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The power of combining oculometric and pupillometric parameters for autism screening in children

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Abstract

Autism Spectrum Disorder is a neurodevelopmental trouble for which no objective biomarker has yet been discovered. The search for an accessible biomarker aims, in particular, for early autism screening, in order to optimize tailored intervention when necessary. In this context, eye-tracking has been now used for numerous years in the field of research on autism as it allows for non-intrusive, no-contact recordings even in very young children. However, individual oculometric parameters, while showing significant differences between groups of autistic and non-autistic individuals, are not discriminative enough for individual screening. In this study, we combined oculometric measures with pupillary parameters obtained simultaneously by the eye-tracker, and used a machine-learning approach to estimate the discriminative performance of such combinations of parameters. Data were obtained in 72 autistic and 93 neurotypical 2-13 years old children observing objects and faces during less than a minute. We used the Weka datamining software, testing 36 machine-learning algorithms without any a priori, in order to describe robust and convergent performance. Moreover, we chose to report only performance associated with high sensitivity, specificity and accuracy. We showed that oculo-pupillometric combinations of parameters allowed to reach outstanding discriminative performance in young children, paving the way for a clinical use.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder affecting around 1% of the population and characterized by atypical social interaction and communication, repetitive behaviors and focused interests¹. Although inclusion of autistic individuals within society has notably improved, an effort is still necessary to optimize individual support, with targeted approach, in order to promote their quality of life while respecting their specificities. As a consequence, improving screening for autism, especially in young children, remains a major objective in research nowadays. Indeed, the younger difficulties linked to autism are revealed, the more can be expected from tailored intervention for positive personal evolution, familial balance, and societal inclusion².

To help for early screening, an objective biomarker would be necessary. Indeed, until now, only expert clinicians can make a diagnosis based on extensive evaluations including detailed developmental history, psychiatric assessment and pediatric, psychological and neurological examinations. Several scientific domains have tried to identify biomarkers, like genetics, metabolomics, neuroimaging or neurophysiology^{2,3}. However, while promising results have been uncovered, a clear and easily tested biomarker still remains elusive. One parameter compromising the identification of such a biomarker is the heterogeneity within the autism spectrum. Moreover, autism reveals itself during infancy or childhood, periods of huge biological, physiological and behavioral maturation. One of the autistic trait robust to heterogeneity and maturation is social interaction atypicality, which is also a hindrance to social inclusion. On the other hand, social adjustment disturbance, via its external manifestations, can be quantified without intrusive, costly or time-consuming methodologies. Indeed, social reciprocity can be measured behaviorally and physiologically, for example with eye-tracking.

Eye-tracking is a very interesting technique in the field of research on autism, as it is non-invasive, without direct contact with the participant, suited for young children, and relatively low-cost. Consequently, the number of studies on ASD using eye-tracking has exploded since the seminal publication of Klin et al. in 2002⁴. This technique gives access to a quantification of ocular exploration, and has been mostly used during the observation of social scenes or stimuli like faces. Human faces are salient social stimuli in our environment, spontaneously capturing our visual attention from early age, and especially the region of the eyes⁵. Faces involve specific brain processing^{6,7}, with a maturation during childhood, from local featural processing to holistic expert processing⁸, this expertise being progressively acquired around 7 to 10 years of age⁹. All these aspects are disturbed in ASD, with social difficulties associated

with atypical exploration of the faces and especially of the eyes^{10,11}. Less time spent on biological motion, faces and eyes have indeed been classically reported (e.g.^{4,5,12}, but see¹³), with a less systematical visual exploration pattern¹⁴. Moreover, when social and non-social contents are presented simultaneously, autistic participants show a preference for non-social stimuli^{15,16}.

These significant differences between ASD and typically-developing (TD) participants have been described at the group level and for several oculometric parameters, like time spent on a defined region, fixation time, or number of fixations for example. However, with the objective of autism screening, this group approach does not allow to characterize each individual. To this end, it is necessary to evaluate the discriminative power of eye-tracking parameters thanks to a classifying approach, i.e. to evaluate if individual diagnosis is correctly predicted by oculometric indices. Methods like ROC (Receiver Operating Curve) analysis can estimate the discriminative power according to sensitivity, specificity and AUC (Area Under the Curve) of these oculometric parameters using machine-learning algorithms. In the last five to ten years, a growing number of studies have tested these approaches with mitigated results¹⁷. Using ROC analysis, discriminant scores (AUC, between 0 and 1) using oculometric parameters can reach from 0.45 till 0.86, depending on the type of stimuli (static vs. dynamic, social vs. non-social), the age and number of participants (e.g. ^{15,18,19}). Several kinds of algorithms have also been used, like SVM (Support Vector Machine) or CNN (Convolutional Neural Networks), with heterogeneous performances and heterogeneous testing conditions (stimuli, age, clinical populations, number of participants, and duration of data acquisition; e.g.²⁰⁻²⁴, for reviews see ^{17,25,26}). These performances can reach up to 0.92 ^{27,28} in a specific age group (8-years old), suggesting a high potential for possible clinical application if these scores can be generalized to younger autistic children. Overall, there is a tendency for better discriminative performances in young children and for social stimuli^{17,19}. However, high discriminative scores are usually obtained for restricted number of participants and age groups, questioning the feasibility of generalization with both high specificity and sensitivity. Another recent and promising trend is the combination of several oculometric parameters to increase discriminative and generalizable performance²⁹⁻³¹, or the combination with other kinds of functional evaluation (e.g. electroencephalography³²).

Interestingly, eye-trackers provide another measure, recorded simultaneously with gaze position, the pupil diameter. This parameter can reflect many processes³³, in particular adjustment of the quantity of light reaching the retina³⁴. If illumination and fixation depth are

controlled, pupil dilates in relation with physiological arousal increase and cognitive processes engagement (e.g.³⁵⁻³⁷). We have recently shown that, in TD children, the pupil was more dilated when they observed faces compared to objects³⁸, and even more if the faces were dynamic (videos) compared to static (images)³⁹. In contrast, in ASD children, dilation of the pupil was reduced compared to their TD peers and was not different as a function of the stimulus category^{38,39}. This result could reflect a reduced physiological arousal in response to face observation in autistic children. Using ROC analysis, we showed that pupillometric parameters could discriminate according to the diagnosis group with a performance (AUC) around 0.75-0.8³⁹.

