Towards telediagnostic procedures in child neuropsychiatry: addressing ADHD diagnosis and autism symptoms through supervised machine learning

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Abstract

Recently there has been an increase in telemedicine applied to child neuropsychiatry, such as the use of online platforms to remotely collect anamnestic and behavioral information. In the present proof-of-concept study, we aimed to understand to what extent information provided by parents and teachers through online questionnaires overlaps with clinicians' diagnostic conclusions on Attention-Deficit/Hyperactivity Disorder (ADHD). Moreover, we intended to explore a possible role played by autism spectrum disorders (ASD) symptoms in this process. We examined parent- and teacher-rated questionnaires collected remotely and an on-site evaluation of intelligence quotients from 342 subjects (18% females), aged 3 to 16 years, referred for suspected ADHD. A machine learning model (decision tree, DT) was built to simulate the clinical process of classifying ADHD/non-ADHD. Differences in ASD symptoms in the DT-identified classes were tested to address their role in performing a diagnostic error using the DT model. The DT identified the decision rules adopted by clinicians to classify ADHD diagnosis and proved accurate in 82% of our subjects. The caregiver-reported ADHD core symptom severity proved the most discriminative information for clinicians during the diagnostic decision process. However, ASD symptoms were a confounding factor when ADHD severity had to be established. Telehealth procedures proved effective in obtaining an automated output regarding a diagnostic risk, reducing the time delay between symptom detection and diagnosis. However, this should not be considered as an alternative to on-site procedures but as automated support for clinical practice, enabling clinicians to allocate more resources to the most complex cases.

1. Introduction

Over the past years, healthcare services have been involved in a progressive digitalization process [1]. The COVID-19 pandemic spurred this trend, increasing the demand for effective telehealth support for mental health [2]. Accordingly, the development and use of online platforms for the collection of anamnestic and behavioral data is steadily increasing in child and adolescent neuropsychiatry [3, 4]. However, the validity and reliability of data collected remotely via computer are still to be ascertained [5]. In fact, while clinical questionnaires are being already delivered through apps on smart devices, the validity of self-reported data might be affected by the uncontrolled settings of administration, which could differ from the original settings of the validated questionnaires [6]. Moreover, remote self-administration prevents users from turning to a clinician for help in properly understanding item content.

Our proof-of-concept study addresses this topic in relation to a diagnosis of attention deficit / hyperactivity disorder (ADHD) as the evaluation process for this condition reflects the trend towards digitalization described above. According to the National Institute for Health and Care Excellence Guidelines [7], an accurate ADHD diagnostic process requires an integration of different instruments and informants.

Within this workflow, ADHD characteristics are investigated –to a certain degree– through parent and teacher reports that could be digitally administered. A recent study has demonstrated that parents and

teachers show similar diagnostic accuracy in predicting a clinical diagnosis when the ADHD Rating Scale-IV threshold to discriminate ADHD/non-ADHD condition is considered [8]. However, parents with lower educational attainment showed worse diagnostic accuracy when compared to both parents with higher education levels and teachers [8]. This effect could potentially be enhanced by remote collection of behavioral data because individuals with lower educational levels may face difficulties accessing digital tools [9].

The purpose of the present study is twofold. First, we aimed to understand to what extent the diagnostic conclusions of expert clinicians overlap with the information provided by parents and teachers in online questionnaires. To do this, we tested a decision tree (DT) classification, an interpretable machine learning (ML) algorithm, to analyze diagnostic data collected at the Scientific Institute “IRCCS Eugenio Medea” Regional Center for ADHD [10]. Here we recently developed the first Italian web-based screening tool to remotely administer digital clinical questionnaires in order to provide timely and effective support for the diagnostic process in the child neuropsychiatry field [11]. Recent evidence has shown the advantages of ML algorithms as well-suited analytic techniques for digitally obtained diagnostic data within the progressive digitalization process under way in clinical practice over the past years [12]. Computer algorithms can be indeed optimized to highlight patterns in remotely collected clinical data that could assign a predicted diagnostic label to each evaluated subject. At this stage, most of the studies employing ML techniques to support the ADHD diagnostic process used “black box” models, providing accurate but not easily interpretable results [13, 14]. However, in the specific case of supporting decisions associated with a diagnosis, model interpretability is of crucial importance in enabling clinicians to integrate qualitative clinical knowledge with algorithms results.

Second, we intended to explore whether caregivers reported a co-presence of autism spectrum disorder (ASD) symptoms. We aimed to understand at which point the presence of autistic features in children clinically referred for ADHD problems could represent a potential confounding factor, also taking into account the considerable behavioral overlap between the two disorders [15, 16].

