Pupil Dilation Progression Modulates Aberrant Social Cognition in Autism Spectrum Disorder

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Progression of pupil dilation (PD) in response to visual stimuli may indicate distinct internal processes. No study has been performed on PD progression during a social cognition task. Here, we describe PD progression during the Movie for the Assessment of Social Cognition (MASC) test in $n = 23$ adolescents with Autism Spectrum Disorder (ASD) and $n = 24$ age, IQ and sex-matched neurotypical controls (NTC). The MASC consists of 43 video sequences depicting human social interactions, each followed by a multiple-choice question concerning characters' mental states. PD progression data were extracted by eye tracking and controlled for fixation behavior. Segmenting PD progression during video sequences by principal component analysis, three sequential PD components were unveiled. In ASD compared with NTC, a distinct PD progression was observed with increased constriction amplitude, increased dilation latency, and increased dilation amplitude that correlated with PD progression components. These components predicted social cognition performance. The first and second PD components correlated positively with MASC behavioral performance in ASD but negatively in NTC. These PD components may be interpreted as indicators of sensory-perceptual processing and attention function. In ASD, aberrant sensory-perceptual processing and attention function could contribute to attenuated social cognition performance. This needs to be tested by additional studies combining the respective cognitive tests and the outlined PD progression analysis. Phasic activity of the locus coeruleus–norepinephrine system is discussed as putatively shared underlying mechanism. *Autism Res* 2019, 12: 1680–1692. © 2019 The Authors. *Autism Research published by International Society for Autism Research* published by Wiley Periodicals, Inc.

Lay Summary: In adolescents with autism, we found an altered pupil dilation during watching scenes of human interactions. Early pupil dilation correlated positively with the number of correct answers to questions about the shown human interactions. Our findings suggest that aberrant sensory processing and attention function may contribute to altered social cognition in autism.

Keywords: attention modulation; eye tracking; pupillary reactivity; biomarker; sensory processing

Introduction

Pupil dilation (PD) is a versatile and accessible indicator of internal processes [Beatty & Lucero-Wagoner, 2000]. Baseline PD reflects general physiological arousal on a slow change rate [Bradley, Miccoli, Escrig, & Lang, 2008], whereas stimulus-evoked PD reflects rapid physiological reactivity in response to stimuli [Beatty & Lucero-Wagoner, 2000]. Stimulus-evoked PD has been related to various internal processes: Sensory-perceptual processing [Bombeke, Duthoo, Mueller, Hopf, & Boehler, 2016; Kang, Huffer, & Wheatley, 2014; Sabatino DiCriscio,

Hu, & Troiani, 2018] as the conversion of an external stimulus to a cognitive percept, attention function [Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Unsworth & Robison, 2017] as the selectivity to an external stimulus or cognitive percept, and social cognition [Jessen, Altvater-Mackensen, & Grossmann, 2016; Kinner et al., 2017] as "the processing of stimuli relevant to understanding agents and their intentions" [Happé, Cook, & Bird, 2017, p. 244]. The interrelation of these processes remains unclear, although they might concurrently affect stimulus-evoked PD. PD has also been related to other internal processes especially cognitive load

[Beatty & Lucero-Wagoner, 2000], decision making [Sirois & Brisson, 2014], and memory [Sara, 2015], which are beyond of our scope as they are expected to be less dependent on stimuli.

In Autism Spectrum Disorder (ASD), research on stimulus-evoked PD has investigated two distinct internal processes depending on the presented stimuli. First, stimulus-evoked PD has been studied in ASD as marker of *social cognition* by the presentation of social cues. Preschoolers and adults with ASD compared with neurotypical controls (NTC) showed attenuated PD to static emotional faces [Anderson, Colombo, & Jill Shaddy, 2006; Gotham et al., 2018]. Attenuated PD in ASD was sometimes specific to subliminally presented faces [Nuske, Vivanti, Hudry, & Dissanayake, 2014] or unfamiliar faces [Nuske, Vivanti, & Dissanayake, 2014], which suggested altered sensory-perceptual processing. However, some studies did not observe attenuated PD to emotional faces [Falck-Ytter, 2008; Nuske, Vivanti, & Dissanayake, 2015]. PD in ASD compared with NTC was also studied during social interaction tasks. Children with ASD showed attenuated PD in a joint attention task, when gaze cues were incongruent to the target location, which correlated positively with the Social Responsiveness Scale (SRS) summary score [Erstenyuk, Swanson, & Siller, 2014]. Adults with ASD showed attenuated PD to observed social pain but not to observed physical pain [Krach et al., 2015]. In ASD, such attenuated PD to social cues has been interpreted as attenuated physiological reactivity during social cognition. It remains understudied which underlying processes moderate this attenuated physiological reactivity to social cues.

Second, stimulus-evoked PD has been studied in ASD as marker of *sensory-perceptual processing* by the presentation of basic sensory stimuli and ambiguous figures. Toddlers with ASD compared with NTC showed *increased* PD during a visual search paradigm, which correlated with increased performance [Blaser, Eglington, Carter, & Kaldy, 2014]. Adults without ASD showed increased PD during a perceptually switching brightness illusion, which correlated positively ($r = 0.70$) with the autism quotient (AQ) [Turi, Burr, & Binda, 2018]. The authors inferred that neurotypical adults with increased AQ scores showed fewer perceptual switches, which was related to the attenuated global-feature bias as aberrant sensory-perceptual processing in ASD [Van der Hallen, Evers, Brewaeys, Van den Noortgate, & Wagemans, 2015]. Across children with and without ASD, decreased PD amplitude in reaction to dark screens was positively correlated with the SRS summary score [DiCriscio & Troiani, 2017]. Children with ASD had decreased PD amplitudes compared with children without ASD. However, in an underpowered study on brightness illusion in adults with ASD, no PD differences compared with NTC were observed (ASD: $n = 11$) [Laeng, Færevaag,

Tanggaard, & von Tetzchner, 2018]. Overall, ASD symptom scores (SRS, AQ) in neurotypical development were associated with altered stimulus-evoked PD during sensory-perceptual processing. In ASD, altered sensory-perceptual processing—as measured by stimulus-evoked PD—may contribute to attenuated physiological reactivity during social cognition.

