**Cognitive, social, and behavioral manifestations of the co-occurrence of Autism Spectrum Disorder and Attention-Deficit /Hyperactivity Disorder: a systematic**   **review**

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**Abstrac**t. Attention-deficit/hyperactivity disorder (ADHD) is one of the most common comorbidity in individuals with autism spectrum disorder (ASD). However, the clinical implications of the co-occurrence of these two disorders are still poorly understood. Based on a pre-registered protocol (PROSPERO CRD42020193880), this systematic review identified ~~36~~ 34 articles, published between January 1st,2014 and September 1st, 2020, on cognitive, adaptive/social, and behavioral manifestations in children and adolescents with a comorbid diagnosis of ASD and ADHD (ASD+). The majority of available studies found a tendency towards a significant poorer cognitive performance in individuals with ASD+ compared to those with ASD alone (ASD-). The analysis of social/adaptive processes suggested that ASD+A is associated with lower functioning in comparison to ASD-. Finally, individuals with ASD+ were more likely to develop emotional/behavioral difficulties, in particular externalizing problems. Overall, co-occurring ASD+ may constitute a distinctive phenotype with a greater vulnerability for cognitive, adaptive dysfunction and mental health symptoms ~~other psychiatric conditions~~, compared to ASD--. These results will inform the setting up and implementation of care pathways for individuals with ADHD and ASD.

**Lay Abstract**

This work aimed to review recent research on the characteristics of individuals who have both ASD and ADHD. ~~36~~ 34 studies were analyzed, and main findings summarized in two content domains focusing on areas that could enhance our understanding of the cognitive and behavioral characteristics of individuals with ASD+ADHD. Results showed that ASD+ADHD represents a high risk co-occurring condition associated with more severe impairments in cognitive functioning, adaptive behavior, and increased vulnerability to present more emotional/behavioral problems. These results will be helpful to provide improved care plans for individuals with both ADHD and ASD.

**Keywords**: autism spectrum disorder; attention-deficit/hyperactivity disorder; comorbidity; neurodevelopmental disorders; systematic review

**1. Introduction**

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are two common neurodevelopmental disorders. A recent meta-analysis of 41 studies in 27 countries reported a worldwide prevalence rate in ADHD of 5-7% in children and adolescents (Polanczyk et al., 2015). In the case of ASD, the median prevalence, based on an epidemiological survey conducted in 37 countries, was 0.97% in primary school children (Fombonne et al., 2021). Even though ASD and ADHD can share some characteristics, they are two distinct disorders in their core symptoms and other phenotypic manifestations, with different diagnostic criteria. ADHD core symptoms include inattention, impulsivity and hyperactivity, whereas ASD is characterized by communication and social interaction difficulties as well as the presence of repetitive and stereotyped patterns of behavior, activities, and interests (APA, 2013).

Empirical evidence suggests that children with ASD generally experience greater deficits in planning and flexibility (Happe et al., 2006; Salcedo-Marin et al., 2013), whereas children with ADHD exhibit more severe problems with inhibitory control and sustained attention (Corbett et al., 2009; Sinzig et al., 2008). In addition, social cognition processes are more affected in children with ASD and they usually experience withdrawal and avoidance of social interactions. In contrast, children with ADHD have less generalized impairments in social cognition, although they present difficulties in social contexts due to deficits in self-regulation that lead to frequent maladaptive behaviors (Bora and Pantelis, 2016; Taurines et al., 2012). Despite these important differences, ASD and ADHD symptoms often present together, and they have a tendency to co-occur in families and share etiological mechanisms such as genetic risk factors and ~~the~~ neurocognitive features (Yerys, 2020).

The co-occurrence of ASD and ADHD was not formally recognized until the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (Diagnostic and Statistical Manual of Mental Disorders, fifth edition, 2013). The co-occurrence

between both disorders is reported between 20 to 70% (Brookman-Frazee et al., 2018; Joshi et al., 2017; Llannes et al., 2020; Lyall et al., 2017; Salazar et al., 2015). This broad range depends on the type of sample (clinical or community, age), the evaluation procedures, the type of informants, the diagnostic criteria utilized as well as specific characteristics of the individuals such as their cognitive level. A recent meta-analysis showed an overall pooled prevalence estimates of 28% for ADHD in ASD population (Lai et al., 2019) that increased with age and ASD severity (Gordon-Lipkin et al., 2018). In addition to being fairly frequent, an increasing body of literature suggests that ASD+ADHD comorbidity increases vulnerability and clinical complexity. Indeed, in the presence of ADHD symptoms, autism seems to be generally associated with more severe impairments in executive functioning, theory of mind, adaptive functioning, greater psychosocial problems and poorer quality of life (Antshel, 2013; Berenguer-Forner et al., 2015; Leitner., 2014; Taurines et al., 2012).

