Social and Nonsocial Autism Symptom Domains in Children and Adolescents with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder: Insights into Their Symptomatological Interplay

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Keywords

Co-occurrence · Autism spectrum disorder · Attention-deficit/hyperactivity disorder · Autism Diagnostic Interview-Revised · Autism Diagnostic Observation Schedule · Differential diagnosis

Abstract

Introduction: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) share overlapping symptomatology, particularly with regard to social impairments (including peer relationship difficulties), and they frequently co-occur. However, the nature of their co-occurrence remains unclear. Therefore, the current study aimed to examine the nature of the transdiagnostic link between ASD and ADHD from a symptomatological point of view measured with the Autism Diagnostic Observation Schedule (ADOS Module 3) and the Autism Diagnostic Interview-Revised (ADI-R). **Methods:** We analyzed the social and nonsocial ASD symptom domain scores from both diagnostic instruments in 4 clinically referred groups (i.e., ASD, ADHD,

ASD + ADHD, and no psychiatric diagnosis) without other co-occurring mental disorders using a two-by-two full-factorial MANOVA design with the factors ASD (yes/no) and ADHD (yes/no). **Results:** We found no ASD by ADHD interaction effects across all symptom domain scores of ADOS and ADI-R, except for ADOS *imagination/creativity*. There were only main effects of the factor ASD but no main effects of ADHD. Follow-up contrasts showed that exclusively, ASD had an impact on the measured symptomatology in case of co-occurring ASD + ADHD. **Conclusion:** Overall, the results support an additive model of the symptomatology across areas of communication, social interaction, and stereotyped behaviors and restricted interests in case of the co-occurrence of ASD and ADHD when assessed with ADOS/ADI-R. Thus, one can assume that the phenotypic overlap of ASD + ADHD may be less complicated than suspected – at least with regard to ASD symptomatology – and that in the presence of ADHD, ASD symptomatology is generally well measurable with best-practice diagnostic instruments.

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Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are common, severely impairing neurodevelopmental disorders which typically onset in early childhood. Although the diagnostic criteria for the 2 disorders clearly point to distinct core symptom sets [1], diagnoses of ASD and ADHD frequently co-occur, and research suggests that there is overlap at the phenotypic level, for instance in clinical symptomatology that is shared by ASD and ADHD [2–4]. Specifically, while social impairments are a hallmark of individuals with ASD, children with ADHD also often exhibit social difficulties that resemble those seen in ASD, such as problems in relating to other people or inappropriate peer-related behaviors [5–10]. Consequently, differentiating between ASD and ADHD is apparently not a trivial undertaking in clinical practice, and the same applies to correctly classifying the co-occurrence of both disorders within the same individual.

Several studies and reviews have focused on the nature of the transdiagnostic link between the 2 conditions from different research perspectives, including genetics, cognition, neurobiology, and clinical symptomatology, but results and hence conclusions are rather mixed [11–13]. In terms of symptomatology, previous research showed that individuals with ASD + ADHD display greater ASD symptom severity than individuals with ASD or ADHD when simple pairwise comparisons are used [14–17]. However, other studies did not find such differences between individuals with ASD + ADHD and for instance those with ASD [10, 18]. Moreover, children with ADHD often present with elevated ASD ratings, particularly with regard to social communication difficulties [19, 20], even to the extent that many individuals could be false-positively categorized as ASD using the Autism Diagnostic Observation Schedule (ADOS) [21] and the Autism Diagnostic Interview-Revised (ADI-R) [22, 23].

Inconsistent findings across studies might be explained by differences in sample composition (e.g., age range, IQ level, gender ratio, or the presence of additional co-occurring mental disorders) or diagnostic procedures used (e.g., DSM vs. International Classification of Diseases [ICD], varying assessment instruments, and categorical vs. dimensional approach). However, they may also reflect methodological shortcomings, such as using only pairwise group comparisons (i.e., ASD vs. ASD + ADHD vs. ADHD) when investigating the co-occurrence of both conditions [24]. To overcome such shortcoming, it is necessary to apply appropriate statistical testing in the

form of a full-factorial design with 4 groups (ASD, ADHD, ASD + ADHD, and controls) enabling computations based on the factors ASD (yes/no) and ADHD (yes/no) and their potential interaction. To our knowledge, this has been done to date only by Tye and colleagues for investigating different cognitive functions [25–28], including emotional face and gaze processing, but not yet in terms of clinical ASD symptomatology.

