SJCAPP

Scandinavian Journal of Child and Adolescent Psychiatry and Psychology
Vol. 1, pp. 3-13 (2013)

Research Article **Open Access**

Exploration of ADHD Subtype Definitions and Co-Occurring Psychopathology in a Missouri Population-Based Large Sibship Sample

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Abstract

Background: There is some debate regarding the utility of Attention-Deficit/ Hyperactivity Disorder (ADHD) subtypes as currently defined. Differences in co-occurring psychopathology among subtypes would support the validity of subtype definitions.
Objective: To explore how ADHD subtype relates to co-occurring psychopathology in a large population-based sample of children and adolescents (n=5744).
Method: Parents completed the Strengths and Weaknesses of ADHD-symptoms and Normal behavior (SWAN) questionnaire, the Child Behavior Checklist (CBCL) and the Social Responsiveness Scale (SRS). Methods including discriminant analysis, principal components analysis, and fractional polynomial regression were used to examine the relationship between ADHD diagnostic subtypes and co-occurring psychopathology.
Results: Children with different ADHD subtypes show differences on several CBCL subscales. A combination of CBCL subscales and SRS score had good ability to discriminate ADHD subtypes. Conversely, for the same overall number of ADHD symptoms, individuals who present with both inattentive and hyperactive/impulsive symptoms exhibit higher severity of co-occurring psychopathology on a summary measure derived from principal components analysis of the CBCL subscales and SRS. This includes some subjects who fail to meet the DSM-IV-TR ADHD symptom criterion due to having less than 6 inattentive and less than six hyperactive-impulsive symptoms, yet have ADHD symptom severity similar to those with the inattentive or hyperactive-impulsive subtype.
Conclusions: Several convergent lines of analysis provide support for the continued use of ADHD subtypes (or current presentation symptom profiles), as evidenced by differences in co-existing psychopathlogy. We also found that current diagnostic criteria may fail to identify a potentially impaired group of individuals who have low-to-moderate levels of both inattention and hyperactivity/impulsivity. Under the upcoming DSM-5, it will be important for clinicians to consider the option of giving an ADHD "not elsewhere classified" diagnosis to such children.

Key Words: ADHD, subtypes, comorbidity

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Introduction

There is some debate regarding the current DSM-IV-TR criteria for Attention-Deficit/Hyperactivity Disorder (ADHD) and its three subtypes (predominantly inattentive, predominantly hyperactive-impulsive, and combined type). First, the correlation between the inattentive and hyperactive-impulsive domains is very high, with evidence of high genetic overlap between separate ADHD subtypes or symptom dimensions (1). Second, from a clinical intervention standpoint, stimulants are the mainstay of pharmacological treatment, regardless of subtype (though educational accommodations will vary slightly depending on which type of symptoms predominate in the school setting). Third, children who present with a meaningful six to ten symptoms could potentially qualify for the inattentive subtype or the hyperactive-impulsive subtype, provided that six or more of these symptoms fall into one category. A more likely event, given the high correlation between the two domains, is that the symptoms would be roughly equally divided, so that the child would not technically qualify for a diagnosis of ADHD (e.g., five symptoms in each category). Below, we will present data suggesting significant impairment in such children. Improved definition and screening methods for ADHD and its subtypes may help ensure that individuals with clinically impairing ADHD symptoms can be identified and treated.

Differences in external (non-ADHD) measures (such as cognitive profiles, genetic associations, and comorbidity patterns) among ADHD subtypes would help validate the current typology. They may suggest differences in etiology and treatment needs between ADHD subtypes. Also, if different ADHD subtypes are associated with different types of co-occurring problems and/or different levels of severity, this may support subtypes as prognostic indicators to guide the monitoring of specific types of co-occurring problems depending upon the ADHD symptom profile.

The Child Behavior Checklist has previously been used to examine comorbid psychopathology in children with ADHD (2-5). Some studies specifically examined differences in CBCL measures among ADHD subtypes (3, 5). Though results vary somewhat between studies, individuals with the combined subtype generally have the highest rates of co-occurring psychopathology where subtype differences are found.

Population-based studies conducted by our own research group investigated the validity of ADHD subtypes through analyses focusing on prevalence (6), sex differences (6), cognitive function (7), comorbidity profiles (8-10), genetics (11-13), and longitudinal course (14). In these analyses, subtypes were defined both according to DSM-IV criteria and via Latent Class Analysis (LCA), a form of mixture modeling that can be used to separate subjects into discrete, more homogeneous groups characterized by specific symptom profiles. Three of these latent classes (labeled severe inattentive, mild combined, and severe combined) show substantial evidence of impairment (5), while those characterized by pure hyperactive-impulsive symptoms show little evidence of impairment. The severe inattentive type shows modest agreement with DSM-IV inattentive subtype, and the severe combined type shows excellent agreement with DSM-IV combined subtype ADHD (8, 15-18). These previous analyses supported inattentive ADHD as a distinct subgroup based on genetic associations and co-occurring problems (5, 7, 8, 11-13), but failed to take into account the fact that overall severity of combined type ADHD compared to inattentive ADHD could account for many of the differences between these two subtypes.

