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Pupil dilation during visuospatial orienting differentiates between autism spectrum disorder and attention-deficit/hyperactivity disorder

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Background: Previous research demonstrated atypical attention in children with attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Regarding visual orienting, findings suggest a differential impairment: Atypical orienting to relatively unexpected targets in ASD, and atypical processing of alerting cues in ADHD. The locus coeruleus-norepinephrine (LC-NE) system plays an important role in exploiting alerting cues to increase attention and task performance. The present study's aim was to examine differential subcortical processes underlying visual orienting in ASD and ADHD with pupil dilation (PD) as index of LC activity. **Methods:** Pupil dilation (PD) progression metrics during visual orienting were calculated for task-evoked PD locked to cue, stimulus onset, and behavioral response. Group differences in PD and reaction time (RT) were compared between children with ASD without ADHD (ASD-) ($N = 18$), ADHD without ASD (ADHD-) ($N = 28$), both disorders (ASD + ADHD) ($N = 14$), and typically developing children (TD) ($N = 31$) using linear mixed models (LMM). To further explore the modulatory role of the LC-NE system group differences in the effect of task-evoked PD metrics on RT were examined exploratively. **Results:** ASD (+ADHD) showed slower orienting responses to relatively unexpected spatial target stimuli as compared to TD, which was accompanied by higher PD amplitudes relative to ADHD− and TD. In ADHD−, shorter cue-evoked PD latencies relative to ASD−, ASD + ADHD, and TD were found. Group differences in the effect of cue- and stimulus-evoked PD amplitudes on RT were found in ASD− relative to TD. **Conclusions:** Study findings provide new evidence for a specific role of the LC-NE system in impaired reflexive orienting responses in ASD, and atypical visual processing of alerting cues in ADHD. **Keywords:** Attention; LC-NE system; attention-deficit/hyperactivity disorder; autism spectrum disorder; pupil dilation.

Introduction

Attention, the ability to 'take possession of the mind in clear and vivid form' (James, 1890, p. 403), enables us to select and focus on internal and external stimuli, either consciously, but also when salient or unexpected stimuli perpetrate our awareness (Corbetta & Shulman, 2002). Based on behavioral ratings, attention problems are ubiquitous among children referred to child and adolescent psychiatry services, regardless of their actual diagnosis (Schmeck et al., 2001). However, behavioral ratings do not differentiate between cognitive and neural mechanisms underlying attention problems. A considerable body of research within the fields of cognitive psychology and neuroscience demonstrated the functional separation between different attentional modules (Raz & Buhle, 2006). Separate attention networks have been derived, which serve the attention functions of *alerting*, *orienting,* and *executive control* (Petersen & Posner, 2012).

Attention symptoms emerge in various psychiatric disorders due to other primary symptoms. In attention-deficit/hyperactivity disorder (ADHD), a persistent pattern of attention symptoms represents the core impairment interfering with daily functioning and/or the development (American Psychiatric Association, 2013). Attention deficits have also been postulated to underlie the emergence of Autism Spectrum Disorder (ASD; Keehn, Müller, & Townsend, 2013). ADHD and ASD are both early onset, highly heritable neurodevelopmental disorders (Faraone et al., 2005; Freitag, 2007), which frequently co-occur (Leitner, 2014), and show phenotypic and etiological overlap (Ghirardi et al., 2018; Reiersen, Constantino, Volk, & Todd, 2007; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008).

In ADHD, impairments in *vigilance*, *alerting,* and *executive control* have been postulated to underlie the clinical phenotype (Berger & Posner, 2000), and of which impairments in executive control have been most robustly demonstrated across studies (Johnson et al., 2008; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Mogg et al., 2015; but see Samyn, Roeyers, Bijtebier & Wiersema, 2017). In ASD, atypical *reorienting* or *disengagement* of attention has been postulated as specific deficit (Elsabbagh et al., 2013), and as an important mechanism underlying impaired joint attention in early development (Keehn et al., 2013). Still, some findings suggest shared impairments in the attention

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networks underlying orienting task performance (Hames et al., 2016; Kratz et al., 2011).

Experimental paradigms that differentiate the attention networks of alerting, orienting, and executive control typically integrate a cued reaction time task with a Flanker task (Fan, McCandliss, Sommer, Raz & Posner, 2002). Orienting, the ability to select information from sensory input, either sensorial or cognitively driven (Corbetta & Shulman, 2002), has two components: moving and engaging attention (*orienting*, or *the cue benefit effect*), and disengaging attention (*reorienting*) (Fan et al., 2012). In ASD, neuropsychological findings suggest that atypical disengagement of attention underlies impaired behavioral performance on gap overlap (Elsabbagh et al., 2013) and cued visuospatial orienting tasks (Keehn et al., 2013; Landry & Parker, 2013). Additionally, slower orienting responses have been observed in ASD (Keehn et al., 2010; Mutreja, Craig, & O'Boyle, 2016). In ADHD, neuropsychological findings suggest orienting and reorienting attention are intact (Huang-Pollock, & Nigg, 2003; Johnson et al., 2008; Mullane, Corkum, Klein, McLaughlin, & Lawrence, 2011). With respect to the neural mechanisms underlying (re)orienting, however, evidence is less consistent. That is, in ADHD findings of combined neuropsychological and event-related potential (ERP), paradigms consistently demonstrated atypical ERP components locked to alerting cues for upcoming targets (Cue-P3; CNV) (Kratz et al., 2011; Ortega, López, Carrasco, Anllo-Vento, & Aboitiz, 2013). In ASD, atypical reorienting has instead been associated with stimulus-locked ERP components (Sokadhze et al., 2016). Indeed, across studies with cognitive-neurophysiological paradigms, altered attentional processing in ADHD most consistently relates to alerting cues; and in ASD to the relative novelty of the stimulus following a cue (Lau-Zhu, Fritz, & McLoughlin, 2019).

