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From Anxious Youth to Depressed Adolescents: Prospective Prediction of 2-Year Depression Symptoms via Attentional Bias Measures

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Anxious youth are at heightened risk for subsequent development of depression; however, little is known regarding which anxious youth are at the highest prospective risk. Biased attentional patterns (e.g., vigilance and avoidance of negative cues) are implicated as key mechanisms in both anxiety and depression. Aberrant attentional patterns may disrupt opportunities to effectively engage with, and learn from, threatening aspects of the environment during development and/or treatment, compounding risk over time. Sixty-seven anxious youth (ages 9–14; 36 female) completed a dot-probe task to assess baseline attentional patterns provoked by fearful–neutral face pairs. The time course of attentional patterns both during and after threat was assessed via eye-tracking and pupilometry. Self-reported depressive and anxiety symptoms were assessed 2 years after the conclusion of a larger psychotherapy treatment trial. Eye-tracking patterns indicating threat avoidance predicted greater 2-year depression scores, over and above baseline and posttreatment symptoms. Sustained, postthreat pupillary avoidance (reflecting preferential neural engagement with the neutral relative to the previously threatening location) predicted additional variance in depression scores, suggesting sustained avoidance in the wake of threat further exacerbated risk. Identical eye-tracking and pupil indices were not predictive of anxiety at 2 years. These biobehavioral markers imply that avoidant attentional processing in the context of anxiety may be a gateway to depression across a key maturational window. Excessive avoidance of threat could interfere with acquisition of adaptive emotion regulation skills during development, culminating in the broad behavioral deactivation that typifies depression. Prevention efforts explicitly targeting avoidant attentional patterns may be warranted.

General Scientific Summary
This article suggests that anxious youth who show attentional patterns characterized by avoidance of threatening information are at higher risk of depression symptoms 2 years later.

Keywords: attentional bias, anxiety, depression, adolescence

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Depression rates increase markedly during the transition to adolescence (Angold, Costello, & Worthman, 1998). Both biological and psychosocial changes characterize the transition from late childhood to early adolescence (occurring at approximately 9–13 years of age) and contribute to the postpubertal increase in depression rates (Cyranowski, Frank, Young, & Shear, 2000). Hormonal changes occurring in adolescence may sensitize the brain to the harmful effects of stress and increase vulnerability to depression

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(Angold & Costello, 2006; Crone & Dahl, 2012; Hyde, Mezulis, & Abramson, 2008), particularly for females (Green, McGinnity, Meltzer, Ford, & Goodman, 2005). Although such peripubertal changes are normative, specific individuals respond to them with cascading detrimental effects. Identifying specific youth at highest risk, and ideally, intervening before adverse developmental trajectories set in, is an unrealized health care goal with substantial public health ramifications (Weissman et al., 1999).

Pediatric anxiety is a key risk factor for subsequent development of depression, with the majority of depressed youth having a history of anxiety (Kessler, Avenevoli, & Merikangas, 2001; Pine, Cohen, Gurley, Brook, & Ma, 1998). However, only a minority of anxious youth go on to develop depression. Identifying biobehavioral markers of prospective depression risk within this high-risk population is therefore critical to prevention efforts, promoting the ability to design mechanistic interventions that target modifiable precursors of depression, and efficiently deliver them to specific patients who need them.

Altered attentional patterns could constitute one mechanistic bridge from anxiety to depression. Aberrant patterns of attention to negative stimuli are posited to play a key role in both anxiety and depression across the life span (de Raedt & Koster, 2010; MacLeod, Mathews, & Tata, 1986; Gerber, Peterson, Pine, Guyer, & Leibenluft, 2008). Although preferential attention *toward* negative stimuli is thought to promote negative affective states and maladaptive cognitions, excessive *avoidance* of threat represents the opposite extreme on an attentional continuum, and may be equally detrimental in that it precludes adaptive engagement with threats and concomitant habituation (Mogg, Bradley, Miles, & Dixon, 2004). Although theoretical accounts have focused primarily on vigilance as an indicator of hyper-engagement with disorder-relevant information (Mathews & MacLeod, 1994), avoidance behavior is also highly clinically relevant in both depression and anxiety, manifesting as persistent avoidance of threatening contexts (e.g., school refusal), social withdrawal, and/or broad behavioral deactivation (Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011). Avoidance during the course of development may result in missed opportunities for threat engagement and processing, habituation, and the acquisition of adaptive, problem-oriented emotion regulation strategies. Compounded over time, the resulting emotion regulation deficits could constitute one developmental mechanism whereby anxious youth become depressed adolescents.

Experimental evidence supports the notion that both attentional extremes—vigilance and avoidance—are linked with symptoms of anxiety and depression in youth. Vigilant patterns are the more widely documented characteristic among anxious youth samples (Shechner et al., 2012) and are particularly evident when early attentional processes are assessed, such as during initial orienting to threat (Shechner et al., 2013) and following brief (e.g., 500 ms) stimulus presentations (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Vigilance toward negative stimuli has also been found in depressed youth and youth at risk for depression, particularly when using reaction time (RT) measures sensitive to slightly later stages of stimulus processing (e.g., Joormann, Talbot, & Gotlib, 2007; Salum et al., 2013). By contrast, avoidant attentional patterns have been found in depressed children when measuring the persistent direction of eye gaze over a more sustained presentation period (Harrison & Gibb, 2014). Avoidant patterns also characterize subsets of anxious samples, including anxious youth with specific (fear-related) anxiety diagnoses (Waters, Bradley, & Mogg, 2014) and adults and children with unfavorable acute outcomes to certain forms of cognitive behavior therapy (CBT; Legerstee et al., 2010; Price, Tone, & Anderson, 2011; Waters, Mogg, & Bradley, 2012).

