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Impact Of Emotional Disorders In The Functionality Of Children And Adolescents With Autism Spectrum Disorders Review

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Abstract

The main object of this review is to understand how emotional disorders develop and how they may interact with the score of functioning or with the severity of symptoms in autism spectrum disorder. We hypothesize that emotional disorders may influence negatively in the functionality of these patients.

This review was based on a systematic research of published articles available up to July 2014. The initial literature search resulted in 149 citations. Of those, 21 met the inclusion criteria. Many of the unselected studies from the initial pool involved samples outside the targeted age range (e.g., adults or pre-school children) or with non-ASD developmental disabilities. This review concluded that comorbid with emotional disorders among patients with ASD may be more common than previously thought. It may have consequent impairment in their psychological profile, social adjustment, adaptive functionality, cognitive and global functioning and should alert clinicians the importance of assessing mood disorders in order to choose the appropriate treatment.

Keywords: Autism spectrum disorder; Emotional disorder; Adolescents

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Introduction

Autism Spectrum Disorder (ASD) is characterized by deficits in social interaction and communication, as well as the presence of stereotyped behaviour and restrictive interests [1]. In the past, all psychiatric issues in children and adults with autism used to be attributed to autism itself. However, an increasing number of studies are arguing about accepting behaviours and symptoms that had been considered additional or associated features of ASD as potential indicators of the presence of comorbidities warranting additional diagnosis.

An instinctive reaction is that comorbidity will generally lead to more severe impairments as a result of the cumulative effects of having more than one disorder [2]. Otherwise, the pathogenic courses that result in comorbidity may be overlapping, but nevertheless, unique. In the example of ASD, research has been delayed to some extent by nosological preconceptions about co-occurring symptomatology, many of which remain largely uncertain [3, 4].

Autism is generally a lifelong condition beginning in childhood and with pathological outcomes in adulthood. Outcomes are often described as difficulties or issues in finance, employment and socialization [5-7]. Findings from these studies indicate substantial progress in the care and treatment of persons with ASD, allowing individuals to get more involved in community life with reduced burden on their families. Despite these advances, living with autism can be difficult [8], particularly during developmental transitions and critical periods of childhood. While all children with ASD exhibit one or more of the core domains (impairments in social interaction, communication and behavioural functioning), some children may have associated problems with mood and affect. Therefore, parenting for some children with ASD can be challenging and can severely impact family functioning as well as the health and wellbeing of caregivers and other family members [9, 10]. Clearly, successful interventions for children with ASD have the potential to greatly affect health outcomes for the child and can have extensive economic benefits by contributing to the child's independence when reaching adulthood.

There is no doubt that comorbid condition can complicate the patient's management. Reliable diagnosis of comorbid psychiatric disorders in children with ASD is of major importance. Emotional disorders are one of the main comorbid disorders often find in this population [11]. In this order, anxiety-related concerns are among the most common presenting problems for children and adolescent with ASD [12]. When other problematic symptoms are recognized as manifestation of a comorbid psychiatric disorders rather than just isolated symptoms, more specific treatment is possible. For this reason, one of the goals of the new DSM-5 classification must be to identify subgroups of ASD, including comorbid disorders and adaptive functioning, which may be important to understand the biological mechanisms, the clinical results and the reactions of the individuals with ASD [13] (Figure 1).

In the field of clinical research on ASD, we have well-established valid tools for the diagnosis of the spectrum disorder with Autism Diagnostic Interview-Revised [ADI-R; [14]] and Autism Diagnostic

Observation Schedule [ADOS; [15]], but a limited repertoire of evidence-based tools for assessing change in day-to-day functioning.

In this paper, we focused on emotional disorders which include: anxiety disorders [including obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD)] and mood disorders (bipolar affective disorder, depression and mania). We strongly believe that these pathologies can influence significantly in the prognosis across the social, familiar, adaptive, cognitive and global functioning of patients with ASD.

The main object of this review is to understand how emotional disorders develop and how they may interact with the score of functioning or with the severity of symptoms in ASD. We hypothesize that emotional disorders may influence negatively in the functionality of these patients. For all the reasons previously exposed, the specific aims of this review are: (1) to summarize the empirical research on the prevalence of emotional disorders in children and adolescent with ASD, (2) to provide which is the impact on the functionality or severity for this patients and (3) to offer future research that could provide better understanding in relation with the impact of emotional disorders in this population.

Methods

This review was based on a systematic research of published articles available up to July 2014. The Psych-Info and Medline online databases were searched using the following key words: ("autism" or "autistic disorder" or "asperger(s)", or "pervasive developmental disorder") AND (anxiety or anxious or mood disorders or bipolar affective disorder or depression or mania or obsessive compulsive disorder (OCD) or post-traumatic stress disorder (PTSD) or comorbidity AND functioning or functionality). Abstracts of identified articles were then screened for the following inclusion criteria (Table 1).

Figure 1 Diagnostic and statistical proposal from the mental diseases manual. 5Th edition (dsm-5). Associated criteria and characteristics to be considered for the characterization of asd [13].

Table 1 Inclusion and exclusion criteria.

Inclusion Criteria

- (a) The target population included children or adolescents (between 6 and 18 years) diagnosed with an ASD including autism, Asperger's Disorder or PDD-NOS.
- (b) Prevalence of any emotional disorder (anxiety or anxious, mood disorders, bipolar affective disorder, depression, mania, OCD or PTSD) in this population.
- (c) Emotional disorders assessment with direct observation or report (from parent, teacher, or child) evaluations.
- (d) The association with score of functioning or any predictor of severity for the ASD. There were no restrictions on minimum sample size. All measures of functionality or autism severity symptoms were included.