In addition to stimulus-evoked PD, the pupillary light reflex (PLR) has also been proposed as indicator of sensory-perceptual processing [Daluwatte, Miles, Sun, & Yao, 2015]. The PLR is a pupillary constriction in response to luminance that peaks around 600 ms [Bergamin & Kardon, 2003]. In ASD, there are contrary findings of attenuated PLR in children [Daluwatte et al., 2013; Fan, Miles, Takahashi, & Yao, 2009] with longer onset latency [Yao, Christ, Miles, & Beversdorf, 2013] versus intensified PLR in infants at-risk for ASD, which was predictive of a future ASD diagnosis [Nyström et al., 2018]. Still, another study did not find PLR-related differences in preschoolers with ASD [Dinalankara, Miles, Nicole Takahashi, & Yao, 2017]. Nonetheless, PLR and PD findings indicated aberrant sensory-perceptual processing in ASD by altered pupillary reactivity. The inter-relation of PLR and PD during sensory-perceptual processing remains unknown but can be investigated by the application of PD progression.

PD progression describes continuous change in stimulus-evoked PD, which delivers temporally dense time series that are visually comparable to electroencephalography data. This allows eliciting different PD components within task trials, which might represent underlying processes that cause PD changes. These PD components are functionally analogous to event-related potentials within electroencephalography data. However, previous studies predominantly aggregated PD progression to mean scores or investigated only specific metrics, for example, dilation latency. In contrast, in a seminal paper, an optimization algorithm differentiated PD progression of neurotypical adults in a temporal attention task (AB task), which revealed two distinct PD components [Wierda, van Rijn, Taatgen, & Martens, 2012]. Another paper differentiated PD progression of neurotypical adults into three sequential components by contrasting task conditions of the Attention Network Task (ANT) [Geva, Zivan, Warsha, & Olchik, 2013]. These PD progression components were not interpreted as indicators of sensory-perceptual processing but as indicators of Posner's attention functions: alerting, orienting, and executive control [Peterson & Posner, 2012]. Phasic alerting describes immediate reactivity to specific stimuli, thus overlapping with sensory-perceptual processing. Orienting is attention allocation to stimuli, whereas executive control describes volitional maintenance of attention. Attention is our central ability to direct cognition to social environments [Corbetta, Patel, & Shulman, 2008]. Thus, attention

function—besides sensory-perceptual processing—is another promising modulator of attenuated physiological reactivity during social cognition in ASD. These modulating effects are expected to be represented in PD progression components during social cognition tasks.

The current study investigates PD progression during social cognition in adolescents with ASD compared with NTC. We want to study the modulating effects of stimulus-evoked PD on social cognition in ASD. Stimulus-evoked PD is differentiated into PD components by a novel PD progression analysis. Based on previous literature [Geva et al., 2013; Kalwani, Joshi, & Gold, 2014; Nyström, Gredebäck, Bölte, & Falck-Ytter, 2015; Wierda et al., 2012], we (1) explore the number of independent components underlying PD progression during watching social scenes. PD progression components are expected to represent several distinct underlying processes relevant to social cognition. In response to criticism of the component extraction method in previous literature [Ambrosini, Vastano, Montefinese, & Ciavarro, 2013], we use a principal component analysis (PCA) as a data-driven component extraction method. (2) We hypothesize an aberrant PD progression in ASD, which is expected to correlate with extracted PD progression components. PD progression in ASD will be related to findings of aberrant sensory-perceptual processing and attention function. We (3) expect PD progression components to differentially predict social cognition performance across and within groups.

Methods
Participants

The total sample (n = 47) included 23 adolescents with ASD and 24 NTC, carefully matched for chronological age, verbal IQ, and gender ratio (see Table 1). Matching was done by drawing a parallelized subsample of a previously published study [Müller, Baumeister, Dziobek, Banaschewski, & Poustka, 2016]. Adolescents with ASD were recruited from the ASD clinical database of the Central Institute of Mental Health (CIMH, Germany) and NTCs by advertisement. NTC and their caregivers confirmed during initial screening that they did not receive psychiatric medication, psychotherapy, or any mental health diagnosis. The Institutional Review Board at the CIMH approved all study procedures. All participants and their caregivers gave informed consent.

Measures

Social cognition was assessed by the Movie for the Assessment of Social Cognition (MASC) [Dziobek et al., 2006]. The measure consists of 43 video sequences depicting four characters eating dinner together. Dominant topics are dating and friendship issues. The social

Table 1. Sample Characteristics

	ASD (n = 23)	NTC (n = 24)	P value
Age	15.9/2.8 [12.7–24.5]	15.8/2.4 [11.6–20.5]	0.846
IQ	100.0/16.1 [70–139]	108.6/14.4 [77–140]	0.064
IQ perceptual	102.7/18.4 [57–135]	110.8/13.8 [81–137]	0.094
IQ verbal	102.4/16.6 [70–133]	103.3/13.9 [77–142]	0.857
Gender	18/5 (male/female)	19/5 (male/female)	-
ADOS—total	10.8/4.7 [4–20]	-	-
ADI-R—total	34.7/14.1 [12–55]	-	-
ADI-R—SI	17.3/6.7 [7–27]	-	-
ADI-R—COM	10.5/5.1 [3–21]	-	-
ADI-R—RRB	4.8/4.4 [0–18]	-	-

Note: Mean/*SD* [min − max]. ASD, Autism Spectrum Disorder; NTC, neurotypical controls; ADOS, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview—Revised; ADI-R subscale scores: SI, social interaction; COM, communication; and RRB, restrictive and repetitive behavior; IQ (perceptual/verbal), cognitive ability as measured by Wechsler Intelligence Scales (WISC-IV, WAIS-IV). *P* value refers to *t*-test group comparisons.