2. Methods

In this retrospective, single-center, observational study, we reported data from the diagnostic process of a sample of children and adolescents referred for suspected ADHD diagnosis at the Scientific Institute “IRCCS Eugenio Medea” – Associazione La Nostra Famiglia in Bosisio Parini (Lecco, Italy) between early 2017 and late 2020. This study was approved by the Institute’s Ethical Review Board (Prot. N. 29/22, “Comitato Etico IRCCS E. Medea — Sezione Scientifica Associazione La Nostra Famiglia”) and all the participants’ legal guardians gave their written informed consent to the children’s participation.

2.1. Participants

Three hundred forty-two children and adolescents (18% females) living in Northern Italy, aged 3 to 16 years, underwent a full neuropsychiatric evaluation and did or did not receive an ADHD and/or ASD

diagnosis in accordance with the DSM-5 criteria [17].

2.2. Procedure

A workflow of the diagnostic procedure is shown in Fig. 1.

[Figure 1: **Diagnostic process scheme]**

2.3. Measures

2.3.1. Remotely collected measures

Socio-anamnestic questionnaire. The following socio-anamnestic information was collected: a) age and sex; b) perinatal risk factors: pregnancy problems, preterm or late birth, extremely high or low birth weight, breastfeeding problems, APGAR score at birth; c) family type (biological / fostering parents, co-parenting / single-parent); d) family socioeconomic status coded according to Hollingshead scale [18].

Parent-report questionnaires. Conners' Parent Rating Scale-Revised (CPRS-R) [19]. The CPRS-R is appropriate for parents with children between the ages of 3 and 17. It consists of items tapping behavioral and emotional problems. Item scores are summed up in symptom scales presenting moderate to high internal reliability, with Cronbach's alphas ranging from .75 to .94 [19]. CPRS-R adjusted scores higher than 60 and 70 indicate moderate and severe clinical risk. For this questionnaire, Oppositional, Cognitive Problems, Hyperactivity, Anxious/Shy, Perfectionism, Social Problems, Psychosomatic Problems, ADHD index, CGI Restless-Impulsive, CGI Emotional Lability, CGI Total, DSM-IV Inattentive, DSM-IV Hyperactive-Impulsive, and DSM-IV Combined were considered.

Child Behavior Checklist for Ages 1.5-5 (CBCL/1½-5) or Child Behavior Checklist for Ages 6–18 (CBCL/6–18) [20]. The CBCL is a questionnaire tapping behavioral and emotional problems in children and adolescents, covering a broad spectrum of psychopathological symptoms. The intraclass correlation coefficient of CBCL is .95; Cronbach's alphas range from .72 to .97 [20]. Symptom scale scores higher than 64 and 69 indicate moderate and severe risk. Scores higher than 59 and 63 on Total Problems, Internalizing Problems, and Externalizing Problems scales indicate moderate and severe risk. In our analyses we included the following scale scores: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Attention Problems, Rule-Breaking Behavior, Aggressive Behavior, Depressive Problems, Anxiety Problems, ADHD Problems, Oppositional Defiant Problems, Internalizing Problems, Externalizing Problems, and Total Problems.

Social Responsiveness Scale (SRS) [21]. The SRS is a questionnaire collecting information on the severity of impairment of a number of social abilities linked to ASD symptoms in children and adolescents. SRS is characterized by high internal consistency (Cronbach's alpha ranging from 0.94 to 0.96) [22]. Scores higher than 59 and 76 indicate moderate and severe risk, respectively. SRS showed a sensitivity and a specificity value of .92 [22]. Social Awareness, Social Cognition, Social Communication,

Social Motivation, Autistic Mannerisms (Restricted Interests and Repetitive Behavior), and Total scores were considered in the analyses.

Teacher-report questionnaire. Conners' Teacher Rating Scale-Revised (CTRS-R) [23]. The CTRS-R measures behavioral problems in children and adolescents aged 3 to 17 years. The CTRS-R showed Cronbach's alpha coefficients higher than .73. Scores higher than 60 and 70 indicate moderate and severe risk, respectively. We considered for the analyses the same scales as for the parent version, except for Psychosomatic Problems (not included in the teacher form).

2.3.2. Measures administered on-site

All the participants underwent a full examination by a medical doctor specialized in child neuropsychiatry. A child psychologist with experience in ADHD and ASD independently confirmed the diagnosis by direct observation of the child and administered neuropsychological and cognitive tests.

