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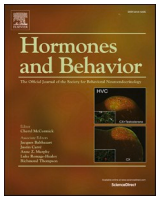

Estradiol effects on an emotional interference task in adolescents with current and remitted depression

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ABSTRACT

Attentional biases to emotional stimuli are thought to reflect vulnerability for mood disorder onset and maintenance. This study examined the association between the endogenous sex hormone estradiol and emotional attentional biases in adolescent females with either current or remitted depression. Three groups of participants (mean age ± SD) completed the Emotional Interrupt Task: 1) 20 adolescent females (15.1 ± 1.83 years) currently diagnosed with Major Depressive Disorder (MDD), 2) 16 adolescent females (16.4 ± 1.31 years) who had experienced at least one episode of MDD in their lifetime but currently met criteria for MDD in remission, and 3) 30 adolescent female (15.4 ± 1.83 years) healthy controls. Attentional interference (AI) scores were calculated as differences in target response reaction time between trials with emotional facial expressions versus neutral facial expressions. Estradiol levels were assayed by Salimetrics LLC using saliva samples collected within 30 min of waking on assessment days. Robust multiple regression with product terms evaluated estradiol's main effect on AI scores, as well as hypothesized estradiol × diagnostic group interactions. Although neither mean estradiol levels nor mean AI scores in the current-MDD and remitted-MDD groups differed from controls, the relationship between estradiol and overall AI score differed between control adolescents and the remitted-MDD group. Specifically, the remitted-MDD adolescents performed worse (i.e., showed greater attentional interference) when they had higher estradiol; no significant relationship existed in the current-MDD group. Because this finding was driven by angry and not happy stimuli, it appears higher estradiol levels were associated with greater susceptibility to the attention-capturing effects of negatively-valenced emotional content in girls at risk for MDD from prior history.

1. Introduction

Depression is among the most common mental health problems in adolescence, as 17 % of adolescents in the United States ages 12–17 have experienced at least one major depressive episode in their lifetime (Substance Abuse and Mental Health Services Administration, 2021). In adulthood, adolescent-onset depression often is associated with a chronic or recurrent illness course, marked by difficulty with interpersonal relationships, increased physical problems, suicide risk (Thapar et al., 2012), and impairment in global functioning (Kertz et al., 2019). Because adolescent-emergent depression is associated with such poor outcomes and few individuals reach full symptomatic recovery (Conradi et al., 2011), researchers have sought to identify factors that influence disorder onset, maintenance, and reoccurrence in teenagers. One particular focus has been biological changes that occur during puberty. After puberty onset, the low prevalence of depression (<1 % in most childhood studies) rises substantially. Disorder prevalence changes to 2:1 for girls versus boys (Thapar et al., 2012) with a peak sex difference at age 16 across the lifespan (Salk et al., 2017). In older women, lower estradiol levels are linked to depression onset (Schmidt, 2005) and

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maintenance (Frey et al., 2008). However, the peri- and post-menopause phases examined in these studies are quite different from puberty, raising questions about whether a comparable relationship exists for teenage girls. Evidence is sparser about estradiol levels' relationship to depression onset, maintenance, and prevention in adolescents, despite evidence that adolescent depression is more closely linked to hormonal changes than to chronological age (Lewis et al., 2018). As such, it is important to understand the mechanisms through which estradiol levels might confer risk or resilience for mood disorder in this age group.

A common feature of depression found in clinical studies is the reliable presence of attentional biases, typically defined as a tendency for attention to be preferentially directed towards or away from different types of stimuli in the environment, such as a lack of attention towards positive information (Elgersma et al., 2018). Depressed persons also demonstrate better recall for depression-specific stimuli and recall more negative than positive stimuli (Fritzsche et al., 2010). Several experimental tasks have been used to measure attentional biases in depression, such as the Emotional Stroop task and the Emotional Dot Probe task. Studies using these paradigms in depressed individuals have produced equivocal results. Some studies have demonstrated attentional biases in depressed individuals (Winer and Salem, 2016; Scher et al., 2005); however, a larger number have failed to show this effect (Gotlib et al., 2004; Fritzsche et al., 2010). Only four studies have examined the association between estradiol and attentional biases. Most of these studies established links between higher estradiol and both greater early automatic visual processing (Lusk et al., 2015), and difficulty suppressing the processing of negative emotional stimuli (Lusk et al., 2017; Graham and Shin, 2018). In contrast, one found combined oral contraceptive use had no influence on attentional bias in healthy women (Scheuringer et al., 2020). We are unaware of any prior study that has examined the relationship of estradiol levels to attentional biases in adolescent females with and without depression.

