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Behavioral characterization of prediction and internal models in adolescents with autistic spectrum disorders

Running title: Prediction and internal models in autism

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Abstract

Autism has been considered as a deficit in prediction of the upcoming event or of the sensory consequences of our own movements. To test this hypothesis, we recorded eye movements from high-functioning autistic adolescent and from age-matched controls during a blanking paradigm. In this paradigm, adolescent were instructed to follow a moving target with their eyes even during its transient disappearance. Given the absence of visual information during the blanking period, eye movements during this period are solely controlled on the basis of the prediction of the ongoing target motion. Typical markers of predictive eye movements such as the number and accuracy of predictive saccades and the predictive reacceleration before target reappearance were identical in the two populations. In addition, the synergy of predictive saccades and smooth pursuit observed during the blanking periods, which is a marker for the quality of internal models about target/eye motions, was comparable between these two populations. These results suggest that, in our large population of high-functioning autistic adolescent, both predictive abilities and internal models are left intact in Autism, at least for low-level sensorimotor transformation.

Keywords: Autism; smooth-pursuit; saccades; prediction; internal models; sensorimotor control; adolescents

4 highlights:

1) We investigated predictive mechanisms during ocular tracking performance in ASD adolescents using a target motion blanking paradigm

2) Anticipatory pursuit responses before target onset and target reappearance after a transient blanking are normal in ASD participants

3) At target reappearance, saccades and pursuit are well coordinated in both groups

4) Predictive mechanisms and internal models for oculomotor control are preserved in adolescents with Autism

Introduction

Making predictions about future sensory events or the consequences of our own actions is a cardinal property of cognitive systems to adapt our behaviors and interact with the environment. Such ability has been largely investigated in motor control where theoretical studies have pointed out the role and the properties of internal models about the dynamics of both inflows and outflows of motor systems (e.g. Miall and Wolpert, 1996; Wolpert and Ghahramani, 2000). In this context, the smooth pursuit system offers a simple but yet powerful empirical framework to investigate these internal models (Barnes and Asselman, 1991; Becker and Fuchs, 1985; Kowler et al., 2014). For instance, in response to a fully predictable moving target, smooth eye movements can be initiated in the correct direction and speed before target motion, a behavior called anticipatory pursuit (Kowler, 1989). If the same target is transiently occluded during steady-state pursuit, the oculomotor system is able to maintain the on-going eye movement during several hundred of ms even though the eye velocity decreases during the blanking period (Becker and Fuchs, 1985; Mitrani and Dimitrov, 1978). In adults, this decrease in eye velocity induces a lag of the eye with respect to the target position that is compensated by saccades, whose total amplitude is inversely proportional to the residual eye velocity (Coppe et al., 2012; Orban de Xivry et al., 2008, 2006). Lastly, when the duration of target blanking is predictable, the pursuit eye velocity starts increasing again before target reappearance (Bennett and Barnes, 2004, 2003; Orban de Xivry et al., 2006). Such anticipatory eye acceleration is another signature of predictive mechanisms based upon an internal representation of the target timing. These trial-by-trial saccadic adjustments and anticipatory pursuit reacceleration are considered as markers of the internal model of both target and eye velocities (Coppe et al., 2012; Ego et al., 2016) that is used by the automatic predictive mechanisms involved in the sensorimotor control of pursuit eye movements (Bogadhi et al., 2013; Orban de Xivry et al., 2013). At a neurophysiological level, empirical evidences highlight the importance of the frontal lobes (Barborica and Ferrera, 2003; Ding et al., 2009; Ferrera and Barborica, 2010; Lencer et al., 2004; Missal and Heinen, 2004) and of the cerebellum (Cerminara et al., 2009; Lisberger,

2009; Wolpert et al., 1998) in building the internal models used for sensorimotor prediction. Because of their neurological substrates, predictive eye movements have been proposed as reliable biomarkers of neurological and psychiatric disorders involving frontal lobes such as schizophrenia (e.g., Benson et al., 2012) or cortical degeneration (e.g., Coppe et al., 2012).

Recently, a lack of ability to predict future events or to build and update internal models of the world and our own actions has been proposed as a theoretical framework to shed light on the cognitive dysfunctions observed in Autism Spectrum Disorders (ASD) (e.g., Gomot and Wicker, 2012; Pellicano and Burr, 2012; Sinha et al., 2014, Quattrocki & Friston, 2014; Van de Cruys et al., 2014; Sevgi et al., 2015). Such inability could impact social, behavioral, cognitive or motor functions and explain some of the clinical hallmarks of this pathology (David et al., 2009). Interestingly, the neural substrates involved in elaborating internal models (i.e., mainly the frontal lobes and the cerebellum) are thought to be particularly affected in ASD (Amaral et al., 2008; Brambilla, 2003; Palmen et al., 2004; Sparks et al., 2002). Empirical evidences supporting the hypothesis of a deficit in prediction in ASD remain, however, highly controversial and mitigated (e.g. Gowen and Hamilton, 2013). A few motor studies reported impairments in predictive control or in internal models in ASD, as illustrated by deficiencies in the temporal coordination between grip and load forces during objects grasping (Schmitz et al., 2003). At perceptual level, the weaker adaptation to complex visual inputs (such as faces or numerosity) in children with ASD compared to typically developing children was taken as evidence of a reduced ability to build internal models of the visual world from their previous, cumulative experience (Pellicano and Burr, 2012). However, several other studies failed to find a significant difference in prediction at both perceptual and motor levels between individuals with and without ASD. Blakemore et al. (2006) for instance, showed that the attenuation of the tickling perception due to self-generation is present in ASD, clearly indicating that they are able to use a sensory prediction. In addition, the ability of children with ASD to acquire and adapt internal models of self-generated movements is as efficient as that of typically developing children (Gidley Larson et al., 2008) even though it relies on different motor coordinates (Haswell et al., 2009; Marko et

al., 2015). Overall, this second series of studies suggest that motor prediction is intact in this pathology.

To resolve these controversies, there is a strong need for a solid experimental framework able to probe the ability of ASD participants to predictively control behaviors. Simple visuomotor transformations such as tracking eye movements appear as a good candidate. It is, indeed, a low-level sensorimotor task that involves automatic predictive mechanisms but allows to alleviate biases introducted by high-level perceptual, motor or cognitive processing. Moreover, the maturation of these predictive mechanisms for ocular tracking is now well understood (Ego et al., 2016, 2013). By estimating pursuit performance for moving targets that are transiently occluded during the steady-state phase of pursuit, contrasted visually-guided (i.e., target present, Ego et al., 2013) and predictive (i.e., target absent, Ego et al., 2016) mechanisms were assessed in a large population of participants spanning from 5 to 20 years old. Both a late maturation of the predictive mechanisms as reflected by lower ability to compensate for late smooth pursuit maturation (Ego et al., 2013) and a weaker accuracy of the internal models governing the synergy between the saccadic and the pursuit systems were observed in young children (<10 years old) (Ego et al., 2016). Interestingly, Ego and collaborators reported that these objective and selective behavioral signatures of the prediction mechanisms can be accurately estimated in severe atypical development, such as in cerebral palsy (Ego et al., 2015).

