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Focus Article

Pupil dilation to emotional expressions in adolescent social anxiety disorder is related to treatment outcome

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ABSTRACT

Atypical attention to potential social threats, such as emotional faces, may be one of the core mechanisms underlying social anxiety disorder (SAD). Pupil dilation is an index of locus coeruleus-noradrenergic activity, and closely linked to attention. In the present study, pupil dilation was studied in adolescents with SAD (N = 26; 22 Female) before the onset of a 12-week cognitive behavioral treatment, and in healthy controls (N = 23). Stimuli were faces with angry or happy emotional expressions. Contrary to our hypothesis, the SAD group did not show hyper-responsiveness to angry compared to happy faces. Instead, an atypical time course of the pupil dilation response was found, resulting in an attenuated response during late time stages. Larger pupil dilation amplitude to *happy faces* before treatment was related to worse treatment response. These results contribute significantly to our understanding of the mechanisms underlying adolescent SAD.

1. Introduction

Social anxiety disorder (SAD) is associated with multiple negative outcomes in academic, professional and social areas (Beesdo, Bittner, & Pine, 2007; Stein & Stein, 2008). The core symptom of the disorder is an intense fear of negative evaluation, which leads the affected individuals to withdraw from social situations. Contemporary theoretical models of SAD hypothesize that a number of cognitive and physiological vulnerability factors underlie the disorder, and contribute to the maintenance of symptoms (Craske, 2003; Lau & Waters, 2017; Mogg & Bradley, 1998; Rapee & Spence, 2004). These vulnerability factors are believed to exist on a continuum within the population, and are not restricted to people with a formal diagnosis of SAD. In particular, SAD has been associated with atypical attention to stimuli which may signal a social threat, such as angry faces, and eyes with direct gaze (Horley, Williams, Gonsalvez, & Gordon, 2003; Kleberg, Högström, & Nord, 2017; Mogg & Bradley, 1998; Weeks, Howell, & Goldin, 2013). Recent research has shown that individuals with SAD are also often vigilant towards social cues that signal a positive social evaluation, such as emotional expressions of happiness or affiliation, which may be driven by a fear of being ridiculed or not meeting expected standards for social behavior (Weeks & Howell, 2014). SAD has a typical onset during childhood and adolescence (Stein, Lim, & Roest, 2017), meaning that it is particularly important to understand the associated vulnerability and maintaining factors and during this time period.

1.1. Attention to threat in anxiety disorders

Previous studies using either eye tracking or manual response time tasks have suggested that SAD is characterized by vigilant attention to potential threat, which leads the affected individuals to orient quickly to threat-related information (Chen & Clarke, 2017; Mogg, Millar, & Bradley, 2000). At later time stages (typically > 500 ms), SAD may be associated with *avoidance*, or a tendency to look away from the perceived threat (Mogg, Bradley, Miles, & Dixon, 2004; Teik, Chen, & Thomas, 2015). A small number of studies suggest that childhood and adolescent SAD and other anxiety disorders are also associated with biased attention to threat-related faces during early time stages, although the evidence for later stage avoidance is less consistent (Dodd, Hudson, & Williams, 2015; In-Albon, Kossowsky, & Schneider, 2010; Roy, Vasa, & Bruck, 2008; Schmidtendorf, Wiedau, & Asbrand, 2018; Schwab & Schienle, 2017; Teik et al., 2015). Eye tracking and manual

Abbreviations: CGI-S, Clinical Global Impression – Severity; SAD, social anxiety disorder; EMI, eye-mouth index; LC-NE, locus coeruleus – noradrenaline; LMM, linear mixed effects model; SPAI-C, Social Phobia and Anxiety Inventory for Children

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response-time studies have been informative about the time scale and spatial allocation of attention to threat in SAD, but are less informative about the physiological underpinnings of attention. Pupil dilation is a measure of attention with a known neurophysiological correlate. The size of the pupil is directly controlled by the balance of sympathetic and parasympathetic innervation of muscles surrounding the iris. In addition to light adaptation, the pupil dilation is closely linked to attention. This attentional component of the pupil dilation is closely linked to activity in the brainstem locus coeruleus-norephinephrine (LC-NE) system (Murphy, Robertson, Balsters, & O'Connell, 2011; Reimer, Froudarakis, & Cadwell, 2014). The neural and cognitive factors driving pupil dilation may shift during stimulus presentation. During the initial stages of processing, pupil dilation may index a bottom-up driven increase in phasic arousal, primarily driven by low-level stimulus characteristics (Marois, Labonté, Parent, & Vachon, 2018; Kleberg, del Bianco & Falck-Ytter, 2018) whereas late stage pupil dilation may be modulated by top-down regulation from higher-order cortical mechanisms (Kinner, Kuchinke, & Dierolf, 2017). For example, it was recently reported that late stage pupil dilation was related to emotion regulation strategies (Kinner et al., 2017) Despite the fact that partly dissociable mechanisms may underlie early and late stage pupil dilation, the time course of the pupil dilation response has rarely been examined in clinical populations.