In the present study, our goal was to evaluate if the combination of pupillometric and oculometric parameters, never explored until now, could improve discrimination performances, paving the way for a useful clinical tool. In order to explore systematically the feasibility of such an approach, we chose not to select a priori either particular eye-tracking parameters or machine learning algorithms. Moreover, to include autistic children whatever their cognitive abilities and from a young age (3-years old), we focused on a very short paradigm (less than 1 min) with presentations of faces and objects and no explicit instructions. We showed that the combination of pupillometric and oculometric parameters was very efficient for data acquired during the observation of faces in young children (under 7-years old), with performances (AUC, sensitivity, specificity and accuracy) above 0.9 for several combinations of parameters and several machine learning algorithms.

2. Results

A total of 72 children with autism spectrum disorders (ASD) and 93 typically developing (TD) children, aged 2 to 13 years-old, were recorded with an eye-tracker while looking at a 52s sequence of visual stimuli (Figure 1). This sequence started with a black and a white screen to evaluate the pupil light reflex, and then randomly alternated objects and faces pictures. Several parameters were extracted from this recording (see Methods): pupillometric parameters linked to the pupil light reflex (evaluated during the black and white slides), pupillometric parameters linked to the object and face presentations, and oculometric parameters linked to the exploration of the screen, the object, the face and the regions of interest of the eyes and the mouth.

A. Stimuli



B. Paradigm



Figure 1: Experimental paradigm. A. Stimuli. A total of four different faces and four different objects were presented, equated in size, luminance and color. B. Paradigm. The sequence started with a 2s black and a 2s white slide, then each stimulus was presented for 4s and preceded by a 2s interstimulus. The interstimulus gray slide was equated in luminance and color to all the faces and objects.

a. Discriminant analysis of individual parameters

We first evaluated how each individual oculometric or pupillometric parameter could discriminate between ASD and TD children. For each parameter, individual parameters performances were evaluated with the ROC analysis. Three scores were calculated: AUC, specificity (true negative rate), and sensitivity (true positive rate). These scores vary from 0 to 1 and are qualified as good if between 0.7 and 0.8, and excellent if between 0.8 and 0.9. In order for a parameter to have a good discriminative power (i.e. correctly classifying ASD and TD children in their own diagnosis group, without too many false positive or false negative), these three scores have to be above 0.7.

Figure 2 shows these scores for the Object stimuli. As can be observed in the top panel, no individual parameter exhibited scores above 0.7 for AUC, specificity and sensitivity. We split the population in two age groups, 2-7 years old and 8-13 years old children. Only one parameter, the total time tracked (TTT) was discriminant for the 8-13 years old group (Figure 2 lower panel).

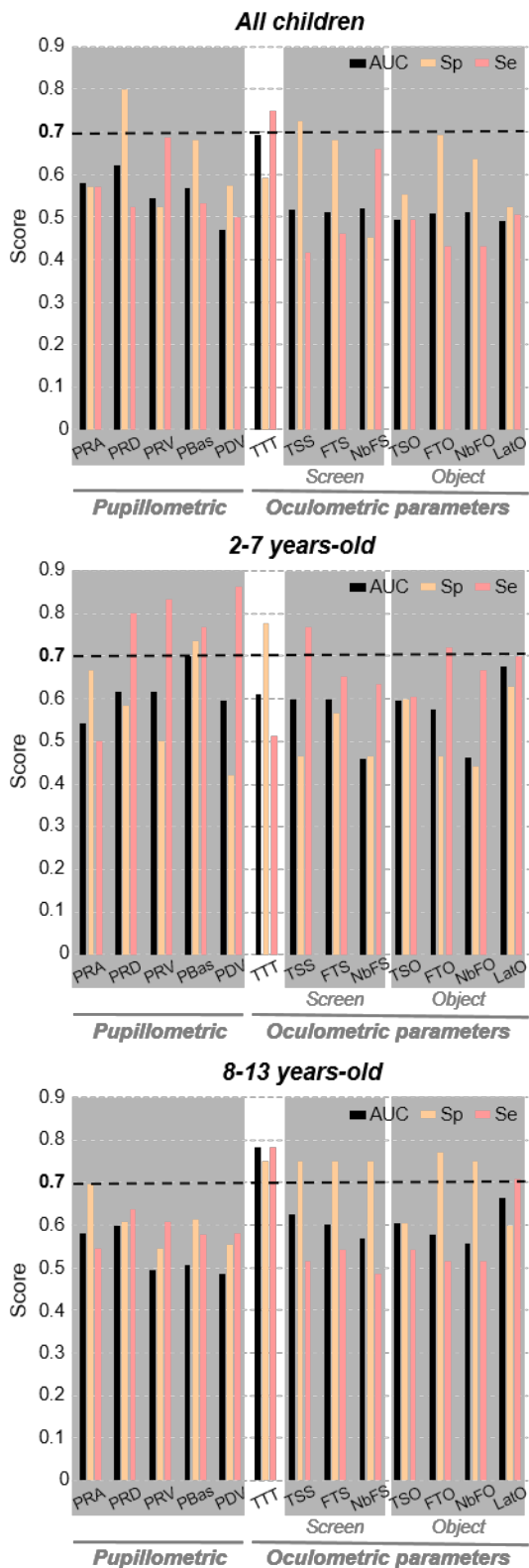


Figure 2: Discriminant analysis scores for the Object stimuli. Area Under the Curve (AUC), specificity (Sp) and sensitivity (Se) scores for each pupillometric and oculometric parameter are represented for the complete population (top panel), the 2-7 years old group (middle panel) and the 8-13 years old group (lower panel). PRA: pupil light reflex amplitude, PRD: pupil light reflex duration, PRV: pupil light reflex velocity, PBas: pupil baseline, PDV: pupil diameter variation, TTT: total time tracked, TSS: time spent on screen, FTS: fixation time on screen, NbFS: number of fixations on screen, TSO: time spent on object, FTO: fixation time on object, NbFO: number of fixations on object, LatO: latency of first entry on object.

Figure 3 shows these scores for the Face stimuli, with more regions of interest (ROIs) as the exploration of the eyes and mouth has been described as affected in ASD participants in some studies (e.g. ^{4,5}). Even with more parameters, only the total time tracked (TTT) for the 8-13 years old group was again exhibiting AUC, specificity and sensitivity scores above 0.7.