An infrequently-used paradigm that can quantify attentional biases is the Emotional Interrupt Task (EIT). The EIT examines the interference of emotional stimuli on basic goal-directed behavior by measuring whether simple target identification reaction time is changed on trials where emotional information preceded and followed those trials. The EIT differs from the Emotional Stroop and Emotional Dot Probe tasks in the sense that the latter both assess the effects of emotional salience on response behavior when emotional information is presented contemporaneously with other information that competes for cognitive resources, while the EIT assesses the effects of emotional interference on subsequent responses to other stimuli. This provides researchers a measure that can be sensitive to influences on cognitive processing time from both bottom-up sensory processes like emotional salience, or top-down influences such as executive attentional mechanisms (Mitchell et al., 2008). The EIT has been used in only six studies since its conception in 2006. Healthy non-patient's responses are consistently slower when responding to a shape if that shape is temporally bracketed by an emotional stimulus, regardless of valence (Mitchell et al., 2006; Rich et al., 2010) – an attentional interference (AI) effect. In contrast, individuals theorized to have emotion processing deficits such as those with psychopathy or severe mood dysregulation have less AI to the emotional distractors (Mitchell et al., 2006, Rich et al., 2010). Although the EIT has not been used as often as the Emotional Stroop or the Emotional Dot Probe tasks, it has promise to add useful new information about attentional bias to researchers' efforts to understand attentional biases in depression.

In the present study, we compared EIT performance of female adolescents with either a current or a past diagnosis of MDD. This study design also offered the opportunity to determine whether there are any relationships between EIT performance and depression, as well as between attentional interference and absolute estradiol levels. Therefore, we also examined the relationship between estradiol levels and AI by EIT emotional distractors, because no prior study has examined if estradiol scores might differ between participant groups defined by the presence or absence of MDD in depressed female adolescents. Study goals were to determine: i) if EIT performance differed for either MDD study group relative to never depressed control adolescent females, ii) if estradiol levels differed between non-depressed, formerly-depressed, or currently-depressed study groups, iii) if estradiol levels predicted EIT performance, and iv) if the relationship between estradiol levels and AI might be different in the three participant groups. We predicted that higher estradiol levels would predict worse performance on the EIT in both the MDD current and the MDD remitted group on negative stimuli. This study is potentially informative because investigators do not yet have a full understanding of whether estradiol might modulate attentional biases in mood disorder in adolescent females. More information about any relationships between these factors is needed to further develop theories about the role of estradiol on this putative neurocognitive risk factor for depression.