Intelligence quotient evaluation. The child's IQ was evaluated through one of the following scales according to age, testability, and ability: Griffiths Mental Development Scales [24], Wechsler Preschool and Primary Scale of Intelligence, Third Edition [25], Wechsler Intelligence Scale for Children, Fourth Edition [26].

2.4. Statistical analyses

Statistical analyses were performed using R version 4.1.2 [27].

2.4.1. The decision tree-based machine learning method

To ascertain which reported features were most relevant in the diagnostic process of ADHD, we used a DT classifier, an flowchart-like structure that is built considering the full dataset "sitting" at the top of the root node and, at each junction, observations satisfying the splitting condition are assigned to the left branch and the others to the right branch [28]. Information gain is used as a node impurity measure to select the attribute and split each node until reaching the last node, the so-called "leaf" [29]. The most frequently observed class in each leaf is considered as a classification prediction by the algorithm [30].

Note that:

- *TP* means *true positive* (hereafter, true ADHD): the rightly predicted subjects as *ADHD subjects;*
- *TN* means *true negative* (true non-ADHD): the rightly predicted subjects as *non-ADHD subjects;*
- *FP* means *false positive* (false ADHD): the wrongly predicted subjects as *ADHD subjects;*
- *FN* means *false negative* (false non-ADHD): the wrongly predicted subjects as *non-ADHD subjects.*

The algorithm performance was evaluated considering the following information:

1. *Classification accuracy*: percentage of correctly performed predictions against the total number of instances;

2. *No information rate (NIR)*: the accuracy achievable by always predicting the majority class label;
3. *P-Value of Acc > NIR*: a hypothesis test result, to evaluate whether the classification accuracy by the algorithm is greater than the rate of the largest class (NIR);
4. *Specificity*: percentage of correctly performed negative predictions (non-ADHD) against the number of subjects without an ADHD diagnosis;
5. *Sensitivity*: percentage of correctly performed positive predictions (ADHD) against the number of subjects with an ADHD diagnosis.

2.4.2. Decision tree for correct/incorrect classifications

Predictions of ADHD/non-ADHD diagnoses performed by the DT algorithm were compared with the actual ADHD/non-ADHD diagnoses by clinicians. To address the clinical characteristics of subjects incorrectly classified by the DT algorithm (in other words, the cases in which the integration of in-person observation, caregiver questionnaires, and psychometric tests administered by the clinicians was discordant with the data resulting exclusively from questionnaires), the whole data set was split into ADHD and non-ADHD children. For each of these groups, correct/incorrect classification was considered as an output variable in two further DTs to identify a rule-based algorithm that could express the properties of misclassified subjects.

2.4.3. Analysis of autism symptoms in correctly/incorrectly classified ADHD children

To disentangle the role of ASD symptoms in correct/incorrect classification of the DT algorithm, subjects with or without an ADHD diagnosis were considered separately in two contingency tables addressing frequencies of correctly/incorrectly classified ADHD and the presence vs absence of an ASD diagnosis as assessed by clinicians. Two Fisher's exact tests were applied to test the association between receiving an ASD diagnosis and being correctly or incorrectly classified as ADHD through the DT algorithm.

In addition, parent-reported ASD symptoms were evaluated in relation to correctly classified/misclassified ADHD subjects. True ADHD / true non-ADHD / false ADHD / false non-ADHD categories were considered as independent variables, and the six SRS scores were considered as dependent variables in separate Kruskal–Wallis tests. To identify what specific couples of medians were significantly different, two-sided pairwise Wilcoxon Rank Sum tests with Bonferroni correction for multiple comparisons were performed. The following group comparisons were considered: a) true ADHD vs false non-ADHD, and b) true non-ADHD vs false ADHD.

3. Results

After performing data cleaning procedures (see the Appendix section), more than 50% of data were missing for 16 subjects, which were therefore excluded from the analyses. The final sample consisted of 326 children and adolescents. The participants' characteristics are shown in Table 1. The male-to-female ratio (5.5:1) in our sample is in line with previous literature [31]. At the end of the diagnostic process

performed by the clinicians, 52% of the sample received an ADHD diagnosis without ASD, 33% of the subjects received neither an ADHD diagnosis nor an ASD diagnosis, 8% of the subjects were diagnosed with ASD without ADHD, and 7% of the children received a comorbid ADHD-ASD diagnosis.

Table 1
Sample descriptive statistics. The location parameter for quantitative variables is the median (± standard deviation).