The dorsal frontoparietal attention network supports orienting attention to central, expected, and exploitable stimuli whereas the ventral frontoparietal attention network facilitates the reallocation of attention to peripheral, unexpected, and explorable stimuli (Corbetta, Patel, & Shulman, 2008; Kim, 2014). Increasing alertness after an alerting cue for an upcoming target is regulated by the subcortical locus coeruleus—norepinephrine (LC-NE) system (Aston-Jones, & Cohen, 2005; Petersen, & Posner, 2012). More specifically, through NE-modulated recruitment of the ventral attention network, the LC-NE system modulates arousal-dependent sensory and cognitive processing of salient information (Vazey, Moorman, & Aston-Jones, 2018), such as an alerting cue, and hence plays a critical role in regulating various attention functions during task performance (Sara, & Bouret, 2012).

Task-evoked pupil dilation (PD) has been shown to index phasic LC activity in monkeys (Joshi, Li, Kalwani, & Gold, 2016) and humans (Murphy, O'Connell, O'Sullivan, Robertson, & Balsters, 2014). Task-evoked phasic LC activity modulates NE-induced adaptive gain in synaptic signal transmission, promoting task engagement (Aston-Jones & Cohen, 2005; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010). Continuous measures of PD during task performance (PD progression) hence connect behavioral performance directly to functional indices of brainstem activity. PD during cognitive tasks has previously been implicated as biomarker in ADHD (Wainstein et al., 2017) and ASD (Blaser, Eglington, Carter, & Kaldy, 2014;), but to the best of our knowledge, no study so far compared PD as index of LC activity during attention performance between ADHD and ASD. Comparing PD progression during a cued visuospatial orienting task allows us to gain further insight into subcortical processes underlying atypical attention in ADHD and ASD. The present study compared PD progression, the cue benefit effect, and reaction time measures between children with ADHD without ASD (ADHD−), ASD without ADHD (ASD−), both disorders (ASD + ADHD), and typically developing children (TD) during a cued visuospatial orienting task. We hypothesized that children with ASD and ASD + ADHD would show atypical phasic PD responses when orienting attention to relatively unexpected spatial locations, and slower reaction times relative to TD and ADHD associated with reflexive orienting (Keehn et al., 2013). Second, we hypothesized that children with ADHD− and ASD + ADHD would show atypical cue-evoked PD responses across alerting cues relative to children with ASD- and TD. Finally, the modulatory role of the LC-NE system in atypical attention and task performance was examined exploratory by comparing group differences in the effect of task-evoked PD on reaction time.

Methods and materials

Participants and ethical considerations

Twenty-eight children with ADHD−, 18 children with ASD−, 14 children with ASD + ADHD, and 31 TD were included. The ethical approval was obtained from the Ethical Committee of the Department of Medicine at the Goethe University Frankfurt (46/16). Informed consent and assent were obtained. Participants were between 8 and 18 years old, with estimated full IQ > 70 (HAWIK-IV; Petermann, 2012; WAIS-IV; Petermann & Petermann, 2007; Table 1). TD showed below clinical cutoff values for the Child Behavior Check List (CBCL) total score (Schmeck et al., 2001; Table 1). ADHD and ASD diagnoses were established according to DSM-5 (American Psychiatric Association, 2013) by experienced clinicians. ADHD diagnosis was additionally confirmed by a semistructured diagnostic interview with a primary caregiver (K-SADS-PL, adapted to DSM-5; Kaufman et al., 1997) and ASD diagnosis with the Autism Diagnostic Observation Schedule (ADOS; Rühl, Bölte, Feineis-Matthews, & Poustka, 2004) and the Autism Diagnostic Interview-Revised (ADI-R; Bölte, Rühl, & Schmötzer, 2006). Exclusion criteria for all samples were current depressive episodes, bipolar disorder, schizophrenia, and conduct