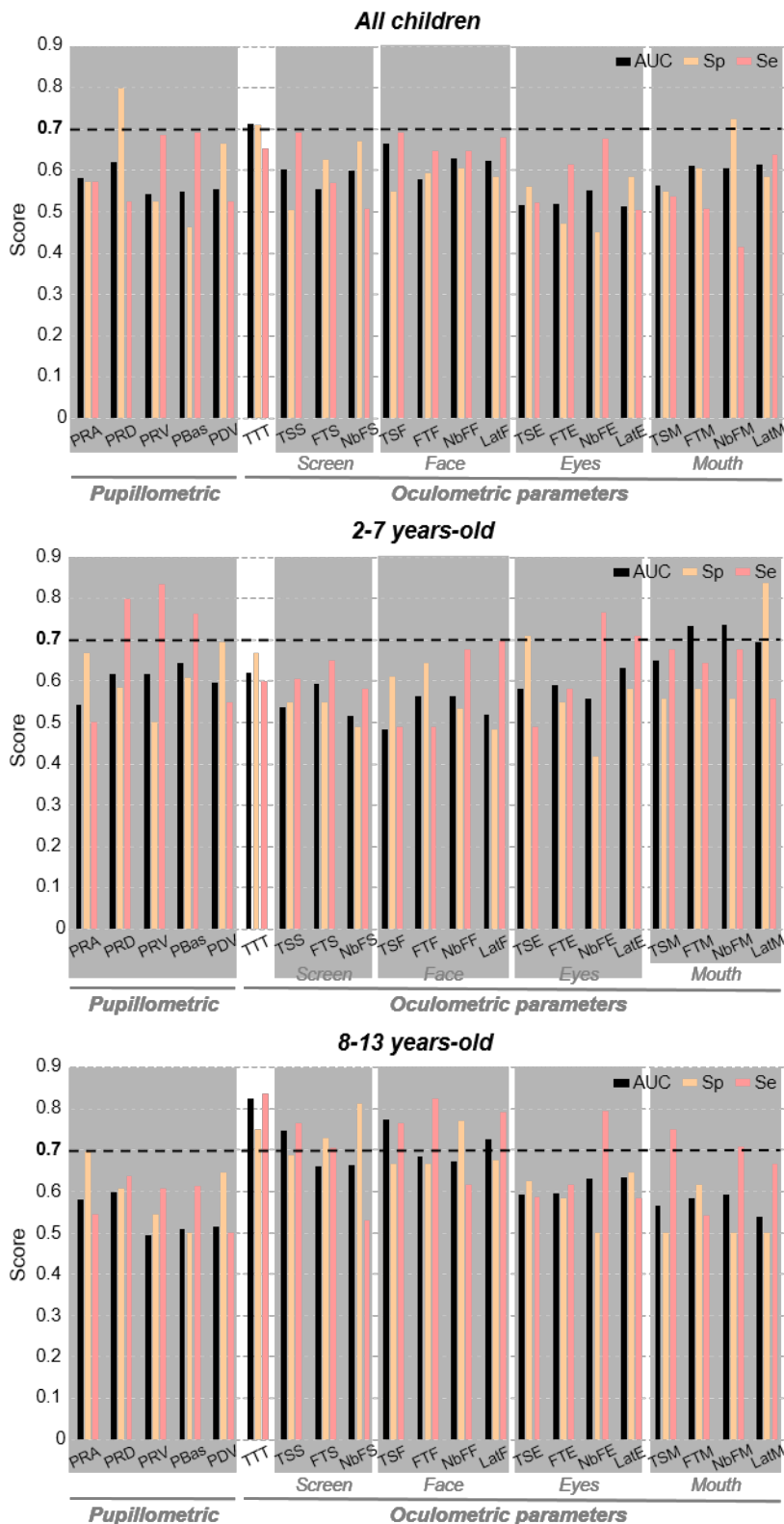


Figure 3: Discriminant analysis scores for the Face stimuli. Area Under the Curve (AUC), specificity (Sp) and sensitivity (Se) scores for each pupillometric and oculometric parameter are represented for the complete population (top panel), the 2-7 years old group (middle panel) and the 8-13 years old group (lower panel). Parameters for the Face/Eyes/Mouth ROIs: time spent on ROI (TSF/TSE/TSM), fixation time on ROI (FTF/FTE/FTM), number of fixations on ROI (NbFF/NbFE/NbFM), LatO: latency of first entry on ROI (LatF/LatE/LatM). See Figure 2 for other abbreviations.

b. Combinations of parameters with machine-learning classification

Even if individual parameters were not discriminant enough to distinguish ASD and TD groups, some had high specificity and other had high sensitivity scores. Therefore, a discriminant analysis based on their combination could prove very effective. Machine learning approaches provide the possibility to test the discriminant performance of such combinations of parameters.

We chose to test combinations without selecting any given parameters based on their individual performances. But to limit the number of possible combinations, we first grouped the parameters according to their nature. We thus obtained 11 new parameters: one based on the pupil light reflex (L); for the Object stimuli: one based on the pupil variation (P), the total time tracked (T), one based on the oculometric measures for the screen exploration (S), and one for the object exploration (O); for the Face stimuli: P, T and S for this category of images, then parameters based on the oculometric exploration of the head (H), eyes (E), and mouth (M).

We analyzed separately these new parameters for the Object and Face stimuli, adding the pupil light reflex to both analyses. It thus resulted in combining 5 parameters for the Object stimuli, and 7 parameters for the Face stimuli. We considered each new parameter individually, then all the combinations of 2 parameters, 3 parameters, etc. In total, 31 combinations were thus tested for the Object stimuli, and 127 for the Face stimuli.

With the same will of exploring discrimination performance without any a priori, we decided not to select any precise machine-learning algorithm. We used the Weka datamining software⁴⁰ that regroups 36 algorithms of different kinds (e.g. logistic regression, random forest, multilayer perceptron). For each of these classifiers, for each combination, we calculated an AUC score, a sensitivity (Se) score, a specificity (Sp) score, and an accuracy (Ac) score (5-fold cross-validation). As for the individual parameters, we looked for combinations that obtained a minimum of 0.7 for each of these four scores.