2. Methods

2.1. Participants

Three groups of participants age 12–18 were included: 1) 20 adolescent females currently diagnosed with Major Depressive Disorder (MDD), 2) 16 adolescent females who had experienced at least one episode of MDD in their lifetime but currently met criteria for MDD in remission, and 3) 30 adolescent female healthy controls. These participants were drawn from a larger study funded by an administrative supplement to R01MH102852 which examined the neural architecture of emotion regulation. All participants were recruited from local newspaper ads, community placed flyers, and social media advertisements. Participants in the current-MDD group were included if they met the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL) criteria for a current major depressive episode. Participants in the remitted-MDD group were included if they met the K-SADS-PL criteria for a past major depressive episode. Participants in the HC group were excluded if they had met the K-SADS-PL criteria for either a current or past major depressive episode. Participants in all study groups were excluded for left-handedness, learning disabilities, an estimated IQ below 80 assessed by the WASI, a lifetime history of schizophrenia, bipolar disorder, psychotic disorder, OCD, autism, any pervasive developmental disorder, PTSD, social phobia, generalized anxiety disorder, Tourette's disorder, ADHD, conduct disorder, current substance use disorder, any neurological disorders, any chromosomal disorders, any autoimmune disorders, brain trauma, brain tumors, any psychotropic medication, or a first degree relative with a lifetime history of schizophrenia or Bipolar I illness. Participants in the MDD-C group and MDD-R group also were excluded if they had a previous failed SSRI treatment, previous or ongoing ECT, or the onset of their MDD was before the age of 10. All guardians of participants gave informed consent, all participants gave informed assent, and all protocols were approved by the Hartford Healthcare ethics committee and were in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association.

2.2. Diagnostic assessment

Participants ages 12–17 and their parent were administered the K-SADS-PL (Chambers et al., 1985) semi-structured interview to confirm the presence or absence of DSM-IV Axis I affective disorders. Parent and child interviews were conducted separately. Participants aged 18 were administered the Structured Clinical Interview for DSM-IV (SCID-IV, First and Gibbon, 2004). A trained research assistant conducted the interview and diagnoses were confirmed in a weekly diagnostic consensus meeting with a licensed clinical psychologist.

2.3. Salivary assessment of estradiol levels

Following informed consent and diagnostic assessment, participants were given saliva sample collection materials and instructions. Evidence supports strong correlation between salivary and blood derived estradiol concentrations across the menstrual cycle which range across studies from $r = 0.60$ to 0.93 (Sakkas et al., 2021; Huang et al., 2023). In addition, many studies in adolescents utilize salivary hormone levels as the collection does not require venipuncture (Granger et al., 2012). Samples were not entrained to any menstrual cycle phase in order to capture naturally-occurring variation in estradiol levels. Data on average age at menarche and hormonal contraception was available for all but 3 participants in the MDD-R group (see Table 1). Average age at menarche and percentage of participants on hormonal contraception did not statistically differ between groups. To confirm that the primary analyses were independent of the influence of adolescents using hormonal contraception, a set of supplementary analyses were run with only cycling participants included.

Saliva samples were obtained within 30 min of waking on the morning of their cognitive testing, consisting of 2 mL of passive drool into a polypropylene cryovial. Samples were analyzed by Salimetrics LLC. The Salimetrics assays have been designed for consistent performance in saliva, including utilizing diluents that control for inconsistency in the passive drool matrix. See online specifications on the salivary estradiol ELISA kits (Salimetrics Estradiol Assay Specifications, 2023). All observed estradiol values were above the 0.1 pg/mL lower limit of assay sensitivity, ranging from 0.42 to 6.11 pg/mL. The participant mean value of estradiol was 1.78 pg/mL (± 1.03). The intra-assay coefficient of variation for estradiol was 5.28 % and the inter-assay coefficient of variation was 1.08 %. The samples were tested twice and the average of the two assayed values were used for hypothesis-testing. Because salivary estradiol levels were positively skewed across the sample, a set of supplementary analyses was conducted using log-transformed values to check the robustness of the results.