Table 1 Sample characteristics of TD, ADHD−, ASD−, and ASD + ADHD

	TD (*N* = 31)	ADHD- (*N* = 28)	ASD- (*N* = 18)	ASD + ADHD (*N* = 14)	Test statistic, degrees of freedom, *p*-value	Group differences
Age, *M* (*SD*)	14.4 (2.7)	13.5 (2.4)	13.8 (2.6)	12.6 (3.0)	K-W χ^2 = 5.32, *df* = 3, *p* = .150	n.s.d.
Sex (*n* female/*n* male)	16/15	3/25	2/16	2/12	χ^2 = 17.34, *df* = 3, *p* < .001	TD> ADHD-, ASD-, ASD + ADHD
pIQ, *M (SD)*	111.4 (14.1)	104.1 (13.8)	107.8 (12.4)	102.5 (14.6)	*F*(3,87) = 2.013, *p* = .118	n.s.d.
vIQ, *M (SD)*	114.6 (11.8)	106.1 (17.6)	105.5 (18.7)	116.5 (17.3)	K-W χ^2 = 8.34, *df* = 3, *p* = .040	TD, ASD + ADHD> ADHD-
CBCL total *t*-score, *M (SD)*	44.8 (7.1)	64.4 (8.2)	63.1 (6.0)	70.6 (7.6)	*F*(3,87) = 56.62, *p* < .001	TD < ADHD-, ASD-, <ASD + ADHD
SRS total raw score, *M (SD)*	14.7 (11.9)	50.9 (18.3)	85.2 (22.4)	107.4 (17.8)	K-W χ^2 = 72.43, *df* = 3, *p* < .001	TD < ADHD- < ASD-, ASD + ADHD
FBB-ADHD inattention symptom severity, *M (SD)*	2.8 (2.8)	13.8 (5.7)	9.2 (5.3)	16.4 (5.2)	K-W χ^2 = 53.29, *df* = 3, *p* < .001	TD < ASD- < ASD + ADHD-, ADHD-
FBB-ADHD hyperactivity/ impulsivity symptom severity, *M (SD)*	1.3 (1.7)	13.5 (6.1)	4.9 (4.2)	13.6 (8.8)	K-W χ^2 = 59.57, *df* = 3, *p* < .001	TD < ASD- < ASD + ADHD, ADHD-

ADHD-, attention-deficit/hyperactivity disorder without comorbid ASD; ASD-, Autism Spectrum Disorder without comorbid ADHD; ASD + ADHD, comorbid ASD and ADHD; CBCL, Child Behavior Checklist; FBB-ADHD, dimensional parent-ratings of ADHD symptoms; K-W χ^2, Kruskal Wallis Chi-Square value; *M* (*SD*), Mean (Standard Deviation); n.s.d., no significant differences; pIQ, performance intelligence quotient; SCQ, Social Communication Checklist; SRS, Social Responsiveness Scale; TD, typically developing children; vIQ, verba lintelligence quotient.

disorder, assessed by the K-SADS-PL (parent interviews). Participants on stimulant medication were asked to withdraw 24 hr before the assessment.

Procedure

Participants completed a visuospatial orienting task in a quiet and dimly lit (110 lux) testing room. Heads were placed on a chin rest to prevent excessive head movements.

Measures

Behavioral ratings. ADHD symptom severity scores were obtained by the ADHD rating scale for parents (FBB-ADHD; Döpfner & Lehmkuhl, 2000). Parents rated ADHD symptom severity during the past six months on 18 items based on DSM-IV and ICD-10 criteria, scaled from 0 (nonexistent) to 3 (strongly pronounced).

ASD symptom severity scores were obtained using the Social Responsiveness Scale (SRS) (Bölte & Poustka, 2008). Parents rated ASD symptom severity during the past six months on 65 items based on DSM-IV-TR criteria and other characteristics indicative of ASD, scaled from 0 (never true) to 3 (almost always true).

Cued visuospatial orienting task. PD progression and RT were recorded during a task based on the Posner cueing paradigm (Posner, 1980) (Figure 1). Participants were instructed to press a button as soon as they detected a tadpole (target), but refrain from responding when a fish (distractor) was detected. Following a 500 ms fixation phase to a central cross surrounded by a circle of puddles, either an arrow (specific cue) or circle (nonspecific cue) was presented for 1000 ms (size of. 3 × 4°), followed by the distractor or target randomly appearing in any of the eight surrounding puddles (size of 2 × 3°; eccentricity of 6°), with presentation times of either 100 or 300 ms. The arrow indicated the puddle in which either the distractor or the target appeared. Cues and fixation cross had the same luminance. Each task consisted of 120 trials.

Recording and preprocessing eye-tracking data. PD progression data were recorded using a Tobii X2-30 binocular eye tracker (Tobii Technology AB, Sweden). A 5-point calibration was done. Display resolution was 1024 × 768 pixels. PD data were preprocessed and analyzed in R statistics 3.4.3 (R Core Team, 2017). First, raw PD data were controlled for fixations. PD data were only included if corresponding fixations were on screen center during baseline and cue presentations, and within stimulus display area (screen center: ±16.3°) during stimulus presentations. Second, PD data were controlled for sampling variation of the eye tracker (30 Hz ± 2 Hz). PD data were included only if corresponding sampling intervals deviated less than 1.5 *SD*s (8.3 ms) from the mean (33.3 ms), and if samples were recorded within the respective trial phase (e.g., samples 1–15 within fixation phase). Third, all PD data of implausible size (PD < 2 or >8 mm) and poor validity rating (range: 1–4) were excluded. Finally, absolute PD was calculated as the mean of both eyes. When tracking was unsuccessful for one eye, only data from the successful eye were selected. PD progression gaps smaller than 100 ms were linearly interpolated. Baseline PD was calculated as trial-specific mean during the fixation phase. Relative PD was calculated as absolute PD divided by baseline PD and applied in all analyses.