For the Object stimuli, when considering the whole population (2-13 years old), only one combination (L/P/T/O) passed this threshold (AUC 0.73, Se 0.73, Sp 0.73, Ac 0.74, for one algorithm only). We then analyzed separately the 2-7 and 8-13 years old age groups. Figure 4A represents these results, each point being the mean of the four scores (performance index) for one given algorithm, and colored if the four scores are above the threshold. The combinations are organized along the x-axis, depending first of the number of children for each combination (bottom gray line) and then as the number of parameters within the combination (more parameters towards the left). In total, the combinations on the left are the one with the most

parameters but with the less children, due to missing data especially for the pupillary measures; combinations on the right are those with the less parameters, in particular oculometric acquisitions only, for which data could be acquired for all or nearly all participants.

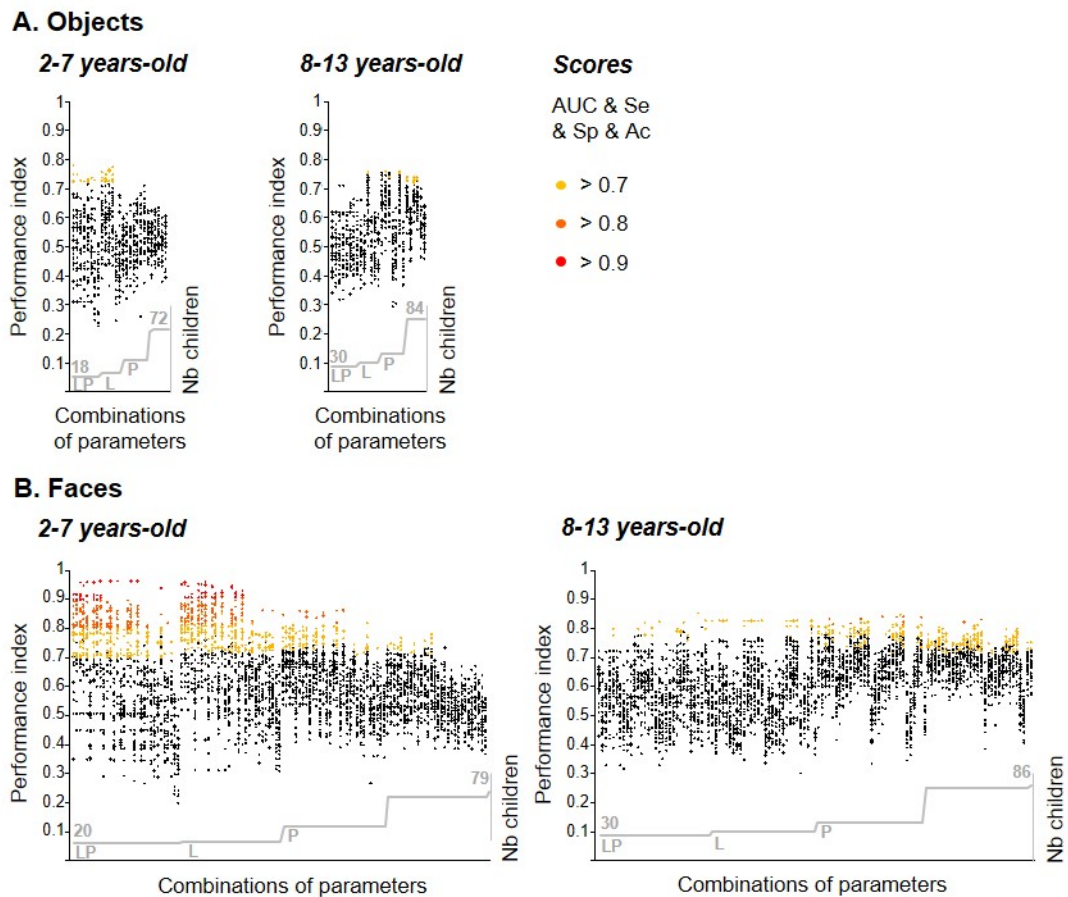


Figure 4: Performance index for all combinations of parameters and all machine-learning algorithms for the Object stimuli (A) and the Face stimuli (B). Each point is the mean of AUC, Se, Sp and Ac. The point is colored if the four scores are above 0.9 (red), 0.8 (orange) or 0.7 (yellow). The combinations of parameters are organized along plateaus of number of children within the data, with less children towards the left and more children towards the right (gray line at the bottom of each panel). Within a plateau, the combinations with the most parameters are towards the left, those with the less parameters towards the right. The plateaus are defined by the presence of the pupillometric parameters (L: pupil light reflex, P: pupil variation) within the combinations.

As can be observed, several combinations of parameters yielded good performances between 0.7 and 0.8. For the 2-7 years old group, these combinations were mostly ones including both pupillometric and oculometric parameters (located on the left of the graph). The pupillometric parameters alone did not discriminate correctly between ASD and TD children, but the pupil light reflex (L) parameter combined with any oculometric parameter or combination of parameters allowed for a good discrimination. For the 8-13 years old group, the combinations

producing good performances contained mainly oculometric parameters (on the right of the graph). These combinations could contain 2, 3 or 4 parameters, mainly oculometric but also sometimes the pupil variation (P). Overall, for the Object stimuli, the strategy of combining parameters did not produce better results than analyzing only the total time tracked (TTT, Figure 2).

For the Face stimuli, analyzing the whole population produced a few combinations with good scores (between 0.71 and 0.74 for the four scores). However, separating the younger and older children (2-7 and 8-13 years old groups) yielded many excellent (scores > 0.8) or outstanding (scores > 0.9) performances. As can be observed in Figure 4B, the best performances were obtained for the 2-7 years old group. Many combinations of parameters were identified by multiple classifiers, leading to scores above 0.7 (even if many classifiers did not lead to a good ASD/TD discrimination). The two parameters both present in most of the combinations with excellent or outstanding performances are pupil light reflex (L) and oculometric exploration of the mouth (M). The two pupil parameters (L and P), alone or together, could not produce a good performance without the combination with oculometric data. Conversely, oculometric data (T, S, E and M, alone or in combinations) could not yield scores above 0.8 without the presence of at least one pupillometric parameter. The results are completely different for the 8-13 years old group. First, no combination reached scores of 0.9. Only 10 combinations reached 0.8 for the four scores (AUC, Se, Sp and Ac), and among them 7 contained the two parameters P (pupil variation) and T (total time tracked). In conclusion, combining T with other parameters only slightly improved the individual performance observed in Figure 3 for the 8-13 years old.

c. Algorithms of classification

The multiplicity of classifiers identifying the same combinations of parameters as excellent or outstanding is reassuring from a clinical point of view: this suggests that the ASD/TD classification is reliable and does not depend on one specific algorithm. However, it would be interesting to know if one or several algorithms are more suited to our clinical data. We thus analyzed the patterns of classification, for the Face stimuli, focusing on the identity of the classifiers. Figure 5 shows the same results as Figure 4B, but bringing out classifiers for which scores of 0.8 or above were obtained (AUC, Se, Sp and Ac) for the 2-7 and 8-13 years old groups.

