# *Resting and Functional Pupil Response Metrics Indicate Features of Reward Sensitivity and ASD in Children*

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ORIGINAL PAPER

# Resting and Functional Pupil Response Metrics Indicate Features of Reward Sensitivity and ASD in Children

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## Abstract

The current study examined the relationship between quantitative measures of reward and punishment sensitivity, features of autism spectrum disorder (ASD), and resting and functional pupil response metrics across a clinically heterogeneous sample. Scores on a parent-report measure of punishment and reward sensitivity were correlated with ASD features. We also assessed whether pupil measurements could be used as a physiologic correlate of reward sensitivity and predictor of ASD diagnosis. In a logistic regression model, pupil dilation metrics, sex, and IQ, correctly classified 86.3% of participants as having an ASD diagnosis versus not. This research highlights individual differences of reward sensitivity associated with ASD features. Results support the use of pupil metrics and other patient-level variables as predictors of ASD diagnostic status.

**Keywords** Autism spectrum disorder · Individual differences · Pupillometry · Motivation · Reward · Punishment sensitivity

## Background

It has been hypothesized that core diagnostic features of autism spectrum disorder (ASD) result from disruptions to neural networks associated with reward processing and motivation (Chevallier et al. 2012; Clements et al. 2018; Dichter et al. 2012c; Kohls et al. 2012a, 2012b; Mundy et al. 2007). This hypothesis has primarily been tested using functional magnetic resonance imaging (fMRI), in which a participant's brain response to various types of rewards are assessed (see Bottini 2018; Clements et al. 2018 for review). Neuroimaging studies have characterized disruptions to reward circuity in response to social rewards (i.e. faces) (Choi et al. 2015; Damiano et al. 2015; Dichter et al. 2012a; Kohls et al. 2012b, 2018) that align with deficits in social motivation (Chevallier et al. 2012) and atypical social approach behaviors. Atypical reward-based responses in ASD have been extended to other classes of rewards including non-social stimuli (Assaf et al. 2013; Cascio et al. 2014; Clements et al. 2018; Dichter et al. 2012b; Solomon et al. 2009; Stavropoulos and Carver 2014) specifically those that are subjectively linked to symptoms of restricted and circumscribed interests (Cascio et al. 2014). The nature of the behavioral requirements to complete an fMRI experiment and the cognition required to assess participants' understanding of abstract reward concepts (i.e. money) frequently limit participation in such studies to only high functioning children. In the current study, we assessed whether quantitative features of reward sensitivity are related to core clinical features of ASD. Thus, there is an identifiable need for novel and scalable methods that reduce task demands while maximizing participant eligibility. In Experiment 1, we assessed reward sensitivity and ASD features in children with and without a diagnosis of ASD using parent-report symptom measures (Sensitivity to Punishment and Sensitivity to Reward Questionnaire for Children, SPSRQ-C; and Social Responsiveness Scale, SRS). In Experiment 2, we explored the relationship between 'resting' or baseline

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pupil diameter (PD) and functional pupil response metrics collected from a passive eye tracking procedure, reward sensitivity, and ASD traits.

Pupil dynamics, including the pupillary light reflex (PLR), have been highlighted as a peripheral marker of underlying physiologic function as well as neurological and neuromuscular disease (Fotiou et al. 2007, 2000; Jain et al. 2011). The pupil has been interpreted as a peripheral physiologic correlate of autonomic arousal and neurotransmitter release, specifically dopaminergic and noradrenergic activity (Bast et al. 2018; Giza et al. 2011; Hellmer and Nyström 2017) that influence motivational drive states. Resting PD is thought to be a sensitive measure of synergistic sympathetic and parasympathetic activity within the autonomic nervous system and related to tonic firing of neurons in the locus coeruleus (Anderson and Colombo 2009; Bast et al. 2018; Fan et al. 2009a; Laeng et al. 2012; Stern et al. 2001). Reactive changes in pupil diameter are influenced by numerous stimulus-driven, or external factors, including ambient light, motion, color and contrast (Ahern and Beatty 1979; Birren et al. 1950; Ellis 1981; Lobato-Rincón et al. 2014). However, changes in pupil response are also known to be influenced by arousal state, cognitive effort and visual attention (Binda et al. 2014, 2013; DiCriscio et al. 2018; Mather et al. 2015; Mathôt and Stigchel 2015; Mathôt et al. 2013) and is linked to activity in a network of brain regions and brainstem nuclei (Beatty and Lucero-Wagoner 2000; Corbett et al. 2006, 2008; Hou et al. 2007; Stenberg 2007). Thus, simple and reflexive changes in pupil diameter represent sensitive and reliable measures of cognitive processes as well as a proxy for underlying neurobiological function. Outside of behavioral research studies on task- or stimulus-induced changes in pupil response in the context of reward (Bijleveld et al. 2009; Mardaga and Hansenne 2009, 2011; Matthys et al. 2004), baseline or resting PD has also been highlighted as a potential physiological marker for arousal state associated with cognitive processes including performance in reward-based paradigms (Aminihajibashi et al. 2019; Gilzenrat et al. 2010; Unsworth and Robison 2015).

Previous eye tracking and pupillometry research has reported differences in measures of resting PD in ASD (Anderson et al. 2013; Anderson and Colombo 2009; Blaser et al. 2014; Martineau et al. 2011), specifically reporting larger baseline pupil size in those individuals with ASD as compared to healthy controls. These findings have been interpreted to reflect dysregulated arousal states within ASD that align with original hypotheses of autism as a disorder of atypical resting-state physiology (Hutt et al. 1964). Other research has focused specifically on the PLR, an automatic and reflexive pupil response following a brief flash of light that serves to control the amount of light falling on the retina. Within ASD, an atypical PLR has been reported (Dinalankara et al. 2017; Fan et al. 2009a) and has been used to discriminate ASD patients from healthy controls. In contrast to the PLR, recent work has focused on characterizing pupil adaptation metrics associated with ASD. Instead of a brief and transient stimulus, sustained monochromatic stimuli are presented and functional response metrics including the amplitude of the peak pupil response are extracted. DiCriscio and Troiani (2017), using a simple eye tracking paradigm, assessed characteristic patterns of pupil dilation and constriction in response to alternating dark and light stimuli across a clinically heterogeneous cohort of children (i.e. with and without ASD and with a broad range of cognitive abilities). Individual differences in functional pupil response metrics were found to be associated with a quantitative measure of ASD traits. Taken together, this research highlights pupillary metrics as potential physiologic correlates of core clinical features of ASD. However, it remains unclear how resting PD and functional pupil responses are associated with other cooccurring cognitive features, such as reward sensitivity, that may be associated with core clinical features of ASD.

The measure we employ here to assess sensitivity to reward and punishment is based on Gray's Reinforcement Sensitivity Theory (RST), which conceptualizes individual differences in variation in the brain's sensitivity to punishing and reinforcing stimuli (Gray 1976, 1982). Revised versions of Gray's original RST (Cogswell et al. 2006; Cooper et al. 2008; Gray and McNaughton 2000; McNaughton and Corr 2004; Smillie et al. 2006) have led to the current understanding of the behavioral inhibition (BIS) and behavioral approach systems (BAS) as interdependent neurobiological systems that influence human behavior in response to signals of reward and punishment.

When considering the RST framework and disruptions to reward and punishment sensitivity in ASD, one could hypothesize a link between disturbances in appetitive behaviors associated with the BAS and symptoms related to social approach. However, research in joint attention across ASD suggests a more complex relationship between BIS/BAS function, approach/avoidance behaviors and a broad range of symptoms associated with social impairment. Reduction in the *initiation* of joint attention in ASD (Dawson et al. 2005; Kasari et al. 1990; Meindl and Cannella-Malone 2011; Mundy et al. 1992, 2007; Mundy 1995) suggests that disturbances in BAS activity and atypical social approach behaviors contribute to joint attention deficits. Deficits in *responding* to joint attention bids from others have also been described (Loveland and Landry 1986; Whalen and Schreibman 2003) and align with disruptions in BIS activity and atypical avoidance behaviors that may contribute to diminished social orienting, symptoms of social withdrawal, aloof behaviors, (Chevallier et al. 2012; Gadow and Garman 2018; Mikami et al. 2019) and comorbid symptoms of anxiety in ASD (Leyfer et al. 2006). Thus, it is unclear whether social features central to ASD are driven solely by BIS

or BAS dysfunction. Furthermore, the restricted and repetitive behavior symptom domain of ASD cannot be fully accounted for within the framework of disturbed approach behaviors and instead may suggest that such symptoms emerge from atypical sensitivity to signals of punishment that call for behavioral modification (Geurts et al. 2009; Yerys et al. 2009). Thus, the heterogeneous and variable phenotypic expression of multiple ASD symptom domains may be attributed to variability in both approach and avoidance behaviors across individuals.