stimuli are presented in a fixed narrative order but vary in content (group discussion, dyadic interaction, and single character close-up) and duration (m = 20.2 sec, SD = 15.3 sec). One PD progression was assessed during each stimulus presentation. Each stimulus is followed by a multiple-choice question presented on-screen with white text on black background regarding the depicted characters' cognition, emotion, or intention. These multiple-choice questions were also read aloud by the experimenter. Participants answered the questions with verbal responses after which the next social stimulus was started. There were no additional inter-stimulus blank screens. Correct answers were aggregated to a sum score that measures social cognition performance. Psychometric properties in adolescent samples and measure's details including sample items are described in the previous validation study [Müller et al., 2016].

All applied measures were validated German versions. ASD diagnostic assessments included the Autism Diagnostic Observation Schedule (ADOS, module 3 or 4), the Autism Diagnostic Interview—Revised (ADI-R) [Lord, Rutter, & Le Couteur, 1994; Lord et al., 2000], and a consensus-based clinical evaluation of ADOS and ADI-R results. This evaluation was done by CIMH's clinical experts that regularly conduct ASD diagnostic assessments during clinical practice but were otherwise not involved in the current study. Seven participants with ASD did not meet ADOS autism spectrum but ADI-R cutoff criteria, yet the clinical experts and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria confirmed the ASD diagnoses. ASD participants below the ADOS cutoff did not show different social cognition performance compared with ASD participants above the cutoff ($t < 1$, P = 0.405; ASD below cutoff: m = 26.7, SD = 4.5; ASD above cutoff: m = 23.3, SD = 7.6).

Cognitive ability (IQ) was assessed by an age-appropriate test—either a four-subtest version of the Wechsler Intelligence Scale for Children or the Wechsler Adult Intelligence Scale [Wechsler, 2004, 2008]. Verbal IQ was estimated by the subtests' similarities and vocabulary, whereas perceptual reasoning IQ was estimated by the subtests block design and matrix reasoning.

Data Acquisition

Noninvasive infrared remote eye tracking was carried out during the social cognition test (MASC). The MASC was implemented in Tobii Pro Studio 3.2 [Tobii Technology, 2012]. Eye-tracking data including PD data were collected by a Tobii TX-300 eye tracker with a 300 Hz sampling rate. Data collection was preceded by a five-point calibration. Environmental luminance default was 200 lx but adapted by adjustable lighting before calibration for optimal eye detection. Participants were seated 65 cm in front of the screen and instructed to watch a movie (MASC, 43 stimuli) while their eye movement was recorded and to answer the associated social cognition questions. Participants had unlimited answering time to prevent stress induction. Thus, test duration varied based on participants' answering speed (ASD: $m = 33.2$ min, $SD = 4.7$; NTC: $m = 30.5$ min, $SD = 2.7$) with a longer duration in the ASD group ($t(44) = 2.38$, $P = 0.021$). However, answering speed did not affect stimulus presentation.

Data Preprocessing

We retrieved 1,865 raw PD progressions (ASD: $n = 881$, NTC: $n = 984$) of 2,021 possible PD progressions (47 participants × 43 stimuli). PD progressions were only analyzed during the stimulus presentation and not during the multiple-choice questions. Raw PD progressions were exported to statistical software R 3.4.3 [R Core Team, 2014]. Each PD progression was truncated to the first 5 sec to pronounce early processes like sensory-perceptual processing and attention function. Each PD progression consisted of 1,500 consecutive points in time (5 sec × 300 Hz).

PD was defined as the mean of both eyes, when both eyes were tracked. When tracking was unsuccessful for one eye, PD was defined as data from the single successful eye. In addition, PD progressions were excluded when more than 50% of PD data in each corresponding trial were missing (ASD: $n = 56$, NTC: $n = 25$). PD progressions were preprocessed by linear filtering with a moving average of 110 ms (33 points). Gaps caused by blinking (<300 ms) were filled by linear interpolation. This resulted in a measure of absolute PD for each point in time that is systematically affected by items' luminance profile, environmental luminance, and participant characteristics. Thus, relative PD served as the dependent variable in all analyses and was calculated by dividing the absolute PD for each point in time by participant's mean PD in each corresponding item.

Fixation Behavior Control

Fixation behavior affects PD estimates, as angular changes between the eye-tracker and pupil affect the pupillary surface that the eye tracker can capture. We implemented a double control for this effect. First, PD data were excluded if the fixation coordinates were not within two standard deviations of mean on-display fixation coordinates as measured in pixels (px; x-axis: $m = 656$ px, $SD = 209$ px; y-axis: $m = 291$ px, $SD = 126$ px). This reduced the analyzed display area to the central 41.6% of the complete display and ensured a uniform angle of eye tracker and pupil. As a result, 16.4% of the PD progression data were excluded. Second, for each stimulus (i.e., truncated video sequences), we calculated a between-group root mean squared error (RMSE) of fixation coordinates by comparing group-specific heatmaps. The heatmaps divided the analyzed display area into 10 × 10 arbitrary units. The RMSE can be interpreted as the mean between-group difference in fixation numbers on units in the analyzed display area. For three stimuli (34, 39, and 43), between-group RMSE deviated from the normal distribution, which the Kolmogorov–Smirnoff test confirmed (stimulus 34: $D = 0.991$, $P = 0.016$; stimulus 39: $D = 0.999$, $P < 0.001$; stimulus 43: $D = 0.991$, $P = 0.016$). These stimuli elicited substantially different between-group fixation behavior and were thus excluded from further analysis (7.9% of the data; RMSE after exclusion: $m = 6.2$, $SD = 1.02$). After fixation behavior control, 1,611 PD progressions (86.4%) remained (ASD: $n = 763$ [86.6%], NTC = 848 [86.1%]). This remaining PD data included $m = 35.8$ ($SD = 7.5$) PD progressions—that is, trials—per participant, which did not differ between groups ($t < 1$, $P = 0.334$; ASD: $m = 34.6$, $SD = 7.9$; NTC: $m = 36.9$, $SD = 7.1$). Figure 1 visualizes between-group fixation behavior of the remaining PD data.