PD progression metrics. Visual inspection of the PD progression revealed three task-evoked PD responses following *cue* and *stimulus onset*, and *behavioral response*, which were used to calculate amplitude (*amp*) (1) and latency (*lat*) PD metrics (2) for each PD response (see Figure 2) following the

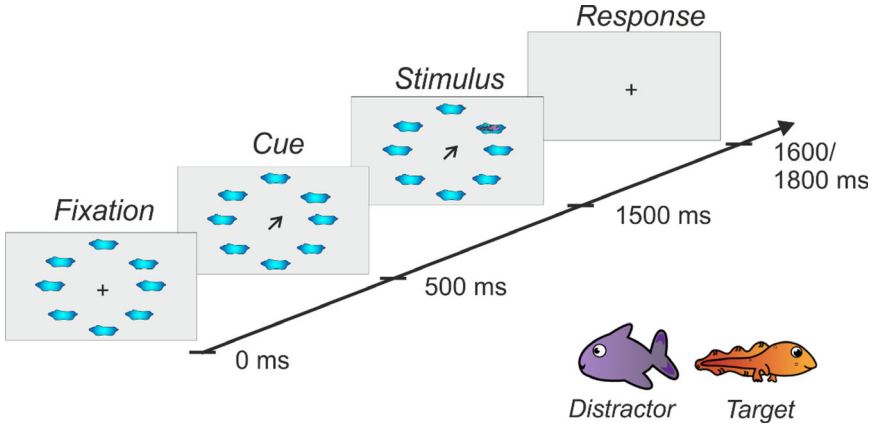

Figure 1 Task design and stimuli [Colour figure can be viewed at wileyonlinelibrary.com]

rationale of previous research (Fan, Miles, Takahashi, & Yao, 2009).

$$\mathrm{amp}(\mathrm{PD}_k) = \max(\mathrm{PD}_{k+1}; \mathrm{PD}_{k+11}) - \min(\mathrm{PD}_{k-10}; \mathrm{PD}_k) \quad (1)$$

$$\mathrm{lat}(\mathrm{PD}_k) = t(\max(\mathrm{PD}_{k+1}; \mathrm{PD}_{k+11})) - t(\min(\mathrm{PD}_{k-10}; \mathrm{PD}_k)) \quad (2)$$

Index k was the within-trial sample (range = 1–90) and was set corresponding to PD responses (cue: $k = 21$, stimulus: $k = 45$, and behavioral response: $k = 67$). Function t retrieved time since trial onset. Time intervals (k–10; $k + 10$) were chosen by visual inspection of the overall PD progression (see Figure 2). Thus, amplitude and latency metrics refer to intervals 330 ms around respective PD responses. In addition, baseline PD for each trial was calculated as mean PD of the first ten samples ($k = 1$–10). Amplitude outliers were excluded based on 95% confidence intervals. Latency metrics were calculated for complete observations only. Correlations among PD progression metrics, ASD– and ADHD symptom severity and RT are displayed in Table S1.

Statistical analysis. Group differences in PD progression metrics and the effect of PD progression metrics on z-standardized reaction time measures (RT) were analyzed by linear mixed models (LMM) with trial number as random slope varying across participants. RT was corrected for premature responses ($x < 200$ ms) (Semmelmann & Weigelt, 2017). A backward approach for model selection was implemented. Full models included dummy-coded group as predictors (ASD: yes, no; ADHD: yes, no), cue (specific cue vs. nonspecific cue), and age and sex as covariates. Stimulus type (distractor vs. target) and stimulus duration times (300 ms vs. 100 ms) were additionally included when analyzing group differences in stimulus and behavioral response PD metrics and RT. Reduced models included dummy-coded group main and interaction effects, cue, and significant interaction and covariate effects of full models. PD progression metrics were included as predictor in our exploratory analysis on group differences in the effect of PD progression metrics on RT. Likelihood ratio tests were used to compare goodness of fit of full models to reduced models and a baseline model. p-Values were false discovery rate (FDR) corrected for the number of estimated models ($k = 30$) (Benjamini & Hochberg, 1995). For the best fitting models, standardized beta coefficients with 95% confidence intervals (CI) of significant predictor and covariate effects are reported. Finally, estimated marginal means or coefficients with corresponding 95% CI were calculated to test for specific ASD- and ADHD group effects in PD metrics, RT, and the effect of PD metrics on RT.

