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Diagnosing ASD in adults without ID: Accuracy of the ADOS-2 and the ADI-R

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Running title: Diagnosis of ASD in adulthood

Abstract

Diagnosing Autism Spectrum Disorder (ASD) in adulthood often represents a challenge in clinical practice. The aim of the present study was to evaluate the sensitivity and specificity of the ADOS and ADI-R in diagnosing ASD in adults. 113 subjects with an IQ of 70 or above were assessed through an extensive clinical evaluation. The ADOS-2 Module 4 and the ADI-R were separately administered by staff members blind to clinical judgment. Our results cautiously confirm the accuracy of ADOS-2 Module 4, while suggest that ADI-R might not be reliable in adults without intellectual disability. Clinicians' training and experience remains of primary importance while assessing adults who could potentially belong to the autism spectrum.

Key words: Autism; Adult; DSM-5; Diagnosis; ADOS; ADI-R

Introduction

According to recent data, the number of diagnoses of Autism Spectrum Disorder (ASD) is constantly increasing (CDC, 2014), and a large number of individuals is beginning to seek formal diagnosis of Autism Spectrum Disorders (ASD) in adulthood (Happé et al. 2016; Howlin and Moss 2012; Mukaetova-Ladinska et al. 2012). The reasons underlying this trend should be at least in part related to the changes occurred in diagnostic criteria and to the increased awareness towards autism (Bent et al. 2016; Hansen 2015; Rutter 2005).

Diagnosing ASD in adulthood for the first time may represent a challenge for clinicians. The difficulties could be partly ascribed to the presence of similarities in symptoms with other psychopathological conditions, such as personality disorders, obsessive-compulsive disorder or social anxiety (Wolf and Ventola 2014). Professionals could also experience difficulties in gaining information about the patient's early development (Lai and Baron-Cohen 2015) and could eventually be misled by previous psychiatric diagnosis in the subject's medical history (Nicolaidis et al. 2014). Additionally, ASD symptoms, even if present since childhood, may not become fully manifest until social demands exceed patients' limited capacities. **As a consequence, some individuals might not meet cut-off for ASD, in particular those with milder symptoms severity and normal range IQ. This could be due to camouflaging of symptoms, or late onset of symptoms that causes the individual to meet criteria for ASD in adulthood (Bargiela et al. 2016; Hull et al. 2017; Lai and Baron Cohen 2015; Rynkiewicz et al. 2016).** Particularly in females, impairments may be over-shadowed by the tendency to suffer from internalizing (e.g. anxiety or depression) rather than externalizing (e.g. hyperactivity or conduct problems) difficulties (Bargiela et al. 2016).

Nonetheless, it is important to recognize ASD symptoms also in adults with milder forms to consequently support them and promote positive outcomes (Lai and Baron Cohen 2015; Pugliese et al. 2015; Interagency Autism Coordinating Committee 2012). The most recent guidelines suggest that the evaluation of adults with suspected ASD should be performed through a multistep and

multidisciplinary assessment (National Institute of Clinical Excellence 2012; Wolf and Ventola 2014). It should be undertaken by trained and competent professionals, considering information of current and past behavior, also including early development. For more complex assessments in adults, it is recommended to support the clinical judgment with standardized instruments, such as the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al. 2012) or the Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994).

The ADOS-2 and the ADI-R are currently considered the most important diagnostic tools for ASD (Falkmer 2013; Ozonoff 2005). The ADOS-2 is a semi-structured observation of the patient and includes five modules used for the evaluation of individuals with different developmental and language levels. It has been extensively demonstrated that it is a reliable and valid instrument to assess the presence of ASD in children, adolescents and adults (Bastiaansen et al. 2011; De Bildt et al. 2004; De Bildt et al. 2016; Kamp-Becker et al. 2013; Langmann et al 2017; Molloy et al. 2011; Risi et al. 2006). However, Module 4, which has been developed for adolescents and adults with fluent language skills, received less psychometric evaluations. Bastiaansen et al. (2011) examined the psychometric properties of ADOS-2 Module 4 in an independent sample of adults without ID with an established diagnosis of ASD compared to other clinical (schizophrenia and psychopathy) and non-clinical groups. The authors concluded that the ADOS-2 could adequately discriminate ASD from psychopathy and typically developed adults, while discrimination from schizophrenia was more difficult. More recently, De Bildt and colleagues (2016) found an improved sensitivity using the revised algorithm. Langmann and co-authors retrospectively investigated the utility of ADOS-2 Module 4 in an independent clinical sample of high-functioning adolescents and adults (Langmann et al. 2017). Both original and revised algorithms demonstrated good sensitivity and specificity, with slightly better results for the revised algorithm.

