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ORIGINAL PAPER

Use of Machine Learning to Identify Children with Autism and Their Motor Abnormalities

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Abstract In the present work, we have undertaken a proof-of-concept study to determine whether a simple upper-limb movement could be useful to accurately classify low-functioning children with autism spectrum disorder (ASD) aged 2–4. To answer this question, we developed a supervised machine-learning method to correctly discriminate 15 preschool children with ASD from 15 typically developing children by means of kinematic analysis of a simple reach-to-drop task. Our method reached a maximum classification accuracy of 96.7 % with seven features related to the goal-oriented part of the movement. These preliminary findings offer insight into a possible motor signature of ASD that may be potentially useful in identifying a well-defined subset of patients, reducing the clinical heterogeneity within the broad behavioral phenotype.

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Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental disorder with multiple causes, courses, and a wide range in symptom severity (Amaral et al. 2008). Although the core features of ASD are persistent deficits in social communication and interaction and the presence of restricted, repetitive patterns of behavior, interests, or activities (DSM V, American Psychiatric Association 2013), it is of great importance not to ignore the motor impairments associated with ASD as they are highly prevalent, at 79 %, and can have a significant impact on quality of life and social development (Lai et al. 2014). Motor abnormalities in ASD may occur very early in development (Teitelbaum et al. 1998, Brian et al. 2008) and be apparent over time (Fournier et al. 2010; Van Waelvelde et al. 2010) being a pervasive feature of the disorder. Recent studies have also provided evidence for the specificity of motor impairments identified in high-functioning children with ASD compared to children with attention deficit/hyperactivity (ADHD) (Izawa et al. 2012; Ament et al. 2014) and to typically developing children matched by nonverbal IQ and receptive language (Whyatt and Craig 2013). Overall, these findings suggest that motor abnormalities could be a consistent marker of ASD (Dowd et al. 2012). A number of different motor deficits have been reported in ASD, including anomalies in walking patterns (e.g., Rinehart and McGinley 2010; Nobile et al. 2011), hand movements such as reaching (e.g., Mari et al. 2003; Glazebrook et al. 2006; Forti et al. 2011), and eye-hand

coordination (e.g., Glazebrook et al. 2009; Crippa et al. 2013). The severity of motor deficits correlates with the degree of social withdrawal and the severity of symptoms (Freitag et al. 2007). Motor control has even been speculated to be crucial for communication and social interaction (Leary and Hill 1996). Indeed, Minshew et al. (2004) proposed that studies on motor function could have significant potential in elucidating the neurobiological basis and even improving the diagnostic definition of ASD.

Currently, the gold standard for the diagnosis of ASD has been formalized with the clinical judgment of symptoms and with semistructured, play-based behavioral observations (Lord et al. 2000) and standardized interviews or questionnaires (e.g., Lord et al. 1994). However, recent studies have started to explore the predictive value of neurobiological as well as behavioral measures in ASD in order to identify a well-defined phenotype of individuals and—possibly—to enable a computer-aided diagnosis perspective. These studies typically implement pattern classification methods that are based on machine-learning algorithms to predict or classify individuals of different groups by maximizing the distance between groups of datasets. Machine learning commonly refers to all procedures that train a computer algorithm to identify a complex pattern of data (i.e., "features") that can then be used to predict group membership of new subjects (e.g., patients vs. controls). Machine-learning techniques based, for example, on support vector machines (SVMs; Vapnik 1995) require a well-characterized dataset in the training phase in order to extract the classification algorithm that best separates the groups (i.e., the "hyperplane" or "decision function"). In the testing phase, the classification algorithm can be used to predict the class membership of a participant not involved in the training procedure (e.g., whether a new child has ASD). Pattern classification methods can also identify complex patterns of anomalies not efficiently recognized by other univariate statistical methods. Thus, the use of pattern recognition methods to predict group membership should not be considered merely in a potentially "diagnostic" perspective but also as a useful tool used to develop objective measures for each individual from a set of sample data. Most of the studies have applied pattern classification methods to neuroanatomical data measured by structural magnetic resonance (MRI; Ecker et al. 2010a, b) or by diffusion tensor imaging (Lange et al. 2010; Ingalhalikar et al. 2011; Deshpande et al. 2013), although Oller et al. (2010) analysis of data regarding automated vocal analysis produced promising results.

In the present work, we have undertaken a proof-of-concept study to determine whether a simple upper-limb movement could be useful to accurately classify low-functioning children with ASD who are between the ages of 2 and 4. In order to answer this question, we developed a supervised machine-learning method to identify preschool children with ASD and correctly discriminate them from typically developing children by means of kinematic analysis of a simple reach, grasp and drop task. We decided to analyze this simple motor task because the motor system can be more easily probed in low-functioning autistic children than systems that underlie complex cognitive functions. In addition to the potential predictive value of our machine-learning method in exploring the clinical relevance of simple upper-limb movement measures in ASD, we could identify a limited set of kinematic characteristics that even suggests the hypothesis of a motor signature of autism.