In a prospective longitudinal study of twins, we found that compared to the inattentive subtype, the diagnosis of combined subtype ADHD (defined by either DSM or LCA) is more stable over time than other subtype diagnoses (14). While combined subtype subjects sometimes switched to inattentive subtype five years later, inattentive subjects tended to remain inattentive if they still had a diagnosis five years later. Again, overall severity could underlie the difference in subtype stability since children with more severe forms of a neurodevelopmental disorder (i.e. combined type ADHD) may be expected to have more persistent symptoms over time. Hurtig and colleagues reach a similar conclusion based on a retrospective study (19). For DSM-5, it has been proposed that ADHD subtypes be replaced by similarly defined "specifiers" of current presentation, in part to emphasize that these categories represent current symptom profile rather than longitudinally stable subtypes (20). Even though the concept of subtypes will be de-emphasized by this change, DSM-5 will likely still require six symptoms in at least one of the two symptom domains in order to meet the overall symptom criterion. A diagnosis of "ADHD Not Elsewhere Classified" has been proposed to classify individuals who do not meet the full symptom criterion due to partial remission status or clinically significant but subthreshold symptoms (e.g., those with five symptoms in each category) (20).

Using additional population-based data from a large sibship sample, the current analysis attempts to further explore the validity of ADHD subtype definitions through the examination of co-occurring psychopathology. If, for example, when controlling for overall severity of total ADHD symptoms, individuals with the inattentive ADHD subtype are more severely affected than combined type on any specific measures of co-occurring psychopathology, this would suggest that inattentive ADHD is a distinct subtype rather than just a less severe form of combined type ADHD. Our focus on population-based samples avoids some of the biases inherent to clinical samples. In particular, children with hyperactive-impulsive symptoms may be brought to clinical attention due to their disruptive behavior at school, while children with predominantly inattentive ADHD (especially those without additional psychopathology warranting clinical attention) may be overlooked because they do not disrupt the classroom.

Methods

Sample

Subjects are from the Missouri Large Sibship Sample (MO-BIGSIBS). Families with four or more children born in the state of Missouri were identified for study using a birth records database (21). As the parent study required genetic material from both parents in a later phase, we only screened families in which both biological parents were available (parents could not be deceased or in prison). Families were excluded at the birth records review or tracking level if the family was known to have twins (due to other studies using twin samples), language difficulty that would prevent English-language telephone screening, or if a parent was deceased. Individual children were excluded during the parent-report telephone screening if the child was adopted or not a full sibling, or had a parent-reported diagnosis of autism, a major hearing impairment, a marked medical illness such as cancer, Down's Syndrome, or intellectual disability ("mental retardation" or IQ less than 70).

As the initial screening phase involved the collection of relatively non-invasive parent-report interview and questionnaire data to be stored in de-identified form, consent was required only from parent participants at this stage. After explanation of study procedures, informed consent was obtained from respondent parents and documented by study staff prior to an initial ADHD screening interview. Parents were informed that phase 1 of the study would include the initial telephone interview plus questionnaires regarding their children. They were also informed that they and their family may later be invited to participate in additional assessments on the basis of their responses to the initial telephone questions. A subset of families was eventually selected for more detailed phenotypic and genetic study, which required written consent from parents and their adult offspring participants, and assent from minor children. The current manuscript uses only the phase 1 parent-report screening data. Ethical approval for this study was obtained through the Washington University Human Research Protection Office, which reviewed and approved the study protocols, including consent procedures.

The MO-BIGSIBS sample includes 22,581 offspring, some of them young adults, with complete data on sex, age at screening, and screening interview ADHD items (21). The current analyses focus on children and adolescents age 7-17 years (n=5,744) at assessment, who have complete data on sex, age, lifetime ADHD symptoms from the screening interview, and relevant questionnaire items. Of the 5,744 subjects, 98% are Caucasian, 2% are African-American, and less than 1% report other races/ethnicities. Fifty-two percent of study subjects are male.

Measures

In the initial screening phase, the best informant parent (usually mother) reported on lifetime occurrence of each of the standard 18 DSM-IV ADHD symptoms for each of their offspring. Each lifetime ADHD symptom was counted as positive only if there was reported impairment at home and/or school at some point in the child's life. The screening questions were taken from the ADHD section of the Missouri Assessment of Genetics Interview for Children (MAGIC), which has excellent reliability for parent-reported ADHD (22). A subset of parent informants subsequently completed several questionnaires regarding the offspring, including the Strengths and Weaknesses of ADHD-symptoms and Normal-behavior (SWAN) scale, the Social Responsiveness Scale (SRS), and the Child Behavior Checklist (CBCL).