Within a full-factorial design, the lack of an interaction effect between the 2 factors ASD and ADHD would support an additive model in which the co-occurrence of both diagnoses (i.e., ASD + ADHD) simply represents a combination of the 2 distinct pathologies. Such model suggests that the symptomatology of patients with ASD + ADHD is impacted by symptoms of ASD in addition to symptoms of ADHD (or vice versa) in a summative manner (for further explanation of additive effects see [29, 30]). By contrast, an interactive model (i.e., the presence of an interaction effect) would suggest that the co-occurrence of both diagnoses represents a separate nosological entity. In case that an additive model is supported, the relative contribution of the 2 factors ASD and ADHD to the symptomatology in the ASD + ADHD group could be further determined by follow-up contrasts [31].

Thus, the current study aimed at investigating social and nonsocial clinical symptomatology in 4 groups (i.e., ASD, ADHD, ASD + ADHD, and no psychiatric diagnosis [ND]) without other co-occurring mental disorders using a two-by-two full-factorial design with the factors ASD (yes/no) and ADHD (yes/no). Here, we focused on core ASD symptom domains since they are the most challenging in the differential and co-occurring diagnostic process [1], particularly the social difficulties seen in both groups (ASD and ADHD). More specifically, we aimed to clarify (i) whether the social and nonsocial clinical symptomatology assessed with best-practice ASD-specific diagnostic instruments (i.e., ADOS and ADI-R) fits with an additive or interactive model of the co-occurrence of ASD + ADHD and (ii) in case that an additive model is supported, which factor(s) (i.e., ASD and/or ADHD diagnosis) is/are related to the symptomatology scores on these instruments. Additionally, we calculated contrasts to (iii) specify the relative impact of the factor ASD and/or ADHD by direct comparison, e.g., the factor ASD adds more to the different ADOS/ADI-R domain scores than the factor ADHD. Considering the recent literature review on the topic by Antshel and Russo [11] and the work by Tye et al. [25–28], we expected to find an “additive” profile regarding ASD symptomatology in case of the co-occurrence of ASD and ADHD.

Table 1. Sample description

	ASD (<i>n</i> = 174)	ADHD (<i>n</i> = 37)	ASD + ADHD (<i>n</i> = 30)	ND (<i>n</i> = 33)	Group differences	
Age					<i>F</i> (3, 270)	<i>p</i> value
M (SD)	10.45 (2.59)	9.68 (2.29)	10.00 (2.03)	9.61 (2.33)	1.880	0.133
Min–max	5–17	6–15	6–14	6–15		
Gender, %					χ^2 (df = 3)	<i>p</i> value
Female	9.2	2.7	16.7	12.1	4.067	0.254
Male	90.8	97.3	83.3	87.9		
IQ*					<i>F</i> (3, 233)	<i>p</i> value
<i>n</i>	154	29	25	29	0.468	0.705
M (SD)	100.92 (19.08)	101.86 (19.34)	96.68 (17.78)	99.24 (15.93)		
Min–max	55–143	72–134	58–124	58–135		

N (total) = 274. ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; ASD + ADHD, co-occurrence of both diagnoses; ND, no psychiatric diagnosis; M, mean; SD, standard deviation; *n*, sample size; ID, intellectual disability. * Considering solely an IQ criterion of <70 as a cutoff for ID, there was the following proportion of ID per group: ADHD (2.8%), ASD (3.8%), ASD + ADHD (11.5%), and ND (3.4%), with no significant differences between groups (*p* = 0.29).

Materials and Methods

Sample

Our sample, including the youth without a psychiatric diagnosis (ND), was derived from a large database of individuals referred to specialized outpatient clinics for children and adolescents and/or adults with ASD. The database was created by 4 of the leading ASD research groups in Germany (Marburg, Dresden, Berlin, and Mannheim) as part of the ASD-Net consortium [32]. It includes 2,453 patients (age in years: $M = 13.56 \pm 10.61$; min = 18 months; max = 72 years; 16.8% female), who were referred with suspected ASD to one of the 4 outpatient clinics. All participants were diagnosed according to the ICD-10 [33], using “gold-standard” best-estimate clinical (BEC) diagnoses [23]. BEC diagnosis was determined by at least 2 experienced clinicians from a multidisciplinary team (which included psychologists and/or psychiatrists) after extensive examination and review of all available information from a patient’s medical record. Medical records included IQ, neuropsychological testing, questionnaires, reports from other institutions, school reports, home videos, ADOS [21], ADI-R [22], and a differential/co-occurring diagnoses algorithm performed by an experienced clinician. Both ADOS and ADI-R were conducted by clinically trained team members at each center who were all licensed to do so.