Methods

Participants

Fifteen preschool-aged children with autism (ASD) were compared to fifteen typically developing (TD) children who were matched by mental age. IQ and mental age were assessed in our institute by using the Griffiths Mental Development Scales (Griffiths 1970) as a part of the routine clinical practice with low-functioning children. A poor score on the Griffiths scales at 1 and/or 2 years has been demonstrated to be a good predictor of impairment at school age (Barnett et al. 2004). All participants had normal or corrected-to-normal vision and were drug-naïve.

The participants in the ASD group were recruited at our institute over an 18-month period. All participants in the clinical group had been previously diagnosed according with the criteria described in the Diagnostic and Statistical Manual of Mental Disorders-IV TR (American Psychiatric Association 2000) by a medical doctor specialized in child neuropsychiatry with expertise in autism. The diagnoses were then confirmed independently by a child psychologist through direct observation and discussion with each child's parents. Seven children had been administered the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2000). The participants in the control group were recruited by local pediatricians and from kindergartens to be mentally age-matched to the clinical sample from the normally developing population. We decided to include, as a comparison group, typically developing children matched by mental age, following the assumption that mental age usually predict ability to understand task instructions, use appropriate strategies and inhibit inappropriate responses (Jarrold and Brock 2004). The TD children had no previous history of social/communicative disorders, developmental abnormalities, or medical disorders with central nervous system implications. All of the participants' legal guardians

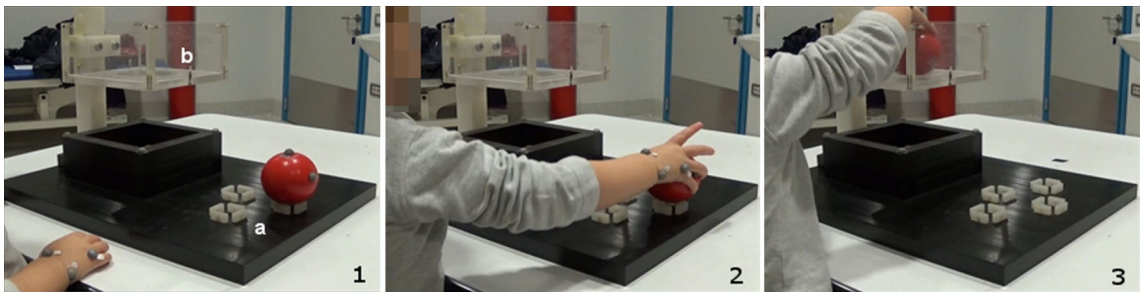

Fig. 1 The experimental task consisted of grasping a rubber ball (**2**) that was placed over a support (see **1**, a); that is, a reach-to-grasp movement before they dropped it in a hole (**3**). The hole (**1**, c) was located inside a see-through *square box* (21 cm high, 20 cm wide) and was large enough not to require fine movements. The goal area is transparent to allow seeing through. 4 markers are placed on the basket under the goal area, 2 on the ball and 3 on each hand (attached to the ulnar and radial surfaces of the participant's wrist and to the hand dorsum on the 4th and 5th metacarpals)

gave their informed written consent prior to the children's participation. The research was approved by the ethics board of our institute in accordance with the Declaration of Helsinki.

Procedure

The participants sat in front of a table of variable height, which was adjusted to the base of the children's trunk. The experimenter sat at the opposite side of the table, and one parent was present in the room. All trials started with the children's hands resting at a set position 20 cm away from the ball support. The experimental task consisted of grasping a rubber ball (6-cm diameter) that was placed over a support (see Fig. 1a); that is, a reach-to-grasp movement before they dropped it in a hole (7-cm diameter). The hole (see Fig. 1b) was located inside a see-through square box (21 cm high, 20 cm wide; see Fig. 1) and was large enough not to require fine movements. Ten trials per participant were conducted: five consecutive trials on the left side (and left hand) and five consecutive trials on the right side (and right hand). The order of trial blocks was counterbalanced between participants. The experimenter performed the task first in order to overtly illustrate the task demand (i.e., reach for the ball, grasp it and drop it in the hole) without any verbal cue. Practice trials, the number of which varied individually, were given to participants before recording in order to verify the children's understanding of the task. The participants were allowed to interrupt the experiment at will in order to rest. The experimental task was simple and interesting enough to ensure the full motivation and compliance of all participants across groups.