Statistical Analysis

The study was designed as a cross-sectional, group comparison study. All analyses were done in the statistical software R 3.4.3 with additional packages [Barton, 2009; Bernaards & Jennrich, 2005; Fox & Weisberg, 2011; Lenth, 2016; Pinheiro, Bates, DebRoy, & Sarkar, 2014; Revelle, 2015; Torchiano, 2015; Wickham, 2007, 2009, 2011; Zeileis & Grothendieck, 2005]. Descriptive statistics were compared by unpaired t-tests.

To test hypothesis 1, we conducted a PCA with varimax rotation on the PD progression. The number of extracted components was based on a visual inspection of the scree plot. We created three new variables as mean PD during high-factor-loading segments on respective components
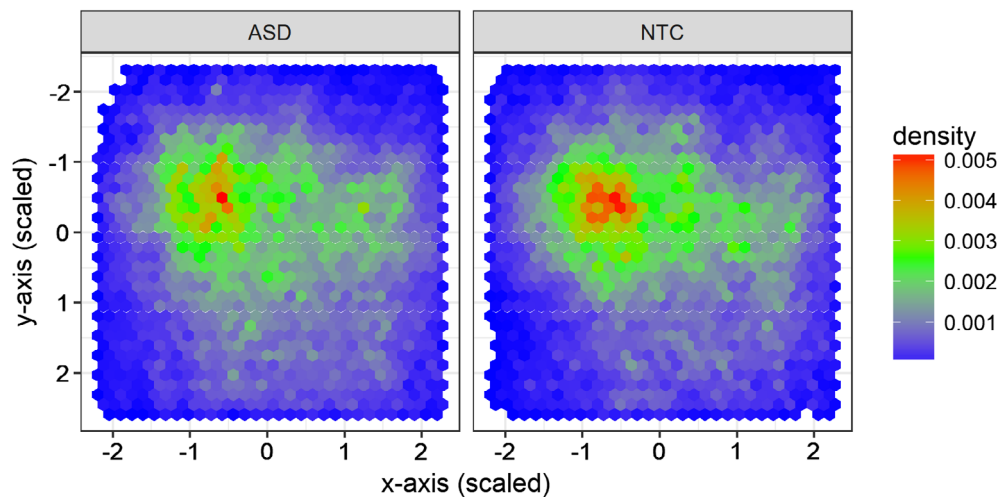
Figure 1. Heatmap of on-screen fixations between groups.

($x > 0.80$). Hereafter, these new variables are called PD components.

For hypothesis 2, a linear mixed model (LMM) tested a distinct PD progression in ASD compared with NTC, with PD as the dependent variable and group affiliation as the fixed-effect, between-group factor. PD progression was partitioned into an arbitrary categorical factor with 10 levels each consisting of 150 consecutive points in time, that is, level A included the points 1 to 150. This partitioned PD progression variable represents a compression of each PD progression into 10 intercorrelated and consecutive PD values (see Supporting Information S1) and was applied as a fixed-effect, within-group factor. PD progression was partitioned to increase the probability of detecting a putative PD-progression × group interaction. Fixed-effect covariates were age, sex, and IQ. Fixed effects were estimated by maximum likelihood. To control for individual variation, stimulus depending on participant was included as a random intercept. Stimulus was also included as a random slope. This LMM was compared with more parsimonious models by χ^2-difference tests.

PD progression metrics were applied to characterize a putatively distinct PD progression in ASD and to relate PD components to previous literature. PD progression metrics—including baseline PD, constriction amplitude, constriction latency, dilation amplitude, and dilation latency—were derived from previous literature. Baseline PD was defined as the mean absolute PD during the first 120 ms corrected for a participant's mean PD in each corresponding item [Nyström et al., 2015]. Constriction/dilation amplitude was defined as relative minimum/maximum dilation measured in relative PD, whereas constriction/dilation latency was defined as the point in time of relative minimum/maximum dilation measured in seconds [DiCriscio & Troiani, 2017]. Group differences in PD progression metrics were estimated by group-specific predicted marginal means of LMMs with the PD

progression metric as the dependent variable. These predicted marginal means were controlled for fixed-effect age, sex, and IQ, as well as random-effect participant. In addition, PD progression metrics were correlated with PD components (derived from PCA, hypothesis 1) by beta coefficients in LMMs with the same covariates and random effect.

Finally, to test hypothesis 3, PD components were related to social cognition by a linear model with social cognition performance as the dependent variable. PD components and group were fixed-effect predictors, as well as two-way interactions of each PD component and group. Effect size was quantified by the coefficient of determination (R^2_{adj}). The linear model was compared with more parsimonious models by χ^2-difference tests.

Results
Behavioral Data

Adolescents with ASD showed reduced social cognition performance compared with NTC ($t(44) = 2.31$, $P = 0.025$, $d = 0.68$; ASD: $m = 23.9$, $SD = 7.2$, $range = 6$–34; NTC: $m = 28.7$, $SD = 6.8$, $range = 10$–37).

PD Progression Components (Hypothesis 1)

An initial, unrotated PCA was run over the PD progression data matrix (1,611 PD progressions × 1,500 points in time). Figure 2 shows the scree plot, which indicated a three-component solution.