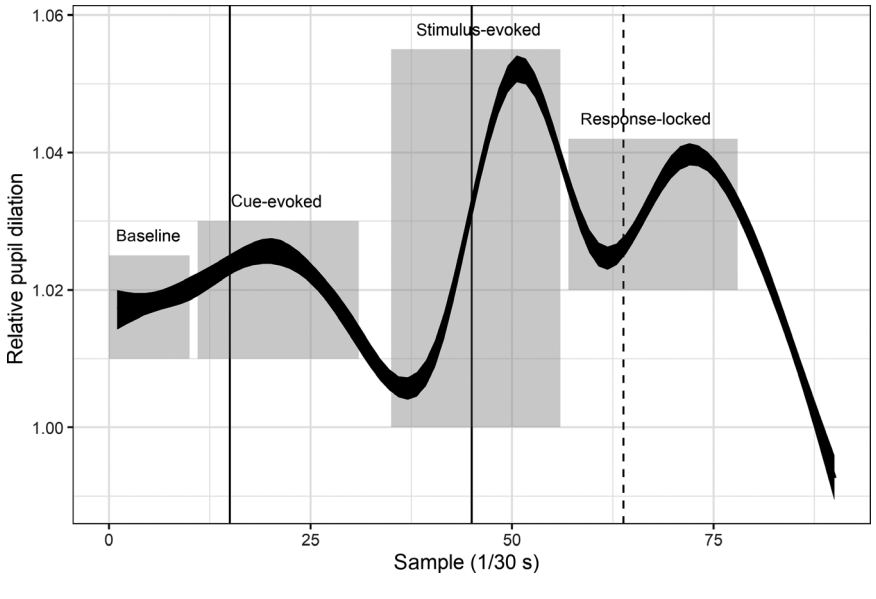

Figure 2 Pupil dilation progression across trials and groups. Black curve represents the 95% confidence interval of relative pupil dilation. Solid vertical lines represent cue (sample 15) and stimulus (sample 45) onset. The dashed vertical line represents median reaction time (565 ms, sample 64). Gray boxes indicate time intervals that were applied to calculate baseline pupil dilation and PD metrics (PD amplitude and latency)

Results

Sample characteristics are reported in Table 1. Groups did not differ in age, sex ratio, and performance IQ scores. Verbal IQ scores were lower in ADHD- compared with TD and ASD + ADHD. All clinical groups scored higher than TD on clinical symptom outcome measures.

Model fit comparison results showed better fit for reduced models compared with full and baseline models in testing group, task, and covariate effects on RT and all PD progression metrics except cue-evoked amplitudes, for which a full and reduced model did not fit the data significantly better than a baseline models (Table S2).

Task and covariates effects on PD progression metrics

Task effects on PD progression metrics are presented in Table 2. Increasing trial numbers predicted smaller baseline PD, and smaller stimulus-evoked-, and response-locked PD amplitudes. Nonspecific cues were associated with shorter cue-evoked- and longer stimulus-evoked latencies, larger stimulus-evoked PD amplitudes, and smaller response-locked PD amplitudes. Longer stimulus presentation times were associated with smaller response-locked PD amplitudes. Distractor stimuli were associated with faster response-locked PD latencies, and smaller response-locked PD amplitudes relative to target stimuli. Concerning covariates, higher age was associated with smaller baseline PD ($\beta = -0.084$, 95% CI: −0.125 – −0.042), and response-locked PD amplitudes ($\beta = -0.033$, 95% CI: −0.063 – −0.004), and longer stimulus-evoked PD latencies, ($\beta = 0.036$, 95% CI: 0.013 – 0.058). Male participants had shorter response-locked PD latencies than females ($\beta = -0.164$, 95% CI: −0.295 – −0.033).

Group differences in RT

Nonspecific cues predicted slower RT ($\beta = 0.45$, 95% CI: 0.38–0.52). Higher age and longer stimulus presentation times were associated with faster RT ($\beta_{age} = -0.06$, 95% CI: −0.10 – −0.01; $\beta_{stim.pres.} = -0.06$, 95% CI: −0.11 – −0.02). No overall ASD− ($\beta_{ASD} = 0.17$, 95% CI: −0.15–0.48) or ADHD group differences in RT were found ($\beta_{ADHD} = 0.06$, 95% CI: −0.23–0.34; $\beta_{ASD*ADHD} = 0.05$, 95% CI: −0.43–0.52). However, results showed 2- and 3-way interaction effects among clinical groups and cue ($\beta_{ADHD*cue} = 0.16$, 95% CI: 0.05–0.26; $\beta_{ASD*cue} = 0.387$, 95% CI: 0.27–0.51; $\beta_{ADHD*ASD*cue} = -0.43$, 95% CI: −0.61 – −0.25). Post hoc comparison showed nonspecific cues predicted slower RT in ASD- and ASD + ADHD, but not in ADHD− relative to TD (ASD− vs. TD: mean diff = 0.56, 95% CI: 0.23–0.88; ASD + ADHD vs. TD: mean diff = 0.39, 95% CI: 0.03–0.74; ADHD vs. TD: mean diff = 0.22, 95% CI: −0.07–0.50; Figure 3). ASD- additionally responded slower across nonspecific cue trials compared with ADHD− (mean diff = 0.34, 95% CI: 0.01–0.67). No group differences in RT in nonspecific cue trials were found between ASD− and ASD + ADHD (mean diff = 0.17, 95% CI: −0.22–0.56), and ADHD− and ASD + ADHD (mean diff = −0.17, 95% CI: −0.53–0.19). Group differences on aggregated RT measures (variability and differential) are provided in Appendix S1.

Group differences in PD progression metrics

Cue-evoked PD latencies differed between groups (Table 2). Post hoc comparisons showed shorter cue-evoked PD latencies in ADHD− relative to TD (mean diff = −0.13, 95% CI: −0.23 – −0.04), ASD− (mean diff = −0.21, 95% CI: −0.33 – −0.10), and ASD + ADHD (mean diff = −0.14, 95% CI: −0.27 – −0.02) (Figure 4). Cue-evoked PD latencies did not differ between ASD- and TD (mean diff = 0.08, 95% CI: −0.03–0.19), ASD + ADHD and TD (mean diff = 0.01, 95% CI: −0.11–0.13), and ASD− and ASD + ADHD (mean diff = 0.07, 95% CI: −0.07–0.21).