Apparatus

An optoelectronic system (The SMART D from BTS Bioengineering® Garbagnate Milanese, Italy) was used to acquire the kinematics data. Three-dimensional kinematic data were collected by eight infrared-motion analysis cameras at 60 Hz (spatial accuracy <0.2 mm), located four per side at 2.5 m from the participants. Passive markers (1 cm) were attached to the ulnar and radial surfaces of the participants' wrists and to the hand dorsum on the fourth and fifth metacarpals (see Fig. 1). Moreover, two markers were placed on the ball and four on the box edges under the goal area. All raw data were first preprocessed with Matlab (Mathworks® Natick, MA, USA); a fifth-order Butterworth, 8-Hz low-pass filter was applied, and movement segmentation and parameters estimation were computed with self-written software.

The overall movement was divided into two sub-movements: *Sub-movement 1*—the movement necessary to reach the ball and place it on its support; *Sub-movement 2*—the movement to transport the ball from its support to the target box hole where the ball was to be dropped. For each of these sub-movements, statistics pertaining to a set of dependent measures was collected: (a) total movement duration (TD), (b) number of movement units[1] (MU), (c) peak velocity (PV), (d) time of PV from sub-movement onset (tPV), (e) peak acceleration (PA), (f) time of PA (tPA), (g) peak deceleration (PD), and (h) time of peak deceleration (tPD). Moreover, final movement accuracy was evaluated by the wrist inclination at the time of the ball drop (delta_WA), calculated as the angle between the palm and the vertical axis of the coordinate system (more precisely, the difference between the WA at the end of the transport phase and the WA at the time of peak deceleration). These 17 kinematic measures were used as input features for the pattern classification procedure.

[1] A movement unit is defined as an acceleration phase followed by a deceleration phase higher than 10 mm/s, starting from the moment at which the increase or decrease in cumulative velocity is over 20 mm/s (Von Hofsten 1991; Thelen et al. 1996).

Data Analysis

After checking that the assumptions were not violated, an analysis of covariance (ANCOVA) was carried out to compare the two groups of children on all kinematic measures with Group (ASD vs. TD) as a between-participant factor, and with IQ and chronological age as between-participant covariates. The alpha level was set to .05 for all data analyses. Effect sizes for ANCOVA are reported using partial eta squared (η_p^2).

The Machine-Learning Method

A pattern classification method based on a machine-learning algorithm was used to classify ASD versus TD by maximizing the distance between the two groups of datasets. A validated supervised machine-learning method (Salvatore et al. 2013) was used. The method involves two different steps: (1) feature selection, the process of selecting a subset of relevant features to be used for classification, and (2) classification, the process of using the selected features to separate the two considered groups of subjects (ASD vs. TD).

Feature Selection

In order to understand which of the collected kinematic features were more discriminative for the ASD versus TD comparison, feature selection was implemented by using a Fisher discriminant ratio (FDR)-based technique (Padilla et al. 2012).

By this technique, for each subject, the collected features and the "label" associated to that subject on a clinical diagnosis basis (i.e., ASD or TD) were considered to calculate a score (FDR score) for each feature.

Specifically, for the feature i, the FDR score was calculated using the following formula:

$$FDR_i = \frac{(\mu_{i-ASD} - \mu_{i-TD})^2}{\sigma^2_{i-ASD} + \sigma^2_{i-TD}}$$

where μ_{i-ASD} and μ_{i-TD} are the mean value of the feature i calculated across the whole ASD and TD datasets, respectively. σ^2_{i-ASD} and σ^2_{i-TD} are the variance of the feature i calculated across the whole ASD and TD datasets, respectively.

Ranked features were then sorted in a decreasing order, from the most to the least discriminative, according to their FDR score.

Classification Algorithm

Classification of ASD and TD subjects was performed using a Support Vector Machine (SVM) approach (Schölkopf et al. 2000; Vapnik 1995, 1998; Vapnik and Chapelle 1999, López et al. 2011), already optimized and validated in a clinical setting (Salvatore et al. 2013).

The aim of the considered SVM is to generate a model able to (1) learn from the selected features of labeled subjects how to discriminate subjects of different groups (binary labeled training datasets), and (2) correctly classify, by means of the same selected features, new unlabeled subjects as belonging to one of the two groups (ASD or TD).

The learning process of the classifier consists of a training phase in which the selected features of the ASD and TD subjects are two training datasets associated to the ASD and TD labels, respectively.

Mathematically, if we have training data consisting of a vector $x_i \in R^N, i = 1, \ldots, N$ and the associated binary label $y_i \in \{\pm 1\}$ (e.g., $+1$ for ASD, -1 for TD), then SVM uses the principle of structural risk minimization to design an optimal hyperplane (OH) that maximizes the distance between the two training groups and that separates them. The lower the distance of a training subject from the OH, the more important that training subject to define the OH. Thus, the distance identifies the "weight" of that training subject in the definition of OH.