The degree to which aberrant attentional patterns are remediated by conventional treatments remains unclear. Psychotherapy, and CBT in particular, is considered a first-line treatment for pediatric anxiety, producing substantial reductions in anxiety for the majority of patients (Silverman, Pina, & Viswesvaran, 2008). However, a substantial minority of patients (e.g., 40%; Walkup et al., 2008) do not respond, and of those who do, some fail to maintain gains, suggesting the risk of progression from anxiety to depression remains high in these youth. Although CBT for anxiety teaches skills to reduce vigilance-related cognitive biases (e.g., overestimation of risk) as well overt behavioral avoidance, it largely relies on the patient's conscious awareness of vigilance and avoidance patterns. Such conscious behaviors may be distinct from the forms of attentional alteration described in the attentional bias literature, which occur relatively automatically on a time course of milliseconds to seconds (Buetti, Juan, Rinck, & Kerzel, 2012; Najmi, Kuckertz, & Amir, 2010). Although there is some limited evidence that CBT for anxiety may reduce vigilance patterns (e.g., Lavy, van den Hout, & Arntz, 1993; Mohlman, Price, & Vietri, 2013; cf. Waters, Wharton, Zimmer-Gembeck, & Craske, 2008), such findings at the group level imply that individuals who begin at the opposite (avoidant) end of the vigilance–avoidance continuum may either persist in this pattern, or may move even further in the avoidant direction following treatment. Avoidant attention could potentially interfere with maximal engagement in key therapy strategies thought to promote enduring reorganization of threat representations in memory (e.g., exposure and habituation; Foa & Kozak, 1986). In that case, acute benefits might still be obtained through a variety of alternative (i.e., nonattentionally mediated) pathways (including both specific and nonspecific factors), but a dormant risk of long-term relapse and/or progression to new symptoms (e.g., depression) could potentially endure in spite of state-of-the-art care. Progression to depression, in particular, might be likely among certain youth if anxiety-focused psychotherapy taught skills effective for the management of anxiety itself, but failed to remediate a core attentional pattern conferring risk for the emergence of depression during the key developmental stage of adolescence.

In the current study, all participants received standardized psychotherapy (CBT or client-centered therapy; CCT) in the context of a larger anxiety treatment trial and, on the whole, exhibited substantial acute decreases in anxiety during both treatments (clinical trial results are presented separately; Silk et al., 2015). If attentional features indeed predict prospective symptoms, even among individuals known to have received high-quality psychotherapy, and over and above any acute treatment benefit, this would strongly imply that existing first-line behavioral interventions are insufficient to ameliorate the specific form of risk contained in certain attentional patterns. Given mounting evidence that attentional patterns themselves are malleable using automated approaches (MacLeod & Clarke, 2015), findings could simultaneously suggest viable targets for alternative intervention/prevention efforts.

To promote the feasibility of clinical translation, we focused current prediction efforts on measures obtained using a relatively inexpensive laboratory set-up (computer, eye-tracker). We assessed visual attentional patterns in eye gaze during fearful–neutral face pair presentations, focusing specifically on overall bias in dwell time (the most consistent marker of depression and depression risk) and bias in initial fixation (an early attentional marker linked to anxiety; for review, see Armstrong & Olatunji, 2012). Eye-tracking measures were selected to index attentional patterns because they provide detailed information about the time course of attention, including indices of both relatively early/automatic (i.e., initial fixation) and relatively late/controlled (i.e., dwell time) components of attention, and were more reliable than RT indices obtained during this version of the task (Price et al., 2015). Fear-related stimuli, which are particularly relevant to anxiety disorders (Cisler & Koster, 2010; Gotlib et al., 2004), were selected to best match concurrent symptoms and treatment targets within the sample at baseline.

Although eye-tracking indices provide a direct assessment of visual attentional mechanisms in the presence of threat, pupilometry was used to provide complementary information on covert neural-attentional processes occurring *in the wake of* threat stimuli, during a sustained postthreat period. Pupil dilation is a peripheral marker of neural engagement that provides a summative index of cognitive and affective processing load. We have previously reported sustained pupil alterations in the aftermath of fearful–neutral face pairs among anxious youth that persisted for > 8 s after threat stimuli were removed (Price et al., 2013), possibly signifying attentional alterations that endure beyond the presence of threat and therefore cannot be measured via conventional behavioral (e.g., eye gaze) patterns. Sustained pupil alterations (increases or decreases) in the aftermath of negative stimuli have also been observed in anxious adults (Oathes, Siegle, & Ray, 2011) and depressed adults and youth (Siegle, Granholm, Ingram, & Matt, 2001; Siegle, Steinhauer, Carter, Ramel, & Thase, 2003; Silk et al., 2007). Like conventional attentional bias markers, pupillary markers can reflect both vigilant (i.e., preferential neural engagement with negative information) and avoidant (preferential engagement with neutral information) patterns, with detrimental effects posited in each case. Increased neural engagement with previously presented negative stimuli may represent a perseverative form of negative attentional orientation (e.g., rumination; Siegle et al., 2003), whereas relatively increased engagement following neutral stimuli may represent persistent attempts at avoidance (Oathes et al., 2011). Pupil dilation persisting in the aftermath of negative stimuli has been shown to prospectively predict acute treatment outcomes in depression with high accuracy (Siegle et al., 2014; Siegle, Steinhauer, Friedman, Thompson, & Thase, 2011), and may also have strong reliability (Siegle et al., 2014), making it an attractive candidate for predicting outcomes at the level of individual patients.

In summary, efforts to identify biomarkers of prospective depression risk among youth have so far been limited. Here we describe findings from one of the first studies to prospectively follow anxious youth (without primary depression at baseline) over a key 2-year developmental window during the transition to adolescence. Depression was assessed on a continuum, consistent with a dimensional approach to uncovering developmental mechanisms of psychological distress (Nigg, 2015) and allowing for incorporation of subclinical forms of depression, which are both impairing and prognostic of subsequent depressive disorders (Compas, Ey, & Grant, 1993). We hypothesized that attentional markers (i.e., eye gaze and pupilometry, indexing perithreat and postthreat attention, respectively) would confer prospective risk of depression during the transition to adolescence, in spite of state-of-the-art treatment for anxiety during youth. This would suggest a key transdiagnostic mechanism that is not remediated by existing first-line treatments.