2.4. Emotional interrupt task

The original Emotional Interrupt task (Mitchell et al., 2006, 2008; Rich et al., 2010) assesses the impact of emotional stimuli on attention. A set of 32 faces were chosen from the Karolinska Directed Emotional Faces (KDEF) Database (Lundqvist et al., 1998), with an equal number of male and female faces. Straight angle facial expressions of angry, happy, and neutral were selected for all chosen identities. Images were cropped to 449 × 337 pixels, then resized to 800 × 600 pixels (~28 × 21 cm). Each facial expression (32 happy, 32 angry, and 32 neutral expressions) was presented twice, paired once with a circle or square, across four randomized blocks for 64 trials of each facial expression type and a total of 192 trials. Fig. 1 depicts an exemplary sequence of stimuli presented to the participant in the Emotional Interrupt Task. Each trial began with the display of a white fixation cross in the middle of the screen for 800 ms, followed by the presentation of a facial expression for 200 ms. A target stimulus of either a white circle or a square then was presented for 150 ms, which was followed by the same picture that had preceded the target shape for 400 ms. A blank screen appeared for 1200 ms between trials. Participants were instructed to respond as quickly and accurately as possible to the target stimulus (circle/square) using left index fingers (computer keyboard letter f) for circles and right index finger (j) for squares. A brief 15,000 ms rest period was provided between the second and third block. The EIT demonstrates stable test-retest reliability and internal consistency across conditions (Bondy et al., 2018). The current study modified the original task by replacing IAPS images with facial expressions of emotion to avoid any familiarity effects from re-using the same IAPS stimuli that was employed in parent R01 experimentation. The task was presented on a Lenovo-M93z-B desktop with a 1920 × 1080 screen resolution using *E*-Prime software (Psychology Software Tools, Pittsburgh, PA).

Table 1
Demographics and clinical data.

	HC	MDD-C	MDD-R	p value
N	30	20	16	
Age, years	15.4 ± 1.83	15.1 ± 1.64	16.4 ± 1.31	0.05[a]
PDS score	7.7 ± 1.51	8.4 ± 0.79	8.3 ± 0.75	0.14
Age at Menarche	11.9 ± 1.92	11.6 ± 1.23	11.8 ± 1.24	0.81
% on Hormonal Contraception	11.5 ± 0.33	10 ± 0.31	38.5 ± 0.51	0.06
IQ Estimate	107.9 ± 10.28	102.6 ± 10.72	103.6 ± 11.03	0.19
BDI T Score	4.4 ± 4.82	25.6 ± 5.98	11.4 ± 12.08	< 0.01[a]
BDI Somatic T Score	2.1 ± 2.89	11.5 ± 3.42	4.9 ± 5.01	< 0.01[a]
BDI Cognitive T score	1.9 ± 2.07	12.6 ± 4.27	6.4 ± 5.75	< 0.01[a]

[a] HC, MDD-C, and MDD-R all significantly ($p \leq 0.05$) differed.

2.5. Measures

Attention interference (AI) scores were computed for happy and angry facial expression types by subtracting mean reaction time on trials with neutral expressions from mean reaction time on trials with the emotional expression in question. Positive scores indicated greater emotion induced attention interference and negative scores indicated emotion induced attention enhancement. Overall AI, which was calculated by subtracting the mean reaction time of all of the emotion trials from the mean reaction time of all of the neutral trials, was used as the primary dependent variable, and post hoc tests examined differential effects of Angry AI or Happy AI scores. Only EIT reaction times between 200 and 1500 ms from correct responses were used in AI score calculation. Because the EIT has only once before been used in adolescents, we inspected overall and participant groups' reaction times to neutral, negative and positive stimuli before hypothesis-testing to see if average AI scores were consistent with those found in adult samples. Particular attention was given to the comparison of performance between the non-MDD control group and the healthy, non-patient adults in prior EIT studies (Mitchell et al., 2006; Mitchell et al., 2008).

2.6. Analyses

All analyses used R 4.1.1 software (R Core Team, USA). To compare our groups on demographic and clinical variables, we used ANOVAs to examine age, Pubertal Development Scale (PDS; Petersen et al., 1988) score, IQ, estradiol levels, and self-reported levels of depressive symptoms. One sample *t*-tests were conducted to assess whether differences in overall emotional AI, angry AI, or happy AI existed for each group and whether these differences were systematically different from zero across the sample. A series of robust multiple regression models with product terms was used to test study predictions. These models were tested using the *Robustbase* R software package (Maechler et al., 2019). This was chosen to ensure the analyses would be robust to outlier values or non-normal distributions when examining relatively smaller sample sizes. In addition to testing for group differences in average AI score or estradiol levels, these models tested whether or not estradiol levels predicted AI scores, and if there were interactions between AI and estradiol levels across currently depressed (MDD-C), remitted-depressed (MDD-R), and never-depressed healthy control (HC) study groups. All robust regression models used attentional interference (AI) scores as the dependent variable. The overall AI score and mean centered estradiol levels were entered as the first predictor terms. Dummy-coded group terms for MDD-C and MDD-R were entered next. Finally, two product terms were included to represent the estradiol × MDD diagnostic group interactions. Post hoc models specific to angry or happy AI scores had the same general structure. Significance level was set at $p < 0.05$. The nature of the interactions between estradiol and other predictors were depicted with additional simple slope post hoc analyses, in which the regression

