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Latent Class Subtyping of Attention-Deficit/Hyperactivity Disorder and Comorbid Conditions

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Abstract

Objective—Genetic studies of attention-deficit/hyperactivity disorder (ADHD) generally use discrete *DSM-IV* subtypes to define diagnostic status. To improve correspondence between phenotypic variance and putative susceptibility genes, multivariate classification methods such as latent class analysis (LCA) have been proposed. The aim of this study was to perform LCA in a sample of 1,010 individuals from a nationwide recruitment of unilineal nuclear families with at least one child with ADHD and another child either affected or clearly unaffected.

Method—LCA models containing one through 10 classes were fitted to data derived from all *DSM-IV* symptoms for ADHD, oppositional defiant disorder, and conduct disorder (CD), as well as seven items that screen for anxiety and depression from the National Initiative for Children's Healthcare Quality Vanderbilt Assessment Scale for Parents.

Results—We replicated six to eight statistically significantly distinct clusters, similar to those described in other cross-cultural studies, mostly stable when comorbidities are included. For all age groups, anxiety and depression are strongly related to Inattentive and Combined types. Externalizing symptoms, especially CD, are strongly associated with the Combined type of ADHD. Oppositional defiant disorder symptoms in young children are associated with either conduct disorder or anxiety-related symptoms.

Conclusions—Methods such as LCA allow inclusion of information about comorbidities to be quantitatively incorporated into genetic studies. LCA also permits incorporation of milder but still impairing phenotypes than are allowed using the *DSM-IV*. Such methods may be essential for analyses of large multicenter datasets and relevant for future clinical classifications. This population-based ADHD classification may help resolve the contradictory results presented in molecular genetic studies.

Keywords

attention-deficit/hyperactivity disorder; latent class analysis; comorbidity; genetics

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Attention-deficit/hyperactivity disorder (ADHD), the most common childhood psychiatric disorder,^{1,2} is increasingly recognized as a heterogeneous syndrome, not a single condition.³ Possible explanations include the proposition that two or more causal pathways are involved.⁴ At the same time, there is little evidence supporting the validity of the *DSM-IV-TR*-defined subtypes of Predominantly Inattentive, Predominantly Hyperactive-Impulsive, and Combined types of ADHD.⁵ Alongside clinical interviews and direct observation, *DSM-IV* diagnosis of ADHD incorporates parent and teacher reports. Variations in interpretation of symptoms and total prevalence are influenced by cultural differences. It is, however, clearly a condition described worldwide.⁶ *DSM-IV* criteria are still the criteria used for clinical decisions.^{1,7} An alternative bottom-up approach, first proposed for ADHD by Hudziak and colleagues,⁸ involves determining the finite number of latent classes best fitting the observed distribution of response items (e.g., the *DSM-IV* symptoms).

The goal of latent class analysis (LCA) is to identify naturally occurring clusters of symptoms without imposition of a cutoff for the number of positive symptoms required for diagnosis (as in *DSM-IV*). LCA⁹ applied to parent reports of ADHD symptoms have repeatedly yielded six to eight clusters that appear to consistently account for the distribution of ADHD-related symptomatology across cultures, types of samples, population type, and diagnostic methods.^{10–12} Indirect evidence of the neurobiological validity of the observed latent classes derives from the demonstration that these clusters show higher heritability estimates than *DSM-IV* subtypes (i.e., monozygotic cotwins are significantly more likely to resemble one another in latent class membership than on *DSM-IV* subtype classification).^{8,10,12–14} The six to eight clusters typically established in LCA including three particularly clinically relevant: severe inattentive, severe combined, and severe hyperactive.^{8,10,12,14} These three clusters correspond roughly to the typically defined *DSM-IV* subtypes.⁵ However, subjects not meeting *DSM-IV* criteria are also often included in clusters. For example, subjects included in the *DSM-IV* ADHD, Predominantly Inattentive type are found to be divided across several latent classes and the severe inattentive latent class contains some *DSM-IV* ADHD, Predominantly Inattentive type cases.¹⁵ The Predominantly Inattentive and Combined LCA-derived types demonstrate clinical stability over time. In contrast, people assigned to the Predominantly Hyperactive-Impulsive type typically evolve to a different subtype over time.⁵

