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Motor synergies: Evidence for a novel motor signature in autism spectrum disorder☆

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ABSTRACT

In autism spectrum disorder (ASD), socio-communicative impairments and stereotypical behaviours are paralleled by sensorimotor deficits. Individuals with ASD show an altered selection of motor parameters, resulting in clumsy and fragmented actions. Here, we investigated inter-joint coordination and motor synergies as a potential substrate of motor control problems in ASD. Synergies enable co-controlling redundant motor degrees of freedom (DoF, e.g. joint angles, muscles) by mapping behavioural goals into a flexible and low-dimensional set of variables. This mechanism simplifies motor control and helps to find unambiguous solutions for motor tasks. In a reaching-grasping paradigm, children with ASD showed reduced coupling between DoF, which correlated with socio-communicative symptoms severity. Impaired synergies may help to frame well-established motor problems in ASD, including impaired motor sequencing and abnormal trial-to-trial motor variability. On the other hand, synergies also provide an effective and compact coding system of observed actions. Impaired synergies may thus jeopardize motor interaction by initiating bottom-up cascade effects, leading to pervasive impairments of social behaviour. Finally, we trained an automatic classification algorithm to distinguish between ASD and typically developing (TD) participants based on reaching-grasping kinematics. Classification accuracy reached up to 0.947. This result corroborates and expands previous accounts claiming that motor-based early recognition is feasible and effective in ASD.

1. Introduction

According to the current diagnostic criteria, autism spectrum disorder (ASD) is characterized by impairments in social communication and interaction (e.g. lack of social-emotional reciprocity, abnormal verbal and non-verbal communication, difficulties in engaging in relationships) and by the presence of restricted interests and repetitive behaviours (e.g. ritualized activities in everyday life, difficulties to cope with changes, stereotypical movements) (American Psychiatric Association, 2013; World Health Organisation, 2012). The outcome severity, developmental trajectories, and prognosis of ASD are highly heterogeneous as symptoms expression varies across the spectrum. For example, socio-communicative difficulties range from subtle problems in understanding the social context and others' mental states (e.g. intentions, emotions, desires and goals) to complete lack of interest in social cues and interaction. Similarly, restricted and repetitive behaviours span across variable degrees of inflexibility in interests and activities and distress with changes. In addition, intellective functioning, language abilities, adaptive behaviours and neuropsychiatric or medical/genetic comorbidities convey additional inter-subject variability in ASD (Constantino & Charman, 2016; Lai, Lombardo, & Baron-Cohen, 2014).

The aetiology of autism is far from being understood, possibly involving a broad range of genetic (Ramaswami & Geschwind, 2018) and environmental factors (Chaste & Leboyer, 2012). In addition, mounting evidence indicates that low-order impairments of sensory processing and motor coding during the early stages of life may impact the acquisition of more complex abilities, including socio-communicative skills and cognitive functions (Gowen & Hamilton, 2013; Moseley & Pulvermüller, 2018). Indeed, a large body of research has clarified pervasive sensorimotor impairments involving posture and

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balance (Bojanek, Wang, White, & Mosconi, 2020; Fournier et al., 2010), gait (Nobile et al., 2011; Rinehart et al., 2006), aiming movements of the upper limb (e.g. pointing and reaching-grasping movements) (Forti et al., 2011; Glazebrook, Elliott, & Lyons, 2006; Stoit, van Schie, Slaats-Willemse, & Buitelaar, 2013), eye-hand coordination (Glazebrook, Gonzalez, Hansen, & Elliott, 2009), force control (Wang et al., 2017, 2015) and handwriting (Beversdorf et al., 2001; Fuentes, Mostofsky, & Bastian, 2009).

These scattered disturbances presumably arise from a limited number of common dysfunctional mechanisms, with long-reaching effects on motor behaviour. Among these, the limited use of predictive information in motor planning is overtly apparent in ASD. Neurotypical subjects model their actions in advance by predicting the future states of their body and the surrounding environment (Wolpert, 1997). Conversely, individuals with ASD exhibit fragmented actions (Cattaneo et al., 2007), scarcely tuned on global purposes (Fabbri-Destro, Cattaneo, Boria, & Rizzolatti, 2009; Scharoun & Bryden, 2016), upcoming perturbations (Jover, Schmitz, Centelles, Chabrol, & Assaiante, 2010; Schmitz, Martineau, Barthélémy, & Assaiante, 2003) and target objects affordance (Campione, Molteni, Piazza, Villa, & Molteni, 2016). Although planning difficulties have been clarified in ASD, the mechanisms through which low-order variables (e.g. muscle activations and joint rotations) are organized in sensorimotor representations supporting motor parameters selection are uncertain.

Motor planning is hierarchically structured (Wolpert, Doya, & Kawato, 2003; Wolpert & Ghahramani, 2000). The representation of a behavioural goal (e.g. reaching for an object) leads to an increasingly detailed specification of motor parameters (e.g. trajectory, velocity, joint rotations and muscle activations). This operation is not trivial as motor degrees of freedom (DoF, e.g. joint angles, muscles) are largely redundant (Bernstein, 1967). To simplify motor control and reduce its computational burden, DoF are not controlled independently but rather co-controlled in blocks commonly called motor synergies. Through the flexible combination of a limited number of motor synergies, the central nervous system governs joint rotations and muscle activations over time, generating rich patterns of motor behaviour (D'Avella, 2016; Overduin, D'Avella, Roh, Carmena, & Bizzi, 2015). For example, muscular activations involved in reaching movements of the upper limb toward different directions could be described by weighted combinations of only 4 to 5 synergies – a substantial reduction of dimensionality if one considers the vast amount of muscles and joints involved in reaching movements (D'Avella, Portone, Fernandez, & Lacquaniti, 2006). It follows that synergies are a conceivable substrate for motor planning. That is, sensorimotor transformations of behavioural goals into appropriate actions may be reduced to the process of distributing appropriate weights across a low-dimensional set of variables. While still neglected in ASD, the organization of motor synergies may unravel one of the dysfunctional core mechanisms underlying the well-established evidence of impaired selection of motor programs.