Method

Participants

Sixty-seven youth (ages 9–13; 29 female) with *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) diagnoses of generalized anxiety disorder, separation anxiety disorder, and/or social phobia were recruited for a larger psychotherapy trial. Results of the treatment trial will be presented separately (Silk et al., 2015); for the present report, we focused on prediction of depressive symptoms that emerge *in spite of* treatment. Sixty-seven youth had usable data from (a) baseline (pretreatment) attentional measures and (b) clinical variables including baseline depression and anxiety symptoms, anxiety symptoms assessed immediately after the acute treatment phase, and depression and anxiety symptoms assessed approximately 2 years following the conclusion of the acute treatment phase (CBT or CCT; see Table 1 and below for further details). Of these, 53 youth also had depressive symptoms assessed acutely posttreatment. Informed consent/assent and study procedures were approved by the University of Pittsburgh Institutional Review Board.

Clinical assessments, treatment, and sample composition. Data come from a large treatment outcome study of pediatric anxiety (clinicaltrials.gov NCT00774150; Silk et al., 2015). In

Table 1
Descriptive Characteristics of the Sample

Characteristic	Anxious youth (n = 67)
Age	11.1 (1.4)
Female, n (%)	36 (53.7%)
Caucasian, n (%)	61 (91.0%)
Baseline diagnoses[a], n (%)	
Separation anxiety disorder	13 (19.4%)
Social phobia	17 (25.4%)
Generalized anxiety disorder	49 (73.1%)
Specific phobia	11 (16.4%)
Major depressive disorder	1 (1.5%)
Baseline SCARED	37.8 (11.01)
Baseline MFQ	20.4 (11.32)
2-year SCARED	17.51 (11.57)
2-year MFQ	11.0 (10.1)

Note. Data presented as mean (standard deviations) unless otherwise noted. SCARED = Screen for Child Anxiety Related Emotional Disorders—child report; MFQ = Mood and Feelings Questionnaire—child report.
[a] Diagnostic groups are partially overlapping due to inclusion of comorbid patients. Primary/principle diagnoses were not designated, meaning that percentages for the 3 diagnostic inclusion groups will not sum to 100.

brief, following a brief phone screen, an intake assessment occurred during which a structured diagnostic interview was administered to the child and his or her parent to confirm presence of an anxiety disorder. Diagnoses were made by trained interviewers using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). Parents and youth were interviewed separately, with interviewers integrating data from both informants to arrive at final diagnoses. Diagnoses were reviewed and supervised by a child psychiatrist (Neal D. Ryan). Participants were excluded if they demonstrated an IQ below 70 as assessed by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), required current ongoing treatment with psychoactive medications including anxiolytics and antidepressants, were acutely suicidal or at risk for harm to self or others, failed to meet MRI safety requirements, or had previously completed a course of CBT. Participants were excluded from the study if they had current, primary major depressive disorder at baseline. Comorbid depressive disorders secondary to anxiety in terms of functional impact were allowed ($n = 1$ in current analyses; no reported results affected by excluding this individual). Additional diagnostic exclusionary criteria included current diagnosis of obsessive–compulsive disorder, posttraumatic stress disorder, conduct disorder, substance abuse or dependence, attention-deficit/hyperactivity disorder combined type or predominantly hyperactive-impulsive type, or lifetime diagnosis of autism or Asperger syndrome (as assessed by the Child Asperger Syndrome Test; Allison et al., 2007), bipolar disorder, psychotic depression, schizophrenia, or schizoaffective disorder.

Patients were randomized to receive 16 sessions (14 with the child, plus 2 parent sessions) of CBT or CCT in a 2:1 ratio. Master's-level and doctoral-level therapists administered both treatments (therapists and treatment were fully crossed). In brief, CBT was delivered using the Coping Cat therapist manual (Kendall & Hedtke, 2006a) and child workbook (Kendall & Hedtke, 2006b). The first eight sessions focused on anxiety-management skills; the second 8 sessions involved the therapist guiding the child through a hierarchy of exposure tasks. CCT (Cohen, Deblinger, Mannarino, & Steer, 2004) is a manualized nondirective, supportive psychotherapy based on humanistic principles. Acceptance, reflection, and nondirective problem solving are key techniques. The intervention was developed to be analogous to typical supportive psychotherapy that anxious children and adolescents receive in the community. Further details of the study protocol and treatment conditions are provided elsewhere (Silk et al., 2015).

Dot-Probe Task

Participants completed the dot-probe task with concurrent eye-tracking and pupilometry assessment, as previously described (Price et al., 2013). After an initial fixation cross in the middle of the screen (500 ms), a fearful and a neutral face pair from the NimStim battery (Tottenham et al., 2009) were presented simultaneously on the top and bottom of the screen for either a short (200 ms) or long (2,000 ms) interval, followed by a probe (dot) replacing one of the faces ("congruent" trials = fearful face location; "incongruent" trials = neutral face location). Participants responded as quickly as possible with a keyboard press to indicate the location of the probe. The dot remained on-screen for the remainder of the trial irrespective of when a response was made (10.6 s for short stimulus trials, 8.8 s for long stimulus trials; each trial = 11.3 s total), allowing for continuous pupilometry assessment of covert attentional processes occurring in the wake of threat (without interference from changes in screen luminescence). For consistency within all analyses, data were restricted to the 32 trials per participant with long (2,000 ms) fearful–neutral face pair presentations, as they provided sufficient time for meaningful eye-tracking analyses (whereas 200-ms presentations do not reliably allow for completion of a single eye movement; Henderson & Hollingworth, 1998).

