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The Impact of Inflammatory Bowel Disease and High Dose Steroid Exposure on Pupillary Responses to Negative Information in Pediatric Depression

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Abstract

Objective—To better understand emotional information processing in pediatric inflammatory bowel disease (IBD) and its relationship with depression. Pediatric IBD is associated with higher rates of depression than seen in other physical diseases and in community samples. In systemic inflammation, proinflammatory cytokines have been implicated in altering activity in brain regions known to affect emotion processing and emotion regulation in depression.

Methods—We examined differences in pupillary responses as a marker of brain function in response to negative emotional information in youths (age 8–17) with IBD both with ($n = 8$) and without ($n = 15$) comorbid depression who were receiving high dose steroid treatment. We compared their responses to each other and to depressed youths without IBD ($n = 20$), and healthy youths ($n = 22$).

Results—Youths with IBD demonstrated greater pupillary responses to the initial presentation of negative emotional stimuli regardless of their depression status ($p = 0.05$). In contrast, depressed youths, regardless of their IBD disease status, demonstrated a greater constriction of the pupil 10 to 12 seconds after exposure to negative stimuli. This constriction was associated with greater depressive severity and lower albumin levels.

Conclusions—IBD may be associated with increased sensitivity to negative emotional stimuli above and beyond depression diagnosis. Depressed youths potentially demonstrate affective blunting, emotional avoidance, or a failure to regulate emotion after exposure to negative emotional information. Thus, there appear to be unique contributions of medical disease and depression to physiological indications of emotional reactivity, but these factors do not appear to interact.

Keywords

inflammatory bowel disease; depression; pupillary responses; steroid medication

INTRODUCTION

Pediatric inflammatory bowel disease (IBD), comprising Ulcerative Colitis (UC) and Crohn's disease (CD), affects 71 in 100,000 children in the United States (1). IBD has an insidious onset most commonly diagnosed between 10 and 20 years of age (2). While CD and UC involve different genetic vulnerabilities, pathological abnormalities, and different regions of involvement in the intestinal tract, both are characterized by both gastrointestinal symptoms such as bloody diarrhea, weight loss, and abdominal pain, as well as extra-intestinal manifestations such as joint pain, uveitis, and erythema nodosum (3,4). In terms of treatment, CD has a more refractory course and whereas in UC, surgical resection can be curative, in CD it is more palliative with a high risk of post-operative disease recurrence. Disease complications in both types of IBD can include pubertal delay and depression (3). In adolescents with either CD or UC, rates of depression have been reported to be as high as 25%, higher than that seen in other physical diseases and in community controls (5–7). Whether depression in pediatric IBD represents the same phenomenon as other childhood depressions but occurs more frequently due to the additional psychosocial stress related to having a physical illness or instead represents a qualitatively different phenomenon, more associated with the unique risk factors of IBD (e.g., increased proinflammatory cytokine function, or treatment with steroids) is unclear. To better understand psychological features of depression in youths with IBD, this study examined effects of IBD and depression, and their interactions on responses to emotional stimuli. Answering this question will be critical to using mechanistic considerations to create and refine treatments for pediatric depression with medical comorbidities such as IBD.

There are multiple reasons to believe that depression in the presence of IBD could differ from other types of depression. In contrast to naturally occurring depressions where psychological and environmental factors are strongly implicated etiological factors, both IBD-related inflammatory proteins (e.g., proinflammatory cytokines), and medications like steroids often used to treat the inflammation, have been implicated in the etiology of this depression (8,9). In animal and human models of systemic inflammation, circulating cytokines have been shown to affect neural functioning by both direct and indirect processes in key brain regions (e.g., amygdala and subgenual cingulate cortex) essential to the regulation of emotion, behavior, and the experience of rewarding outcomes (10–12).