In this study, we used an ecological and self-explanatory motor task to record reaching kinematics in children with ASD of pre-school age. In addition to general measures of motor performance (e.g. movement time and relative time to peak velocity), we assessed DoF control and motor synergies by applying principal component analysis (PCA) to extract the linear correlations between upper limb joint angles excursions. Kinematic measures were then correlated with autism severity, as indexed by the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000; Lord, Rutter, DiLavore, & Risi, 1999). The distribution of motor impairments across individuals may help to explain the large inter-subject variability of socio-communicative symptoms, possibly supporting a causal link between early motor dysfunction and atypical development. However, only a few studies have attempted to frame inter-individual differences of ASD symptoms as a function of motor impairments, with mixed results (Cavallo et al., 2018; Cook, Blakemore, & Press, 2013). In contrast, standardized assessments of autistic symptoms are often only used to assign group labels (i.e. ASD vs. neurotypical). This approach has prevented understanding the impact of motor differences in the heterogeneous expression of ASD symptoms. Finally, research on motor impairments in ASD has attracted growing attention over the latest years for their potential use as early diagnostic predictors (S. R. Harris, 2017). Importantly, by boosting prompt interventions, early recognition was shown to positively impact the clinical outcome and quality of life (Bradshaw, Steiner, Gengoux, & Koegel, 2015; Howlin, Magiati, & Charman, 2009; Volkmar & Editorial, 2014). Recent results indicate that automatic classification algorithms fed with movement kinematics effectively discriminate between adults with ASD and neurotypical counterparts (Cavallo et al., 2021; Li, Sharma, Meng, Purushwalkam, & Gowen, 2017; Vabalas, Gowen, Poliakoff, & Casson, 2019, 2020). However, only a few studies have attempted motor-based automatic classification of ASD vs. typically developing (TD) children as young as preschool-age (Alcañiz Raya et al., 2020; Anzulewicz, Sobota, & Delafield-Butt, 2016; Crippa, Salvatore, Perego, Forti, & Nobile, 2015; Perego, Forti, Crippa, Valli, & Reni, 2009). Building on this evidence, we designed an automatic classification algorithm to discriminate between ASD and TD participants based on motor features. Moreover, to provide practical information for translational purposes, we evaluated motor-based classification under conditions of few trials or only end-effector kinematics available. Moving from the automatic classification approach, we developed a fine-grained analysis of motor impairments at single subject level, revealing which features made one participant closer to the ASD vs. TD group. By this approach, we aimed to move toward personalized assessment of sensorimotor impairments in ASD.

2. Methods

2.1. Participants

Participants were 13 children with ASD (5 females) aged 44 to 82 months (mean = 66.231; SD = 11.562) and 13 TD children (9 females) aged 43 to 71 months (mean = 60.077; SD = 9.543) (Table 1). Groups were matched for age ($t_{24} = 1.480$, $p = 0.152$). All participants had normal or corrected-to-normal vision. Children with ASD were recruited at a local outpatient clinic for neurodevelopmental disorders, while TD children were recruited at a local kindergarten school. Diagnosis of ASD was provided by an experienced clinician according to the ICD-10 (World Health Organisation, 2012) and DSM-5 criteria (American Psychiatric Association, 2013). Handedness was assessed before all the experimental procedures by asking participants to pick up a felt-tip pen and draw freely on a sheet of paper and confirmed by children's caregivers and/or clinicians. Two children (one in the ASD group and one in the TD group) were left-handed and two children in the ASD group did not have a clear handedness. All the other participants were right-handed. All participants' parents or legal guardians provided written informed consent before children participated in the study. The study was designed according to the declaration of Helsinki and approved by the local ethical committee, ref.: EM185-2020_UniFe/170686_EM2.

2.2. Clinical assessement

ADOS was administered to all participants in both groups to corroborate clinical diagnosis and capture variation of symptoms severity across the ASD group. ADOS is a semi-structured standardized behavioural assessment of social interactions, communication and play. It consists of four different modules administered based on individual expressive language skills and developmental levels. Each module includes different age-appropriate activities, ranging from playful to verbal tasks. The examiner codes the observed behaviours and three scores are derived overall, namely a Communication score, a Reciprocal Social Interaction score and a Total score (i.e. the sum of Communication and Reciprocal Social Interaction scores). ADOS is acknowledged as a 'gold standard' for ASD diagnosis and a recent review reported an overall sensitivity of 0.94 and specificity of 0.80 calculated on 12 studies

Table 1
Demographic and clinical data (F84.9: Pervasive developmental disorder, unspecified; F84.0: Autistic disorder; F84.5: Asperger syndrome; F80.2: Mixed receptive-expressive language disorder; G40.8: Other epilepsy and recurrent seizures).