Pupil dilation to emotional faces has previously been used to study atypical processing of emotional faces in conditions such as depression (Burkhouse, Owens, & Feurer, 2016), vulnerability to post-traumatic stress disorder (PTSD) (Woody, Burkhouse, & Siegle, 2017), and autism (Falck-Ytter, 2008; Nuske, Vivanti, Hudry, & Dissanayake, 2014); Galazka et al., 2019) To our knowledge, only one study has investigated pupil dilation to emotional faces in adolescent SAD. Keil and colleagues recently reported blunted pupil dilation responses to emotional faces in children with SAD aged 10–13 years (Keil, Hepach, & Vierrath, 2018). Another study reported highly typical pupil dilation in adolescents with subclinical social anxiety(Kadosh, Haller, & Schliephake, 2018), and Price, Rosen, Siegle, Ladouceur, Tang and Allen (2016) reported that children in a group with mixed anxiety disorders (mean age 10 years) had increased pupil dilation compared to healthy controls when viewing angry faces, but reduced pupil dilation to neutral faces, with differences being most evident during later phases of the trial.

1.2. Is pupil dilation to facial emotion related to treatment response in SAD?

Cognitive behavioral therapy (CBT) is a gold standard treatment for adolescent SAD (Pilling, Mayo-Wilson, & Mavranezouli, 2013). Despite the fact that CBT is effective, as many as 50% of patients still fulfill diagnostic criteria after treatment, and the risk of remission is high (Stein & Stein, 2008). It has been suggested that atypical attention to threat is a maintaining factor underlying SAD symptomatology (Mogg & Bradley, 1998; Rapee & Spence, 2004). If this is correct, suboptimal treatment outcome may be related to specific patterns of atypical attention. This theory has been tested in a small number of studies in child samples using manual response time measures (Waters, Mogg, & Bradley, 2012; Waters, Bradley, & Mogg, 2014), and in adult samples with functional magnet resonance imaging (fMRI). For example, Månsson, Frick, & Boraxbekk (2015) reported that better response to CBT treatment in adults was predicted by a weaker coupling between the amygdala and dorsal anterior cingulate cortex (dACC), suggesting that enhanced threat-related activity at baseline is a risk factor for worse treatment outcome. In childhood samples, manual response time studies have suggested that *enhanced* attention to threat at treatment baseline is linked to better outcome (Waters et al., 2012). To our knowledge, no study has examined pupil dilation as a predictor of treatment response in adolescent SAD.

1.3. Hypotheses

The aim of the present study was to examine pupil dilation to threat related (i.e. angry) and positive (i.e. happy) emotional faces in adolescents with SAD. We expected individuals with SAD to show a larger pupil dilation response (larger amplitude and slope) compared to the non-clinical control group. We expected this effect to be strongest for angry faces. Furthermore, we expected larger pupil dilation responses at baseline (pre-treatment) to relate to better response to CBT treatment. Although pupil dilation was the main focus of the study, we also analyzed the distribution of fixation time within the face, since this may affect pupil dilation.

2. Methods

2.1. Participants

Individuals with SAD were recruited from a clinical trial evaluating the efficacy of cognitive behavioral therapy (CBT) for adolescents with SAD (Nordh, Vigerland, & Öst, 2017). From an initial sample of 30 participants in the clinical trial, 27 chose to participate in the present study. Of these individuals, one was excluded because of low data quality (see *Data Reduction*). In addition, one individual who was initially recruited to the non-clinical control group fulfilled criteria for a diagnosis of SAD according to the clinical assessment, and was therefore included in the SAD group. To sum up, 26 individuals (22 female) were included in the SAD group. Of these, 23 completed the clinical assessment post treatment and 22 the assessment at six months follow up.

Two individuals were treated with selective serotonin reuptake inhibitors (SSRIs) at baseline, and continued this treatment at the post- and follow up visits. The average pupil dilation values (slope and amplitude) of these participants were within +/- 1 SD of the group means, indicating that they were no outliers in the data. These individuals were therefore retained in the analyses. Three additional participants had started medication at either the post- or follow up visit with SSRIs or psychostimulants (see Table 1). All significant relations related to treatment outcome remained when these individuals were removed from analysis.