The RST framework has been previously related to peripheral somatic markers of autonomic response (Colder et al. 2011; De Pascalis et al. 1996; Mardaga and Hansenne 2009, 2009, 2011; Norris et al. 2007); however, has not been related to pupillary measurements. Previous work showing greater baseline PD (Anderson et al. 2013; Anderson and Colombo 2009) and meaningful variability in reflexive pupil response (DiCriscio and Troiani 2017; Fan et al. 2009a) in ASD has suggested atypical or discordant autonomic arousal may drive these differences; however, it remains unclear how pupil measurements may be associated with individual differences in the context of RST.

In Experiment 1, we aimed to assess the relationship between sensitivity to punishment and reward and ASD features in a clinically heterogeneous pediatric sample of children with and without ASD, including children with mild to moderate intellectual disability (Russell et al. 2019). Based on previous research in this area (Luman et al. 2012; Van den Berg et al. 2011), we predicted a significant linear relationship between SRS and SPSRQ-C scores. In Experiment 2, we assessed resting PD and functional pupil response metrics in the absence of specific stimuli and/or subjective content as a physiologic correlate of reward sensitivity and core clinical features of ASD. Based on previous work in ASD and other neurodevelopmental phenotypes (Anderson and Colombo 2009; DiCriscio and Troiani 2017; Nuske et al. 2014), we predicted significant relationships between pupil measurements, SPSRQ-C and SRS scores. Specifically, we predicted that resting PD and the amplitude of pupil response would scale with the presence of ASD features. We also assessed whether measures of PD and features of reward sensitivity could serve as potential predictors of ASD diagnostic status using logistic regression procedures across Experiments 1 and 2.

## Experiment 1

### Methods

#### Participants and General Procedure

Participants (N = 89; mean age = 8.48 ± 2.25; 54 males) included children 5 through 14 years of age. We used a broad recruitment strategy in order to obtain a cohort with a wide range of ASD traits. This included identifying participants based on patient referral to our neurodevelopmental pediatric clinic, as well as from health system wide advertisement. The vast majority of patients (> 85%) receiving clinical care at our neurodevelopmental pediatric clinic consent/assent to a clinic-wide research protocol, which gives permission to access the patient's health record and allows for recontact for additional research. ASD and comorbid diagnoses for this study were determined based on a DSM-5 clinical diagnosis from a diagnostic team at the authors' home institution. After receiving a referral to our neurodevelopment clinic, patients undergo assessment by a multi-disciplinary team that includes neurodevelopment pediatricians, clinical psychologists, behavioral specialists, and speech pathologists. The clinical team may sometimes utilize an assessment tool such as the ADOS or ADI-R, but diagnoses are ultimately made by the clinicians using DSM-5 criteria for ASD after a comprehensive evaluation of the patient. All patient diagnoses, including ASD and any comorbidities, are entered into the patient's digital health record and available for this study.

Of the entire sample described above, n = 43 individuals (48% of sample) had a clinical diagnosis of ASD (34 males). Results of a Pearson $\chi^2$ assessing the association between sex and ASD diagnosis indicated that sex was not independent of diagnostic status [$\chi^2(1) = 10.36$, $p = 0.001$]. It is important to note that of the n = 43 individuals with ASD that were included in the current study, n = 16 also had attention deficit hyperactive disorder (ADHD), n = 8 had a speech and/or language diagnosis, n = 5 had a diagnosis of intellectual disability and learning disability, and n = 7 had a co-occurring behavioral and/or emotional diagnosis (i.e. anxiety, oppositional defiance, mood dysregulation disorder, social anxiety, etc.). Of the n = 46 individuals without ASD (i.e. non-ASD), n = 2 had a history of a behavioral and/or emotional diagnosis, n = 1 had a previous diagnosis of ADHD, n = 2 had a diagnosis of a learning disability, and n = 1 had a diagnosis of a motor coordination disorder.

Participants were recruited as a part of a larger study that also gathered eye tracking (see Experiment 2) and additional cognitive and behavioral data. All participants assented to protocols approved by the Institutional Review Board (IRB) at the authors' home institution. On the day of research testing, all participants completed a cognitive assessment to document IQ (WASI-II: Wechsler abbreviated scale of intelligence, 2nd edition, Wechsler and Hsiao-pin 2011; (K-BIT: Kaufman Brief Intelligence Test, 2nd edition, Kaufman and Kaufman 2004). Both the K-BIT and WASI are administered as a part of clinical research protocols at the authors' home institution. While our initial research assessment procedures included administration of the WASI as a cognitive measure, we adapted our testing procedures to align with clinical assessment procedures and included the administration of the K-BIT. If an IQ test was completed during their

**Table 1** (A) Range and means (SDs) for cognitive and parent-report measures (N = 89); (B) range and means (SDs) for subset of individuals with ASD Dx (i.e. n = 43 of N = 89); and (C) range and means (SDs) for subset of individuals without an ASD Dx (i.e. n = 46 of N = 89)

| (A) N = 89 individuals with and without ASD | | | | | | (B) ASD (n = 43 of N = 89) | | | (C) Non-ASD (n = 46 of N = 89) | | | p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex (male:female): 54:35 | | | | | | Sex (male:female): 34:9 | | | Sex (male:female): 20:26 | | | ** |
| | $\bar{x}$ ($\sigma_{\bar{x}}$) | Range | | Median | IQR | $\bar{x}$ ($\sigma_{\bar{x}}$) | Range | | $\bar{x}$ ($\sigma_{\bar{x}}$) | Range | | |
| | | Min | Max | | $Q_3$–$Q_1$ | | Min | Max | | Min | Max | |
| Age | 8.48 (2.25) | 5 | 14 | 8 | 3 | 8.34 (1.74) | 6 | 13 | 8.65 (2.61) | 5 | 14 | – |
| FSIQ | 95.12 (20.29) | 40 | 131 | 96 | 27 | 87.88 (22.06) | 40 | 131 | 101.89 (15.93) | 48 | 128 | ** |
| SRS-2 (Total T-Score) | 63.72 (14.91) | 34 | 91 | 62 | 23 | 73.48 (12.42) | 44 | 91 | 54.97 (10.85) | 34 | 79 | ** |
| SRS-2 (Raw Score) | | | | | | | | | | | | |
| Total | 67.36 (40.10) | 3 | 154 | 61 | 72 | 92.49 (31.80) | 15 | 154 | 41.61(28.82) | 3 | 113 | ** |
| SCI | 55.24 (32.17) | 3 | 122 | 53 | 53 | 74.26 (26.32) | 12 | 122 | 35.48 (23.6) | 3 | 95 | ** |
| RBRI | 12.12 (8.73) | 0 | 34 | 12 | 15 | 18.23 (6.60) | 2 | 34 | 6.13 (5.96) | 0 | 24 | ** |
| Social Awareness | 9.61 (4.47) | 0 | 20 | 9 | 7 | 12.19 (3.93) | 3 | 20 | 7.02 (3.38) | 0 | 15 | ** |
| Social Cognition | 12.62 (7.81) | 0 | 28 | 12 | 13 | 17.16 (6.23) | 3 | 28 | 7.89 (6.00) | 0 | 21 | ** |
| Social Communication | 22.21 (14.11) | 1 | 55 | 21 | 23 | 30.21(11.70) | 1 | 55 | 13.80 (10.42) | 1 | 40 | ** |
| Social Motivation | 10.87 (7.33) | 0 | 29 | 11 | 12 | 14.70 (6.78) | 1 | 29 | 6.89 (5.42) | 0 | 23 | ** |
| SPSRQ-C | | | | | | | | | | | | |
| Punishment | 2.67 (0.67) | 1.53 | 4.73 | 2.80 | 1.17 | 2.94 (0.78) | 1.53 | 4.73 | 2.59 (0.52) | 1.6 | 4.07 | * |
| Reward | 3.12 (0.50) | 2.11 | 4.33 | 3.22 | 0.78 | 3.21 (0.48) | 2.11 | 4.33 | 3.07 (0.50) | 2.22 | 4.22 | – |

*SRS SCI* social communication impairment, *RBRI* SRS repetitive behaviors and restricted interests, *Soc Awr* social awareness, *Soc Cog* social cognition, *Soc Com* social communication, *Soc Mot* social motivation

– $p$-value > 0.05, NS; *$p$-value < 0.05; **$p$-value < 0.01

clinic appointment that day (n = 21), we used the clinically ascertained IQ score. Given that FSIQ was assessed using different tests, we have run analyses outlined below using standardized measures of FSIQ. Results from this analyses including standardized FSIQ are identical to those reported below.

### Parent-Report Symptom Measures and Scoring

Parents were asked to complete parent-report forms of questionnaires (e.g. reporting based on their child's behavior). Questionnaires were administered electronically via laptop computer supplied to parents at the research visit. Scores on all parent-report and cognitive measures can be found in Table 1. Additionally, group comparisons (ASD versus non-ASD) on demographic variables (i.e. age and FSIQ) as well as parent-report measures can be found in Table 1 (see last column in Table 1).