Attentional Predictor Variables

Eye-tracking. An ISCAN RK-786, (ISCAN Inc., Woburn, MA) affixed to a table top, was used to track eye movements and pupillary motility continuously at 60 Hz. Eye fixations were defined as eye positions stable within 1° of visual angle for at least 100 ms and were used to calculate 2 bias scores (difference scores) representing the following gaze patterns: (a) percentage of trials with initial fixations falling within regions of interest defined by the fearful versus neutral face locations (an "early" index of initial attentional capture) and (b) percentage of dwell time spent fixating on fearful versus neutral faces (an index of overall attentional preference throughout the face presentation).

Both eye-tracking indices reflect a continuum from avoidance of threat (i.e., gaze preference for neutral information) to vigilance (gaze preference for threat information), and were calculated such that larger scores indicate greater vigilance and smaller (negative) scores indicate avoidance of threat. Trials with incorrect responses, comprised of > 50% blinks, or with no detectable fixations prior to manual response were excluded prior to analysis (16% of trials). Participants ($n = 3$) were excluded from the reported sample if they had < 10 usable trials. Excluded participants did not differ from included participants on any clinical or demographic variable in Table 1 (ps > .1).

Pupillary motility. Pupil diameter values were cleaned using our lab's standard procedures to remove blinks, as previously described (Price et al., 2013). Pupillary responses were baseline-corrected within each trial by subtracting mean pupil diameter during the first 10 samples (167 ms) from the remainder of the trial. Baseline-corrected pupil diameter values were then averaged across all trials during a temporal window of interest corresponding to postthreat probe presentation, that is, from probe onset until the conclusion of the trial (an 8.8-s window; incongruent and congruent trials averaged separately). Resulting means were outlier-corrected prior to analysis using a Winsorizing approach in which values outside 1.5 interquartile ranges from the 25th or 75th percentiles of the distribution were rescaled to the last valid value within that range.

For consistency with eye-tracking indices, which represent bias toward/away from threat in a single measure, pupil bias scores were quantified on the basis of the dot-probe attentional manipulation, which orients attention toward (congruent trials) or away from (incongruent trials) the previous threat location. Pupil bias was calculated as: average pupil diameter (expressed as change from baseline), averaged across the probe period, for congruent—incongruent trials. Akin to the eye-tracking bias scores, larger values indicate relatively greater neural engagement (pupil dilation) with the location of threat (i.e., postthreat vigilance), and smaller (negative) values indicate relatively greater neural engagement with the neutral location (postthreat avoidance).

For post hoc pupilometry time-series analyses, a test statistic (specifically, correlation with 2-year depression; or independent samples t test in the extreme-groups comparison analysis) was calculated at every timepoint within the mean pupil waveform. To hold Type I error at $p < .05$ across all timepoints, Guthrie and Buchwald's (1991) Monte Carlo simulation technique was used to identify the duration of the temporal window over which a series of contiguous point-by-point t tests or correlation coefficients could be considered significant given the observed temporal autocorrelation of the waveform, as described previously (Siegle et al., 2003; Siegle, Steinhauer, Stenger, Konecky, & Carter, 2003; Siegle, Steinhauer, & Thase, 2004). A minimum duration of 2.97 s (178 samples) was identified using this technique.

An additional post hoc analysis of pupil data was used to aid in interpreting pupil findings through neural "source localization" in a subset of subjects (n = 43) with usable functional MRI (fMRI) data collected during an identical task (see the online supplemental material). Although prediction analyses were intentionally constrained to measures obtainable with a relatively inexpensive laboratory set-up, fMRI data were used to provide potentially disambiguating information regarding the interpretation of primary pupil findings.

Dependent Variables

The primary outcome was depressive symptoms 2-years posttreatment, assessed on a continuum via the Mood and Feelings Questionnaire—Child report (MFQ; Kent, Vostanis, & Feehan, 1997). To assess specificity for progression to depression, anxiety symptoms at 2-years posttreatment were also assessed via the child-report Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997).

Covariates

Baseline MFQ and SCARED scores, acute posttreatment SCARED scores (a primary marker of therapy response), and therapy condition (CBT or CCT) were controlled in all regression analyses. Because the acute treatment phase targeted anxiety specifically and primary depression constituted a study exclusion, acute posttreatment MFQ scores were inconsistently obtained and were available from only a subset (n = 53) of participants. Regression analyses were repeated controlling for posttreatment MFQ within this subsample (see the online supplemental material). In exploratory analyses, pretreatment age, gender, and the Age × Gender interaction (a potential proxy for pubertal development, given that girls enter puberty earlier than boys) were explored as additional developmental covariates.

Analytic Strategy

Bivariate correlations were used for preliminary interrogation of relationships between attentional predictors, covariates, and dependent variables. For primary prediction analyses, hierarchical linear regression was used to identify predictors of MFQ scores at 2-years posttreatment. For comparison, SCARED scores at 2-years were used as a secondary endpoint. Unless otherwise noted, predictors were entered as follows—Step 1: baseline depression (MFQ) and anxiety (SCARED) scores, posttreatment anxiety (SCARED), and therapy condition; Step 2: eye-tracking bias measures (dwell time bias and initial fixation bias); Step 3: pupil bias.