Variable	Total sample	ADHD stratification		ASD stratification	
		ADHD	non - ADHD	ASD	non-ASD
Age	9 (± 2)	9 (± 2)	8 (± 2)	8 (± 2)	9 (± 2)
Sex	m = 83%	m = 89%	m = 75%	m = 86%	m = 83%
N. of Perinatal Problems	f = 17%	f = 11%	f = 25%	f = 14%	f = 17%
SES	1 (± 1)	1 (± 1)	1 (± 1)	1 (± 1)	1 (± 1)
IQ	50 (± 18)	50 (± 17)	50 (± 19)	50 (± 19)	50 (± 18)
	96 (± 16)	96 (± 15)	96 (± 17)	97 (± 16)	96 (± 16)

[Table 1: **Sample descriptive statistics]**

3.1. Decision tree for ADHD diagnosis

DT results are shown in Fig. 2.

[Figure 2: **ADHD decision tree results]**

The DT showed an 82% accuracy (95% confidence interval = 78%-86%); this result was significant (NIR = 59%, $p < 0.001$). The model had an 80% specificity and an 84% sensitivity.

3.2. Decision tree for correct / incorrect classifications

Correct (true ADHD and true non-ADHD) and incorrect (false ADHD and false non-ADHD) classifications were considered in the two groups of clinician-diagnosed ADHD and non-ADHD, separately.

Figure 3 shows the DT results regarding true ADHD / false non-ADHD classification, with a DT accuracy of 97% (95% confidence interval = 93%-99%); this result was significant (NIR = 84%, $p < 0.001$). The model had a 100% specificity and a 96% sensitivity.

[Figure 3: **decision tree results for true ADHD and false non-ADHD]**

Figure 4 shows the DT results regarding true non-ADHD / false ADHD classification. The DT accuracy was 95% (95% confidence interval = 90%-98%); this result was significant (NIR = 80%, $p < 0.001$). The model had a 100% specificity and a 94% sensitivity.

[Figure 4: **decision tree results for true non-ADHD and false ADHD]**

A rule-based interpretation of the results presented in Figs. 3 and 4 is shown in Table 2.

Table 2
Rules for incorrect decision tree-performed classifications.

False non - ADHD class	**● If CTRS-R ADHD index < 60, or** **● If CTRS-R ADHD index > 59, and CPRS-R DSM - Combined < 63, and CTRS-R CGI - Total < 69.**
False ADHD class	● CPRS-R CGI - Total > 59, and CTRS-R ADHD index < 60, and CBCL - ADHD Problems < 54, or ● CPRS-R CGI - Total > 59, and CTRS-R ADHD index > 59, and CPRS-R - DSM Combined > 64.

[Table 2: **Rules for incorrect decision tree-performed classifications**]

3.3. Analysis of autism symptoms in correctly / incorrectly classified ADHD children

Table 3 shows significant results on Fisher's exact test.

Table 3
ADHD and ASD contingency table. Fisher's exact test addressed the association between categorical ASD diagnosis and false non-ADHD/true ADHD. p-value = 0.029.

	Misclassified as non-ADHD	Correctly classified as ADHD
Absence of ASD	18%	82%
Presence of ASD	0%	100%

[Table 3: **ADHD and ASD contingency table]**

The Kruskal–Wallis tests by ranks were all significant, except for the Social Motivation problems scale. Autism symptoms were reported to be higher in the true ADHD group compared to the false non-ADHD group, and in the false ADHD group compared to the true non-ADHD group. Hence, the DT algorithm highlighted a tendency towards an ADHD diagnosis when parents reported elevated ASD symptoms.

Results regarding the SRS subscales are shown in Figures A1-A5 in the Appendix section. As an example, Fig. 5 shows the total score results.

[Figure 5: **Total ASD symptoms**]

4. Discussion

Over the last few years, the digital innovation process and the COVID-19 pandemic spurred an increasing request for telehealth procedures [32, 33]. The first steps of the diagnostic process for ADHD may fit this trend, since a thorough information collection regarding children's behaviors could be potentially performed remotely [11].

The first aim of the present study was to explore whether and to what extent the clinical diagnosis of ADHD by expert clinicians agreed with symptoms as rated by parents and teachers through online administered questionnaires. To this end, we tested a DT, given its notable interpretability and the suitability for digitally collected data [12].

Our algorithm reached a very good accuracy (82%) in correctly identifying children which either did or did not receive a diagnosis of ADHD at the end of the clinical evaluation. The present accuracy is in line with previous ML works which highlighted the possibility of accurately discriminating subjects with and without ADHD [13, 34, 35]. However, earlier research was based on biological, neurophysiological, or behavioral data collected on-site. To our knowledge, the present study provided first preliminary evidence that data collected through telehealth might be valuable to support the clinical practice of diagnosing ADHD.