The ADI-R, a diagnostic interview administered to caregivers, appears as a valid instrument independently from age and level of functioning (De Bildt et al. 2004). Studies reported diagnostic

stability of the ADI-R over lifetime in non-ID samples (Mazefsky and Oswald 2006; Moss et al. 2008; Soke et al. 2011). However, to our knowledge, its utility in adulthood has been examined only by Sappok et al. (2013). In particular, the authors investigated the applicability and validity of both ADOS-2 (Modules 1 to 4) and ADI-R in a sample of adults with ID in a clinical setting. The authors observed that the ADI-R could be a reliable tool for the assessment of ASD in adults with intellectual disability.

Moving from the scarcity of evidence in literature, we aimed at evaluating the accuracy and the validity of the two main standardized instruments (ADOS-2 and ADI-R) in diagnosing ASD in adults with average or above-average intelligence.

Methods

Setting

The Laboratorio Autismo, University of Pavia, Italy, is a center specialized in the diagnosis of ASD in adulthood. Research staff is composed by licensed medical doctors and psychiatrists. Patients can be referred to Laboratorio Autismo by professionals, such as physicians or psychologists, relatives, or by means of self-referral.

Participants

From June 2013 to December 2016, 262 people were referred to the Laboratorio Autismo of the University of Pavia, Italy. Among these patients, 113 met the following inclusion criteria: age of 18 years or above; IQ of 70 or above; good comprehension of spoken and written Italian language. Patients meeting the inclusion criteria were consequently enrolled into the present study (Figure 1). Written informed consent was obtained from all participants. The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki.

@@ Figure 1 about here @@

The sample was mainly composed of males (72.6% of the sample) and the mean age at evaluation was 28.47 ± 10.16 years old, while ages ranged from 18 to 55 years. IQ ranged from 76 to 145 and mean IQ was 112.71 ± 17.38 . Thirty-six patients were self-referred, 42 were referred by relatives, and 35 were referred by a specialist. Of note, 42 patients (37.2%) had already received a non-ASD psychiatric diagnosis. ADOS-2 was administered to all 113 patients, while only 84 parents or caregivers were available for the ADI-R.

Clinical evaluation and diagnostic classification

Each patient was extensively evaluated by a senior psychiatrist (PP) and a licensed medical doctor (LF or MR) with wide clinical expertise in diagnosing and treating adults with ASD. The staff collected a complete psychopathological and clinical history from the patients and their caregivers, focusing on past and present core symptoms of ASD. In particular, the clinicians focused on the following aspects: verbal and nonverbal communicative behaviors, quantity and quality of relationships, social connections, presence of vocal or movement stereotypes, insistence on sameness, restrictive and pervasive interests, rituals, hypo- or hypersensoriality. Based on the psychiatric assessment, additional standardized interviews, such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-II; First et al. 1997), have been performed to verify the presence of other psychiatric conditions. The diagnostic procedure was completed with the evaluation of the Intelligence Quotient (IQ) through the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981) or the Raven's Standard Progressive Matrices (Raven 1941).

The definitive clinical diagnoses were finally performed according to the DSM-5 criteria through a consensus meeting among the staff members. Severity levels for criterion A ("Persistent deficits in social communication and social interaction across multiple context") and B ("Restricted, repetitive patterns of behavior, interests, or activities") were specified for those individuals who received an ASD diagnosis. According to DSM-5, individuals with level 1 of severity require support; people

with level 2 of severity require substantial support; subjects with level 3 of severity require very substantial support.