The three-factor solution of orthogonal rotated factors explained 72% of the total sample variance (RC1 = 17%, RC2 = 19%, RC3 = 36%; RC, rotated component). This solution indicates a good model fit based on off-diagonal values of 0.96. Residuals had an RMS of 0.09, which indicates the extraction of enough components. Figure 3 displays the factor loadings of the three-factor solution.
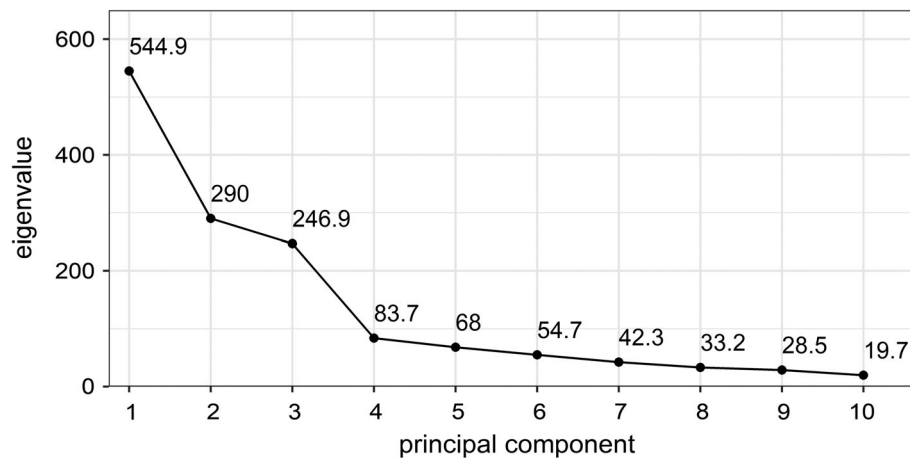
Figure 2. Scree plot of the PD progression.

All three components showed distinctive, high factor loading segments ($x > 0.80$) across the PD progression: a first segment during 0.49–1.28 sec, a second segment during 1.70–2.52 sec, and a third segment during 2.94–-4.58 sec. PD components (RC1, RC2, and RC3) defined as the mean PD during these segments did not differ between groups with all $ts < 1$.

Distinct PD Progression Between Groups (Hypothesis 2)

The LMM with PD-progression × group interaction (full model) showed a significantly better fit than a more parsimonious model without the interaction term ($\chi^2(9) = 7804$, $P < 0.001$; see Table 2). This interaction indicated a distinct PD progression in ASD, as PD differed across the progression depending on group. This is visualized in Figure 4.

The distinct PD progression in ASD was further characterized by group differences in predefined progression metrics: groups differed on three of the five progression metrics by comparing predicted marginal means of

standardized measures. The ASD group exhibited increased constriction amplitude ($t(39) = 2.16$, $P = 0.036$; ASD: $m = 0.93$, $SE = 0.005$; NTC: $m = 0.95$, $SE = 0.004$), increased dilation latency ($t(40) = 3.54$, $P = 0.016$; ASD: $m = 3.20$ sec, $SE = 0.09$; NTC: $m = 2.91$ sec, $SE = 0.08$), and subsequently increased dilation amplitude ($t(40) = -2.11$, $P = 0.041$; ASD: $m = 1.06$, $SE = 0.003$; NTC: $m = 1.05$ sec, $SE = 0.002$). There were no group differences for constriction latency ($t(40) < 1$) or baseline PD ($t(40) = 1.20$, $P = 0.236$).

PD Progression Metrics Indicate PD Components

Correlation patterns and loading the points in time on their respective components suggested an association of PD components with PD progression *metrics* (see Table 3). The first PD component was negatively correlated with dilation amplitude and latency and substantially positively correlated with constriction amplitude. The second component did not substantially correlate with any PD progression metric. The third PD component was
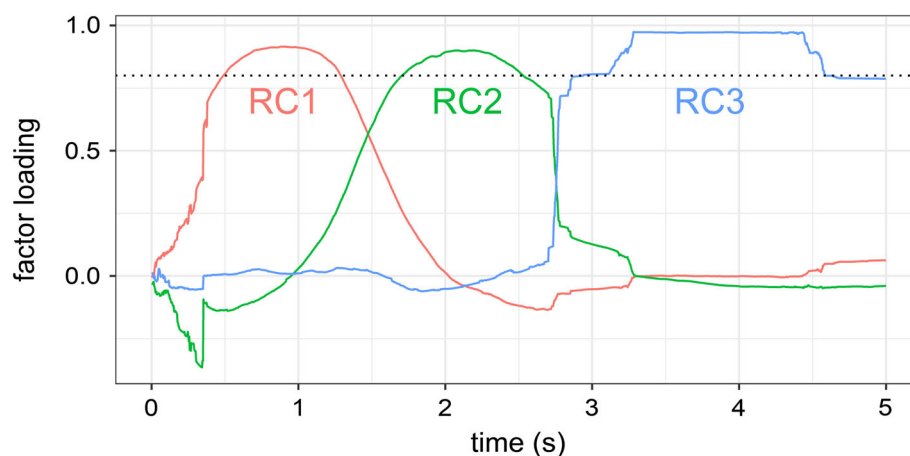

Figure 3. Factor loadings of PD on the derived components over time. The dotted line represents high factor loading with $x > 0.80$. RC1, rotated component 1; RC2, rotated component; RC3, rotated component 3.