For the purpose of the current study, our sample was selected according to the following criteria: (i) referred for a clinical ASD diagnostic assessment, (ii) complete data of ADOS Module 3 (ADOS-M3) and ADI-R, (iii) age of 4–18 years, (iv) verbally fluent, (v) BEC diagnosis of ASD (F84.0, F84.1, or F84.5) but no ADHD, (vi) BEC diagnosis of ADHD (all subtypes F90.0 or F98.8) but no ASD, (vii) co-occurring ASD + ADHD, and (viii) no psychiatric diagnosis (ND). The patients with ASD, ADHD, and ASD + ADHD had no other psychiatric diagnoses. To keep the sample representative of the common population in ASD specialty clinics, there were no exclusion criteria regarding IQ or gender. This resulted in a sample of *n* = 274 individuals (age in years: $M = 10.20$

± 2.48 , min = 5, max = 17; 10% female), including *n* = 174 patients with ASD, *n* = 37 with ADHD, *n* = 30 with ASD + ADHD, and *n* = 33 with ND. The 4 groups did not differ in age (*p* = 0.133), IQ (*p* = 0.705), or gender distribution (*p* = 0.254; see Table 1).

Measures

Our analyses included the domain scores of the so-called gold-standard instruments in diagnosing ASD: ADOS [21, 34] and ADI-R [35, 36]. Both are based on ASD criteria of ICD-10 [33] and DSM-IV-TR [37] and can be used to obtain information about ASD symptoms across different behavioral domains.

The ADOS is a well-established, standardized, semi-structured observational instrument. It consists of 4 modules whose application depends on the patient’s expressive language and developmental levels. The current analyses focused on ADOS-M3, which is used for verbally fluent children and adolescents, and it evaluates language and communication, reciprocal social interaction (SI), play/imagination, and stereotyped behaviors and restricted interests (RRB). The ADOS-M3 contains a set of standardized scenarios that an ADOS-trained clinician walks through with the patient. Afterward, the patient’s behavior is rated on 28 items. These item codes are converted according to the ADOS manual so that each item is rated on a 3-point scale from 0 = no abnormality to 2 = moderate to severe abnormality. The ADOS-M3 yields 4 domain scores, which are the sum of certain of the 28 items: communication (Com), SI, imagination/creativity, RRB, and a total score (sum of the domain scores Com and SI) [21, 34, 38]. Other abnormal behaviors (section E of the ADOS-M3) were not included as no domain score can be built. For the German version [38] found adequate internal consistency, sensitivity, and specificity.

The ADI-R is a semi-structured parent interview with 93 items on ASD symptoms covering lifetime and early-childhood behavior. The items are rated by a trained clinician and converted according to the ADI-R manual so that each item is rated on a 3-point scale from 0 = no abnormality to 2 = moderate to severe abnormality. The ADI-R yields 4 domain scores, created from subsets of the

Table 2. ADOS-M3 2 × 2 ANOVA for the factors ASD and ADHD

ADOS domains	ASD (<i>n</i> = 174) M (SD)	ADHD (<i>n</i> = 37) M (SD)	ASD + ADHD (<i>n</i> = 30) M (SD)	ND (<i>n</i> = 33) M (SD)	ANOVA <i>F</i> (1, 270) with (η^2)					
					ASD		ADHD		ASD × ADHD	
Com	3.88 (1.71)	1.16 (1.17)	3.87 (2.10)	1.91 (1.63)	79.928 ***	(0.228)	2.110 (0.008)	1.972 (0.007)		
SI	7.83 (2.71)	3.49 (2.56)	8.60 (2.69)	3.70 (2.87)	120.852 ***	(0.309)	0.447 (0.002)	1.366 (0.005)		
Total score (Com + SI)	11.71 (3.93)	4.65 (3.51)	12.47 (4.55)	5.61 (4.12)	127.426 ***	(0.321)	0.026 (0.000)	1.939 (0.007)		
Imagination/creativity	1.14 (0.75)	0.62 (0.59)	1.30 (0.84)	0.94 (0.70)	14.915 ***	(0.052)	0.499 (0.002)	4.303 *	(0.016)	
RRB	1.09 (1.25)	0.32 (0.53)	1.03 (1.43)	0.48 (0.80)	13.556 ***	(0.048)	0.376 (0.001)	0.081 (0.000)		