As investigators conduct molecular genetic studies, the question of handling comorbidities remains unsettled. One approach has been to exclude them as much as possible, but that can result in minimizing the influence of genetic factors,¹⁶ because only sporadic cases remain. In some psychopathologies such as conduct disorder (CD) and ADHD in a Colombian isolate and anxiety and depression in women, a single gene or set of genes influences more than one disorder or set of traits,^{17,18} respectively. Comorbidities are the rule in ADHD.^{1,19} Externalizing and internalizing disorders vary in their frequencies in the ADHD population among different studies and populations.^{20,21} Externalizing disorders, such as CD and oppositional defiant disorder (ODD), occur with frequencies up to 50%.²² An estimated 20% of children diagnosed with ADHD have CD and 30% to 45% have ODD.^{1,22–25} Among the internalizing disorders, the prevalence of co-occurrence is somewhat lower, with 10% to 20% of children with ADHD exhibiting mood disorders.^{1,20,26,27} In addition, the association of ADHD with both depressive disorders and anxiety disorders has been replicated by new epidemiological studies.^{28,29} It is now clear that assessment of the underlying structure of these disorders, to discriminate natural symptom aggregation across ADHD domains and provide insight into the cause of comorbidity, is necessary to better understand the psychopathology of these entities.

CD and antisocial behaviors, as comorbidities in ADHD, have been better defined in terms of genetic association.^{22,30,31} A recent study¹⁷ supports the hypothesis that major genes underlie a broad behavioral phenotype in some families that may manifest as a range of symptoms

including ADHD, disruptive behaviors, and alcohol abuse or dependence. These data are consistent with the notion that different behavioral phenotypes comprise a nosological entity and that the concept of comorbidity is inadequate.^{17,22}

The picture is less clear for internalizing disorders. Anxiety and depression may have different phenotypic expressions modified by comorbidity with ADHD or by genetic and environmental factors modifying the final phenotype.¹⁸ A special consideration is necessary for ODD, which is not only highly comorbid with ADHD but is also a predictor of two different developmental trajectories ending in either CD or anxiety. The path that the ODD phenotype selects is dictated by complex interactions between genetics and environment.^{24,32}

In preparation for molecular genetic studies, we performed LCA in a sample of nuclear families with at least one child with ADHD and at least one other child either clearly affected or clearly unaffected and no more than one affected parent. Our analyses include all *DSM-IV* symptoms for ADHD, ODD, and CD, as well as seven screening items for anxiety and depression, as contained in the National Initiative for Children's Healthcare Quality Vanderbilt Assessment Scale for Parents (VAS-P).^{33,34} We hypothesized that LCA would improve the fit of diagnostic subtypes relative to *DSM-IV* for our sample, which included children, adolescents, and adults. We also hypothesized that comorbidity information incorporated into the LCA would provide ADHD phenotypes useful for genetic analysis because LCA permits incorporation of milder phenotypes than are allowed in the *DSM-IV* framework.