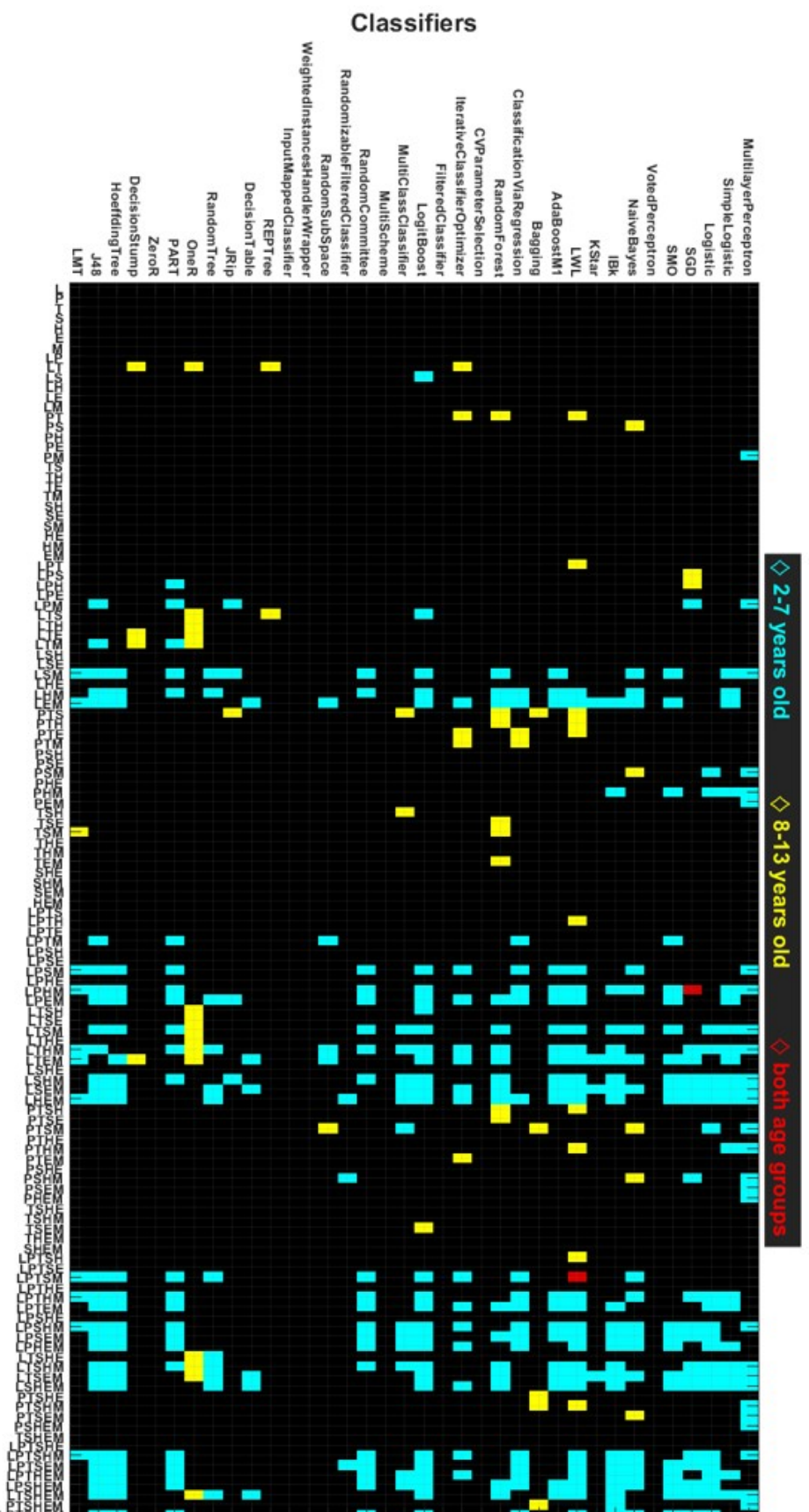


Figure 5: Classifiers with AUC, sensitivity, specificity and accuracy scores above 0.8 as a function of combinations of parameters for 2-7 years old (cyan), 8-13 years old (yellow) or both groups (red). Pupilometric parameters: pupil light reflex (L) and pupil variation (P); oculometric parameters: total time tracked (T), exploration of the screen (S), head (H), eyes (E), and mouth (M). IBk: K-nearest neighbours, LMT: Logistic Model Tree, LWL: Locally Weighted Learning, OneR: One Rule, SGD: Stochastic Gradient Descent, SMO: Sequential minimal optimization.

A few classifiers never provided any good discrimination whatever the parameter or combination of parameters. For the 2-7 years old group, many combinations of parameters were identified as discriminant by many classifiers but no classifier identified all these combinations. The five algorithms identifying the most combinations as discriminant were LogitBoost (30 combinations), J48 (29), Multilayer Perceptron (27), Hoeffding Tree (26), and Locally Weighted Learning (25). The pattern was different for the 8-13 years old group, with less common combinations identified and less algorithms picking up several combinations. The best algorithms for this age group were OneR (15 combinations), Locally Weighted Learning (10), and Random forest (8). Some classifiers were specific for one age group (e.g. J48 and Multilayer Perceptron for the 2-7 years old group, and OneR and Decision Stump for the 8-13 years old group), but others worked for both groups. Only two individual classifier x combination cases allowed for an excellent discrimination of both the 2-7 and 8-13 years old (Locally Weighted Learning x LPTSM and Stochastic Gradient Descent x LPHM).

d. Loss of data and clinical implications

For young children (2-7 years old group), the machine-learning classification could discriminate ASD and TD children with a performance up to 0.964 (AUC ~1, Se 0.95, Sp 0.95, Ac 0.96). However, these good performances were obtained only for combinations in which pupillometric parameters were present, and for many children these data could not be acquired. If these children could not be recorded because of their age or clinical characteristics, it would diminish the possible clinical use of our discrimination approach. We thus explored how age and clinical scores could affect data acquisition.

