Are Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder Different Manifestations of One Overarching Disorder? Cognitive and Symptom Evidence From a Clinical and Population-Based Sample


Objective: Autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur. Given the heterogeneity of both disorders, several more homogeneous ASD–ADHD comorbidity subgroups may exist. The current study examined whether such subgroups exist, and whether their overlap or distinctiveness in associated comorbid symptoms and cognitive profiles gives support for a gradient overarching disorder hypothesis or a separate disorders hypothesis. Method: Latent class analysis was performed on Social Communication Questionnaire (SCQ) and Conners’ Parent Rating Scale (CPRS-R: L) data for 644 children and adolescents (5 through 17 years of age). Classes were compared for comorbid symptoms and cognitive profiles of motor speed and variability, executive functioning, attention, emotion recognition, and detail-focused processing style. Results: Latent class analysis revealed five classes: two without behavioral problems, one with only ADHD behavior, and two with both clinical symptom levels of ASD and ADHD but with one domain more prominent than the other (ADHD[+ASD] and ASD[+ADHD]). In accordance with the gradient overarching disorder hypothesis were the presence of an ADHD class without ASD symptoms and the absence of an ASD class without ADHD symptoms, as well as cognitive functioning of the simple ADHD class being less impaired than that of both comorbid classes. In conflict with this hypothesis was that there was some specificity of cognitive deficits across classes. Conclusions: The overlapping cognitive deficits may be used to further unravel the shared etiological underpinnings of ASD and ADHD, and the nonoverlapping deficits may indicate why some children develop ADHD despite their enhanced risk for ASD. The two subtypes of children with both ASD and ADHD behavior will most likely benefit from different clinical approaches. J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(11):1160–1172. Key Words: autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), latent class analysis (LCA), heterogeneity, cognition
ASD fall within the range of 30% to 80%, whereas the presence of ASD is estimated in 20% to 50% of the patients with ADHD. Features such as poor social skills, language delay, sensory oversensitivity, attention problems, oppositional defiant behavior, and emotion regulation problems are frequently disclosed in both ASD and ADHD. Furthermore, there is an increasing number of studies documenting various patterns of association between ASD and ADHD and an overlap between ASD and ADHD with respect to genetic factors and cognitive functions linked to a familial vulnerability for ASD and ADHD (intermediate phenotypes), such as in executive functioning, motor speed and variability, emotion recognition, and detail-focused processing. These findings suggest that there are shared etiological pathways for ASD and ADHD, and that patients with one of both disorders should be routinely checked for the presence of the other disorder. Furthermore, as the clinical presentation of both disorders is strongly influenced by age, this monitoring should occur on a regular basis.

Although the current psychiatric classification scheme prevents a diagnosis of ADHD in the context of ASD, based on the assumption that ASD mimics or even causes symptoms of ADHD, a comorbid diagnosis of ASD and ADHD can be made in the upcoming DSM-5. This is a significant step forward and will likely boost research on the shared and specific pathways related to comorbid ASD and ADHD. However, given that both separate disorders are rather heterogeneous in symptom presentation, associated cognitive deficits, and underlying etiological factors, it is likely that children with a comorbid diagnosis of ASD and ADHD form a very heterogeneous group as well. This might hinder both clinical interventions as well as scientific studies on the etiology of comorbid ASD and ADHD.

Identification of more homogeneous subgroups of patients with ASD as well as ADHD may be achieved using an empirical bottom-up approach, such as a latent class analysis (LCA). This statistical method allows classification into classes on the basis of type and severity of ASD and ADHD symptoms, composing mutually exclusive classes. By using quantitative symptom measures reflecting the nature and severity of ASD and ADHD symptoms, justice is done to the continuously distributed nature of symptoms of both ASD and ADHD within the population. This approach has already been successfully applied in the separate research fields of ASD and ADHD, and has with greater precision disclosed clinically relevant, more homogeneous subtypes of both disorders. Of great interest is the study of Reiersen et al. that examined ASD traits in several population-derived ADHD latent classes. Almost all classes (except one class that merely showed hyperactive symptoms) showed more ASD symptoms than the class without ADHD symptoms. However, among the various ADHD classes, the severity of ASD traits clearly differed, with the class having the most severe ADHD symptoms also displaying the most severe ASD symptoms. Using DSM-IV derived ADHD subtypes, less distinctions between the subtypes were present, with no significant difference between the ADHD predominantly inattentive subtype and the ADHD predominantly hyperactive-impulsive subtype. This study shows that empirically defined symptom classes may be more useful in examining comorbidity patterns across the continuum of symptom severity. However, since no previous study has used both ASD and ADHD symptom measures in a LCA, it is as yet unknown to what extent mutually exclusive ASD–ADHD classes can be identified.