The CBCL covers a wide range of problem behaviors (23), and the SRS is a 65-item quantitative measure of autistic traits (24, 25). SRS score is highly correlated with algorithm scores from the Autism Diagnostic Interview-Revised (ADI-R) (24). The SWAN (26)

includes 18 items based on DSM-IV ADHD symptoms plus additional items assessing oppositional-defiant behaviors (9 items) and three items related to sluggish cognitive tempo. SWAN items are scored on a seven-point scale (-3 to +3) in which positive scores indicate the presence of problem behaviors and negative scores indicate better than average behaviors.

Data from the SWAN was used to define *current* DSM-IV-like ADHD diagnoses, and data from the screener was used to define *lifetime* DSM-IV-like ADHD diagnoses. It was not possible to apply strict DSM-IV criteria in determining ADHD diagnoses since information about age-of-onset and current impairment specifically from ADHD symptoms was not collected. However, the lifetime ADHD symptom data from the screening interview and current symptom data from the SWAN allowed us to assign subjects to ADHD-like diagnoses using the DSM-IV ADHD symptom criterion. From the screener data, a diagnosis of Lifetime DSM-IV inattentive ADHD (DSM-Life-IA) was assigned if there were at least six lifetime inattentive (IA) symptoms and less than six lifetime hyperactive-impulsive (HI) symptoms based on the screening interview. Lifetime DSM-IV hyperactive-impulsive type (DSM-Life-HI) was assigned if there were at least six HI symptoms but less than six IA symptoms. Lifetime combined type ADHD (DSM-Life-C) was assigned if there were at least six symptoms in each of the two categories (IA and HI).

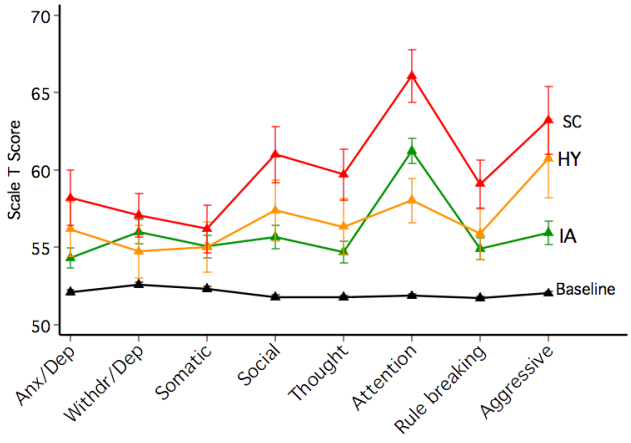

Figure 1. Mean CBCL subscale T-Scores for children and adolescents with DSM-IV Inattentive (IA), Hyperactive-Impulsive (HY), and combined type (SC) ADHD. The SC subtype consistently scores higher than the IA or HY subtypes.

Using similar algorithms, current DSM-IV-like diagnoses (DSM-IA, DSM-HI, and DSM-C) were assigned using the DSM-IV ADHD symptom items from the SWAN. SWAN-based ADHD symptoms were counted as present if the parent rated the child at a level of 1 or higher, an actually stringent cutoff that typically corresponds to the 90th-95th percentile for each item (21).

Data Analysis

Analyses were conducted using STATA 12 and SAS 9.3. We used ANOVA to Compare CBCL syndrome subscale T-scores across the four subject groups (unaffected individuals and the three ADHD subtypes), with a conservative Bonferoni correction for multiple testing and with standard errors adjusted for clustering by family. Conversely, we considered whether a rule could be developed from the SRS and CBCL subscale data, to distinguish DSM-IV inattentive and hyperactive-impulsive subtypes, again taking into account the known correlation between the two symptom domains. To that purpose, we use seemingly-unrelated bivariate probit regression with the robust clustering option (on family), beginning with a full model consisting of age, SRS, and the eight CBCL syndrome scale scores. This allowed us to test if the relationship between specific variables (e.g., age or subscale score) and the liability to HI was the same as with the liability to IA. The analyses were conducted separately for males and females. The output from this analysis consists of two predicted means (probit scale, akin to predicted scores from linear regression) for each individual subject, one for IA and one for HI. Receiver Operating Characteristics (ROC) Curves were used to assess the sensitivity and specificity of these probit scores in predicting elevated IA and HI symptoms. The two probit scores were then used in a linear discriminant analysis to assess the ability to distinguish between DSM-IV ADHD subtypes.

Table 1. Parameter estimates for females, ordered bivariate probit regression, predicting inattentive and hyperactive-impulsive symptom counts.
* = Retained for subsequent analyses.