First we considered the oculometric data. For TD children, only 2 out of 93 children could not be recorded, and these children were among the youngest (3 and 3.9 years old). For ASD children, 7 out of 72 children could not be recorded. Their age was not significantly different from the age of the recorded children (mean \pm std: 6.7 ± 2.6 vs. 7.8 ± 2.7 years old, t-test $p > 0.1$). The CARS scores, reflecting the severity of autism⁴¹, were not different between the non-recorded and recorded ASD children (mean \pm std: 33.7 ± 5.2 vs. 31.2 ± 6.2 , t-test $p > 0.3$), while there was a tendency for a lower developmental quotient (DQ) in non-recorded ASD children (mean \pm std: 52 ± 16 vs. 78 ± 26 , t-test $p = 0.061$ uncorrected).

For the pupillometric data, we considered separately the recording of the pupil light reflex, and the pupil variation elicited by face or object observation. The pupil light reflex was the part of

the experiment for which we had the most data loss. In TD children, 58 out of 93 children could not be recorded and were younger than the children recorded (mean \pm std: 6.9 ± 2.6 vs. 8.4 ± 2.4 years old, t-test $p=0.003$). In ASD children, 51 out of 72 children could not be recorded. They were not different from the recorded children with respect to age (mean \pm std: 7.6 ± 2.5 vs. 7.8 ± 3.1 years old, t-test $p>0.3$) or CARS scores (mean \pm std: 31.4 ± 6 vs. 31.7 ± 6.5 , t-test $p>0.8$). However, there was a tendency for a lower DQ in non-recorded children (mean \pm std: 70.4 ± 27.1 vs. 88.9 ± 19.2 , t-test $p=0.046$ uncorrected). For the pupil variation, 39 out 93 TD children could not be recorded and were younger than the children recorded (mean \pm std: 6.9 ± 2.6 vs. 7.9 ± 2.5 years old, t-test $p=0.040$). 33 out of 72 ASD children could not be recorded but were not significantly different from the recorded children (mean \pm std: age 7.7 ± 2.7 vs. 7.6 ± 2.7 years old, t-test $p>0.4$; CARS 30.9 ± 5.3 vs. 32 ± 6.7 , t-test $p>0.4$; DQ 71.4 ± 29.4 vs. 79.3 ± 23.3 , t-test $p>0.3$).

To summarize, in TD children loss of data was observed in young children. However, for ASD children, loss of data was not linked to age or autism severity, but there was a tendency for an effect of developmental quotient.

3. Discussion

This study was the first to combine oculometric and pupillometric parameters with the goal of discriminating ASD and TD children with a non-invasive and short paradigm. Our main result was that combining these two kinds of recordings indeed improved discriminative performance, especially for young children and for social stimuli.

Processing of social information is evolving with maturation and exposure. It is now well documented that face processing involves specialized circuits and mechanisms^{6,7} that become efficient from 8 years old⁹, when children start being considered as face experts. Intuitively we could have expected that discrimination between ASD and TD children would have been easier after 8 years old due to this expertise especially developed in TD children. On the contrary, our best performances were obtained for children below 8 years old, suggesting that machine-learning algorithms picked on characteristics of non-expert face processing.

However, considering age in our analyses led to a decrease in the number of participants in each groups. Outstanding performances obtained in our analyses should thus be interpreted with caution, as they reflect the ability of machine-learning algorithms to categorize 2-7 years old children within two small diagnostic groups (10-12 TD children vs 10 ASD children). A larger

number of participants will be needed to confirm this classification, before a generalization and application to describe autistic characteristics. In particular, the small number of participants in our analysis prevented us to analyze if wrongly classified autistic children would correspond to a specific clinical profile. However, two aspects were really encouraging about the performances we obtained. First, we only reported results for which AUC, specificity, sensitivity and accuracy (based on 5-fold cross-validation) were all above 0.7, 0.8 or 0.9 thresholds, so without bias towards false positive or negative classification. Second, although the machine-learning algorithms we tested had very heterogeneous approaches, models and/or processing, a majority converged towards the identification of the same combinations of parameters with excellent or outstanding performances.

Very interestingly, only combinations of pupillometric and oculometric parameters led to better performances than the ones obtained with single parameters in our protocol (Figures 2 and 3). The combinations of pupillometric parameters with each other, or of oculometric parameters with each other, did not produce an interesting gain of performance. This result suggests that the type of information picked up by the algorithms is of different nature, and previous studies combining different kinds of signal already suggested that such a combinatory approach could be successful^{31,32}. However, for oculometric and pupillometric parameters it could be less expected than for the combination of oculometric parameters and EEG or kinematics parameters for example^{31,32}. Indeed gaze and pupil diameter could partially reflect similar cerebral mechanisms, as eye movements are guided by attentional factors⁴², pupil dilation is correlated to attentional engagement^{33,43}, and pupil diameter is sensitive to eye movements⁴⁴. On the other hand, we already showed, in a previous study reporting part of the same data, that there was no correlation between oculometric and pupillometric parameters³⁹. This oculo-pupillometric combination is optimal for practical use as the recordings rely on only one eye-tracker, facilitating the acquisition especially in ASD children.

It should be noted, however, that for children above 8 years old, the combination approach led to a very small gain in performance compared to the discrimination based only on the total time tracked by the eye-tracker. This parameter reflects the ability of the children to stay calm and oriented towards the screen (and thus the eye-tracker). This ability increases with age in neurotypical children⁴⁵, but not as much in autistic children (in our sample, linear coefficient for TTT between 0 and 4s as a function of age in years: 0.18 and 0.15 for Objects and Faces respectively in TD children, with a R2 of 0.26 and 0.21 respectively; 0.13 and 0.09, with R2 of 0.08 and 0.04, for ASD children). Yet, this parameter may not be specific to autism.