Exclusion Criteria

- * Unpublished dissertations or studies published more than 20 years ago. Secondary reviews were excluded, as well as studies not published in English.

For brevity, the following abbreviations are used throughout this review: Autistic Disorder (AD), Asperger's Disorder/Syndrome (AS), Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), High-Functioning Autism (HFA), and Autism Spectrum Disorder (ASD).

The initial literature search resulted in 149 citations. Of those, 21 met the inclusion criteria. Many of the unselected studies from the initial pool involved samples outside the targeted age range (e.g., adults or pre-school children) or with non-ASD developmental

disabilities. The second phase, which systematically examined the three major autism journals, identified four additional articles. Because the purpose of the studies varied, they were classified into four broad categories according to their primary question in relation with the functionality: cognitive and executive functioning, social and family functioning assessment, global assessment of functioning or quality of life and other measure of autism severity symptoms. It should be noted that some of the studies addressed more than one domain. In this case, the

studies were grouped and reviewed according to their primary research question.

Results

Cognitive and executive functioning

In this review, the authors focus on measures used in ASD clinical studies in order to evaluate the functionality (**Table 2,2b**). Out of the 25 studies, 6 of them focused their primary research question according with the cognitive and 2, with the executive functioning scores. Six studies reported information about the prevalence and the impact in the functioning being the main comorbidity the anxiety disorder [11, 16-18]. The range of anxiety disorders was between 39,2 to 42,7 % [11, 16]. All of these studies used different measures in order to assess the anxiety comorbidity and the ASD diagnosis. Weisbrodt et al. [19] and Thede & Coolidge [20] used clinical evaluations which included interviews by child psychiatrists according to DSM-IV criteria. The rest of them [11, 16-18] confirmed the diagnosis with at least one of the assessment criteria described on the **Table 2,2b**. Simonoff et al. [11] and Hollocks et al. [17] used the same sample of patients. As we can see on the **Table 2** and according with the main results, Sukhodolsky et al. [16] and Weisbrodt et al. [19] found a positive correlation; children with higher IQ were found to experience the most severe anxiety. On the other hand, Simonoff et al. [11] found that ASD diagnosis, IQ, and adaptive behavior were not associated with the presence of an anxiety disorder. Similarly, Pearson et al. [18] concluded that verbal IQ was not found to have any correlation with anxiety disorders according to the parent reports of the population in the sample.

Regarding executive functioning, Hollocks et al. [17] indicated a significant association between poorer executive functioning and higher levels of anxiety, but is not associated with depression. However, Thede & Coolidge [20] found no significant differences in executive functioning between the AS and HFA.

Mukaddes et al. [21] and Simonoff et al. [22] reported information about comorbidity with depressive disorder and severe mood dysregulation and problems (SMP). They used the same sample so the results should not be interpreted independently (**Table 2**). Simonoff et al. [22] is the one and only study that evaluated the SMP in patients with ASD. They found that intellectual ability and adaptive functioning did not predict SMP and relationships between SMP and tests of executive function were not significant after controlling for IQ.

Global functioning and quality of life

Out of the 25 studies, 5 of them are described in this section. Mattila et al. [23], Mazzone et al. [24] and White et al. [25] focused their primary research question in accordance to the Children's Global Assessment Scale (CGAS), Farrugia [26] used the life interference measure (LIM) and Van Steensel et al. [27] used the EuroQol-5D.

Four studies reported information about co-morbidity with anxiety disorder [23, 25-27]. As it is shown in the **table 3**, all of these studies used different measures to assess the ASD diagnosis and anxiety comorbidity. In the study of Farrugia [26],

the diagnoses from the community were accepted and were not confirmed as part of the study. However, the rest of the studies confirmed the diagnosis with at least one assessment. All the studies with the exception of Mattila et al. [23], all the other studies used different control samples (**Table 3**). White et al. [25] used ASD with anxiety comorbidity without cognitive behavioural therapy (CBT) intervention to compare with a similar sample of patients who were receiving CBT. Regarding the main results, Farrugia [26] found that the correlations among anxiety symptoms, negative automatic thoughts, behavioral problems and overall impairment were significantly higher in the AS group than in either comparison group. In the same way, Mattila et al. [23] found that oppositional defiant disorder (ODD), major depressive disorder and anxiety disorders as comorbid conditions indicated significantly lower levels of functioning. Similarly, in the study of Van Steensel et al. [27] the results showed that higher anxiety severity scores on the ADOS, were associated with a lower quality of life, irrespective of the sample group. Although all of them showed similar results, they used different functionality scales (**Table 6**). On the other hand, White et al. [25] found that there was no relationship between Developmental Disability (DD)-CGAS scores and parent-reported anxiety scores, adaptive behaviour scores, or educational placement. Mazzone et al. [24] was the only study that considered the association between functioning and depressive symptoms. The results showed that higher levels of depressive symptoms increase the risk of poorer global functioning. There was no significant association between IQ and mood symptoms, behavioural problems or global functioning.

Psychosocial and/or family functioning

Out of the 25 studies, 5 of them [28-32], focused their primary research question accordingly with the psychosocial or family functioning. The measures used for assessing this sort of functioning were very heterogeneous between the different studies (**Table 6**). Only Bauminger et al. [32] focused their main functioning assessment on family evaluation.