METHOD

We recruited participants by advertising in national ADHD-related publications in the United States and on the NIH/NHGRI Web page (<http://www.genome.gov/ADHD>). Eligible families included an ADHD proband between 7 and 18 years of age at enrollment with at least one unaffected or one affected sibling. In addition, at least one parent had to be available to participate with information available regarding both parents. Self-referred families or families from a health care provider underwent an initial screening interview by telephone. Consent forms approved by the National Human Genome Research Institute Institutional Review Board were mailed to families. Once signed consent was obtained, the first telephone interview evaluation included extensive questions regarding pregnancy and birth history for the proband and siblings. If the family met initial inclusion criteria, then rating scales were sent. These scales included the focus of the present report, the VAS-P used for all family members, and scales for adults only (Wender Utah Rating Scale³⁵ and Conners Adult ADHD Rating Scale³⁶) and the Strengths and Weaknesses of Attention and Normal Behavior³⁷ for children and adolescents only. Questionnaires and eligibility criteria for each family and family member were reviewed by a clinical team consisting of a registered nurse coordinator (J.Z.B.), two registered nurses (P.E., J.J.), and a clinical social worker (L.N.), all with extensive training in behavioral conditions and ADHD research. The few questionable cases ($n = 18$) were reviewed by a board-certified child neurologist with extensive clinical and research expertise in ADHD (M.T.A.).

Parents underwent a full structured psychiatric interview regarding each offspring (Diagnostic Interview for Children and Adolescents IV-Revised Parents Version [DICA]).³⁸ The Structured Clinical Interview for *DSM-IV*³⁹ was administered to all siblings 18 years or older. Pedigrees were obtained from all of the families. We excluded bilineal families (both parents with ADHD). Families were also excluded if the proband met *DSM-IV* criteria for Tourette's disorder, obsessive-compulsive disorder, pervasive developmental disorders, psychotic disorders, mood disorders with psychotic features, posttraumatic stress disorder, previous diagnosis of lead toxicity, neurological conditions, known genetic syndromes, mental retardation, hydrocephaly, known prenatal drug exposure, cardiac surgery, or prematurity

(birth weight <2,500 g). For major depression, we excluded families only if both proband and sibling had a lifetime history. Participants were classified into one of four mutually exclusive categories: definitely ADHD, definitely unaffected, possibly ADHD, and unknown. Definitely affected subjects generally met full *DSM-IV* ADHD criteria during childhood, with onset before age 7 years, and with persistence of clearly impairing symptoms in more than one setting. In rare cases of disagreement between an individual's self-report of symptoms and collateral reports, the supervising child neurologist (M.T.A.) reviewed all of the clinical information and requested collateral information to probe more deeply for evidence of early impairment. Individuals were classified as possibly affected if they failed to meet *DSM-IV* ADHD criteria, particularly with respect to unequivocal impairment (criterion D) or by meeting only five criteria A symptoms instead of six in childhood. Individuals reported by relatives to meet ADHD criteria, but for whom interviews were unavailable, were also classified as possibly affected ($n = 30$). Individuals who did not meet *DSM-IV* criteria for ADHD by history or our evaluation were classified as definitely unaffected. The unknown category ($n = 8$) applied to those subjects for whom evaluations could not be completed.

VAS-P

The VAS-P³⁴ includes all 18 *DSM-IV* criteria for ADHD, all 8 criteria for ODD,¹⁴ criteria for CD, and 7 items taken from the Pediatric Behavior Scale⁴⁰ that screen for anxiety and depression. The wording was simplified to slightly below third grade reading level.³⁴ Parents are asked to rate the severity of each behavior on a four-point scale with 0 indicating that a behavior “never” occurs and 3 indicating that the behavior occurs “very often.” Items are positive if scores of 2 or 3 (“often” or “very often,” respectively) are selected. The reliability, factor structure, and concurrent validity of the VAS-P were found to be acceptable and consistent with *DSM-IV*³⁴ and NIMH Diagnostic Interview Schedule for Children-IV⁴¹ ratings of ADHD. Although a relationship has been confirmed between the VAS-P comorbid symptoms and measurements of impairment, the concurrent validity has not been tested. We sought to assess the consistency of the VAS-P comorbid items with the DICA,³⁸ whose psychometric properties have been extensively studied.^{42,43} Pairwise correlations were performed between the VAS-P ODD and CD symptom severity totals and the DICA ODD and CD positive symptom totals. Because the anxiety and depression items of the VAS-P do not have an exact equivalent in the DICA, pairwise correlations were performed using the major depressive disorder, dysthymic disorder, separation anxiety disorder, and generalized anxiety disorder sections of the DICA.