The healthy control group was recruited from the Swedish population register from which randomly chosen adolescents between 13 and 17 years, living in the Stockholm region, were contacted by mail and invited to participate. Initially, 25 individuals agreed to participate in the healthy control group. Of these, one was excluded because of low data quality, and one because of a diagnosis of SAD (see above). After exclusions, 23 healthy individuals were included in the control group. These individuals were matched to the SAD group on gender and age (see Table 1),

Participants were assessed by a clinical psychologist using the MINI-KID (Sheehan, Sheehan, & Shytle, 2010), a semi-structured diagnostic interview for mental disorders. Exclusion criteria were initiation or dose modification of psychotropic drug within the past 6 weeks, current psychosis, eating disorder, severe depression, suicidal behavior or other current severe mental disorder including autism spectrum disorder, or current substance or alcohol abuse. Individuals in the control group were excluded if the clinical interview indicated any present mental disorder.

IQ was assessed using the General Ability Index (GAI), from the Wechsler Intelligence Scale for Children, 4th. Ed (Wechsler, 2003) or the Wechsler Adult Intelligence Scale, 4th. Ed (Wechsler, 2008), depending on the child's age. An assessment of IQ was completed during the same visit as the experimental procedures in the ASD and control groups. Individuals with SAD were invited to complete the IQ assessment during a later visit within six months of the experiment.

Table 1
Demographics, clinical information and number of included trials in the study.

Measure	SAD (*N = 27*)	Control (N = 23)	GROUP COMPARISON
Gender (female/male)	22/4	20/3	*ns*
Age	15.0 (1.2)	15.5 (1.2)	*NS*
Clinical Measures			
IQ	108.2(13.4)[a]	105.7(13.2)	*NS*
SRS	50.9 (19.8)	19.2 (10.1)	SAD > CONTROL***
SPAI-C BASELINE	34.5 (7.8)	9.5 (7.9)	SAD > CONTROL***
SPAI-C POST[b]	24.66 (11.69)	–	–
SPAI-C FU6[c]	22.15 (11.30)	–	–
CGI-S BASELINE	4.69 (0.74)	–	–
CGI-S POST[b]	3.32 (1.36)	–	–
CGI-S FU6[d]	3 (1.48)	–	–
Valid Trials / Participant			
Angry	6.6 (2.7)	7.7(1.9)	*NS*
Happy	6.6(2.6)	7.4(1.5)	*NS*
%Correctly identified expressions			
Angry	96.2% (6.4)	98.3% (4.9)	*NS*
Happy	98.9% (3.3)	98.7%(5.6)	*NS*
Psychotropic medication (baseline)			
SSRIs (fluoxetine, sertraline)	2	0	–
Psychotropic medication (post treatment)		0	–
SSRIs (fluoxetine, sertraline)	4	–	–
Psychostimulants (concerta)	1	–	–
Psychotropic medication (follow-up)			
SSRIs (fluoxetine, sertraline)	5	–	–
Psychostimulants (ritaline)	1	–	–

SSRIs = Selective serotonin reuptake inhibitors.
[a] *N = 17.*
[b] *N = 23.*
[c] *N = 21.*
[d] *N = 22.*
*** P < .001 (independent samples *t*-test). NS = non-significant.

Seventeen participants with SAD agreed to participate in the assessment. No group difference was found between individuals in the SAD and control groups on age, gender distribution or IQ (see Table 1).

Self-reported social anxiety level was measured by the Social Phobia and Anxiety Inventory for Children (SPAI-C (Beidel, Turner, Hamlin, & Morris, 2000)), a widely used scale with high internal consistency ($\alpha = .95$) shown to correlate strongly with clinician ratings of social anxiety (Cederlund & Öst, 2013). Symptom severity was also rated by a clinical psychologist using the Clinical Global Impression Scale-Severity (CGI-S) (Guy, 1976), a well validated clinical rating instrument for SAD symptoms with scores ranging from 1 to 8, with higher scores representing higher symptom severity. The CGI-S was administered at baseline by the clinical psychologist responsible for the subsequent treatment, and at the post-treatment and six months follow up visits by a clinical psychologist not involved in the treatment. The sample size is similar or slightly larger than most previous eye tracking studies of social attention in SAD (Horley et al., 2003; Keil et al., 2018; Teik et al., 2015), and had 80% power to detect medium to large effect sizes at (equivalent to Cohens $d \approx 0.7$ for group comparisons or $r \approx 0.5$ for the analyses of treatment effects). Effects of this magnitude has previously been reported in previous studies of pupil dilation in clinical conditions (Keil et al., 2018; Nuske et al., 2014), and were therefore expected.