Predictor of Inattentive Symptom Count	Coefficient	Standard Error	z	p	95% CI
* SRS	0.022	0.003	8.19	<0.001	0.017 to 0.027
* Anxious/Depressed	-0.025	0.009	-2.91	0.004	-0.042 to -0.008
* Withdrawn/Depressed	-0.030	0.007	-4.48	<0.001	-0.043 to -0.017
* Somatic Complaints	0.022	0.006	3.60	<0.001	0.010 to 0.034
* Attention problems	0.149	0.008	18.35	<0.001	0.133 to 0.165
* Rule-Breaking	0.030	0.008	3.82	<0.001	0.015 to 0.045
Age	-0.020	0.009	-2.32	0.020	-0.037 to -0.003
Social Problems	-0.012	0.009	-1.36	0.175	-0.029 to 0.005
Thought Problems	-0.020	0.008	-2.44	0.015	-0.036 to -0.004
Aggressive Behavior	-0.011	0.009	-1.43	0.154	-0.027 to 0.004
Predictor of Hyperac-tive-Impulsive Symptom Count	**Coefficient**	**Standard Error**	**z**	**p**	**95% CI**
* Age	-0.031	0.009	-3.25	0.001	-0.049 to -0.012
* SRS	0.021	0.003	7.86	<0.001	0.015 to 0.026
* Withdrawn/Depressed	-0.067	0.008	-7.94	<0.001	-0.084 to -0.051
* Thought Problems	0.021	0.008	2.76	0.006	0.006 to 0.036
* Attention Problems	0.057	0.007	8.28	<0.001	0.044 to 0.071
* Aggressive Behavior	0.055	0.009	6.30	<0.001	0.038 to 0.072
Social Problems	0.009	0.009	1.00	0.319	-0.009 to 0.027
Somatic Complaints	0.013	0.006	2.04	0.041	0.001 to 0.025
Anxious/Depressed	0.003	0.009	0.35	0.724	-0.014 to 0.020
Rule-Breaking	-0.007	0.009	-0.78	0.434	-0.025 to 0.011

Table 2. Parameter estimates for males, ordered bivariate probit regression, predicting inattentive and hyperactive symptom counts.
* = Retained for subsequent analyses.

Predictor of Inattentive Symptom Count	Coefficient	Standard Error	z	p	95% CI
* SRS	0.021	0.002	9.84	<0.001	0.017 to 0.025
* Anxious/Depressed	-0.027	0.007	-3.74	<0.001	-0.042 to -0.013
* Withdrawn/Depressed	-0.017	0.006	-2.78	0.005	-0.029 to -0.005
* Thought Problems	0.028	0.007	-3.86	<0.001	-0.043 to -0.014
* Attention problems	0.159	0.008	19.31	<0.001	0.143 to 0.176
Somatic Complaints	0.001	0.007	0.22	0.827	-0.012 to 0.015
Social Problems	-0.006	0.008	-0.67	0.501	0.022 to 0.011
Age	0.000	0.008	0.04	0.968	-0.015 to 0.016
Rule-Breaking	0.016	0.008	1.85	0.065	-0.001 to 0.032
Aggressive Behavior	-0.012	0.007	-1.63	0.103	-0.026 to 0.002
Predictor of Hyperac-tive-Impulsive Symptom Count	**Coefficient**	**Standard Error**	**z**	**p**	**95% CI**
* Age	-0.059	0.008	-7.02	<0.001	-0.075 to -0.042
* SRS	0.019	0.002	8.78	<0.001	0.015 to 0.024
* Withdrawn/Depressed	-0.060	0.007	-8.57	<0.001	-0.073 to -0.046
* Attention Problems	0.087	0.006	13.76	<0.001	0.075 to 0.100
* Aggressive Behavior	0.045	0.007	6.25	<0.001	0.031 to 0.059
Anxious/Depressed	-0.015	0.007	-2.03	0.042	-0.029 to -0.001
Somatic Complaints	-0.012	0.007	-1.85	0.064	-0.025 to 0.001
Social Problems	0.011	0.008	1.35	0.178	-0.005 to 0.027
Thought Problems	0.013	0.007	1.88	0.060	-0.001 to 0.026
Rule-Breaking	-0.004	0.008	-0.54	0.590	-0.021 to 0.012

Given the relatively high levels of correlation between them, we also conducted a principal components analysis of SRS total score and CBCL subscale scores in a preliminary assessment of whether a summary measure of these individual scales and subscales could be used to distinguish between ADHD subtypes. We implemented principal components analysis using the principal-component factor (pcf) method available in STATA, which analyzes a correlation matrix in which the communalities (numbers on the diagonal of the correlation matrix) are assumed to be 1. We examined the relationship between the first unrotated factor from this analysis and the first factor from the SWAN principal components analysis for individuals with only inattentive symptoms, only hyperactive-impulsive symptoms, and both types of symptoms.

Results

Thirteen percent of the 5,744 subjects meet symptom criteria for *lifetime* ADHD based on the screening interview, and 11% for *current* ADHD based on the SWAN. The *current* inattentive group (DSM-IA) includes 119 females and 213 males, the hyperactive-impulsive (DSM-HI) group includes 26 females and 52 males, and the combined type ADHD group (DSM-C) includes 31 females and 94 males. The baseline (currently unaffected) group includes 2,602 females and 2,527 males.