Based on the methodology calibrated in these previous works, our objective was to test the prediction hypothesis in ASD in the context of ocular tracking. We investigated a large group of children and adolescent ASD, reasonning that a late maturation shall impact the ASD, but not the matched control, group. Here, we show on the contrary that ASD children and adolescents exhibit similar performance to typically-developing age-matched control but much better performance than 6 years old children, suggesting that automatic predictive mechanisms may in fact be intact in this pathology. This result calls for a more careful and restrictive definition of the prediction hypothesis in ASD.

Methods

Participants

Eye movements were recorded in 40 participants with Autism Spectrum Disorder (ASD) with no intellectual impairment and in 35 age-matched control participants (see Table 1). ASD participants were recruited at the Autism Center of Reference, a specialized clinical center from the Pediatric Psychiatry Unit of the Marseille University Hospital. All participants had normal, or corrected-to-normal vision. They were all evaluated with a WAIS (III/IV) or a WASI test and performance IQ were higher than 70 for all participants (ASD participant included). A statistical difference was found between IQ scores of the two groups (T test 2 tailed, p=0.003) but not between ages (p=0.47). None of the participant with ASD was taking medication susceptible to affect their eye movements at the time of testing. All of them have been evaluated using the ADOS scale and were also asked to complete the Empathy Quotient (EQ) self-report questionnaire (Baron-Cohen and Weelwright, 2004) (see Table 1). Among the 40 ASD participants, only 3 showed clinical signs of attentional deficits during the clinical evaluation but were still included in the study.

Group	Age (years)	N	N males	Performance IQ	ADOS Communication	ADOS Social interaction	EQ
ASD	10 to 29y (16.4 +/- 4.2y)	40	36	98 +/- 36	3.3 +/-3.8	7 +/- 2.6	27.5+/-10.9
Ctrl	10 to 28y (15.7 +/- 4.1y)	35	21	108 +/- 38			

Table 1: Participants description. For the two groups, we indicate the range and mean (+/- SD) age, the total number and the number of males and the performance scores for IQ. For the ASD group, we report the scores (mean +/- SD) obtained with the ADOS scale on two items (Communication, Social Interaction) and the EQ scale.

All procedures were approved by the local Ethics Committee and were conducted in accordance with the Declaration of Helsinki. All participants, or their representatives signed an informed consent. All experiments took place in the local Clinical Unit.

For one particular analysis (Figure 6E,F), results from participants with ASD were also compared to those of 60 control participants (aged 5 to 34y) who participated in a very similar previous study (Ego et al., 2016) using the same procedures and identical set-ups. Our objective was to compare the difference in oculomotor parameters between autistic children and age-matched controls to the change in parameters due to development.

Experimental Setup

Participants were seated on a chair with their head restrained by a chin-rest and faced a computer screen (47.5 x 30 cm) placed 57 cm away from them. Eye movements of both eyes were recorded at 500 Hz using an infrared eye tracker (Eyelink 2, SR Research, Ottawa, Canada) for the first 44 participants (28 ASD and 16 control participants). For the 31 additional participants, eye movements were recorded at 1000 Hz using an Eyelink 1000 (12 ASD and 8 control participants). We checked that all pursuit and saccades parameters were not significantly different between the two recording systems.

Behavioral paradigm

The paradigm was similar to the one used in Ego et al. (2016) (Figure 1). Participants had to pursue a red dot (0.6 deg) displayed at the center of a green bird (horizontal width: 4 deg) that moved horizontally on the video screen. All trials started with an initial fixation period (1 s) on one side of the screen at a position randomly selected between +/-19 and +/-22 degrees of eccentricity. At the end of the fixation period, the target disappeared for 0.3 s (gap period), reappeared and then immediately started to move at 20 deg/s to the other side (i.e. towards the center of the screen) for 2 s. The gap period was introduced to shorten the pursuit onset latency. In the test trials, after 0.6 s, the target disappeared (blanking period) for 0.8 s and then reappeared for the last 0.6 s, as illustrated in Fig. 1. Each participant completed 6 blocks of 20 trials. For the first two trials and two other trials randomly placed in the block, the target was continuously kept visible (control trials) to reinforce the continuous motion of the target (no gap and no blanking period). The direction of the target motion was kept constant within a block but randomized across blocks.

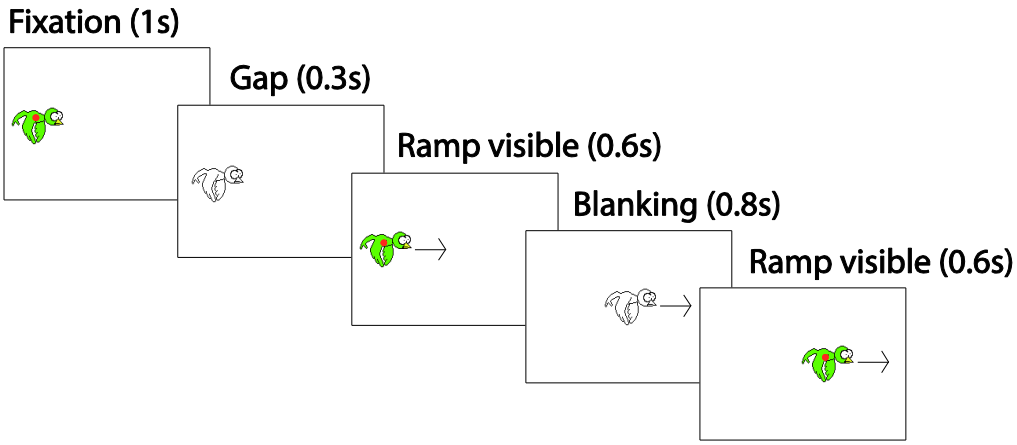

Figure 1

Figure 1: *Time course of a test trial. After 1s of fixation and a gap period (target blanked for 0.3 s), the target started to move horizontally at a constant velocity of 20deg/s. 0.6 s later the target was blanked for 0.8 s (blanking period) and then reappeared and continued moving for another 0.6 s.*

Data analysis

Eye position signals were low-pass filtered at 50 Hz. Time-series from the recordings with the Eyelink 2 were filtered again using a median filter with a 50 ms interval. No additional filtering was applied on the data collected with the Eyelink 1000. All remaining data analysis were similar to the ones described in Ego et al. (2016). They are briefly summarized below. First, eye velocity and acceleration signals were derived from position signals using a central difference algorithm. Saccades were detected using an acceleration criterion of 500 deg/s² and removed from the velocity traces to analyze the smooth pursuit component of visual tracking behavior.