Each individual was also independently evaluated by means of the ADOS-2 Module 4 and the ADI-R, if parents or caregivers of the patients were available. The ADOS-2 and the ADI-R were administered by two separate staff members (NB and CP) who met standard requirements for research reliability and who were blind to the consensus clinical diagnoses. Each interview or direct observation was performed by one assessor; no interrater reliability was then computed.

Assessment instruments

Autism Diagnostic Observation Schedule-2 (ADOS-2)

The ADOS-2 is a semi-structured observation of individuals who may belong to the autism spectrum (Lord et al., 2012). It is composed by different domains: Communication, Reciprocal Social Interaction, Communication+Social, Imagination/Creativity, and Stereotyped Behaviors and Restricted Interests. The ADOS-2 consists of five modules, addressed to children and adults according to their developmental and language levels. For the purpose of the present study, all subjects were evaluated by means of Module 4, which is used for adolescents or adults with normal intelligence and good verbal fluency. Different cutoffs are used to classify individuals into the autism spectrum or into autism. As proposed by Lord et al. (2012) in the original diagnostic algorithm, we considered the ADOS-2 suggestive of a diagnosis of ASD if the subject met the cutoff values for the autism spectrum in the Communication domain (score of 2 or above), Social domain (4 or above), as well as in the Communication+Social domain (7 or above). Imagination/Creativity, and Stereotyped Behaviors and Restricted Interests domains were not considered in the final scoring. We also evaluated the accuracy and utility of the revised algorithm of ADOS-2 Module 4, as proposed by Hus and Lord (2014). In the revised algorithm, a score of 8 or above in the sum of Social Affect (SA) and Restricted and Repetitive Behaviors (RRB) domains is considered suggestive of a diagnosis of ASD.

Autism Diagnostic Interview-Revised (ADI-R)

The ADI-R is a semi-structured parent interview that covers all three major areas of impairment in autism (quality of reciprocal social interaction; communication; repetitive, restricted, and stereotyped patterns of behavior) (Lord et al. 1994). A prominent part of the interview focuses on the period between the ages of 4 and 5 years, when differences among individuals with different levels of functioning can be better observed and compared. The ADI-R is considered positive for a diagnosis of ASD if the scores in the three domains exceed the cutoff values. The total cutoff score for the communication and language domain is 8 for verbal subjects. For all subjects, the cutoff for the social interaction domain is 10, and the cutoff for restricted and repetitive behaviors is 3. Additionally, some abnormality in at least one area should be present by 36 months of age. We also used an alternative algorithm for PDD-NOS: we considered the ADI-R positive for a diagnosis if the scores exceeded the cutoffs in at least two of the three main domains, with maximum one point below the threshold on the third scale.

Statistical analysis

Demographic variables of the studied population were presented as mean and standard deviations, percentages or counts as appropriate. Data were tested for normal distribution and homogeneity of variance using Kolmogorov-Smirnov and Levene's tests before statistical procedures were applied. Agreement among the assessment tools and between the assessment tools and clinical judgment were computed by means of Cohen's *k*. We used the Landis's cutoffs (Landis and Koch 1977) to interpret Cohen's *k* value (0: no agreement; 0–0.2: slight; 0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; 0.81–1: almost perfect agreement). Receiver Operating Characteristic (ROC) analyses were used to evaluate the accuracy of the different diagnostic measures. We used the classification proposed by Hosmer and Lemeshow (2000) for the interpretation of AUC values (0.5: no discrimination; 0.7–0.79: acceptable; 0.8–0.89: excellent; ≥ 0.9 outstanding). Results were considered

statistically significant at the $p \leq 0.05$ level, and all tests were two tailed. Statistical analysis was performed using SPSS 21.0 software packages (SPSS, Chicago, IL).

Results

Clinical diagnoses and agreement among the diagnostic instruments

General characteristics of the sample are depicted in Table 1. After the evaluation, 78 people (69.03% of the sample) received a clinical diagnosis of ASD according to DSM-5 criteria. **Severity levels were distributed** as follows: as concerns criterion A, 43 individuals had level 1 (55.1%); 34 had level 2 (43.6%) and one level 3 (1.3%); as concerns criterion B, 48 individuals had level 1 (61.5%), 29 had level 2 (37.2%) and one person had level 3 of severity (1.3%).