As seen in previous studies, subjects with combined type ADHD have more severe psychopathology than other ADHD subtypes (Figure 1). Not surprisingly, the highest separation is attained for the CBCL attention problems and aggressive behavior subscales. There are no statistical differences between the DSM-HI and DSM-IA subtypes on the social problems and rule-breaking behavior subscales. Although clearly different from baseline, we find no difference between the DSM-IA, DSM-HI, and DSM-C subtypes on the withdrawn/depressed and the somatic complaints subscales. Finally, there is a gradual increase in severity on the anxious/depressed subscale, in the order baseline < DSM-IA < DSM-HI < DSM-C, but without clear group separation.

Bivariate ordered probit regression models are summarized in Tables 1-2. In females, when predicting inattentive symptom counts, we retained SRS score as well as scores on five CBCL subscales: anxious/depressed, withdrawn/depressed, somatic complaints, attention problems, and rule-breaking. In the model for hyperactivity symptoms, we retained age, SRS and four CBCL subscales: withdrawn/ depressed, thought problems, attention problems, and aggressive behavior. The *residual* correlation (between the IA and HI latent dimensions) was 0.33 (95% CI: 0.27 – 0.41). Follow-up ROC analyses for these two models to predict the presence or absence of six of more inattentive or hyperactive-impulsive symptoms, respectively, show good specificity and sensitivity (AUC=0.93 and 0.90).

The residual correlation between the IA and HI latent dimensions was comparable in the male subsample (0.39, 95% CI: 0.33 – 0.45). There were significant associations of the latent inattentive dimension with SRS score and scores on the CBCL subscales for anxious/depressed, withdrawn/ depressed, thought problems and attention problems. For the HI dimension, age, SRS and the CBCL subscale scores for withdrawn/depressed, attention problems and aggressive behavior were significant. Follow-up ROC analyses using the predicted values from these models to predict the presence or absence of six or more inattentive or hyperactive-impulsive symptoms show, as for females, good specificity and sensitivity (AUC=0.93 and 0.91, for inattention and hyperactivity-impulsivity, respectively).

We then used linear discriminant analysis to assess the ability to distinguish between ADHD subtypes using information from age, gender, the SRS and the CBCL subscales (Table 4). The measures used in the discriminant analyses are the predicted means (probit) from the models described previously. Note that different predictors are used depending on the outcome measure (e.g., inattentive vs. hyperactive/ impulsive symptoms) and gender, as described above. Based on these measures which were not designed to assess ADHD, the ability to discriminate between unaffected and the combined subtype was very good, with positive predictive values (PPV) and negative predictive values (NPV) over 83% and 96%, respectively. In females, the lowest PPV was observed for discriminating between the inattentive and combined subtypes. In males, the lowest PPV was for the contrast between the hyperactive/impulsive and combined subtypes.

Table 3. Principal Components Analysis of SWAN items. (N=5744 children) Principal components analysis of the 18 SWAN ADHD symptom items yields the well documented two factor solution, accounting for approximately 80% of the variance. The first principal component is severity score, with loadings approximately equal. The second associates positive loadings to inattentive items and negative loadings to hyperactivity items. Abbreviated version of item content is shown in the left column.

Swan Item	Factor 1	Factor 2	Uniqueness
1. Careless mistakes	0.80	0.36	0.23
2. Sustain attention	0.85	0.28	0.19
3. Listen	0.86	0.14	0.25
4. Finish work	0.83	0.37	0.17
5. Organize tasks	0.82	0.41	0.16
6. Sustain effort	0.82	0.35	0.21
7. Keep track of things	0.82	0.35	0.20
8. Ignore stimuli	0.79	0.17	0.34
9. Remember activities	0.83	0.26	0.23
10. Sit still	0.86	-0.20	0.23
11. Stay seated	0.87	-0.21	0.19
12. Running/Climbing	0.79	-0.22	0.33
13. Play quietly	0.82	-0.35	0.20
14. Control activity	0.85	-0.35	0.16
15. Control talking	0.80	-0.37	0.23
16. Control blurting	0.83	-0.32	0.21
17. Await turn	0.84	-0.35	0.17
18. Control intruding	0.80	-0.33	0.26

Table 4. Percentage correct ADHD subtype classification based on scores derived from age, gender, SRS, and CBCL subscales. Base=baseline (unaffected); IA=inattentive subtype; HI= hyperactive-impulsive subtype; CB= combined subtype ADHD. Linear discriminant analysis readily distinguishes between ADHD subtypes using information from age, gender, SRS score and CBCL subscales. The ability to discriminate between unaffected and combined subtype ADHD was very good, with positive predictive values (PPV) and negative predictive values (NPV) over 83% and 96%, respectively. In females, the lowest PPV was observed for discriminating between inattentive and combined subtypes. In males, the lowest PPV was for the contrast between the hyperactive/impulsive and combined subtypes