As one could expect, among all the collected measures, the core parent- and teacher-reported ADHD symptom severity was the most discriminative information for the DT classification. Ratings on DSM-oriented ADHD scales of both the informants showed a crucial relevance for the clinicians' diagnostic decision. This is interesting if we consider that the DT assigns the same "weight" to all the considered input variables (i.e., anamnestic, cognitive, behavioral). Moreover, although the algorithm was totally naïve about the questionnaire cutoffs, in the upper nodes the DT identified scores that are in line with moderate and severe risk for ADHD, respectively 64 and 70 [19, 23]. These findings thus extend –for the first time, in a telehealth setting– recent findings which showed that caregivers' reports could reliably predict ADHD diagnosis [8].

Interestingly, in 18% of the cases, clinicians reached a different diagnostic conclusion compared to that resulting from the algorithm. Specifically, in case of "extreme" scores on caregivers' reports, the clinicians rely mostly on both their direct observation of the patient, cognitive performance, and clinical interview for their decision.

The second aim of this study was to understand whether the co-presence of ASD symptoms as described by caregivers could represent a potential confounding factor, given the considerable overlap in symptom presentation [36]. In our sample, 12% of children diagnosed with ADHD were also clinically diagnosed with ASD. This is in line with recent evidence [37].

It is important to keep in mind that the DT only relied on caregivers' reports of ADHD core symptoms and often associated oppositional symptoms [38]. As one could expect, ASD symptoms were not selected by the algorithm as discriminant information for a correct ADHD classification. Nevertheless, all participants clinically diagnosed with comorbid ADHD-ASD were correctly recognized as ADHD by the DT algorithm;

conversely, not all participants with a clinical diagnosis of ADHD without an ASD diagnosis were correctly classified as ADHD. This therefore showed that both parents and teachers provided more severe ratings of ADHD in children who were later diagnosed with a comorbid ADHD-ASD by clinicians. The present finding is in line with a recent review, which reported higher externalizing difficulties in children with ASD [36] and with previous evidence describing an additive effect of symptom severity in children with ADHD/ASD comorbid state [39, 40].

Consistently, the analysis of social abilities among the four groups sorted by the DT showed that participants with higher ratings of social cognition, communication problems, and autistic mannerisms on SRS were classified as having ADHD, leading to many false positives for the algorithm. These traits, with the addition of social awareness, were conversely lower in children misclassified as non-ADHD by the algorithm. Despite representing a novelty for what concerns the analytic approach, this finding may corroborate previous evidence. Indeed, social functioning atypicalities, a hallmark of ASD, are often reported in ADHD, too [40]. Although research suggests that the mechanisms underlying these difficulties are different [40], social impairment in the two conditions may look alike at phenotypic level to non-clinical observers such as parents. Hence, impaired social functioning can be reported by parents of children referred for suspected ADHD, influencing the DT results. An interesting exception to this trend is social motivation scores on SRS. All the four classes presented indeed typical levels of social motivation, which is in line with a recent work reporting comparable scores in social motivation between children with ADHD only and neurotypical peers [41].To our knowledge, the present study addressed for the first time the impact of ASD features on an ML algorithm classification of ADHD. Against the background of recent developments of digitalized procedures supporting diagnostic decisions, the confounding effect of non-core associated symptoms needs to be further investigated in future studies.

4.1. Conclusion

Online information collection and screening procedures should not be merely considered as an alternative to on-site diagnostic practice. Instead, telehealth can help effectively collect reliable caregivers' reports and obtain a subsequent automated output regarding a diagnostic risk factor [11]. Special attention should be given not only to the development of accurate diagnostic classification models but also to the factors that might lead to diagnostic misclassification. Lastly, if the first diagnostic steps are optimized, a reduction of the time delay between initial symptom detection and diagnosis could be achieved, enabling clinicians to focus on the most complex cases.

4.2. Limitations

Some limitations of the present preliminary study should be considered. Our sample included children and adolescents from the same area (Northern Italy) referred by their pediatricians for suspected ADHD. Thus, it is not known whether our results could be generalized to other populations.

Furthermore, our analysis exclusively addressed the potentially confounding effects of autism symptoms in ADHD classification. However, there are several conditions commonly associated with ADHD [42].

Additional research addressing the impact of these symptoms and conditions in predicting ADHD is needed.

4.3. Future directions

Future research focused on the development of online platforms for remotely performed data collection is needed [11]. Developments of ML predictive models could also offer clinicians prompt feedback about the diagnostic risks associated with questionnaire scores. If proven valid, these procedures could be readily implemented also for other neurodevelopmental conditions.