**Social Responsiveness Scale-2nd Edition (SRS-2)** The Social Responsiveness Scale-2nd Edition (SRS-2; Constantino et al. 2003; Frazier et al. 2013) is most frequently used as a parent-report measure assessing the presence and severity of symptoms of social impairment associated with ASD. In addition to a Total score reflecting overall impairments and social communication impairments (SCI), the SRS-2 generates scores across five subscales (Social Cognition, Social Motivation, Social Awareness, Social Communication, and Restricted Interests and Repetitive Behaviors).

SRS-2 Total T-scores can be used to assess symptom severity based upon a provided range: (1) ≤ 59 T-score: within normal limits/not clinically significant; (2) 60–65 T-score: mild range; (3) 66–75 T-score: moderate range; (4) ≥ 76 T-score: severe range. Of our included ASD sample, n = 34 of 43 had reported SRS T-scores above the cutoff of T ≥ 60 the mean SRS T-score for those participants with a diagnosis of ASD (n = 43) was 73.4 ± 12.42 (max = 91; min = 44). Consistent with the idea that ASD features are present in individuals that do not meet criteria for a clinical diagnosis of ASD, the mean SRS total T-score for participants without a clinical diagnosis of ASD (i.e. non-ASD; n = 46) was 54.97 ± 10.85 (max = 79; min = 34). Thus, our final sample included children with and without a clinical diagnosis of ASD, with a wide range of cognitive functioning and clinically relevant phenotypic traits. Additional information regarding SRS-2 Total T-scores and raw scores are reported in Table 1.

**Table 2** Internal consistency (Cronbach's α) of SPSRQ-C Punishment and Reward (entire sample, N = 89; ASD subsample, n = 43; non-ASD subsample, n = 46)

| SPSRQ-C | Cronbach's α | | |
|---|---|---|---|
| | Entire sample | Sample separated by Dx | |
| | N = 89 | ASD n = 43 | Non-ASD n = 46 |
| Punishment | 0.886 | 0.878 | 0.888 |
| Reward | 0.789 | 0.808 | 0.786 |

**Sensitivity to Punishment and Sensitivity to Reward Questionnaire/- for Children (SPSRQ-C)** The Sensitivity to Punishment and Sensitivity to Reward Questionnaire for Children (SPSRQ-C; Colder and O'Connor 2004) is a 33-item parent-report measure with responses provided on a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). A 2-factor model of the SPSRQ-C results in two subscales: Punishment and Reward (Colder and O'Connor 2004; Luman et al. 2012). The Punishment subscale is linked to the BIS and the Reward subscale is linked to the BAS. Group average SPSRQ-C scores can be found in Table 1. Internal consistency of the SPSRQ-C, based on Cronbach's alpha, within our sample is reported in Table 2 and is consistent with previous research (Ezpeleta et al. 2017; Van den Berg et al. 2010). Additionally, we assessed the internal consistency of the SPSRQ-C separately for our ASD and non-ASD subsamples and found these reliability measures to be consistent across both groups.

### Data Analysis

Our main analyses focused on (1) investigating the relationship between individual differences in ASD features and measures of reward sensitivity and (2) identifying whether measures of reward sensitivity significantly predicted the presence of an ASD diagnosis. A partial correlation, controlling for age, FSIQ, and sex, between SRS and SPSRQ-C scores was used to assess the relationship between reward sensitivity and ASD features. SPSRQ-C scores, as well as FSIQ and sex, were entered into a binary logistic regression in order to model the relationship between demographic variables and behavioral features of reward and punishment sensitivity to predict the probability of having an ASD diagnosis (Chan 2004; Kalil et al. 2010; Osborne 2016). It is important to note that raw SRS scores were used for all primary analyses in order to provide greater variability of scores at the lower and higher end of the measure across our clinically heterogeneous sample (Bölte et al. 2008; Constantino and Gruber 2005; Duvekot et al. 2015; Moreno-De-Luca et al. 2015).

Before completing our primary analyses, we determined whether there were relationships that may impact interpretation between our demographic variables (i.e. child's age and FSIQ) and parent-report measures using Pearson, pairwise correlation with correction for multiple comparisons. Age was not found to be related to SRS scores ($p$'s > 0.21) nor SPSRQ-C scores ($p$'s > 0.88). FSIQ was found to be related to SRS Total score ($r = -0.23$, $p = 0.033$) as well as all subscale scores ($p$'s < 0.04) with the exception of the Social Awareness subscale ($r = -0.18$, $p = 0.09$, NS) and the Social Motivation subscale ($r = -0.17$, $p = 0.12$, NS). FSIQ was not found to be related to SPSRQ-C scores ($p$'s > 0.26). Complete results from these correlation analyses, which include relationships between SRS and SPSRQ-C scores, can be found in Supplement 1, Table 1 for Experiment 1.

We also assessed the distribution of parental report measures. SRS Total raw scores deviated from a normal distribution based on results of Shapiro–Wilks tests of normality ($p = 0.001$). SPSRQ-C Reward ($p = 0.207$, NS) and SPSRQ-C Punishment ($p = 0.09$) did not deviate from a normal distribution. SRS Total raw scores for the entire sample roughly demonstrated a bimodal distribution. We also assessed the distribution of SRS raw scores separately for those with and without an ASD diagnosis. SRS raw scores in those individuals with an ASD diagnosis demonstrated a moderately left skewed distribution, −0.678 (SE = 0.36), while those without an ASD diagnosis demonstrated a moderately right skewed distribution, 0.810 (SE = 0.35). Follow-up t-tests comparing SRS Total T-scores and Total raw scores between individuals with and without an ASD diagnosis indicated significantly higher SRS Total T-scores and [$t(87) = 7.587$, $p < 0.0001$] and SRS Total raw scores [$t(87) = -7.918$, $p < 0.0001$] in those individuals with an ASD diagnosis (SRS Total raw mean = 92.49 ± 31.80) than those without (SRS Total raw mean = 41.61 ± 28.82). To address concerns of normality and the distribution of SRS scores within our included sample, SRS scores were log transformed. These transformed scores were used in analyses outlined below.

Despite the fact that SPSRQ-C scores did not deviate from a normal distribution, we also evaluated the distribution of SPSRQ-C scores within our sample. SPSRQ-C Punishment scores appeared unimodal and were only mildly skewed, 0.351 (SE = 0.255). SPSRQ-C Reward scores also appeared unimodal with no indication of skewness, −0.095 (SE = 0.255). We assessed group differences in SPSRQ-C scores in individuals with an ASD diagnosis versus those without. SPSRQ-C Punishment scores were significantly higher in those individuals with an ASD diagnosis as compared to those who did not have an ASD diagnosis, $t(87) = -2.33$, $p = 0.022$. SPSRQ-C Reward scores did not differ between individuals with and without an ASD diagnosis, $t(87) = -1.31$, $p = 0.192$, NS.

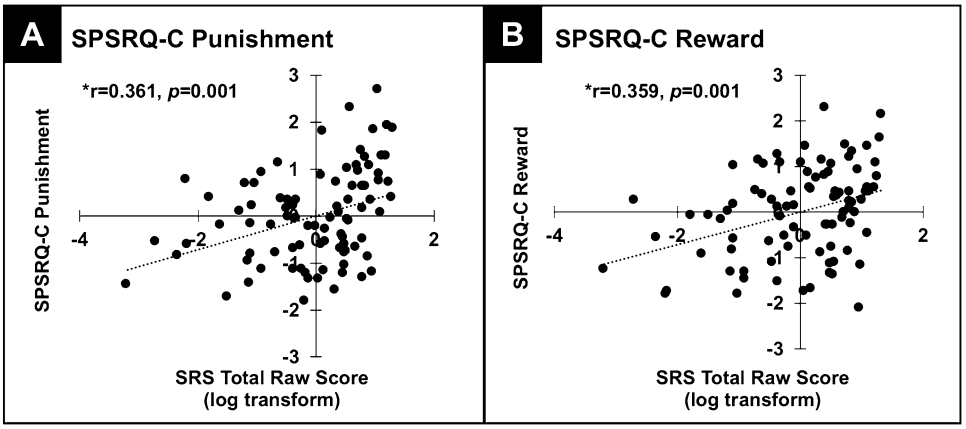


**Fig. 1** Results of a partial correlation (age, FSIQ, and sex) indicating a significant relationship between **a** SPSRQ-C Punishment and SRS Total raw score (log transform) (r = 0.361, $p = 0.001$) and **b** SPSRQ-C Reward and SRS Total raw score (log transform) (r = 0.359, $p = 0.001$)