Yet, there are also reasons to suggest that depression with IBD may be similar to other depressions. For example, brain regions affected by cytokines such as the amygdala have also been implicated in endogenous depression in the absence of physical illness (13–15). In fact, children with depression who do not have IBD demonstrate decreased pupillary responses, following initial exposure to negative stimuli (16). This decreased physiological reactivity could reflect multiple relevant neural mechanisms from decreased amygdala activity to decreased prefrontal regulatory function (16).

No identified research has examined the impact of IBD and its treatment on the processing of negative emotional information. Furthermore, it is unclear whether or not youths with pediatric IBD who are in active treatment process emotional information the same or differently when compared to youths diagnosed with depression.

Pupillary responses reflect cognitive and emotional information processing. The pupil is highly innervated by cortical and limbic brain regions involved in both cognitive and emotional processing (17,18). Thus, stimulation of limbic regions, such as the amygdala, increases pupil dilation (19), as does stimulation of the midbrain reticular formation (20), which receives afferent projections from the frontal cortex and sends efferent projections to the ocular motor nuclei, particularly structures such as the anterior cingulate cortex, which

are implicated in emotion regulation (21). Pupil size increases with processing demands and in response to emotional information (see 22,23 for reviews). Furthermore, pupil dilation persists if the cognitive and emotional processing is sustained (24). Pupil dilation also provides information regarding the time course of cognitive and emotional load with high temporal resolution (25,26).

Thus, we examined pupillary responses to emotional stimuli in a sample of youths with high medical burden including having IBD and high dose steroid treatment, with and without comorbid depression. We compared the pattern of pupillary responses during emotional information processing in youths with IBD to youths with depression without IBD or steroid exposure, and healthy comparison youths. Primary questions included the unique and interacting effects of IBD, depression, and their interactions on the time course of responses to negative information in this pediatric sample. Our hypothesis was that due to the different etiology, youths with IBD and depression would appear different from other depressed youths. Our secondary hypothesis was that the degree of steroid exposure and inflammation would be associated with pupillary responses to negative information.

METHODS

Participants

The sample consisted of a total of 65 youths (63% female, 37% male, ages 8 – 17 years, $M = 13.5$ years, $SD = 2.50$). The sample was divided into four groups: youths with IBD and no depressive disorder ($n = 15$); youths with IBD and major or minor depressive disorder ($n = 8$); youths with major depressive disorder but no IBD ($n = 20$); and healthy comparison youths ($n = 22$). This study was approved by the University of Pittsburgh Institutional Review Board. Before participating in the study, all subjects and their parents were required to sign assents and informed consents, respectively, in compliance with the requirements of the University of Pittsburgh Institutional Review Board (see Table 1 for descriptive characteristics of the sample).

Twenty three youths with IBD were recruited during their pediatric gastroenterology medical appointments or inpatient hospitalization for an IBD flare to participate in this study and met inclusion criteria. Fourteen participants were previously diagnosed with Crohn's disease and nine were diagnosed with ulcerative colitis confirmed via biopsy by a gastroenterologist. IBD patients also had to have received high-dose oral (prednisone) or parenteral (IV) steroid treatment for acute flares (equivalent dose of ≥ 20 mg/day prednisone) for at least one week. Exclusion criteria for participants with IBD included: 1) history of non-psychiatric CNS disorders, mental retardation, significant developmental delay, learning or attention problems requiring special education or medication; 2) current or past bipolar, psychotic disorder, or eating disorders; 3) substance abuse disorders within one month of the assessment by history; and 4) active medical conditions other than IBD by history and medical records. Participants in the IBD group were considered depressed if they met DSM-IV criteria (26) for either major ($n = 3$) or minor depression ($n = 5$). One of the IBD youth with major depression also met criteria for generalized anxiety disorder.