Joshi et al. [28] and Wozniak & Biederman [31] focused on mood disorder in patients with ASD and the impact on the functionality. The diagnostic measures were similar on both studies. However, as it is shows in the **table 4**, the samples characteristics and the control group were very different. Regarding the main results, Joshi et al. [28] examined not only the social functioning, but also the clinical and familiar correlates of bipolar disorder when it occurs with and without ASD comorbidity in a well-characterized, research-referred population of youth with bipolar disorder. Wozniak & Biederman [31] systematically investigated the overlap between mania and PDD in a consecutive sample of referred youths, examining its prevalence and correlates. According with the purpose of this review, the results found by Joshi et al. [28] were inconsistent. Wozniak & Biederman [31] found that the functioning of children with PDD+ mania was poorer than PDD group, as evidenced by their scores on the social adjustment inventory for children and adolescents (SAICA) and the global assessment of functioning (GAF) (**Table 6**).

The rest of the studies described in this section assessed the

association between the social functioning and its comorbidity with anxiety [29, 30, 32]. They used different ASD diagnostic agreements (**Table 4**). According with the main results, Meyer et al. [29] concluded that anxiety was related to deficits in social awareness and experience. In the opposite effect direction, Bellini [30] found that physiological arousal and social skills deficits combined contributed to a significant variance in symptoms of social anxiety. Finally, Bauminger et al. [32] investigated the relationship between internalizing and externalizing (I-E) behaviors and family variables, including both parenting stress and quality of attachment relations. The results were inconsistent according with the purpose of this review (**Table 4**).

Measures of symptoms severity or adaptive functioning

In the last section, we found 7 studies that describe the impact on the functionality through the severity of symptoms, using a range variability of measures (**Table 5**).

Bradley et al. [33], Van Steensel et al. [34] and Gadow et al. [35] evaluated the comorbidity with anxiety disorders. The sample of patients and the diagnosis measures were also very different (**Table 5**). According to the main results found on their studies, Gadow et al. [35] reported that the severity of ASD appeared to be negatively associated with psychiatric symptoms. The following studies were inconsistent relating to this review; Bradley et al. [33] concluded that the children with AD had an average of 5.25 clinically significant disorders based on cut-off scores on the diagnostic assessment of the severely handicapped-II (DASH-II) (**Table 6**) compared to an average of 1.25 for the non-AD group. The goal of the Van Steensel et al. [34] study was to estimate the societal costs of children with high-functioning ASD and comorbid anxiety disorder and to explore whether costs are associated with the type/severity of ASD or anxiety disorder. They found that the mean of severity score of an anxiety disorder did not differ between the ASD+ anxiety disorder and anxiety disorder group.

Regarding comorbidity with mood disorders, we found 3 studies [2, 36, 37]. As we can see in **table 5**, they used very different samples, diagnosis and control groups. Relating to the main results, Simonoff et al. [36] and Munesue et al. [37] found more consistent results than Gadow et al. [2] (**Table 5**). Simonoff et al. [36] concluded that lower IQ and adaptive functioning predicted higher hyperactivity and total difficulties scores. In the same way, Munesue et al. [37] established that patients with mood disorder showed significantly lower scores on the Tokyo autistic behaviour scale (TABS) (**table 6**) than those without mood disorder.

Finally, Pfeiffer et al. [38] was the only study that evaluated both, comorbidity between anxiety and depression disorder. They found that there were no significant relationships between depression and overall adaptive behaviour or anxiety and overall adaptive behaviour.

Discussion

Based on the data presented in these studies collectively, there is no doubt that emotional problems are quite prevalent in young

people with ASD. Variables such as specific ASD diagnosis, level of cognitive and global functioning, degree of social and family impairment, adaptive functioning and severity of symptoms likely have an influence on the individual's experience of emotional problems. Unfortunately, there is little clarity on how best to assess the functionality in this population and the direct impact of the emotional disorders in the youth patients with ASD functioning. The studies summarized in this review have addressed a broad range of questions about the functionality impact of emotional disorders in young people with ASD. The main strength of this review is that our intent was to not only summarize the available empirical literature, but also emphasize the need for consistent future research.

Methodology issues

By addressing methodological issues that limit the findings of the extant literature, future studies can contribute noticeably to our better understanding of the impact of emotional disorders in this population and answer more pointed scientific questions. Many of the reviewed studies [e.g., [17, 22, 33]], reported using 'gold standard' diagnostic tools for ASD [i.e., ADI-R [14] and ADOS [15]]. Some studies did not employ any independent confirmation of the diagnoses, instead they included children based solely on previous clinical diagnoses of ASD [e.g., [21, 26, 30]]. Other studies, such as Gadow et al. [35], used rigorous diagnostic evaluation procedures (e.g., interview, observations) and established inter-diagnostician reliability, but did not use the ADI-R or ADOS, which were designed specifically for the assessment of autism and other spectrum conditions.

The studies reviewed demonstrated little consistency in terms of how comorbidity disorders were measured. Research on the applicability of traditional measures of childhood emotional symptoms is sorely needed. If valid and reliable measures cannot be identified, new measures will need to be developed in order to accurately capture symptoms of emotional problems in people with ASD. For example, previous reports have supported the validity of the mania diagnosis in non-PDD children when examining clinical correlates [31] as well as external validators such as the Child Behavior Checklist (CBCL) [39], but not in PDD children. Until we have consensus on 'best practice' measurements, a healthy scepticism is called, with respect to the precision of the tools we currently have for measuring childhood emotional problems when evaluating children with ASD. In the same way, the functionality measures described in this review were very heterogeneous and with a widespread variability across the different studies. Further research is necessary for assess the impact on functionality (global scores, cognitive, social, adaptive functioning. etc.) in this population.

A methodological concern seen in most of the studies is the inclusion of mixed ASD samples, comprised of youth with AD, AS, and PDD-NOS. Also, given differences in cognitive functioning usually associated with ASD subtypes, future studies should examine how diagnosis might independently be associated with emotional disorders.