Effects are from 2 × 2 ANOVA with ASD (yes/no) and ADHD (yes/no) as factors. ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; ASD + ADHD, co-occurrence of both diagnoses; ND, no psychiatric diagnosis; RRB, stereotyped behaviors and restricted interests; M, mean; SD, standard deviation; *n*, sample size; η^2 , eta square for effect size; SI, social interaction; Com, communication; ADOS-M3, Autism Diagnostic Observation Schedule Module 3. *** $p < 0.001$. * $p < 0.05$.

Table 3. ADOS-M3 – comparison of the main factors

ADOS domains	Contrast score	<i>t</i> (270)		Factor comparison ^a
Com	2.72	8.913 ***		ASD > ADHD
SI	4.34	8.854 ***		ASD > ADHD
Total score (Com + SI)	7.06	9.818 ***		ASD > ADHD
Imagination/creativity ^b	–	–		–
RRB	0.77	3.683 ***		ASD > ADHD

ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; ASD + ADHD, co-occurrence of both diagnoses; ND, no psychiatric diagnosis; RRB, stereotyped behaviors and restricted interests; SI, social interaction; Com, communication; ADOS-M3, Autism Diagnostic Observation Schedule Module 3. *** $p < 0.001$. ^a The calculation was performed on the assumption that the difference in the sum of mean values from the ADOS subscales between children with or without ASD disorder does not deviate from the difference in the sum of mean values in children with or without ADHD ([ASD/ADHD + ASD] – [ADHD + Control] = [ASD/ADHD + ADHD] – [ASD + control]). After solving the equations, the following contrast weights resulted: ND, 0; ASD, 1; ADHD, –1 and ASD/ADHD, 0. ^b Contrasts could not be computed due to the significant interaction in the ANOVA (Table 2).

93 items: Com, SI, RRB, and abnormality of development evident at or before 36 months of life. The last domain was not considered in this study due to many missing values. The interrater reliability of the domain SI was reported to be $r_{\text{kw}} = 0.75$; for Com, $r_{\text{kw}} = 0.77$; and for RRB, $r_{\text{kw}} = 0.80$ [38, 39]. The internal consistency was reported to be $\alpha = 0.91$ for the domain SI, $\alpha = 0.83$ for Com, and $\alpha = 0.64$ for the domain RRB [38].

Data Analysis

The domain scores of ADOS and ADI-R were analyzed using two-way MANOVAs, followed by univariate ANOVAs with the between-subject factors ASD (yes/no) and ADHD (yes/no). A possible additive model of ASD and ADHD would be supported by the absence of an interaction effect. In such case, contrasts were calculated to compare the contribution of the 2 factors to the ASD symptomatology when ASD and ADHD co-occur. The calculations were computed on the assumption that the difference in the sum of mean values from the ADOS and ADI-R domain scores

between children and adolescents with or without ASD does not deviate from the difference in the sum of mean values in those with or without ADHD ([ASD + ADHD + ASD] – [ADHD + ND] = [ASD + ADHD + ADHD] – [(ASD + ND)]). The equation results in the following contrast weights: ND = 0; ASD = 1; ADHD = –1; and ASD + ADHD = 0 [31]. All analyses were computed with SPSS (IBM SPSS Statistics, Version 25) using a significance level of 5%.

Results

ADOS

The 2 × 2 MANOVA revealed no overall interaction effect between the factors ASD (yes/no) and ADHD (yes/no) across all 5 ADOS domain scores. There was however a main effect of ASD ($F(4, 267) = 31.916$; $p < 0.001$;

Fig. 1. ADOS and ADI-R symptom domain scores. See main text for results. Means and SEMs are given. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; ASD + ADHD, co-occurrence of both diagnoses; ND, no psychiatric disorder; RRB, stereotyped behaviors and restricted interests; ADOS, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview-Revised.

partial $\eta^2 = 0.323$) but not of ADHD ($p = 0.140$). Table 2 shows the follow-up 2×2 univariate ANOVAs, confirming the main effects for the factor ASD on each of the ADOS domains. As expected, no main effects were found for the factor ADHD (all $p > 0.147$). To further specify the impact of ASD and/or ADHD on each of the ADOS domains, additional contrasts were calculated, except for the domain *imagination/creativity* due to the significant interaction effect ($p = 0.039$) which points to a lack of an additive model with regard to this symptom domain (Fig. 1). Note however that this interaction effect would not survive correction for multiple comparisons. Table 3 shows that the factor ASD had indeed stronger impact than that of ADHD on all ADOS domains.