Control trials (for which the target was continuously visible) were sorted out from the data set and not analyzed as we focused on the difference in predictive behavior between the two groups of participants. For the quantitative analysis, we defined four successive time periods: T1 for the three first test trials, T2 for the next four, T3 for the next four and, finally T4 for the last five test trials. Using different sized bins allowed us to take into account both the fact that it takes three trials to observe anticipatory eye movements at the beginning of a

block design protocole (Bennet et al., 2010) and the timing of the interleaved control trials. Such binning has been calibrated in previous studies (Coppé et al., 2012; Ego et al., 2016).

In the test trials, we first measured the visually-guided steady-state pursuit gain defined as the ratio between the mean eye velocity (averaged over a 50ms interval centered at 100ms before target blanking) and the target velocity. When a pursued target disappears, the eye velocity decreases exponentially until a plateau called residual velocity (Becker and Fuchs, 1985). After just a few trials and when the timing of target reappearance is known, the pursuit eye velocity can begin to increase prior to target reappearance (Bennett and Barnes, 2003). Such predictive smooth response was evaluated using the residual gain (computed on a 50ms interval centered 500ms after target disappearance) and the predictive recovery. The predictive recovery is defined as the slope of the regression line fitted on a 150ms interval of the de-saccaded eye velocity trace, starting 100ms before and ending 50ms after target reappearance. Predictive saccades are saccades triggered in absence of visual information and the latencies of which range between 120 and 800ms after target disappearance (see Orban de Xivry et al., 2009). To construct heat maps of saccades endpoints, all saccades endpoints (time of offset and landing position) were replaced by 3D Gaussian curves. Heat maps of participant groups were constructed with the sum of all Gaussians representing the saccades endpoints divided by their maximum. Colors represent the height of the resulting sum (see Ego et al. (2016) for more details). Note that one autistic kid did not exhibit many saccades during the occlusion and his data had to be removed from the analyses of the precision of predictive saccades.

Saccade-pursuit interaction was studied using both the saccadic eye displacement (SAD) and smooth pursuit eye displacement (SED) during blanking. SAD is defined as the sum of the amplitudes of the saccades triggered during blanking. The difference between the total eye displacement and SAD is called SED. Both SAD and SED were normalized with target displacement. The relationship between SAD and SED was quantified using the slope of the regression line as well as the root mean square error (RMSE). For this particular analysis, performances of ASD participants were compared to the one of the control group of this paper (Ctrl 1) and two groups from a similar previous study (Ego et al., 2016): Ctrl 2 is a

group of age-matched control children (the 40 participants with the closest age) and Young is a group of 10 younger control children (aged 5 to 7 years).

For all analyses, no directional biases were observed in the data and thus data from both directions were collapsed. Repeated measures ANOVA's were performed with groups as between participants factor and periods as within-participants factor. All analyses were performed using Matlab. Regressions were computed using the *robustfit* function.

Lastly, we performed a group-size analysis to estimate the statistical power of our study. Deficits in motor coordination for high-functioning autistic children compared to age-matched control were shown to have an effect size of 1.2 (Cohen's d) (see Fournier et al. (2010), for a meta-analysis). It is however almost impossible to infer the expected size effect using different sensorimotor tasks, as for instance the variability sources can be totally different. Instead, we reasoned that impairment in internal model function would correspond to a developmental delay of internal model formation of several years. For instance, in cognitive studies, this developmental delay can be up to 7 years (e.g. Baron-Cohen (1989). In our previous study (Ego et al., 2016), for a difference of three years (5-7 *vs* 10-12 years old), we found an effect size of 1.4 (Cohen's d). Therefore, if we expect delayed internal model formation such as suggested by others, we can reasonably expect an effect size of 1 between ASD and TD children. To detect such effect size with a 90% power (which is higher than the usual 80% power required), one needs to have at least 21 participants per group. Our groups are larger than that, allowing for a robust statistical analysis.

Results

The ability to track moving targets that transiently disappear is at the core of this study. Here, we are interested in comparing the tracking ability of participants with ASD and aged-matched controls. Typical oculomotor responses from one control and one ASD participant are displayed in Figure 2. These two trials have similar characteristics. Both participants tracked the moving target accurately when it was visible. Indeed, the eye velocity is close to target velocity for both participants during the first part of the trial (between the two grey

areas Figure 2C and 2D). Then, when the target was blanked (beginning of the second grey area), the eye velocity of both participants rapidly dropped by about 50%. Eye velocity started to increase again around target reappearance time (Figure 2C and 2D). In addition, both participants use a combination of smooth pursuit and saccades to pursue the invisible target (Figure 2A and B). Below, the pursuit, saccadic behavior and the interaction between both types of eye movements in participants with ASD will be compared to the one of age-matched control participants.

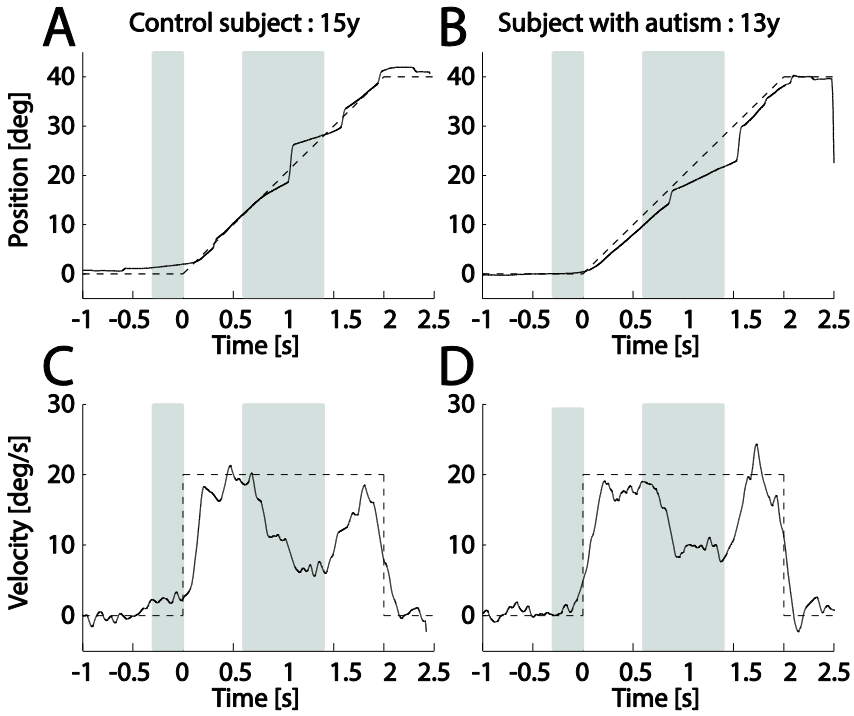

Figure 2: *Typical trials. Position vs. time of the eye for a typical trial from a control participant (A) and a participant with Autism (B). C and D: The corresponding desaccaded eye velocities. Dashed lines represent respectively the target position and velocity. Grey areas represent the time periods when the target is not visible.*

The mean desaccaded eye velocities for both groups for the first and last trials of the blocks are illustrated in Figure 3. The pursuit of participants with ASD (in orange) is very similar to the one observed in controls (in blue). Overall, both ASD and controls are able to follow the target at the correct velocity when visible (just before the second grey bar in Figure 3A and B). This translates into a visually-guided pursuit gain close to one for both groups (Figure 4A, Controls: 0.952±0.02; ASD: 0.95±0.017 (mean±SE); main effect of group:

F(1,73)=0.0005, p=0.98). The gain of visually-guided pursuit was not correlated with the performance IQ (N=75, R=0.07, p=0.57).