The majority of the studies reviewed used clinic-based samples

[e.g.,[30, 35]] or samples recruited from a variety of other sources (e.g., autism support groups) [e.g., [18, 38]]. In contrast, Simonoff et al. [11] drew their ASD sample from a large population-derived, non-clinical cohort. Clinical samples are often needed to accrue an adequate number of participants and for ensuring statistical power, but such samples can make it difficult to generalize findings. Clinical-based samples are likely not representative of all children with ASD in many important aspects, such as degree of parental investment, level of behavior disturbance, and previous treatment exposure. Further studies using non-clinical, community based and school samples are needed to evaluate the prevalence and the impact of emotional disorders in the broader ASD population.

Other limitation of this study is related to the fact that the majority of them are cross-sectional [e.g.,[24, 29]] and to understand the developmental change and to clarify the clinical phenotypic manifestation across the lifespan and the direction of the association between the risk factors (emotional disorders) and the outcome (functionality) [e.g.,[30, 32]] longitudinal studies are needed. For example, the results of the study of Bauminger et al. [32] were inconsistent because they concluded that parenting stress emerged as the most important predictor of children's I-E problems but, the inverse association between the impact of the I-E problems in the parenting stress were not analyzed.

Main results

The most important clinically relevant question in this review is the degree to which emotional disorders in children with ASD, affect the functionality of their lives, in other words, how co-occurring emotional problems affect the prognosis for the functionality in children with ASD. For answering this question, our study found only three primary studies, White et al. [25], Wozniak & Biederman [31] and Munesue et al. [37], in which they compared the functionality between a group of patients with ASD+ and emotional disorders and a group of patients with ASD without the emotional disorders. They studied the comorbidity with anxiety disorder, mania and mood disorders respectively. Wozniak & Biederman [31] and Munesue et al. [37] determined a significant negative association between ASD and the comorbidity with emotional disorders. These results were consistent with our hypothesis; affecting considerably the functionality scores. According with the study of White et al. [25], they supported the importance of assessing global functioning in addition to symptom change and treatment response in clinical trials. In a previous review, White et al. [40] obtained the anxiety comorbidity estimated ranging from 11% to 84%.

The secondary studies provided more information about the impairment in patients with ASD and emotional disorders, but the association with a comparative group of patients with ASD and without the risk factors is needed.

Cognitive ability for children with ASD can range from low to high across any range of severity for the condition [41, 42]. Lower IQ

may interact with the severity of the child's autism to increase the need for assistance with activities of daily living [43]. Intellectual disability (ID) is one of the most common co-occurring disorders in ASD [44, 45] and is an important predictor of outcome [5-8]. Several research studies have established the impact of general IQ on adaptive (daily life) functions in ASD samples [46], but little is known in relation with the impact of comorbid disorders on cognitive functions in this population. According with the results of this review, there is controversy in the conclusions across the different studies. The results of some studies indicated that children with ASD may experience anxiety symptoms which are similar to those seen in non-ASD clinical samples, but that the presentation of anxiety symptoms in this population may be affected by cognitive functioning. Thus, Sukhodolsky et al. [16] found that children with higher IQ and greater social impairment experience the most severe anxiety. This hypothesis is reinforced by Gadow et al. [35] and Weisbrot et al. [19]. On the other hand, Simonoff et al. [11], Pearson et al. [18] and Simonoff et al. [22] found no significant association. Mazzone et al. [24] supported this hypothesis; they concluded that there was no significant association between IQ and mood symptoms, behavioural problems or global functioning.

Regarding executive functioning, Hollocks et al. [17] contrarily to Thede & Coolidge [20] suggested that poor executive functioning is one factor associated with the high prevalence of anxiety disorder in children and adolescents with ASD.

Assessment of global functioning is an important consideration in treatment outcome research; yet, there is little guidance on its evidence-based assessment for children with ASD [25]. Outcome measures sensitive to change in global functioning designed for use in the ASD population are needed [47]. Wagner et al. [48] addressed this need by modifying the CGAS [49]. In this review, many studies showed that higher anxiety severity, major depression, mania and bipolar disorder as comorbid conditions indicated significantly lower levels of functioning or lower quality of life [23, 24, 27, 28, 31]. In contrast, the only primary study of White et al. [25] found no relationship between DD-CGAS and anxiety scores.

Concerning to psychosocial functioning and according with the primary study of Wozniak & Biederman [31], there was a negative correlation between comorbidity with mania and scores on the SAICA. Using different measures, Meyer et al. [29] and Bellini [30] supported this finding, but they studied anxiety comorbidity. Alternatively, Hollocks et al. [17] found that social cognition ability was not associated with either anxiety or depression.

Relating to symptoms severity and adaptive functioning, (Table 5) the majority of the studies were inconsistent with the objective of this review. Only Simonoff et al. [36] and Munesue et al. [37] found a consistent correlation. In examining the role of risk factors, Simonoff et al. [36] found that lower IQ and adaptive functioning predicted higher hyperactivity and total difficulties scores., in addition, Munesue et al. [37] concluded that mood disorder showed significantly lower scores on the TABS [50],

than those without mood disorder, although scores on high-functioning autism spectrum screening questionnaire (ASSQ) [51], and autism-spectrum quotient (AQ) [52], were not significant. A limitation of these studies was that the clinical scientists often used measures that targeted specific problem areas (e.g. anxiety, depression, aggressive behaviour) rather than global functioning, and most often, these measures have been developed for individuals without ASD [53, 54]. Because individuals with ASD do not typically present a unified, prominent problematic symptom or behaviour, but rather a myriad, a narrow focus on improvement in a single symptom domain may fail to capture the full range of possible functioning or change. Although measuring change in the targeted behavioural domains is methodologically necessary, future research is needed because the full range of a

participant's abilities and deficits may not be captured if global measures are not included.