Considering that the studies carried out before DSM-5 were not based on ASD participants having a formal ADHD diagnosis but rather ADHD symptoms, an overview of the studies published after the DSM-5 was implemented allows us to address the profile of comorbid ASD and ADHD. Thus, the present study aimed to carry out a systematic review of recent (published in or after 2014) studies exploring the characteristics of children and adolescents with ASD+ADHD in different domains that have relevance for improving the diagnosis and treatment. The research questions of this systematic review were as follows:

- What are the characteristics of the cognitive phenotype of co-occurring ASD+ADHD? Are there more deficits in executive, sensorial, and social processing in individuals with ADHD+ASD in comparison to those with ASD alone?

- What are the characteristics of the behavioral phenotype of co-occurring ASD+ADHD? Are there more severe impairments in adaptive/social skills and more emotional/behavioral in co-occurring ASD+ADHD than those observed in ASD alone?

Based on previous literature published before the formal diagnosis of ASD+ADHD was allowed, our first hypothesis was that children with ASD+ will experience greater executive and social cognition deficits compared to those with ASD- (Antshel et al., 2013; Berenguer el al., 2015; Taurines et al., 2012). The second hypothesis was that individuals with ASD+ present poorer adaptive/social skills and more emotional/behavioral difficulties, requiring greater treatment needs, compared to those with ASD- - (Gillman et al., 2000; Leitner, 2014).

**2. Materials and Methods**

The protocol of this systematic review was pre-registered in PROSPERO (CRD42020193880), and the methods were developed following the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) guidelines (Moher et al., 2015).

**2.1. Inclusion and exclusion criteria**

The complexity and significance of ASD+ADHD has sufficient power to explore research questions within this subgroup regarding to ASD-only. The primary aim was to identify the developmental profile of ASD+ADHD. Thus, we identified publications based on the following inclusion criteria: 1) empirical quantitative studies (cross-sectional, case-control, cohort study) with at least one group of participants with a comorbid diagnosis of ASD+ADHD (primary diagnosis of ASD) and another group with ASD-only, according to the ICD-9, ICD-10, DSM-IV, DSM-IV TR, or DSM-5 criteria; 2) studies with data on ASD and ADHD symptoms, cognitive functioning, adaptive and social skills, comorbidity, or academic competence of individuals with co-occurring ASD+ADHD; 3) mean age of participants ≤ 18 years; 4) studies published between January 1st 2014 and September 1st 2020 that had not been included in previous reviews on the topic before the implementation of the DSM-5 (Antshel et al., 2013; Gargaro et al., 2011; Leitner, 2014; Rommelse et al., 2011; Taurines et al., 2012), expanding the information from other recent reviews that focused only on the neuropsychological profile of individuals with ASD+ADHD (Berenguer et al., 2018a; Craig et al., 2016). Articles were excluded if they: 1) did not include quantitative data and a formal peer-review process (i.e., editorials, extended abstracts, doctoral dissertations, symposium papers, research abstracts, book chapters, or proceedings, systematic reviews, and survey papers); 2) focused on molecular genetics, neuroimaging/neurophysiological data, medical conditions, interventions (pharmacological, psychological). These topics were beyond the scope of the present systematic review and are covered in other publications (Antshel et al., 2016; Antshel and Russo, 2019; Yerys, 2020); 3) case series with fewer than 10 participants.

**2.2. Search strategy**

PubMed, PsycINFO, and the Educational Resources Information Center (ERIC) were searched for peer-reviewed articles published in English between January 1st 2014 and September 1st 2020.

 The following combination of search terms was used in the systematic searches: (“autis\*” or “autistic disorder” or “pervasive developmental disorder” or “autism spectrum disorder” or “Asperger syndrome” or “high functioning autism” or “ASD”), combined with ("attention deficit\*" or “ADHD” or “attention-deficit/hyperactivity disorder” or “hyperkinetic disorder” or “hyperactiv\*” or “inattentive” or “impulsiv\*”) and (“child\*” or “adolescen\*” or “teen\*”). Variations in the syntax of the search terms and Medical Subject Headings (or equivalents) were used according to the specific database.

Two authors independently searched and reviewed all the references via the platform Covidence. Potential disagreement between authors during the selection process was resolved in regular meetings that were held to carefully discuss titles/abstracts in the first phase and full-texts in the second phase to ensure agreement.

**2.3 Study quality assessment**

The quality of the reporting of included studies was assessed with a standardized and validated set of criteria based on the “STROBE Reporting Guidelines for writing and reading observational studies in epidemiology” (Von Elm et al., 2014). The evaluation included 19 items related to the introduction (3 items; justification of the study, well described aims and clear hypothesis/expectations), methods (9 items; e.g., replicable protocol, number of participants, inclusion-exclusion criteria; detailed description of methods of measurement), results (2 items; appropriate analyses plan and clear results presentation), and discussion sections (4 items; e.g., results discussed according the literature, limitations shown) as well as other information (1 item about ethics). For each criterion, two of the authors assigned scores of 2, 1, or 0, depending on whether it was completely fulfilled, partially fulfilled, or not fulfilled at all. A second quality tool was added as an additional tool to assess the methodology of the studies. The checklist from the Centre for Evidence Based Management (CEBMA, 2014, <https://www.cebma.org>) includes 12 items (e.g., accuracy of the research question, methods sufficient to address it, recruitment description and potential bias, use of power calculation, validity of measures, statistical analyses, identification of confounding variables and generalizability of results) and each item can be scored 0 or 1, with total higher scores indicating better quality. ~~(Appendix B).~~ Two authors rated the studies and resolved disagreements through discussion until a consensus was achieved. Tables in Appendix A and B report the appraisal of the reporting of the studies and their methodological quality, respectively.