Statistical Analyses

LCA models containing one through 12 classes were fitted to the data using Latent GOLD 3.0.1 software (Statistical Innovations, Belmont, MA). Latent GOLD uses both expectation/maximization and Newton-Raphson algorithms to find the maximum likelihood of each model after estimating model parameters.⁹ To avoid local solutions (a well-known problem in LCA), we used a multiple starting value set as automatically implemented in Latent GOLD. Because we had sparse contingency tables, we estimated p values associated with L^2 statistics (500 replicates) rather than relying on asymptotic p values. To obtain a bootstrap estimate of the p value corresponding to the difference in log-likelihood value between two nested models, such as two models with different numbers of latent classes or different number of discrete factors, we followed a procedure in which the $-2LL$ -difference statistic is defined as $-2 \cdot (LLH0 - LLH1)$, where $H0$ refers to the more restricted hypothesized model (e.g., a K -class model) and $H1$ to the more general model (e.g., a model with $K + 1$ classes).⁴⁴ Replication samples were generated from the probability distribution defined by the maximum likelihood estimates under $H0$. The estimated bootstrap p value is defined as the proportion of bootstrap samples with a larger $-2LL$ -difference value than the original sample.⁴⁴ This approach was comparable overall

with selection of the best fitting model when using parsimony criteria such as the Bayes information criterion.

As covariates for the model, we used sex, ADHD medication use, and age. Age was included as a continuous variable, as a categorical variable based on deciles (e.g., 1–10, 10–20), and as a categorical variable using the age ranges we previously used (i.e., children ages 4–11, adolescents 12–17, adults 18 years or older).²² Our final models used the latter approach because it resulted in smaller bivariate residuals, as described further below. We used the age variable as a covariate to define clustering membership in the whole group without establishing any conditional age-based stratification. Decisions obtained after testing these models controlling the effect of age on symptoms and comorbidities did not affect the general conclusions presented here. VAS-P items were treated as ordinal variables to capture any residual variance caused by differences in symptom severity.

Initially, the presence of interactions between variables and the basic assumption of local independence of the standard latent class model was not supported. Next, we relaxed the local independence assumption allowing for interactions between variables and for direct effects of covariates on variables.⁴⁵ Latent GOLD calculates bivariate variable-variable and variable-covariate residuals that can be used to detect which pairs of observed variables are more strongly related. Therefore, bivariate residuals >3.84 were included iteratively for each model to identify significant correlations between the associated variable-variable and variable-covariate pairs inside each class (for 1 *df*, bivariate residuals >3.84 indicate statistical significance at the .05 level).

The procedure described above was performed in two sets of analyses. The first included only the 18 ADHD items. The second included all of the VAS-P items. We also included both adults and children in one set of preliminary analyses; however, the proportion of adults and children in each cluster was not evenly distributed. An analysis of variance revealed significant differences among the three age groups in severity of total inattentive, hyperactivity, ODD, and CD symptoms ($p < .001$ for each). Because Levene's test for homogeneity of variances revealed unequal variances in the mean of total internalizing symptoms, the Brown-Forsythe test, which does not assume equal variances, was used for testing anxiety and depressive symptoms. The three age groups did not differ significantly in the total sum of anxiety and depressive symptoms ($p = .92$).

Because of differences in symptom endorsement among the three age groups, we performed the LCAs separately for the three age groups. VAS-P CD items 37, 38, 39, and 40 (has broken into someone else's home, business, or car; has stayed out at night without permission; has run away from home overnight; has forced someone into sexual activity, respectively) were not endorsed for any of the children ages 4 to 11. Because these questions had zero variance, they were removed from the analysis for the children. Likewise, question 40 was negatively answered for all of the adolescents, and this item was removed for the analysis of this age group.