Conclusion

Children with ASD and emotional disorders may suffer from two disorders. Comorbid with emotional disorders among patients with ASD may be more common than previously thought. It may have consequent impairment in their psychological profile, social adjustment, adaptive functionality, cognitive and global functioning and should alert clinicians to the importance of assessing mood disorders in order to choose the appropriate treatment. Identification of the comorbid condition may have important therapeutic and scientific implication. Future researches are needed to understand how emotional disorders develop and how they may interact with the score of functioning in this population.

Table 2 Cognitive functioning.

Year	Author	Comorbidity Measures	N	Sample Characteristics	Control Group	Main Results
2010	Mukaddes NM et al. (a) (A)	(K-SADS-PL-T) (Orvaschel and Puig-Antich, 1987)	60	AS (30) IQ>70	AD(30) IQ>70	(I) AS group displayed greater comorbidity with depressive disorders and ADHD-CT, they also had higher range of IQ score. From a clinical perspective, it could be concluded that both disorders involve a high risk for developing psychiatric disorders, with AS patients at greater risk for depression.
2012	Simonoff et al. (b)(1) (A,B)	PONS ((Santosh, 2006);SDQ CAPA (Angold & Costello,2000)	91	ASD 16 year (91), 12 year (79)	None	(NA) Prevalence of High-SMP was 26,37% (N=24). This study concluded that severe mood problems were associated with current and earlier emotional problems. Intellectual ability and adaptive functioning did not predict to SMP. Relationships between SMP and tests of executive function were not significant after controlling for IQ.
2006	Person et al. (a) (A,B)	PIC-R (Wirt, 1984).	51	AD (26), PDD-NOS (25). Age range:4–18 (M: 10)	None	(NA) After controlling for verbal IQ, the children with AD had significantly more social difficulties, atypical behaviours, and social withdrawal (the core symptoms of autism), than did the children with PDD-NOS. No significant differences found between children with PDD-NOS and AD on anxiety symptoms, although both groups approached clinical significance.
2008	Sukhodolsky et al.(a) (A)	(CASI) (Gadow & Sprafkin, 1997a,b)	171	AD (151), AS (6), PDD-NOS (14). Age range: 5–14 (M: 8) [C]	None	(P) 73 (43%) met screening cut-off criteria for at least one anxiety disorder. Higher levels of anxiety associated with higher IQ, functional language use, and stereotyped behaviours.
2005	Weisbrot et al. (a) (A)	(ECI-4; Gadow & Sprafkin,1997a) (CSI-4;Gadow&Sprafkin, 2002). (CBCL; Achenbach 1991a),	483	PDD-NOS (209), AD (170), AS (104). Age range: 3–12	Non-ASD, (326)	(P) Children with AS earned higher ratings on several anxiety items than children diagnosed with AD. Children with the highest levels of anxiety had higher mean IQ scores than did the low anxious ASD group.
2008	Simonoff et al.(c) (A,C)	(CAPA)	112	AD (62), PDD-NOS (50). Age range:10–14 (M: 11) [R]	None	(NA) 41.9% met criteria for at least one anxiety disorder. ASD diagnosis (AD or PDD-NOS), IQ, and adaptive behaviour were not associated with the presence of an anxiety disorder. These results indicate that anxiety disorders are common in the broader ASD population, not just clinical cases.

Table 2b Executive functioning.

2014	Hollocks MJ et al. ^{(1)(a) (A,B,C)}	SDQ, PONS	90	ASD (90) Range of age: 14-16	None	(N) Results indicated a significant association between poorer executive functioning and higher levels of anxiety, but not depression. (NA) In contrast, social cognition ability was not associated with either anxiety or depression. This may suggest that poor executive functioning is one factor associated with the high prevalence of anxiety disorder in children and adolescents with ASD.
2006	Thede and Coolidge ^{(2) (A)}	CPNI; (Coolidge, 2002)	31	AS (16), HFA (15). Age range: 5-17 (M: 10)	Age, gender matched TD* (31)	(I) Children with AS had more symptoms of anxiety than did children with HFA; 10 of 16 children with AS had elevated GAD scale scores. ASD children (AS and HFA combined) showed greater deficits than the control children on the Executive Function scale of the CPNI. However, there were no significant differences in executive functioning between the AS and HFA children

Cognitive Functioning: (a) The Wechsler Abbreviated Scale of Intelligence (Wechsler,1999) (b) Adaptive functioning (Vineland Adaptive Behaviour Scales composite score) (c) WISC-III UK version,30 Raven_s Standard matrix (SPM) or Coloured Progressive matrices (CPM) . Executive functioning measures: (1) Opposite worlds, Trail making [Reitan, 1958], Numbers backwards, Card sorting task. (2) Coolidge Personality and Neuropsychological Inventory. Correlation: (P) Positive (comorbidity is associated with high functionality) (I) Inconsistent (with the goal of this review) (N) Negative (comorbidity is associated with poor functionality) (NA) No association. ASD Diagnosis :(A)Clinical Diagnosed (DSM-IV) . (B) ADI-R (Le Couteur et al., 1989) and/or ADOS-G (Lord et al., 2000) (C) SCQ (Goodman,2003) *TP (Typical Development)

Table 3 Global functioning and quality of life.