2.2. CBT treatment protocol

Participants in the SAD group took part in a 12-week therapist guided CBT treatment as part of an ongoing treatment study, with treatment starting after the experimental assessment (Nordh et al., 2017). The treatment protocol was based on Rapee and Heimbergs CBT model (Rapee & Heimberg, 1997), and incorporated standard treatment components such as exposure, focus shifting, reducing safety behaviors, social skills training and coping skills. The treatment included both internet-based modules and live group sessions. The treatment typically started within a week after the experimental assessment. Treatment fidelity was ensured by a 1-day course on how to conduct the treatment for all therapists in the study, weekly supervision, manualized group-sessions and the highly standardized content of the online modules.

2.3. Experimental stimuli

Stimuli were images of still faces from the Karolinska Directed Emotional Faces (KDEF) data set (Lundqvist, Flyckt, & Öhman, 1998). Participants viewed 20 images of actors (50% male) of which 50% showed an angry, and 50% a happy expression (see Fig. 1). Stimuli were presented in randomized order. Our aim was to select stimuli that were easily identified, in order to avoid mental effort associated with

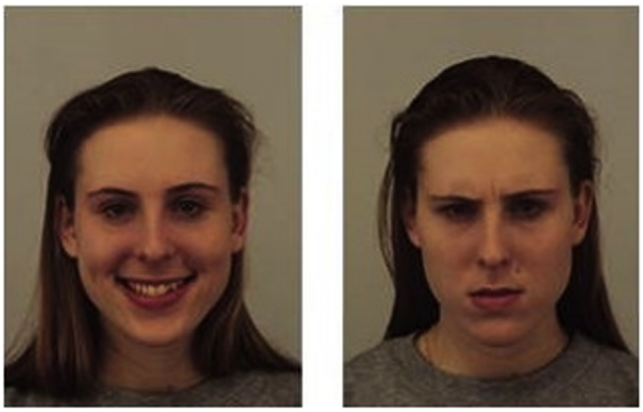

Fig. 1. Example of happy (left) and angry (right) stimuli.

emotion recognition as a confounding variable. Each actor appeared twice, once with each expression, resulting in 10 images with each emotional expression. The stimuli extended approximately 19° vertically and 14° horizontally, and were presented on a 17" monitor at a screen resolution of 1280 × 1024 at an ambient illuminance of approximately 700 lux. The same actors showed both emotions, so that differences between faces in low-level visual characteristics or idiosyncratic facial features would not cause any differences between conditions. To confirm this, we ran all pupillometry analyses with 'actor' added as a predictor in the model. As expected, this did not change any of the results. We also measured local luminance of the stimuli (in candela per square millimeter, cd/mm^2) using a Hagner Universal Photometer (B Hagner AB, Solna, Sweden) that measures local luminance within 1° of the visual field. Luminance was measured from a distance of 70 cm at a point between the eyes, and at the center of the image. Angry and happy faces did not differ in luminance at either location ($p > .35$; paired samples *t*-test).

Although our main interest was emotional faces, we initially included neutral faces as additional control stimuli. However, there was a significant difference in luminance between happy and neutral faces ($p. < .05$), which makes direct comparisons between neutral and emotional faces difficult. Neutral faces were therefore not included in the analysis, but the data are presented as a supplementary material.

2.4. Experimental procedure

Stimuli were presented during 4000 ms, and were preceded by a fixation cross on a light gray screen for 1000 ms. Directly after stimulus offset, participants were asked to indicate whether the person showed on the screen was feeling angry, happy, or emotionally neutral.

2.5. Recording and processing of pupil and gaze data data

Data were recorded on a Tobii TX300 eye tracker (Tobii INC, Danderyd, Sweden) at a sample rate of 120 hz and were analyzed in custom scripts written in MATLAB (Mathworks, INC). Pupil size of the right and left eye were averaged. Samples with gaze coordinates outside the face were rejected. We interpolated linearly over gaps smaller than 150 ms. A moving median filter with a window size of 80 ms was applied to the data. A dispersion based fixation filter (Tobii Fixation Filter) with velocity and duration threshold parameters set to 35 pixels was used to identify fixations in the gaze data.