Results

Bivariate Relationships

The correlation matrix for predictor variables, covariates, and dependent variables is presented in Table 2. Higher depressive symptoms at 2 years (the primary outcome) were associated

Table 2
Correlation Matrix

	Attentional features					Covariates							Dependent variables	
Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Δ Pupil diameter (congruent trials)	—	.354**	.618**	−.068	.158	.073	−.203	−.201	−.074	.099	.063	.062	−.036	−.092
2. Δ Pupil diameter (incongruent trials)		—	−.517**	−.209	.238	.072	−.073	−.055	−.046	.065	.249	.182	.338**	.085
3. Pupil bias (probe period)			—	.113	−.055	.006	−.125	−.138	−.029	.036	−.152	−.096	−.317**	−.156
4. Dwell time bias				—	.183	.034	−.030	−.010	−.161	−.160	−.045	−.104	−.341**	−.134
5. Initial fixation bias					—	.123	−.037	−.005	.047	.061	−.076	−.019	−.102	−.121
6. Baseline age						—	−.153	−.022	.039	.111	.160	.152	.164	.065
7. Gender							—	.984**	−.115	.157	.196	.262*	.273*	.385**
8. Baseline Age × Gender								—	−.115	.162	.208	.292*	.293*	.402**
9. Baseline MFQ									—	.474**	.357**	.210	.069	.051
10. Baseline SCARED										—	.184	.459**	.265*	.364**
11. Posttreatment MFQ											—	.558**	.331*	.320*
12. Posttreatment SCARED												—	.419**	.603**
13. 2-year MFQ													—	.658**
14. 2-year SCARED														—

Note. MFQ = Mood and Feelings Questionnaire; SCARED = Screen for Child Anxiety Related Emotional Disorders.
* $p < .05$ level (2-tailed). ** $p < .01$ level (2-tailed).

with two indices of avoidant attention (see Figure 1): more avoidant eye gaze patterns across the trial (dwell time bias: $r = -.341$, $p = .005$) and lesser differential pupil diameter (pupil bias) for congruent compared to incongruent trials ($r = -.317$; $p = .01$), which was driven by a relationship with increased pupil diameter during incongruent trials ($r = .338$; $p = .005$).

To explore the timing of the observed pupil correlation during incongruent trials, a post hoc time-series analysis was conducted. Significant correlations between pupil diameter and 2-year depression began at the point of probe onset and continued almost continuously throughout the remaining 8.8 s of the trial, with the peak correlation coefficient ($r = .35$) occurring 4.1 s after probe onset (i.e., > 3 s after the average manual response time of 840 ms). Similarly, when comparing the top and bottom quartile of 2-year MFQ scorers, significant pupil differences commenced shortly after probe onset and were sustained nearly continuously throughout the remaining 8.8 s of the trial (Figure 1).

Hierarchical Regressions Predicting 2-Year Outcomes

In primary prediction analyses, after controlling for baseline depression and anxiety, treatment group, and posttreatment anxiety (Step 1: $\Delta R^2 = .19$, $\Delta F_{4,62} = 3.7$, $p = .01$), eye-tracking bias measures (Step 2) explained significant additional variance in 2-year MFQ scores ($\Delta R^2 = .09$, $\Delta F_{2,60} = 3.9$, $p = .03$). Likewise, pupil bias explained significant variance in 2-year MFQ scores at Step 2 after controlling for clinical covariates at Step 1 ($\Delta R^2 = .07$, $\Delta F_{7,59} = 4.5$, $p = .01$). In a final hierarchical model, pupil bias was added at Step 3 (after controlling eye-tracking bias indices at Step 2) and explained further significant variance in 2-year MFQ scores, above both clinical and eye-tracking measures ($\Delta R^2 = .07$, $\Delta F_{1,59} = 5.9$, $p = .02$). At Step 3, 35% of variance was explained (adjusted $R^2 = .27$; $F_{7,59} = 4.5$, $p < .001$), and greater 2-year MFQ scores were predicted by more avoidant eye-tracking bias ($\beta = -.26$, 95% CI [−.48, −.04], $p = .02$) and more avoidant pupil bias ($\beta = -.26$, 95% CI [−.48, −.05], $p = .02$), controlling for all other variables.