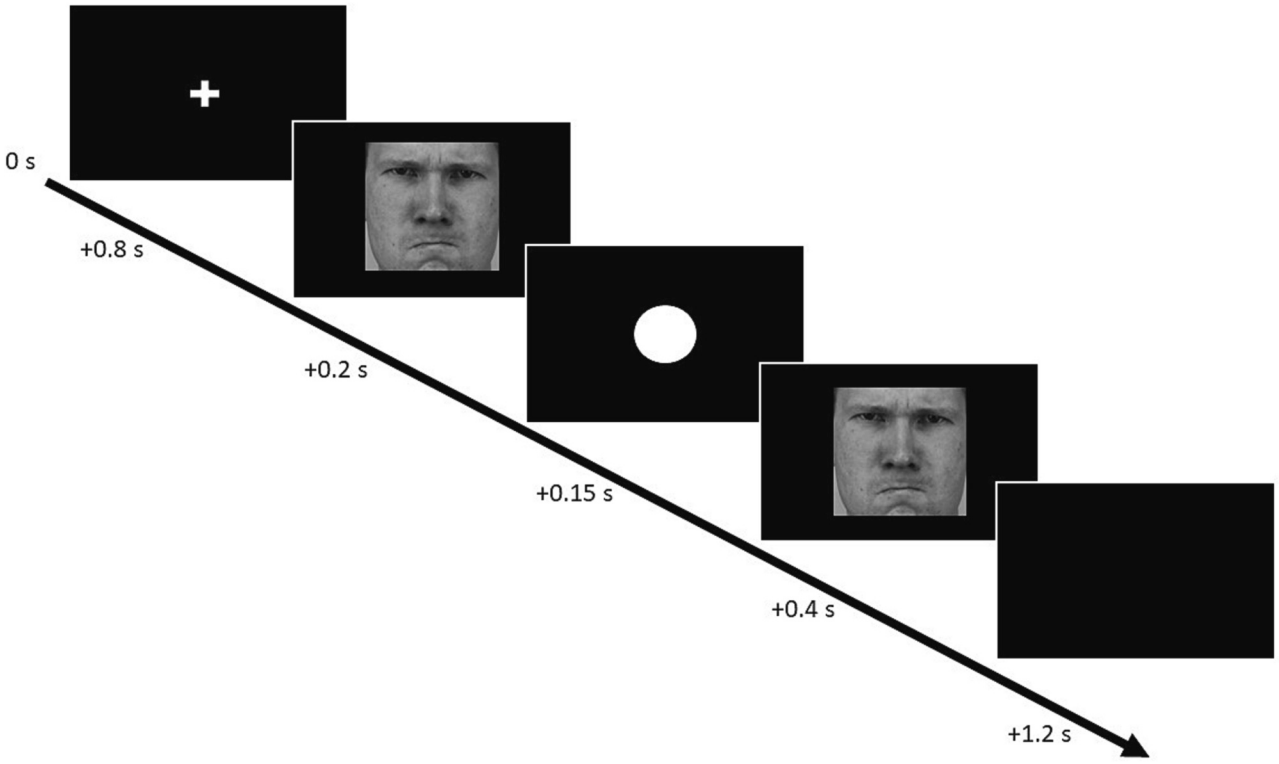

Fig. 1. Exemplary Sequence of the Emotional Interrupt Task.

of the outcome variable (AI) on the predictor (estradiol levels) were plotted separately for MDD-C, MDD-R, and HC groups.