The remaining patients were diagnosed with schizotypal personality disorder (5 cases), obsessive-compulsive disorder (5), attenuated psychosis syndrome (3), schizophrenia (2), schizoid personality disorder (2), borderline personality disorder (2), avoidant personality disorder (1 case), depressive personality disorders (1), substance abuse (1), narcissistic personality disorder (1), factitious disorder (1), and other diagnoses (4). Of note, seven patients did not satisfy the criteria for any psychiatric diagnosis.

@@Table 1 about here @@

Clinical consensus judgment showed a substantial agreement both with traditional ($k=0.66$, $p < 0.0001$) and revised algorithm ($k=0.61$, $p < 0.0001$) of ADOS-2. On the contrary, ADI-R total algorithm fairly agreed with clinical evaluation ($k=0.23$, $p=0.002$). As concerns ADI-R algorithm for PDD-NOS, the agreement with clinical consensus judgment was fair but higher ($k=0.40$, $p < 0.0001$). Agreement between ADOS-2 and ADI-R was fair ($k=0.23$, $p=0.007$). Finally, considering an exceedance of cutoffs at both ADOS-2 (original algorithm) and ADI-R (algorithm for autism), the agreement with clinical judgment was also fair ($k=0.25$; $p=0.001$).

Diagnostic accuracy of ADOS-2, ADI-R, and subscales

Table 2 reports sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of cutoff criteria of the algorithms for ADOS-2 and ADI-R compared to the consensus clinical classification performed according to the DSM-5 criteria. Single subscales for each test were also examined.

The diagnostic accuracy of ADOS-2 and ADI-R were tested by means of ROC curves. According to the original algorithm of ADOS-2 Module 4 (Figure 2), ROC curves showed an excellent discriminant validity for the Communication+Social domain (AUC=0.84, SE=0.04, $p<0.0001$, 95% CI 0.76 to 0.93). Considering the two domains singularly, they both showed an acceptable accuracy, with an AUC=0.79 (SE=0.05, $p<0.0001$, 95% CI 0.69 to 0.90) for the Social Interaction domain and an AUC=0.76 (SE=0.05, $p<0.0001$, 95% CI 0.66 to 0.87) for the Communication domain. The revised algorithm of ADOS-2 also showed an excellent discriminant validity (AUC=0.81, SE=0.05, $p<0.0001$, 95% CI 0.71 to 0.90).

@@Figure 2 about here@@

Accuracy of ADI-R was almost acceptable (AUC=0.69, SE=0.06, $p=0.01$, CI 05% 0.57 to 0.81). Considering ADI-R single domains (Figure 3), ROC curves showed an acceptable discriminant validity for all domains. The highest values of AUC were found in Qualitative Abnormalities in Reciprocal Social Interaction (AUC=0.75, SE=0.06, $p<0.01$, 95% CI 0.62 to 0.87), and Abnormalities of Behavior Evident at or Before 36 months (AUC=0.75, SE=0.06, $p<0.01$, 95% CI 0.63 to 0.86). A good accuracy was also found in the Qualitative Abnormalities in Communication domain (AUC=0.74, SE=0.06, $p<0.01$, 95% CI 0.61 to 0.87). On the contrary, we observed a poor accuracy AUC in the Restricted, Repetitive and Stereotyped Patterns of Behavior domain (AUC=0.62, SE=0.08, $p=0.13$, 95% CI 0.46 to 0.77). Finally, considering the algorithm of ADI-R for PDD-NOS, we found a good discriminant validity (AUC=0.78, SE=0.06, $p<0.01$, 95% CI 0.67 to 0.89).

We computed a sensitivity analysis excluding the nine participants with a borderline intellectual functioning (IQ between 70 and 85) according to the DSM-IV-TR criteria (APA, 2000). We did not find any substantial difference from the overall analysis.