By examining the overlap and distinctiveness of associated traits (such as comorbidity patterns and cognitive problems) between the various ASD–ADHD classes, several hypotheses can be tested. First of all, it has recently been postulated that ASD and ADHD are different manifestations of one overarching disorder (overarching disorder hypothesis [H1]). If true, symptomatic expression can be regarded as “noise,” and classes (if at all identified) will not show distinctiveness in associated traits. Second, a variant of this hypothesis states that ADHD may best be seen as a milder, less severe subtype within the ASD spectrum (gradient overarching disorder hypothesis [H2]). LCA will then identify at least one ADHD class without ASD symptoms, but no ASD class without ADHD symptoms, and all classes will show rather similar associated traits, with the lowest severity in the ADHD class without ASD symptoms and highest severity in the ASD with ADHD class. Alternatively, ASD and ADHD do not constitute different expressions of one overarching disorder. In this case, the LCA will identify at least some classes with pure ADHD or ASD symptoms. Furthermore, the classes will be more different than similar in...
terms of associated traits (distinct disorders hypothesis [H0]). Some previous studies using DSM-IV defined subgroups of patients support the gradient overarching disorder hypothesis, with ASD children having more severe but similar types of cognitive problems compared to children with ADHD.\(^{5,21-24}\) In contrast, there is also evidence for the (partly) distinct disorder hypothesis, with ASD children having cognitive problems that are qualitative different from those of children with ADHD.\(^{25-27}\) However, because these studies used DSM-IV defined (hence heterogeneous) groups of patients and because ADHD was not always assessed in children with ASD,\(^{7}\) group comparisons may have been significantly obscured.

Therefore, the current study set out to examine whether different ASD–ADHD homogeneous classes exist, and whether their overlap or distinctiveness in associated traits (comorbid symptoms such as oppositional behavior, emotional lability, anxiety, perfectionism, psychosomatic complaints, and cognitive profiles) gave support for the (gradient) overarching disorder hypotheses or for the (partly) separate disorders hypothesis. Continuous ASD and ADHD symptom questionnaire data was available for 644 children and adolescents between 5 and 17 years of age from a clinical and population-based sample. Given the distinct developmental characteristics of both disorders, the influence of age was taken into account. A large variety of cognitive domains was assessed, most robustly associated with ASD (e.g., identification of facial emotions, cognitive flexibility, and detail-focused processing) or ADHD (e.g., motor speed and variability, inhibition, verbal and visual attention, and verbal and visual–spatial working memory), as documented in previous studies.\(^{7,9-11}\) LCA was used to identify phenotypical homogeneous classes, and we examined to what extent overlap and specificity in comorbid symptoms and cognitive profiles existed between the classes.

**METHOD**

**Participants**

The study was approved by the Central Committee on Research involving Human Subjects (CCMO) and participants were enrolled between January 2009 and July 2011. Eligible participants were 370 children from a random population cohort study (Schoolkids Project Interrelating DNA and Endophenotype Research [SPIDER]) and 274 children from a clinical ASD-ADHD genetic study (Biological Origins of Autism [BOA]). The BOA cohort consisted of siblings, including DSM-IV–based ASD, ADHD and ASD+ADHD cases, and nonaffected siblings.\(^{28}\) All children and adolescents were between 5 and 17 years of age, of white ethnicity, and had an estimated total IQ of at least 70 on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale (WISC-III), or Wechsler Adult Intelligence Scale (WAIS-III).\(^{29,31}\) Exclusion criteria were epilepsy, known genetic or chromosomal disorders (such as Down syndrome), brain damage, and problems with vision or hearing. After complete description of the study to the parents, written informed consent was obtained.