Gender	Contrast	Base	IA	HI	CB	PPV	NPV
Females	Base vs. IA	93%	80%	--	--	80%	93%
	Base vs. HI	88%	--	65%	--	65%	88%
	Base vs. CB	96%	--	--	89%	89%	96%
	IA vs. HI	--	75%	87%	--	87%	75%
	IA vs. CB	--	78%	--	56%	56%	78%
	HI vs. CB	--	--	78%	74%	74%	78%
Males	Base vs. IA	89%	73%	--	--	73%	89%
	Base vs. HI	89%	--	73%	--	74%	90%
	Base vs. CB	95%	--	--	83%	83%	96%
	IA vs. HI	--	76%	67%	--	67%	76%
	IA vs. CB	--	77%	--	67%	67%	77%
	HI vs. CB	--	--	74%	66%	65%	73%

A principal components analysis of the 18 SWAN current ADHD symptom items yields the well documented two factor solution, accounting for approximately 80% of the variance (Table 3). The factor loadings are remarkably close to what we observe for the lifetime ADHD screener data. The first component represents "severity", with approximately uniform factor loadings across all items. The second component assigns a positive loading to inattentive items and a negative loading to hyperactive-impulsive items, and differentiates between predominantly inattentive versus hyperactive-impulsive, with the same overall level of severity. The factor loadings are fairly uniform, but not identical. Thus, the correlation between simple symptom counts and factor scores is very high (>95%), but imperfect. The implication is that a number of children could be "misdiagnosed" under a simple counting scheme that assigns equal weight to all items (in Figure 2, a number of such "misdiagnoses" are visible).

There are strong correlations and partial correlations between the SRS total score and CBCL subscores (Table 5). Figure 3 plots the predicted first factor score (without rotation) derived from these measures, against the first factor score for the 18 SWAN ADHD items. Three curves are shown, for individuals with zero hyperactive/impulsive symptoms (green), zero inattentive symptoms (orange), and at least one symptom of each category (red). Inasmuch as SWAN Factor 1 correlates very highly with the actual number of symptoms, this shows that, for the same number of symptoms, individuals who present with both inattentive and hyperactive/impulsive symptoms also tend to present with higher severity with respect to a summary score of the SRS and the CBCL subscales. Note that at low SWAN severity scores, the lines are almost flat, and the mean SRS-CBCL factor scores are not different between groups. At higher SWAN severity scores, the slopes of the lines increase and there is a statistically significant separation of the predicted SRS-CBCL severity factor scores between groups, with the lowest severity in the HI-only group, intermediate severity in the IA-only group, and the highest severity in the group with both IA and HI symptoms.

There are 250 individuals in our sample with at total of at least 6 current DSM-IV ADHD symptoms, who do not meet criteria for a specific DSM-IV ADHD subtype. On average, these 250 individuals have four inattentive and three hyperactive-impulsive symptoms. In Figure 2, these subjects would be near the

Table 5. Correlations (bottom) and partial correlations (top) between SRS score and CBCL subscale scores.
All correlations significant with p < 0.0001 (Bonferoni adjusted). Correlations between the SRS score and CBCL scales on N = 4982; Correlations between CBCL subscales on N = 5737. Only partial correlations greater than 0.10 are shown. Note that while the overall correlation shows Rule-breaking (Rule) is positively correlated with the Anxious/Depressed (Anx/Dep) scale, the partial correlation indicates these two scales are negatively correlated after controlling for other psychopathology. CBCL subscale abbreviations: Attention= Attention problems; Thought= Thought problems; Anx/Dep= Anxious/Depressed; With/Dep=Withdrawn/Depresssed; Somatic=Somatic complaints; Social= Social problems; Rule= Rule-breaking; Aggr=Aggressive behavior

	SRS	Attention	Thought	Anx/Dep	With/Dep	Somatic	Social	Rule	Aggr
SRS	-- --	*0.2874*	*0.1302*		*0.3398*		*0.2891*		
Attention	0.6300	-- --	*0.1769*				*0.1410*	*0.1253*	*0.1647*
Thought	0.5305	0.5133	-- --	*0.1574*		*0.1719*			
Anx/Dep	0.5399	0.4037	0.4892	-- --	*0.2387*	*0.1970*	*0.2700*	*- 0.1203*	*0.1368*
With/Dep	0.6140	0.4098	0.4118	0.5438	-- --	*0.1372*		*0.1308*	
Somatic	0.3539	0.3160	0.4119	0.4617	0.3882	-- --			
Social	0.6728	0.5801	0.4918	0.6071	0.5092	0.4145	-- --		*0.2236*
Rule	0.4354	0.5040	0.3982	0.3073	0.3757	0.2728	0.4409	-- --	*0.5246*
Aggr	0.5700	0.5967	0.4934	0.5006	0.4390	0.3706	0.6274	0.6867	-- --

center of the scatter-plot, just below the affection cut-off by DSM-IV symptom criteria. Interestingly, this group appears to have higher severity of co-occurring psychopathology than pure inattentive or pure hyperactive-impulsive subjects with equivalent total ADHD severity (Figure 3).

