak J, Heath A, Madden P et al. (1998), The latent class and factor analysis of *DSM-IV* ADHD in girls. *J Am Acad Child Adolesc Psychiatry* 37:848–857

Hudziak J, Todd R (1993), Familial subtyping attention deficit hyperactivity disorder. *Curr Opin Psychiatry* 6:489–493

Kendler KS, Eaves LJ, Walters EE, Neale MC, Heath AC, Kessler RC (1996), The identification and validation of distinct depressive syndromes in a population-based sample of female twins. *Arch Gen Psychiatry* 53:391–399

Levy F, Hay DA, McStephen M, Wood C, Waldman I (1997), Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry* 36:737–744

Madden PA, Bucholz KK, Dinwiddie SH et al. (1997), Nicotine withdrawal in women. *Addiction* 92:889–902

Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT (1995), Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. *Am J Psychiatry* 152:1793–1799

Sherman DK, Iacono WG, McGue MK (1997a), Attention-deficit hyperactivity disorder dimensions: a twin study of inattention and impulsivity-hyperactivity. *J Am Acad Child Adolesc Psychiatry* 36:745–753

Sherman DK, McGue MK, Iacono WG (1997b), Twin concordance for attention deficit hyperactivity disorder: a comparison of teachers' and mothers' reports. *Am J Psychiatry* 154:532–535

Silberg J, Meyer J, Pickles A et al. (1996), Heterogeneity among juvenile antisocial behaviors: findings from the Virginia Twin Study of Adolescent Behavioral Development. *Ciba Found Symp* 194:76–86

Stevenson J (1992), Evidence for a genetic etiology in hyperactivity in children. *Behav Genet* 22:337–344

van den Oord EJ, Boomsma DI, Verhulst FC (1994), A study of problem behaviors in 10- to 15-year-old biologically related and unrelated international adoptees. *Behav Genet* 24:193–205