Our results are the first step to consider using the oculo-pupillometric combination approach in a clinical context. We obtained outstanding performances, with very high sensitivity and specificity exigence, which are necessary criteria for potential autism screening. Other critical expectations for clinical transfer are met by our protocol: first we used a unique non-invasive and non-intrusive material; second our paradigm was very short (less than one minute) and could be even shorter as only the social stimuli proved to be useful for discriminative performance; the protocol can be standardized, contrary to real life situations²⁹. One aspect could be improved however, as our performances rely on good quality of both gaze and pupil acquisition: indeed, we observed a significant loss of pupil data in our study. The absence of correlation between this loss of data and ASD severity suggests that this approach is compatible with the heterogeneity of autistic population and points rather towards a material failure. Indeed, we used a rather old eye-tracker system which was not yet optimized for pupil detection, contrary to modern material relying on both dark and light pupil detection. We could thus expect shortly a clinical transfer for autism screening in young children based on up-to-date eye-tracking acquisition during face observation.

4. Methods

a. Participants

This study included 93 typically developing (TD) children (50 boys and 43 girls, mean age 7.5 years) and 72 children with autism spectrum disorders (ASD) (64 boys and 8 girls, mean age 7.4 years), aged 2 to 13 years-old (see details in Table S1). The children with ASD were recruited in the Child Psychiatry Centre of the University Hospital of Tours, in the Centre-Val de Loire regional Autism Resource Center, and in the Pediatric Centre of Paris Nord (CPPN). All the children gave verbal consent and the parents provided written informed consent according to institutional guidelines. The experiment conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2008) and was approved by the local ethics committee before it started (n°2012-A00520-43).

Exclusion criteria were neurological disorders (including seizures), neurologic impairment in motor or sensory function, or genetically defined disorders. The diagnosis of ASD was made by clinicians according to ICD10 criteria and using the Autism Diagnostic Observation Schedule-Generic (ADOS-G⁴⁶) and/or the Autism Diagnostic Interview-Revised (ADI-R⁴⁷), and the Childhood Autism Rating Scale (CARS⁴¹). Developmental quotient (DQ) was assessed

by the Echelles Différentielles d'Efficiences Intellectuelles (EDEI-R⁴⁸) or the Wechsler Intelligence Scale for Children⁴⁹ (WISC III and WISC IV). Due to the multi-sites recruitment, CARS and DQ scores were only assessed respectively in 64 and 40 out of 72 ASD children (Table 1).

b. Stimuli

The two categories of stimuli consisted in objects (4 photos) and faces (4 photos; Figure 1A). The chosen objects were toys, with an overall vertical symmetry in order to match some characteristics of faces. The faces were of two men and two women with a neutral expression. The overall size (19.2 x 13.2°) of the objects and faces were matched, as well as their luminance (10 lux), and color (Red, Green, Blue values =212, 233, 250). Each image was associated with an inter-stimuli gray image with a fixation cross, presented before the image of interest, and matched in luminance. The mean luminance of the images was around 10 lux in order to optimize the pupil diameter recordings (see SI of ³⁹).

Black and white slides were also used in order to test for the pupil light reflex.

c. Material and protocol

The children were seated comfortably in an armchair in front of a computer screen at a distance of about 90 cm. When necessary, a child booster seat was fitted in the armchair in order to support the child. The screen was coupled with a head-free binocular eye-tracking system (FaceLAB[®]) with a 60Hz data acquisition frequency. GazeTracker[®] software was used to present the stimuli and acquire the data. The reliability of oculometric and pupillometric measurements was tested beforehand (see SI of ³⁹). A calibration procedure of the eye-tracker was performed at the beginning of each acquisition.

The protocol started with the presentation of a 2s black screen, followed by a 2s white screen in order to measure a pupil light reflex. Then a succession of gray slides (2s) followed by a stimulus (4s, object or face) was presented (Figure 1B). Each stimulus was presented only once, in a randomized order.

d. Data extraction, pre-processing and parameters

For each stimulus, Regions of Interest (ROIs) were defined: the whole computer screen (as the tracking allows to follow the eyes a little bit beyond the screen borders), the object, the face, and the eyes and mouth regions. GazeTracker® provided both the raw oculometric and pupillometric data, as well as parameters like tracking time and fixation time applied or not to the different ROIs.

Data pre-processing was performed in Excel and Matlab as described previously^{39,45}. For the pupil recordings, pre-processing aimed at suppressing artefacts and blinks, thanks to median filtering and interpolation of small times windows corresponding to data loss, artefacts or blinks.

Several parameters were calculated for the pupil recordings. For the pupil light reflex (measured during the black and white slides), three parameters were extracted, thanks to a logistic curve fitting, inflexion points and “plateau” detection: the amplitude (PRA for Pupil light Reflex Amplitude), duration (PRD) and velocity (PRV). The pupil baseline (PBas) parameter was recorded during the gray slides presented before each object or face stimulus. It was estimated as the median value of the last “plateau” of at least 200ms before the stimulus presentation (“plateau” defined as successive pupil diameter values < 0.01 mm). If no “plateau” was found, then the baseline value was estimated as the median value of the last second before the stimulus presentation. Lastly, the pupil diameter variation (PDV) was estimated for each stimulus presentation as the median value, recorded from 2s to 4s, minus the baseline for the previous gray slide.

A list of parameters was also extracted for the oculometric recordings: the total time tracked (TTT, corresponding to the duration of the tracking of the eyes by the eye-tracker); for the Screen ROI: time spent (STS), fixation time (FTS) and number of fixations (NbFS); for the Object/Face/Eyes/Mouth ROIs: time spent (STO/STF/STE/STM), fixation time (FTO/FTF/FTE/FTM), number of fixations (NbFO/NbFF/NbFE/NbFM) and latency of the first entry (LatO/LatF/LatE/LatM) in the ROI.

e. Discriminant analysis and datamining

For each participant, all the previously described parameters were extracted and calculated for 4 objects and 4 faces. Among these 4 values for each parameter, outliers were removed (>1.5 interquartile range). The total time tracked (TTT) was a value between 0s (no tracking possible)

and 4s (tracking during the whole stimulus presentation). But only stimuli for which the TTT exceeded 2s were kept for the other parameters in order to have enough time for a proper evaluation. All the oculometric parameters (except latency) were pondered by the TTT. Finally, each parameter was averaged for the 4 objects and for the 4 faces so that only one set of parameters was considered by category and by participant.