**Table 3** Partial correlations (age, FSIQ, and sex) between log transformed SRS raw scores and SPSRQ-C Punishment and Reward subscale scores

| Control variables | SRS Total | SRS SCI | RBRI | Soc Awr | Soc Cog | Soc Com | Soc Mot | SPSRQ-C Punishment | SPSRQ-C Reward |
|---|---|---|---|---|---|---|---|---|---|
| Age, FSIQ, and sex | | | | | | | | | |
| SRS Total | 1.00 – | | | | | | | | |
| SRS SCI | **0.996**** | 1.00 – | | | | | | | |
| RBRI | **0.903**** | **0.864**** | 1.00 – | | | | | | |
| Soc Awr | **0.851**** | **0.851**** | **0.764**** | 1.00 – | | | | | |
| Soc Cog | **0.911**** | **0.905**** | **0.839**** | **0.734**** | 1.00 – | | | | |
| Soc Com | **0.954**** | **0.965**** | **0.818**** | **0.783**** | **0.862**** | 1.00 – | | | |
| Soc Mot | **0.878**** | **0.885**** | **0.774**** | **0.723**** | **0.720**** | **0.833**** | 1.00 – | | |
| SPSRQ-C Punishment | **0.361**** | **0.372**** | **0.295*** | **0.307**** | **0.271*** | **0.359**** | **0.448**** | 1.00 – | |
| SPSRQ-C Reward | **0.359**** | **0.356**** | **0.360**** | **0.416**** | **0.316**** | **0.310**** | **0.323**** | **0.301**** | 1.00 – |

Significant *p*-values are given in bold

*SRS SCI* social communication impairment, *RBRI* SRS repetitive behaviors and restricted interests, *Soc Awr* social awareness, *Soc Cog* social cognition, *Soc Com* social communication, *Soc Mot* social motivation

*Correlation is significant at the 0.05 level (two-tailed); **Correlation is significant at the 0.01 level (two-tailed)

## Results

### Relationship Between Reward Responsivity and ASD Features

We examined the relationship between SRS scores and SPSRQ-C scores via partial correlation, controlling for age, FSIQ, and sex. SRS Total raw score was found to be significantly related to SPSRQ-C Punishment (r = 0.361, $p = 0.001$) (see Fig. 1a) as well as SPSRQ-C Reward (r = 0.359, $p = 0.001$). SPSRQ-C Punishment and SPSRQ-C Reward was also found to be significantly related to all SRS subscales ($p$'s < 0.016, see Table 3).

### Binary Logistic Regression

A binary logistic regression was performed to model the effects of SPSRQ-C Punishment, SPSRQ-C Reward, FSIQ, age, and sex on predicting diagnostic status or the probability of having an ASD diagnosis. Best subsets general

**Table 4** Binary logistic regression predicting ASD Dx including FSIQ, sex, and SPSRQ-C Punishment as predictors

| Observed | Predicted | | |
|---|---|---|---|
| | Diagnosis | | % Correct |
| | Non-ASD | ASD | |
| Non-ASD | 34 | 12 | 73.9 |
| ASD | 12 | 31 | 72.1 |
| **Overall %** | | | **73.0** |
| [$\chi^2(3) = 28.497$, $p < 0.0001$] | | | |
| Nagelkerke $R^2 = 0.37$ | | | |
| Hosmer and Lemeshow Goodness-of-fit (GOF) test $\chi^2(8) = 7.139$, $p = 0.522$, NS | | | |

| | β | SE | Exp(β) | 95% Confidence interval for Exp(β) | | Wald | *p*-value |
|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | |
| Sex | **1.870** | **0.562** | **6.486** | **2.155** | **19.524** | **11.057** | **0.001**** |
| FSIQ | **−0.036** | **0.013** | **0.964** | **0.940** | **0.989** | **7.796** | **0.005**** |
| SPSRQ-C Punishment | **0.973** | **0.407** | **2.645** | **1.191** | **5.875** | **5.707** | **0.017*** |
| Constant | −0.450 | 1.714 | 0.637 | | | 0.069 | 0.793 |

[Analysis of deviance]

| | Deviance Resid | Df Resid | Deviance | *p*-value |
|---|---|---|---|---|
| FSIQ | **9.748** | **86** | **101.332** | **0.002**** |
| SPSRQ-C Punishment | **6.562** | **85** | **94.782** | **0.010**** |
| Constant | – | 88 | 123.279 | |

[Box–Tidwell transformation]

| | MLE (λ) | z | *p*-value |
|---|---|---|---|
| FSIQ | 1.040 | −0.078 | 0.938, NS |
| SPSRQ-C Punishment | 1.643 | 0.422 | 0.673, NS |

Significant results are given in bold

*$p$-value < 0.05; **$p$-value < 0.01

**Table 5** (A) Range and means (SDs) for subset with parent-report measures *and* eye tracking data that were included in analysis for Experiment 2 (N = 73); (B) range and means (SDs) for subset of individuals with ASD Dx (i.e. n = 43 of N = 73); and (C) range and means (SDs) for subset of individuals without an ASD Dx (i.e. n = 30 of N = 73)

| (A) N = 73 individuals with and without ASD | | | | | | (B) ASD (n = 43 of N = 73) | | | (C) Non-ASD (n = 30 of N = 73) | | | p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex (male:female): 45:28 | | | | | | Sex (male:female): 34:9 | | | Sex (male:female) 11:19 | | | ** |
| | $\bar{x}$ ($\sigma_{\bar{x}}$) | Range | | Median | IQR | $\bar{x}$ ($\sigma_{\bar{x}}$) | Range | | $\bar{x}$ ($\sigma_{\bar{x}}$) | Range | | |
| | | Min | Max | | $Q_3$–$Q_1$ | | Min | Max | | Min | Max | |
| Age | 8.53 (2.02) | 5 | 13 | 8 | 3 | 8.34 (1.74) | 6 | 13 | 8.83 (2.39) | 5 | 13 | – |
| IQ and parent-report measures | | | | | | | | | | | | |
| FSIQ | 95.53 (20.60) | 40 | 131 | 100 | 29 | 87.88 (22.06) | 40 | 131 | 106.5 (12.35) | 82 | 128 | ** |
| SRS-2 (Total T-Score) | 66.1 (15.38) | 37 | 91 | 70 | 26 | 73.48 (12.42) | 44 | 91 | 54.3 (9.98) | 39 | 74 | ** |
| SRS-2 (Raw Score) | | | | | | | | | | | | |
| Total | 73.31 (39.08) | 6 | 154 | 82 | 65 | 92.49 (31.80) | 15 | 154 | 41.3 (24.93) | 6 | 95 | ** |
| SCI | 59.90 (31.31) | 5 | 122 | 67 | 50 | 74.26 (26.32) | 12 | 122 | 35.50 (20.35) | 5 | 74 | ** |
| RBRI | 13.41 (8.68) | 0 | 34 | 15 | 15 | 18.23 (6.60) | 2 | 34 | 5.80 (5.65) | 0 | 24 | ** |
| Social awareness | 10.35 (4.29) | 0 | 20 | 10 | 7 | 12.19 (3.93) | 3 | 20 | 7.43 (2.90) | 0 | 12 | ** |
| Social cognition | 13.72 (7.67) | 0 | 28 | 14 | 13 | 17.16 (6.23) | 3 | 28 | 7.93 (5.58) | 0 | 20 | ** |
| Social communication | 24.08 (13.90) | 1 | 55 | 26 | 22 | 30.21 (11.70) | 1 | 55 | 13.53 (9.14) | 1 | 33 | ** |
| Social motivation | 11.75 (7.38) | 1 | 29 | 12 | 13 | 14.70 (6.78) | 1 | 29 | 6.60 (4.95) | 1 | 23 | ** |
| SPSRQ-C | | | | | | | | | | | | |
| Punishment | 2.75 (0.76) | 1.53 | 4.73 | 3.22 | 1.10 | 2.94 (0.78) | 1.53 | 4.73 | 2.42 (0.55) | 1.67 | 3.60 | * |
| Reward | 3.16 (0.48) | 2.11 | 4.33 | 2.73 | 0.64 | 3.21 (0.48) | 2.11 | 4.33 | 3.11 (0.49) | 2.28 | 4.22 | – |
| Pupil measures | | | | | | | | | | | | |
| Resting PD (mm) | 3.86 (0.67) | 2.72 | 5.83 | 3.73 | 0.91 | 4.02 (0.72) | 2.77 | 5.83 | 3.63 (0.50) | 2.72 | 4.83 | * |
| Amplitude of dilation, $A_D$ (mm) | 1.34 (0.64) | 0.16 | 2.44 | 1.42 | 1.16 | 1.01 (0.08) | 0.16 | 2.07 | 1.85 (0.41) | 0.91 | 2.43 | ** |
| Amplitude of constriction, $A_C$ (mm) | 1.36 (0.85) | 0.12 | 2.92 | 1.27 | 1.65 | 0.94 (0.11) | 0.12 | 2.76 | 1.99 (0.60) | 0.62 | 2.92 | ** |