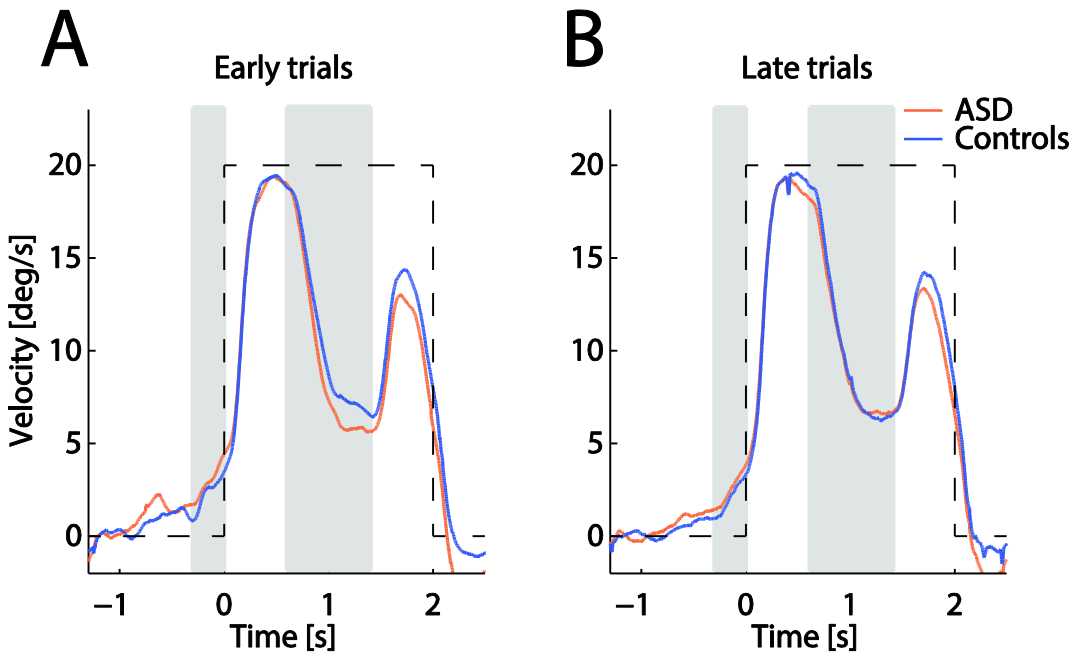

Figure 3: *Mean desaccaded eye velocity for both ASD (orange) and control (blue) groups during the first (A) and last trials (B) of each block. The black dashed traces indicate target velocity profile. Grey bars represent the initial (gap) and late blanking periods (i.e. target invisible).*

When the target disappears, the eye velocity begins to decrease until it reaches a plateau (called residual velocity) at about 30% of target velocity, similar in the two groups (Figure 3A and B). The residual gain was about 0.35 and did not differ between groups (Figure 4B, F(1,73)=1.9, p=0.17) and was not correlated with the performance IQ (N=75, R=0.1, p=0.4). After a few trials, participants learned the timing of target reappearance and started anticipating it. Participants stopped to decelerate their eyes earlier in order to catch the target faster after target reappearance (see difference between Figure 3A,B). The tendency to increase the eye velocity in anticipation of target reappearance is reflected by the predictive recovery (eye acceleration at the end of the blanking period) that becomes positive after the first period (T1) (see Figure 4C). Such predictive recovery did not differ between groups (Figure 4C, F(1,73)=0.39, p=0.53) but was weakly correlated with the performance IQ (R=0.24, p=0.035). Therefore, we added the IQ as a co-variate of the

predictive recovery and still failed to find a significant differences across the groups (ANCOVA: main effect of group when controlling for IQ: F(1,71)=.054, p=0.82). Overall, our results show that predictive smooth pursuit is not altered in autism. This is further demonstrated by the similar anticipatory pursuit initiation observed during the initial gap that is, before target onset. Because of anticipatory tracking, eye velocity already reached nearly 20% of target velocity at target motion onset. There was no statistical differences between the two groups (F(1,73)=0.23 , p=0.63) nor between the successive blocks (F(3,219)=1.37 , p=0.25).

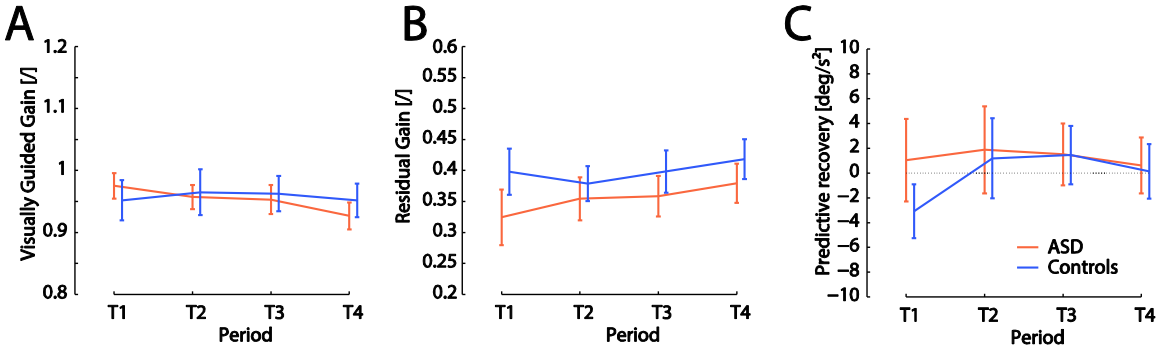

Figure 4: *Predictive smooth pursuit. A: Evolution of the visually guided pursuit gain through trials of a block for the ASD (in orange) and control group (in blue). B: Evolution of the residual gain through the block. C: Evolution of the predictive recovery through the block. On each panel, data points are the average per group computed on the mean per participant and error bars are standard errors of the means.*

Predictive saccades are preserved in autism

The two groups of participants use a combination of smooth pursuit and saccades to pursue the blanked target, as illustrated in Figure 2A,B. While predictive smooth pursuit is similar between groups, the saccades might exhibit different characteristics. To test whether there were differences in saccadic behavior during target blanking, we computed the number of saccades occurring during this period. This is represented by the heat maps of saccades endpoints, which reflect the time and position of saccadic ends. First, the number of saccades did not differ between groups (Figure 5A,B, Mann-Whitney test: U = 700, p = 0.2). Second, heat maps were qualitatively similar (Figure 5E and F). This was quantified using the position error with respect to the position of the blanked target at the end of the predictive saccades (triggered during blanking) which is similar between both groups (Figure 5C,

F(1,72)=0.047, p=0.83) and was not correlated with the IQ (N=75, R=0.15, p=0.2). The variability of this position error was also similar between groups (Figure 5D, F(1,72)=2.98, p=0.09) and was correlated with the participants' IQ (N=75, R=-0.31, p=0.007). This result was confirmed when the difference in IQ between the two groups was taken into account (main effect of group when taking QI as covariate: F(1,71)=0.73, p=0.39). The similarity of both heat maps and position errors at the end of predictive saccades showed that the two groups used a similar strategy to track the invisible target. Thus, both ASD and control participants used predictive saccades to orient the eyes ahead of the target.