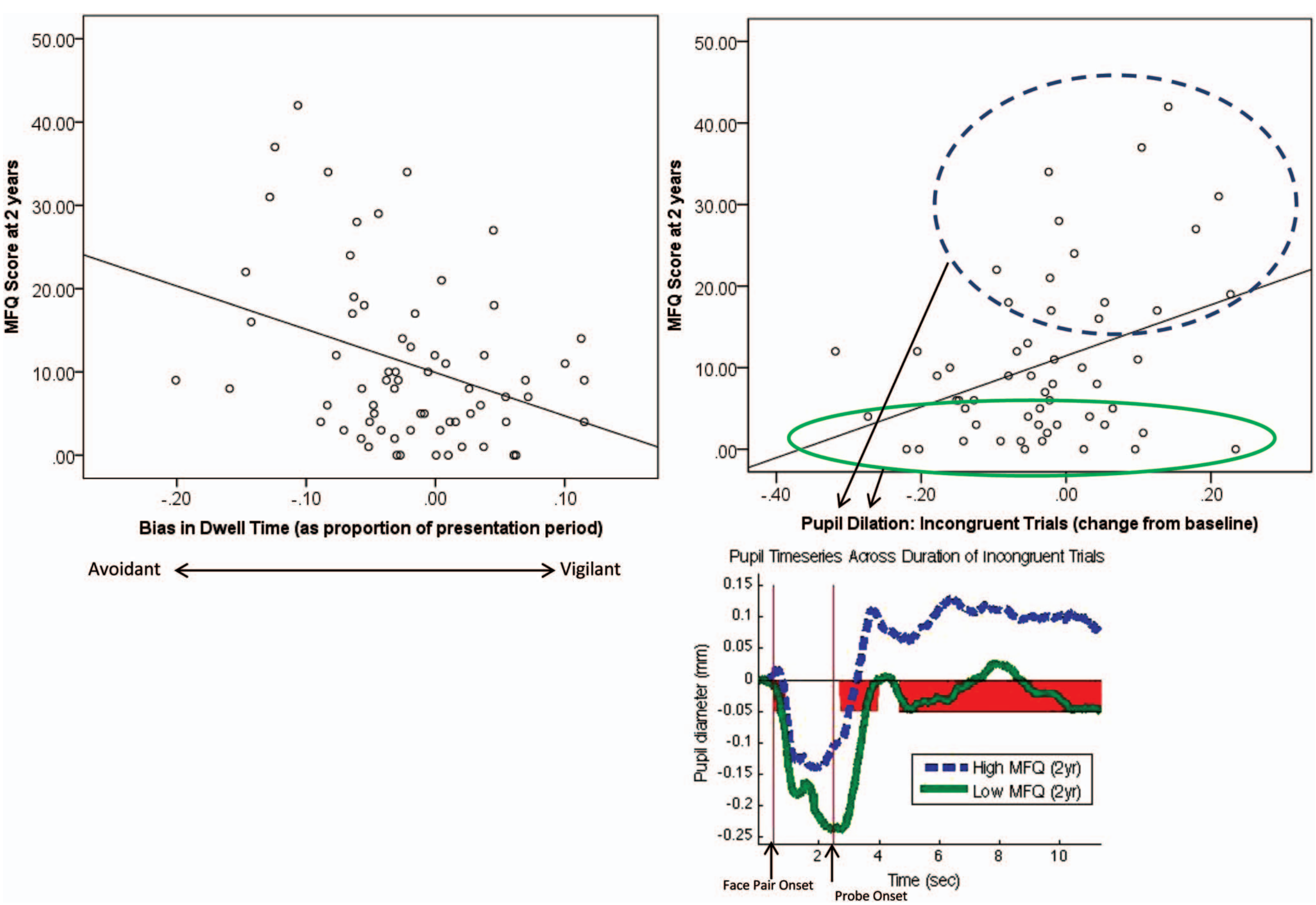

Figure 1. Scatterplots for attentional variables predicting 2-year depression. Time-series plot depicts pupil diameter (expressed as change from baseline) in top and bottom quartiles of the 2-year Mood and Feelings Questionnaire (child report; MFQ), with red (dark gray) shading indicating timepoints with significant group difference. Initial dip during face presentation is driven by pupillary light reflex. See the online article for the color version of this figure.

All significant findings above were upheld when posttreatment depression was covaried in participants with available data (see the online supplemental material for details).

Parallel regression analyses for 2-year anxiety revealed no significant effects for attentional predictors at any step (dwell time bias, initial fixation bias, pupil bias; *p*s $>$ .2). As above, baseline depression and anxiety, treatment group, and posttreatment anxiety collectively predicted 2-year anxiety (Step 1: $\Delta R^2 = .39$, $\Delta F_{4,62} = 10.0$, $p < .001$) but Steps 2 and 3 did not improve prediction (Step 2: $\Delta R^2 = .02$, $\Delta F_{2,60} = .81$, $p = .45$; Step 3: $\Delta R^2 = .01$, $\Delta F_{1,592} = 1.41$, $p = .24$), and no interaction effects were significant (see the online supplemental material).

Interaction effects among covariates, and between covariates and attentional features, were not significant predictors of 2-year depression or anxiety, suggesting covariates in the model were valid (see the online supplemental material). Of particular note, relationships between attentional features and 2-year depression were not moderated by psychotherapy treatment condition (see the online supplemental material).

Developmental Factors

Exploratory regression analyses examining the influence of age, gender, and Age × Gender interactions suggested observed relationships were not better explained by these demographic factors. Consistent with the clinical developmental literature, female gender and the Age × Gender interaction (i.e., older girls, relative to younger girls and boys at any age) were associated with greater symptomatology (depression and anxiety) at 2-years (see Table 1). However, although age, gender and Age × Gender interactions collectively explained 12% of variance in 2-year depression (Step 1: $\Delta R^2 = .12$, $\Delta F_{3,63} = 2.81$, $p = .05$), these indices were no longer significant once clinical and attentional variables were entered (as above; *p*s $>$ .1), and both avoidant dwell time bias ($\beta = -.27$, 95% CI [−.49, −.05], $p = .02$) and avoidant pupil bias ($\beta = -.24$, 95% CI [−.46, −.03], $p = .03$) remained predictive in the final model. Age and gender did not moderate any attentional feature to predict 2-year depression or anxiety (see the online supplemental material).

Discussion

More than 2 years after a laboratory assessment of attention to threat among anxious youth, youth depression scores were predicted by avoidant gaze patterns, over and above variance explained by baseline clinical and demographic measures, and in spite of treatment-related effects (therapy condition, acute posttreatment symptoms). Depression severity was further predicted by a sustained, avoidant pattern of pupil dilation in the aftermath of threat, suggesting that persistent cognitive efforts at postthreat avoidance further compounded this risk. Findings were specific for depression, while anxiety at 2 years was related to clinical but not attentional measures. Although the total variance explained in the final model was modest (35%; 20% for attentional/pupilometry measures alone), it is nevertheless notable that measures taken during a simple laboratory task were predictive of prospective depressive scores in spite of an intervening 2-year period of life events and developmental/pubertal progress. This long-term pattern suggests the attentional measures captured a key mechanism in the progression from pediatric anxiety to adolescent depression.