[@@Figure 3 about here@@](#)

Discussion

Given the lack of studies investigating the reliability of the main standardized instruments in adulthood, we aimed at evaluating the sensitivity and specificity of ADOS-2 and ADI-R for the diagnosis of ASD in adults. Our study reported data regarding the evaluation of adult subjects without ID who have referred to an Italian University center for first formal diagnosis of ASD. Of note, only the 31% of the sample was referred by a specialist; the remaining part was referred by parents or relatives, or self-referred. After an exhaustive assessment, focused on ASD core symptoms at the moment of evaluation and during patients' early development, about 69% of our sample met DSM-5 diagnostic criteria for ASD.

Our results provide evidence for substantial agreement between the clinical diagnosis and the ADOS-2 scores (both using the original and the revised algorithm), showing also good sensitivity and specificity. AUC values of the ROC curves for the Communication+Social Interaction domain (original algorithm) and for the SA+RRB domain (revised algorithm) were both suggestive of excellent accuracy, without any significant difference ($z = -0.50$). Our findings are in line with previous studies which evaluated the discriminant validity of ADOS-2 Module 4 in samples of adults with average or above-average intelligence (Bastiaansen et al. 2011; De Bildt et al. 2016; Hus and Lord 2014; Kamp-Becker et al. 2013; Langmann et al. 2017; Pugliese et al. 2015), cautiously suggesting that it could be a reliable instrument also for first evaluations of adults.

The ADI-R is a semi-structured interview generally administered to caregivers. Our sample was composed by adults (mean age: 28.47) and unfortunately in about 26% of cases we have not been

able to contact parents or caregivers. The agreement between ADI-R and clinical diagnosis was poor, correctly classifying into the spectrum only 55% of our sample. The agreement between ADOS-2 and ADI-R score was fair. It could be hypothesized that the ADI-R may not capture essential features in older people, as already acknowledged by Seltzer et al. (2003). Of note, ADI-R presented good specificity, but lacked in sensitivity: several patients who received a diagnosis of ASD after the clinical assessment did not actually exceed the ADI-R cutoffs in at least one scale. **However, considering the PDD-NOS algorithm, the accuracy of ADI-R improved: in fact, it could correctly classify the 71% of our sample.**

It is also worth mentioning that most of the items of the ADI-R focuses on the period between the ages of 4 and 5 years (Lord et al. 1994). For adults, the quality of informant's recall might not be detailed or reliable due to the long time elapsed from subject's childhood to the current assessment (Lai and Baron-Cohen 2015). Additionally, it is possible that individuals with high cognitive abilities may have developed camouflaging or compensating strategies during their childhood, thus being able to mask the core ASD symptoms.

Our results are in contrast with the findings reported by Sappok et al. (2013) who evaluated the diagnostic utility of ADI-R in adults with ID. Sappok et al. found less specificity (0.80), but extremely high sensitivity (0.87) compared to our sample. This discrepancy could be partly explained by the characteristics of Sappok's sample: all patients recruited in the study had a diagnosis of ID and a long history of developmental delay. Consequently, parents or caregivers were probably more prone to recall information about the abnormal developmental history of the patients, and may have undergone through several previous evaluations. However, our findings partially mirror the conclusions of recent studies, which evaluated the discriminant validity of ADI-R in children, finding high specificity, but moderate to low sensitivity (De Bildt et al. 2015; Zander et al. 2015). Also, the low degree of agreement between ADI-R and ADOS is consistent with the findings of previous studies (De Bildt et al. 2004; Gray et al. 2007; Papanikolaou et al. 2008; Ventola et al. 2006).

The Restricted, Repetitive Behaviors and Interests represented the less specific scale of the ADI-R. On the contrary, all the other domains presented good discriminant validity. The limited utility of the stereotyped behaviors domain is in line with the findings of Mazefsky and Oswald (2006), who analyzed the agreement between single ADI-R scales and clinical diagnosis in children. The high number of false positive at this scale (12 out of 19 non-ASD patients) could find an explanation in the characteristics of our sample, which may be considered a general clinical population. Stereotypes and rituals, in fact, may be present also in other psychiatric conditions, such as obsessive compulsive disorder or psychosis. Finally, previous studies showed an improvement in Restricted, Repetitive and Stereotyped Patterns of Behavior domain in adults with ASD, in particular in the repetitive use of objects, complex mannerisms and unusual preoccupations (Seltzer et al. 2003). Additionally, it was found that adults with IQ scores of 70 or higher appear to improve much more than those with a comorbid ID (Piven et al. 1996; Esbensen et al. 2009).