**Measures**

ASD and ADHD symptom measures (parent reports) were taken from the Social Communication Questionnaire (SCQ, Lifetime version) and the Conners’ Parent Rating Scale—Revised: Long version (CPRS-R:L). The SCQ and the CPRS-R:L are both validated instruments for screening ASD and ADHD.\(^{32,33}\)

**Procedure**

The tasks described in Supplement 1 and Figure S1 (available online) were part of the broader neuropsychological assessment batteries used in the BOA and SPIDER projects. Children completed the battery in approximately 2 hours, and the order of task administration was counterbalanced. Because of time constraints, not all tasks were administered to all children. Full-Scale IQ was prorated by four subtests of the WPPSI, WISC-III, or WAIS-III;\(^ {28,31}\) Block Design, Picture Completion, Similarities, and either Vocabulary (BOA) or Arithmetic (SPIDER). These subtests are known to correlate between 0.90 and 0.95 with Full-Scale IQ.\(^ {34,35}\) Parents were invited to fill in several questionnaires concerning their youngster’s behavior.

**Data Analyses**

To identify homogeneous symptom classes, LCA was used on the raw subscale outcomes of the SCQ (Social Interaction, Communication and Stereotypic Behavior) and the t scores of the following 10 scales of the CPRS-R:L: Inattention, Restlessness, Cognitive Problems, Hyperactivity, Oppositional Behavior, Emotional Lability, Anxiety, Perfectionism and Psychosomatic Complaints. Subscales that represented the total of other subscales (Global Index Total) and subscales that restructured the items by DSM criteria (DSM-IV Inattention, DSM-IV Hyperactivity-Impulsivity, and DSM-IV Total) were excluded to prevent overrepresentation of these items. The LCA was carried out using Mplus version 6.11.\(^ {36}\) Both the probability for a child to belong to each of the classes and the conditional
probabilities for children in a particular class to show specific behavior were estimated. Children could be admitted to only one of the classes. Class differences with respect to sex, age, and IQ were analyzed to check for possible confounders. If differences were detected, only age was implemented as a covariate in further analyses on cognitive data, as both IQ and sex are inherently confounded with ASD and ADHD, and therefore could not be separated from the effects of the disorders.37 Class-by-age interaction effects were examined and, if significant, analyzed post hoc and reported. If nonsignificant, these interactions were dropped from the model. Next, mean factor sum scores of all behavioral domains were computed and were presented in a line chart, so that quantitative differences between classes could be examined. Size and significance of differences were determined with a multivariate analysis of variance (MANOVA), after which the Bonferroni correction for multiple testing was used for all post hoc comparisons.

Secondly, the underlying cognitive profiles of the classes were examined. All variables were successfully normalized and standardized into z scores by applying a Van der Waerden transformation (SPSS version 18).38 Effect sizes were defined in terms of percentage of variance explained ($\eta^2$). Small, medium and large effects were defined in variances of 0.01, 0.06, and 0.14 respectively.39 Some of the outcome measures were mirrored, so that the scores of all variables would imply the same: a higher z-score was indicative of a better performance. The classes were compared for each domain separately using analyses of covariance (ANCOVAs) with class membership as a fixed factor, age as a covariate and speed, accuracy or variability separately for each domain as dependent variable. Correction for multiple comparisons was applied according to the false discovery rate (FDR) controlling procedure to the analyses with a $p$ value setting of 0.05.40 Only the effects that remained significant after the FDR correction were reported.

RESULTS

Identifying Homogeneous Symptom Classes

The LCA was based on fit and accuracy measures and revealed a solution with five classes.41 Five classes had the best fitting BIC (126554) and SSA BIC (121572), $p$ values on the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test and Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (for both, $p = 0.003$). The behavioral profiles of the classes are presented in Figure 1. For the sake of clarity, the classes were labeled. Classes 1 and 2 could be viewed as normative groups, showing hardly any problems on the separate behavioral domains. Therefore, these classes were labeled “normal” ($n = 268$ and $n = 150$). Next, class 3 was best referred to as “ADHD,” with only ADHD behavioral problems ($n = 109$). Here, both DSM-IV–oriented CPRS subscales for

![FIGURE 1](image-url)
ADHD (inattentive and hyperactive-impulsive behavior) were above the clinical cut-offs, whereas the SCQ total score was substantially below the cut-off (Table 1). Classes 4 and 5 contained children who scored high on both ADHD (CPRS) as well as ASD symptoms (SCQ). In class 4, the ADHD symptoms were more prominent than the ASD symptoms, with CPRS subscales substantially above the cut-off, and a SCQ-total score slightly above the clinical cut-off (Table 1). Therefore, class 4 was described as “ADHD(+ASD)” (n = 58). In contrast, in class 5, ASD symptoms were more prominent than ADHD symptoms, with the SCQ total score being substantially above the clinical cut-off, the CPRS-Hyperactive-Impulsive subscale just above the cut-off, and the CPRS-Inattention subscale slightly below cut-off (Table 1). Therefore, class 5 was described as “ASD(+ADHD)” (n = 59). No class with only ASD behavior was identified.