**3. Results**

Overall, 3,604 potentially relevant references were initially identified (1,851 in PubMed, 1,213 in PsycINFO, and 540 in ERIC). Of these, 1,455 were excluded due to duplication. Of the remaining 2,149 references, titles/abstracts were screened by two authors according to the inclusion and exclusion criteria and 2,073 were discarded as deemed not pertinent (i.e., studies on interventions; etiology; comorbidity with medical conditions; adult population; prevalence). Then, 76 full-text were screened by two authors and, after consensus was reached, a total of ~~34~~ 32 articles were selected as pertinent. Finally, with the addition of two other studies located through references from other publications, a total of 34 ~~36~~ studies were included in this systematic review (Figure 1).

**-Insert Figure 1-** Fig. 1 PRISMA flowchart of the search strategy

In the 34 ~~36~~ studies selected, ~~three~~ two main content domains and several subdomains were identified: 1) cognitive phenotype, including the subdomains of executive functioning (EF), sensory processing, and social cognition; 2) behavioral phenotype, including adaptive/social skills and emotional/behavioral. Out of the 34 ~~36~~ included studies, ~~17~~ 15 focused on cognitive phenotype (Biscaldi et al., 2016; Dajani et al., 2016; Dellapiazza et al., 2020; Gargaro et al., 2018; Kado et al., 2020; Lundervold et al., 2016; Salunkhe et al., 2018; Sanz et al., 2017; Seernani et al., 2020; ~~Tye et al., 2014a,b;~~ Tye et al., 2016; Unterrainer et al., 2016; Van der Meer et al., 2016; Oerlemans et al., 2014; Wadington et al., 2018 a,b), , 15 on behavioral phenotype (Ashwood et al., 2015; Avni et al., 2018; Carta et al., 2020; Chen et al., 2015; Chiang et al., 2018; Magnusdottir et al., 2016; McClain et al., 2017; McFayden et al., 2020; Ng et al., 2019b; Rao and Landa, 2014; Salley et al., 2015; Scandurra et al, 2019; So et al., 2017; Turygin et al., 2015; Yamawaki et al., 2020)~~, five on symptoms of mental health disorders (Carta et al., 2020; Chen et al., 2015; McClain et al., 2017; So et al., 2017; Yamawaki et al., 2020) and~~ ~~five~~ and four on multiple outcomes (Berenguer et al., 2018b; Colombi and Ghaziuddin, 2017; Ng et al., 2019a~~,b~~; Craig et al., 2015).

Supplementary tables 1 and 2 ~~, 2, and 2 3~~ report the participants characteristics, measures used, and main findings of each study included in the systematic review in relation to cognitive processes (EF and social cognition) and behavioral functioning ( adaptive/social skills ~~characteristics~~, and emotional/behavioral difficulties) ~~symptoms of mental disorders~~, respectively. Tables in appendix A and B report the appraisal of the reporting of the studies and their methodological quality, respectively. The main findings across studies are summarized in the following subsections, and in the cases where the information was available, exploratory forest plots figure are presented.

**3.1. Cognitive phenotype of co-occurring ASD+ADHD**

19 ~~Twenty~~ studies focused on the analysis of cognitive, sensory, and social cognition processing: EF (Berenguer et al., 2018b; Colombi and Ghazziuddin, 2017; Dajani et al., 2016; Gargaro et al, 2018; Kado et al., 2020; Ng et al., 2019a; Salunkhe et al., 2018; Unterrainer et al., 2016; Van der Meer et al., 2016), variability in reaction time (Biscaldi et al., 2016; Lundervold et al., 2016; Salunkhe et al., 2018; Sernani et al., 2020; Tye et al., 2016), Theory of Mind (ToM) and emotion recognition (ER) (Colombi and Ghazziuddin, 2017; Oerlemans et al., 2014; Wadington et al., 2018 a,b), and sensorial processing (Dellapiazza et al., 2020; Sanz et al., 2017). The majority had a cross-sectional design, including three clinical groups (ASD, ADHD, ASD+ADHD). In total, the median number of participants was 160 ~~161~~, aged between 5 and 15, and ~~80.7%~~ 79% were males. Participants’ cognitive levels were reported in all studies, with mean global IQ scores ranging from 78 to 120. ~~Fifteen~~ Fourteen studies were conducted in Europe, three in North America, one in Japan and another one in Australia.

*Executive Functioning.* The retrieved studies explored the possible cognitive phenotypes to explain the main ADHD symptoms (Barkley, 2005) and the restrictive interests and repetitive behaviors present in ASD (Lopez et al., 2005): working memory (WM), attention, response inhibition, planning, and cognitive flexibility.