As implemented in Latent GOLD, individuals are assigned posterior membership probabilities for belonging to each cluster based on their symptom profiles. Cases are then assigned to the cluster for which the posterior membership probability is highest. Based on this assignment, we compared cluster membership to our *DSM-IV*-based best estimate clinical diagnoses of ADHD.

RESULTS

Characteristics of the Sample

The total sample consisted of 1,010 individuals, 55% of whom were male; 10.6% were ages 4 to 11 years at intake, 26.6% were 12 to 17 years, and 62.8% were 18 years and older. Based on our clinical assessment, 49.6% of subjects were affected with ADHD, 46.6% were unaffected, and 3.8% had an indeterminate diagnosis.

Comparison Between VAS-P and DICA Symptom Totals

Significant correlations ($p < .0001$) were seen between the VAS-P inattention, hyperactivity-impulsivity, ODD, and CD components and the DICA. The anxiety/depression items of the VAS-P showed significant correlation with major depressive disorder ($p < .001$), separation anxiety disorder ($p < .0001$), and generalized anxiety disorder ($p < .0001$) sections of the DICA. The DICA dysthymic disorder items were not significantly correlated ($p < .05$) with the VAS-P anxiety/depression items.

LCA of ADHD

LCA using the 18 VAS-P items in 107 children revealed a best fit for a five-cluster model and LCA in 269 adolescents produced a six-cluster model as the best fit; LCA using the 18 VAS-P items in 634 adult subjects found a seven-cluster model fit the data best. Figure 1 shows the symptom endorsement probabilities for the latent classes in each age group, respectively. Common to all of the age groups were clusters demonstrating severe combined ADHD symptoms, moderate combined symptoms, mild inattentive symptoms, and few ADHD symptoms. A talkative-hyperactive cluster was found in 4- to 11-year-olds; a similar group was found in the adults but with lower symptom severity. This group was not found in the adolescents. Two symptom clusters were found in the adult and adolescent age groups but not in 4- to 11-year-olds: a severe inattentive ADHD cluster and a mild combined ADHD cluster. With the exception of the three symptom clusters mentioned above (talkative-impulsive, severe inattentive, and mild combined), similar clustering trends were found in the three age groups. However, the older age groups showed a marked decrease in symptom severity scores for hyperactivity questions 11 to 13.

As shown in Figure 2, we compared ADHD status as defined by the *DSM-IV* best estimate and posterior cluster membership (described in the figures following the convention established in Figure 1). The proportion of ADHD cases affected in particular clusters was similar between age groups with the exception of the mild combined ADHD symptom cluster. All of the individuals who were assigned to the severe combined and the severe inattentive groups had *DSM-IV* ADHD. Most of the individuals assigned to the moderate combined group had *DSM-IV* ADHD. The proportion of affected individuals in the mild combined cluster differed between adults and adolescents. Adolescents assigned to this cluster were largely affected with *DSM-IV* ADHD; adults assigned to this cluster were a mixture of affected and unaffected individuals.

LCA of VAS-P ADHD and Comorbid Symptoms

In LCA of ADHD and comorbid symptoms in children ages 4 to 11, a six-cluster model showed the best fit; seven-cluster models provided the best fits for the adolescents and adults. Figure 3 shows symptom endorsement probabilities for latent classes in each age group. Figure 4 shows affection status of cases by posterior cluster assignment. Overall, the pattern of ADHD symptom endorsement among the clusters resembled the LCAs limited to only ADHD symptoms. Inclusion of comorbid symptoms appeared to separate certain ADHD subgroups.