The remaining 42 participants without IBD were from a longitudinal study of neurobehavioral factors in pediatric affective disorder (see reference 27 for details) on whom pupillary responses have already been published (16). Twenty-two participants were low-risk comparison youths, and 20 participants had a current primary diagnosis of major depressive disorder based on the DSM-IV (28). Details regarding psychiatric comorbidity and factors used in determining low-risk status have been described elsewhere (16). In brief, eleven participants in the major depression group also had a comorbid anxiety disorder. Comparison youths had no lifetime psychopathology and no first-degree relatives with a

lifetime episode of mood or psychotic disorder, and no second-degree relatives with a lifetime history of childhood-onset, recurrent, psychotic, or bipolar depression or schizoaffective or schizophrenic disorder, and no more than 20% of their second degree relatives had a lifetime single episode of major depression. Exclusionary criteria for both low-risk comparison youths and youths with major depressive disorder but no IBD included the use of any medication with central nervous system effects within the 2 weeks preceding the assessment (subjects could not be on steroids), significant medical illness (e.g., severe asthma requiring daily medication), extreme obesity (weight greater than 150% of ideal body weight), or growth failure (height or weight below the third percentile).

Recruitment and Diagnostic Interviews

Youths diagnosed with IBD were recruited from the Inflammatory Bowel Disease Center at Children's Hospital of Pittsburgh. Youths with IBD were recruited during either an outpatient visit or medical hospitalization for an IBD flare. Data acquisition was performed over a total period of 19 months between 08/2006 and 03/2008. Youths with major depression without IBD were recruited from inpatient and outpatient clinics and community advertisements. Comparison youths were recruited from community advertisements. Data acquisition was performed between 01/2004 and 04/2008. Lifetime and present DSM-IV diagnoses for all participants were assessed using the Schedule for Affective Disorders and Schizophrenia in School Age Children – Present and Lifetime Version (29).

Pupil Assessment

Pupillary responses were assessed in a moderately lit room (1.54 foot-candles illuminance). Youths without IBD were assessed in the morning whereas time of day was not controlled for youths with IBD who completed pupillary assessment after the diagnostic interview and completion of self-report questionnaires. For all participants, the stimuli were in lowercase letters approximately 1.59 cm high subtending 0.76° of visual angle, displayed in dark gray on a light gray computer screen. Reaction times were recorded via a modified game pad containing three buttons arranged in a triangle so that respondents' fingers were nearly equidistant from each possible response. The mapping of game pad buttons to responses was counterbalanced across participants. Pupil size was recorded with an ISCAN headmounted RK-726 or a table-mounted RK-464 eye-tracker at 60 Hz (every 16.7 msec). The resolution for a typical participant was better than 0.05 mm pupil diameter.

Word Valence Identification Task

Participants were instructed to identify the emotional valence of 22 positive, 22 negative, and 22 neutral words, chosen from a corpus of emotional words normed for use with children (21), by pressing a corresponding button for each valence. Words from each category were balanced for length and frequency. Each trial included a 1-sec fixation mask, followed by the word for 5 sec, followed by a mask for 6 sec.

Data Selection, Cleaning, and Reduction

Data were cleaned by our lab's standard methods (26). Trials comprising more than 50% blinks were removed. Linear interpolations replaced blinks throughout the data set. Data were smoothed using a 10-point weighted average filter. The average pupil diameter over the 167 msec (10 samples) preceding the onset of the stimulus was subtracted from pupil diameter after stimulus onset to produce stimulus-related pupil dilation waveforms.

Measures

Participants completed several self-report and clinician rated measures. The Mood and Feelings questionnaire (30) is a 34 item questionnaire designed to have high sensitivity and

specificity in screening for depression in children age 8–18 (31). The questionnaire was used to evaluate participants' levels of depressive symptoms on the day of the assessment.

The Pediatric Crohn's Disease Activity Index (PCDAI; 32) and the Pediatric Ulcerative Colitis Disease Activity Index (PUCDAI; 33) were used to assess IBD severity. The PCDAI and PUCDAI include measures in three illness domains that are routinely collected as part of the medical visit: (a) self-reports of pain and functional disability, (b) clinician-rated severity, and (c) objective data such as blood tests, weight, and growth charting.

