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Clinical characteristics of children with ASD and comorbid ADHD: association with social impairment and externalizing and internalizing behaviours

AUTHOR NOTE

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Author Contributions

FD and LAT conceived the study, contributed to the collection, analysis, and interpretation of the data, and drafted the manuscript. AB is the PI of the ELENA cohort and also participated in the design of the current study, drafted the work, and critically revised it for the principal intellectual content. CM analysed and interpreted the data. All authors read and approved the final version to be published.

Declarations

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Conflict of Interest

The authors have no conflict of interest to declare.

Ethical Approval

The study and informed consent procedure have been approved by the Ethics Committee on the Research of Human Subjects at Marseille Mediterranean and the National Commission for Computing and Liberties (CNIL. number DR-2015-393).

Informed Consent

Signed informed consent is obtained from all participating families.

1 **Clinical characteristics of children with ASD and comorbid ADHD: association with**
2 **social impairment and externalizing and internalizing behaviours**

3
4 **Highlights**

5 - Children with neurodevelopmental disorder presented a higher level of social impairment and
6 externalizing/internalizing behaviours than typically developing children.

7 - Internalizing behaviours were more often associated with ASD severity and externalizing behaviours with
8 ADHD severity.

9 - Our results stress the importance of checking for comorbidities during the diagnosis of ASD or ADHD and to
10 take into account such comorbidities in the intervention plan.

11 **Abstract**

12 Background

13 Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are frequently occurring
14 conditions that are often associated (ASD+ADHD). However, there are few comparative studies concerning the
15 clinical presentation in patients formally diagnosed with both ASD and ADHD. Here, we aimed to 1) compare
16 social impairment and externalizing/internalizing behavioural problems across four groups of children:
17 ASD+ADHD, ASD alone, ADHD alone, and typical development and 2) examine their bidirectional relationship
18 with ASD and/or ADHD symptoms.

19 Methods

20 This study included 186 participants from 6 to 12 years of age: single ASD ($n = 98$), ASD+ADHD ($n = 29$),
21 single ADHD ($n = 28$), and TD ($n = 31$).

22 Results

1 The results showed that children in the ASD+ADHD and single ASD groups had a higher level of social
2 impairment than those in the single ADHD group. In addition, children in the single ADHD group presented a
3 greater attention deficit than those in the single ASD group. Externalizing /internalizing behaviours were more
4 frequent in all groups with neuro-developmental disorders than in typical development. In addition, externalizing
5 behavioural problems were related to ADHD severity in the ASD+ADHD and single ADHD groups, whereas
6 internalizing behaviours were related to ASD severity.

7 Conclusions

8 These findings highlight the specific needs of children who have both ASD and ADHD and underscore the
9 necessity of individualizing their interventions.

10

What this paper adds?

11 The present study focused on the comorbidity between autism spectrum disorder and attention deficit
12 hyperactivity disorder. This condition remain not much explore in literature because the co-existing diagnosis is
13 only possible since the publication of the DSM-5, in 2013. Our study, based on a population with a reliable
14 diagnostic of ASD+ADHD, showed that additional comorbidities, such as internalizing/externalizing behaviours
15 or social impairments, are frequent in neurodevelopmental disorder (NDD), which tend to complex clinical
16 profiles and interventions aims'. In particular, internalizing behaviours were more often associated with ASD
17 severity and externalizing behaviours with ADHD severity. This underlies the necessity of searching for the
18 presence of comorbidities during the diagnosis of NDD.

19

Keywords

20 autism spectrum disorders, attention deficit disorder, comorbidities, children, social impairments.

21

1. Introduction

Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are frequently occurring comorbid conditions, but their association has only recently been recognized in medical classification through the DSM-5 (American Psychiatric Association, 2013). The prevalence rates of comorbid ADHD symptoms in ASD range from 37 to 85%, suggesting that ADHD is the most frequent comorbid condition in ASD (Lecavalier et al., 2019; Murray, 2010; Simonoff et al., 2008; van der Meer et al., 2012). ASD with comorbid ADHD is more frequently found in males, with the sex ratio being 3:1 in single ADHD and 4:1 in single ASD (Fombonne, 2009; Kern et al., 2015). Moreover, it has been reported that individuals with ASD and comorbid ADHD (ASD+ADHD) have more severe ASD symptoms, lower intellectual functioning, and more psychiatric comorbidities than individuals with single ASD alone (Craig et al., 2015; Jang et al., 2013; Yamawaki et al., 2020). Thus, the association of ASD and ADHD could worsen the developmental course of such children, making it important to investigate their clinical characteristics and behaviours.