2.6. Data reduction

Pupil dilation can be divided into an early phase, where the change in pupil size is primarily (but not exclusively) reflecting adaptation to changes in light, and a late phase, where the change in pupil size is primarily driven by attentional processes (Bast, Poustka, & Freitag, 2018; Bradley, Miccoli, Escrig, & Lang, 2008; Laeng, Sirois, & Gredebäck, 2012). The trial interval was divided into an early (1–1249 ms) and a late (1250–4000 ms) phase. These time intervals were defined based on earlier studies (Bradley et al., 2008) as well as on visual inspection of the average pupil waveform (see Fig. 2). For each participant, an estimate of baseline pupil size was calculated by taking the average pupil size during a 750 ms period preceding each valid trial. Two metrics of the pupil dilation response were extracted. The *amplitude* was defined as the average pupil size during the late phase, expressed as change in percentage from baseline pupil size. To examine the temporal change of the pupil dilation, we analyzed the *slope* of the pupil dilation response. Separate slope measures were extracted for the early and late phases. In line with previous studies (Naber, Frassle, Rutishauser, & Einhauser, 2013; Rigato, Rieger, & Romei, 2016), we operationalized the slope as the unstandardized beta coefficient of a linear regression line fitted on the pupil data. Within each trial, the pupillary data from the phase of interest was first aggregated into 30 discrete bins and the regression line was fitted on these data. Trials were rejected if the participant had valid gaze data from the face during less than 30% of the trial. We also excluded trials if the participant failed to identify the expressed emotion, to control for the possibility that potential difficulties with explicit emotion recognition could drive the hypothesized pupil dilation effects. Finally, trials were rejected it the pupil dilation amplitude exceeded 25%, since larger amplitudes are physiologically unlikely (Beatty & Lucero-Wagoner, 2002)

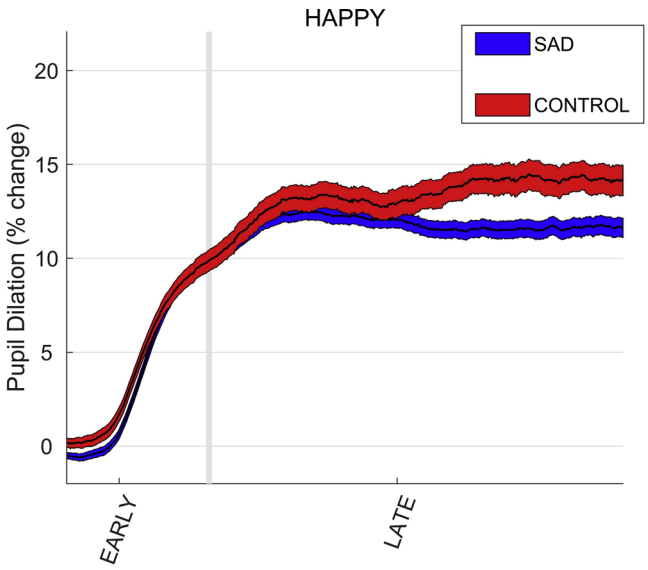

Fig. 2. Pupil dilation during early (1–1249 ms after stimulus onset) and late (1250–4000 ms after onset) phases in participants with SAD and controls. The pupil curve shows mean pupil dilation as a function of time with 95% confidence intervals.

Participants contributing less than four valid trials in either the happy or angry condition were excluded from analysis ($n = 3$). We also examined the spatial distribution of gaze using the eye-mouth index (EMI) defined as total fixation time at the eyes relative to the total fixation time at the eyes and mouth combined, to examine whether any group- or individual differences in visual scanning could explain effects on pupil dilation

2.7. Statistical analysis

All analyses were conducted in MATLAB. Data were analyzed using linear mixed effects models (LMMs) with random intercepts for participant. Main effects of group were analyzed using models with the equation $Y \sim$ Group + Emotion + (1| ID), where *Y* represents amplitude or slope, depending on the analysis. To examine the relation between treatment response and pupil dilation metrics, we fitted a series of LMMs with pupil dilation metrics (amplitude or slope) at treatment baseline as dependent variables, emotion (angry or happy) and symptom measures (CGI or SPAI-C) post treatment as predictors. Pre-treatment symptom measures were added as covariates in the analyses (e.g. $Y \sim$ Emotion + Symptoms pre-treatment + Symptoms post-treatment + (1|ID)). Separate analyses were conducted for self- and clinician ratings. Interaction terms between emotion and group (in analyses of group differences) and emotion and symptom levels post treatment (in analyses of the relation between pupil dilation and treatment response) were included in the models, but dropped when they were not statistically significant. We tested the significance of main and interaction effects by comparing models including the effect to a model without the effect of interest using likelihood ratio tests (LRT). LRT:s are preferable to ANOVAs for testing the significance of LMMs with an unbalanced number of trials per participant (Baayen, Davidson, & Bates, 2008). However, all significant effects remained when *F*-tests

were used.