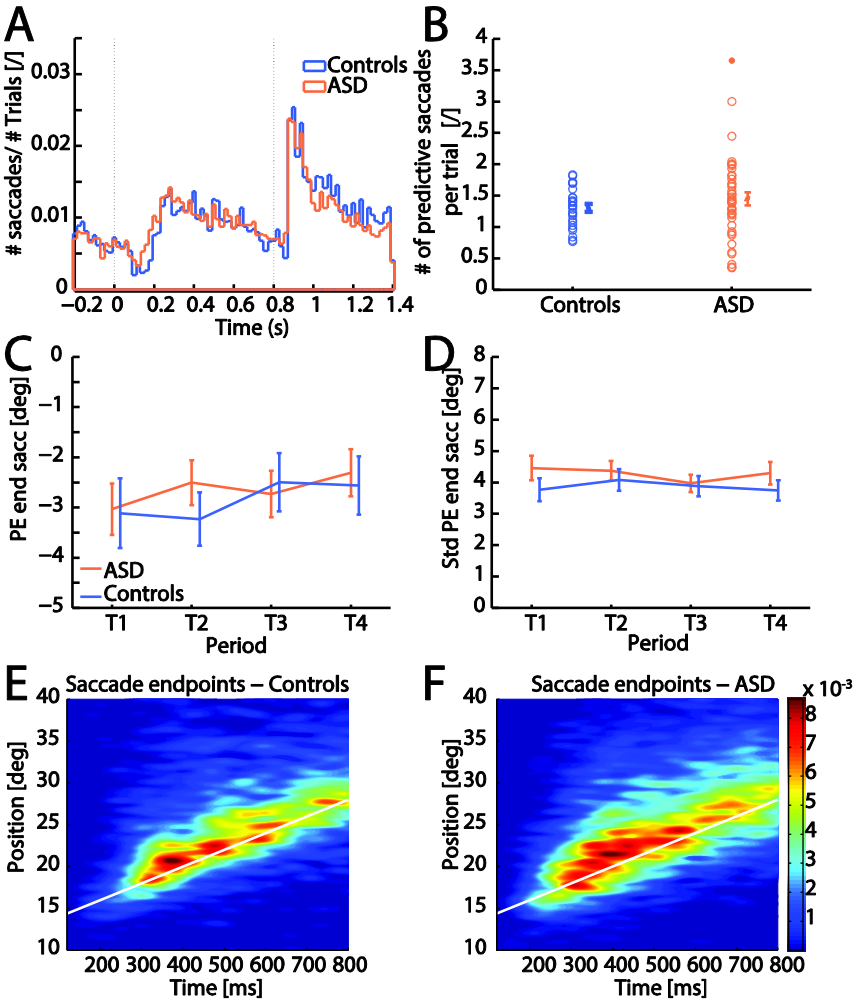

Figure 5: *Predictive saccades. A: Histogram of the number of saccades executed during the blanking period by both groups (ASD in orange and controls in blue). B: Number of predictive saccades per trial per group. Data points are means per subject. Error bars are standard errors of the mean C: Evolution through trials of a block of the position error at the end of predictive saccades for both groups. D: Evolution through trials of a block of the standard deviation of the position error at the end of predictive saccades for both groups. On panels C and D, data points are the means per subject and error bars are standard errors of the mean. E: Heat map of the position of predictive saccades endpoints versus time during the blanking of the target for control subjects. F: Heat map of predictive saccades endpoints for subjects with autism. On panels A, B, E and F, the time zero corresponds to the target disappearance*

and 0.8 s is the time of target reappearance. On panels E and F, the white line is the virtual (not visible) target position. The red colors represent the time and space where the saccades land with the higher frequency. The dark blue color is used for the combinations location/timing where no saccade lands.

Saccade-pursuit interaction during blanking shows that internal models are preserved in Autism

The decrease in eye velocity observed at target disappearance largely varied between trials. In order to ensure that position error is minimum at target reappearance, the amplitude of the saccades needs to be adjusted for each trial separately, in function of the decay in eye velocity. That is, the amplitude of predictive saccades should be larger when the residual eye velocity is lower (Figure 6A) and smaller when residual eye velocity is higher (Figure 6B). In Figure 6C,D, for each participant, the normalized saccadic eye displacement is plotted as a function of the normalized pursuit eye displacement for each trial. Ideally, when the predictive pursuit movement is really small (e.g., SED = 0.2 Figure 6A and C), the saccade displacement should be high (e.g., SAD = 0.7 Figure 6A and C). The black line connecting (0,1) to (1,0) with a slope of -1 indicates the optimal relationship between saccadic and pursuit displacements. Along this line, and for each trial, the sum of smooth pursuit and saccadic eye displacement exactly corresponds to the target displacement, leading to a zero position error at target reappearance. The observed relationship between SAD and SED is presented for one illustrative participant with ASD (Figure 6C) and one control participant (Figure 6D).

Given that there is no visual information available, this compensation can only be based upon an internal estimate of the eye (and target) displacement during the blanking period. The strength of the relationship (slope and RMSE) between pursuit and saccadic eye movement, as computed participant-by-participant gives a measure of the quality of these internal models. This slope slightly differs between the ASD and the control group (ASD vs Ctrl 1: Mann-Whitney: $U = 700$, $p = 0.038$). However, this difference was very small compared to the change in slope with age observed in a previous study, using the same methods and protocols (Ego et al., 2016). These previous data have been replotted in Figure 6E and F, for comparison with the current results for both the slope and RMSE of the relationship between saccade and pursuit. Our objective was to compare the difference in

these relationships between autistic children and age-matched controls (current study) to the change in parameters due to development (Ego et al., 2016). Indeed, the difference between ASD and Ctrl 1 is much smaller than the difference observed between aged-matched controls (Ctrl 2) and the younger children (Young) (Figure 6E, permutation test: $p< 0.0014$). Indeed, the slopes observed in ASD children were not statistically different from the slopes observed in the two age-matched control groups (Tukey-Kramer test, ASD vs. Ctrl 1: $p=0.21$; ASD vs. Ctrl 2: $p=0.94$) but were larger than the slopes observed in younger children ($p=0.003$). Similarly, the RMSE (the other parameter for the quality of the saccade-pursuit interaction) of ASD children exhibited the same pattern (Figure 6F). Namely, the difference in RMSE between ASD and Ctrl 1 was significantly smaller (permutation test, $p=0.003$) than the change of RMSE observed with development (Ctrl 2 vs. Young). The value of RMSE in the ASD group was similar to the one of the two age-matched control groups (Tukey-Kramer test, ASD vs. Ctrl1: $p = 0.11$; ASD vs. Ctrl2: $p = 0.9$) but differed from the younger children (ASD vs. Young: $p = 0.011$).