#Subject	Group	ADOS	ADOS module	Age (months)	Gender	Diagnosis	Co-morbidity	Handedness
1	ASD	8	3	63	F	F84.9		Right
2	ASD	12	2	63	F	F84.9		Right
3	ASD	12	2	82	M	F84.9	F80.2	Right
4	ASD	23	2	74	F	F84.0		Right
5	ASD	14	2	57	F	F84.9	F80.2	Left
6	ASD	14	3	78	M	F84.9	G40.8	N.D.
7	ASD	20	1	78	M	F84.0		Right
8	ASD	13	3	62	M	F84.0		Right
9	ASD	9	3	69	M	F84.5	F80.2	Right
10	ASD	11	3	49	F	F84.0		Right
11	ASD	16	1	44	M	F84.0		N.D.
12	ASD	17	3	66	M	F84.0		Right
13	ASD	12	3	76	M	F84.9	F80.2	Right
14	TD	2	3	70	F			Right
15	TD	0	3	61	F			Right
16	TD	3	2	43	F			Right
17	TD	0	3	67	M			Left
18	TD	0	3	67	F			Right
19	TD	0	3	59	F			Right
20	TD	0	2	47	M			Right
21	TD	0	2	50	F			Right
22	TD	0	3	71	F			Right
23	TD	0	3	61	M			Right
24	TD	0	3	68	F			Right
25	TD	3	2	50	F			Right
26	TD	0	3	67	M			Right

(Randall et al., 2018). Children in the ASD group fulfilled the diagnostic cut-off on the ADOS score, while TD participants scored below this threshold.

2.3. Procedures

Participants seated on a children-size chair (height = 30 cm) in front of a table (height = 60 cm), where two buttons marked the initial position of the right and left hand at the beginning of each trial. On the experimenter's vocal command ("ready…go"), children were instructed to reach for and grasp a felt-tip pen (length = 140 mm, diameter = 13 mm) to complete a figure printed on a sheet of paper (A4 size, 210 × 297 cm). The two buttons were positioned symmetrically 20 cm away from the midline of the table and 10 cm from its edge. The paper sheet was positioned in a vertical orientation, with its centre 20 cm away from the line passing through the two buttons. The felt-tip pen was placed on top of the paper sheet, with its midpoint lying on the centre of the sheet and its tip pointing toward one out of four possible orientations (upward right, upward left, downward right, downward left). The four orientations were used to add more variability to the task and avoid the use of stereotyped actions. Over and above ecological, this paradigm provides the valuable advantage of being self-explanatory. That is, children of preschool age know perfectly well how to manipulate a felt-tip pen to draw on a sheet of paper, with no need for detailed task description. Eight blocks of 5 trials each were recorded throughout 2 sessions of 4 blocks each (10 trials per pen orientation overall). Blocks order was randomized across participants. Children were free to use any grip strategy, including using either the right or the left hand to grasp the felt-tip pen.

2.4. Data collection and processing

Movement kinematics were recorded with an optoelectronic motion capture system (Qualysis AB, Göteborg, Sweden) composed of three infrared cameras sampling at 200 Hz. Data were low-pass filtered offline at 10 Hz with a 3rd order Butterworth filter. Ten passive markers were attached symmetrically to the upper limbs (head of the second metacarpal bone, radial styloid, ulnar styloid, lateral humeral epicondyle, shoulder acromion) and one to the manubrium of the sternum (Fig. 1A). In three right-handed participants with ASD, markers on the left arm could not be placed due to compliance problems; trials performed with the left hand by these participants were discarded. Accurate marker labelling in kinematic recordings was verified by offline visual inspection. The reference system was oriented with the x-axis along the longitudinal axis of the movement, the y-axis along the lateral axis and the z-axis along the elevation axis. Kinematic analyses were conducted on the trajectories of the markers attached to the arm employed to reach the felt-tip pen in each trial. The reaching movement onset was defined as the moment in which the tangential velocity of the ulnar marker started increasing for at least 100 ms, while movement offset was set when the participant started lifting the felt-tip pen, i.e. when the tangential velocity of the ulnar marker started increasing again for at least 50 ms after it had fallen below the 20% of its peak (Fig. 1B). The goodness of these criteria was assessed through visual inspection of individual trials.

The upper limb was modelled as a kinematic chain composed of five segments, which roughly corresponded to the clavicula, humerus, forearm, a segment connecting the ulnar and radial markers and the hand (Fig. 1A). The five segments were articulated through nine joint angles. The cart2sph Matlab function was used to compute the azimuth (φ) and elevation (λ) angles of the clavicula, humerus, forearm and hand. Except for the clavicula φ and λ angles, all other angles were computed as intersegmental angles by subtracting the φ or λ angle of the proximal segment (e.g. the humerus φ angle was computed by subtracting the clavicula φ angle from the absolute φ angle of the humerus segment). Pronosupination was calculated as the λ angle of the segment connecting the ulnar and radial markers after the coordinates of both markers were rotated by the forearm φ angle around the z-axis (see Supplementary material 1).

PCA was used to investigate motor synergies between joint angles. This analysis captures linear correlations among DoF and uncovers some latent variables (principal components, PCs) which govern groups of DoF, each corresponding to a motor synergy. PCA was trial-wise applied to angular displacements after time-normalization over 200 points. Additionally, angular displacements were centred and normalized in amplitude using the formula $(\theta_i\text{-m})/SD$, where θ_i is the angular displacement at the ith time point and m and SD are the mean and