Results additionally demonstrated an interaction effect between ASD and cue on stimulus-evoked PD amplitudes, in the absence of an ASD main effect (Table 2). Stronger stimulus-evoked PD amplitude responses were observed in ASD (+ADHD) relative to TD and ADHD- following nonspecific relative to specific cues (Figure 5).

Group differences in the effect of PD progression metrics on RT

Full models estimating group differences in the effect of baseline PD, and response-locked PD amplitudes, and cue latency on RT showed better fit than reduced and baseline models. Reduced models estimating group differences in the effect of the other PD progression metrics on RT showed better fit than full and baseline models (Table S3).

Results demonstrated 3- and 4-way interactions between the effects of cue-evoked PD amplitudes, cue type, ASD, and ADHD on RT, driven by the ASD group (Table S4). Post hoc comparison showed that only in ASD- larger cue-evoked PD amplitudes across nonspecific cue trials were associated with faster RT relative to TD (coef diff = −2.58, 95% CI: −4.84 – −0.33). In contrast, larger cue-evoked PD amplitudes across specific cue trials were associated with slower RT in ASD- relative to TD (coef diff = 2.28, 95% CI: 0.15–4.40). The effect of cue-evoked PD amplitudes on RT did not differ between ASD- and ADHD- (coef $diff_{nonspec} = -1.89$, 95% CI: −4.30–0.51; coef $diff_{spec} = 2.07$, 95% CI: −0.03–4.18), and ASD- and ASD + ADHD (coef $diff_{nonspec} = -2.24$, 95% CI: −4.96–0.47; coef $diff_{spec} = 1.28$, 95% CI: −1.12–3.71).

The effect of stimulus-evoked PD amplitudes on RT differed between ASD relative to ADHD and TD for

Table 2 Group and task parameter effects on PD progression metrices

Dependent variable	ASD [1 vs. 0]		ADHD [1 vs. 0]		cue [nonspecific vs. specific]		ASD*ADHD		ASD*cue		Trial number [1–120]		Stimulus type [target vs. distractor]		Stimulus presentation time [300 vs. 100]	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Baseline PD	0.099	−0.208–0.406	0.062	−0.211–0.334	[b]	[b]	−0.218	−0.674–0.238	[b]	[b]	−0.004	−0.005–−0.003	[c]	[c]	[c]	[c]
Cue amplitude	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Cue latency	0.081	−0.030–0.191	−0.134	−0.227–−0.041	−0.129	−0.188–−0.070	0.063	−0.102–0.228	[b]	[b]	[b]	[b]	[c]	[c]	[c]	[c]
Stimulus amplitude	−0.172	−0.404–0.061	−0.092	−0.289–0.106	0.167	0.110–0.222	0.173	−0.163–0.509	0.188	0.090–0.286	−0.002	−0.003–−0.001	[b]	[b]	[b]	[b]
Stimulus latency	−0.039	−0.204–0.127	0.103	−0.048–0.255	0.127	0.042–0.213	0.002	−0.246–0.249	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
Response amplitude	−0.127	−0.346–0.093	0.007	−0.189–0.202	−0.089	−0.129–−0.049	0.093	−0.233–0.420	[b]	[b].	−0.002	−0.003–−0.001	−0.274	−0.314–−0.234	−0.052	−0.092–−0.012
Response latency	−0.010	−0.145–0.166	0.095	−0.043–0.232	0.039	−0.015–−0.094	−0.032	−0.257–0.192	[b]	[b]	[b]	[b]	−0.317	−0.371–−0.262	[b]	[b]

95% CI, 95% Confidence Intervals; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; β, standardized beta regression coefficient.
[a]Full and reduced model fit not better than baseline model.
[b]Not significant in full model, best model fit for reduced model.
[c]Not included in full model because of relevance.

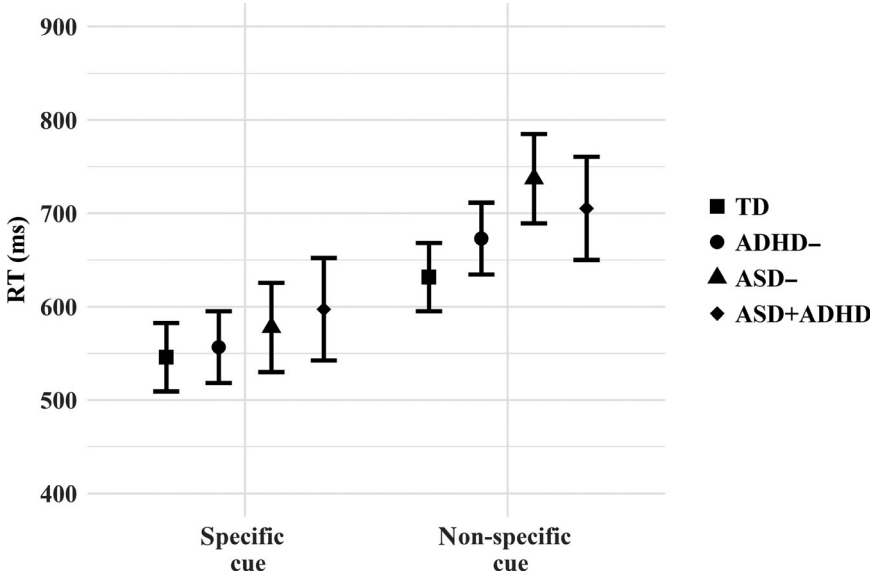

Figure 3 Slower reaction times after nonspecific cue in ASD relative to ADHD- and TD and in ASD + ADHD relative to TD. Error bars represent 95% confidence intervals. ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; RT, median reaction time; and TD, typically developing