Discussion

This analysis supports the continued use of ADHD subtypes, or "presentations", as they may be called in DSM-5 (20), as suggested by differences in co-occurring psychopathology. As different psychopathology subscales were more or less associated with IA versus HI symptoms (and with ADHD subtypes), the pattern of ADHD symptom presentation may inform clinicians about risk for various co-occurring conditions and overall severity or impairment. We observe ADHD subtype differences in severity of co-occurring psychopathology, not only at the extreme, but also in the range of mild to moderately severe ADHD. Children with low-level symptoms in both the inattentive and the hyperactive-impulsive domain, but with a significant number of total symptoms overall, are likely to be just as impaired (or more impaired) than individuals with the same overall total ADHD severity but with symptoms in only one of the two domains.

Our results underscore the fact that current diagnostic criteria may fail to identify a potentially impaired group of children with significant levels of both inattention and hyperactivity-impulsivity. These children, who could be classified as ADHD Not Otherwise Specified (ADHD-NOS) according to DSM-IV, have significant impairment and co-occurring problems. As these individuals have, on average, 4 inattentive and 3 hyperactive-impulsive symptoms, they could also be described as having a mild combined subtype of ADHD. In a separate Missouri population-based sample, analyses indicated that a "mild combined" form of ADHD was one of 3 clinically impaired latent class ADHD subtypes (5), and was also characterized by elevated levels of autistic traits (9). On the other hand, it could be argued that some children with moderate ADHD symptoms may not have true ADHD but rather another disorder with symptoms that overlap with ADHD. Arguably, depression or oppositional-defiant disorder, for example, might respectively lead to high internalizing or externalizing symptoms, and mimic the pure inattentive or pure hyperactive-impulsive ADHD subtype. Differences in comorbid psychopathology between subtypes (Figure 3) could be due to the inclusion of individuals with disorders other than ADHD that mimic ADHD symptoms.

The CBCL and the SRS did rather well in distinguishing ADHD subtypes in this population-based sample, even though they were not designed for that purpose. This supports the use of quantitative measures of ADHD (such as the SWAN) and other forms of psychopathology (i.e., SRS, CBCL) in order to obtain a more complete picture of overall severity and co-occurring problems. In particular, even after removing SRS items with wording that may pick up on ADHD-like symptoms, SRS scores remain mildly elevated for hyperactive-impulsive and inattentive

ADHD, and even further elevated in combined type ADHD (9). Children with ADHD symptoms plus very high (clinically elevated) SRS scores may have a combination of ADHD plus a true autism spectrum disorder. However, it may be that moderately elevated SRS scores in the context of ADHD are sometimes indicators of general psychosocial impairment, social impairment directly due to ADHD symptoms, and/or social anxiety symptoms, resulting in SRS scores that are above normal but not in a range indicating a clinical diagnosis of autism spectrum disorder. The SRS may be a measure of overall level of psychopathology across its entire scoring range, such that children with the highest severity levels of ADHD, or even the highest levels of overall psychopathology, will always show some autistic-like social impairment. Within this conceptualization, children with autism might be considered to have the most severe and pervasive form of childhood psychopathology.

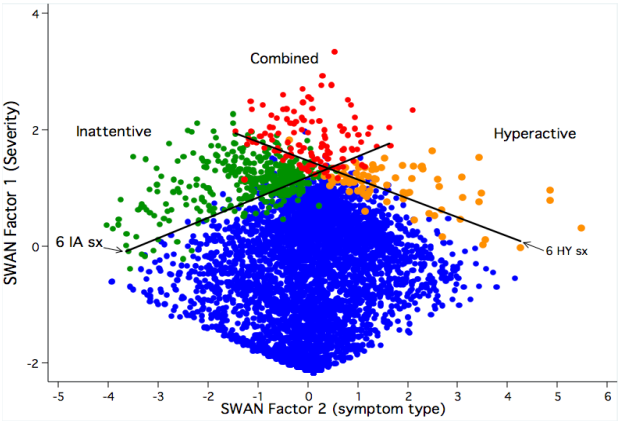

Figure 2. Relationship between severity and symptom type factors derived from the SWAN, and DSM-IV diagnosis. Each circle is an observation. Color indicates DSM-IV subtype (Blue= No diagnosis, Green= Inattentive, Orange= Hyperactive-Impulsive, Red= Combined type ADHD). Black lines: Created using linear regression of factor 2 on factor 1, using only those subjects with exactly 6 inattentive or exactly 6 hyperactive-impulsive symptoms. Some individuals in the center of the plot do not meet the DSM-IV symptom criterion (<6 symptoms in both categories), but actually have a total severity factor score equal to some individuals classified as having inattentive or hyperactive-impulsive type ADHD.