Declarations

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Figures

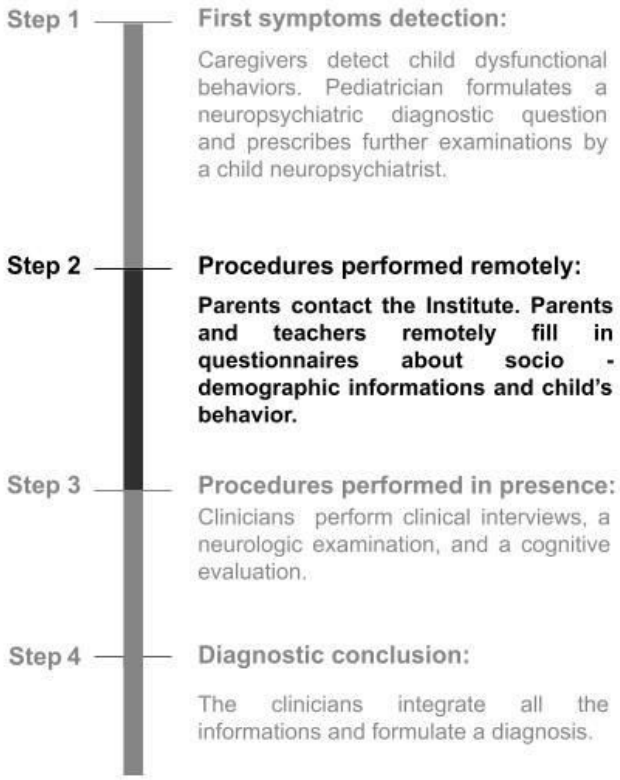

Figure 1

Diagnostic process scheme. Graphic design of diagnostic process at the Regional Center for ADHD.