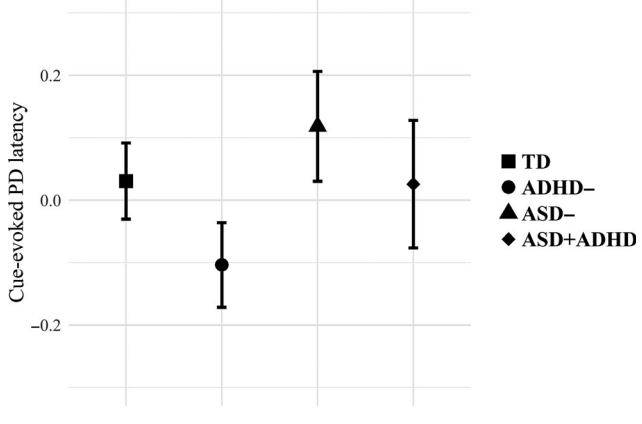

Figure 4 Shorter cue-evoked PD latencies in ADHD- relative to ASD-, ASD + ADHD, and TD. Error bars represent 95% confidence intervals. ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; PD, pupil dilation; and TD, typically developing

different cue types (Table S4). Post hoc comparison showed that larger stimulus-evoked PD amplitudes across specific cue trials predicted slower RT in ASD relative to TD and ADHD (coef diff = 1.81, 95% CI: 0.04–2.97). Across nonspecific cue trials, the effect of stimulus-evoked amplitudes on RT did not differ between ASD and TD and ADHD (coef diff = −1.35, 95% CI: −0.27–2.97). No other group differences were found (Table S4).

Discussion

Previous cognitive and neuropsychological findings suggested different attention impairments related to visual orienting in ADHD and ASD: the processing of alerting cues in ADHD and processing and orienting to relatively unexpected targets in ASD (Lau-Zhu, Fritz, & McLoughlin, 2019). The LC-NE system is implicated in exploiting alerting cues to increase alertness and detecting task-relevant stimuli (Aston-Jones, & Cohen, 2005; Petersen, & Posner, 2012), and as such in modulating the optimal attentional state during visual orienting. The goal of the present study was to elucidate whether differential subcortical processes underlie visual orienting in ASD and ADHD. Pupil dilation (PD) progression to index LC activity and reaction times (RT) to index response execution were compared between children with ASD-, ADHD-, ASD + ADHD, and TD. Study findings supported moderately slower orienting responses in ASD- and ASD + ADHD to relatively unexpected spatial locations, accompanied by slightly higher PD amplitudes, and slightly shorter cue-evoked PD latencies in ADHD without comorbid ASD.

Our findings of moderately slower RT in ASD and ASD + ADHD when orienting attention to relatively unexpected locations corroborate previous findings of impaired reflexive, rather than voluntary orienting responses in children and adults with ASD (Keehn et al., 2013). Furthermore, our results provide new evidence for slightly increased PD in ASD related to reflexive orienting. Increased PD in ASD has been proposed to reflect a persistent *hyperphasic* state, promoting an enhanced attentional focus, albeit at the expense of impeding attentional disengagement (Aston-Jones, Iba, Clayton, Rajkowski, & Cohen, 2007; Kaldy, Giserman, Carter, & Blaser, 2016). Increased PD in ASD has been previously observed in a visual search task (Blaser, Eglington, Carter, & Kaldy, 2014), during which participants searched for target stimuli amidst several competitors. In the present study, participants needed to engage and subsequently move their focus of attention either voluntary based on a specific (i.e., spatially directive)

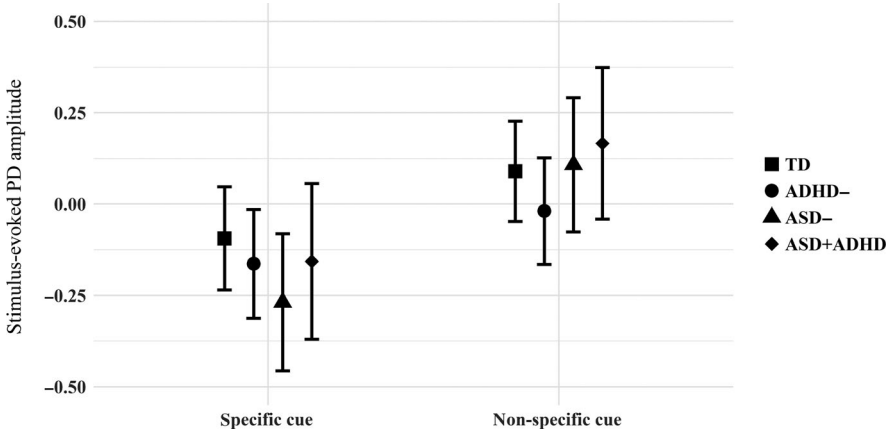

Figure 5 Stronger stimulus-evoked PD amplitude responses in ASD(+ADHD) relative to TD and ADHD after nonspecific relative to specific cues. Error bars represent 95% Confidence Intervals. ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; PD, pupil dilation; and TD, typically developing