A MANOVA using class as fixed factor and all behavioral domains as dependent variables revealed that, as expected, the five classes differed significantly on all behavioral subscales (for all, p < .001). Next, all classes were reciprocally compared on the separate behavioral domains using Bonferroni corrected post hoc comparisons. Only 14 of 130 comparisons did not reach significance. Roughly, the nonsignificant differences were between the ADHD-only class and the ASD(+ADHD) class on the ADHD-behavioral domains (Figure 1, middle), or on the comorbid behavioral domains, such as Anxiety and Perfectionism (Figure 1, right side). When corrected for the influence of age, no changes in differences between the classes were found. Comparisons between the two Normal classes (classes 1 and 2) were considered theoretically irrelevant. Hence, these classes were considered as one class in further analysis. To check whether this would affect further analyses in any possible way, both classes were compared on demographic characteristics as well as on all cognitive outcome measures.

None of those comparisons reached significance (for all, p > .05); classes 1 and 2 clearly differed only on a behavioral level, most likely ranging from normal to super-normal behavior but without meaningful cognitive differences. The distribution of all children across the distinct classes, as well as the sex, age, population, and IQ distributions are provided in Table 1.

Cognitive Profiles of the Distinct Classes
To test in which cognitive domains the classes overlapped or differed, separate ANCOVAs were used for each cognitive domain, with age as a covariate. Results are also presented in Figure 2. Baseline Speed and Variability. A significant but small effect of class was found for speed (F [3,611] = 4.91, p = .002, $\eta^2_p = 0.02$) and variability (F [3,611] = 3.41, p = .017, $\eta^2_p = 0.02$). Pairwise comparisons indicated that the ASD(+ADHD) class responded significantly slower and more variable than the normal class (p = .001 and p = .008, respectively). The ADHD-only and ADHD(+ASD) groups formed intermediate classes that did not differ from the other classes.

Identification of Facial Emotions. Significant medium and small effects of class were found for speed (F [3,379] = 7.52, p < .001, $\eta^2_p = 0.06$) and accuracy (F [3,379] = 5.39, p = .001, $\eta^2_p = .04$), respectively. Pairwise comparisons revealed that responses in the ASD(+ADHD) class were significantly slower and less accurate than the normal class (for both, p < .001) and significantly slower than the ADHD class (p = .001). The ADHD(+ASD) class was also slower than the normal class (p = .007), and formed an intermediate class that did not differ from the other classes regarding accuracy.

Inhibition and Cognitive Flexibility. No significant effect of class was found for speed or accuracy in motor inhibition (F [3,605] = 2.14, p = .09, $\eta^2_p = 0.01$ and F [3,605] = 0.92, p = .432, $\eta^2_p = 0.005$, respectively) or in cognitive flexibility (F [3,605] = 1.19, p = .31, $\eta^2_p = 0.006$ and F [3,605] = 0.60, p = .614, $\eta^2_p = 0.003$, respectively).

Visuo-Spatial and Verbal Attention. Small significant effects of class were found for accuracy in the forward trials for visuo-spatial attention [F [3,607] = 7.95, p < .001, $\eta^2_p = 0.04$] and verbal attention [F [3,623] = 10.04, p < .001, $\eta^2_p = 0.05$], respectively. Pairwise comparisons for the visuo-spatial task indicated that the ADHD(+ASD) class performed worse than the Normal class and ADHD-only class (p < .001 and p = .013, respectively) and the ASD(+ADHD) class performed worse in comparison to the normal class (p = .003). Furthermore, all classes performed worse than the normal class in the verbal attention task (p = .007 for the ADHD-class, p < .001 for the comorbid classes). Other group differences did not reach significance. A small but significant class by age interaction effect was found in the forward trials for visuo-spatial attention (F
children (F larger class differences in older than in younger compared to both comorbid classes, resulting in analyses indicated that the age effect was stronger in the normal and ADHD-only classes compared to both comorbid classes, resulting in larger class differences in older than in younger children (F [1,449] = 8.50, p = .004, $\eta_p^2 = .02$ for the normal class compared to the ASD [+ADHD] class, F [1,455] = 5.34, p = .021, $\eta_p^2 = .01$ for the normal class compared to the ADHD [+ASD] class, F [1,149] = 7.64, p = .006, $\eta_p^2 = .05$ for the ADHD class compared to the ASD [+ADHD] class, and F [1,155] = 4.09, p = .045, $\eta_p^2 = .03$ for the ADHD-only class compared to the ADHD [+ASD] class).  