Social communication deficits in ASD cover deficits in socio-emotional reciprocity and nonverbal communication used for social interaction and developing, maintaining, and understanding relationships (American Psychiatric Association, 2013). Such deficits, generally typical of ASD, are also observed in ADHD, in which individuals are faced with social problems as they encounter global interpersonal difficulties with peers, parents, and siblings (Greene et al., 2001). Although studies concerning social impairment in ADHD are more limited than those on ASD, several have reported comparable social deficits in the two conditions. Rommelse et al. (2018) emphasized that social difficulties are common in both conditions from the early stages of development and that this clinical dimension cannot allow a differential diagnosis. Individuals with ASD and those with ADHD share the same social deficits and both have difficulties in social interactions with peers (Kern et al., 2015) and poor socialisation skills (Avni et al., 2018). Studies comparing individuals with ASD+ADHD to those with a single diagnosis have suggested greater impairment in their social adaptation (Avni et al., 2018). Several studies found specific social impairment in children with ASD+ADHD, including greater social communication deficits, problems with social awareness (Factor et al., 2017), and social behavioural challenges (McVey et al., 2018). In her review, Leitner et al. (2014) highlighted that psychosocial problems are more prevalent in children with ASD+ADHD, regardless of the behavioural dimensions that were examined. However, these findings are difficult to generalize because there was significant disparity in the assessment of social impairments across the reviewed studies. Although there is evidence that children with ASD+ADHD

1 show greater social impairment than children with a single-diagnosis, there is no consensus concerning the
2 determinants of such results. One hypothesis is that social impairment, generally attributed to ASD, may be
3 greater in cases of comorbid ADHD due to attention deficit-related symptoms and low verbal intellectual
4 quotient (Sokolova et al., 2017), as well as by shared theory of mind's deficits (Kern et al., 2015; Leitner, 2014)
5 and associated anxiety (McVey et al., 2018). In parallel, studies focusing on social difficulties in children with
6 ADHD have emphasized that they may be due to ASD-related symptoms and not only ADHD symptoms
7 (Grzadzinski et al., 2011). One limitation of these studies is that children with ASD had comorbid ADHD traits
8 and no ascertained diagnosis of ADHD.

9 The high prevalence of externalizing behaviours in children with ADHD is broadly reported in the literature
10 (Carta et al., 2020; McRae et al., 2019; Noordermeer et al., 2017). Relative to children with ASD alone, those
11 with ASD+ADHD appear to display more externalizing problems, such as aggressive and oppositional
12 behaviours (Berenguer et al., 2018; Craig et al., 2015; Matsushima et al., 2008). Similarly, Lecavalier et al.
13 (2019) showed an elevated prevalence of a range of behavioural problems in a large sample of 658 children with
14 ASD. Indeed, 81% of the children with ASD had ADHD, and within this group of children, 46% also had
15 oppositional disorders and 12% conduct disorders. Van Steensel et al. (2013) also reported that children with
16 ASD+ADHD have a higher level of oppositional behaviours than those with ASD or ADHD alone. Moreover, a
17 study that compared externalizing behavioural problems in children with ASD ($n = 255$), ADHD ($n = 40$), or
18 ASD+ADHD ($n = 47$) found that the rate of tantrum behaviours was higher in the ASD+ADHD group (Goldin et
19 al., 2013). For some authors, the occurrence of externalizing behavioural problems in children with
20 ASD+ADHD may be due to the clinical severity of the ASD (Berenguer et al., 2018; Green et al., 2015),
21 especially high levels of restricted and repetitive behaviours (Avni et al., 2018). Conversely, other studies have
22 supported that externalizing behaviours in children with ASD+ADHD are related to the clinical severity of
23 ADHD (Craig et al., 2015; Yerys et al., 2009). Finally, inconsistencies in the existing literature concerning the
24 factors related to externalizing behaviours in children with ASD+ADHD are obstacles to the individualization of
25 interventions, and further studies are required.

26 In the literature, internalizing behaviours are reported to be a frequent condition in children with ASD (Gjevik et
27 al., 2015; Lecavalier et al., 2019; van Steensel et al., 2013). Shephard et al (2019) found similar clinical patterns
28 in children with ASD and those with anxiety, creating difficulties in the differential diagnosis, especially in early
29 stages of life. Anxiety disorders have been reported to co-occur in 42% of children with ASD and mood