The OH can then be used as model to classify new subjects, i.e., subjects for which the label is unknown.

Mathematically, the model used for the identification of the binary label y' of a new subject x, as a result of the classification of that new subject, is given by the following function:

$$y'(x) = \sum_{i=1}^{N} a_i \cdot y_i \cdot k(x, x_i) + b$$

a_i being the weight of the training subject x_i, y_i being the binary label of the training subject i, $k(x, x_i)$ being a linear kernel function, b being a threshold parameter called bias, and N being the number of training subjects. We chose to employ a linear kernel because it represents the more general form of a decision function and because it ensures better computational efficiency.

In this study, the whole machine-learning method was implemented on the Matlab platform (Matlab version R2013b, The MathWorks, Natick, MA). In particular, we used functions of the biolearning toolbox of Matlab to implement the classification algorithm.

Performance of the Classification Algorithm

Performance of the classification algorithm was assessed by using a cross-validation strategy. In general, cross validation involves splitting the original dataset into two complementary subsets: a training set and a testing set. The training set is a set of data associated to a label and used to perform the

training of the classifier (as already described in the previous section); the testing set is a set of data not associated to a label and used to perform the validation of the classifier. By considering different partitions of the data, multiple rounds of cross-validation can then be performed.

In a particular case of cross-validation, called leave-one-out (LOO) cross-validation, the testing set is solely composed of one sample of the original dataset and the training set is made up of the remaining samples of the original dataset ($N - 1$). Therefore, if we want to test all N samples in the original dataset, then it is sufficient that the number of rounds to be performed equals the number N of samples in the original dataset. LOO is a widely used validation approach in literature because it has been proven able to return an almost unbiased estimate of the probability of error (e.g., Vapnik 1998; Chapelle et al. 1999).

In this study, validation of the classifier for the ASD versus TD comparison was performed by using an LOO cross-validation strategy for a number i of selected features running from one to the whole number of features (i.e., 17). A schematic description of the whole procedure is shown in Fig. 2.

In order to quantify the performance of the proposed classification algorithm, the accuracy, specificity, and sensitivity rates were computed. Accuracy of classification measures the rate of correctly classified samples in both positive (ASD) and negative (TD) classes. Specificity and sensitivity measure the rate of correctly classified samples in the positive (ASD) and in the negative (TD) class, respectively.

Mathematically, the accuracy, specificity and sensitivity of the classifier when the first i selected features are used, were computed as follows:

$$Accuracy_i = \frac{N^{CC}}{N}$$

$$Specificity_i = \frac{N_{TD}^{CC}}{N_{TD}^{CC} + N_{TD}^{IC}}$$

$$Sensitivity_i = \frac{N_{ASD}^{CC}}{N_{ASD}^{CC} + N_{ASD}^{IC}}$$

where N is the total number of classified subjects; N^{CC} is the total number of correctly classified (CC) subjects, N_{TD}^{CC} is the number of TD samples that were CC as belonging to the TD gr (true negatives), N_{TD}^{IC} is the number of TD samples that were incorrectly classified (IC) as belonging to the ASD class (false positives); N_{ASD}^{CC} is the number of ASD samples that were CC as belonging to the ASD class (true positives), N_{ASD}^{IC} is the number of ASD samples that were IC as belonging to the TD class (false negatives).

We then studied the dependency of accuracy, specificity, and sensitivity on the number i of selected features.

The maximum values reached for accuracy, specificity, and sensitivity, referred to as maximum accuracy, specificity, and sensitivity, allowed the definition of the most discriminative features.

Overall mean accuracy, specificity, and sensitivity rates were calculated as mean values of accuracy, specificity, and sensitivity as follows:

$$Overall\ mean\ accuracy = \frac{1}{F} \cdot \sum_{i=1}^{F} Accuracy_i$$

$$Overall\ mean\ specificity = \frac{1}{F} \cdot \sum_{i=1}^{F} Specificity_i$$

$$Overall\ mean\ sensitivity = \frac{1}{F} \cdot \sum_{i=1}^{F} Sensitivity_i$$

where F is the whole number of features (17).

Results

Data on the demographic, cognitive, and clinical characteristics of the participants are summarized in Table 1.