Outlier observations, defined as standardized residuals outside the +/−3.25 SD range were excluded. Significance levels were set to 0.05. Interaction effects were followed up with Bonferroni corrected pairwise comparisons. Unstandardized *b*-coefficients are reported as estimates of the observed effects. No centering of the predictor variables was used.

3. Results

3.1. Preliminary analysis

As expected, participants were close to ceiling level in emotion recognition, and no group differences were found in emotion recognition performance. These data are shown in Table 1. Participants with SAD did not differ from controls in baseline pupil size [t (48) = .39; p = .702]. No group difference was found on the EMI [χ^2 = 0.92, p = 0.631, b = 3.75, SE = 4.85]. There was also no group x emotion interaction on the EMI [χ^2 = 0.11, p = 0.947, b = 0.71, SE = 3.70]. Female faces elicited larger pupil dilation amplitudes than male faces [χ^2 = 67.16, p < 0.001, b = −2.83, SE = 0. 34], but there were no interactions between group and model gender, or model gender and any of the clinical measures (all p > .20). Model gender had no effect on early or late phase slope (p > .20). Model gender was therefore not included as a factor in the analysis.

3.2. Main analysis

3.2.1. Group comparisons

The average pupil waveform is shown in Fig. 2. For descriptive statistics, see Table 2.

Amplitude. As expected, larger pupil dilation amplitude was found for angry as compared to happy faces in the SAD [χ^2 = 7.24, p = 0.007, b = 1.39, SE = 0.51] and control groups [χ^2 = 8.10, p = 0.004, b = 1.45, SE = 0.51]. No difference was found between the SAD group and controls in pupil dilation amplitude [χ^2 = 0.13, p = 0.715, b = 0.03, SE = 0.80]. No group x emotion interaction effect was found, [χ^2 = 0.15, p = 0.700, b = 0.26, SE = 0. 68].

Slope: Early Phase. A main effect of emotion was found [χ^2 = 11.46, p = 0.001, b = 0.06, SE = 0.02], driven by steeper slope for angry, as compared to happy faces. The SAD and control groups did not differ in early phase slope, [χ^2 = 0.04, p = 0.840, b = −0.01, SE = 0.04], and there was no significant interaction between group and emotion, [χ^2 = 2.14, p = 0.143, b = -0.05, SE = 0.03],

Slope: Late Phase. No main effect of emotion was found, [χ^2 = 0.53, p = 0.465, b = −0.01, SE = 0.02. The SAD and control groups differed in late phase slope [χ^2 = 4.44, p = 0.035, b = 0. 06, SE = 0.03, an effect driven by lower slopes in the SAD group. This effect was not qualified by a group x emotion interaction, [χ^2 = 3.43, p = 0.064, b = −0.06, SE = 0.03].

3.2.2. Relation to treatment response

Pupil dilation amplitude at baseline predicted higher symptom severity post treatment, as measured with clinician ratings [χ^2 = 4.62, p = 0.032, b = 0.93, SE = 0.04] as well as patient ratings [χ^2 = 4.06, p = 0.044, b = 0.09, SE = 0.04]. An interaction between emotion and clinician rated symptom severity post treatment was also found, [χ^2 = 4.54, p = 0.033, b = 0.86, SE = 0.40]. Follow-up tests revealed that pupil dilation amplitude to happy faces was linked to higher symptom severity post treatment, [χ^2 = 9.23, p = 0.002, b = 1.39, SE = 0.41], whereas no relation was found for angry faces, [χ^2 = 0.65, p = 0.419, b = 0.38, SE = 0.46]. The interaction effect between emotion and self-rated symptom severity post treatment was not significant, [χ^2 = 2.07, p = 0.150, b = 0.06, SE = 0.04]. These results are shown in Figs. 3 and 4.