. Young: $p = 0.001$).

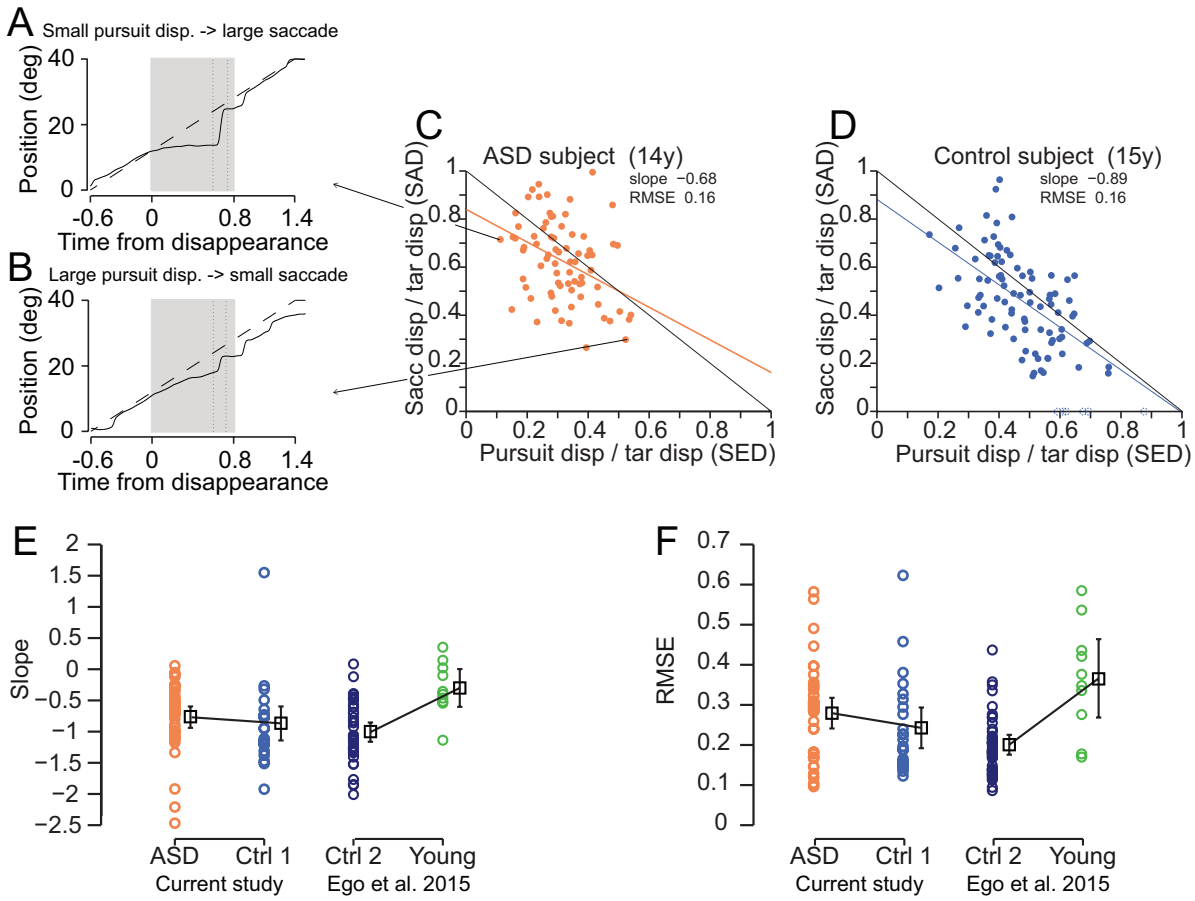

Figure 6: *Saccade-pursuit interaction. A: Position of the eye vs. time for a single trial from an ASD adolescent. On this trial, smooth eye velocity during blanking is very low and a large saccade is executed. B: Position of the eye for another trial from the same participant. In this trial, the eye is relatively close to the target (dashed black trace) and a smaller saccade is executed. On these two last panels, the grey rectangles represent the time periods of target blanking. C and D: Two typical examples of the trial-by-trial relationship between the saccadic eye displacement (SAD) and the smooth eye displacement (SED) for an ASD participant and a control, respectively. On these two panels, each dot represents one trial. The color lines represent the linear fits. The black lines represent the optimal compensation with a slope equal to -1. In panel C, the two trials corresponding to panels A and B are linked with them thanks to a thin black line and arrow. E: Slope of the regression line characterizing the saccade-pursuit interaction for the ASD group and the control group (Ctrls1) of the present study. For comparisons purpose, data from typically developing children of the same age (Ctrl2) and of a younger age (Young, 5-7 years old) are represented. These data are taken from Ego et al.* (Ego et al., 2016). *F: Quality of the linear fits between SAD and SED represented by the root mean square error (RMSE). On the two last panels, open disks are the means per subject. Squares are the means per group computed with the means per participant. Error bars represent 95% confidence intervals of the mean.*

While the slope parameter used to quantify saccade-pursuit interaction was not related to the measured performance IQ of the participants (correlation between slope and IQ: r=-0.04, p=0.7), we found that the RMSE was significantly correlated with IQ (both groups: r=-0.4, p=0.0004; ASD: r=-0.4, p=0.01; Ctrl: r=-0.26, p=0.14). Namely, the RMSE

became smaller with increasing IQ. Therefore, we added the IQ as an additional co-variate in the analysis of the RMSE but still did not find a significant difference in RMSE between ASD and control children (ANCOVA: main effect of group: $F(1,71)=0.044$, $p=.83$; interaction between IQ and group: $F(1,71)=0.009$, $p=0.92$). In other words, the small difference observed between ASD and controls for the RMSE parameters was likely due to the small difference in IQ between the two groups.

Position error at reappearance

As we previously reported, the position error at reappearance provides a global performance index on the predictive tracking during blanking (Ego et al., 2016). The similarity between control and ASD participants in the position error (Figure 7, $F(1,73) = 0.01$, $p=0.92$) further supports our conclusion that there is no deficit in prediction for the ASD children. This parameter was not correlated with the IQ of the participants ($N=75$, $R=0.09$, $p=0.42$).