1 disorders in 8% (Lecavalier et al., 2019). Relative to children with ASD or ADHD alone, children with
2 ASD+ADHD have been reported to have higher rates of anxiety symptoms (Avni et al., 2018; Lecavalier et al.,
3 2019) and more severe depressive symptoms (Jang et al., 2013). Rommelse et al. (2018) emphasized that self-
4 regulation problems are common in both ASD and ADHD from the early stages of development and that they do
5 not allow a differential diagnosis. Conversely, other studies found that children with a ADHD alone had similar
6 emotional problems (Craig et al., 2015) and anxiety symptoms (Grzadzinski et al., 2011) as children with
7 ASD+ADHD. One study separately considering each diagnosis in children (single ASD or ADHD) found that
8 the occurrence of routines was predictive for internalizing behaviours (McRae et al., 2019). Such internalizing
9 behaviours can also manifest as psychosomatic disorders, such as sleep disturbance and anxiety, which are
10 frequently reported for both clinical conditions (Kern et al., 2015). Both children with single ASD and single
11 ADHD exhibit internalizing behaviours, but they appear to be more severe in ASD+ADHD. However, Carta et
12 al. (2020) found similar level of internalizing behaviours in the three clinical groups. Currently, there is no
13 consensus concerning the factors that increase internalizing behaviours in ASD+ADHD. Avni et al. (Avni et al.,
14 2018) attributed their increase to ADHD symptoms, whereas Lecavalier et al. (Lecavalier et al., 2019) attributed
15 them to cognitive deficits. Consequently, another challenge is to determine the factors related to internalizing
16 behaviours in children with ASD+ADHD to propose adapted personalized intervention (Jang et al., 2013).

17 Research on children with ASD+ADHD has increased since the DSM-5 acknowledged its nosological validity
18 (American Psychiatric Association, 2013). However, data remain scarce and they are conflicting. Further studies
19 are thus required to investigate whether certain components of their clinical presentation are more severe than in
20 single ASD or single ADHD. The comorbidity between ASD and ADHD raises many issues in professional
21 routines in terms of awareness of the children's specific needs and individualization of their interventions. This
22 requires well-designed comparative clinical studies between children with ASD+ADHD, those with ASD or
23 ADHD alone, and typically developing children (TD).

24 Here, our first aim was to compare the level of social impairment and externalizing/internalizing behavioural
25 problems across four groups of children according to their diagnosis: ASD+ADHD, ASD alone, ADHD alone,
26 and TD. Based on previous studies, we hypothesized that: 1) The group with ASD+ADHD would have more
27 severe social impairment and externalizing/internalizing behavioural problems than the three others, 2) the
28 groups with ASD+ADHD and ADHD alone would show more externalizing behavioural problems than those
29 with ASD alone or TD, and 3) the groups with ASD+ADHD and ASD or ADHD alone would show more severe

1 social impairment and internalizing behavioural problems than the TD group. Our second aim was to examine
2 the bidirectional relationship between ASD and ADHD symptoms within the ASD+ADHD group and clinical
3 characteristics, such as social impairment and externalizing/internalizing behavioural problems. We expected
4 that a higher level of ASD and ADHD symptoms in the group with ASD+ADHD would be associated with
5 greater severity in social impairment and externalizing/internalizing behavioural problems.

6 2. Methods

7 2.1 Participants

8 This study extended our previous findings to examine sensory and attention processing in four subgroups of
9 children: single ASD, single ADHD, ASD+ADHD, and TD (Dellapiazza et al., 2020). We collected more data to
10 increase the number of participants with ASD and comorbid ADHD. Our sample included 186 participants from
11 6 to 12 years of age, divided into the four groups described below.

12 *The ASD+ADHD group* (N = 29) consisted of children recruited from the ELENA cohort, a large multicentric,
13 longitudinal, prospective cohort of children diagnosed with ASD for which the protocol has already been
14 extensively described (Baghdadli et al., 2019). The ASD diagnosis was confirmed by a multidisciplinary team
15 using a standardized clinical approach. This standard process relied on DSM-5 (American Psychiatric
16 Association, 2013) criteria and consisted of the Autism Diagnostic Observation Schedule 2 (ADOS 2 ; Lord et
17 al., 2012), the Autism Diagnostic Interview-Revised (ADI-R ; Le Couteur et al., 2003), the Vineland second
18 version (VABS-II ; Sparrow et al., 2005) and the direct psychological assessment of intellectual functioning.

19 For this study, we used a subsample of 29 participants recruited from the ELENA cohort for which the inclusion
20 criteria were being from 6 to 12 years of age with comorbid ADHD clinically ascertained by experienced
21 psychiatrists on the basis of DSM-5 criteria (American Psychiatric Association, 2013) . We excluded participants
22 with genetic syndromes or a best-estimate intelligence quotient (IQ) < 80.

23 *The single ASD group* (n = 96) was also a subsample recruited from the ELENA cohort. We excluded children
24 who had an ADHD diagnosis according to DSM-5 criteria (American Psychiatric Association, 2013), a genetic
25 syndrome, or a best-estimate IQ < 80.