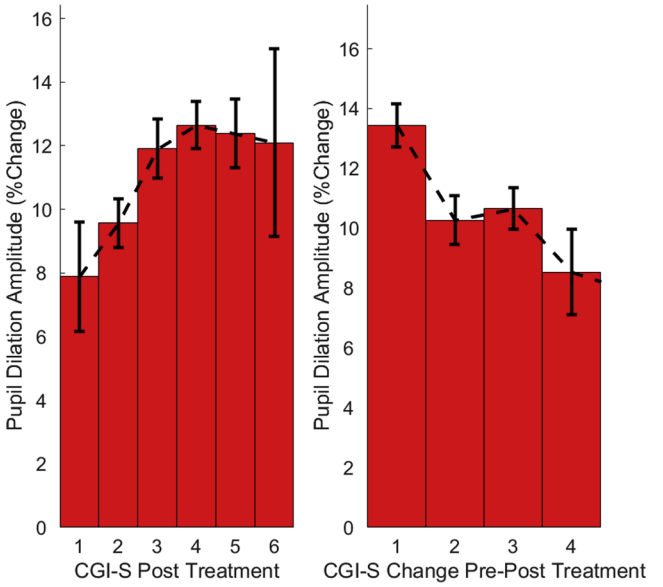

Fig. 3. Left: Average pupil dilation amplitude to happy faces before treatment and clinician-rated symptoms post treatment (CGI-S). Right: Average pupil dilation amplitude to happy faces before treatment and clinician-rated change score (pre-post treatment).

In a second step, we examined the relation between pupil dilation amplitude and symptom severity at six months follow up. This analysis showed no main effects of either clinician rated [χ^2 = 2.69, p = 0.101, b = 0.63, SE = 0.38], or patient rated symptoms [χ^2 = 2.92, p = 0.087, b = 0.10, SE = 0.06]. The interaction effects between emotion and self-rated symptom severity at six months follow up were not significant for clinician-rated [χ^2 = 2.69, p = 0.101, b = 0.63, SE = 0.38] or patient-rated symptoms [χ^2 = 3.37, p = 0.066, b = 0.09, SE = 0.05].

To examine the possibility that the study may have been underpowered to detect interaction effects between emotion and symptom severity measures, we conducted post-hoc power analyses of the observed effects using Monte Carlo based simulations (*Supplementary materials*). These analyses showed that, while the power to detect relations of the observed magnitude between pupil dilation amplitude and symptom severity was generally adequate (79.80–90.10%), the power to detect interaction effects was low at post treatment and follow-up. Therefore, in an exploratory analysis, we ran the analysis for happy and angry faces separately for the follow-up data and for self-

Table 2
Pupil dilation amplitude and slope in adolescents with SAD (N = 26) and healthy controls (N = 23). 95% confidence intervals of the means are bootstrapped with 1000 simulations.

	SAD		CONTROL		GROUP DIFFERENCE
	MEAN (SD)	95% CI	MEAN (SD)	95% CI	
AMPLITUDE	11.8 (5.3)	11.3–12.3	12.0 (5.6)	11.5–12.5	*NS*
SLOPE (EARLY PHASE)	0.38 (0.33)	0.34–0.41	0.35 (0.26)	0.32-0.38	*NS*
SLOPE (LATE PHASE)	0.01 (0.03)	−0.02–0.03	0.07 (0.03)	0.04–1.0	< .05

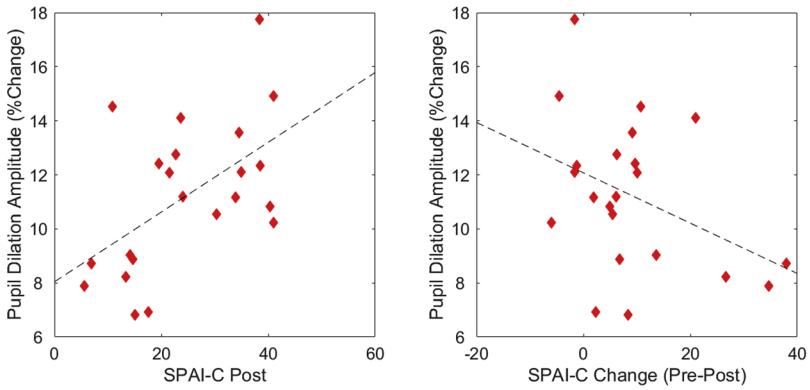

Fig. 4. *Left:* Pupil dilation amplitude to happy faces and self-rated SAD symptoms (SPAI-C). *Right:* Change score (pre-post treatment) in self-rated SAD symptoms. Markers represent individual participants.

rated symtom levels post treatment. This analysis showed that pupil dilation amplitude to happy faces before treatment was related to higher symptom severity at six months follow up using both clinician [$\chi^2 = 5.40$, p = 0.020, b = 1.01, SE = 0.41 and patient ratings [$\chi^2 = 5.36$, $p = 0.021$, b = 0.12, $SE = 0.05$], whereas pupil dilation amplitude to angry faces did not [clinician ratings: $\chi^2 = 0.57$, $p = 0.451$, $b = 0.32$, SE = 0.42; patient ratings: $\chi^2 = 1.29$, $p = 0.256$, $b = 0.06$, $SE = 0.05$]. Additional analyses showed that higher pupil dilation amplitude to happy faces before treatment baseline predicted higher self-rated symptoms post treatment [$\chi^2 = 6.36$, p = 0.012, b = 0.12, SE = 0.05], see Figure 3, whereas no relation was found for angry faces [$\chi^2 = 1.29$, p = 0.256, b = 0.06, SE = 0.05]. Early and late phase slope did not predict symptom severity post treatment or at six months follow-up (all $p > .15$; see Supplementary materials).