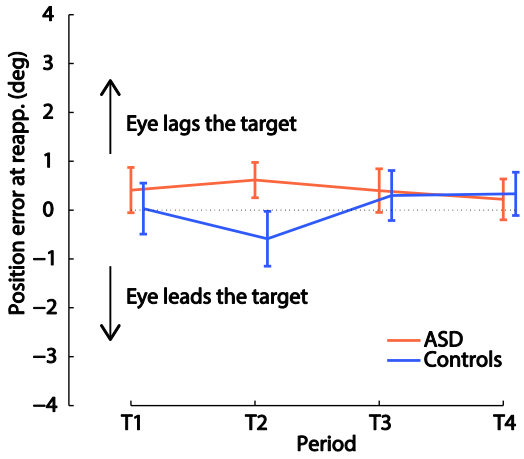

Figure 7: *Evolution of the position error at reappearance through trials of a block for the ASD group (in orange) and the control group (in blue). Data points are the mean per group computed with the mean per subject. Error bars represent standard errors of the mean.*

Discussion

Using a normative approach of both sensory-driven and predictive pursuit, we show that ocular tracking performance is indistinguishable between two large groups of ASD and matched typically developing adolescents. More specifically, our results demonstrate that

predictive mechanisms driving smooth pursuit before target motion initiation as well as during target blanking are intact in children and adolescents with ASD. Moreover, all oculomotor signatures of internal models about target and eye motions are normal as well. It could be argued that prediction is not that important for the pursuit during target blanking or that the task is not difficult enough. However, prediction is the only driving mechanism of the smooth pursuit response during the 800ms of the occlusion given that there is no visual feedback and that eye movements cannot be driven by proprioception. In addition, the predictive behavior observed during the blanking periods has been shown to be really sensitive to brain maturation (Ego et al., 2016). Therefore, we believe that if ASD is associated with a delay in the maturation of the brain structures supporting predictive oculomotor behavior, our task would be sensitive enough to detect such a deficit. Our findings thus clearly indicate that, at least for low-level sensorimotor skills, predictive mechanisms are not affected in high-functioning ASD children and adolescents. They argue against a recent and popular hypothesis that views autism as a general deficit of prediction mechanisms (e.g., Gomot and Wicker, 2012; Pellicano and Burr, 2012; Sinha et al., 2014). Results will be discussed in regards to the existing, controversial literature on the sensorimotor and cognitive aspects of oculomotor control in ASD and their neural bases.

Is there a deficit in oculomotor control in Autism?

Whether or not children with ASD exhibit a specific deficit in the control of eye movements is still debated. Overall, smooth pursuit in ASD has not been well documented (see Rommelse et al., 2008 for a review). In a large group of adolescent and young adults, Takarae et al. (2004) investigated open- and closed-loop pursuit performance during rectilinear (i.e. identical to the current paradigm) and sinusoidal target motions. They reported a small (~10%) but systematic decrease in pursuit gain of both phases in the older sub-group of the ASD cohort. This reduction was interpreted as an evidence for a maturational disturbance of the frontal lobe, as originaly proposed using different saccadic tasks (Goldberg et al., 2002; see below). It shall be noticed however that no deficit in pursuit gain was observed between the younger ASD and control participants (<16 years old). The

small difference observed between the two older groups (>16 years old) was due to the fact that pursuit gain did not further improve with age in ASD as it did in control participants. Consistent with an intact pursuit in young ASD, Kemner et al. (2004) reported normal closed-loop pursuit gain in a group of adolescents (i.e., mean age ~16 years old) diagnosed with pervasive developmental disorders. Thus, our results are coherent with these previous studies showing normal pursuit in ASD of similar age and IQ distributions. By contrast to the previous studies, our study also revealed that the absolute performance was nearly perfect (i.e. a closed-loop gain ~1) in both groups, suggesting a normal tracking oculomotor control in high-functioning ASD. We moreover observed that predictive saccades naturally occurring during the blanking phase of pursuit were identical between the two groups. This result is consistent with those of Takarae et al. (2004) and of Kemner et al. (2004) reporting normal saccadic behavior during rectilinear and sinusoidal tracking. It is also consistent with previous studies showing a nearly normal control of visually-driven saccades in adolescent ASD participants (Goldberg et al., 2002; Landry and Bryson, 2004, Rosenhall et al., 1988; van der Geest et al., 2001). Using state-of-the-art eye movement recording techniques, our study strongly supports the view of an intact low-level oculomotor system in the autistic pathology, evidencing the functional integrity of cerebellar-brainstem networks underpinning oculomotor control (Nowinski et al., 2005).

Is there a cognitive deficit in ocular behavior control?

Ocular behaviors have been also extensively used to probe cognitive deficits in ASD (see Benson and Fletcher-Watson, 2011; Falck-Ytter et al., 2013; Rommelse et al., 2008 for recent reviews). An influential study by Goldberg et al (2002) used a set of standard saccadic tasks to disentangle sensorimotor and cognitive aspects of oculomotor control in this population. As stated above, the fact that memory-guided saccades and anti-saccades, but not visually-guided, reflexive saccades, were selectively disturbed in a large group of high-functioning ASD adolescents was taken as evidence for neurodevelopmental abnormalities affecting the prefrontal (e.g., FEFs) and frontal (dlPFC) cortical areas known for their role in the cognitive control of saccadic eye movements. Interestingly, Goldberg et al. (2002) also

asked their participants to look back and forth between two alternatively illuminated targets and found fewer predictive saccades in the population of ASD adolescents. Whereas such task would allow testing predictive abilities regarding the timing of saccades, it provides little information on the internal models used for such prediction.

Surprisingly, the impact of cognitive mechanisms upon smooth pursuit eye movements has been barely investigated in ASD. Aitkin et al. (2013) reported normal pursuit behavior during a complex task requiring both prediction and cognitive processing about the perceptual organization of the visual scene. The presence of a cue (barrier) on the visual tracking path elicited similar anticipatory eye movements in participants with ASD and in typically developing participants. The T-maze task used by Aitkin et al. (2013) did not involve learning or memory mechanisms as the participants had to judge the most probable target trajectory online. Still, their results are consistent with ours that, during transient target occlusion, adolescents with ASD exhibit both a normal decrease in tracking velocity during blanking periods and a normal anticipatory eye acceleration before target reappearance, as compared to typically developing teenagers. Moreover, in our oculomotor task, anticipatory pursuit during target initiation and reappearance involves both learning and memory processing about the timing and the kinematics of the different phases of the target trajectory (Bennett et al., 2010, 2007; Bogadhi et al., 2013; Madelain and Krauzlis, 2003; Montagnini et al., 2006; Orban de Xivry et al., 2006). This is demonstrated by the small but significant improvement of the tracking performance over the successive blocks (see Ego et al., 2015, 2016). Yet, no difference between ASD and controls was reported here, suggesting that they were able to build and update an internal representation of target motion dynamics. Lastly, the coordination between two types of eye movements (saccade and pursuit) was not different between the two groups, further demonstrating the accuracy of such internal model (Orban de Xivry et al., 2008, 2006). Overall, using both pursuit and saccade markers, we establish that predictive eye movements are preserved in ASD even when it is necessary to estimate both the timing and the velocity of the sensory events from the previous trials.