cue, or reflexively following a spatially nondirective cue. In the present study, Increased PD in ASD was furthermore selectively evoked by targets following reflexive orienting. Apart from an enhanced focus, increased PD may index increased task difficulty or cognitive load (Rondeel, van Steenbergen, Holland, & van Knippenberg, 2015). The increased PD responses in ASD observed in the present study may thus reflect a higher effort to control the focus of attention during reflexive orienting in ASD.

In ADHD, slightly shorter cue-evoked latencies were observed relative to all groups, which can be interpreted as faster but also attenuated cue processing (Isabella et al., 2019). Support for faster processing is provided by findings suggesting children with ADHD benefit relatively more from alerting cues to improve task performance (Johnson et al., 2008; Samyn et al., 2017). In the present study, however, cue-evoked latencies were not associated with task performance, and faster cue-evoked latencies were hence unrelated to faster responses. Alternatively, shorter processing times may indicate that children with ADHD invested less attentional resources in processing alerting cues. Attenuated cue processing in ADHD has been observed previously in ERP paradigms (Kratz et al., 2011; Ortega, López, Carrasco, Anllo-Vento, & Aboitiz, 2013), and corroborates the hypothesis on poor state regulation in ADHD, that predicts children with ADHD will allocate less attentional resources when processing an alerting cue (van der Meere, 2006).

A limitation of the present study design was that the effect of an alerting cue could not be compared with a baseline condition, because trials without alerting cues were lacking. To further unravel subcortical processes underlying cue processing in ADHD, future studies should compare tonic-, task-evoked PD, and task performance between trials with and without alerting cues. Other limitations of the present study were the small sample of children with comorbid ASD and ADHD ($N = 13$), which was accounted for in our statistical analysis by including ASD and ADHD as dichotomous predictors. Males were overrepresented in all clinical groups relative to TD (Table 1). Sex was included as covariate in our main analyses, but replication of our findings using more balanced designs is warranted. Finally, it should be emphasized that ADHD-specific differences in cue-evoked PD latencies did not correlate with RT. A previous finding suggests that, in contrast with task-evoked PD amplitudes, task-evoked PD latencies and RT may reflect largely independent processes (Isabella et al., 2019). In the present study, only response-locked PD latencies correlated with RT (Table S1). Correlations between PD metrics and PD amplitudes were thus additionally lacking. Within ASD-, however, cue- and stimulus-evoked PD amplitudes correlated with RT. Taken together, the lack of correlations across groups except for cue- and stimulus-evoked PD amplitudes within ASD- may additionally indicate an increased effort to optimize task performance in children with ASD- (Rondeel, van Steenbergen, Holland, & van Knippenberg, 2015). Nevertheless, to further examine how the LC-NE system modulates attention and task performance future studies should examine other, and more sensitive measures of (disorder-specific) response execution in addition to RT (Karalunas et al., 2018).

Conclusion and future directions

In sum, using a rather novel approach to analyse PD progression, the present study provided new evidence for a specific role of the LC-NE system in impaired reflexive orienting responses in ASD (independent of ADHD), indexed by increased PD amplitudes, and atypical processing of alerting cues in ADHD, as indexed by shorter cue-evoked PD latencies.

Future studies may further compare the role of the LC-NE system in atypical attention in ASD and

ADHD and other psychiatric disorders, and address the impact of tonic LC activity on phasic discharge during task performance. Furthermore, connecting PD responses to cortical measures of attention could increase our understanding on how the LC-NE dysfunction influences cognitive performance on a neural systems level. Finally, comparing tonic and task-evoked PD across different experimental paradigms will help to unravel during which specific experimental manipulations disorder-specific LC dysregulation can be measured optimally. Unravelling the conditions during which attention problems arise within and across diagnostic boundaries is not only important to differentiate between separate cognitive and neural mechanisms underlying attention problems, but may also help to improve behavioural and pharmacological interventions in clinical practice.

Supporting information

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

Appendix S1. Group differences on aggregated RT measures.
Table S1. Pearson's correlation coefficients between mean PD progression metrices, ADHD and ASD symptom severity ratings and reaction times across clinical groups.
Table S2. Model fit comparison results of group- and task parameter effects on PD progression metrics- and reaction time.
Table S3. Model fit comparison results of group differences in the effect of PD progression metrics on reaction time.
Table S4. Group differences in the effect of PD progression metrices on reaction time.

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Key points

- Previous findings suggest different attention processes during visuospatial orienting task performance in ASD and ADHD.
- This is the first study to compare pupil dilations (PD) as an index of LC activity between ASD and ADHD during visuospatial orienting.
- PD during visuospatial orienting differentiated between ASD and ADHD, suggesting different subcortical processes in ASD and ADHD.

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