*SRS SCI* social communication impairment, *RBRI* SRS repetitive behaviors and restricted interests, *Soc Awr* social awareness, *Soc Cog* social cognition, *Soc Com* social communication, *Soc Mot* social motivation, *Resting PD* resting pupil diameter, $A_D$amplitude of pupil dilation (in mm), $A_C$ amplitude of pupil constriction (in mm)

– $p$-value > 0.05, NS; *$p$-value < 0.05; **$p$-value < 0.01

**Table 6** Partial correlation (age, FSIQ, an sex) between log transformed SRS raw scores, SPSRQ-C Punishment and Reward subscale scores, and log transformed metrics of PD

| Control variables Age, FSIQ, and sex | SRS Total | SRS SCI | RBRI | Social Awr | Social Cog | Social Com | Social Mot | SPSRQ-C Punish | SPSRQ-C Reward | Resting PD | $A_D$ | $A_C$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SRS Total | 1.00 – | | | | | | | | | | | |
| SRS SCI | 0.993** | 1.00 – | | | | | | | | | | |
| RBRI | 0.883** | 0.828** | 1.00 – | | | | | | | | | |
| Social Awr | 0.866** | 0.872** | 0.703** | 1.00 – | | | | | | | | |
| Social Cog | 0.902** | 0.892** | 0.808** | 0.714** | 1.00 – | | | | | | | |
| Social Com | 0.933** | 0.947** | 0.754** | 0.790** | 0.794** | 1.00 – | | | | | | |
| Social Mot | 0.842** | 0.855** | 0.695** | 0.674** | 0.673** | 0.779** | 1.00 – | | | | | |
| SPSRQ-C Punish | 0.453** | 0.471** | 0.345** | 0.423** | 0.362** | 0.417** | 0.555** | 1.00 – | | | | |
| SPSRQ-C Reward | 0.285** | **0.285*** | **0.276*** | 0.325** | 0.192 | 0.227 | **0.281*** | 0.343** | 1.00 – | | | |
| Resting PD | 0.334** | 0.329** | **0.293*** | **0.242*** | **0.251*** | **0.278*** | **0.298*** | 0.353** | 0.415** | 1.00 – | | |
| $A_D$ | −0.399** | −0.381** | −0.419** | −0.340** | −0.350** | −0.315** | −0.388** | −0.403** | **−0.246*** | −0.114 | 1.00 – | |
| $A_C$ | −0.414** | −0.400** | −0.403** | −0.373** | −0.338** | −0.324** | −0.419** | −0.557** | −0.350** | −0.401** | 0.762** | 1.00 – |

Significant *p*-values are given in bold

It is important to note that none of the Experiment 1 participants with ASD (n = 43) had to be excluded from Experiment 2

*SRS SCI* social communication impairment; *RBRI* SRS repetitive behaviors and restricted interests, *Soc Awr* social awareness, *Soc Cog* social cognition, *Soc Com* social communication, *Soc Mot* social motivation, *Resting PD* resting pupil diameter, $A_D$ = amplitude of pupil dilation, $A_C$ amplitude of pupil constriction

*Correlation is significant at the 0.05 level (two-tailed); **Correlation is significant at the 0.01 level (two-tailed)

linear modeling procedures in R Studio, including SPSRQ-C Punishment, SPSRQ-C Reward, FSIQ, age, and sex, were used to evaluate predictors to be included in the best fitting regression model (Kalil et al. 2010; Osborne 2016). A model including FSIQ, sex, and SPSRQ-C Punishment was noted to minimize error variance and potential prediction error based on Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), and coefficient of determination (Adjusted $R^2$). Results from model fitting procedures are outlined in Supplement 1, Table 2 for Experiment 1.

The logistic regression model was significant [$\chi^2(3) = 28.947$, $p < 0.0001$, Nagelkerke $R^2 = 0.37$] and correctly classified 73.0% of cases as having an ASD diagnosis. FSIQ, sex, and SPSRQ-C Punishment were noted to be significant predictors of diagnostic status in our sample (see Table 4 for complete results). Results of Hosmer and Lemeshow Goodness-of-fit (GOF) test indicated no evidence of lack of fit in our reported model [$\chi^2(8) = 7.14$, p = 0.522, NS]. Finally, results from Box–Tidwell procedures to assess linearity between our continuous predictors and the logit transformation of our binary response variable based on diagnosis did not suggest the presence of nonlinear effects within our model ($p$'s > 0.67, NS). Additional information regarding our model fitting procedures and regression analyses can be found in the supplement. Specifically, in our supplement for Experiment 1, we included additional regressional analyses that evaluate potential interaction effects between our predictors (see Supplement 1, Tables 3, 4, 5 for Experiment 1).

We extended the results above and also modeled the relationship between FSIQ, sex, and SPSRQ-C Punishment in predicting the probability of an SRS T-score ≥ 60 (cut-off for mild symptoms) (Constantino et al. 2003; Frazier et al. 2013). A logistic regression model including FSIQ, sex, and SPSRQ-C Punishment was found to be significant [$\chi^2(3) = 14.886$, $p = 0.002$, Nagelkerke $R^2 = 0.21$] and correctly classified 70.8% of cases as having SRS T-score ≥ 60. Results of Hosmer and Lemeshow Goodness-of-fit (GOF) test indicated no evidence of lack of fit in the model [$\chi^2(8) = 74.206$, p = 0.838, NS]. SPSRQ-C Punishment was found to be a significant predictor of clinically significant ASD features. Results from this analysis are also included in the Supplementary Material (see Supplement 1, Table 6 for Experiment 1).

#### Experiment 1 Conclusions

Results outlined above (1) demonstrate a significant linear relationship between individual differences in reward and punishment sensitivity based on parental report questionnaires and ASD and (2) model the relationship between demographic variables (i.e. sex and FSIQ) and features of reward and punishment sensitivity as predictors of ASD diagnostic status across a clinically heterogeneous pediatric sample. While this research contributes to the growing body of literature on atypical reward sensitivity and core ASD features, the results described above are based on parent-report measures. Outside of the use of parental-report metrics, neuroimaging methods have consistently documented atypical reward response in ASD; however, neuroimaging is expensive and difficult to implement in individuals with significant behavioral and cognitive impairments. Thus, there is a need for sensitive and objective measures of reward sensitivity associated with clinically relevant ASD features. In the next experiment, we extended previous research on differences in baseline PD in ASD (Anderson and Colombo 2009; Fan et al. 2009b) and meaningful variability in functional pupil response metrics (i.e. characteristic patterns of reflexive dilation and constriction) associated with clinical ASD features (DiCriscio and Troiani 2017). We explored whether resting PD and functional pupil changes in response to alternating light and dark conditions were associated with reward and punishment sensitivity and quantitative measures of ASD features.

## Experiment 2

### Methods

#### Participants and General Procedure

In addition to parent-report (i.e. SPSRQ-C and SRS) and cognitive measures outlined in Experiment 1, a subset of participants (N = 73, mean age = 8.53 ± 2.02, n = 45 males) successfully completed an eye tracking session at the time of their in-person research appointment (i.e. n = 4 participants from our sample in Experiment 1 did not complete the eye tracking task, n = 12 non-ASD participants from Experiment 1 were excluded from the analysis for Experiment 2 due to unsuccessful completion of our eye tracking task).[1] None of the Experiment 1 participants with ASD (n = 43) had to be excluded from Experiment 2. Thus, of the larger sample included in Experiment 2, n = 43 individuals (58% of sample) had a diagnosis of ASD (34 males). Results of a Pearson $\chi^2$ assessing the association between sex and ASD diagnosis

[1] To be included in analyses, we required participants to maintain fixation on screen during the baseline period and successfully complete at least 50% of trials across dark and light conditions in our eye tracking task. After excluding 12 participants, the average percent of trials successfully completed was 76.7 15.1 (average with ASD diagnosis = 72.7 15.6; average without ASD = 82.6 +/− 12.4; t(71) = −2.84, $p = 0.002$). Unusable trials were due to failure of tracking caused by child noncompliance (closing eyes or averting gaze away from screen) or recording failure during the task.

indicated that sex was not independent of diagnostic status [$\chi^2(1) = 9.34$, $p = 0.002$]. See Table 5 for demographics and scores on parent-report measures for larger sample and ASD and non-ASD subsamples included in Experiment 2. Group comparisons (ASD versus non-ASD) on demographic variables (i.e. age and FSIQ) as well as parent-report and pupillometric measures for those individuals included in Experiment 2 can be found in Table 5 (see last column in Table 5).