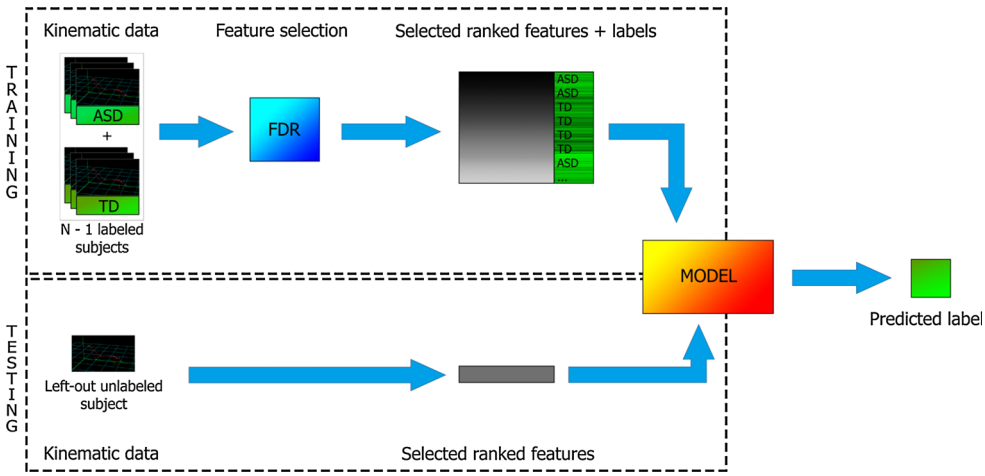

Fig. 2 Flowchart of preprocessing, support vector regression and leave-one-subject-out procedures

Table 1 Demographics of the participants

	ASD	TD	t (1, 28)	*p*
N	15	15		
Females:males	3:12	2:13		
Chronological age[a]	3.5 ± 7.7 (2.8–4.6)	2.6 ± 5.2 (1.7–2.9)	−4.55	<.001
Mental age[a]	2.6 ± 5.7 (1.7–3.4)	2.7 ± 5.9 (1.6–3.2)	.513	n.s.
IQ[b]	75 ± 13.4 (51–96)	105 ± 12.7 (81–119)	6.52	<.001
ADOS[c]				
Social	11 ± 2.2	–		
Communication	7 ± 1.5	–		
SBRI[d]	2 ± 1.6	–		

ASD autism group, *TD* typically developing group; IQ and mental age were assessed using the Griffiths Mental Development Scales (Griffiths 1970)

[a] Mean years; months ± standard deviation (range)

[b] Mean ± standard deviation (range)

[c] ADOS autism diagnostic observation schedule, Lord et al. (2000)

[d] Stereotyped Behavior and Restricted Interests scale

The validity of mental age matching was confirmed ($p > 0.05$). Gender was also balanced between groups, as there were 3 girls in the ASD group and 2 girls in the healthy control group ($\chi^2(1) = .240$; $p > 0.05$). As expected, IQ and chronological age were not balanced across groups (both $p < 0.001$). Table 2 shows kinematic feature values of the two groups of children included in the study (ASD vs. TD) and the results of ANCOVA calculated on all kinematic measures. We found several significant group differences based on the kinematic variables even after having controlled for between-participant differences in IQ and chronological age.

The Machine-Learning Method

Classification Algorithm

In Fig. 3, the optimal hyper-plane separating ASD from TD participants is shown as a representative example of the training phase of the machine-learning method.

Performance of the Classification Algorithm

In Table 3, the accuracy, specificity, and sensitivity of the machine-learning method for the comparison of ASD versus TD are reported.

The machine-learning method was able to successfully classify participants by diagnosis. The classification accuracy reached a maximum accuracy of 96.7 % (specificity 93.8 % and sensitivity 100 %) by using seven features selected by the Fisher discriminant ratio-based technique. Overall mean accuracy, specificity, and sensitivity rates were also calculated over a number of selected features ranging from one to 17 (the whole number of features). The overall mean classification accuracy (specificity/sensitivity) was 84.9 % (mean specificity 89.1 % and mean sensitivity 82.2 %).

Table 2 Kinematic data were initially analyzed through an ANCOVA with Group (ASD vs. TD) as a between-participant factor, and with IQ and chronological age as covariates