Autism has been associated to scattered morphological and functional brain changes (Amaral et al., 2008; Auzias et al., 2014; Bailey et al., 1998; Brambilla, 2003; Brun et al.,

2015; Courchesne et al., 2007; Peters et al., 2013). The correlation of these cerebral changes with specific alterations of sensory, motor or cognitive abilities is, however strongly disputed such that, a well-accepted view of functional brain changes in ASD is far from being reached. Behavioral performances related to well-documented neuronal mechanisms can be a powerful guide when searching for specific brain developmental abnormalities. In human and non-human primates, pursuit maintenance during target occlusion sustains neuronal activity in a network of cortical (e.g. MST, FEF/SEF, dlPFC areas) and cerebellar (e.g. Floculus) areas (Lisberger, 2009; Ono, 2014; Orban de Xivry and Lefèvre, 2007). Moreover, anticipatory tracking responses have been associated with predictive neuronal activities in the prefrontal oculomotor fields (FEF/SEF) (Barborica and Ferrera, 2003; de Hemptinne et al., 2008; Ding et al., 2009; Ferrera and Barborica, 2010; Lencer et al., 2004; Missal and Heinen, 2004). The nearly perfect anticipatory tracking responses that we reported in ASD (see also Aitkin et al., 2013) suggest that such frontal and cerebellar networks are functionally intact in high-functioning ASD adolescents. In the same vein, internal models driving both anticipatory pursuit and saccades during occlusion have been associated to computations performed in the parietal cortex and the cerebellum (Lisberger, 2009; Orban de Xivry et al., 2013). The absence of behavioral deficits in the present study argues for a functional integrity of the fronto-cerebellar networks in ASD (Hashimoto et al., 2000; Luna et al., 2002).

Conclusion: Is there a general deficit of predictive mechanisms in Autism?

Autistic spectrum disorders remain largely a mystery and has therefore generated a number of theories trying to explain their cognitive disabilities within a single, generic computational framework. Just to mention a few recent propositions, autism was considered as an excessive neural variability (Dinstein et al., 2015), an over-specificity during learning (Harris et al., 2015) or a change in the balance between excitation and inhibition (Rosenberg et al., 2015). These theories aim at proposing that ASD may broadly alter neural computation rather than narrowly impacting individual systems. Recently, Sinha et al. (2014) proposed that a generic deficit in predictive mechanisms is a cardinal feature of ASD. Such deficient

predictive abilities might be related to an abnormal ability to build internal models build from the past history of sensory evidence or action (Pellicano and Burr, 2012). On the contrary, we and others (Aitkin et al., 2013) found that predictive mechanisms and internal models involved in the control of tracking behavior are preserved in high-functioning, adolescent patients with ASD. A vast repertoire of sensorimotor and cognitive skills relies on predictive mechanisms. We show here that some of them may be intact. It is thus critical that future studies attempt to decipher which prediction-based behaviors are specifically impaired or spared in ASD. Saccadic and pursuit eye movements are powerful behavioral probes to delineate low and high cognitive computations that are specifically affected in ASD.

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FIGURE CAPTIONS

Figure 1: Time course of a test trial. After 1s of fixation and a gap period (target blanked for 0.3 s), the target started to move horizontally at a constant velocity of 20deg/s. 0.6 s later the target was blanked for 0.8 s (blanking period) and then reappeared and continued moving for another 0.6 s.

Figure 2: *Typical trials. Position vs. time of the eye for a typical trial from a control participant (A) and a participant with Autism (B). C and D: The corresponding desaccaded eye velocities. Dashed lines represent respectively the target position and velocity. Grey areas represent the time periods when the target is not visible.*

Figure 3: *Mean desaccaded eye velocity for both ASD (orange) and control (blue) groups during the first (A) and last trials (B) of each block. The black dashed traces indicate target velocity profile. Grey bars represent the initial (gap) and late blanking periods (i.e. target invisible).*

Figure 4: *Predictive smooth pursuit. A: Evolution of the visually guided pursuit gain through trials of a block for the ASD (in orange) and control group (in blue). B: Evolution of the residual gain through the block. C: Evolution of the predictive recovery through the block. On each panel, data points are the average per group computed on the mean per participant and error bars are standard errors of the means.*

Figure 5: *Predictive saccades. A: Histogram of the number of saccades executed during the blanking period by both groups (ASD in orange and controls in blue). B: Number of predictive saccades per trial per group. Data points are means per subject. Error bars are standard errors of the mean C: Evolution through trials of a block of the position error at the end of predictive saccades for both groups. D: Evolution through trials of a block of the standard deviation of the position error at the end of predictive saccades for both groups. On panels C and D, data points are the means per subject and error bars are standard errors of the mean. E: Heat map of the position of predictive saccades endpoints versus time during the blanking of the target for control subjects. F: Heat map of predictive saccades endpoints for subjects with autism. On panels A, B, E and F, the time zero corresponds to the target disappearance and 0.8 s is the time of target reappearance. On panels E and F, the white line is the virtual (not visible) target position. The red colors represent the time and space where the saccades land with the higher frequency. The dark blue color is used for the combinations location/timing where no saccade lands.*

Figure 6: *Saccade-pursuit interaction. A: Position of the eye vs. time for a single trial from an ASD adolescent. On this trial, smooth eye velocity during blanking is very low and a large saccade is executed. B: Position of the eye for another trial from the same participant. In this trial, the eye is relatively close to the target (dashed black trace) and a smaller saccade is executed. On these two last panels, the grey rectangles represent the time periods of target blanking. C and D: Two typical examples of the trial-by-trial relationship between the saccadic eye displacement (SAD) and the smooth eye displacement (SED) for an ASD participant and a control, respectively. On these two panels, each dot represents one trial. The color lines represent the linear fits. The black lines represent the optimal compensation with a slope equal to -1. In panel C, the two trials corresponding to panels A and B are linked with them thanks to a thin black line and arrow. E: Slope of the regression line characterizing the saccade-pursuit interaction for the ASD group and the control group (Ctrls1) of the present study. For comparisons purpose, data from typically developing children of the same age (Ctrl2) and of a younger age (Young, 5-7 years old) are represented. These data are taken from Ego et al.* (Ego et al., 2016)*. F: Quality of the linear fits between SAD and SED represented by the root mean square error (RMSE). On the two last panels, open disks are*

the means per subject. Squares are the means per group computed with the means per participant. Error bars represent 95% confidence intervals of the mean.

Figure 7: *Evolution of the position error at reappearance through trials of a block for the ASD group (in orange) and the control group (in blue). Data points are the mean per group computed with the mean per subject. Error bars represent standard errors of the mean.*