While previous studies have utilized stimulus sets with specific subjective content (i.e. faces or social images) in order to characterize atypical reward sensitivity in ASD (Choi et al. 2015; Dichter et al. 2012b; Kohls et al. 2012b; Stavropoulos and Carver 2014), we utilized a previously validated, passive eye tracking task using monochromatic stimuli (black, white, gray) (see DiCriscio and Troiani 2017) in order to quantify functional pupil response metrics as physiologic correlates of punishment and reward sensitivity associated with ASD. Eye movements and pupil diameter were recorded using a Tobii X120 binocular eye-tracking system (Tobii Technology AB, Danderyd, Sweden), which monitors eye gaze as well as pupil dilation. The system is a stand-alone eye tracking unit that monitors eye gaze patterns and pupil diameter at rate of 60 Hz by using infrared light to produce reflection patterns on the corneas. The eye tracker then monitors the movements of these reflections relative to eye position. Multiple sensors assess eye movements and pupil diameter using bright and dark tracking. Tobii eye trackers adjust pupil measurements based upon measured distance between the eye and the sensor in order to accurately measure pupil size. Individual measurements regarding the position of the eyes and optical distortions between the cornea and the lens as well as other gaze artifacts (i.e. blinks and head movement) are accounted for as a part of the Tobii recording. In addition to automated correction procedures implemented within the Tobii recording system, experimenters continuously monitored eye gaze for each individual. Participants were instructed to maintain eye gaze within a gray outlined square at the center of the screen.

Participants completed a passive viewing eye tracking task during which alternating dark (black screen) and light (white screen) stimuli were displayed. Prior to the start of the eye tracking task, a gray screen was presented for 10 s from which resting PD was extracted. After this gray screen, alternating dark (i.e. black screen) and light (i.e. white screen) stimuli were displayed across a ~ 2.5-min task (24 trials total; 12 each for dark and light conditions). Each stimulus screen was presented for 5 s. Participants were instructed to remain still and to maintain gaze in the center location of the screen. Stimuli were presented on a 21.5-in. display monitor via Tobii Studio that allowed for concurrent eye gaze monitoring and pupillometry data acquisition. Testing was done in a quiet, darkened room separate from an experimenter control room via a wall with a two-way mirror. Across each testing session, one experimenter was positioned within the control room while a second experimenter was in the testing room with the participant. The experimenter in the testing room explained all instructions to the participant and ensured the participant remained focused and on task throughout the session. All participants were positioned at a distance of 55–65 cm from the display screen and completed the standard Tobii Studio, 5 point calibration procedure prior to the start of testing.

See Table 5 for descriptive statistics for average resting and functional measures of pupil response for larger sample, ASD and non-ASD subsamples included in Experiment 2. Results of between-groups (ASD versus non-ASD) comparisons for all cognitive, parent-report, and pupil response metrics are also included in Table 5. We wish to note that all analyses outlined below were repeated, including the average percent of trials successfully completed as a covariate, and yielded similar results.

### Eye Tracking–Resting PD and Pupil Response Metrics

Data was exported from Tobii Studio and analysis proceeded using MATLAB, R Studio (https://www.r-project.org/), and SPSS. In the event of missing data from one pupil, missing values were replaced with the recorded value for the other eye. In the event of missing values for both eyes, a linear interpolation was used. Pupil data was averaged and smoothed using a low pass (15 Hz) filter. Average resting PD was extracted from the 10 s gray screen presented at the start of the task.

Differences in sustained pupil response across dark and light conditions (i.e. the *amplitude* of dilation: $A_D$ or constriction: $A_C$) were measured as changes in pupil diameter relative to the average baseline pupil diameter (resting PD) measured at the start of the task. Measures of reflexive changes in pupil response transitioning from one condition to the other were then averaged across each condition. DiCriscio and Troiani (2017) extracted amplitude metrics *as well as* latency to reach maximum dilation and constriction; however, results indicated amplitude metrics to be a significant predictor of ASD features as compared to latency metrics. Thus, we focused analysis on pupil amplitude measures in the current study.

### Data Analysis

We next focused on (1) investigating the relationship between individual differences in resting PD, functional pupil response metrics ($A_C$, $A_D$), ASD features and measures of reward sensitivity, and (2) identifying whether resting and/or functional pupil metrics significantly predicted the presence of an ASD diagnosis. Pupil metrics, as well

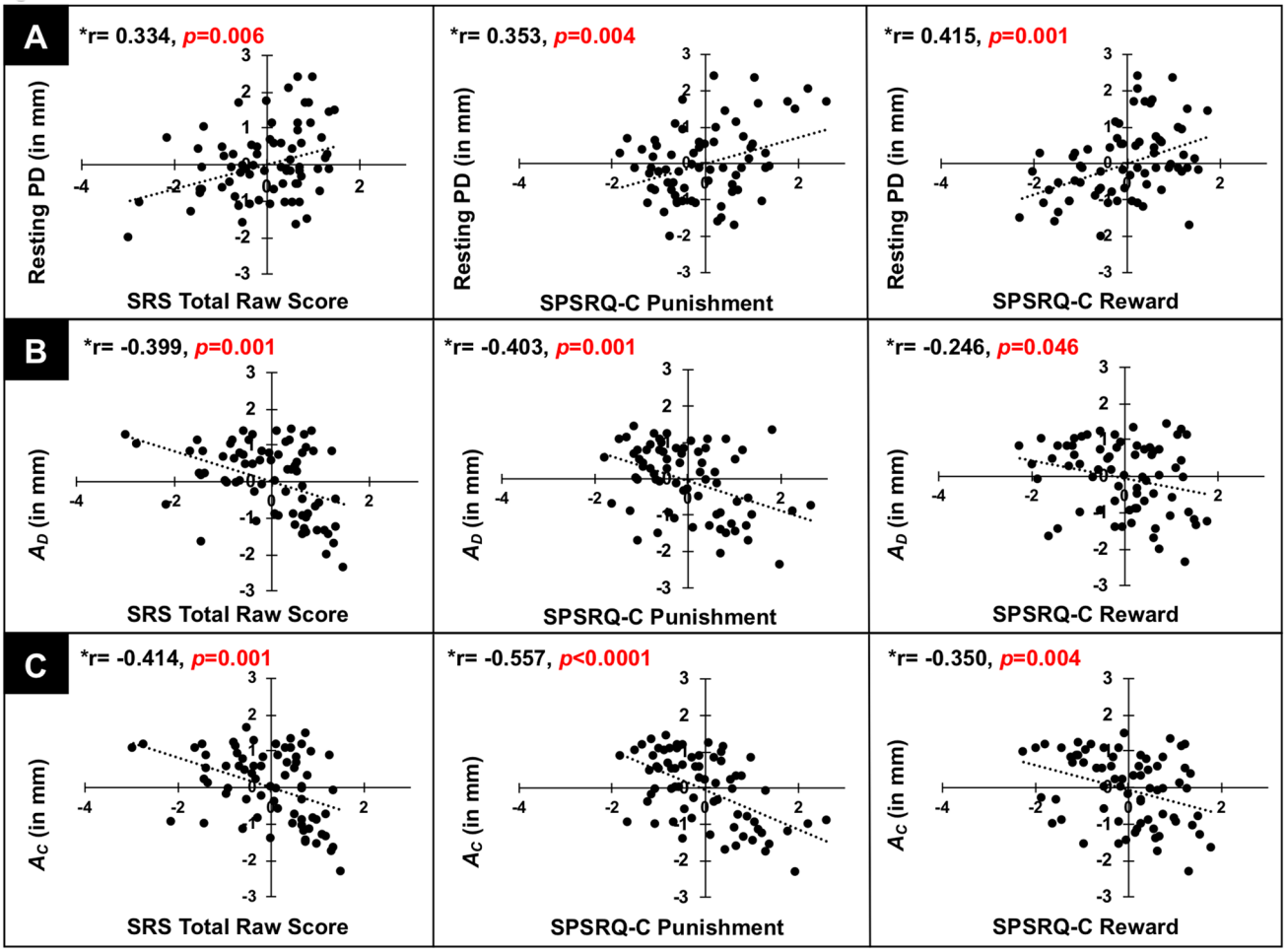


**Fig. 2** Results of a partial correlation (age, FSIQ, and sex) indicating a significant relationship between **a** resting PD (Ø), SPSRQ-C Punishment, SPSRQ-C Reward, and SRS Total raw score (log transform), **b** amplitude of dilation during dark adaptation ($A_D$) SPSRQ-C Punishment, SPSRQ-C Reward, and SRS Total raw score (log transform), and **c** amplitude of constriction during light adaptation ($A_C$) SPSRQ-C Punishment, SPSRQ-C Reward, and SRS Total raw score (log transform)

as FSIQ, age, and sex, were entered into a binary logistic regression to identify whether these objective metrics significantly predicted the presence of an ASD diagnosis. Please note that all pupil metrics (resting PD, $A_C$, and $A_D$) deviated from a normal distribution based on results of Shapiro–Wilks tests of normality ($p$'s $< 0.005$). Pupil metrics were log transformed and transformed variables were used across all analyses reported below.