Year	Author	Comorbidity Measures	N	Sample Characteristics	Control Group	Main Results
2012	Van Steensel FJ et al. (c) (B)	(ADIS-C=P) (Silverman and Albano, 1996) ; CSBQ (ASD-like symptoms)	115	ASD (115) Age M:11.37 years	Anxiety D (122) M-Age: 12,79.	(N) Higher anxiety severity scores on the ADIS, as well as higher scores on the CSBQ (ASD-like behaviours), were associated with a lower quality of life, irrespective of group. However, whether anxiety increases ASD (symptoms), ASD (symptoms) cause anxiety, or both (symptoms exacerbating one another), is unclear. The results of this study support a highly similar phenotype of anxiety disorders in children with ASD. No group differences in quality of life were found according to parental or child report.
2006	Farrugia et al. (a) (A)	Spence Children's Anxiety Scale (SCAS; Spence, 1998)	29	AS. Age range: 12-16 (M: 13)	Anxiety disordered (34);TD (30)	(N)Self-reported symptoms of anxiety were equivalent to those of teens with anxiety disorders; anxiety symptoms, neg. automatic thoughts were significantly higher than in control group. The correlations among anxiety symptoms, negative automatic thoughts, behavioural problems and overall impairment were significantly higher in the AS group than in either comparison group.
2013	White et al. (d) (B)	CATS; Schniering & Rapee, 2002)	30	ASD + Anxiety Disorder.(15) CBT 14 weeks treatment	ASD + Anxiety Disorder (15)	(NA)DD-CGAS scores were strongly correlated with parent-reported degree of ASD-related impairment and pragmatic communication. Contrary to what we hypothesized, there was no relationship between DD-CGAS scores and parent-reported anxiety scores, adaptive behaviour scores, or educational placement. DD-CGAS scores were also negatively correlated with verbal IQ, as expected.
2010	Mattila ML et al. (b) (B)	Anxiety Disorders Interview Schedule—Child/ Parent Version (ADIS-/P)	50	ASD/AS (50) Range of age (9-16)	None	(N)The results support common (prevalence 74%) and often multiple comorbid psychiatric disorders in AS/HFA; behavioral disorders were shown in 44%, anxiety disorders in 42% and tic disorders in 26%. Oppositional defiant disorder, major depressive disorder and anxiety disorders as comorbid conditions indicated significantly lower levels of functioning
2013	Mazzone et al. (b) (A,B)	(K-SADS-E)	30	AS/HFA (30)	Major Depression (30) TD (35)	(N)The presence of internalizing symptoms was reported in 18,9% of the AS/HFA group, in 18,9% of the MD group and in 3,9 % of the TD group. AS/HFA group reported higher depression symptoms compared to the TD group. Higher level of depression symptoms increase the risk of poorer global functioning. There was no significant association between IQ and mood symptoms, behavioural problems or global functioning.

Functioning Measures: (a) The Life Interference Measure (LIM; Lyneham et al. 2003) ; (b) Children Global assessment Scale (CGAS)(Shaffer et al.,1983) ; (c) *The EuroQol-5D* (EuroQol group, 1990); (d) DD-CGAS(Wagner et al,2007) . ASD Diagnosis :(A)Clinical Diagnosed (DSM-IV) . (B) ADI-R (Le Couteur et al., 1989) and/or ADOS-G (Lord et al., 2000). Correlation: (P) Positive (comorbidity is associated with high functionality) (I) Inconsistent (with the goal of this review) (N) Negative (comorbidity is associated with poor functionality) (NA) No association.

Table 4 Psychosocial and family functioning.

Year	Author	Comorbidity Measures	N	Sample Characteristics	Control Group	Main Results
2006	Meyer et al. (D) (a)	BASC (Reynolds & Kamphaus, 1998)	31	AS. Age range: 7–13 (M: 10)	TD (33)	(N) This study examined the associations between information processing, social functioning and psychological functioning, including co-occurring psychiatric disorders. Teens with AS and their parents reported higher levels of anxiety than did the control group. Anxiety was related to deficits in social awareness and experience. Cognitive and social-cognitive abilities were associated with aspects of social information processing tendencies, but not with emotional and behavioural difficulties
2006	Bellini et al. (A)*(b)	(SAS-A; LaGreca, 1999); (MASC; March, 1999)	41	AD (19), AS (16), PDD-NOS (6). Age range: 12–18 (M: 14); No MR	None	(N) Social skill deficits and physiological hyperarousal combined, contributed to variance in symptoms of social anxiety in teens with ASD.
2013	Joshi G et al. (C) (c,d)	(CBCL) (Achenbach, 1991) (K-SADS-E))	155	BD+ASD(47)	BD (155)	(I) Thirty percent (47/155) of the bipolar I probands met criteria for ASD. The age at onset of bipolar I disorder was significantly earlier in the presence of ASD comorbidity and significantly poorer GAF scores than BPD-I probands. BPD-I + ASD probands had significantly more impaired scores on all CBCL subscales compared to BPD-I probands except for the somatic complaints scale. However Bipolar I probands has significantly poorer SAICA scores independent of comorbid with ASD. Bipolar I disorder comorbidity with ASD represents a very severe psychopathologic state in youth.
1997	Wozniak J. et al. (C) (c)	(K-SADS-E) ; (CBC [Achenbach, 1991]	190	PDD + mania (14), mania without PDD (114)	PDD without mania (52)	(N) The 14 children with both PDD + mania represented 21% of the PDD subjects and 11% of all manic subjects. Functioning of children with PDD+mania was very poor as evidenced by their scores on the SAICA, GAF and CBCL clinical subscales. These scores, plus the high rate of hospitalization associated, suggest that PDD+mania is a highly disabling condition, warranting further study and attention.
2010	Bauminger N et al. (A,B) (e)	(CBC)	77	HFA (23) Israel HFA (20) USA Rate of age (8-12)	TD(22) Israel, TD (20) USA	(I) Children with ASD exhibited significantly greater levels of psychopathology as assessed by the CBC and parents of children with ASD exhibited higher parenting stress as assessed by the Parenting Stress Index [Abidin, 1995]. Parenting stress emerged as the most important predictor of children's I-E problems.