To confirm results, we did supplementary analyses using log-transformed estradiol values, which are often employed to ensure findings are robust to the sometimes non-normal distribution found for estradiol assay data. We also re-examined the data excluding the individuals on hormonal contraception to ensure results were independent of adolescents on hormonal contraception. In addition, we re-analyzed the data using age or pubertal status as covariates to ensure any findings could not be better explained by developmental differences across the study groups. Finally, we also re-inspected the data after excluding HC's with a depression history from analyses, as defined by the Family History Screener (Weissman et al., 2000), to confirm that familial risk did not affect study findings. Finally, post hoc power analyses were done to inform the level of Type II error rate control.

3. Results

3.1. Demographics and clinical characteristics

Participant details by group are presented in Table 1. One-way ANOVA showed the MDD-R participants were slightly older, but pubertal status measured by the PDS did not significantly differ between groups. As expected by study design, depression severity measured by the Beck Depression Inventory II (Beck et al., 1996) was higher in the two MDD groups, with currently depressed teens having the highest BDI-II scores.

3.2. EIT task performance and group differences

Table 2 lists mean AI scores calculated for each group, along with the results of testing whether those scores statistically differed from zero for each group. AI scores were computed by subtracting mean reaction time on trials with neutral expressions from mean reaction time on trials with an emotional expression, with positive scores indicating AI and negative scores indicating attentional enhancement. There was a wide range of scores across participants. Only valence-specific AI subscores statistically differed from zero. Testing of Angry and Happy sub-scores revealed different interference effects by emotional valence. Detection of the target stimulus was quicker in non-patient control with angry-valenced stimuli, while detection of the target stimulus was slowed in MDD-R group participants with happy-valenced stimuli. Direct comparison found no differences in overall emotional AI scores between healthy controls and the MDD-C group ($p = 0.73$), or between healthy controls and the MDD-R group ($p = 0.94$).

3.3. Estradiol group differences

Mean estradiol levels did not differ across study groups (all p values >0.48). Mean estradiol levels ± SD for each group were as follows: the

Table 2
Group performance on the emotional interrupt task.

	HC			MDD-C			MDD-R		
Variable	Mean	*t*	*p*	Mean	*t*	*p*	Mean	*t*	*p*
Emotional AI	−4.008	1.066	0.29	−0.236	0.053	0.96	−6.761	1.536	0.15
Angry AI	−9.871	2.3017	0.03[a]	4.058	0.797	0.44	−3.705	0.728	0.48
Happy AI	1.624	0.387	0.70	−4.449	0.953	0.35	−9.616	2.089	0.05[a]

[a] AI scores significantly ($p \leq 0.05$) differed from zero using a one-sample *t*-test.

HC group was 2.00 ± 0.95 pg/mL, the MDD-C group was 1.52 ± 1.23 pg/mL, and the MDD-R group was 1.67 ± 0.85 pg/mL.

3.4. Relationships between estradiol and overall emotional attentional interference score

There was no main effect of estradiol level on overall emotional AI ($p = 0.63$) scores when all group data were aggregated for analysis. However, interaction tests (see Fig. 2) found the relationship between estradiol and AI for the MDD-R group differed from their relationship in control group adolescents ($p = 0.02$). This AI/estradiol relationship did not statistically differ between the control adolescents and the MDD-C group ($p = 0.33$).

3.5. Post-hoc simple slope analyses to characterize interaction effects

Post hoc simple slope analyses revealed directionally opposing relationships between overall AI score and estradiol level in the MDD-R group compared to the other two study groups. Although there was a range of AI scores across estradiol levels for every group, female adolescents in the MDD-R group with higher estradiol levels had worse scores of overall attentional interference ($r = 0.53$, $p = 0.03$), evidenced by a greater positive score (see Fig. 3). In contrast, the association between AI and estradiol was essentially flat for control participants ($r = -0.18$, $p = 0.34$) and female adolescents in the MDD-C group ($r = -0.15$, $p = 0.52$).