## Results

### Relationship Between Resting PD, $A_C$, $A_D$, Reward Responsivity and SRS Scores in Children

Partial correlations (controlling for age, sex, and FSIQ) were used to assess the relationships between SRS, SPSRQ-C scores, and resting and functional pupil response metrics. Resting PD was found to be significantly correlated with SRS Total raw score ($r = 0.334$, $p = 0.006$), SPSRQ-C Punishment ($r = 0.353$, $p = 0.004$), and SPSRQ-C Reward ($r = 0.415$, $p = 0.001$) (see Fig. 2a). $A_D$ was found to be related to SRS Total raw score ($r = -0.399$, $p = 0.001$), SPSRQ-C Punishment ($r = -0.403$, $p = 0.001$), as well as SPSRQ-C Reward ($r = -0.246$, $p = 0.046$) (see Fig. 2b). Similarly, $A_C$ was also found to be significantly related to SRS Total raw score ($r = -0.414$, $p = 0.001$), SPSRQ-C Punishment ($r = -0.557$, $p < 0.0001$), and SPSRQ-C Reward ($r = -0.350$, $p = 0.004$) (see Fig. 2c). Complete results from this correlation analyses, including SRS subscale scores, are reported in Table 6.

These results align with the correlations reported in Experiment 1 and suggest a novel relationship between resting PD, functional pupil response metrics, quantitative measures of reward sensitivity, and ASD features. Complete results from a Pearson, pairwise correlation with correction

**Table 7** Binary logistic regression predicting ASD Dx including FSIQ, sex, age, resting PD, and $A_D$ as predictors

| | Predicted | | |
|---|---|---|---|
| | Diagnosis | | % Correct |
| | Non-ASD | ASD | |
| Observed | | | |
| Non-ASD | 24 | 5 | 82.8 |
| ASD | 5 | 39 | 88.6 |
| Overall % | | | **86.3** |
| [$\chi^2(4) = 51.849$, $p < 0.0001$] | | | |
| Nagelkerke $R^2 = 0.69$ | | | |
| Hosmer and Lemeshow Goodness-of-fit (GOF) test $\chi^2(8) = 3.034$, $p = 0.932$, NS | | | |

| | β | SE | Exp(β) | 95% Confidence interval for Exp(β) | | Wald | *p*-value |
|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | |
| FSIQ | **1.673** | **0.786** | **0.948** | **0.903** | **0.995** | **4.628** | **0.033*** |
| Resting PD | 2.555 | 2.526 | 12.878 | 0.091 | 1819.612 | 1.023 | 0.312 |
| Amplitude of dilation ($A_D$) | **−6.789** | **2.059** | **0.001** | **0.000** | **0.064** | **10.872** | **0.001**** |
| Constant | 5.601 | 5.038 | 270.827 | | | 1.236 | |

[Analysis of deviance]

| | Deviance Resid | Df Resid | Deviance | *p*-value |
|---|---|---|---|---|
| Sex | **11.152** | **71** | **98.095** | **0.0008**** |
| FSIQ | **15.337** | **70** | **86.943** | **< 0.0001**** |
| Resting PD | **5.669** | **69** | **71.607** | **0.0172*** |
| Amplitude of dilation ($A_D$) | **19.691** | **68** | **65.938** | **< 0.0001**** |
| Constant | | 72 | 46.247 | |

[Box–Tidwell transformation]

| | MLE (λ) | z | *p*-value |
|---|---|---|---|
| FSIQ | 0.934 | 0.158 | 0.875, NS |
| Resting PD | 1.686 | 0.263 | 0.793, NS |
| Amplitude of dilation ($A_D$) | 1.109 | −0.442 | 0.658, NS |

Significant results are given in bold

*$p$-value < 0.05; **$p$-value < 0.01

for multiple comparisons, including SRS subscale scores, SPSRQ-C scores, pupil metrics, FSIQ, and age are reported in correlation tables provided as Supplementary Material for the larger sample (N = 73) (see Supplement 2, Table 1 for Experiment 2) as well as our ASD subsample (e.g. n = 43 of 73) (see Supplement 2, Table 2 for Experiment 2).

### Binary Logistic Regression

Given the results reported above, we explored whether measures of resting PD and functional pupil response metrics could be substituted into logistic regression analyses and function as physiological correlates of SPSRQ-C scores and significant predictors of ASD diagnostic status. A binary logistic regression was performed to assess the effects of resting PD, $A_D$, $A_C$, FSIQ, age and sex on predicting the presence of an ASD diagnosis. Best subsets general linear modeling procedures in R Studio, including Resting PD, Amplitude of pupil dilation ($A_D$), Amplitude of pupil constriction ($A_C$), FSIQ, age, and sex, were used to evaluate possible predictors to be included in the best fitting regression model (Kalil et al. 2010; Osborne 2016). A model including FSIQ, sex, Resting PD and $A_D$ was noted to minimize error variance and potential prediction error based on Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), coefficient of determination (Adjusted $R^2$). Results from model fitting procedures are outlined in Supplement 2, Table 3 for Experiment 2.

The logistic regression model was significant [$\chi^2(4) = 51.85$, $p < 0.0001$, Nagelkerke $R^2 = 0.69$] and correctly classified 86.3% of cases as having an ASD diagnosis (see Table 7). A model including resting and functional metrics of pupil response indicated that measures of pupil dilation during dark adaptation, as compared to resting PD and pupil response during light adaptation, are a significant predictor of diagnosis. Results of Hosmer and Lemeshow Goodness-of-fit (GOF) test indicated no evidence of lack of fit in our reported model [$\chi^2(8) = 3.03$, $p = 0.932$, NS]. Finally, results from Box–Tidwell procedures to assess linearity between our continuous predictors and the logit transformation of our binary response variable based on diagnosis did not suggest the presence of nonlinear effects within our model ($p$'s > 0.66, NS). Additional information regarding our model fitting procedures and regression analyses for Experiment 2 can be found in the supplement. Specifically, in our supplement for Experiment 2, we included additional regressional analyses that evaluate potential interaction effects between FSIQ and pupil metrics (see Supplement 2, Table 5 for Experiment 2).

As in Experiment 1, we also modeled the relationship between FSIQ, sex, and $A_D$ in predicting the probability of an SRS T-score ≥ 60 (cutoff for mild symptoms) (Constantino et al. 2003; Frazier et al. 2013). A logistic regression model including FSIQ, sex, and $A_D$ was found to be significant [$\chi^2(3) = 24.238$, $p < 0.0001$, Nagelkerke $R^2 = 0.38$] and correctly classified 76.7% of cases as having SRS T-scores ≥ 60. Results of Hosmer and Lemeshow Goodness-of-fit (GOF) test indicated no evidence of lack of fit in the model [$\chi^2(8) = 9.79$, $p = 0.280$, NS]. $A_D$ was found to be a significant predictor of clinically significant ASD features as defined by the SRS. Results from this analysis are also included in the Supplementary Material (see Supplement 2, Table 6 for Experiment 2).

## Discussion

The current research aimed to characterize the relationship between measures of reward and punishment sensitivity, eye tracking metrics including resting PD and functional pupil response, and quantitative measures of ASD features. Specifically, we aimed to explore whether PD could function as a peripheral objective measure of reward sensitivity that differentiates individuals with and without a diagnosis of ASD. We report significant relationships across SPSRQ-C and SRS scores as well as pupil measurements in a heterogeneous sample of children with and without ASD, demonstrating that individual differences in measures of punishment and reward sensitivity scale with the presence of ASD features.

We report a significant linear relationship between measures of punishment and reward sensitivity and SRS scores. Additionally, results from a binary logistic regression highlighted SPSRQ-C Punishment as a significant predictor of an ASD diagnosis. The Punishment subscale of both the SPSRQ and SPSRQ-C is theoretically linked to the BIS, reflecting behavioral inhibition, avoidance, and sensitivity to signals of punishment, non-reward, denial, and novelty (Luman et al. 2012; Vandeweghe et al. 2016). Increased sensitivity to signals of negative reinforcement would result in altered behavioral inhibition and/or negative affective or behavioral responses (i.e. withdrawal, fear or anxiety) to novel situations and social interactions (Carver and White 1994; Gray 1994). This definition aligns with core diagnostic features associated with ASD, including diminished social reciprocity, social orienting, reduced response to bids for joint attention, and observations of co-occurring anxiety, social withdrawal and aloof behavior (Chevallier et al. 2012; Constantino 2011; Mundy et al. 2007; Sherer and Schreibman 2005; South et al. 2011). Thus, behavioral features associated with behavioral inhibition and punishment sensitivity may significantly influence the development and clinical presentation of core ASD features.