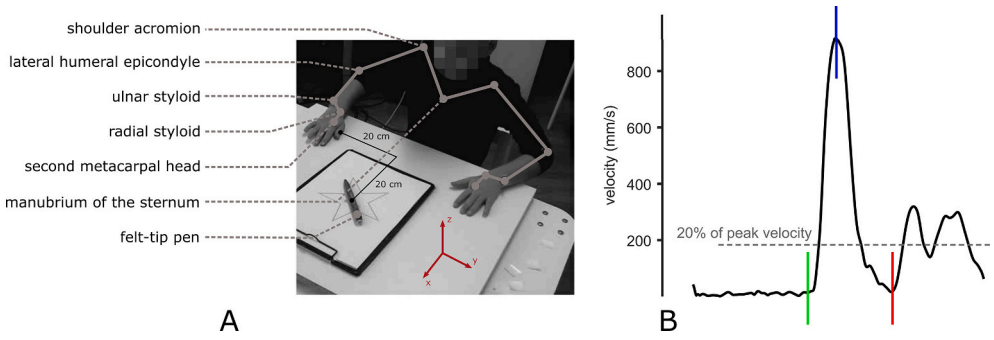

Fig. 1. A: Kinematic model and markers position. B: Example of velocity profile. The green, blue and red cursors indicate reaching movement onset, peak velocity and movement offset, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

standard deviation of θ during each trial (i.e. z-score normalization). This procedure allows accounting for the different ranges of motion of each joint (Berret, Bonnetblanc, Papaxanthis, & Pozzo, 2009). The variance accounted for (VAF) by the first three PCs was extracted from each trial. Based on previously published data (Bockemühl, Troje, & Dürr, 2010), this number of PCs was assumed as adequate to explain most of the variance for a 3-dimensional movement.

2.5. Group-wise data analysis

A mixed-effect ANOVA was carried out on movement time, relative time to peak velocity (i.e. the ratio between absolute time to peak velocity and movement time), standard deviation (SD) of trajectory length and cumulative VAF by the first three PCs. The Shapiro-Wilk test was used to assess normality. Movement time and relative time to peak velocity provide general information about planning and control of movements. Faster movement time and larger relative time to peak velocity (i.e. resulting in a more symmetrical bell-shaped velocity profile) are commonly associated with movements planned in a feedforward manner, with a reduced contribution from feedback control mechanisms (Arbib, 1981; Desmurget & Grafton, 2000; Glover, 2004; Woodworth, 1899). Conversely, greater involvement of visual and/or proprioceptive feedback control mechanisms generates slower movements, with a longer deceleration phase, resulting in a more asymmetric bell-shaped velocity profile and a smaller time to peak velocity. SD in trajectory length provides a measure of consistency in motor performance. Movements planned on the basis of stable internal models are expected to be more consistent across trials (Harris & Wolpert, 1998). The cumulative VAF by the first three PCs indexes the degree of linear correlation among joints angular displacements: A value close to 100% would indicate that no more than three synergies govern the nine DoF included in the model. On the contrary, a lower value would suggest that DoF are controlled in a more independent fashion. The ANOVA model consisted of a between-group factor GROUP (ASD, TD) and a within-group factor PEN_ORIENTATION (upward right, upward left, downward right, downward left). Because pen orientation did not interact with the factor group (see Results), the four positions were collapsed in subsequent analysis. Within the ASD group, the average movement time, relative time to peak velocity, SD in trajectory length and cumulative VAF by the first three PCs observed in each participant were correlated with the ADOS Total score using non-parametric Spearman correlation.

2.6. Automatic classification

Support Vector Machine (SVM) was used to perform the automatic classification of each participant in the ASD or TD group (Fig. 2). An SVM classifier must first be fitted to a training dataset, which contains labelled examples from each class (e.g. the diagnostic group, ASD vs. TD). During training, the algorithm maximizes the distance between the examples of each class presented in the training dataset. Then, the trained SVM can be used to classify previously unseen data presented in a test dataset, e.g. data taken from a participant not included in the training dataset. In this study, an SVM with a Radial Basis Function (RBF) was designed in Python using the Scikit-learn library (Pedregosa et al., 2011). Seventeen kinematic features (Table 2) were extracted from each trial and included in the main dataset, in which rows corresponded to trials and columns to features. The training dataset was obtained after the exclusion of the rows corresponding to an individual participant's trials from the main dataset. The data of the excluded participant formed the test dataset. This procedure was repeated for each participant. Each feature in the training dataset was z-normalized, while features in the test dataset were normalized on their corresponding mean and standard deviation in the training dataset. At each iteration, the C and γ hyperparameters were optimized through a grid search procedure (grid parameters were set as: $C = 1, 10, 100$; $\gamma = 0.01, 0.001, 0.0001$). The accuracy of the trained SVM, defined as the proportion of correctly classified trials, was then assessed on the test dataset. Additional analyses included evaluating classification

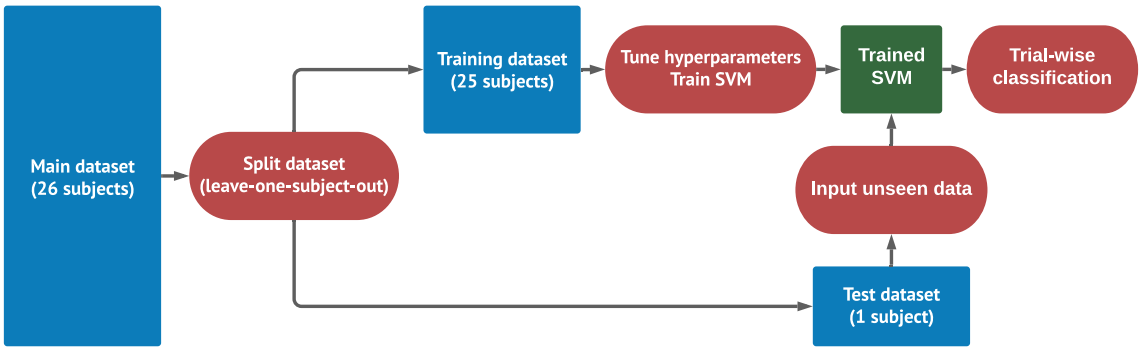

Fig. 2. Pipeline for automatic classification. The procedure illustrated here was repeated for each participant.