**Visuo-Spatial and Verbal Working Memory.** Small but significant effects of class were found for accuracy in the backward trials for both visuo-spatial working memory (F [3,581] = 5.10, p = .002, $\eta_p^2 = 0.03$) and verbal working memory (F [3,623] = 5.68, p = .001, $\eta_p^2 = 0.03$). Pairwise comparisons indicated that in the visuo-spatial task, the ADHD (+ASD) class performed worse than the normal class (p < .001). In the verbal working memory task, the ADHD-class performed worse than the normal class (p < .001). The ASD (+ADHD) class formed an intermediate group that did not differ from the other classes regarding both visuo-spatial and verbal working memory. A small but significant class by age interaction effect was found in the backward trials for visuo-spatial working memory (F [3,581] = 5.37, p = .001, $\eta_p^2 = .03$). Post hoc analyses indicated that the effect of age was stronger in the normal class than in the three clinical classes, with larger class differences in older than in younger children (F [1,428] = 12.16, p = .001, $\eta_p^2 = .03$) and verbal working memory (F [3,623] = 5.68, p = .001, $\eta_p^2 = 0.03$).
5.19, \( p = .023, \eta^2 = 0.01 \) for the normal class compared to the ADHD(+ASD) class).

**Detail-Focused Processing Style.** A small but significant effect of class was found for accuracy (\( F_{[3,634]} = 6.93, p < .001, \eta^2 = 0.03 \)) (also when processing speed or IQ was implemented as a covariate; \( p < .001 \) and \( p = .003 \), respectively). Pairwise comparisons revealed that the ADHD(+ASD) class performed significantly worse compared to the normal class and the ASD(+ADHD) class (for both, \( p < .001 \)). The ADHD-only class formed an intermediate group.

**FIGURE 2** Differences between the classes on measures of baseline speed, the identification of facial emotions, inhibition, cognitive flexibility, attention, working memory, and detail-focused processing style. Note: (a) Baseline Speed: Group differences presented were based on a mean age of 9.9 years. (b) Identification of Facial Emotions: Group differences presented were based on a mean age of 10.2 years. (c) Motor Inhibition: Group differences presented were based on a mean age of 9.9 years. (d) Cognitive Flexibility: Group differences presented were based on a mean age of 9.9 years. (e) Attention: Group differences presented were based on a mean age of 9.9 years. (f) Working Memory: Group differences presented were based on a mean age of 9.9 years. (g) Detail-focused processing style: Group differences presented were based on a mean age of 9.9 years. Normal refers to the classes with no behavioral problems. Attention-deficit/hyperactivity disorder (ADHD) refers to the class with behavioral problems in ADHD only. ADHD(+ASD) refers to the children who most prominently show severe ADHD symptoms, but who also show autism spectrum disorder (ASD) symptoms. ASD(+ADHD) refers to the class with profound ASD symptoms, but who also show ADHD symptoms. The means are adjusted for the covariate age and error bars represent 1 standard error.
FIGURE 2 Continued

(c) ASD and ADHD in One Overarching Disorder?

(d) ASD and ADHD in One Overarching Disorder?

(e) ASD and ADHD in One Overarching Disorder?
that did not differ from any of the other groups. The ASD(+ADHD) class showed the highest score (although not significantly different from the normal class), indicating a detail-focused processing style. A small but significant class-by-age interaction effect was found for accuracy ($F_{[3,631]} = 4.83, p = .002, \eta^2_p = 0.02$). Post hoc analyses indicated that the effect of age was stronger in normal and ADHD-only classes compared to the ADHD(ASD) class, resulting in larger class differences in older than in younger children ($F_{[1,471]} = 14.84, p < .001, \eta^2_p = 0.03$ for the normal class compared to the ADHD[+ASD] class, and $F_{[1,163]} = 5.27, p = .023, \eta^2_p = 0.03$ for the ADHD-only class compared to the ADHD[+ASD] class).