Of particular interest in the current study was the linear relationship between measures of pupil adaptation (amplitude of dilation), reward and punishment sensitivity, and

ASD features. Given the significant linear relationships between SRS and SPSRQ-C scores and PD, resting PD and functional pupil metrics were then substituted into a binary logistic regression for the parental report measures. In this adapted regression model, the amplitude of pupil dilation during dark adaptation, FSIQ, and sex could be used to predict ASD diagnostic status. These results emphasize that individual differences in reward sensitivity may be tied to physiologic indicators (pupil metrics) that can be objectively measured and potentially predictive of diagnosis. Thus, eye tracking technology and passive paradigms with minimal task demands may be used to extract meaningful oculomotor metrics that may serve as useful proxies for physiologic correlates of co-occurring cognitive features such as reward sensitivity and ASD features in children with ASD.

Differences in pupil dynamics have been noted in ASD. Atypical baseline PD, prior to the onset of a stimulus, has been reported in individuals with ASD and shown to be a significant predictor of diagnostic group membership (Anderson and Colombo 2009; Lynch et al. 2018). Specifically, individuals with ASD exhibit larger resting PD as compared to peers (Anderson and Colombo 2009; Blaser et al. 2014). Other studies have demonstrated differences in pupil response metrics during cognitive and perceptual tasks (Blaser et al. 2014; Martineau et al. 2011; Nuske et al. 2016). However, a majority of this previous work focused on comparisons between ASD and matched control groups and did not explore the relationship between pupil measures and individual differences in ASD features and co-occurring traits (DiCriscio et al. 2019b, 2019a). The work presented here extends previous research (DiCriscio and Troiani 2017) assessing meaningful variability in pupil adaptation metrics associated with quantitative measures of clinically relevant ASD traits. Specifically, the current research demonstrates the utility of functional pupil response metrics and patient level variables as potential diagnostic predictors. Additionally, to our knowledge, this is the first study to characterize the link between resting and functional pupil response metrics and quantitative features of reward sensitivity in ASD.

We wish to highlight that Reward and Punishment subscales were significantly correlated across Experiments 1 and 2 which is consistent with previous research that has reported significant relationships between the subscales of the SPSRQ-C (Van den Berg et al. 2010) as well as relationship between the BIS/BAS. More modern interpretations of Gray's original RST framework hypothesizes interdependent biological subsystems (Corr 2002) that modulate responses to signals of reward and punishment. Research in the general population suggests that there is meaningful variability in the function and sensitivity of these behavioral response systems (Ezpeleta et al. 2017). Thus, there may exist a broad spectrum of BIS/BAS response profiles (i.e. low-BIS/high-BAS to high-BIS/low-BAS) rather than mutually exclusive behavioral components that can be singularly assessed. Additional research is necessary in order to determine the specific relationships between distinct features of reward and punishment sensitivity, versus a cumulative index of reinforcement sensitivity, and ASD.

It remains unclear how individual differences in arousal or reward sensitivity mediates the relationship between BIS/BAS function and the different domains of ASD features. Here, we find several significant relationships between SPSRQ-C and SRS scores. Although the SRS is thought to be primarily a measure of social symptoms, it does contain an RBRI subscale. The RBRI subscale of the SRS was correlated with both SPSRQ-C Punishment and Reward; however, the relationship between SPSRQ-C Reward and the RBRI subscale was not found to be significant in the subsample (in Experiment 2). Thus, it's unclear as to whether BIS/BAS function is related to a cumulative sum of ASD symptoms (i.e. overall symptom severity), specific symptom domains (i.e. social features or repetitive behaviors), or another complex behavioral phenotype that goes beyond traditional diagnostic categories (i.e. ASD versus non-ASD). Previous work in ASD has suggested that BIS/BAS function is primarily related to social features (Chevallier et al. 2012; Kasari et al. 1990; Mundy et al. 2007; Mundy 1995) but not necessarily the features of RBRI. However, assessments of BIS activity in the context of ADHD/ODD symptoms have been linked to non-social behaviors (Geurts et al. 2009; Luman et al. 2012; Yerys et al. 2009). Future studies should continue to dimensionally assess sensitivities to punishment and reward in order to better understand which aspect of the BIS/BAS may differentially scale with pupil metrics and the range of social and non-social impairments seen in ASD.

While the current results highlight a significant relationship between features of reward sensitivity, ASD traits, and pupil response, the functional form of the relationship between BIS/BAS activity and ASD features remains unclear. Adapted versions of the classic Yerkes–Dodson law, describing the inverted U-shape relationship between arousal and behavioral performance, have been proposed to describe the neurocognitive development of reward processing regions (Van Leijenhorst et al. 2010) and the function of reward circuitry associated with clinically significant behavioral traits in ADHD (Plichta and Scheres 2014). In the current research, our limited sample size left us underpowered to explore a multivariate, nonlinear model of arousal via PD, reward sensitivity, and ASD symptomology. Further, while we did explore potential interaction effects between our predictors (i.e. FSIQ, SPSRQ-C Punishment, and pupil metrics) across Experiments 1 and 2, we were unable to identify interaction variables as significant predictors of the probability of ASD diagnosis. Additional research in much larger samples is necessary in order to comprehensively quantify (a) the functional form of the relationship between

reward sensitivity and core symptoms of ASD and (b) how this relationship is reflected in pupil measurements.

The focus of the current study was to quantitatively assess the relationship between features of reward sensitivity, ASD traits, and resting and functional pupil response metrics across a clinically heterogeneous sample. In addition to identifying those with and without ASD, we reported various co-occurring conditions across our included sample (i.e. ASD and non-ASD). The clinical characterization of our current sample relied on documentation of pre-existing diagnoses and ASD features assessed via a clinical research measure (SRS; Constantino et al. 2003; Frazier et al. 2013). The sample characteristics, described in the methods section, are representative of the diversity of children seen at our neurodevelopment clinic. However, it is important to acknowledge the potential impact of co-occurring conditions on the interpretation of reported results. It remains unclear whether the reported results, specifically in regards to pupil response metrics associated with ASD traits, are specific to ASD or neurodevelopmental symptoms more broadly. We also wish to acknowledge that we did not case–control match ASD and non-ASD participants and it is important to note that the distribution of ASD features in our current sample, as assessed by the SRS, was roughly bimodal, with many more children with a clinical diagnosis of ASD scoring higher than those without a clinical diagnosis. There were also individuals with ASD that scored below the suggested SRS cutoff for ASD and individuals without ASD that scored within the range that suggests mild to moderate features of ASD. In order to more comprehensively characterize the sensitivity and specificity of pupil response metrics in distinguishing those with ASD as compared to healthy controls or those with mild neurodevelopmental features, it is necessary to gather pupil measurements on a larger number of children to understand the precise relationship between SRS, clinical diagnosis (including 'borderline' cases as well as those with co-occurring conditions), and the potential utility of pupil metrics and reward responsivity.

There are additional limitations in the present study that should be acknowledged and addressed as a part of future research. Our sample included a wide age range as well as a large proportion of males with ASD; however, we were underpowered to subset our groups by age as well as diagnostic features and other demographic variables. Sex differences in ASD features and punishment and reward sensitivity were not central to the current research; however, sex differences in core clinical features, comorbid symptoms and in phenotypic variability continue to be a relevant topic across research in ASD. Age related changes in the development and expression of core ASD features across males and females have also been reported (Halladay et al. 2015; Van Wijngaarden-Cremers et al. 2014). Furthermore, pupil size is linked to arousal state, which can be impacted by age and other demographic variables (Loewenfeld 1999). Our sample left us underpowered to comprehensively assess age-related effects on pupil dynamics and behavioral features of reward response associated with ASD. Thus, additional research in larger cohorts and using scalable methods similar to those proposed here is necessary to specifically assess the effects of demographic and patient-level variables, such as sex and age, on pupil dynamics and behavioral features of reward response associated with ASD. Finally, we also chose to use the SPSRQ-C, but other measures of reward sensitivity exist (Carver and White 1994; Van den Berg et al. 2010). Future work should assess whether these results are consistent across different measures of reward sensitivity.

The current research makes a substantial contribution to current knowledge regarding punishment and reward sensitivity associated with core clinical features of ASD. Our results underscore the significant contributions of behavioral features outside of the core diagnostic criteria of ASD to the development and expression of clinically relevant features. This work also emphasizes that eye tracking technology can capture peripheral measures in patients with below and above average cognitive ability (Russell et al. 2019), indicating promise for future use in clinical trials of heterogeneous populations. Quantitative approaches are necessary in order to comprehensively characterize meaningful variability across behavioral features in order to identify factors that may moderate clinical outcomes across the ASD phenotype.

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**Author Contributions** ASD and VT designed the research. ASD programmed the task and collected the data. ASD analyzed the data with guidance from VT. ASD and VT interpreted the data. ASD drafted the manuscript. ASD and VT critically revised the manuscript. All authors have read and approved the final version of the manuscript. All authors reviewed the manuscript.

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**Data Availability** Datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request and the acquisition of appropriate permissions.

## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964

Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

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