Table 2. Comparison of LMMs With PD as Dependent Variable

Model	Type	Model syntax	dfs	AIC	BIC	χ^2	P value
(1) Baseline	Random intercept/slope (0 predictors)	Fixed: ~1 Random: ~stimulus|participant	5	5,569,480	5,569,542		
(2) Covariates	Random intercept/slope (0 predictors, 3 covariates)	Fixed: ~1 Covariates: + age + sex + IQ Random: ~stimulus|participant	8	5,569,483	5,569,583	2.66 (1 vs. 2)	0.447
(3) Group effect	Random intercept/slope (1 predictor, 3 covariates)	Fixed: ~group Covariates: + age + sex + IQ Random: ~stimulus|participant)	9	5,569,479	5,569,591	6.31 (2 vs. 3)	0.012
(4) Main effects	Random intercept/slope (2 predictors, 3 covariates)	Fixed: ~group + PD-progression Covariates: + age + sex + IQ Random: ~stimulus|participant	19	5,436,595	5,436,832	132,903 (3 vs. 4)	<0.001
(5) Interaction	Random intercept/slope (2 predictors, 3 covariates, group × PD-prog. interaction)	Fixed: ~group * PD-progression Covariates: + age + sex + IQ Random: ~stimulus|participant	28	5,428,809	5,429,159	7,804 (4 vs. 5)	<0.001

Note: Model syntax is reported as defined in R statistics' nlme package [Pinheiro et al., 2014]. There is no consensus about degrees of freedom (df) in LMMs. Here, df equals the number of estimated parameters by the model. AIC, Akaike information criterion; BIC, Bayesian information criterion. PD progression was partitioned into a categorical factor with 10 levels and applied as fixed within group factor. Group affiliation was the fixed between group factor. Compared model numbers are shown in brackets after χ^2-value.

positively correlated with dilation latency but negatively correlated with constriction amplitude. This is an inverse correlation pattern compared with the first PD component.

PD Components Modulate Social Cognition Performance (Hypothesis 3)

The linear model with PD components × group interaction as a predictor of social cognition performance had a significantly better fit than a model without the interactions ($\chi^2(3) = 8.76$, $P = 0.033$, $R^2_{adj} = 0.18$; Table 4).

Insignificant main effects are explained by crossover interactions (Fig. 5). Comparing group-specific beta coefficients, predicting social cognition performance by first

PD component was positive in ASD ($\beta = 0.41$) but negative in NTC ($\beta = -0.22$). Similarly, by second PD component, social cognition performance prediction was positive in ASD ($\beta = 0.31$) and negative in NTC ($\beta = -0.30$). This relationship was reversed for third PD component (ASD: $\beta = -0.20$, NTC: $\beta = 0.20$). However, the interaction of third PD component and group was not significant in the overall model.

Discussion

We investigated PD progression as modulator of social cognition performance. We found a distinct PD progression in ASD that correlated with retrieved PD progression
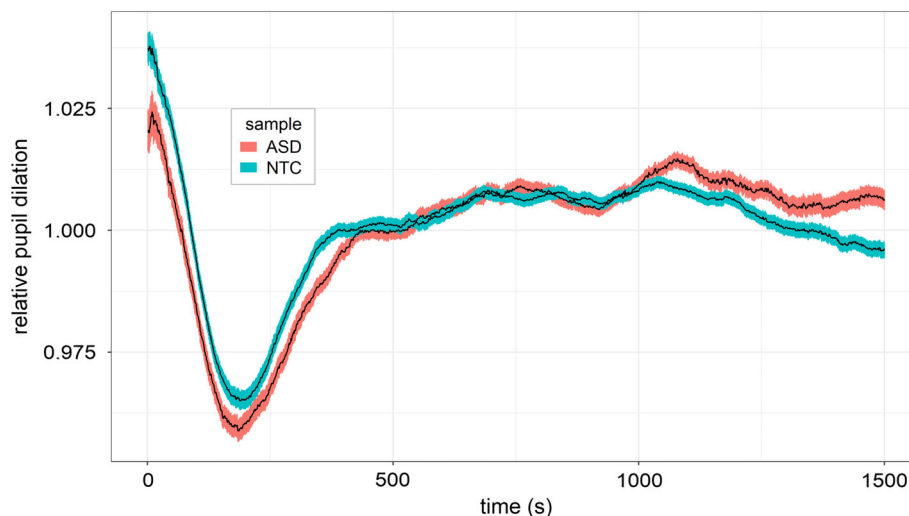

Figure 4. Comparison of PD progression. Colored shaded areas represent standard errors. ASD, Autism Spectrum Disorder; NTC, neurotypical controls.

Table 3. Intercorrelations of PD Components and Correlations With PD Progression Metrics

	RC1	RC2	RC3	rpd	d_{amp}	d_{lat}	c_{amp}	c_{lat}
PD components								
First (RC1)	1							
Second (RC2)	−0.43 (0.03)	1						
Third (RC3)	−0.61 (0.02)	−0.23 (0.03)	1					
PD progression metrics								
Relative baseline (rpd)	0.20 (0.03)	−0.18 (0.03)	−0.37 (0.03)	1				
Dilation amplitude (d_{amp})	−0.12 (0.03)	0.07 (0.03)	0.09 (0.03)	−0.13 (0.03)	1			
Dilation latency (d_{lat})	−0.36 (0.04)	−0.20 (0.04)	0.54 (0.03)	*−0.05 (0.04)*	*0.02 (0.04)*	1		
Constriction amplitude (c_{amp})	0.74 (0.02)	−0.33 (0.03)	−0.56 (0.03)	0.48 (0.04)	−0.17 (0.04)	−0.24 (0.05)	1	
Constriction latency (c_{lat})	−0.16 (0.03)	−0.12 (0.03)	*0.03 (0.03)*	0.51 (0.03)	−0.09 (0.04)	0.16 (0.04)	*0.04 (0.05)*	1

Note: Beta-coefficient (standard error). Nonsignificant coefficients are marked in italics. Beta coefficients and standard errors are estimated in LMMs across groups with the column variable as predictor and the row variable as dependent variable. LMMs were controlled for covariates (group, age, sex, and IQ) and random effects of participants. RC1, rotated component 1; RC2, rotated component; RC3, rotated component 3.

components. Two PD components differentially correlated with social cognition performance in ASD and NTC.