In 4- to 11-year-olds, the severe combined cluster split into two clusters, one with high anxiety symptom endorsements and one with low anxiety. Those with higher anxiety also had higher ODD compared to the group with lower anxiety. In 12- to 17-year-olds, the symptom endorsements for ADHD items appear similar after addition of comorbid symptoms, the exception being the disappearance of a cluster corresponding to mild inattentive symptoms. There the two groups displaying severe combined ADHD symptoms appeared to differ most dramatically on externalizing symptoms, although there were differences in internalizing symptoms to a lesser extent. The two groups displaying predominantly inattentive symptoms differed in the extent of internalizing symptoms.

In adults, like adolescents, a cluster demonstrating mild inattentive symptoms was no longer present when comorbid symptoms were added to the analysis. The cluster size of the talkative-impulsive group also decreased after comorbid symptoms were added. In addition, in the adult group, both internalizing and externalizing symptoms appeared to differentiate clusters displaying similar ADHD symptoms. The two moderate combined ADHD groups in adults (Fig. 3C) appeared to differ most notably in internalizing symptoms.

DISCUSSION

Using the 18 VAS-P items for inattention, impulsivity, and hyperactivity, we produced similar clustering patterns (i.e., six to eight clusters and similar cluster definitions), as shown in other LCA studies of ADHD symptoms.^{8,10–14,46} Because the VAS-P has not been used for this purpose in adults and symptom severities are known to differ among age groups, we performed LCA separately for children, adolescents, and adults. Although the age groups differed on certain hyperactivity symptoms, overall the symptom-clustering patterns between age groups were strikingly similar.

Adding comorbidities had little effect on the cluster distributions. This comparability of symptom profiles among age groups with a broad range of internalizing and externalizing symptoms supports the use of LCA in genetic cohorts that include both adults and children.

We used a specific ascertainment process, particular features of which are recruitment of patients based on a voluntary agreement to participate in a study that did not involve help seeking or interventions, making the presence of familial clustering a condition for participating in the study, recruitment not targeting any particular population (participating families came from throughout the United States), most families were successfully enrolled in a standard program of clinical support and were not actively seeking additional support or intervention, and prevalence of comorbidities such as CD was low (3%) compared to clinically referred samples, but similar to the epidemiological prevalence.²⁵

A limitation of our study is that because this sample is family based, the LCA independence assumption is violated. To address this, we created a covariate controlling for coancestry. Maximization of models while considering this covariate did not incur any qualitative change in clustering. Differences among models with the coancestry covariate present and absent were compared by means of parametric bootstrap. In addition, empirical analyses on multigenerational and extended pedigrees in which only a small number of categories are present have confirmed our view that this violation of LCA assumption is not fatal (data not shown).

Beyond replicating the basic clustering pattern found in other studies, we also confirmed the observation⁴⁷ that a substantial proportion of individuals who are classified as unaffected according to *DSM-IV* criteria nevertheless cluster in latent categories exhibiting symptoms associated with clinical impairment. These results suggest that the application of *DSM-IV* ADHD criteria likely underestimates the prevalence of clinically impaired individuals, some

of whom may carry genetic risk factors for ADHD. Volk et al.¹⁵ also found that despite not meeting formal *DSM-IV* criteria, individuals clustering in the mild combined latent class, a form of ADHD undetected by current *DSM-IV* criteria, showed evidence of educational and psychological impairment. Thus, the extension of LCA methods to clinical settings may have utility in allowing the identification of individuals who could benefit from clinical attention. Results from LCA using Dutch twins with the Conners Rating Scale show stability across informants, suggesting that more stable phenotypes may be accessible for genotyping using a multi-informant approach.⁴⁸ In addition, LCAs have already demonstrated the utility of the population-based phenotype approach to identified potential genetic markers for ADHD.^{49, 50} The traditional classification according to the *DSM-IV* criteria, useful in clinical assessment, may introduce uncertainty into studies of subtype etiology. Todd et al.^{49,50} reported a significant association between specific clusters using LCA and some *ADHA* candidate genes. Those associations were not previously found in the same data using the traditional approach and subtype classification according to the *DSM-IV*. Use of alternative population-based defined ADHD subtypes may help to resolve some of the variation in results presented for candidate gene association studies in ADHD.