Enquiry of WM in children with ASD+ADHD reported mixed findings. Performance on the WISC-IV working memory index (WMI), which comprises digit span and letter-number sequencing subtests, was significantly poorer in children with ASD+ADHD compared to children with ASD alone, with medium effect size (Columbi and Ghaziuddin, 2017). In contrast, other studies (Ng et al., 2019a; Salunkhe et al., 2018) did not find any significant WMI differences between the ASD and ASD+ADHD groups. Several factors may have influenced the results, including possible medications effects (Ng et al., 2019a) or computerized tasks (Salunkhe et al., 2018).

Presumably, comorbid ADHD could negatively influence attentional processes, therefore ASD+ADHD and ADHD groups are expected to have more attention problems than the ASD group. Indeed, one study (Lundervold et al., 2016) investigated the performance of ~~both ASD~~  ASD and ASD+ADHD groups on the continuous performance test (CPT). The ASD+ADHD group was found to be less judicious with more omission errors, and less consistent on visual search than the pure ASD group. Another finding suggested a particular attention-processing profile of the ASD+ADHD and ADHD groups (Gargaro et al., 2018). ~~Both groups with ADHD~~ ASD+ADHD and ADHD groups experienced significantly slower RT in attention switching, defined as the ability to disengage from one task to undertake another, whereas children with ASD-only did not exhibit these types of impairments (p < 0.01).

Data on organizing and planning showed that ASD and ASD+ADHD had a similar performance, with no significant differences (Colombi and Ghaziuddin, 2017). Unterrainer et al. (2016) did not find significant differences in global performance in TOL between ASD and ASD+ADHD groups. However, from a developmental approach, children with ASD+ADHD were found slightly more impaired and less accurate at younger ages in global performance on the computerized London Tower task, while at older ages their results were similar to TD. Thus, the expected greater difficulty for the addition of both diagnoses in ASD+ADHD was not present, at least in older children, suggesting delayed development.

In another study (Kado et al., 2020), two steps of the Wisconsin card sorting test (KWCST) were used to analyze the age-related differences of EF. The second step is separated by a short pause, during which the examinee is given instructions. Subsequently, all of the cards are sorted again in order to assess if the experience in the first step and the instructions are effectively applied. For improvements between the first and second step within each group, both scores were compared. In the comparison of KWCST performance by age among children with ASD, ASD+ and TD, the older ASD+ADHD children obtained significantly more categories of achievement (d=0.68, CI [-1.06, -0.31]) and less perseverative errors (d=0.58, CI [-0.52, 1.72]) than the ASD children in the first step. However, younger ASD+ADHD children showed on the second step a worse performance than ASD children regarding the number of responses (d= 0.78, CI [-2.98, 1.30]). The findings of the two previous studies indicated that younger ASD+ADHD individuals struggle to sustain attention and older ASD-only individuals have flexibility problems, suggesting that impulsivity symptoms of ADHD are likely to have a ´protective´ effect against behavioral rigidity.

A visual search task was selected to compare temporal processing in ADHD, ASD, ASD+ADHD and TD groups in overall search performance and intra-subject variability (ISV) (Seernani et al., 2020). The results showed that the ASD-only group exhibited significantly better search performance (slower mean fixation duration, d= 0.34, CI [-12.69, 11.99]) while ASD+ADHD group showed increased ISV (more entry time to cue, d= 0.90, CI [-0.97, -0.26]). ~~In particular, the ASD+ADHD group showed significantly more variability in initiation of search (d= 0.60), had slower mean RT (d= 1.12) and fewer number of fixations (d=0.55) than ASD-only group.~~

~~In another investigation,~~ ISV in RT ~~(Biscaldi et al., 2016)~~ also proved to be inconsistently high across a range of tasks in ASD+ADHD children, although the difference was non-significant, SSRT and N-Back task RT were slower in ASD+ADHD than the ASD group (Biscaldi et al., 2016). The profile of the differences between the ASD-only group and the TD group was similar to the profile of differences between the ASD+ADHD and ASD-only subgroups, indicating that the impairments in ASD could be due to the comorbidity with ADHD. In a subsequent study that included an additional group of children with ADHD (Salunkhe et al., 2018), patients with ASD+ADHD or ADHD, but not ASD alone, presented high ISV levels across different tasks and temporal processing deficits (comparison of ISV between the two groups with ASD, d= 1.02). Even more, ASD+ADHD participants, in comparison to ASD-only individuals, showed worse variability indexes in slow tasks (mean RT, d= 1.02, CI [-60,06, 58.01]) and fast incentive tasks (mean RT, d= 0.39, CI [-49.37, 48.58]). Whilst RT is a potential marker of ASD+ADHD comorbidity in slow and less rewarding conditions, it had no discrimination power in faster and more rewarding conditions (Tye et al., 2016).