1 *The single ADHD group (n = 28)* was recruited from the Department of Child and Adolescent Psychiatry of the
2 University Hospital of Montpellier during consultations. Experienced child psychiatrists used DSM-5 criteria
3 and a medical report to diagnose ADHD and exclude ASD.

4 *The TD group (n = 31)* consisted of children in mainstream school and without any medical history of
5 neurodevelopmental disorders matched for age with the other clinical groups. These children were selected after
6 parental agreement to participate. The absence of history of neurodevelopmental disorders was confirmed by
7 asking parents if they have ever been concerned about their child's development and whether their child has ever
8 been diagnosed with a neurodevelopmental disorder. In addition, SRS-2 and CBCL scales were used to
9 systematically screen for ASD and ADHD, respectively. None of the children in this group, met the clinical
10 threshold on these scales.

11 Exclusion criteria for each group were having sensory deficits (blindness and auditory deficit) and to have
12 received a medication for attention deficit.

13 **2.2 Measures**

14 *Social impairment* was assessed using the SRS-2, a 65-item questionnaire measuring ASD trait severity
15 (Constantino & Gruber, 2012). For the present study, we utilized the school-age form (from 2.5 to 18 years),
16 which assesses social impairment on five subscales: Social Awareness (ability to pick up on social cues), Social
17 Cognition (ability to interpret social cues), Social Communication (includes expressive social communication),
18 Social Motivation (to engage in social communication), and Restricted Interests and Repetitive Behaviours
19 (RIRB; includes stereotypical behaviour). Each question was rated from 1 (Not True) to 4 (Almost Always
20 True). The Total composite score (T) (M = 50, SD = 10) was used to assess the severity of symptoms. T-scores \geq
21 90 indicate extremely severe social impairment. Total scores of ≤ 59 correspond to the average range, 60 to 65 a
22 mild degree of impairment, 66 to 75 a moderate degree of impairment, and 76 or higher, a severe degree of
23 impairment. The internal consistency was 0.95.

24 *Externalizing and internalizing behavioural problems* were assessed using the Child Behaviour Checklist
25 (Achenbach & Rescorla, 2001), a standardized caregiver-report exploring emotional and behavioural problems
26 in children and adolescents aged from 6 to 18 years. The CBCL provides two scales of child behaviour:
27 internalizing and externalizing problems. The internalizing scale consists of five subscales: anxious/depressed,

1 withdrawn/depressed, somatic complaints, social problems and thoughts problems. The externalizing scale
2 consists of three subscales: rule-breaking behaviour, attention problems and aggressive behaviour. The CBCL
3 also provides a score for ADHD, called the DSM-oriented scale. T-scores based on age and sex were obtained;
4 T-scores ≥ 70 are considered clinically significant and T-scores from 65 to 69 borderline clinically significant.
5 Internal consistency ranged from 0.72 to 0.91, the inter-rater reliability from 0.63 to 0.88, and the test-reliability
6 was 0.90.

7 *The best-estimate IQ* was assessed from psychometric scales, depending on the age of each participant. The non-
8 verbal cognitive level was estimated from the “fluid reasoning” dimension of the WISC-V (Wechsler, 2014a)
9 and the WPPSI-IV (Wechsler, 2014b), “perceptual reasoning” dimension of the WISC-IV (Wechsler, 2014b),
10 and the “performance IQ” of the WPPSI-III (Wechsler, 2002) or “simultaneous process” of the K-ABC II
11 (Kaufman & Kaufman, 2004).

12 A standardized parental questionnaire was used to collect the following information about the children: birth
13 date, other neurodevelopmental disorders, sensory deficits, and medication used for ADHD.

14 **2.3 Procedure**

15 Parents of the children recruited from the ELENA cohort were asked to complete the CBCL and SRS-2
16 questionnaires electronically on a web database. Parents of the children in the ADHD and TD groups were asked
17 to complete the CBCL and SRS-2 questionnaires in print format and to return them to the research team. The
18 intellectual level was assessed during diagnosis for the children recruited from the ELENA cohort (with single
19 ASD or ASD+ADHD) and those with ADHD alone. The intellectual level of the children with TD was not
20 assessed and considered to be normal when the grade level matched the chronological age. Informed consent
21 forms were completed by all parents and the data were anonymized.

22 **2.4 Statistical analyses**

23 Descriptive statistics were analysed to characterize each group (ASD, ASD+ADHD, ADHD, and TD). Bivariate
24 analyses, consisting of Chi-square tests of associations for categorical variables and one-way ANOVA or the
25 Kruskal-Wallis non-parametric test for continuous variables, were conducted to assess intergroup comparisons.
26 For significant differences, a Bonferroni correction was applied for 2-by-2 comparisons. Association between

1 the SRS-2 score and externalising and internalising behaviours scores were then analysed in the ASD and
2 ASD+ADHD groups using Pearson's or Spearman's correlation coefficient, as were associations between the
3 attention deficit score (DSM-5 scale) and social impairment and externalising and internalising behaviours
4 scores. Statistical analyses were performed using SAS 9.3 software. A two-sided $p < 0.05$ was considered to be
5 statistically significant.