Participants' daily steroid dose (mg/day) was extracted from their medical records and reported as prednisone-equivalents. In addition, we calculated an index of participants' cumulative steroid load for the current IBD symptom flare. Steroid load was calculated by multiplying the daily dosage by the number of days participants were on the dose.

Laboratory Assessment

Labs drawn at the assessment time point for IBD participants were all part of routine hospital care and were processed using standard hospital protocols: Erythrocyte sedimentation rate (ESR; mm/hr), and albumin (g/dL) were selected as markers of the immune systems inflammatory response. All laboratory tests were performed by the clinical laboratory at Children's Hospital of Pittsburgh of UPMC.

Data Analysis

Following a similar analysis to the one we used to compare healthy and depressed non-IBD participants (16) we conducted general linear mixed model analyses with an autoregressive covariance structure using "early" (3 to 6 seconds – during the stimulus) and "late" (10 to 12 seconds – after the stimulus was removed) *a priori* regions of temporal interest in pupillary responses as the dependent variables. Subject was treated as a random effect. Fixed effects included depression diagnosis (major or minor depressive disorder vs. no depressive disorder), disease status (IBD vs. No IBD), and a disease status x depression diagnosis interaction. An *a priori* simple comparison comparing youths with IBD and major or minor depression to youths with major depressive disorder was also conducted. Zero order correlations were used to examine associations among pupillary responses to negative stimuli, inflammatory markers, and steroid exposure.

RESULTS

Descriptive Characterization of Sample

The IBD sample consisted of both CD ($n = 14$) and UC ($n = 9$) and demonstrated a range of IBD severity with 30.5% having inactive IBD, 39% Mild IBD, and 30% Moderate/Severe IBD as indexed by the PCDAI or the PUCDAI depending on the IBD type. On average participants were on $M(SD) = 28.21(9.81)$ mg/day of steroids; the average level of overall steroid exposure (steroid load) during the current symptom flare was $M(SD) = 1121.09(1019.07)$. On average, IBD participants also demonstrated albumin levels within the normal range $M(SD) = 3.60(0.71)$ g/dL and elevated ESR $M(SD) = 25.22(17.43)$. In terms of depressive severity, IBD depressed youths demonstrated low levels of depressive severity $M(SD) = 13.50(6.48)$, and depressed youths without IBD demonstrated low to moderate levels of depressive severity $M(SD) = 19.20(12.13)$ (see Table 1 for descriptive statistics by group). All four groups did not statistically differ in their ages. Furthermore, IBD depressed youths did not statistically differ from IBD youths with no depression in terms of age, disease severity, albumin levels, ESR, steroid dose, or steroid load.

Pupillary Responses: A priori Temporal Regions of Interest

Figure 1 shows pupillary responses to negative words for each group. Regions of *a priori* interest are highlighted below the x-axis. *A priori* temporal region-of-interest analyses revealed that youths with IBD demonstrated significantly greater early pupillary responses to negatively valenced words compared to youths without IBD regardless of depression diagnosis (Youths with IBD: $M = 0.16$ mm, $SE = 0.03$ vs. Youths without IBD: $M = 0.09$ mm, $SE = 0.03$, Cohen's $d = 0.41$; $F = 3.95$, $df = 1, 61$, $p = 0.05$) see Figure 2. There were small and non-significant effects of depression diagnosis ($F = 0.28$, $df = 1, 61$, $p = 0.60$) and IBD x depression ($F = 0.59$, $df = 1, 61$, $p = 0.45$). When analyzed separately, youths with IBD and major or minor depressive disorder ($M = .19$ mm, $SE = 0.05$) displayed a larger standardized difference in early pupil magnitude compared to youths with major depressive disorder ($M = 0.08$ mm, $SE = 0.03$, Cohen's $d = 0.80$) than was present in the full-sample analysis, but due to lower power in this subset, the difference was not statistically significant ($t(26) = 1.76$, $p = 0.09$).