Table 2
Kinematic features included in the dataset for automatic recognition.

Kinematic feature (units)	Description
Movement time (ms)	Time difference from movement onset to movement offset
Peak acceleration (mm/s^2)	Maximum acceleration from movement onset to peak velocity
Peak velocity (mm/s)	Maximum velocity from movement onset to movement offset
Peak deceleration (mm/s^2)	Maximum deceleration from peak velocity to movement offset
Relative time to peak acceleration (%)	Time to peak acceleration divided by movement time
Relative time to peak velocity (%)	Time to peak velocity divided by movement time
Relative time to peak deceleration (%)	Time to peak deceleration divided by movement time
Distance along the x-axis at movement offset (mm)	Relative position of the hand on the x-axis with respect to the position at movement onset
Distance along the y-axis at movement offset (mm)	Relative position of the hand on the y-axis with respect to the position at movement onset
Z-elevation at movement offset (mm)	Hand absolute position at movement offset along the z-axis
Distance along the x-axis at peak velocity (%)	Proportion of total displacement of the hand on the x-axis already covered at peak velocity with respect to total displacement on the same axis
Distance along the y-axis at peak velocity (%)	Proportion of total displacement of the hand on the y-axis already covered at peak velocity with respect to total displacement on the same axis
Z-elevation at peak velocity (mm)	Hand absolute position at peak velocity along the z-axis
Trajectory length (mm)	Overall trajectory length from movement onset to movement offset
VAF1 (%)	VAF by the first PC
VAF2 (%)	Cumulative VAF by the first two PCs
VAF3 (%)	Cumulative VAF by the first three PCs

robustness in presence of information loss either in terms of trials available in the test dataset (Supplementary material 2) or features (Supplementary material 3). The importance of each feature for accurate classification was also assessed in each participant (Supplementary material 4).

2.7. ROC curve

The proportion of positive responses provided by the SVM in each participant was taken as an estimate of ASD diagnosis probability. This value was used to build a receiving operating characteristic (ROC) curve. ROC curves are commonly used to plot the true positive rate (TPR, i.e. sensitivity) against the false positive rate (FPR, i.e. 1-specificity) of binary classifiers when the discrimination threshold is varied. The area under curve (AUC) indexes the overall accuracy of the classifier (i.e. in a perfect classifier the ROC curve is a square, whereas in a random classifier it is a diagonal line from the left bottom to the top right corners). ROC curves also provide information about the optimal threshold for the classifier, that is, the one optimizing TPR and FPR.

3. Results

Mixed-effect ANOVA showed a significant effect of GROUP in movement time ($mean_{TD}$ = 839.506, SE_{TD} = 23.981, $mean_{ASD}$ = 743.681, SE_{ASD} = 23.937, $F_{1,24}$ = 8.276, p = 0.008), relative time to peak velocity ($mean_{TD}$ = 0.463, SE_{TD} = 0.012, $mean_{ASD}$ = 0.503, SE_{ASD} = 0.011, $F_{1,24}$ = 5.217, p = 0.031), SD of trajectory length ($mean_{TD}$ = 34.221, SE_{TD} = 3.172, $mean_{ASD}$ = 45.961, SE_{ASD} = 3.973, $F_{1,24}$ = 10.5029, p = 0.0034) and VAF by the first three PCs ($mean_{TD}$ = 98.204, SE_{TD} = 0.100, $mean_{ASD}$ = 97.529, SE_{ASD} = 0.217, $F_{1,24}$ = 8.200, p = 0.009) (Fig. 3). Additionally, a significant effect of PEN_ORIENTATION was observed in MT ($F_{3,72}$ = 5.228, p = 0.002). No PEN_ORIENTATION by GROUP interactions were detected. Because the SD of trajectory length and the cumulative VAF by the first three PCs were not normally distributed, results were confirmed using permutation tests (5000 permutations, main effect of group: p = 0.001, p = 0.002, respectively). The cumulative VAF by the first three PCs showed a significant negative correlation with the ADOS Total score ($\rho = -0.650$, $p = 0.016$) (Fig. 4D). No other correlation was significant (movement time vs. ADOS: ρ = 0.039, p = n.s.; relative time to peak velocity vs. ADOS: $\rho = 0.257$, p = n.s.; SD of trajectory length vs. ADOS: ρ = 0.138, p = n.s.). The SVM classifier had an average accuracy of 0.739. Specifically, accuracy resulted larger than 0.7 in 15 children; between 0.6 and 0.7 in 6 children; lower than 0.6 in the remaining 5 children. The ROC curve had an AUC of 0.947, with a sensitivity of 0.846 and a specificity of 0.923 at its optimal operating point (Fig. 5).

4. Discussion

While pervasive motor difficulties were observed in ASD, their mechanisms are not fully understood, nor is their relationship with socio-communicative symptoms. In this work, we assessed upper limb kinematics in children with ASD and TD children and investigated their relationship with symptoms severity. Besides general kinematic measures (i.e. movement time, time to peak velocity, spatial variability), we evaluated inter-joint coordination and motor synergies. As motor synergies are crucial for mapping behavioural goals into coordinated motor patterns, we reasoned that this approach would shed more light on the mechanisms of impaired selection of motor programs in ASD.