6 3. Results

7 The sample included 186 children from 6 to 12 years and 11 months of age (mean age 9.1 ± 1.8 years). They had
8 a diagnosis of ASD ($n = 98$), ADHD ($n = 28$), or comorbid ASD+ADHD ($n = 29$) or had TD ($n = 31$). Intergroup
9 comparisons showed no differences in age (ASD: mean age 9.1 ± 1.9 , ADHD: mean age 9.2 ± 1.8 ,
10 ASD+ADHD: mean age 8.5 ± 1.6 , TD: mean age 9.3 ± 1.6) or gender. There were 81.6% males in the single
11 ASD group, 82.1% in the single ADHD group, 75.9% in the ASD+ADHD group, and 61.3% in the TD group.
12 No differences were found in nonverbal cognitive level (all $p > 0.05$). No significant difference were presented
13 between ASD and ASD+ADHD groups on clinical characteristics (ADOS severity score, VABS-II and ADI)
14 described in Table 1.

15 [Insert Table 1]

16 Intergroup comparisons showed significant differences in SRS-2 and CBCL scores (Table 2). *Post hoc* analysis
17 showed higher scores for SRS-2 and CBCL in the three groups with neurodevelopmental disorder (NDD) than in
18 the TD group, except for social motivation, for which the ADHD group had scores comparable to those of the
19 TD group. As expected, the ASD+ADHD and ADHD groups had higher CBCL attention problems scores than
20 the single ASD group ($p < 0.05$). The ASD and ASD+ADHD groups had higher SRS-2 scores (for each
21 dimension) than the single ADHD group ($p < 0.05$), except for social awareness, for which the ADHD group
22 had lower scores than the TD, ASD, and ASD+ADHD groups.

23 [Insert Table 2]

24 Correlations between the SRS-2 and CBCL scores performed by group are presented in Table 3.

25 **For the ASD group**, all the SRS-2 scores correlated from moderate to high with the CBCL internalizing
26 behaviours, thoughts problems and attention problems scores. In this group, the SRS-2 total score correlated with
27 all CBCL internalizing scores, CBCL externalizing behaviours, attention problems and aggressive behaviours.

1 RIRB score and social motivation correlated from moderate to high with all CBCL internalizing and attention
2 problems. Overall, for the ASD group, as the severity of ASD increased, all internalizing behaviours and CBCL
3 externalizing behaviours also increased (except rule breaking behaviours).

4 **For the ASD+ADHD group**, the SRS-2 total score and social communication score highly correlated with the
5 CBCL internalizing behaviours score, withdraw depressed, somatic complaints. The CBCL ADHD DSM-
6 oriented score highly correlated with the CBCL attention problems and aggressive behaviours. However, there is
7 no significant correlation between CBCL ADHD DSM-oriented score and the SRS-2 score (all $p > 0.05$).
8 Overall, for the ASD+ADHD group, as the severity of ASD increased, internalizing behaviours, withdraw
9 depressed and somatic complaints increased and as the severity of ADHD increased, attention problems and
10 aggressive behaviours also increased.

11 **For the ADHD group**, the CBCL ADHD DSM-oriented score highly correlated with the CBCL internalizing
12 behaviours (anxious depressed, withdraw depressed, social problems, thoughts problems), externalizing
13 behaviours (rule breaking behaviours, aggressive behaviours) and social impairment (SRS-2 total score, $r = 0.52$,
14 $p < 0.01$; social cognition, $r = 0.39$, $p < 0.05$; social communication, $r = 0.46$, $p < 0.05$; RIRB, $r = 0.60$, $p <$
15 0.001). Overall for the ADHD group, when ADHD severity increased, internalizing, externalizing and social
16 impairments increased too.

17

18 [Insert Table 3]

19

20 4. Discussion

21 Overall, our results show that children with NDDs have more severe social impairment and
22 externalizing/internalizing behaviours than children with TD. As expected, social impairment was more likely to
23 occur in children with ASD alone or ASD+ADHD than in those with ADHD alone. In addition, attention
24 problems were more prevalent for children with ADHD alone or ASD+ADHD than in those with ASD alone.
25 The prevalence of externalizing/internalizing behaviours was high in the three groups with NDD. Thus, the
26 ASD+ADHD group showed scores similar to those of the ASD and ADHD groups. Thus, we did not confirm
27 this part of our hypothesis. However, the correlation analysis revealed that internalizing behaviours are more
28 highly related to ASD severity and that externalizing behaviours are more often associated with ADHD severity.