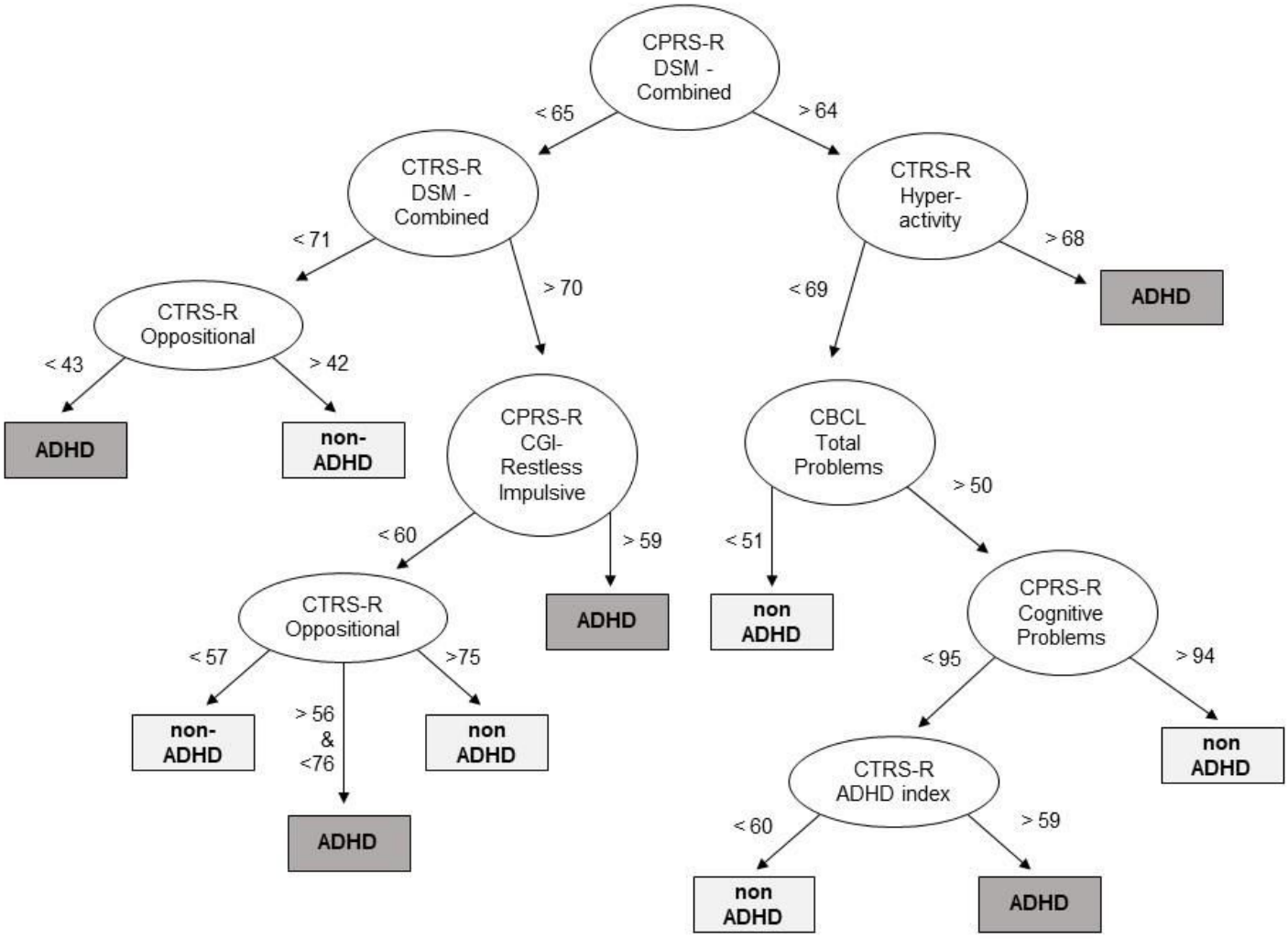

Figure 2

ADHD decision tree results. Representation of the machine learning algorithm results.

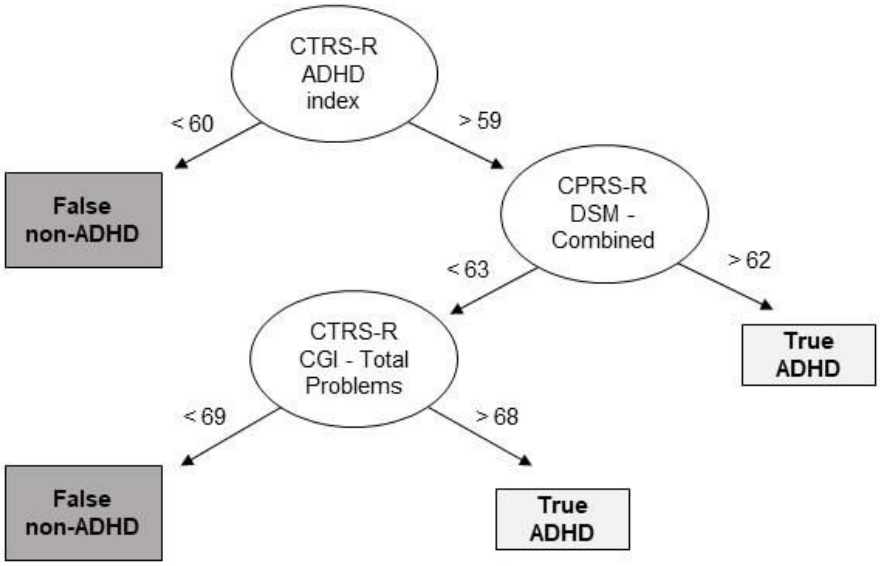

Figure 3

decision tree results for true ADHD and false non-ADHD. Representation of the machine learning algorithm results.