ADI-R

The 2×2 MANOVA revealed no overall interaction effect between the factors ASD and ADHD across all ADI-R domain scores ($p = 0.757$). Similar to the ADOS

domains, there was a main effect of ASD ($F(3, 268) = 20.088$; $p < 0.001$; partial $\eta^2 = 0.184$) but not of ADHD ($p = 0.555$). Table 4 shows the follow-up 2×2 univariate ANOVAs, confirming the main effects for the factor ASD on the 3 analyzed ADI-R domains. No effects for the factor ADHD (all $p > 0.571$) or interaction effects (all $p > 0.253$) were found (Table 4). The calculated contrasts showed again that the factor ASD was more strongly related to all ADI-R domains than the factor ADHD (Table 5).

Discussion

The main objective of this study was to determine the extent to which the co-occurrence of ASD and ADHD impacts on social and nonsocial clinical symptomatology as assessed with best-practice ASD-specific diagnostic instruments among clinically referred children and adoles-

Table 4. ADI-R 2 × 2 ANOVA for the factors ASD and ADHD

ADI-R domains	ASD (<i>n</i> = 174) M (SD)	ADHD (<i>n</i> = 37) M (SD)	ASD + ADHD (<i>n</i> = 30) M (SD)	ND (<i>n</i> = 33) M (SD)	ANOVA <i>F</i> (1, 270) with (η^2)					
					ASD		ADHD		ASD × ADHD	
SI	16.43 (6.00)	9.38 (6.28)	16.10 (5.76)	10.03 (6.88)	47.685 ***	(0.150)	0.268	(0.001)	0.029	(0.000)
Com	12.45 (5.27)	6.92 (4.12)	11.13 (4.27)	7.36 (4.72)	36.390 ***	(0.119)	1.310	(0.005)	0.323	(0.001)
RRB	4.31 (2.47)	2.16 (1.68)	4.40 (2.87)	2.15 (1.62)	36.586 ***	(0.119)	0.019	(0.000)	0.012	(0.000)

Effects are from 2 × 2 ANOVA with ASD (yes/no) and ADHD (yes/no) as factors. ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; ASD + ADHD, co-occurrence of both diagnoses; ND, no psychiatric diagnosis; RRB, stereotyped behaviors and restricted interests; M, mean; SD, standard deviation; *n*, sample size; η^2 , eta square for effect size; ADI-R, Autism Diagnostic Interview-Revised; SI, social interaction; Com, communication. *** *p* < 0.001.

Table 5. ADI-R – comparison of the main factors

ADI-R domains	Contrast score	<i>t</i> (270)	Factor comparison ^a
SI	7.05	6.365 ***	ASD > ADHD
Com	5.54	6.155 ***	ASD > ADHD
RRB	2.15	5.069 ***	ASD > ADHD

ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; ASD + ADHD, co-occurrence of both diagnoses; ND, no psychiatric diagnosis; RRB, stereotyped behaviors and restricted interests; ADI-R, Autism Diagnostic Interview-Revised; SI, social interaction; Com, communication. *** *p* < 0.001. ^a The calculation was performed on the assumption that the difference in the sum of mean values from the ADOS subscales between children with or without ASD disorder does not deviate from the difference in the sum of mean values in children with or without ADHD ([ASD/ADHD + ASD] – [ADHD + Control] = [ASD/ADHD + ADHD] – [ASD + control]). After solving the equations, the following contrast weights resulted: ND, 0; ASD, 1; ADHD, –1; and ASD/ADHD, 0.

cents using a full-factorial group design. To do so, we assessed and compared children and adolescents of 4 groups (i.e., ASD, ADHD, ASD + ADHD, and ND) who had no additional psychiatric diagnoses. While the groups did not differ in age, gender, and IQ, they differed in their expression across most of the ASD symptom domains measured with ADOS and ADI-R. Notably, we found no interaction effect for the factors ASD and ADHD, except for the domain *imagination/creativity* on the ADOS. Thus, overall, our findings would rather support an additive model for ASD-like symptomatology in case of the co-occurrence of ASD and ADHD.