Youths with major or minor depressive disorder demonstrated lower pupillary responses to negative words during the late period compared to youths with no depressive disorder regardless of disease status (Youths with depression: $M = -0.01$ mm, $SE = 0.02$ vs. Youths without depression: $M = 0.04$ mm, $SE = 0.02$, Cohen's $d = .44$; $F = 4.45$, $df = 1, 61$, $p = 0.04$) see Figure 2. There were no effects of disease status ($F = 0.80$, $df = 1, 61$, $p = 0.37$) or disease status x depression interaction ($F = 0.05$, $df = 1, 61$, $p = 0.82$) in this window. When analyzed separately, youths with IBD and major or minor depressive disorder ($M = -0.02$ mm, $SE = 0.03$) did not significantly differ in their pupillary responses during the late period when compared to youths with major depressive disorder ($M = -0.01$ mm, $SE = 0.02$) ($t(26) = 0.53$, $p = 0.59$, Cohen's $d = 0.11$). These findings indicate that youths with IBD and major or minor depression demonstrate decreased cognitive-affective load in response to negative stimuli that is comparable to youths with major depressive disorder.

Correlation of Pupil Responses with Depression Symptoms, Inflammatory Markers, and Steroid Intake

Depressive symptoms were inversely related to late pupillary responses to negative words, such that youths with greater depressive severity had less late pupillary responses to negative words ($r = -0.26$, $p = 0.04$). As shown in Figure 3, larger inflammatory response (as indexed by low albumin levels) was associated with smaller pupillary responses during the late period in youths with IBD ($r(17) = 0.75$, $p = 0.001$). No other relationships of albumin (early: $r(18) = 0.08$, $p = 0.76$), ESR (early: $r(18) = 0.13$, $p = 0.59$; late: $r(18) = 0.18$, $p = 0.47$), steroid dose (early: $r(23) = 0.00$, $p = 0.94$; late: $r(23) = 0.10$, $p = 0.63$), or steroid load (early: $r(21) = 0.00$, $p = 1.00$; late: $r(21) = 0.19$, $p = 0.41$) were associated with pupillary responses in the early or late period.

DISCUSSION

A substantial portion of youths with IBD experience increased symptoms of depression, potentially as a result of the influence of proinflammatory cytokines on CNS activity (5,12,34) and the effects of high dose corticosteroid treatment for IBD flares (35–38). However, it is unclear whether such medically induced depressions differ from other more endogenous depressions in regard to their psychological effects, e.g., how youths process negative emotional information. We found that youths with IBD (regardless of their depression diagnosis) demonstrated greater pupillary responses during the initial processing of negative emotional words relative to youths without IBD (regardless of their depression diagnosis). Tentative evidence suggested that youths with IBD and depression demonstrated greater initial processing than youths with depression alone, however we were not

adequately powered to detect this effect. IBD inflammation and steroid exposure were not associated with the observed early reactivity to negative emotional words so this result could be driven more by psychological aspects of medical illness (e.g., the stress of medical burden) than steroid or cytokine function in particular. Also, as in our original examination of depressed youths without IBD (16), depressed youths (regardless of their IBD diagnosis), demonstrated decreased pupillary responses 10 to 12 seconds after initial exposure to negative words compared to non-depressed youths (regardless of their IBD diagnosis). Moreover, youths with more severe depressive symptoms, and youths with greater chronic inflammation demonstrated a more marked decrease in late pupillary responses to negative words. Counter to predictions, steroid exposure was not associated with late pupillary responses.

The exaggerated initial pupil response to negative emotional words in youths with IBD could suggest that these youths experience more cognitive or emotional load in response to negative emotional stimuli when compared to youths who are not experiencing this devastating illness. Increased pupillary response could reflect either greater emotional reactivity or greater mobilization of resources associated with cognitive control and emotion regulation. Either explanation is consistent with research demonstrating that adolescents who experience early-life adversity (e.g., a life threatening illness) and recent chronic stressors (e.g., disruptions in social life and family conflict) demonstrate the greater release of cortisol during acute exposure to social stress independent of their diagnosis of depression (39). Unexpectedly, this increased processing was not associated with peripheral markers of inflammation or the steroid exposure potentially suggesting that proinflammatory cytokines and steroids are not directly associated with altered CNS activity in response to emotional stimuli. It is possible that unmeasured disease factors that are influenced by the proinflammatory cytokines and steroid exposure, such as psychosocial stress and decreased sleep, are influencing participants' CNS response to negative emotional stimuli. The very small observed effects suggest that failure to observe results was potentially due to low power to detect such mediating contributions.