The domain regarding the Evidence of abnormalities at or before 36 months deserves to be critically discussed for its poor sensitivity. In 26 out of 65 ASD patients no abnormalities could be detected before three years of age, in spite of a clinical classification into the autism spectrum. A possible explanation could again rely in the poor trustworthiness of informants. We have to consider that the individuals examined in our study belonged to the higher-functioning part of the autistic spectrum, with good general cognitive ability and low severity of symptoms, who were evaluated for the first time between 18 and 55 years; thus, it is unlikely that some early abnormalities could be noticed without a consequent evaluation or that they would not be reported at the moment of the interview. A possible explanation could be related also to the changes occurred in the diagnostic criteria. While DSM-IV-TR required an onset of the impairments before the age of three years, according to DSM-5 “ASD symptoms must be present in the early developmental period, but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in

later life". Thus, a clinical diagnosis could be formulated also for those individuals who did not completely show ASD symptoms during their childhood.

Finally, when both ADOS-2 and ADI-R were suggestive for a diagnosis of ASD, we obtained a significant increase in specificity (100%), with a consequent decrease in sensitivity (42.2%), as already reported for children (De Bildt et al. 2013). This finding confirms that the combination of the two gold standard instruments is useful to avoid false diagnoses, but it lacks the ability to investigate the mildest forms of the spectrum.

The major strength of our paper is that we evaluated the usefulness of both main standardized instruments in diagnosing ASD in adults. Additionally, clinical assessors were blind to the results of the ADOS-2 and ADI-R. We thus avoided the risk of generating low specificity values due to the naturalistic design of the study, as already suggested by previous studies that evaluated the ADOS in clinical settings (Bastiaansen et al. 2011; Mazefsky and Oswald 2006; Molloy et al. 2011; Sappok et al. 2013). However, several limitations should be considered. First, the sample size is relatively small and wider samples are needed to replicate our findings. The assessment process was conducted only by psychiatrists and medical doctors highly specialized in ASD in adulthood, and not by a multidisciplinary team, as suggested by guidelines (National Institute of Clinical Excellence 2012). Some important aspects, such as adaptive functioning, were not evaluated in detail and a systematic investigation through the administration of standardized tools was possible only in a small part of our sample. Moreover, we focused only on the evaluation of suspected ASD with average or above-average intelligence, thus limiting the extension of our results to populations with lower intellectual functioning. **Finally, it is important to consider the difficulties encountered in performing an assessment in adults with normal IQ. The development of compensation strategies during the life-course, in fact, is frequent in this population. Consequently, the high levels of skills and abilities could have masked the ASD core symptoms during the standardized observation.**

The diagnosis of ASD is a complex and time consuming process, that should involve different professionals. In adults with average intelligence, in particular, it could be challenging for clinicians to discriminate ASD from other conditions with similar symptomatology and to collect information about the early development of the patients (Lai and Baron Cohen 2015). From our results, it is possible to confirm the reliability of ADOS-2 Module 4 for diagnosis of ASD in clinical practice. On the contrary, it could be cautiously asserted that the ADI-R algorithm lacks of accuracy in the diagnosis of adults seeking first formal diagnosis of ASD.

In conclusion, our results drew attention to the critical points of the diagnostic assessment of ASD in adults, especially in the mildest form of the spectrum, when information about patients' developmental profile are not always reliable. It appears desirable to carefully consider the possible evolution of core symptoms of ASD in adulthood. Additionally, it is important to underline that the design of our research does not completely reflect clinical practice. In our study, in fact, ADOS and ADI-R were administered by clinicians who were blind to the clinical consensus judgment. On the contrary, in everyday practice, professionals are more likely to integrate the results of ADOS and ADI-R with a comprehensive clinical and psychopathological evaluation for the formulation of an accurate diagnosis. We thus believe that the use of standardized diagnostic instruments could be useful in the evaluation of adults with ASD without ID. However, given our findings, it is important for professionals who work with this particular population to be even more critical towards the mere results of the standardized instruments. In conclusion, training and experience remains of primary importance while assessing an adult who could potentially belong to the autism spectrum.