Concerning hypothesis 1, three independent components were derived from the PD progression. These PD components were temporally subsequent and may be interpreted as follows: The first PD component (RC1) indicates sensory-perceptual processing. This is supported by a correlation of RC1 and constriction amplitude that implied the PLR (see Fig. 4). In addition, the temporal occurrence of RC1 is similar to stimulus-evoked PD in previous studies on sensory-perceptual processing [Nyström et al., 2018; Turi et al., 2018]. The second PD component (RC2) indicates attention function. Previous literature specified RC2 as orienting attention function [Geva et al., 2013], which allocates attention to stimuli that evoked (pupillary) reactivity [Dragone et al., 2018; Mather, Clewett, Sakaki, & Harley, 2016]. In our data, this is supported by the negative correlation of RC1 and RC2, as well as their temporal succession. However, RC2 did not substantially correlate with PD metrics and thus needs further validation. The third PD component (RC3) represents a contrary process compared with RC1 regarding correlation patterns. This suggests a complementary

Table 4. Linear Model of PD Components on Social Cognition Performance

	Sum squares	F value	P value
Group	172.3	3.87	0.056*
First (RC1)	36.5	0.82	0.371
Second (RC2)	2.6	0.06	0.809
Third (RC3)	98.6	2.21	0.145
RC1 × group	234.3	5.26	0.027**
RC2 × group	179.8	4.03	0.052*
RC2 × group	32.09	0.72	0.401
(residuals)	1,616.9		

Note: RC1, rotated component 1; RC2, rotated component; RC3, rotated component 3.
*$P < 0.1$; **$P < 0.05$.

process to (bottom-up) sensory-perceptual processing like (top-down) executive control. This is in line with previous research that associated RC3 with a volitional, top-down process [Geng, Blumenfeld, Tyson, & Minzenberg, 2015; Geva et al., 2013; Wierda et al., 2012].

Previous studies also discussed a two-component PD progression model compared with our three PD components [Mill, O'Connor, & Dobbins, 2016; Wetzel, Buttelmann, Schieler, & Widmann, 2016]. These two components were interpreted as a sensory component and a subsequent cognitive component. A two-component model would have resulted from our data by collapsing RC1 and RC2. However, the three-component solution fit the data better than a two-component solution (see scree plot, Fig. 2). Three PD components were also observed in neurotypical adults during the ANT but only interpreted in regard to attention function [Geva et al., 2013]. We propose that sensory-perceptual processing (RC1), orienting attention function (RC2), and executive control (RC3) may underlie our PD progression components.

Concerning hypothesis 2, a distinct PD progression in ASD compared with NTC was found and characterized by increased constriction amplitude, dilation latency, and dilation amplitude. First, increased constriction amplitude implies an enhanced PLR in adolescents with ASD. This contrasts previously reported attenuated PLR in children with ASD [Daluwatte et al., 2013; Fan et al., 2009] but supports findings of enhanced PLR predicting a later ASD diagnosis in at-risk infants [Nyström et al., 2018]. Second, increased dilation latency—to our knowledge—has not been reported in ASD. We proposed orienting attention function to be reflected in RC2 (see above), which is temporally overlapping with dilation latency. Thus, increased PD latency may indicate delayed orienting in ASD, which has been meta-analytically confirmed for behavioral tasks [Landry & Parker, 2013]. Third, increased dilation amplitude has been reported for toddlers with ASD during sensory-perceptual processing [Blaser et al., 2014] but not for adolescents with ASD in
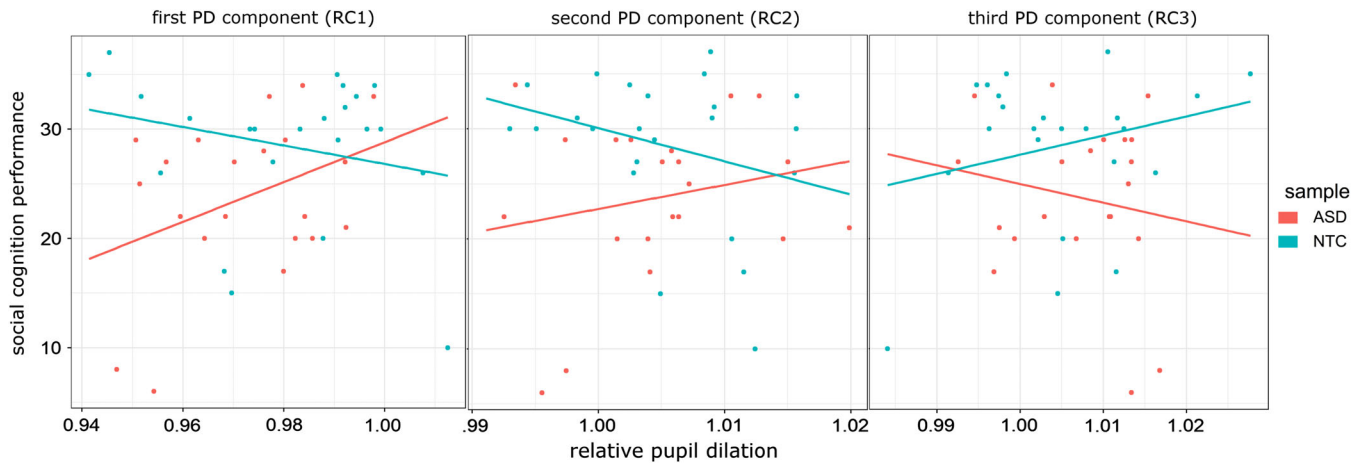
Figure 5. Interrelation of PD and social cognition performance. ASD, Autism Spectrum Disorder; NTC, neurotypical controls; RC1, rotated component 1; RC2, rotated component; RC3, rotated component 3.

response to social cues. In fact, most studies in ASD reported attenuated dilation amplitude in response to social cues [Anderson et al., 2006; Gotham et al., 2018; Nuske, Vivanti, & Dissanayake, 2014], which was interpreted as attenuated physiological reactivity. However, these studies predominantly aggregated PD progression to mean scores and thus might have missed temporal PD progression dynamics. By the analysis of PD progression, we concluded that attenuated physiological reactivity to social cues in ASD could be due to altered sensory-perceptual processing with pronounced PLR and delayed orienting.