Children with ASD moved faster and showed a more symmetrical bell-shaped velocity profile. In addition, the length of the hand trajectory was more variable across trials. Because in the nervous system noise scales with signal amplitude (i.e. signal-dependent noise) (Clamann, 1969; Matthews, 1996), fast, ballistic and explosive movements in children with ASD may have amplified spatial variability. Consistent with previous work (Gowen & Hamilton, 2013), out-scaled and unpredictable movements indicate problems in motor planning and prospective motor control. In addition, the different shape of the velocity profile indicates a distinct use of feedback control strategies in the two groups. TD children showed a longer deceleration epoch, enabling visual/proprioceptive feedback corrections. In contrast, children with ASD decelerated for a shorter time, consistent with previous findings showing low reliance on feedback information (especially visual) (Forti et al., 2011; Glazebrook et al., 2009; Stoit et al., 2013).

The VAF by the first three PCs was lower in children with ASD than in TD children, suggesting a weaker coupling between joints and more independent DoF control. This result indicates, for the first time, that motor synergies are impaired in ASD. Consequences on motor control can be far-reaching. Motor synergies promote differentiated and flexible sensorimotor transformations. The differential distribution of weights across a small set of synergies gives rise to fine-tuned motor behaviours. A dysfunction of this mechanism may result in the adoption of suboptimal strategies for handling DoF. One could be learning one-by-one the motor commands that must be delivered to individual DoF for each specific task. However, given the number of variables involved, this strategy would require a great deal of practice (D'Avella, 2016). Children with ASD may avoid this time-consuming learning process by deploying poorly differentiated and overlearned motor strategies (e.g. moving the hand to grasp an object regardless of subsequent manipulations), rather than scaling motor parameters in a task-dependent fashion (e.g. tailoring motor parameters to subsequent manipulations when grasping an object). A consequence of this is evident in fragmented action chains: Rather than adjusting their movements on global action purposes, they execute each action segment as an isolated instance (Cattaneo et al., 2007; Fabbri-Destro et al., 2009; Scharoun & Bryden, 2016). While this finding was often interpreted as a lack of prospective modelling (Gowen & Hamilton, 2013), the impairment of motor synergies may represent a hard-wired substrate – rather than merely a computational one – underlying poor tailoring of low-order motor

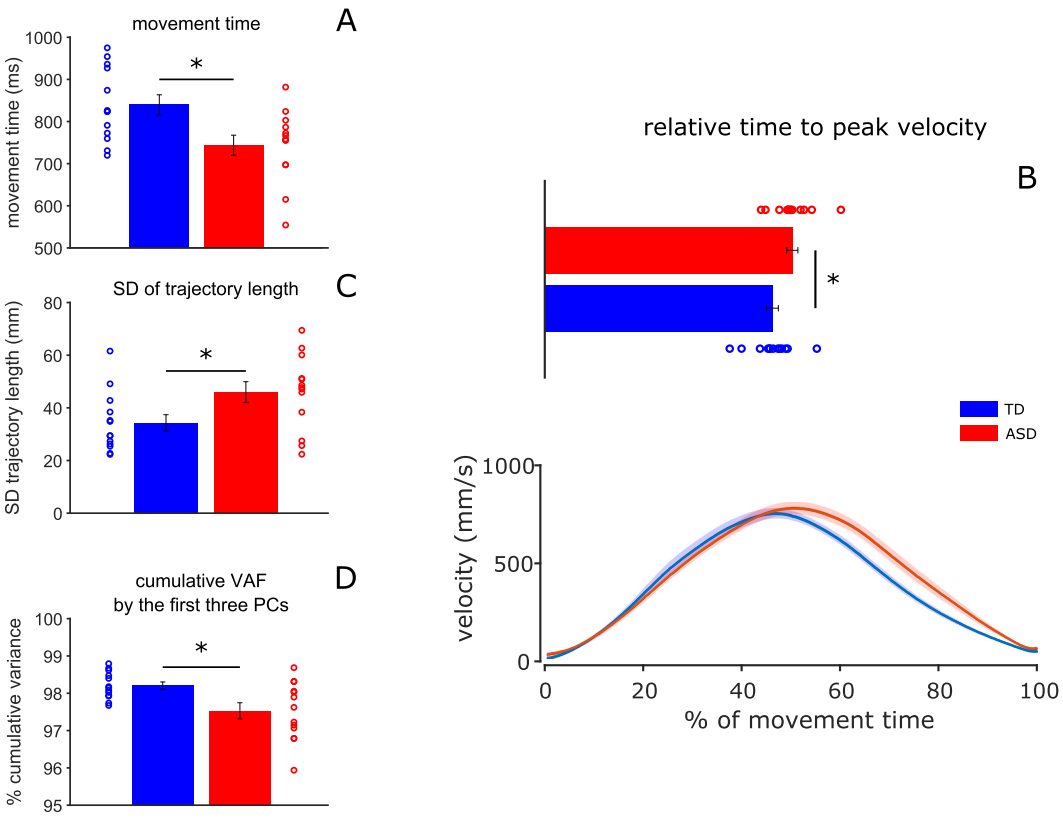

Fig. 3. A: Movement time. B: Relative time to peak velocity (upward panel) and time-normalized velocity profile in the two groups (downward panel). The shaded areas indicate standard errors. C: SD of trajectory length. D: cumulative VAF explained by the first three PCs. Vertical bars indicate standard errors. Horizontal bars with asterisks indicate significant group differences. Circles denote individual subjects' data.

variables on global outcomes of actions in ASD. Otherwise, another dysfunctional strategy consists in mapping each behavioural task into a whole set of muscular activations (D'Avella, 2016). Although effective in coordinating DoF, this strategy would entail learning a new motor program for each behavioural goal rather than adjusting an existing combination of synergies. Importantly, adopting these extreme solutions (or a mixture of them) for handling DoF may lead to personalized compensation mechanisms, becoming apparent as idiosyncratic motor strategies previously observed in children with ASD (Cavallo et al., 2018).