Although adding the symptoms of common comorbid conditions did not have much effect on the underlying clustering patterns, LCA supports some observations regarding comorbid conditions. Our group has already demonstrated the presence of genetic linkage between ODD, CD, and alcohol and nicotine abuse with specific genetic markers in a sample ascertained in a genetic isolate from ADHD probands.¹⁷ ADHD plus CD is a comorbid subgroup characterized by earlier age at onset, poor school performance, high male-to-female ratio, greater risk for drinking while driving, subsequent substance abuse, development of antisocial personality, and decreased likelihood of eventual remission compared to individuals affected by ADHD alone.⁵¹ Although consensus has yet to be attained regarding whether ADHD plus CD should be considered a separate entity, some have suggested that it is a distinct clinical subtype.⁵² In our population, the frequency of CD is lower compared with other studies.^{22,53} However, the distribution of clusters still fits similar patterns described by other investigators.²² In our population, most of the individuals affected with CD correspond to the combined subtype in all ages.

Another interesting finding in our clinical sample was the pattern of splitting of the severe combined ADHD cluster when externalizing (ODD and CD) and internalizing (anxiety disorders and depression) symptoms were included in the LCA. A previous LCA study in a sample of female twins also found that ODD symptoms are not only associated in the context of ADHD combined type but also in a subgroup of ADHD predominantly inattentive type.¹⁴

Different patterns of splitting were noted in the three age groups. In children, severe cases of ADHD with high levels of ODD endorsement appeared to differ primarily to internalizing behaviors, particularly in those items most directly related to anxiety. This pattern was not seen in adolescents and adults. In these age groups, severe cases were largely distinguished by the presence or absence of externalizing behaviors.

We did not find correlations between the diagnosis of dysthymic disorder per the DICA and the screening criteria for internalizing disorders in the VAS-P.³⁴ Similar patterns of behaviors may represent different psychopathologies, and parents sometimes underreport internalizing symptoms in their children or adolescents.^{24,54} The causal relationship between anxiety disorder and ADHD is unclear, although its implications for diagnosis, etiology, and intervention have long been described in the literature.^{24,28,29,54} One possibility is that common genetic loci may confer increased risk of both internalizing disorders and ADHD. Levy⁵⁵ suggested a mechanism whereby differences in mesolimbic system function may play a role in the expression of anxiety in patients with ADHD.

In summary, our data suggest that LCA can feasibly allow the combination of internalizing and externalizing symptoms for future tests of hypotheses regarding specific genetic risk factors.

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Fig. 1.

Latent class analysis for 18 items of the Vanderbilt Assessment Scale for Parents (VAS-P) for children (A), adolescents (B), and adults (C). Each figure shows the latent classes endorsement probabilities (y-axes) for every VAS-P item (symptoms). ADHD = attention-deficit/hyperactivity disorder.

Fig. 2. Comparison of attention-deficit/hyperactivity disorder (ADHD) status as defined by the *DSM-IV* best estimate and posterior cluster membership (each cluster equals 100%).

Fig. 3.

Latent class analysis (LCA) using attention-deficit/hyperactivity disorder (ADHD) plus comorbidity (oppositional defiant disorder [ODD], conduct disorder [CD], anxiety disorder [AD]), Vanderbilt Assessment Scale for Parents items, for children (A), adolescents (B), and adults (C). Each figure shows the latent class endorsement probabilities (y-axes) for every VAS-P item (symptoms).

Fig. 4.

Comparison of attention-deficit/hyperactivity disorder (ADHD) status as defined by *DSM-IV* best estimate and posterior cluster membership when considering ADHD plus comorbidity (oppositional defiant disorder [ODD], conduct disorder [CD], and anxiety disorder [AD]), Vanderbilt Assessment Scale for Parents items (each cluster equals 100%).