In contrast, increased dilation amplitude occurs late in PD progression and likely was not captured in previous studies that applied shorter stimulus presentation times. Increased dilation amplitude in ASD may be a compensatory top-down upregulation of physiological reactivity but was found to be unrelated to social cognition performance (see below).

The locus coeruleus–norepinephrine (LC-NE) system has been established as underlying biological system of PD progression [Samuels & Szabadi, 2008]. Phasic LC activity causes cortical NE release that modulates the signal-to-noise ratio in synaptic signal transmission [Aston-Jones & Cohen, 2005]. Phasic LC-NE activity and stimulus-evoked PD were closely correlated during an oddball task in neurotypical adults [Murphy, O'Connell, O'Sullivan, Robertson, & Balsters, 2014]. Phasic LC-NE activity has been related to sensory-perceptual processing [Mohammed, Kulasekara, Ootsuka, & Blessing, 2016], orienting attention function [Hermans et al., 2011; Suzuki & Tanaka, 2017], and social cognition [Corbetta et al., 2008].

In neurotypical development, LC α2-autoreceptors reduced tonic activity and increased phasic reactivity [Minzenberg, Watrous, Yoon, Ursu, & Carter, 2008]. As

baseline PD measures tonic LC activity and stimulus-evoked PD measures phasic LC reactivity [Joshi, Li, Kalwani, & Gold, 2016], this was reflected in our data by a negative correlation of baseline PD with RC2 and RC3. In addition, phasic LC-NE activity was found to stimulate the temporoparietal junction (TPJ) to initiate ventral frontoparietal attention, which is associated with orienting attention function [Corbetta et al., 2008; Geng & Vossel, 2013; Walz et al., 2013]. Thus, aberrant phasic LC-NE activity may affect attention modulation of social cognition in ASD. Attenuated phasic LC reactivity may mitigate NE-induced adaptive gain in LC-NE projections like ACC, anterior insula, amygdala, and TPJ [Corbetta et al., 2008; Samuels & Szabadi, 2008; Suzuki & Tanaka, 2017]. These brain areas constitute functional neural networks of attention function [Aston-Jones & Cohen, 2005; Corbetta et al., 2008; Peterson & Posner, 2012] as well as social cognition [Odriozola et al., 2015; Schuwerk, Schurz, Muller, Rupprecht, & Sommer, 2017]. Taken together, aberrant phasic LC-NE activity is a promising underlying mechanism of aberrant PD progression and aberrant social cognition performance in ASD [Bast, Poustka, & Freitag, 2018].

Concerning hypothesis 3, two PD progression components (RC1, RC2) predicted social cognition performance. The main effects of these PD components were superimposed by crossover interactions of group and PD components. In ASD, decreased RC1 and RC2 were associated with lower social cognition performance. This could be explained by the proposed underlying mechanism of aberrant phasic LC-NE activity. This may impair sensory-perceptual processing of salient social cues as indicated by decreased RC1. This may also impair orienting attention function to those social cues as indicated by decreased RC2 [Kane et al., 2017; Pajkossy, Szőllősi, Demeter, & Racsmány, 2017; Suzuki &

Tanaka, 2017]. Together, attenuated sensory-perceptual processing and attenuated orienting attention function is proposed to contribute to attenuated social cognition performance in ASD.

Contrasting findings were observed in NTC. In NTC, higher RC1 and RC2 were associated with lower social cognition performance. This contrast—compared with ASD—can be explained by the inverted u-shaped relationship of phasic LC-NE reactivity and performance [Aston-Jones & Cohen, 2005; Gilzenrat et al., 2010]: In ASD, default phasic LC-NE reactivity is proposed to be attenuated so that higher reactivity is associated with better performance. In NTC, default phasic LC-NE reactivity usually is optimal so that higher reactivity impairs performance (see Fig. 5).

Our conclusions are limited. We did not apply direct measures of sensory-perceptual processing and attention function, which would have allowed to externally validate PD components. Moreover, aberrant phasic LC-NE activity in ASD as an underlying mechanism requires empirical validation in future studies. Neuromelanin-weighted magnetic resonance imaging scans have recently been applied to successfully track individual LC locations [Clewett, Huang, Velasco, Lee, & Mather, 2018]. Future studies in ASD could individually locate LC activity and compare it with concurrent PD progression in sensory-perceptual processing and attention function paradigms. In addition, we included some individuals in the ASD who did not meet ADOS autism spectrum cutoff criteria. ASD diagnosis might be questioned for these individuals, which could have attenuated the observed group effects. Finally, the effects of PD progression components on social cognition performance should be interpreted with caution. Although our samples were matched for age, sex, and IQ, these covariates might still have a residual mediating effect that could be explored in future studies with larger sample sizes.

In adolescents with ASD, a distinct PD progression correlated with attenuated social cognition performance. The distinct PD progression was characterized by increased constriction amplitude, dilation latency, and amplitude. ASD-specific PD progression was discussed to indicate attenuated sensory-perceptual processing of (RC1) and orienting attention to (RC2) social stimuli. Attenuated phasic LC-NE activity was proposed as a shared underlying mechanism. We showed that PD progression analysis during social scenes is a feasible method to study underlying processes and their modulation of higher order social cognition performance. More generally, we introduced a novel data-driven approach in the autism field to condense information-rich PD progression data into distinct components by PCA. As a result, complex PD progression can be separated into few putatively meaningful variables, which might represent underlying processes and mechanisms. This may hold potential as a clinical tool, as PD progression can be easily and unobtrusively assessed by

modern eye trackers (e.g., Tobii TX-300) even during other assessments (electroencephalography, functional magnetic resonance imaging, clinical interview). After further validation, PD progression components could be promising diagnostic markers and clinical outcome measures.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplements 1. Correlation matrix of the partitioned PD progression variable.