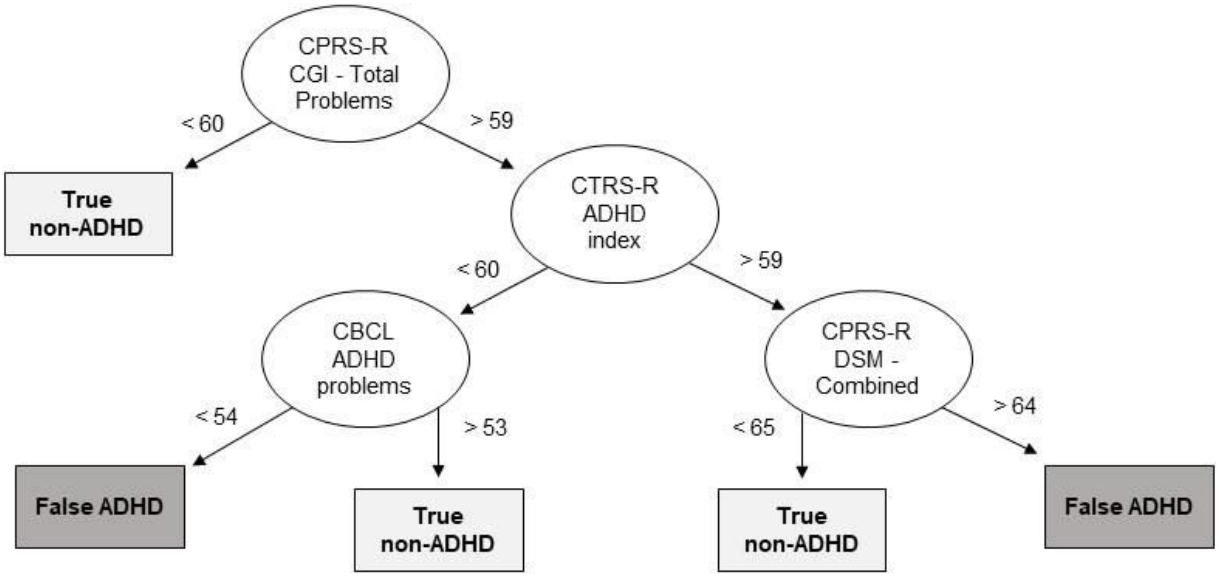

Figure 4

decision tree results for true non-ADHD and false ADHD. Representation of the machine learning algorithm results.

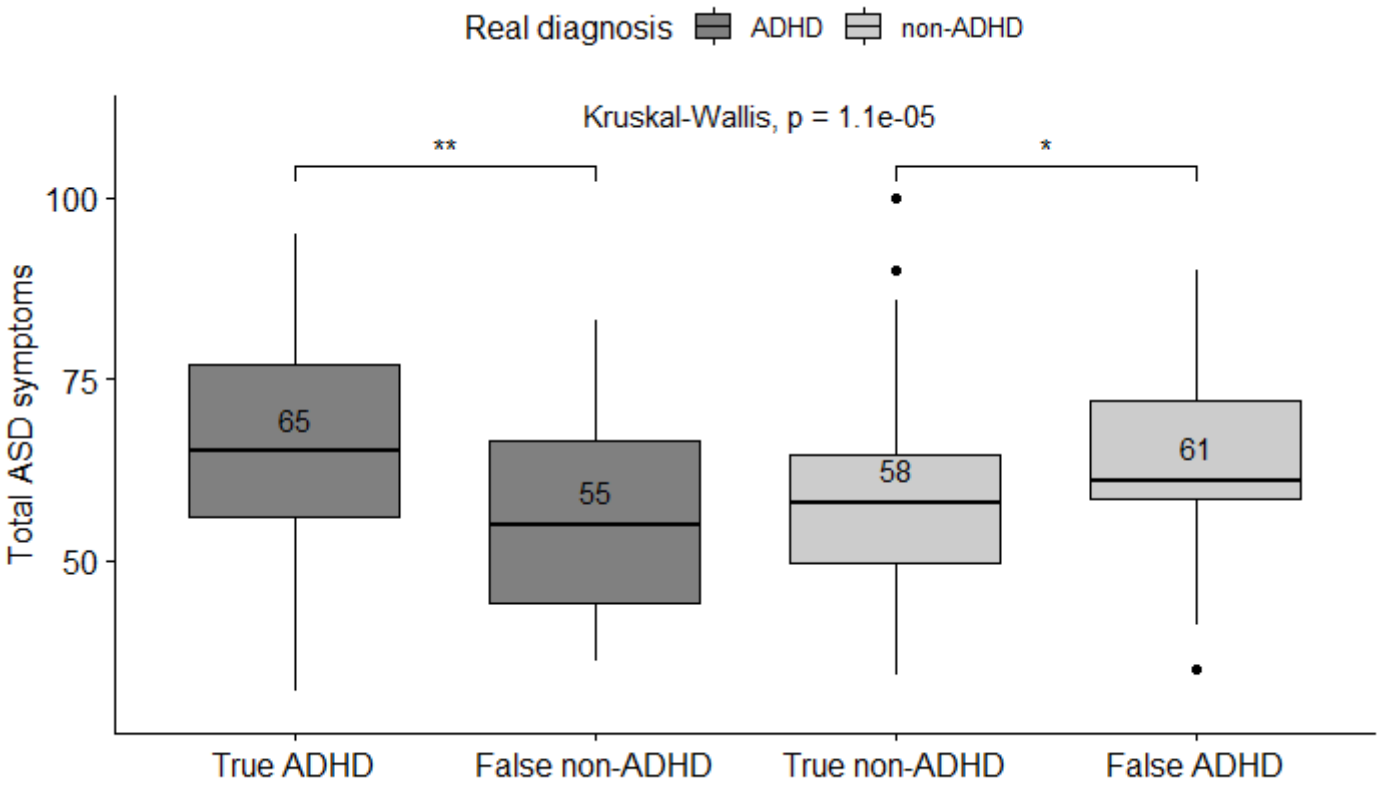

Figure 5

Total ASD symptoms. Differences in total ASD symptoms measured through SRS in the four classes. Note: median values are shown in the boxplots. * $p < 0.05$, ** $p < 0.01$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 3Appendix.docx