**DISCUSSION**

This study examined whether different ASD-ADHD symptom classes exist and whether their overlap or distinctiveness in associated traits (comorbid symptoms and cognitive functions) gave support for the (gradient) overarching disorder hypothesis or for the (partly) distinct disorders hypothesis. If the gradient overarching disorder hypothesis is accurate, LCA would identify at least one ADHD class with no or only minor ASD symptoms and no ASD class without ADHD symptoms. This is exactly what we found. Three patient classes could be distinguished from two normal classes: one class with ADHD symptoms only, one class with clinical levels of ADHD but also clinically elevated levels of ASD symptoms (ADHD(+ASD)), and one class
with clinically high levels of ASD symptoms but also clinically elevated levels of ADHD symptoms (ASD(+ADHD)). As hypothesized, no class with exclusive ASD symptoms was revealed; all children who expressed ASD behavior also presented the less severe “precursor” of ADHD behavior. This finding is in accordance with the higher prevalence of children with ASD who meet criteria for ADHD (up to 80% in literature), compared to the ASD rate in children with ADHD (up to 50% in both the literature and our sample).3,4 These data are also in line with previous studies addressing ASD symptoms in children with ADHD, in which LCA revealed that the most severe ADHD classes were also the classes with the most severe ASD symptoms (however, note that these studies examined ASD symptoms in ADHD-defined classes, thereby excluding the possibility of finding ASD classes without ADHD symptoms).6,20

It may seem in contrast to the (gradient) overarching disorder hypothesis that the level of ADHD symptoms, as well as the level of oppositional and emotional lability symptoms, were significantly lower in the ASD(+ADHD) class compared to the ADHD(ASD) class. However, ADHD symptoms may actually lead to somewhat better ratings on social interaction in children with ASD, partly because of the increased talkativeness seen with ADHD. Furthermore, some forms of oppositional behavior may be more closely related to ADHD, whereas others may be more related to resistance to change (a feature typical of ASD), so the degree of ADHD and ASD symptoms may affect which aspects of ODD are most likely to be endorsed. Because of poor communication skills, symptoms of emotional lability may be more difficult to detect in children with higher ASD symptoms. Hence, lower ratings on emotional lability in the ASD (+ADHD) group may be partly explained because emotional lability goes undetected by the measures used. Based on the currently defined classes, the ADHD-only group was indeed the mildest-affected class within the spectrum, but no such severity distinction could be made between both comorbid ASD–ADHD classes; they appeared qualitatively different. As yet, no previous studies have examined the ADHD symptoms in ASD-defined classes to compare our findings with. The current novel findings suggest that at least two ASD–ADHD comorbidity classes exist that are not merely dissociable on a quantitative basis.

The cognitive profiles, on the one hand, further supported for the gradient overarching disorder hypothesis, but on the other hand possible support for the distinct disorder hypothesis emerged as well. That is, the cognitive functioning in the simple ADHD class could overall be considered at an intermediate level, performing somewhat below the normal class and better than the two comorbid classes. This was best visible in the domains of motor slowness and variability, visuo-spatial and verbal attention, and emotion recognition. However, qualitative differences were also clearly observed, which should perhaps not be too surprising, as ADHD and ASD are partly defined by specific cognitive problems (i.e., inattentiveness versus detail-focused processing, respectively). Working memory deficits were significantly more pronounced in both primarily ADHD classes compared to the primarily ASD class, and a detail-focused cognitive style (reflected in normal to superior block design performance) appears to be present in the ASD(+ADHD) class only. This apparent double dissociation between both comorbid classes suggests that dysfunctions in the information-processing style found in the ASD(+ADHD) class cannot be seen merely as the sum of dysfunctions in the ADHD-only and the ADHD (+ASD) classes. Apparently, different ASD–ADHD comorbid subtypes exists, with overlap but also qualitative difference in cognitive deficits. Similarly, recent studies comparing persons with ASD, ADHD, or ASD+ADHD to controls reported evidence for both specific as well as overarching deficits.24,25 In any case, our cognitive findings are in contrast to the hypothesis that ASD and ADHD are interchangeable manifestations of the same overarching disorder, and symptomatic expression can be regarded as “noise,” in which case no cognitive differences between the classes were predicted. The overlapping cognitive deficits may be used to further unravel the shared etiological underpinnings of ASD and ADHD, whereas the non-overlapping deficits may indicate why some children develop ADHD despite their enhanced risk for ASD and vice versa.