Mapping behavioural goals into redundant DoF also allows multiple solutions for motor tasks. When movements are repeated over and over, this presumably becomes apparent and contributes to motor variability. Importantly, ambiguous motor responses may impact the maturation of sensorimotor maps in young children. During early contacts with the external world, re-entrant information in sensorimotor loops helps to create a rich and differentiated repertoire of cortical representations linking patterns of motor commands and sensory expectations (Von Hofsten, 1991; Von Hofsten & Rönnqvist, 1988; Von Hofsten & Rosander, 2018). Noisy re-entrant information may impact this process, leading to poorly differentiated, broadly tuned cortical maps. Interestingly, more distributed brain activation was reported in ASD participants during simple finger movements, suggesting a scattered organization of cortical maps (Müller, Pierce, Ambrose, Allen, & Courchesne, 2001).

The significant correlation between VAF by the first three PCs and the ADOS Total score suggests that the degree of synergies impairment is related to the clinical outcome. So far, few studies have explored the relationship between ASD symptoms and motor impairments, which were mainly indexed by end-effector kinematics (e.g. hand velocity and acceleration), retrieving mixed results (Cavallo et al., 2018; Cook et al., 2013). Synergies index more global properties of motor control, which entail transforming the end-effector trajectory into an unambiguous pattern of DoF recruitment. Therefore, they may better capture the relationship between motor control problems and symptoms severity. Early sensorimotor experience shapes brain circuits and provides a scaffold of basic skills deemed crucial for subsequent differentiation of complex abilities and behaviours (Hensch, 2005; Hubel & Wiesel, 1970; Le Grand, Mondloch, Maurer, & Brent, 2001; Von Hofsten, 2009). Therefore, motor difficulties may initiate a bottom-up pathogenetic cascade, ranging from basic movement abnormalities to pervasive atypical development (Bhat, Landa, & Galloway, J. C. (Cole)., 2011; Cook, 2016; Leblanc & Fagiolini, 2011; Moseley & Pulvermüller, 2018). In this context, difficulties in encoding others' actions may constitute a pivotal mechanism through which low-level motor problems eventually affect socio-cognitive skills. As a matter of facts, flexible and differentiated sensorimotor representations not only promote proficient self-initiated motor behaviour, but also helps to map actions observed in other individuals (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). Conversely, adopting idiosyncratic strategies for handling DoF may reduce the degree of kinematic similarity with neurotypical individuals and jeopardize others' actions encoding (Aglioti, Cesari, Romani, & Urgesi, 2008; Hilt et al., 2020). As for self-initiated actions, mapping others' motor behaviour into a low-dimensional set of weighted synergies provides valuable advantages: While a low-level DoF-based coding system would lack robustness against noise, inter-subject variability and visual occlusions, goal-directed coding would require specific knowledge of observed action classes (D'Ausilio, Bartoli, & Maffongelli, 2015). Synergies-based coding represents a compromise between these extreme solutions, which provides both adequate information about low-level DoF recruitment and about actions-goals. Consistent with this coding system, TD children can