Functioning Measures: (a) Social encoding errors on the video and Why Kids Do Things (WKDT: Crick and Dodge,1996) (b) Physical Symptoms subscale of MASC and The Social Skills Rating System (SSRS; Gresham & Elliot,1990) (c) [Social Adjustment Inventory for Children and Adolescents (SAICA) (Orvaschel and Walsh, 1984), Global Functioning (GAF) (d) Moos family environment Scale (FES). (Moos RH et al. 1974) ; (e) Mother-child relationship qualities.[Inventory of Parent and Peer Attachment [IPPA;Armsden & Greenberg, 1987]. ASD Diagnosis:(A)Clinical Diagnosed (DSM-IV) . (B) ADI-R (Le Couteur et al., 1989) and/or ADOS-G (Lord et al., 2000) (C) Diagnosis based on DSM-III-R criteria.(D) Autism Spectrum Screebibg Questionare (ASSQ: Enlers et al.,1999) and Australian Scale for Asperger's Syndrome (ASAS: Attwood,1998) *Previous diagnosis. Correlation: (P) Positive (comorbidity is associated with high functionality) (I) Inconsistent (with the goal of this review) (N) Negative (comorbidity is associated with poor functionality) (NA) No association.

Table 5 Symptoms severity and adaptive functioning.

Year	Author	Comorbidity Measures	N	Sample Characteristics	Control Group	Main Results
2005	Gadow et al. (A) (a)	(CSI-4; Gadow & Sprafkin, 2002)	301	AD.(103), AS (80), PDD-NOS (118). Age range: 6-12 (M: 8); Clinic referrals	Non-ASD referrals (181); regular ed (404); special ed (60)	(NA) 25.2% and 19.5% of males and females, respectively, with ASD screened positive for generalized anxiety disorder. The authors reported that severity of ASD appeared to be negatively associated with psychiatric symptoms such that children with AD were generally rated as having fewer and less severe psychiatric symptoms.
2004	Bradley et al.(B) (b)	(DASH-II; Matson, 1995)	12	AD. Age range: 12-20 (M: 16); FSIQb75 [M]	Learning disabled (17) TD (16)	(I) 42% (n=5) of sample reached clinical significance for anxiety problems, compared to 0% of mentally retarded sample without autism. The children with AD had an average of 5.25 clinically significant disorders (excluding AD) based on cut-off scores on the DASH-II, compared to an average of 1.25 for the non-AD group.
2013	Van Steensel FJ et al. (A,B) (c)	(ADIS-C=P)	73	ASD+ Anxiety D-group (73)	Anxiety-Group (34)	(I) The mean of severity score of an anxiety disorder did not differ between the ASD+AD- and AD-group. For the ASD-subtypes (autistic disorder, Asperger's disorder or PDD-NOS), no differences were found with respect to the number of anxiety disorders, anxiety severity scores, or the presentation of anxiety disorders.
2013	Simonoff et al (A,B) (d)	(SDQ). (CAPA)	81	ASD (81) 12-16-year	None	(N) Prevalence for emotional problem was 34,5 % at 12 years and 30,7 % at 16 years. Lower IQ and adaptive functioning predicted higher hyperactivity and total difficulties scores. Greater emotional problems at 16 were predicted by poorer maternal mental health, family-based deprivation and lower social class.
2005	Pfeiffer et al.(A) (e)	(RCMAS; Reynolds & Richmond, 1978) and (CDI; Kovacs, 1978)- Parent Version	50	AS. Age range: 6-17 (M: 9)	None	(NA) There were no significant relationships between depression and overall adaptive behaviour or anxiety and overall adaptive behaviour. However, the data supports positive relationships between anxiety and sensory defensiveness in all age ranges and a relationship between depression and hyposensitivity in older children. Stronger inverse relationships were apparent between specific adaptive behaviours including: (a) symptoms of depression and functional academics, leisure, social skills; (b) anxiety and functional academics; and (c) both sensory hyper- and hyposensitivity and community use and social skills).
2012	Gadow et al.(A,B) (a)	(CSI-4) , (DICA-P; Reich 2000)	287	ASD + ADHD (74), ASD-/ADHD(107), CMTD+ADHD (47), ADHD Only(59)	TD (Mother) (169) (Teacher) (173)	(I) The ASD group obtained more severe ratings for all depression symptoms from both, mother and teacher than controls. They also found little relation between IQ or verbal ability and global depression scores in children with ASD. Severity of depression symptoms was for the most part comparable for boys with ASD with and without ADHD, which raises a number of interesting questions about pathogenic processes that result in ASD and their role in mood dysregulation as well as criteria for depression in ASD.
2007	Munesue T et al. (C) (d)	Hospital according to DSM-IV	44	HFA + MD (16) Range of Age (12-29)	HFA (28) Range of age (8-38)	(N) Sixteen patients (36.4%) were diagnosed with mood disorder (MD). The major comorbid mood disorder in patients with high-functioning ASD is bipolar disorder and not major depressive disorder. Rate of mood disorder in first- and second-degree relatives, and IQs were not significantly different between the two groups. Patients with mood disorder showed significantly lower scores on TABS than those without mood disorder, although scores on ASSQ and AQ were not significantly different between the two groups.