1 In contrast to our hypothesis, the severity of social impairment was comparable between the ASD+ADHD and
2 ASD groups. Social impairment is generally considered to be typical of ASD (Grzadzinski et al., 2011).
3 However, our results reinforce those of previous studies (Rommelse et al. 2018) that found significant social
4 difficulties in children with ADHD, suggesting that this cannot be the only dimension used to confirm a
5 diagnosis of ASD. Although significant social problems were found in the ADHD group, they were greater in
6 both the ASD and ASD+ADHD groups, as illustrated by higher SRS-2 scores, also supporting the relevance of
7 the SRS scale in the differential diagnosis.

8 We hypothesized that the single ADHD and ASD+ADHD groups would exhibit more externalizing behaviours
9 than the single ASD and TD groups. We found the externalizing scores to be comparable between the three
10 groups with NDDs relative to the TD group, except for the attention score, for which the ASD+ADHD and
11 single ADHD groups had higher scores than the single ASD group. Moreover, the percentage of externalizing
12 behaviours was higher in the single ADHD group (75%) than in the single ASD (45%) and ASD+ADHD (38%)
13 groups. Our results agree with those of the literature, which highlight a high percentage of externalizing
14 behaviours in ADHD (Carta et al., 2020; McRae et al., 2019; Noordermeer et al., 2017). However, our results
15 differ from those of past studies, which showed more externalizing behaviour in ASD+ADHD than ASD
16 (Berenguer et al., 2018; Craig et al., 2015; Matsushima et al., 2008) or ADHD (Goldin et al., 2013; van Steensel
17 et al., 2013) alone. In addition, our results reinforce the evidence that the percentage of externalizing behavioural
18 problems is related to the degree of ADHD symptom severity in the ASD+ADHD and ADHD groups (Craig et
19 al., 2015; Yerys et al., 2009).

20 Similarly, our results confirm that the three groups with NDD present more internalizing behavioural problems
21 than children with TD. This result highlights that internalizing behaviours, commonly found in ASD (Gjevik et
22 al., 2015; Lecavalier et al., 2019; van Steensel et al., 2013), are also found in ADHD. This result is concordant
23 with those of past studies, which showed that children with a single diagnosis of ASD or ADHD presented
24 similar emotional problems and anxiety symptoms as children with ASD+ADHD (Carta et al., 2020; Craig et al.,
25 2015; Grzadzinski et al., 2011). Internalizing behaviours in the ASD+ADHD group were associated with ASD
26 severity and the association was particularly strong for the domain of restricted, stereotyped, and repetitive
27 behaviours. It was previously suggested that such restricted and repetitive behaviours help individuals with ASD
28 to cope with their anxiety (McRae et al., 2019; White et al., 2009). We also observed that ADHD severity was
29 highly associated with internalizing behaviours, which highlight the relevance of taking into account these

1 difficulties in this population, which are generally less studied than externalizing behaviours (McRae et al.,
2 2019; Noordermeer et al., 2017).

3 One strength of our study was the comparison of three clinical groups to a TD group matched for age. In
4 addition, we recruited the children with ASD (single or with comorbid ADHD) from the ELENA cohort, for
5 which they were rigorously diagnosed. The children with single ADHD were also thoroughly diagnosed. In
6 addition, we studied comorbidity using the SRS-2 and CBCL, which were standardized and validated
7 questionnaires for clinical research and practice.

8 However, our study also had several limitations. Although the diagnoses were performed in the context of a
9 clinical examination by experienced clinicians, the information on comorbidities was mainly collected by
10 parental questionnaires. Indeed, as reported by Moens et al. (2018) there is negative bias concerning child
11 behaviours in parents reports. We haven't collected parent's socioeconomic status, which may influence
12 questionnaires responses validity. In addition, there was a risk of selection bias related to the recruitment of
13 participants from different sources (Child and Adolescent Psychiatry Department for the ADHD group and Elena
14 cohort for the ASD group), but this risk was limited by the standardization of the diagnostic process for the two
15 groups. Furthermore, the children with NDD had an IQ > 80 to allow comparison with the TD group and, thus,
16 we cannot generalize our findings to lower-functioning children. The differences in recruitment sources also
17 explain differences in groups' sample size and the size of the groups ASD+ADHD and single ADHD was
18 limited. Larger studies will thus be necessary to investigate the clinical characteristics of the ASD+ADHD
19 group.