Finally, two studies reported data from ecological scales of EF in daily life. The first of them(Dajani et al., 2016) conducted a latent profile analysis that included a combination of EF indicators. In the ASD+ADHD group, 92% of children were classified as having impaired EF, compared to 47% of the children with ASD and 63% of the children with ADHD. The second study (Berenguer et al., 2018b) showed that the group with ASD+ADHD, as well as the ADHD group, experienced significantly more deficits in WM, planning, and monitoring than the group with ASD-only. In addition, the ASD+ADHD group showed significantly worse levels on inhibition and shift than the ASD group.

**-insert Figure 2- Fig 2. Forest plot summarizing the results of the studies on executive functions**

*Sensorial Processing*. Research comparing children with ASD+ADHD to individuals with a single diagnosis showed that the co-occurring condition presented an overall atypical sensorial processing (SP) in auditory (d= 1.09, CI [-0.29, 2.53]) and multisensorial processing (d= 0.70, CI [-0.27, 1.63]) (Dellapiazza et al., 2020). The comparison of the ASD, ADHD, and ASD+ADHD groups on the parents’ and teachers’ ratings of SP, social participation, and praxis revealed interesting differences (Sanz et al., 2017). In the home context, the ASD+ADHD group obtained a higher level of body awareness dysfunction than the ASD group (d= 0.9, CI [-3.03, 0.37]), alongside greater social participation dysfunction (SOC) than the ADHD group (d=1.4, CI [-3.62, 0.50]). In the classroom context, the ASD+ADHD group obtained worse scores than the ADHD group on SOC (d= 2.3, CI [-4.18, -0.55]) and hearing (d=1.52, CI [-3.66, 0.62]). In contrast, the ADHD group did not obtain worse scores than the ASD group on any variable. Therefore, three components of SP were significantly more affected in ASD+ADHD than in ASD alone.

*Social Cognition.* Some support was found for the hypothesis that the presence of ADHD in children with ASD associates greater impairments in affective prosody than in children with ASD alone (Oerlemans et al., 2014). Also, significant differences were noted among the clinical groups (ASD-only and ASD+ADHD) in several elements of facial emotion recognition such as happiness recognition and % total errors affective prosody recognition. Similarly, children with ASD+ADHD showed less development of empathy, measured by “reading the mind in the eyes”, than children with ASD alone, with differences between groups close to significance (Colombi and Ghaziuddin, 2017).

In another study (Waddington et al., 2018a), whilst no significant differences were found in emotion recognition (ER) between the ASD+ADHD, ASD-only, and ADHD-only groups, the comorbid group presented the greatest discrepancy with the control group on speed of visual ER (p=0.007; d=0.39), speed of auditory ER (p<0.001; d=0.77) and accuracy of auditory ER (p=0.05; d=0.75). Moreover, four subgroups of children were identified according to their visual and auditory ER skills finding a link between and an increased risk of ASD as well as ADHD (Waddington et al., 2018b). Specifically, all subgroups included patients with diagnoses of ASD-only, ADHD-only, and ASD+ADHD. However, the lowest performing subgroup included the highest percentage of patients (66.07%) and the lowest percentage of controls (10.09%), scoring the highest on ASD/ADHD measures.

Parent ratings were also used to assess the application of ToM skills in everyday social contexts in different domains, such as early skills, social references and understanding basic emotions, meta-representations, and second-order inferences (Berenguer et al., 2018b). The comparative analyses among ASD, ADHD, ASD+ADHD, and control groups showed a similar deficit in the application of ToM skills in both groups with ASD, whose results were worse than those obtained for the ADHD-only group.

**-insert Figure 3- Fig 3. Forest plot summarizing the results of the studies on social cognition**

**3.2. ~~Adaptive/social~~ Behavioral phenotype of co-occurring ASD+ADHD**

~~Ten~~ 19 studies dealt with the behavioral functioning ~~adaptive/social characteristics~~ of children and adolescents with ASD+ADHD:adaptive/social characteristics (Ashwood et al., 2015; Avni et al., 2018; Chiang et al., 2018; Craig et al., 2015; Magnusdottir et al., 2016; McFayden et al., 2020; Ng et al., 2019 a,b; Rao and Landa, 2014; Salley et al., 2015; Scandurra et al, 2019; Turygin et al., 2015) and emotional/behavioral difficulties (Berenguer et al., 2018b; Carta et al., 2020; Craig et al., 2015; Chen et al., 2015; McClain et al., 2017; So et al., 2017; Yamawaki et al., 2020). Most of the studies had a cross-sectional design; fourteen of them included three clinical groups and four studies had ASD and ASD+ADHD groups. In total, the median number of participants was 169, aged between 2 to 18 years and 81.5% of males in the samples. Participants’ cognitive levels were reported in twelve studies with mean IQ scores ranging from 72 to 111. Six studies were conducted in Europe, six in North America, one in Israel, two in Japan and another two in Taiwan. Please see supplementary table 2.