Varieties of models exist to explain the co-occurrence of psychiatric disorders, such as ASD + ADHD, but only

very few of such models have been sufficiently tested so far [29]. Therefore, existing findings have led some authors to suggest that it might be near impossible to determine whether ASD symptoms in ADHD represent ADHD, co-occurring ASD or even a completely separate disorder [40, 41]. However, a recent literature review on the topic concludes that the co-occurrence of ASD and ADHD indicates an “additive” profile of the 2 conditions [11]. Interestingly, the review did not include the work by Tye and colleagues who used a two-by-two factorial design (ASD yes/no; ADHD yes/no) in a small sample of boys (8–13 years) investigating face/gaze processing [27], emotion processing [28], executive functions [25], and response time variability [26]. While the authors found distinct abnormalities for ASD as well as ADHD across these different cognitive domains, they did not reveal any significant interaction effects between ADHD and ASD diagnosis on these measures, suggesting an additive co-occurrence of the unique disorders. Thus, our phenotypic data corroborate and extend the existing literature in support of an additive model regarding ASD-like symptomatology in children and adolescents with ASD + ADHD.

The follow-up contrasts that we calculated to specify the impact of the factor ASD and the factor ADHD in case of co-occurrence showed that exclusively the factor ASD contributed to the clinical symptomatology assessed by ADOS and ADI-R. The factor ADHD had no impact. That is not entirely surprising given that ADOS and ADI-R have been developed specifically for assessing ASD symptomatology, and this should result in higher symptom scores among individuals with ASD than those with ADHD. However, previous studies have clearly shown that ADHD groups may exhibit ASD-like symptoms and SI and Com impairments, like peer relationship problems

[4], and they could even meet ASD cutoffs on the ADOS and ADI-R [23]. The other way around, a co-occurring ADHD diagnosis or elevated ADHD-like symptoms can aggravate maladaptive behavior in individuals with ASD, resulting in a higher autistic trait and externalizing problems [17]. Taken together, these findings highlight that social difficulties are not unique to ASD but should also be recognized as being part of the ADHD condition. Interestingly, a recent meta-analysis suggests that diagnostic subtypes of ADHD may differ with regard to their social difficulties [42]. While children with the combined type of ADHD are significantly more impaired than groups with predominantly inattentive or hyperactive/impulsive symptoms in overall social functioning, prosocial behavior, and peer relationships (i.e., disliked by others), children with the inattentive type show higher levels of shy and passive social behavior than the combined type.

The finding of higher ASD symptom domain scores in both groups with ASD (ASD and ASD + ADHD) than those in the 2 groups without ASD (ADHD and ND) is in line with some of the previous findings that are based on pairwise group comparisons [10, 23]. However, results on (no) differences regarding ASD symptomatology between ASD and ASD + ADHD are still rather mixed. In line with our findings here, Yerys and colleagues [17], for example, found no phenotypic differences between ASD and ASD + ADHD when measured with ADOS and ADI-R. Yet their groups differed on other instruments, such as the Social Responsiveness Scale, with the ASD + ADHD group having more ASD symptoms than those of the pure ASD group [17]. Others found higher ASD severity scores in individuals with ASD + ADHD than those with ASD across different domains measured with the ADI-R but not with ADOS [10, 15, 16]. These inconsistent findings are likely caused by not only the heterogeneous nature of clinical samples in general but also by various study-related differences, like inclusion/exclusion of (other) co-occurring disorders, definition of ADHD status (e.g., elevated symptoms vs. clinical diagnosis), patients' age range, or ASD assessment instruments used (e.g., screening questionnaires vs. ADOS/ADI-R, incl. different ADOS modules). This highlights once again that methodological differences and potential shortcomings clearly limit the comparability between studies and thus replication of findings, precluding firm conclusions.