4. Discussion

The aim of the current study was to examine pupil dilation responses to emotional faces in adolescent social anxiety. Our results suggest that adolescent SAD is characterized by an atypical time course of the pupil dilation response to both angry and happy faces, and that pupil dilation amplitude before CBT treatment is related to subsequent treatment outcome. These results are discussed in turn.

Contrary to our hypothesis, the SAD and control groups did not differ in overall amplitude of the pupil dilation response to angry faces. Instead, we found an atypical time course of the pupil dilation response to both angry and happy faces. During the late phase, SAD individuals differed from the non-clinical controls in terms of a lower slope (i.e. an attenuated pupil response) to both angry and happy faces. This temporal pattern can give clues about implicated brain functions. At early time stages, the pupil dilation response is closely linked to phasic LC-NE activity, and is closely related to a ventral frontotemporal brain network which is activated during bottom-up driven attentional processes (Aston-Jones & Cohen, 2005; Marois et al., 2018). At later time stages of processing, pupil dilation is also influenced by top-down modulation from prefrontal cortical areas (Bast et al., 2018). For example, voluntary emotion regulation (a process that requires top-down control) has been found to influence pupil dilation response during late, but not early stages (Kinner et al., 2017). Our results therefore point to a role of atypical top-down modulation. It is possible that the observed attenuated pupil dilation during later time stages reflects cognitive avoidance strategies commonly seen in SAD (Rapee & Spence, 2004), or an attempt to downregulate emotion by means of distraction (Kinner et al., 2017). Interestingly, a recent study in a sample of young children with SAD (10–13 years) also reported attenuated pupil dilation (Keil et al., 2018). Importantly, although we replicated previous findings that the earliest phase of the pupil dilation response is modulated by the emotional valence of the observed stimuli (Bradley et al., 2008), the early phase slope did not differ between the SAD and control groups. Adolescence is a period of intense cognitive and brain development. An important question for future studies is to examine how pupil dilation and arousal more generally changes during development in individuals with SAD.

Consistent with our hypothesis, we found that increased pupil dilation amplitude before the onset of a CBT treatment program predicted a less favorable treatment outcome, as measured with both clinician and patient ratings. Contrary to our hypothesis however, this relation was driven by responses to happy, but not to angry faces. These results suggest that hyperarousal during processing of happy facial expression is a risk factor for responding less well to CBT. Recent theories have suggested that SAD is characterized by threat responses to social cues that signal *both* positive and negative evaluations (Weeks & Howell, 2014). According to the fear of positive evaluation theory of SAD (Weeks & Howell, 2014), individuals with SAD often perceive affiliative cues as threatening, since they signal the possibility of not living up to expected social standards. Our results are consistent with this theory, and suggests that atypical attention to affiliative cues (i.e. happy faces) may contribute to symptom maintenance. In contrast to the pupil dilation amplitude, the time course (slope) of the pupil dilation amplitude was not related to treatment outcome. Together, these findings suggest that pupil dilation metrics could be promising as biomarkers for adolescent SAD.

4.1. Limitations and methodological considerations

The study has a number of limitations. The sample size is small, meaning that more studies with larger samples will be needed to reach definitive conclusions. Particularly, analysis had low statistical power to detect interaction effects between emotion and subsequent symptom severity. Another limitation is that the relation between pupil dilation and treatment response is purely correlational, meaning that the direction of causality can't be established. Importantly however, we were able to rule out a number of confounding explanations for the results. The relative distribution of gaze between the eyes and mouth did not differ between groups or emotions. Stimuli were matched for local luminance as well as for low-level visual characteristics. Together, this suggests that individual differences in gaze behavior or idiosyncratic features of the stimuli are unlikely to explain the results.

4.2. Implications

Our results suggest that pupil dilation to emotional faces may be a useful indicator of atypical attention in SAD. Our results also suggest that increased arousal to affiliative cues (happy faces) is a risk factor for less favorable response to CBT treatment. Together, these findings can contribute to a better understanding of the attentional mechanisms

related to SAD, as well as to an understanding of the mechanisms underlying response to CBT treatment.

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. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr: 2015/1383-31, with amendment 2016/1183-32).

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.janxdis.2019.04.006.

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