3.6. Supplementary analyses

The study supplement describes post hoc analyses that separated angry AI from happy AI scores, examined naturally-cycling participants and log transformed estradiol levels, tested models in which age or pubertal development scores were added as covariates, and assessed the effects of removing individuals in the HC group with a familial history of depression. Further analyses of angry and happy AI sub-scores revealed that the significant study group × estradiol level interaction found for overall AI scores clearly was driven by negatively-valenced angry stimuli. All supplemental analyses done only on angry stimuli provided the same results as overall AI. In contrast, analyses that focused on happy stimuli were non-significant. Otherwise, no meaningful differences emerged from these analyses to alter study findings. Post hoc power analyses for conventional regression with 6 predictors for $N = 66$ participants provided 81.1 % power for omnibus R^2 values >0.19. The primary model $R^2 = 0.09$, while angry AI and happy AI supplemental analyses R^2 values were 0.15 and 0.11, respectively. As such, this study cannot confidently reject the null hypothesis of no effects if any of the group differences, associations, or interactions were of "small" or "medium" size.

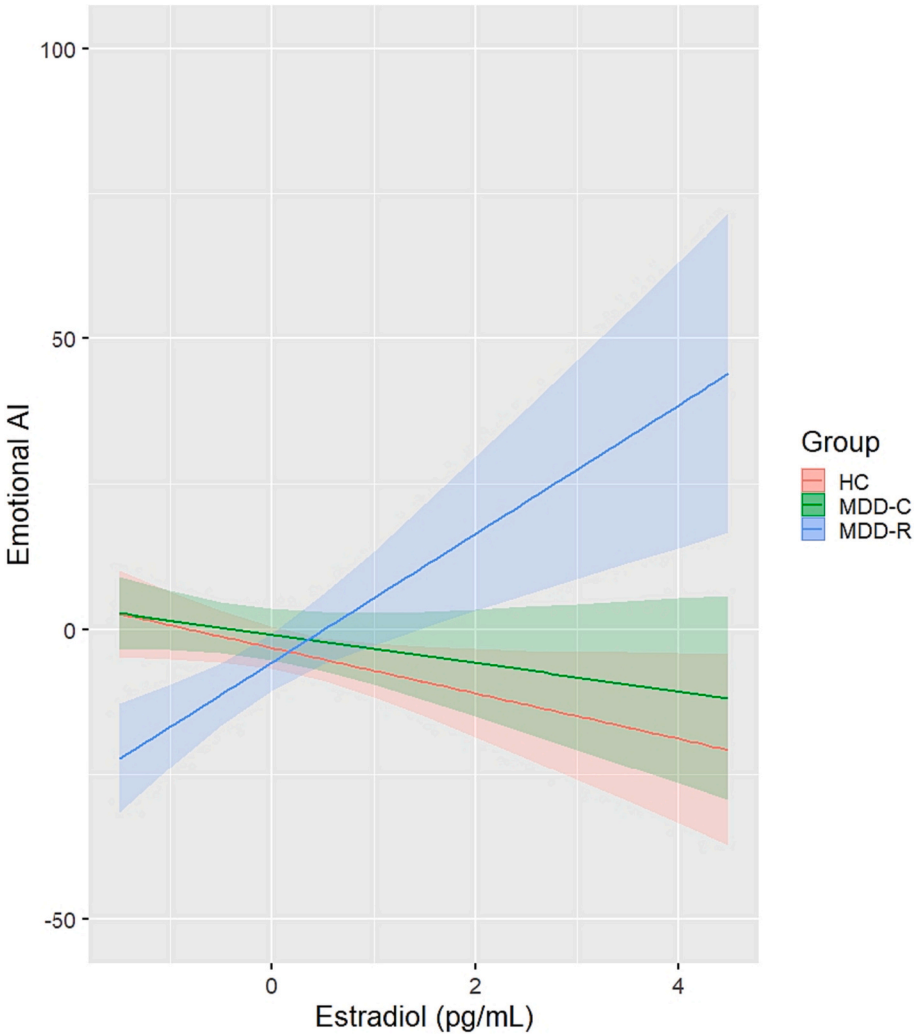

Fig. 2. Interactions between estradiol and diagnosis on overall emotional AI.