		ASD	TD	F(1, 26)	Sig.	η_p^2
Submovement 1						
Movement units	M (SD)	1.91 (0.62)	1.70 (0.37)	<1.0	n.s.	.012
Total movement duration	M (SD)	0.69 (0.14)	0.66 (0.12)	<1.0	n.s.	.010
Peak velocity	M (SD)	0.46 (0.12)	0.59 (0.17)	5,626	**<0.05**	.178
Time of peak velocity	M (SD)	0.34 (0.07)	0.31 (0.04)	<1.0	n.s.	.036
Peak acceleration	M (SD)	3.18 (0.93)	4.26 (1.52)	7,884	**<0.01**	.233
Time of peak acceleration	M (SD)	0.21 (0.07)	0.16 (0.05)	<1.0	n.s.	.031
Peak deceleration	M (SD)	−3.59 (1.28)	−3.93 (1.44)	<1.0	n.s.	.067
Time of peak deceleration	M (SD)	0.47 (0.08)	0.44 (0.06)	<1.0	n.s.	.017
Submovement 2						
Movement units	M (SD)	3.45 (1.78)	1.76 (0.39)	4,408	**<0.05**	.145
Total movement duration	M (SD)	1.35 (0.44)	0.79 (0.15)	13,832	**=0.001**	.347
Peak velocity	M (SD)	0.61 (0.15)	0.76 (0.16)	13,475	**=0.001**	.341
Time of peak velocity	M (SD)	0.41 (0.14)	0.31 (0.05)	18.501	**<0.001**	.416
Peak acceleration	M (SD)	3.85 (1.13)	5.58 (1.94)	12,416	**<0.01**	.323
Time of peak acceleration	M (SD)	0.23 (0.20)	0.13 (0.04)	6,303	**<0.05**	.195
Pick deceleration	M (SD)	−3.29 (1.15)	−4.27 (1.88)	2,632	n.s.	.092
Time of peak deceleration	M (SD)	0.75 (0.24)	0.51 (0.11)	26,652	**<0.001**	.506
Wrist angle	M (SD)	−4.25 (16.34)	−25 (12.40)	6,604	**<0.05**	.203

Bold value indicates significant contrasts

The alpha level was set to .05 for all data analyses. Table depicts group means and standard deviations for kinematic variables, values of *F* test, *p* values and effect sizes reported using partial eta squared (η_p^2)

ASD autism group, *TD* typically developing group

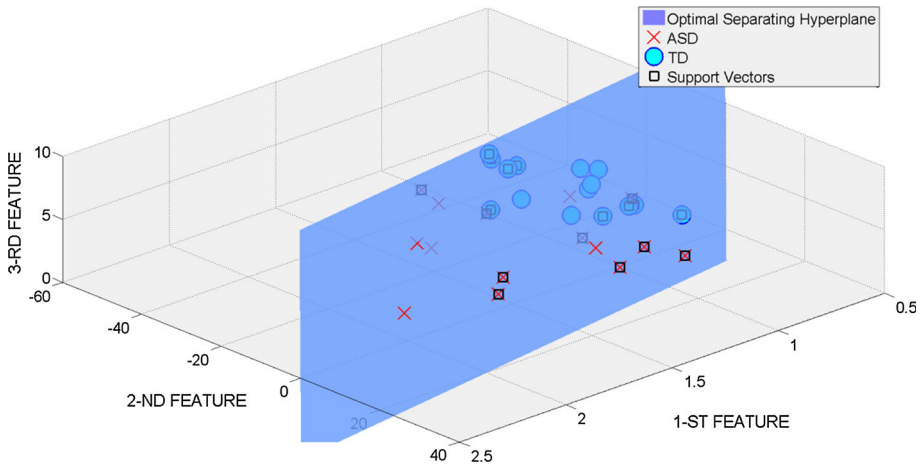

Fig. 3 Optimal separating hyper-plane for the autism group (ASD) versus typically developing groups (TD) (1st, 2nd and 3rd components) is shown as a representative example of the training phase of the machine-learning method

Table 3 Accuracy, specificity and densitivity rates of SVM using LOO validation

	Maximum accuracy (%) (# selected features) Overall mean accuracy (%)	Maximum specificity (%) (# selected features) Overall mean specificity (%)	Maximum sensitivity (%) (# selected features) Overall mean sensitivity (%)
ASD versus TD	96.7 (7) 84.9	93.8 (7) 89.1	100.0 (7) 82.2

ASD autism group, *TD* typically developing group. The maximum values reached by accuracy, specificity and sensitivity were referred to as maximum accuracy, specificity and sensitivity rates. Accuracy, specificity and sensitivity reached their maximum values using 7 features, all related to the second part of the movement—Sub movement 2: (1) Total Duration; (2) delta Wrist Angle; (3) number of Movement Units; (4) time of Peak Deceleration; (5) Peak Acceleration; (6) time of Peak Velocity; (7) Peak Velocity

In Fig. 4, the dependence of the metrics on the number of considered features is shown. The resulting data are shown for a number of features ranging from one to 17. As expected, accuracy, specificity, and sensitivity rates increase with the number of selected features, reaching their maximum values when considering seven selected features.