When specifically viewed at the individual cognitive domains, it is remarkable that response slowness and variability were most pronounced in the ASD(+ADHD) class and not observed in the ADHD-only class. Increased response variability is considered to be one of the most robust and best replicated cognitive features of ADHD as defined by the DSM nomenclature.42-44 Cur-
rent findings based on latent classes suggest that response variability in ADHD actually re-enacts the presence of comorbid disorders such as ASD, as has been reported previously.\textsuperscript{45} Noteworthy, verbal and visual attention were affected in all clinical classes. This finding may imply that a dysfunction in attention is indicative for neurodevelopmental disorders in general, unable to differentiate between ASD and ADHD, as has been reported before.\textsuperscript{3} In contrast, impaired social cognition is a substantially affirmed prime deficit specific for ASD.\textsuperscript{46} The severity of the deficit in social cognition was most pronounced in the ASD(+ADHD) class, followed by the ADHD(+ASD) class, but was not present in the ADHD-only class. Previous studies documenting on social cognition deficits in ADHD\textsuperscript{47-49} may therefore possibly be explained by elevated levels of ASD symptoms in these ADHD patients. Similarly, a local processing style, reflected by a normal to superior block pattern performance, was only apparent in the ASD(+ADHD) class and not in both primarily ADHD classes, which performed intermediately or more poorly than the normal and ASD(+ADHD) classes. This normal-to-superior performance clearly stands out against the background of poorer performance of this class on almost all other domains measured, and is in line with previous studies.\textsuperscript{26,50} Importantly, this feature was absent in the ADHD (+ASD) class, suggesting that the origins of the ASD symptoms in this class are at least partially different from the origins of the ASD symptoms in the ASD(+ADHD) class. Conversely, working memory deficits appeared mainly to be related to ADHD symptoms, being impaired in both ADHD classes but not to that degree in the ASD(+ADHD) class. However, given that there was no class with ASD symptoms only, it remains uncertain whether ASD symptoms are truly unrelated to working memory deficits. In any case, the strong relation between ADHD symptoms and working memory deficits concurs with previous studies\textsuperscript{24,25} and suggests that working memory performance may shed more light on the causal pathways for ADHD. None of the classes showed problems in inhibition or cognitive flexibility, which was probably because of the predictable nature of the task, in which children always had to respond. Previously, this same task also did not differentiate between ADHD and controls,\textsuperscript{51} suggesting that a more unpredictable nature of inhibitory control and cognitive flexibility may be more applicable in distin-

guishing patients from normally developing children.\textsuperscript{52} Finally, class differences between the normal class and severely affected classes on visuospatial attention, visuo-spatial working memory, and a detail-focused cognitive style were greater among older compared to younger children. This may suggest that, within the limitations of this cross-sectional design, children in the normal class improve certain skills more during maturation than children in the (severely) affected classes. However, this needs to be further analyzed with the help of a longitudinal research design.

Some limitations of this study warrant consideration. First, boys were overrepresented in the three affected classes, whereas they were underrepresented in the normal class. This was likely due to the fact that ASD and ADHD are more frequently diagnosed in boys than in girls.\textsuperscript{53} However, as this overrepresentation was present in all patient classes, this did not affect comparisons between those classes. Second, questionnaires were used to collect information on behavioral problems. In comparison with clinical interviews, questionnaires tend to overestimate the degree of comorbidity, as questionnaires do not allow for further explanation of questions. Interviews may improve the correct interpretation of questions, and more precisely distinguish normal-range behavior from clinical-range behavior.\textsuperscript{54} However, the possible comorbidity overestimation cannot account for the cognitive differences in the distinct classes, nor can it explain the presence of an ADHD-only class and the absence of an ASD-only class. Third, the nature of our samples might have prevented us from detecting a “pure ASD” class. ASD without ADHD symptoms might be underrepresented in clinical samples and may also be relatively rare in population samples. Therefore, very large population-based samples might be best to examine this issue further. Future studies in a purely population-based sample may be designed to include both cognitive and symptom measures in tandem in latent class analyses or related statistical approaches, to further increase the etiological homogeneity of the distinct classes. Fourth, children in the currently defined ADHD-only class were younger and also most mildly affected within the spectrum. It is of great interest whether a majority of these children have a childhood-limited form of ADHD, whereas the children in both comorbid ASD-ADHD classes may have more persistent
ADHD symptoms, thus setting new targets for a longitudinal research design.