Consistent with previous research on depressed youth (16), we observed that youths with depression, regardless of their IBD disease status, demonstrated a blunted or decreased pupillary response 10 to 12 seconds following initial exposure to negative words compared to non-depressed youth with and without IBD. These data could suggest that depressed youth engage in decreased regulatory control in response to negative emotional information, or avoid processing of negative emotional information (16). To the extent that depression in our IBD participants is due to their disease, early psychological vulnerability factors for depression such as rumination and worry may not be the primary determinants of this phenomenon. Though this finding suggests that such responses are not unique to endogenous depression it does not rule out a role for cytokine function entirely as proinflammatory cytokines have been also been associated with depression in the absence of IBD (40). Consistent with this idea, both depressive severity and increased inflammation in IBD participants were associated with decreased pupillary responses during the 10 to 12 seconds after the initial exposure to negative words. In adult IBD, research has identified comparable disruptions in central autonomic functioning that are associated with markers of chronic inflammation (41). Specifically, lower levels of albumin and higher levels of ESR have been associated with pupillary hyperreflexia which was associated with longer UC disease duration (41). Taken together, this suggests that markers of more severe illnesses are associated with greater alterations in cognitive-emotional processing that may potentially affect the duration of IBD illness. Alternatively, proinflammatory cytokines may lead to greater autonomic dysfunction which ultimately confers greater risk of developing autoimmune disorders (42,43). This research implies that the observed abnormal pupil

response to emotional stimuli may potentially represent a risk factor for developing IBD instead of being a result of IBD disease related factors.

Steroid exposure, which has previously been associated with increased depressive severity (8), was not linked to decreased pupillary response following initial exposure to negative words. This may suggest that steroids do not alter CNS activity directly, but instead may induce depression via some alternate means, for example by dysregulating sleep (37).

The current investigation has several limitations that warrant consideration. Of particular note, we had low power to detect relevant group differences; further investigation is clearly warranted to follow up on our initial and suggestive observations. Similarly, low levels of depressive severity and symptomatology amongst our nominally depressed groups, particularly within the IBD sample could have obscured true effects of affective disorder. Moreover, our IBD sample was heterogeneous in nature, being composed of both UC and CD. Furthermore, there was significant variability in the degrees of IBD activity. Low levels of IBD activity may have significantly reduced our ability to detect the effect of cytokines on CNS activity during emotional processing. Given that we were only able to obtain serum samples from youths diagnosed with IBD, we were significantly underpowered to detect small to moderate correlations between IBD disease factors and pupillary responses during exposure to negative emotional stimuli; however we were adequately powered to detect large effect sizes. Given the need to taper steroid dosage in IBD youth that responded to treatment, it is likely that the level of steroid exposure at the time of the assessment could have varied considerably across participants. This would have further reduced our ability to detect associations among pupillary responses, steroid exposure, and proinflammatory cytokines. It was not feasible, in the current study, to examine unique contributions of inflammation and steroid intake as withholding steroid treatment from patients with IBD can lead to greater disease complications ultimately requiring surgery. Though the pupil provides a marker of overall CNS activity with excellent temporal resolution, it does not allow for the spatial localization of brain regions that may be functioning abnormally in IBD, and is also affected by autonomic nervous system variation which may diverge from CNS activity. Thus these data suggest that further work with technologies better suited for unique measurement of CNS function and spatial localization, e.g., functional magnetic resonance imaging, are warranted. We did not assess other factors that have observed associations with pupillary reactivity such as gender, puberty, environmental stressors, genetic vulnerability, sleep disturbance, or interfering pain.