Besides calculating the accuracy of the SVM method, we were particularly interested in identifying which kinematic features contributed toward the classification. Our analysis showed that seven of 17 features were sufficient to classify autism with a 96.7 % accuracy rate. All of these seven kinematic features are related to the second part of the movement, *sub-movement 2* (i.e., the movement to transport the ball from a support to the target hole in which the ball was to be dropped): (1) total duration; (2) delta wrist angle; (3) number of movement units; (4) time of peak deceleration; (5) peak acceleration; (6) time of peak velocity; and (7) peak velocity. Finally, the most discriminative features between the two groups when considering all of the N rounds (30) of the LOO cross-validation strategy are reported here in descending order: Total Duration sub movement 2, Delta Wrist Angle, Movement Units sub movement 2, time of Peak Deceleration sub movement 2, Peak Acceleration sub movement 2, time of Peak Velocity sub movement 2, Peak Velocity sub movement 2, Peak Velocity sub movement 1, time of Peak Acceleration sub movement 1, Peak Acceleration sub movement 1, time of Peak Acceleration sub movement 2, Peak Deceleration sub movement 2, time of Peak Velocity sub movement 1, Movement Units sub movement 1, time of Peak Deceleration sub movement 1, Peak Deceleration sub movement 1, Total Duration sub movement 1.

Discussion

Autism spectrum disorder is currently diagnosed on the basis of symptoms as qualitatively judged by clinicians and by means of semistructured observations (ADOS) and standardized interviews or questionnaires (ADI-R). Given this gold standard for the diagnosis of ASD, the use of pattern recognition methods to predict group membership has recently attracted strong attention, not only from a computer-aided diagnosis perspective, but also as suitable tool to define objective, quantitative measures of the disorder. Previous works have investigated the predictive value of neurobiological and behavioral measures in patients with ASD. The purpose of the present study was to explore the ability of the kinematic analysis of a simple upper-limb movement to correctly discriminate young low-functioning children with ASD from typically developing

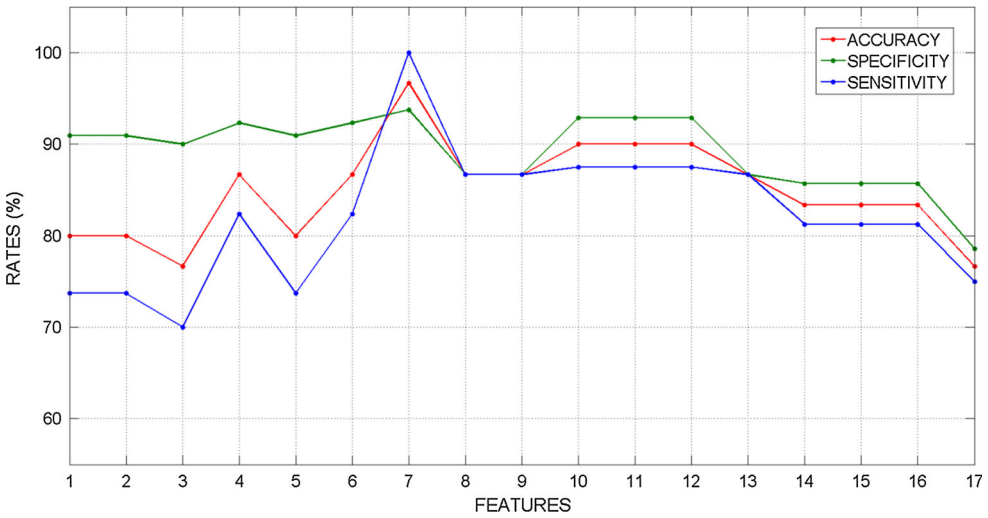

Fig. 4 Graph showing classification accuracy, specificity and sensitivity rates (%) of SVM (Y-axis) in relation of the number of considered features (X-axis). As expected, accuracy, specificity and sensitivity rates increased with the number of selected features. The classification accuracy reached a maximum accuracy of 96.7 % (specificity 93.8 %, and sensitivity 100 %) utilizing seven features. All of these seven kinematic features are related to the second part of the movement—sub-movement 2—the movement to transport the ball from a support to the target hole in which the ball was to be dropped. Such suggests that goal-oriented movements may be critical in separating children with ASD from typically developing children

children. To achieve this goal, we applied our validated supervised machine-learning procedure (Salvatore et al. 2013) to the kinematic analysis of a simple reach, grasp, and drop task performed by preschool children with ASD in comparison to their mental-age-matched, typically developing peers.