*Adaptive/social characteristics.* Although currently there is no universal definition of the concept of "adaptive", the most widely held view refers to an individual's ability to perform skills independently in order to meet personal needs and environmental demands (Price, Morris, & Costello, 2018). The comparison of the adaptive behavior of ASD-only, ASD+ADHD, and ADHD-only groups (Turygin et al., 2015) showed that from early childhood, the adaptive skills of young children with ASD and ASD+ADHD differed from those of the ADHD-only group in several domains: adaptive, motor, communication and personal/social. However, there were no significant differences between ~~both~~ the ASD-only and ASD+ADHD groups~~, with and without ADHD~~. Several studies in mid-childhood (Ashwood et al., 2015; Craig et al., 2015; Scandurra et al., 2019) have supported a general tendency towards a worse adaptive general profile (communication, daily living skills, and socialization) in the ASD and ASD+ADHD groups than in the ADHD-only group. In any case, the differences between ASD+ADHD and ASD-only individuals did not reach statistical significance. Nevertheless, other data (Rao & Landa, 2014) indicated significant differences on all VABS subscales, with mild to impaired ranges in the ASD-only group, while the mean scores were severely impaired on the socialization and daily living domains in ASD+ADHD. The ASD+ADHD group also had greater delays in social awareness (d=0.76, CI [-3.66, 2.19]), social communication (d=0.77, CI [-3.92, 2.50]) and social motivation (d=0.70, CI [-3.83, 2.41]).

In addition (Chiang et al., 2018), the analysis of various indicators demonstrated that ADHD negatively impacted all domains of school adaptationThe comorbid group also exhibited worse attitudes towards school work (d= 0.79, CI [-0.93, -0.65]), more school interaction problems (d= 0.57, CI [-0.67, -0.48]) and more school behavioral problems (d=0.76, CI [-0.85, -0.70]).

Parent ratings of day-to-day social behavior highlighted more severe attentional problems in children with ASD+ADHD and ADHD-only compared to those with ASD alone, being close to statistical significance (p=0.06, Ng et al., 2019a). Furthermore, ADHD symptoms showed a different association with social impairments in children with ADHD versus children with ASD+ADHD. Specifically, caregiver ratings of hyperactivity/impulsivity were the main explanatory factor of the Social Responsiveness Scale total scores in the ADHD group, whereas reports of inattentiveness were the strongest explanatory factor in the comorbid group (Ng et al., 2019b). When examining possible predictors of social communication and interaction problems, comorbid ASD+ADHD, but not ASD alone or ADHD alone, could predict global social impairment. This effect ~~that~~ may be increased by the presence of sluggish cognitive tempo, measured with the Slugglish Cognitive Tempo subscale (SCT) derived from four items on the CBCL (McFayden et al., 2020). However, some results suggested the possibility that the negative effect of ADHD on ASD children in the communication domain and VABS general composite score of adaptive functioning is limited to high functioning boys (Magnusdottir et al., 2016).

The influence of the severity of ADHD symptoms on adaptive skills has been explored across several psychiatric disorders, ASD among them. The comparison between four groups (ASD, ASD+ADHD, ASD+anxiety, and ASD+ADHD+anxiety) (Avni et al., 2018) noted that participants with ASD-only experienced a higher adaptive functioning than the comorbid groups. Specifically, ASD+ADHD participants showed significant impairments in socialization compared to ASD-only. Moreover, the presence of two comorbidities, ASD+ADHD+anxiety, associated more deficits, affecting the socialization and daily living domains (d=0.89, CI [-0.86, 2.65] and d=0.62, CI [-1.19, 2.44], respectively).

**-insert Figure 4- Fig 4. Forest plot summarizing the results of the studies on adaptive/social skills**

*Emotional/behavioral difficulties.* The assessment of mental health difficulties in patients with ASD-only, ADHD-only, and with both disorders in a large sample reported that patients with ASD+ADHD had a greater risk of experiencing bipolar disorder (3.4% vs 1.2% vs 4.0% vs 0.1%, p < 0.001), depressive disorder (6.4% vs 5.6% vs 7.7% vs 0.6%, p < 0.001), anxiety disorder (17.4% vs 18.3% vs 7.3% vs 0.5%, p < 0.001), disruptive behavior disorder (8.2% vs 6.7% vs 2.1% vs 0.1%, p < 0.001), and tic disorder (7.1% vs 5.5% vs 3.6% vs 0.8%, p < 0.001) compared to ADHD-alone, ASD-alone and TD (Chen et al., 2015). However, no significant differences were found regarding the prevalence and severity of internet addiction in adolescents with ASD+ADHD, ASD or ADHD alone (So et al., 2017).