These limitations notwithstanding, we observed differences in pupillary responses associated with IBD and depression which could have important implications. Youths with IBD who are receiving treatment with exogenous steroids display pupillary changes consistent with greater CNS activity shortly after presentation of negative emotional words relative to individuals without IBD. In contrast, youths who are depressed regardless of the etiology of the depressive episode demonstrate decreased pupillary responses seconds after their initial exposure to negative emotional stimuli, potentially reflecting affective blunting, emotional avoidance, or decreased cognitive control. Thus, there appear to be unique contributions of medical disease and depression to physiological indications of emotional reactivity, but these factors do not appear to interact. Replication could suggest that it may be important to target additional aspects of reactivity to emotional information in treatments for depression in youths with high medical burden compared to other depressed youths. Future studies working to disentangle the effects of high dose steroid exposure and active IBD disease processes on pediatric depression should consider including alternate comparison groups such as newly diagnosed patients with as yet untreated active disease and patients whose disease is being treated with other biological agents or 5-ASA derivatives. Furthermore, given the prevalent biological differences between UC and CD as well as the

subset of UC patients that can subsequently develop CD, future studies should work to adequately sample pediatric populations with both diseases.

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Glossary

CD	Crohn's disease
CNS	central nervous system
DSM-IV	Diagnostic and Statistical Manual, Fourth Edition
ESR	Erythrocyte Sedimentation Rate
Hz	Hertz
IBD	Inflammatory Bowel Disease
PCDAI	Pediatric Crohn's Disease Activity Index
PUCDAI	Pediatric Ulcerative Colitis Disease Activity Index
UC	Ulcerative Colitis

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Figure 1. Pupillary responses to negative words in youths with IBD and no depressive disorder, youths with IBD and major or minor depressive disorder, youths with major depressive disorder, and comparison youths. Regions of a priori interest are indicated by shaded bands below the x-axis.

Figure 2.
Group differences in pupillary responses to negative words during the early (3 to 6 seconds – during the stimulus) and “late” (10 to 12 seconds – after the stimulus was removed) regions of temporal interest.

Figure 3. Association between the immune system's inflammatory response and papillary responses occurring 10 to 12 seconds after the initial presentation of negative emotional stimuli.

Table 1

Demographic Characteristics of Study Participants

Characteristic	Inflammatory Bowel Disease						No Inflammatory Bowel Disease					
	IBD Depressed (n=8)			IBD Non-Depressed (n=15)			Major Depression Group (n=20)			Comparison Group (n=22)		
	N	%		N	%		N	%		N	%	
Female	6	75		7	47		14	70		14	70	
Major Depressive Disorder	3	38		0	0		20	100		0	0	
Minor Depressive Disorder	5	63		0	0		0	0		0	0	
IBD Disease Type												
Crohn's Disease	6	75		8	53							
Ulcerative Colitis	2	25		7	47							
IBD Severity												
Inactive	1	12.5		6	40							
Mild IBD	3	37.5		6	40							
Moderate/Severe IBD	4	50		3	20							
Type of Corticosteroid Treatment												
Systemic Administration	8	100		14	93							
Topical Administration	2	25		3	20							
	M	SD		M	SD		M	SD		M	SD	
Age	13.7	2.1		14.4	2.3		13.8	2.5		12.7	2.6	
Mood and Feelings Questionnaire Score	13.5	6.5		7.0	6.5		19.2	12.1		3.1	5.5	
Pediatric Ulcerative Colitis Disease Activity Index	47.5	47		9.3	7.9							
Pediatric Crohn's Disease Activity Index	32.1	12.6		22.8	12.6							
Albumin (g/dL)	3.6	0.9		3.6	0.6							
Erythrocyte sedimentation rate	19	13.6		29.2	19.0							
Steroid dose (mg/day)	30	7.56		27.3	10.7							
Steroid load	928.1	566.0		1224.0	1199.6							