20 This study has several clinical implications. First, our results reveal that children with NDD exhibit both greater
21 social impairment and more severe externalizing/internalizing behaviours than TD children. These results stress
22 the importance of checking for comorbidities during the diagnosis of ASD and to take into account such
23 comorbidities in the intervention plan. We found that ADHD symptom severity in the ADHD group was
24 strongly associated with internalizing behaviours, implying the importance of professionals to search for anxiety
25 issues, which are less systematically investigated in individuals with ADHD than externalizing behaviours.
26 Internalizing behaviours in the ASD group were strongly associated with restricted and repetitive behaviours,
27 suggesting that they also need to be managed in individuals with ASD, such as the current practice for anxiety.

1 Further studies will be necessary to better understand the specific clinical characteristics of ADHD in ASD on a
2 larger sample. It will be important to prospectively examine adaptive trajectories in samples with ASD and
3 ADHD to describe clinical changes and their determinants.

4 5. Conclusion

5 In conclusion, this study focused on comorbidities across groups of children with ASD+ADHD, ASD or ADHD
6 alone, or TD. Groups with NDD presented a higher level of social impairment and externalizing/internalizing
7 behaviours than TD children. In particular, internalizing behaviours were more often associated with ASD
8 severity and externalizing behaviours with ADHD severity. This underlies the necessity of searching for the
9 presence of comorbidities during the diagnosis of NDD. The ASD+ADHD association has only been recently
10 recognized in medical classification and future studies are needed to prospectively follow and describe clinical
11 changes and their determinants in this population.

12

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18 **Author Contributions**

19 FD and LAT conceived the study, contributed to the collection, analysis, and interpretation of the data, and
20 drafted the manuscript. AB is the PI of the ELENA cohort and also participated in the design of the current
21 study, drafted the work, and critically revised it for the principal intellectual content. CM analysed and
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23

23 **Declarations**

24

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1

Conflict of Interest

2 The authors have no conflict of interest to declare.

3

Ethical Approval

4 The study and informed consent procedure have been approved by the Ethics Committee on the Research of
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7

Informed Consent

8 Signed informed consent is obtained from all participating families.

9

10

List of Abbreviations

11 ADHD : Attention Deficit Hyperactivity Disorder

12 ADI-R : Autism Diagnostic Interview- Revised

13 ADOS : Autism Diagnostic Observation Schedule

14 ASD : Autism Spectrum Disorder

15 ASD+ADHD : Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder

16 CBCL: Child Behaviour Checklist

17 DSM : Diagnostic and Statistical Manual of Mental Disorders

18 NDD : Neurodevelopmental disorder

19 IQ: Intellectual quotient

20 SRS : Social Responsivness Scale

21 TD : Typical Development

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Table 1. Clinical characteristics for ASD and ASD+ADHD groups and intergroup comparisons.

	ASD <i>n</i> = 98	ASD+ADHD <i>n</i> = 29	<i>p</i> -value intergroup comparison
	Mean (SD)	Mean (SD)	
ADOS CSS	6.4 (2.2)	6.5 (2.2)	0.9
VABS-II			
Communication	82.5 (13.6)	81.8 (10.8)	0.7
Socialization	74.1 (9.6)	71.9 (6.8)	0.2
Daily living skills	78.8 (10.5)	78.9 (9.9)	0.9
ADI-R			
Communication	12.4 (5.8)	11.1 (3.9)	0.3
Social interaction	15.5 (6.3)	14.8 (5.4)	0.6
RIRB	5.5 (2.5)	5.4 (2.2)	0.7

ASD, autism spectrum disorder; ASD+ADHD, comorbidity form; SD, standard deviation; ADOS CSS, autism diagnostic observation schedule calibrate severity scale; VABS-II, Vineland second version; ADI-R, autism diagnostic interview-revised; RIRB, restrictive interest and repetitive behaviours.

Table 2. SRS-2 and CBCL scores for each group and intergroup comparisons.