The detrimental impact of avoidance patterns was consistent across both perithreat (eye-tracking) and postthreat (pupilometry) indices, in spite of quite distinct forms of information obtained with these methods. During incongruent trials, which encourage an avoidant response by orienting attention away from the previous location of threat, elevated pupil dilation in youth at highest depression risk was sustained across a $>$ 8-s poststimulus period (Figure 1). In conjunction with explicitly avoidant eye gaze patterns, this pattern suggests possible persistent cognitive efforts to sustain attention (e.g., mental focus) in the “safe” (i.e., previously neutral) relative to the “dangerous” (i.e., previously threatening) context, even when actual visual attentional avoidance of threat was no longer necessary or, indeed, possible (given that no threat remained on-screen). Avoidant pupillary responses (i.e., reduced responses to negative relative to neutral trial types) have previously been reported in adults with high self-reported worry (Oathes et al., 2011) and depressed youth (Silk et al., 2007). Just as in the current dataset, the alterations began in the wake of stimuli, and persisted for several seconds after stimuli were removed from view and responses were made. Such patterns could indicate preferential recruitment of elaborative processing and/or cognitive control mechanisms in the wake of neutral relative to negative information. To promote clinical translation, we opted to restrict primary regression analyses to measures that can be obtained quickly and inexpensively in a relatively simple laboratory set-up (and, increasingly, using handheld and/or mobile devices). However, in a supplementary analysis conducted among a subset of participants who performed the same task during functional neuroimaging (see the online supplemental material), pupil values during incongruent trials tracked with larger responses in a right posterior parietal region implicated in sustaining visual attention (Malhotra, Coulthard, & Husain, 2009). This statistical relationship across individuals further links the observed pupil pattern to an attentional control mechanism pertinent to sustained attention, helping to rule out alternative explanations (e.g., arousal, emotional responding).

Given that dwell time and pupil bias explained distinct variance in outcome, youth at highest prospective depression risk exhibited the cumulative burden of behavioral avoidance during threat presentation, plus sustained avoidance attempts in the wake of threat. These two avoidant tendencies, in aggregate, could serve to prohibit active engagement with threats, while decreasing availability of cognitive resources for learning and applying more adaptive forms of emotion regulation in the wake of a threatening encounter (e.g., problem solving, consideration of actual rather than feared outcomes). When combined with increasing stress sensitivity and normative psychosocial changes during the peripubertal period, avoidant attention could propagate more widespread withdrawal from an increasingly “threatening” (e.g., interpersonally) environment, thereby setting the stage for depression to emerge in adolescence.

The existing literature in both anxiety and depression suggests that time course is a key factor in attentional bias effects (de Raedt & Koster, 2010; Mogg et al., 2004). Our methodology enables separation of distinct components of visual attention (initial fixation, dwell time bias throughout the “intermediate” 2-s stimulus presentation, and sustained postthreat processing). Findings suggest that depression was predicted by a pervasive pattern of avoidance at intermediate and late stages of processing, while initial orienting at the earliest stages did not prospectively predict depression or anxiety. Concurrent anxiety has been most reliably linked to early attentional features (e.g., response times to brief 500-ms stimuli, initial fixations in eye gaze; Bantin, Stevens, Gerlach, & Hermann, 2015; Bar-Haim et al., 2007; Gamble & Rapee, 2010; Price, Siegle, & Mohlman, 2012), with a smaller literature suggesting a switch to avoidance of threat occurring at later processing stages (Mogg et al., 2004). Depression has been linked primarily to later stages of attention (e.g., response times to stimuli presented for 1,000-ms or longer, dwell time bias, disengagement difficulty; Kellough, Beevers, Ellis, & Wells, 2008; Leyman, De Raedt, Schacht, & Koster, 2007), although a recent meta-analysis found that both early and late attentional components may be equally affected (Peckham, McHugh, & Otto, 2010). Nevertheless, difficulty disengaging from negative stimuli is often considered the most reliable pattern among currently depressed adults, and may also characterize groups of children and adults at elevated risk of depression (Gotlib & Joormann, 2010). *Vigilance* toward negative stimuli, particularly during late stages of processing, is therefore a key depression marker.

However, using methods more akin to the present study, currently depressed children have shown avoidant eye gaze patterns (specifically, avoidance of sad faces) persisting continuously for up to 20 s of face viewing (Harrison & Gibb, 2014). This avoidant pattern in eye gaze has been posited to be developmentally mediated. Specifically, although avoidance of sad faces may be a normative feature of infancy (Montague & Walker-Andrews, 2001), providing effective mood regulation at this age (Termine & Izard, 1988), depressed children may continue to apply this strategy without the same benefit (possibly due to increasing capacity for abstract cognition), whereas depressed adults may no longer be able to resist attending toward negative information at all (resulting in vigilant patterns). Within the constrained age range of the current study, age (and gender) did not better explain the relationship between avoidance and prospective depression. The sample was specifically selected to capture the high-risk peripubertal window where depression often emerges, meaning that youth may have undergone relatively homogenous (though substantial) changes across the follow-up period. A broader developmental perspective may be required to reveal whether developmental factors do indeed moderate the nature of attentional risks for depression. Nevertheless, developmental changes over time were an important element of the current findings, as avoidant tendencies manifested in depressive symptoms only after the passage of time and maturational progress.

Previous studies in currently depressed individuals suggest attentional biases pertain specifically to sad/dysphoric stimuli, whereas threat-related stimuli elicit attentional biases in currently anxious individuals (Gotlib et al., 2004). Our study included assessment in a currently anxious cohort using threat-related stimuli (fearful faces). It is notable that attentional features were nevertheless predictive of depression, suggesting threat-related stimuli may have greater relevance to depression when placed within a developmental framework, just as anxiety itself is predictive of future depression in spite of separable foci of symptoms and cognition. However, the failure to include dysphoric stimuli in the current study means that we cannot speak to the specificity of our findings to fearful faces and may have missed attentional patterns with even greater relevance to depression development. In addition, our study used fearful faces as a threat cue because they reliably activate fear-processing regions of the brain (Whalen et al., 2001) and have transdiagnostic relevance to fear perception through the implication that a generic, unspecified threat is present. This design decision stands in contrast to many studies using angry or disgusted faces to connote a social form of threat directed at the participant; however, there is evidence that fearful and angry faces elicit comparable eye-tracking bias patterns during the dot-probe (Mogg, Garner, & Bradley, 2007). In the future, inclusion of multiple stimulus types would help to disambiguate the relative relevance of various threatening and dysphoric cues in the transition from anxiety to depression.