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Table 1. General characteristics of the sample (n=113).

	ASD group n=78	Non-ASD group n=35	Total sample n=113
Age	26.45±9.46	32.97±10.35	28.47±10.16
Gender, male (%)	57 (73.1)	35 (71.4)	82 (72.6)
IQ	111.14±17.79	116.67±15.90	112.71±17.38
Criterion A, severity n=78		--	--
Level 1 (%)	43 (55.13)	--	--
Level 2 (%)	34 (43.59)	--	--
Level 3 (%)	1 (1.28)	--	--
Criterion B, severity n=78		--	--
Level 1 (%)	48 (61.54)	--	--
Level 2 (%)	29 (37.18)	--	--
Level 3 (%)	1 (1.28)	--	--
Other diagnoses	--	n=35	--
Schizophrenia spectrum (%)	--	5 (14.3)	--
Obsessive-compulsive disorder (%)	--	5 (14.3)	--
Personality disorders (%)	--	12 (34.3)	--
Other (%)	--	6 (17.1)	--
No psychiatric diagnosis (%)	--	7 (20)	--
ADOS -2 (Original algorithm) n=78		n=35	n=113
Communication	3.09±1.50	1.29±1.18	2.53±1.64
Reciprocal social interaction	6.53±2.38	3.40±1.90	5.56±2.66
Communication+Social	9.61±3.65	4.69±2.87	8.09±4.11
Creativity	0.97±0.74	0.74±0.70	0.90±0.73
Restricted and repetitive behaviors	1.54±1.23	0.86±1.06	1.33±1.22
ADOS -2 (Revised algorithm) n=78		n=35	n=113
Social Affect	9.64±3.34	4.97±3.32	8.19±3.97
Restricted and Repetitive Behaviors	2.03±1.43	0.94±0.97	1.69±1.40
SA+RRB	11.67±4.27	5.91±3.56	9.88±4.85
ADI-R n=65		n=19	n=84
Qualitative abnormalities in communication	9.34±3.45	6.05±4.05	8.59±3.83
Qualitative abnormalities in reciprocal social interaction	12.26±4.48	6.16±3.47	10.88±4.97
Restricted, repetitive and stereotyped patterns of behavior	4.68±2.31	3.16±1.89	4.33±2.30
Abnormalities of behavior evident at or before 36 months	1.25±1.31	0.05±0.23	0.98±1.26

Table 2. Sensitivity and specificity of ADOS-2, ADI-R, and subscales.

	Sensitivity	Specificity	Correct classification	PPV	NPV
ADOS-2 (Original algorithm)	85.9	82.9	84.96	91.8	72.5
Communication	89.7	62.9	81.42	84.3	73.3
Reciprocal Social Interaction	96.2	62.9	85.84	85.2	88
ADOS-2 (Revised algorithm,)	87.2	74.3	83.19	88.3	72.2
ADI-R (Autism algorithm)	43.1	94.7	54.76	96.6	32.7
Qualitative Abnormalities in Communication	69.2	78.9	71.43	91.8	42.9
Qualitative Abnormalities in Reciprocal Social Interaction	70.8	78.9	72.62	92	44.1
Restricted, repetitive and stereotyped patterns of behavior	86.2	36.8	75	82.4	43.8
Abnormalities of behavior evident at or before 36 months	60	89.5	66.67	95.1	39.5
ADI-R (PDD-NOS algorithm)	66.2	89.5	71.43	95.6	43.6
ADOS-2 and ADI-R	42.2	100	55.42	100	33.9

NPV: Negative Predictive Value; PPV: Positive Predictive Value

Figure captions

Figure 1. Flow diagram of included and excluded participants.

Figure 2. ROC curves of the ADOS-2 and domains considered in the diagnostic algorithm.

Figure 3. ROC curves of the ADI-R and domains considered in the diagnostic algorithm.