ROC (Receiver Operating Curve) analysis was conducted on the whole population or in subgroups based on the age (separating 2-7 and 8-13 years old). The separation in two age groups was conducted to obtain groups with approximatively the same number of participants (Table 1), while at the same time reflecting the transition in face processing expertise⁹. Area under the curve (AUC), sensitivity (Se) and specificity (Sp) were estimated for individual parameters.

Datamining and machine learning was performed using Weka software⁴⁰ (Waikato environment for knowledge analysis, <https://www.cs.waikato.ac.nz/ml/weka/>). It allowed to test for the discriminant power of combination of parameters. All the combinations between oculometric and pupillometric parameters were tested separately for the object stimuli and the face stimuli (with the pupil light reflex parameters added to each category). For each combination, AUC, Se, Sp and accuracy (Ac) based on 5-fold cross-validation were calculated to evaluate the discrimination performances for all classifiers (n=36) proposed by Weka software. For purpose of representation, a performance index was calculated as the mean of AUC, Se, Sp and Ac.

f. Statistics

The effect of age, CARS and DQ scores on loss of data were tested by t-tests, corrected for the number of tests by subgroups of children.

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Figures legends

Figure 1: Experimental paradigm. A. Stimuli. A total of four different faces and four different objects were presented, equated in size, luminance and color. B. Paradigm. The sequence started with a 2s black and a 2s white slide, then each stimulus was presented for 4s and preceded by a 2s interstimulus. The interstimulus gray slide was equated in luminance and color to all the faces and objects.

Figure 2: Discriminant analysis scores for the Object stimuli. Area Under the Curve (AUC), specificity (Sp) and sensitivity (Se) scores for each pupillometric and oculometric parameter are represented for the complete population (top panel), the 2-7 years old group (middle panel) and the 8-13 years old group (lower panel). PRA: pupil light reflex amplitude, PRD: pupil light reflex duration, PRV: pupil light reflex velocity, PBas: pupil baseline, PDV: pupil diameter variation, TTT: total time tracked, TSS: time spent on screen, FTS: fixation time on screen, NbFS: number of fixations on screen, TSO: time spent on object, FTO: fixation time on object, NbFO: number of fixations on object, LatO: latency of first entry on object.

Figure 3: Discriminant analysis scores for the Face stimuli. Area Under the Curve (AUC), specificity (Sp) and sensitivity (Se) scores for each pupillometric and oculometric parameter are represented for the complete population (top panel), the 2-7 years old group (middle panel) and the 8-13 years old group (lower panel). Parameters for the Face/Eyes/Mouth ROIs: time spent on ROI (TSF/TSE/TSM), fixation time on ROI (FTF/FTE/FTM), number of fixations on ROI (NbFF/NbFE/NbFM), LatO: latency of first entry on ROI (LatF/LatE/LatM). See Figure 2 for other abbreviations.

Figure 4: Performance index for all combinations of parameters and all machine-learning algorithms for the Object stimuli (A) and the Face stimuli (B). Each point is the mean of AUC, Se, Sp and Ac. The point is colored if the four scores are above 0.9 (red), 0.8 (orange) or 0.7 (yellow). The combinations of parameters are organized along plateaus of number of children within the data, with less children towards the left and more children towards the right (gray line at the bottom of each panel). Within a plateau, the combinations with the most parameters are towards the left, those with the less parameters towards the right. The plateaus

are defined by the presence of the pupillometric parameters (L: pupil light reflex, P: pupil variation) within the combinations.

Figure 5: Classifiers with AUC, sensitivity, specificity and accuracy scores above 0.8 as a function of combinations of parameters for 2-7 years old (cyan), 8-13 years old (yellow) or both groups (red). Pupillometric parameters: pupil light reflex (L) and pupil variation (P) ; oculometric parameters: total time tracked (T), exploration of the screen (S), head (H), eyes (E), and mouth (M). IBk: K-nearest neighbours, LMT: Logistic Model Tree, LWL: Locally Weighted Learning, OneR: One Rule, SGD: Stochastic Gradient Descent, SMO: Sequential minimal optimization.

Table

		2-7 years old			8-13 years old			ALL		
		♀	♂	All	♀	♂	All	♀	♂	All
TD	n	21	29	50	22	21	43	43	50	93
	Age range (years)	2.8 - 7.7	2.7 - 7.4	2.7 - 7.7	8.5 - 13	8 - 12.1	8 - 13	2.8 - 13	2.7 - 12.1	2.8 - 13
	Mean age ± SD	5.6 ± 1.4	5.3 ± 1.3	5.4 ± 1.3	10.2 ± 1.3	9.5 ± 1.1	9.8 ± 1.2	7.9 ± 2.7	7 ± 2.4	7.5 ± 2.6
ASD	n	4	37	41	4	27	31	8	64	72
	Age range (years)	2.7 - 4.6	3.3 - 7.9	2.7 - 7.9	8.3 - 13.1	8.3 - 13.1	8.3 - 13.1	2.7 - 13.1	3.3 - 13.1	2.7 - 13.1
	Mean age ± SD	3.9 ± 0.9	5.9 ± 1.2	5.7 ± 1.3	10.3 ± 2.1	10.3 ± 1.6	10.3 ± 1.6	7.1 ± 3.7	7.7 ± 2.6	7.6 ± 2.7
	CARS score mean ± SD	41 ± 4 (n=3)	32 ± 6 (n=35)	33 ± 6 (n=38)	27 ± 5 (n=4)	30 ± 4 (n=22)	29 ± 4 (n=26)	33 ± 8 (n=7)	31 ± 6 (n=57)	31 ± 6 (n=64)
	DQ mean ± SD	(n=0)	76 ± 33 (n=20)	76 ± 33 (n=20)	75 ± 14 (n=4)	75 ± 19 (n=16)	75 ± 18 (n=20)	75 ± 14 (n=4)	76 ± 27 (n=36)	76 ± 26 (n=40)

Table 1: Characteristics of the populations. ASD: Autism Spectrum Disorder, CARS: Childhood Autism Rating Scale, DQ: Developmental Quotient, SD: standard deviation, TD: typically-developing.