REFERENCES


MEASURES

Four of the tasks described below were selected from the Amsterdam Neuropsychological Tasks (ANT) program. Each computer task contained an instruction trial in which the examiner provided a typical item of the task and a separate practice session. Test–retest reliability and validity of the computerized ANT tasks are satisfactory and have been described and illustrated elsewhere.

Baseline Speed and Variability

This task was used to measure the speed and variability of motor output, comparable to a simple reaction time task. When a fixation cross in the center of a computer screen changed into a white square, children pressed a key as quickly as possible (Figure S1a, available online). To prevent anticipation strategies, the time interval between a response and the emergence of the next square varied randomly between 500 and 2500 milliseconds. Dependent measures were response speed (mean reaction time in ms) and variability (SD of reaction time in milliseconds).

Identification of Facial Emotions

This task was used to measure the capacity to identify facial emotional expressions. Four blocks represented different target emotions: happiness, sadness, anger, or anxiety. Children had to judge whether a face expressed the specified target emotion by pressing a yes/no-button as quickly and accurately as possible (Figure S1b, available online). The order of the targeted emotions was randomly assigned. Dependent measures were mean reaction time and accuracy for all targeted emotions together.

Inhibition and Cognitive Flexibility

This task consisted of three blocks in which the first block measured baseline speed and accuracy. Children had to press a key as soon as they noticed a green circle on the left or the right of a fixation cross. They were instructed to press a key on the same side as the stimulus was presented (Figure S1c, available online). In the second block, the circles were colored red, and children had to press a key on the opposite side. Motor inhibition was calculated as the difference in percentage of errors or in mean reaction time between blocks one and two. Finally in the third block, both green and red circles appeared in a random order, and both same-side (compatible) and opposite side (incompatible) responses were required. This was hypothesized to demand higher levels of cognitive flexibility. Cognitive flexibility was calculated as the difference in percentage of errors or mean reaction time between block 1 and the compatible trials of block 3.

Visuo-Spatial and Verbal Attention

The forward parts of both the Visuo-Spatial Attention task and the Digit Span task of the the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale (WISC-III), or Wechsler Adult Intelligence Scale (WAIS-III) were used to obtain an indication of visuo-spatial and verbal attention. In the Visuo-Spatial Attention task, stimuli consisted of nine squares, presented in a three-by-three square (Figure S1d, available online). During each trial, a sequence of these squares was pointed at, and the children were instructed to exactly reproduce the sequence. In the Digit Span task, children had to repeat a sequence of verbally presented numbers. In both tasks, the difficulty level increased after each succeeded trial. Dependent variables were the total number of correct sequences in identical order, for both tasks separately.

Visuo-Spatial and Verbal Working Memory

The backward parts of the Visuo-Spatial Attention task and the Digit Span task were used to obtain an indication of working memory. Here, children were asked to reproduce the verbal and visuo-spatial sequences (such as described above) in backwards order (Figure S1d). Again, the sequence increased if a child reproduced the previous trial successfully. Dependent measures were the total number of correct sequences in backward order, for both tasks separately.

Detail-Focused Processing Style

The Block Design task of the WISC-III or WAIS-III was used to measure detail-focused (local) processing. Children had to copy geometric white-and-red designs using four to nine plastic cubes. All cubes had two completely white, two completely red and two diagonally white-and-red sides. Dependent measure was the score based on the amount of correct and timely completed geometric designs.
FIGURE S1  Examples of stimuli from the cognitive tasks. Note: a. Baseline speed and variability (fixation and signal). b. Facial emotion recognition. c. Inhibition and cognitive flexibility (left compatible and right compatible trials, left incompatible and right incompatible trials). d. Visuo-spatial attention and working memory.
REFERENCES