The SVM algorithm reached a good mean individual classification in the comparisons between children with ASD and healthy controls (overall mean accuracy = 84.9 %, with overall mean specificity = 89.1 % and overall mean sensitivity = 82.2 %), with a maximum accuracy of 96.7 % (with maximum specificity of 93.8 % and maximum sensitivity of 100 %). The classification accuracy that was achieved in this study is consistent with previous SVM applications to MRI data (Ecker et al. 2010a, b) and to diffusion tensor imaging (DTI) data (Ingalhalikar et al. 2011; Deshpande et al. 2013) or with quadratic discriminant function application on diffusion tensor asymmetries (Lange et al. 2010). Our results are also consistent with the findings of Oller et al. (2010), who derived algorithms that were based on linear discriminant analysis by using an automated analysis of the acoustic characteristics of babble and early language to discriminate typical from language disordered development, such as autism or language delay. Thus, the present findings clearly show the feasibility and the applicability of our SVM method in correctly classifying preschool children with ASD on the basis of a motor task. Indeed, an autism diagnosis is particularly difficult in young, low-functioning children with autism, even using the gold standard diagnostic procedure. Our motor measure might have potential clinical application in such cases, thus providing useful information for clinicians to support a diagnostic decision. A point of relevance of our work, in fact, is that we decided to study the predictive value of a simple reach, grasp, and drop task, because the motor system can be more easily evaluated (i.e., even in young low-functioning children with ASD) than other more complex systems (e.g., cognitive functions). Indeed, because of the easiness and self-explanatory nature of the task, all participants were able to fully understand the experimental demand and to complete the movement successfully. Furthermore, kinematics analysis provides a constraint-free, non-intrusive environment for a challenging clinical population such as ASD in comparison with a magnetic resonance examination that is mostly used in previous pattern-recognition applications. Lastly, kinematic analysis is also a more convenient and less expensive technology than MRI to implement in a clinical setting equipped with an opto-electronic system to acquire kinematic data. Indeed, the task can be easily administered by any professional who works with children. Testing sessions last 15 min, and data analysis can be performed by a trained bioengineer in approximately 30 min for each subject.

Using feature selection, we also found the best classification accuracy of 96.7 % with seven features which had the highest discriminative ability between the groups. All of these seven kinematic features are related to the second part of the movement—*sub-movement 2*—in which the child transported the ball from a support to the target hole

where the ball was to be dropped. This suggests that goal-oriented movements may be critical in separating children with ASD from typically developing children. More specifically, the top three features within the seven kinematic characteristics of *sub-movement 2*—time duration, movement units, and wrist angle—indicate respectively slower and more fragmented movements in children with ASD with inappropriate hand inclination for ball-drops during the final phases of hand transport. Thus, our results extend previous investigations in ASD that report the difficulty of translating intention into a motor chain leading to the action goal (Cattaneo et al. 2007; Fabbri-Destro et al. 2009; Forti et al. 2011). These findings demonstrate that a limited set of kinematic characteristics could reliably identify children with ASD in order to describe a well-defined phenotype of individuals within a complex and highly heterogeneous disorder, even suggesting a possible motor signature of autism related to disrupted planning movement sequences.

Despite our promising results, some methodological limitations of the present exploratory study should be considered. The main limitation is related to the small sample sizes of participant groups; the present findings, therefore, need to be replicated in a larger sample in order to validate the present SVM method by using a data set upon which it has not trained. Another potential limitation of this study is that our SVM classification is highly specific to the sample employed in training the classifier (i.e., preschool children with ASD). Future studies involving females with ASD, children with high-functioning autism, and adult patients are needed to generalize our findings to the heterogeneous spectrum of the disorder. Although we found that our significant between-groups differences were not dependent on IQ and chronological age, it could be worthwhile in future studies to train the computer algorithm with data from age-matched typically developing participants as well. Unfortunately, we did not collect ADOS scores from the entire clinical sample; thus, we could not perform a correlation analysis between our significant findings and the clinical characteristics of children with ASD. Future extensions of this work should also include other neurodevelopmental conditions (e.g., intellectual disability, developmental delays without intellectual disability, or developmental coordination disorders) in order to verify the classifier specificity to ASD, rather than a neurodevelopmental disorder in general. Indeed, some studies have recently indicated the specificity of motor difficulties in older high-functioning children with ASD compared to children with ADHD (Izawa et al. 2012; Ament et al. 2014) and to healthy children matched by nonverbal IQ and receptive language (Whyatt and Craig 2013). Finally, it should be noted that the predictive values of classification methods are restrained by the base rate of neurodevelopmental disorder in the population (Bishop 2010; Heneghan 2010; Yerys and Pennington 2011). Therefore, caution is needed when comparing classification-based accuracy values to the conventional diagnostic measures.

Nevertheless, although the present results should be considered preliminary, this study represents a "proof-of-concept" that kinematic analysis of simple upper-limb movement can reliably identify preschool-aged, low-functioning children with ASD. The significant predictive value of our SVM classification approach might be valuable to support the clinical practice of diagnosing ASD, thus encouraging a computer-aided diagnosis perspective. Moreover, our findings offer insight on a possible motor signature of autism that is potentially useful to identify a well-defined subset of patients, thus reducing the clinical heterogeneity within the broad behavioral phenotype. This may guide further exploration of neuropathology of the disorder with neuroimaging techniques or genetic analysis.

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