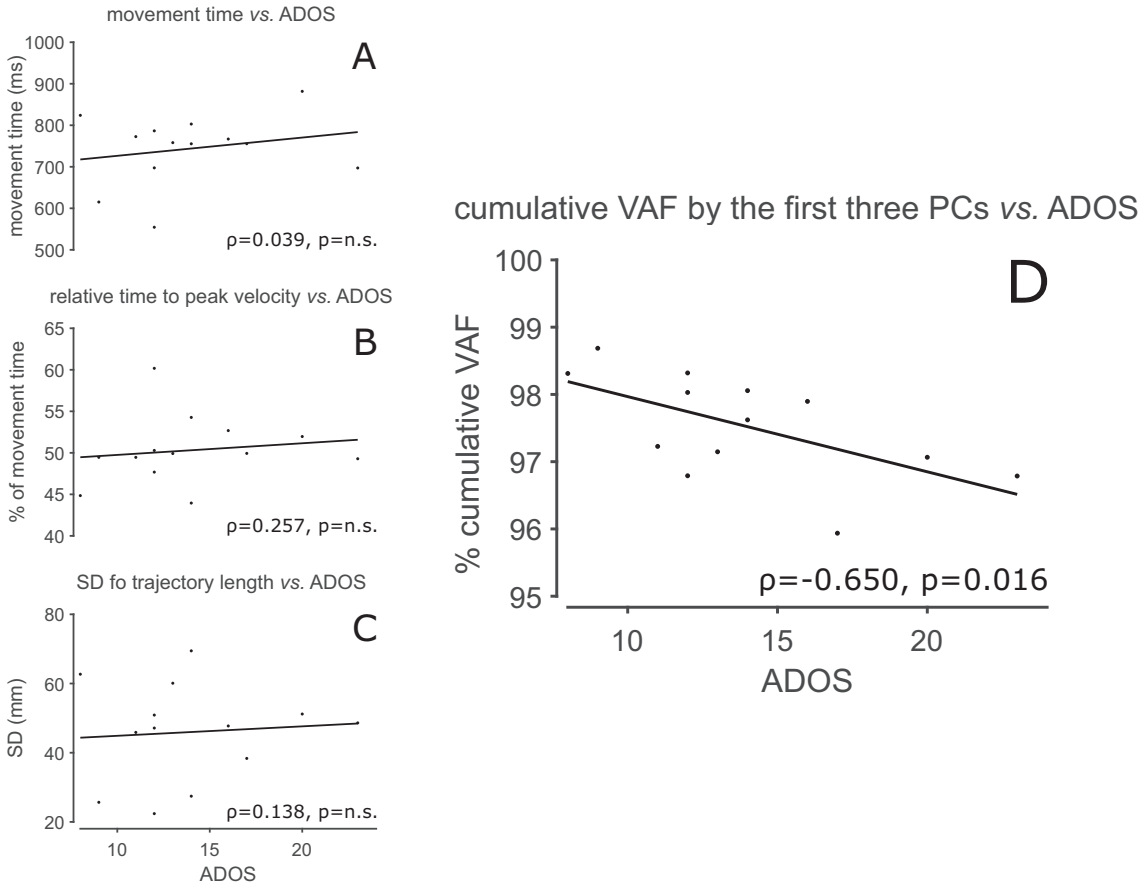

Fig. 4. Correlations between kinematic variables and ADOS Total score. A: Movement time. B: Time to peak velocity. C: SD of trajectory length. D: cumulative VAF explained by the first three PCs.

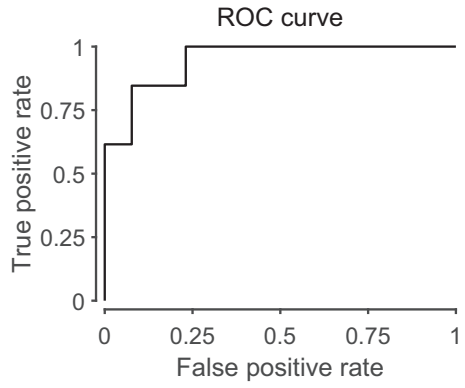

Fig. 5. ROC curve.

switch flexibly from imitating motor strategies to action goals (Gergely, Bekkering, & Király, 2002). In contrast, children with ASD are biased toward imitating action goals while neglecting motor strategies (Hobson & Hobson, 2008) and extracting actions meaning from contextual cues rather than from observed kinematics (Boria et al., 2009). Problems in mapping actions into motor synergies may thus impact not only self-initiated behaviour, but also the encoding of actions observed in other individuals and, in turn, affect social cognition.

In recent years, sensorimotor impairments in ASD have attracted growing interest due to their potential translational applications. Motor difficulties assessed in high-risk infants (i.e. siblings of children with ASD) within the first year of life accurately predict ASD diagnosis in the following years (Canu et al., 2020; Harris, 2017) and automatic classification based on movement kinematics enables accurate discrimination between ASD and TD participants (Alcañiz Raya et al., 2020; Anzulewicz et al., 2016; Cavallo et al., 2021; Crippa et al., 2015; Li et al., 2017; Perego et al., 2009; Vabalas et al., 2019, 2020). Our results on motor based-automatic classification add to this previous evidence, showing sensitivity and specificity similar to the most popular standardized diagnostic assessments (i.e. 0.94 and 0.80, respectively, for ADOS; 0.80 and 0.88 for Childhood Autism Rating Scale) (Randall et al., 2018). Importantly, we split the main dataset by separating trials of one subject (test dataset) from all the other data (training dataset), so the data in the test dataset belonged to a participant that was never seen before by the classifier. Accordingly, the classifier accuracy was tested in a context that simulates as much as possible the diagnosis of a new patient in everyday life clinical settings. To provide further indications for clinical practice and feasibility, we tested changes of classification accuracy as the number of trials available in the test dataset varied (see Supplementary material 2) and using features derived from the ulnar marker only (see Supplementary material 3). Results support the feasibility of motor-based classification in settings with limited time resources and poorly compliant patients. Children with ASD are indeed poorly compliant when required to wear something new or unusual (e.g. bends, plaster). As such, they might feel uncomfortable with many kinematic markers attached to their body. Feature importance substantially confirmed the results obtained with univariate statistics (see Supplementary material 4): Features indexing spatial displacement at peak velocity and movement offset and cumulative VAF by the first three PCs provided a significant contribution for classification.

In conclusion, although the sample size was relatively small and likely not able to capture the full heterogeneity of ASD, a novel

relationship was found between a robust index of motor coordination and ASD severity. In this regards, future research will have to evaluate intellectual disability, which is an important source of inter-subject variability in ASD that seems to impact motor planning and coordination (Glazebrook, Elliott, & Szatmari, 2008; Mari, Castiello, Marks, Marraffa, & Prior, 2003). At the same time, while we focused on the differences between children with ASD and TD children, motor deficits are observed across different neurodevelopmental disorders (Hudry, Chetcuti, & Hocking, 2020). The inclusion of additional diagnostic classes (e.g. developmental coordination disorder, attention deficit with hyperactivity disorders) would facilitate a dimensional acknowledgment of atypical development, in which motor difficulties may represent a common pathogenetic mechanism for these conditions. Finally, our findings on impaired DoF coordination could be only the tip of the iceberg of a general motor problem affecting the complex coordination required for voluntary action. In this sense, speech and language coordination share key similarity with upper limb action (Fazio et al., 2009). Interestingly, language difficulties and delays are often involved in ASD (Eigsti, De Marchena, Schuh, & Kelley, 2011), and future efforts should build on the inestimable legacy of Jacques Mehler to understand how difficulties in low-level aspects of motor coordination interact with innate mechanisms subserving the acquisition of linguistic skills (Gervain & Mehler, 2010).

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cognition.2021.104652.

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