This study has some limitations. We could not confirm true DSM-IV ADHD diagnoses given the absence of age-of-onset and current impairment data, but the purpose of the current analyses was to examine the relationship between ADHD symptoms and co-occurring psychopathology, not to determine prevalence of categorical diagnoses defined exactly as in DSM-IV. Because we did not consider age-of-onset or impairment criteria, our estimated SWAN-based ADHD prevalence (11%) could be slightly higher than the number meeting full criteria for true DSM-IV ADHD. However, *lifetime* ADHD symptoms were not considered positive unless impairment at home and/or school was reported, and 95% of subjects classified as having *current* ADHD based on the SWAN had at least one lifetime impairing ADHD symptom on the telephone screening interview, indicating that most had a history of impairment from their ADHD symptoms. Therefore, we expect our estimates to be close to the true prevalence of DSM-IV ADHD (with consideration of impairment) in Missouri children. Reasonably consistent with our estimates, the United States Centers for Disease Control and Prevention (CDC) reported an ADHD prevalence of 10.8 percent for 4-to-17-year-old children in Missouri for the year 2007 based on parent-reported history of ADHD diagnosis (27), and an estimated 6.7 percent of Missouri 14-to-17-year-old children were taking medication for ADHD in 2007-2008 (28). It may also be argued that our method of ascertainment (large families) might limit the generalizability of this study. Although our sample is not subject to the referral bias that occurs with clinic-based samples, our sample was selected based on large family size and availability of parents for potential future genetic study. There is also the possibility that parents who have ADHD symptoms themselves might be less likely to return questionnaires. However, we found no evidence for selection bias based on ADHD diagnosis in this sample (21). The sample is also almost entirely Caucasian, so it is unclear whether the current findings are generalizable to individuals of other racial and ethnic backgrounds. Also, we were unable to control for socioeconomic factors since we did not have socioeconomic data regarding the study subjects.

ADHD subtypes are useful concepts in terms of understanding a child's symptoms and formulating appropriate educational plans and behavioral interventions. However, the requirement that a child meet a specific DSM-IV ADHD subtype category in order to be diagnosed and treated is not satisfactory. The current study suggests it may be important to consider both overall severity and relative contribution of inattentive vs. hyperactive-impulsive symptoms. Indeed, if only total severity is used, it is possible that some clinically impaired individuals with impairing inattentive-only symptoms might be missed. However if at

least 6 symptoms in one or the other symptom category is required, then clinically impaired individuals with just a few symptoms in each category (i.e., 5 inattentive plus 5 hyperactive-impulsive symptoms) may be missed. These individuals may be best identified by measures of total severity (i.e., a total symptom count or a quantitative symptom rating based on an instrument such as the SWAN).

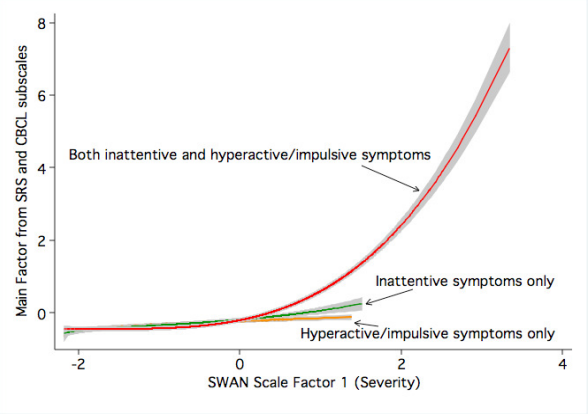

Figure 3. Plot of the first factor score from a factor analysis of SRS total score and CBCL subscores, against the first factor score for the 18 SWAN ADHD symptoms. The curves were built using fractional polynomials (shaded area: approximate 99% confidence interval) and indicate predicted mean SRS-CBCL factor score given the SWAN severity score. Three curves are shown, for individuals with zero hyperactive/impulsive symptoms (green), zero inattentive symptoms (orange), and at least one symptom of each category (red). Inasmuch as SWAN Factor 1 correlates very highly with the overall number of symptoms, this shows that, for the same number of symptoms, individuals who present with both inattentive and hyperactive/ impulsive symptoms tend to present with higher severity with respect to the SRS score and CBCL subscales.

In terms of clinical relevance, we found that children with mild to moderate ADHD symptoms may have different levels of co-occurring psychopathology depending on ADHD subtype, those with both inattentive and hyperactive-impulsive symptoms having the highest overall levels. Also, children and adolescents who have several ADHD symptoms but do not technically meet current ADHD criteria due to lack of 6 symptoms in one or the other symptom category should not be overlooked. In the DSM-IV context, such individuals could be given a diagnosis of ADHD Not Otherwise Specified (NOS) if they have clinically significant impairment from their ADHD symptoms. Proposed changes for DSM-5 include replacement of ADHD-NOS by a "Not Elsewhere Classified (NEC)" diagnosis which could be used to describe individuals who fail to meet the full ADHD criteria due to sub-threshold number of symptoms (20). It will be important for clinicians to consider using the new ADHD-NEC diagnosis for clinically impaired individuals who have approximately 6-10 total ADHD symptoms but less than six symptoms in each of the two symptom domains.

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Acknowledgements

This work is dedicated to Richard D. Todd, Ph.D., M.D., who initiated data collection for this project. Dr. Todd died from complications of leukemia August 22, 2008. This work was supported by award numbers R01-MH-067921 (PI-RDT, then AAT), R01-MH-083823 (PI-AAT), and K08-MH-080287 (PI-AMR) from the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIMH or the National Institutes of Health.