The ASD+ADHD problems profile has been explored using the strengths and difficulties questionnaire (SDQ). The total problem score was significantly higher in the comorbid group than in the group with ASD alone (Berenguer et al., 2018b). The ASD+ADHD, as the ADHD-only group, had more hyperactivity symptoms than the ASD-only group (d=1.18, CI [-1.31, 0.55]), while peer relations were more affected in the ASD-only and ASD+ADHD groups than in the ADHD group (d=1.62, CI [2.11, -1.13]). Also (Yamawaki et al., 2020) higher scores were reported in the comorbid group, compared to the ASD-only, on the SDQ subscales of hyperactivity (d=1.12, CI [-1.62, -0.64]), and conduct problems (d=0.94, CI [-1.31, 2.49]). The greater severity of problems in the comorbid condition was also supported by studies analyzing an extensive profile of behaviors with the child behavior checklist (CBCL). Thus, externalization and other subscales such as conduct (d=0.99, CI [-2.37, 0.38]), aggressive (d=0.89, CI [-2.42, 0.64]), and thought problems (d=0.94; C I [-2.95, 1.07]) were more affected in the ASD+ADHD than the ASD group (Carta et al., 2020; Craig et al., 2015). Moreover, using the Conners rating scale, more impairments in ODD (d=1.15, CI [-4.06, 1.76]), cognitive problems (d=1.05, CI [-4.18, 2,08]), anxiety (d= 1.96, CI [-3.52, 1.60]), perfectionism (d= 1.28, CI [-3.93, 1.38]), social problems (d=1.01 , CI [-4.74, 2.73]), and emotional lability (d=1.18, CI [-4.15, 1.79]) were reported for the ASD+ADHD group than the ASD-only (Craig et al., 2015).

The majority of studies highlight more severe attention and hyperactivity/impulsivity problems in individuals with ASD+ compared to those with a single diagnosis. However, a recent study (McClain et al., 2017) reported unexpected results, suggesting that ASD+ADHD exhibited similar levels of ADHD symptoms to children with ASD or ADHD alone, which is at odds with previous findings , as the authors themselves point out.

**-insert Figure 4- Fig 4. Forest plot summarizing the results of the studies on emotional/behavioral difficulties**

**4. Discussion**

The DSM-5 provided official support for the diagnosis of co-occurring ASD+ADHD, prompting a progressive increase in research on the characteristics of individuals with the double diagnosis. The present systematic review summarizes the main findings from recent empirical literature. It included 35 studies focusing on areas that could enhance our understanding of the cognitive and behavioral characteristics of individuals with ASD+ADHD . However, the results can be considered as preliminary, considering the limited number of investigations carried out.

Our findings extend those of previous non-systematic reviews (Antshel et al., 2016; Antshel and Russo, 2019; Taurines et al., 2012; Yerys, 2020) showing that ASD+ADHD individuals display severe impairments in cognitive functioning. EF and RT indexes continue to be the main focus of studies addressing cognitive domains, followed by studies about ToM and ER. However, research on sensorial processing is limited (two studies) despite that the hypo/hypersensitivity to visual, tactile and auditory input is included within DSM-5 diagnostic criteria for ASD (American Psychiatric Association, 2013). The presence of ADHD had a negative impact on inhibitory and attentional control as well as on increased ISV in RTs, providing evidence that the severity of the neuropsychological dysfunction is greater in the ADHD and ASD+ADHD groups than in the ASD and TD groups. On the other hand, some inconsistencies in the results for WM processes do not allow us to firmly establish more pronounced impairments in ASD+ADHD, compared to one single diagnosis. The ability to mentally manipulate information for a time seems to be more impaired in children with ASD+ADHD, compared to children with ASD only. However, in two studies, no significant differences were found between the two groups of children with ASD, possibly due to the influence of factors related to the computerized presentation of the tasks or medication.

Furthermore, studies on executive processes of planning and flexibility with a developmental perspective, pointed out that the results of older ASD+ADHD children tended to match those of the control group. This finding suggests that, over time, impulsivity which is characteristic of ADHD may counteract the inflexibility observed in ASD. In other words, the presence of ADHD symptoms in ASD could favor cognitive flexibility. Regarding sensory processing, the ~~few~~ data ~~available from the studies~~ reviewed suggests an overall atypical sensory processing and greater auditory impairments in individuals with ASD+ADHD, compared to the ASD group. In fact, more than 60% of children with ADHD exhibit atypical sensory processing (Mimouni-Bloch et al., 2018), particularly on scales of the Sensory Processing Measure, with small to medium effect sizes (Pfeiffer et al., 2015). These deficits may contribute to the inaccurate behavioral and learning responses (Shimizu et al., 2014).

The results also suggested the greater overall deficit in social cognition in the comorbid diagnosis. Direct comparisons of the groups with ASD, ADHD, and ASD+ADHD on ER and ToM tasks showed that the latter group was associated with more pronounced impairments in reading other people's emotions, feelings, and affective prosody, as well as less development of empathy. The problems with RT speed, inhibition, and attention that are often present in ADHD may partly explain the deficits in social processing tasks.

We expected that individuals with ASD+ADHD would present poorer adaptive/social functioning and more emotional/behavioral difficulties (Gillman et al., 2000; Leitner, 2014). Overall, the ASD+ADHD condition ~~clearly associated~~ seemed to exhibit many adaptive and social problems in the communication, daily living skills, and socialization domains that are often present since early childhood. Although the results of the studies on this area are not totally consistent, the general trend showed more severe impairments in individuals with ASD+ADHD in comparison to those with a single diagnosis of ASD or ADHD, Furthermore, co-occurring ASD+ADHD, but not an ASD diagnosis alone, predicted greater adaptive and social impairments, with inattention being the most important predictor of social responsiveness.