The findings of the current study should be interpreted in light of some limitations. First, while our study sample stems from a large database of individuals referred to specialized outpatient clinics for ASD, we were only able

to include relatively few female patients. Although the prevalence of ASD and ADHD is considerably lower in girls than boys, the present findings might not fully apply to female patients. Thus, future work should focus more strongly on differences and similarities in symptom expression in ASD, ADHD, and the co-occurrence of both conditions, specifically in female patients who are still underrepresented in this line of research [43]. Second, our ND group was recruited via the outpatient clinics too, which may have biased our findings to some extent. Notably, as shown in Figure 1, the ND group was not entirely free of ASD symptoms and scored at least numerically higher on most of the ASD symptom domains than the ADHD group. As such, this group is not representative for typically developing children. Third, we restricted our analyses to participants who completed the ADOS-M3 (i.e., nonverbal individuals were not included) and who were free of other co-occurring psychiatric diagnoses. Thus, our sample was deliberately preselected, which limits its representativeness. Fourth, it has to be considered that the present data are based on the ADOS but not the more recent ADOS-2 manual [44]. This is because data collection spanned across a relatively long time period, dating back to when the German version of the ADOS-2 was not yet available. Therefore, our results cannot easily be generalized to DSM-5 criteria. Fifth, we did not include ADHD symptoms in our analyses that are considered to be core to the ADHD diagnosis as ADHD-related clinical data were not available for the entire sample. Thus, follow-up studies should preferably utilize additional assessment instruments for ADHD-specific symptomatology and also extend the research focus on other relevant (e.g., etiological) factors, including neurobiological and neurocognitive parameters [13], as well as investigate different ADHD subtypes [42]. It should also be noted that our ADHD group represents a preselected and less representative subsample of patients with ADHD as this group consisted of children who were seen in outpatient clinics for ASD due to ASD concerns by their parents. The data for the present study were obtained during routine clinical evaluations at ASD specialty clinics using "gold-standard" ASD diagnostic instruments, such as ADOS and ADI-R. In this context, the co-occurrence of ASD and ADHD arises particularly frequently and in many complex cases. Using ADOS and ADI-R, clinicians are able to detect ASD-like symptomatology in ADHD patients, including social communication and peer relationship problems [23]; therefore, this assessment approach is of high ecological and economic advantage as it is a pragmatic one. Moreover, since we recruited a clinical

rather than a research population, this study sample is unique and likely most relevant to practitioners. Nevertheless, the symptomatological data at hand provide only information at the on-average group level but is less informative for the (differential) diagnostic process on an individual case-by-case basis, which would be ideal in the context of personalized medicine.

In conclusion, the current study investigated the co-occurrence of ASD and ADHD from a symptomatological perspective measured with the “gold-standard” instruments for assessing ASD in clinical practice. We provide further evidence in support of an additive model for this co-occurrence with regard to the core ASD symptom domains. Hence, clinically, ASD + ADHD should not be seen necessarily as a separate subgroup or subtype, and therefore, one can assume that the phenotypic overlap in the ASD + ADHD group is probably less complicated than suspected. As mentioned above, while even in the presence of ADHD, ASD-like symptoms, including social deficits, are on average well measurable with ADOS and ADI-R; ADHD (co-occurring or differential) should still be evaluated with ADHD-specific instruments. Notably, individuals referred to outpatient clinics specialized for ASD are not routinely screened for ADHD as part of the evaluation procedure, which is largely due to pragmatic considerations (e.g., financial and personnel resources or time resources of patient and families). Therefore, one can contemplate developing an ADHD screening score based on ADOS/ADI-R to guide the decision-making about the additional effort of evaluating a patient also for ADHD not only clinically but also data-driven. Finally, the sensitivity and specificity of both ADOS and ADI-R for diagnosing ASD in case of maximal bias due to co-occurring ADHD should be examined to substantiate our findings from another perspective.

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Statement of Ethics

The study was carried out in accordance with the recommendations of good clinical practice and in accordance with the Declaration of Helsinki and national legislation. This study protocol was reviewed and approved by the Ethics Committee of the Charité Berlin, approval number EA4/129/19. Written informed consent was not required for this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.T.M. analyzed the data, prepared the tables and figures, and drafted the manuscript. V.R. and A.B. conceived the study, revised the manuscript, and assisted in statistical methodology. N.W., S.S., L.P., and I.K.-B. provided data for the study and revised the manuscript. G.K. contributed to revising the manuscript. All the authors read, commented on drafts of the paper, and approved the final manuscript and its submission.

Data Availability Statement

The datasets generated for this study are available on reasonable request in line with the data sharing policy of the ASD-Net consortium.

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