Symptoms severity: (a) CSI-4; Gadow & Sprafkin, 2002 (b) DASH-II; Matson, 1995 (c) Anxiety Severity score (ADIS-C=P) (d) Adaptive Functioning (Vineland Adaptive Behaviour Scales composite score) (e) Sensory Profile for children (Dunn, 1999). The Adolescent/Adult Sensory Profile (Brown & Dunn, 2002) ,Adaptive Behavior Assessment System: Parent Version. (ABAS) and (SFA) (Dunn, 1999) (d) Severity of Autism [Score of TABS, ASSQ and AQ]. ASD Diagnosis: (A)Clinical Diagnosed (DSM-IV) . (B) ADI-R (Le Couteur et al., 1989) and/or ADOS-G (Lord et al., 2000) (C) (TABS; Kurita and Miyake, 1990), (ASSQ; Ehlers et al., 1999), and (AQ; Baron-Cohen et al., 2001). Correlation: (P) Positive (comorbidity is associated with high functionality) (I) Inconsistent (with the goal of this review) (N) Negative (comorbidity is associated with poor functionality) (NA) No association.

Table 6 Functionality measures.

Year	Author	Functionality	Functionality Measures
2010	Mukaddes NM et al.	Cognitive	Rate of Cognitive Functioning (IQ, Verbal IQ, Performance IQ) (WISC-R)
2012	Simonoff et al.	Cognitive & Executive	Rate of cognitive function (IQ). Vineland Adaptive Behaviour Scales composite score & card sort and trail making
2005	Weisbrod et al.	Cognitive & Severity	Range of Cognitive functioning (IQ) & Early Childhood Inventory-4 and Scoring formats for DSM-IV criteria.
2006	Person et al.	Social & Cognitive	Emotional functioning and Social Skills: Personality Inventory for Children-Revised (Subscale Scores) & Rate of cognitive functioning: Verbal IQ
2008	Sukhodolsky et al.	Cognitive	Range of cognitive functioning (IQ, functional language use, and stereotyped behaviors.)
2008	Simonoff et al.	Cognitive	WISC-III UK version, 30 Raven's Standard matrix (SPM) or Coloured Progressive matrices (CPM)
2006	Thede and Coolidge	Executive	Parent-report measures of psychological and executive functioning: Coolidge Personality and Neuropsychological Inventory.
2014	Hollocks MJ et al.	Cognitive & Executive	(Wechsler,1999) Social cognitive Measure [Frith-Happé animations (Abell, Happe, & Frith, 2000; Castelli, Frith, Happe, & Frith, 2002, Strange stories (Happé, 1994), & Opposite worlds, Trail making [Reitan, 1958], Numbers backwards, Card sorting task.
2012	Van Steensel et al.	Quality of Life (QoL)	EuroQol-5D
2006	Farrugia et al	Severity & QoL	Strengths and Difficulties Questionnaire (SDQ; Goodman,1997) & Life Interference Measure (LIM; Lyneham, Abbott, & Rapee, 2003)
2013	White et al.	Global & Severity	DD-CGAS(Wagner et al,2007), Clinical Global Impresions-Improvement (CGI-I), & Children Communication Checklist-2(CCC-2) Child and Adolescent Symptom Inventory ASD Anxiety Scale, Social Responsiveness Scale, Vineland Adaptative Behaviour Scale. Scholl placement.
2010	Mattila ML et al.	Global	[Children's Global Assessment Scale(GAF)]
2013	Mazzone et al	Global & Cognitive	Children Global assessment Scale (CGAS)(Shaffer et al.,1983) & Rate of cognitive functioning (IQ)
2006	Meyer et al.	Social	Range of cognitive and Social cognitive ability: Social encoding errors on the video and Why Kids Do Things (WKDT: Crick and Dodge,1996)
2006	Bellini	Social	Physiological arousal (Physical Symptoms subscale of MASC) and The Social Skills Rating System (SSRS; Gresham & Elliot,1990)
2013	Joshi G et al.	Social & Global & Family	Psychosocial functioning [Social Adjustment Inventory for Children and Adolescents (SAICA) (Orvaschel and Walsh, 1984) & (GAF) & (FES). (Moos RH et al. 1974)]
1997	Wozniak J. et al.	Social & global	Psychosocial functioning [Social Adjustment Inventory for Children and Adolescents (SAICA) (Orvaschel and Walsh, 1984) & GAF
2010	Bauminger N et al.	Cognitive & Family	(VIQ of 80 or Peabody Picture and Vocabulary Test [PPVT; Dunn & Dunn, 1997] & Mother-child relationship qualities. [IPPA;Armsden & Greenberg, 1987].
2005	Gadow et al.	Severity	Child Symptom Inventory-4 (CSI-4; Gadow & Sprafkin, 2002)
2004	Bradley et al.	Severity	Diagnostic Assessment for the Severely Handicapped (DASH-II; Matson, 1995)
2013	Van Steensel et al.	Severity	Anxiety Severity score (ADIS-C=P): ranging from 0 to 8, and summing the ratings of all anxiety disorders.
2013	Simonoff et al	Cognitive & Adaptive	Rate of cognitive function (IQ) and Adaptative Functioning. (Vineland Adaptive Behaviour Scales composite score
2005	Pfeiffer et al.	Adaptive	Sensory Profile for children (Dunn, 1999). The Adolescent/Adult Sensory Profile (Brown & Dunn, 2002) Adaptive Behavior Assessment System: Parent Version. (ABAS) School Function Assessment (SFA) (Dunn, 1999)
2012	Gadow et al.	Severity & Cognitive	Severity of Symtoms [Child Symptom Inventory-4 (CSI-4)] Neuropsychological Measures [The Wechsler Abbreviated Scale of Intelligence (Wechsler,1999)]
2007	Munesue T et al.	Severity & cognitive	Rate of Cognitive Functioning [Wechsler Intelligence Scale (FIQ,VIQ,PIQ)] Severity ofAutism [Score of TABS, ASSQ and AQ)

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