The comorbid group tended to present more externalizing problems than the group with ASD-only, and often similar levels of emotional and behavioral difficulties to those individuals with ADHD. The findings are in line with a cohort study of ASD-only participants (Mansour et al., 2017) where ASD severity did not contribute to emotional and behavioral impairments and by contrast, greater ADHD severity was significantly related to anxiety, depression, somatic complaints and social problems. The majority of the seven studies that addressed the comorbidity with other mental health difficulties relied the assessment on parent/teacher reported questionnaires such as SDQ or CBCL while rarely used clinical standardized interviews. Another study which used ICD-9 (Chen et al, 2019), the dual diagnosis has been identified as a risk factor for developing psychiatric conditions such as bipolar disorder or depressive disorder in adolescence, compared to ASD or ADHD alone. Despite this, the reviewed literature does not inform potential factors that predict the presence, continuity and change of frequent mental disorders in this co-occurring condition.

Summarizing, individuals with ASD+ should be considered a particularly vulnerable group, which deserves specific clinical attention. The identification of their specific clinical characteristics should inform treatment interventions. In school-aged children, psychoeducational areas to target may include working memory and cognitive flexibility-training, coupled with self-regulation strategies which contribute to enhance academic outcomes of students with ADHD (Moore et al., 2018). In addition, even though the tolerability and efficacy/effectiveness of ADHD pharmacotherapy in individuals with ASD+ individuals is lower compared those with ADHD- , there is support for its use in the treatment of inattentive and hyperactive/impulsive symptoms in individuals with ASD+ (Rodrigues et al., 2020).

**5. Limitations and Future Perspectives**

Some limitations were found in the research design of the reviewed studies. In spite of the time elapsed since the introduction of the DSM-5, the majority of studies used various diagnostic classification systems. In contrast, only a small percentage of studies applied the most updated criteria from the DSM-5 to diagnose ASD and ADHD. Sample sizes were generally small and homogeneous, including mainly male participants. Nevertheless, the gender proportion was representative of the prevalence of males of the disorder. The studies were not age-matched which limits the generalizability of our findings and they frequently included participants with a level of intellectual functioning ranging from low average to above average, so the conclusions cannot be extrapolated to children or adolescents with ASD+ADHD and intellectual disability. Future research could use larger samples and include groups of girls, individuals with intellectual disability as well as differentiate between ADHD presentations (combined, inattentive and impulsive/hyperactive) that have not received enough attention. Another limitation has to do with the developmental stage addressed in the studies. The focus was on mid-childhood and pre-adolescence. However, identifying and providing information about the specific co-morbid group, with an emphasis on early childhood and the preschool period, will help to develop early intervention strategies.

 In addition, some studies suggest differentiated developmental trajectories for the ASD versus the ASD+ADHD conditions, although these findings rely on cross-sectional designs. There is a lack of studies that analyze the course of ASD+ADHD over time. In the future, prospective designs will make it possible to examine how clinical diagnoses of ASD and ASD+ADHD differ in cognitive, and behavior domains throughout the lifespan and to identify mediators involved in different trajectories. The study of educational needs is another challenge for the research in next years. Despite its importance in socio-personal adjustment the topic has not been considered until now.

Finally, the co-occurrence of ASD and ADHD seems to be supported, at least partly, by shared genetic contribution (Ghirardi et al., 2018) and neuro-cognitive networks, (Bethlehem et al., 2017). The results of genetic, neuropsychological and neuroimaging studies suggest possible pathophysiological links between ASD and ADHD affecting key fronto-striatal and fronto-parietal circuits that are important for performing EF and complex cognitive functions as attentional process (Rommelse et al., 2011). In this sense, there is an evident need in the upcoming years for a better understanding of the etiology of this comorbid condition and determine the shared and distinctive genetic and neurobiological basis as well as the complex interactions with environmental factors (e.g poverty, socio-cultural deprivation, poor parenting). It is possible that cognitive and behavioral phenotypes of comorbid individuals are linked to brain abnormalities of ASD and ADHD. In fact, using functional magnetic resonance imaging during a vigilance task, common and different underlying pathophysiology in brain function of youth with ASD and youth with ADHD have been identified (Cristakou et al., 2013). Another recent study suggested that the pathophysiology of ASD+ADHD could also be related to somatosensory deficits and delayed maturation of the left postcentral gyrus (Mizuno et al., 2019) . Furthermore, one exploratory pilot study (Waltes et al., 2019) found that ASD variants of the glutamatergic system interact with biological and psychosocial risk factors influencing the risk for ADHD common comorbidities. On the one hand, the identification of brain-based biomarkers could assist in diagnosis process and monitoring the treatment effectivity. On the other hand, this line of inquiry would allow to identify profiles of individuals with ASD at genetic or familial risk for ADHD and to predict long term outcomes for children with the co-occurring disorder.

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