	ASD <i>n</i> = 98		ASD+ADHD <i>n</i> = 29		ADHD <i>n</i> = 28		TD <i>n</i> = 31		<i>p</i> -value intergroup comparison	<i>Post hoc</i> test ^a
	Mean (SD)	% clinical range	Mean (SD)	% clinical range	Mean (SD)	% clinical range	Mean (SD)	% clinical range		
TOTAL SRS-2	78.5 (10.5)		79.0 (7.10)		69.5 (7.5)		59.1 (2.5)		0.0001	TD<ADHD<ASD+ADHD,ASD
Social awareness	71.4 (11.5)		73.3 (10.8)		63.5 (6.7)		70.3 (5.4)		0.0001	ADHD<TD, ASD+ADHD,ASD
Social cognition	75.5 (11.1)		77.2 (8.8)		73.1 (7.0)		63.9 (4.7)		0.0001	TD<ADHD<ASD+ADHD,ASD
Social communication	77.6 (9.3)		78.7 (7.5)		68.4 (8.3)		59.1 (3.0)		0.0001	TD<ADHD<ASD+ADHD,ASD
Social motivation	71.2 (12.5)		69.0 (10.4)		61.8 (7.8)		56.7 (3.9)		0.0001	TD, ADHD<ASD+ADHD, ASD
RIRB	78.4 (10.3)		77.7 (8.7)		66.5 (12.5)		45.2 (4.7)		0.0001	TD<ADHD<ASD+ADHD,ASD
CBCL Internalizing	18.6 (9.8)	72%	20.3 (10.2)	80%	15.8 (7.7)	64%	5.7 (5.1)	13%	0.0001	TD<ALL
Anxious depressed	9.8 (5.6)	43%	10.2 (4.4)	42%	8.5 (4.0)	32%	3.1 (3.2)	3%	0.0001	TD<ALL
Withdrawn depressed	5.1 (3.5)	39%	5.2 (3.3)	38%	3.3 (2.7)	10%	1.5 (1.5)	3%	0.0001	TD<ALL
Somatic complaints	3.7 (3.2)	17%	4.9 (4.0)	27%	4.1 (3.4)	25%	1.1 (1.4)	0%	0.0001	TD<ALL
Social problems	8.4 (4.3)	35%	9.7 (3.5)	58%	7.9 (3.1)	29%	1.4 (1.7)	0%	0.0001	TD<ALL
Thought problems	7.9 (4.5)	50%	7.8 (4.1)	54%	6.2 (5.2)	39%	1.1 (1.5)	0%	0.0001	TD<ALL
CBCL Externalizing	15.6 (9.2)	45%	14.4 (8.2)	38%	20.4 (9.6)	75%	4.3 (4.1)	3%	0.0001	TD<ALL
Attention problems	9.7 (4.1)	32%	12.1 (3.6)	58%	12.3 (3.8)	50%	1.7 (2.1)	0%	0.0001	TD<ASD<ASD+ADHD, ADHD
Rule breaking behaviors	3.8 (3.1)	14%	3.4 (2.8)	7%	4.9 (3.1)	25%	1.2 (1.2)	0%	0.0001	TD<ALL
Aggressive behavior	11.8 (6.7)	28%	11.0 (6.3)	19%	15.5 (7.2)	43%	3.1 (3.3)	0%	0.0001	TD<ALL
ADHD DSM-oriented	7.7 (3.1)	23%	9.4 (2.3)	39%	10.4 (2.9)	63%	1.6 (1.7)	0%	0.0001	TD<ASD<ASD+ADHD, ADHD

ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; TD, typical development; ASD+ADHD, comorbidity form; ALL, all other groups.

^aBonferroni correction.

Table 3. Correlation between ASD and ADHD severity and internalizing/externalizing behaviours (CBCL scores) by clinical group.

		CBCL internalizing	Anxious depressed	Withdraw depressed	Somatic complaints	Social problems	Thoughts problems	CBCL externalizing	Attention problems	Rule breaking behaviors	Aggressive behaviors
ASD	SRS-2 total score	.54***	.35*	.46***	.37**	.39**	.61***	.31*	.42**	-	.30*
	Social awareness	.30*	-	-	-	-	.46***	.39**	.33*	.37**	.34*
	Social cognition	.43**	.30*	.31*	.33*	-	.46***	-	.40**	-	.32*
	Social communication	.36*	-	.45**	-	-	.47***	-	.34**	-	-
	Social motivation	.52***	.33*	.48***	.34*	.31*	.43**	-	.32*	-	-
	RIRB	.59***	.45***	.40**	.36*	.36*	.61***	-	.48***	-	-
ASD+ADHD	SRS-2 total score	.51*	-	.46*	.46*	-	-	-	-	-	-
	Social awareness	-	-	-	-	-	-	-	-	-	-
	Social cognition	-	-	-	-	-	-	-	-	-	-
	Social communication	.58*	-	.62**	.55*	-	-	-	-	-	-
	Social motivation	-	-	.64**	-	-	-	-	-	-	-
	RIRB	-	-	-	-	-	-	-	-	-	-
	CBCL ADHD DSM - oriented	-	-	-	-	-	-	-	.52**	-	.49**
ADHD	CBCL ADHD DSM - oriented	.58**	.51**	.53**	-	.68***	.49**	.75***		.51**	.73***

*p<0.05, **p<0.01, ***p<0.001, - no significant effect

ASD, autism spectrum disorder ; ADHD, attention deficit hyperactivity disorder ; SRS, social responsiveness scale ; CBCL, child behavior checklist ; RIRB, restrictive interest repetitive behavior ; DSM, diagnostic and statistical manual of mental disorders