In summary, although our findings diverge in some respects from attentional patterns described previously in depression, they were obtained using an individual differences approach and prospective symptom assessment. These design features extend the literature, which is dominated by cross-sectional, group-level comparisons. Findings suggest that it is a persistent pattern of avoidance across the majority of a 2-s time course, coupled with further sustained avoidance in the wake of threat, that confers the highest prospective risk. Although first-line psychotherapies could effectively ameliorate and/or compensate for some of the attentional aberrations observed in cross-sectional studies, sustained avoidance of threat may have a specific, insidious effect over time (e.g., lost opportunities for habituation and adaptive problem solving, compounded over the course of development), leaving youth vulnerable to depression even when they show acute treatment benefits.

Previous studies of acute psychotherapy outcome have suggested that anxious individuals showing avoidant attentional patterns are not as well-suited for certain forms of psychotherapy as youth at the vigilant end of the spectrum (Legerstee et al., 2010; Price et al., 2011; Waters et al., 2012). Consistent with this, one possible interpretation of the current findings is that avoidant youth did poorly in psychotherapy and were therefore less buffered against subsequent depression. However, several pieces of evidence argue against this interpretation. The current effects were specific for depression (whereas the treatments targeted anxiety), and were not apparent immediately after treatment (Table 1), suggesting the longer-term transition to adolescence (and concomitant increased depression risk) were key. Furthermore, whereas both treatment conditions in the current trial produced substantial decreases in primary anxiety outcomes (Silk et al., 2015), the impact of attentional features persisted after controlling for these treatment-related effects. Findings therefore suggest that the attentional assessment captured a long-term form of risk that was relatively impervious to the acute beneficial effects of the treatments. In other words, anxious youth exhibiting avoidant attentional features continued to be at risk for prospective depression, irrespective of how well the treatment ameliorated their symptoms acutely. Clinically, this suggests that alternative and/or adjunctive treatments may be needed for this subset of anxious youth, even when psychotherapy succeeds in reducing symptoms. These youth may be at particular risk of falling through the cracks of clinical care, as they may show initial reductions in symptoms that fail to protect them from further development of depression once developmental risk factors (e.g., increased stress reactivity, psychosocial stressors) are brought to bear.

Our findings could have implications for novel treatment development, particularly in light of growing interest in mechanistic treatments targeting attentional patterns (e.g., attentional bias modification; ABM; MacLeod & Clarke, 2015). The vast majority of ABM studies in anxious patients have trained attention away from threat (toward neutral information), invoking an attentional goal state akin to the pattern that conferred risk in our study. Although several studies showed immediate and short-term (e.g., at 4-month follow-up) benefits on anxiety measures (Amir et al., 2009; Schmidt, Richey, Buckner, & Timpano, 2009), more recent findings have been mixed (Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015), and no published study has examined clinical effects (depression or anxiety) at longer-term follow-up. In the context of pediatric anxiety, it may be important to consider the possible detrimental effects of training in an avoidance pattern. However, the attentional pattern instilled by ABM (designed to remediate relatively early/automatic aspects of attention) may differ substantively from the risk pattern observed here (i.e., sustained avoidance in eye gaze and pupilometry persisting across a ~10-s period). In addition, avoidant attentional patterns may be detrimental only when they arise spontaneously, but not when they occur as the result of a specific attentional training procedure. Avoidant patterns that arise on their own may be far more generalized, potentially indexing an innate, widespread, and pervasive tendency to withdraw from emotional cues (e.g., potentially both positive and negative cues), across longer spans of time. Even so, our findings could implicate the need for an alternative form of ABM tailored to the individual (e.g., training toward threat in avoidant individuals, particularly for late/sustained time points).

More broadly, findings highlight the importance and detrimental impact of attentional avoidance of threat, which has received less attention in the literature than the opposing pattern (vigilance toward threat; Bar-Haim et al., 2007), but is paramount in clinical manifestations of both anxiety and depression (behavioral and emotional avoidance attempts, social withdrawal). Attentional avoidance is posited to maintain emotional difficulties over time due to decreased elaborative processing of threat, decreased active coping, and reduced opportunities for fear habituation/extinction (Foa & Kozak, 1986; Mogg et al., 2004). By focusing on a key maturational window when risk of depression onset is high, the current study suggests these missed opportunities for threat engagement and processing, compounded over time, may constitute one developmental mechanism whereby anxious youth progress to depression.

Limitations

The assessment of biased attention in laboratory studies is constrained by suboptimal reliability (Price et al., 2015), which limits power and risks underestimation of the true impact of attentional mechanisms. This limitation further constrains the ability to infer clinically meaningful information about individual patients. By contrast, pupilometry is reliable (Siegle et al., 2014) and has been used to classify clinical outcomes of individual patients with high accuracy (Siegle et al., 2011); however, given diffuse neural inputs (Beatty, 1986), its meaning can be difficult using the current assessment measures to individual patients to interpret in isolation. Here, we sought to combine the strengths of each approach. However, modest effect sizes for prediction suggest additional measures and/or refinements of current measures would be needed to facilitate clinical translation. In particular, inclusion of dysphoric stimuli (rather than threat-related alone) may improve relevance for depression. Findings may not generalize beyond the specific task design (e.g., 2-s fearful–neutral face pairs) and clinical population recruited here. Finally, the present findings await replication in a larger sample with a wider range of anxiety presentations and depression-related outcomes and a more naturalistic, treatment-free follow-up period.

Conclusions

Among anxious youth, laboratory assessments of attention—using measures feasible to obtain in a typical clinical setting—were predictive of depression scores at a delay of more than 2 years. Persistent avoidance of threat, both during and after threat presentation, emerged as a robust mechanism conferring risk for the transition from pediatric anxiety to adolescent depression, in spite of state-of-the-art behavioral treatment. Anxious youth exhibiting attentional avoidance might benefit from increased clinical attention and preventative efforts, including potential attempts to directly remediate avoidant attention itself. Such efforts could help forestall the onset of depression, a condition that is costly, disabling, and highly enduring across the life span (Weissman et al., 1999).

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