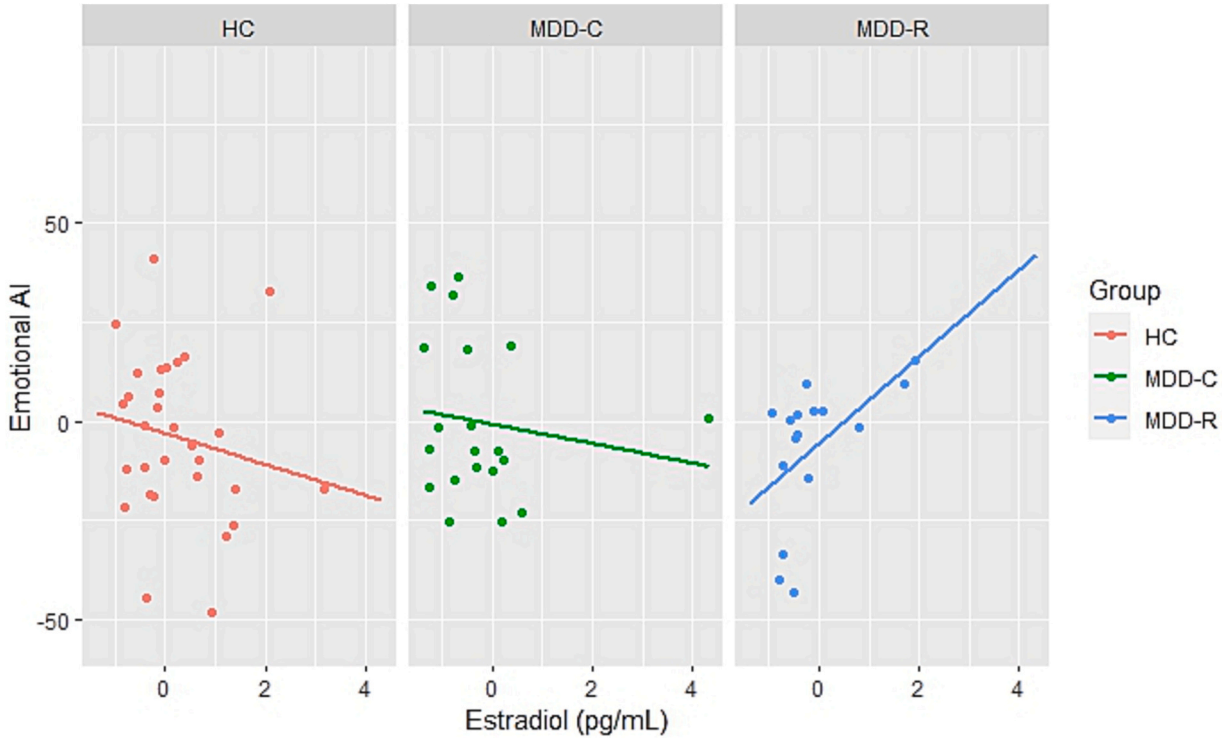

Fig. 3. Scatterplot of estradiol and diagnosis on overall emotional AI.

4. Discussion

This study is the first to examine the relationship between adolescent females' estradiol levels and their EIT attentional interference measurements of emotion-related attentional bias. It also is the first to contrast this relationship among groups of adolescent girls with current depression, remitted depression, and no lifetime histories of depression. The main study finding was that higher estradiol levels were associated with greater susceptibility to the attention-capturing effects of negatively-valenced emotional content in girls at risk for depression from a prior history of MDD when compared to never-depressed adolescents. This was shown by a longer latency to respond when the EIT task target stimulus was preceded and followed by angry, but not happy, faces. This same association was not seen in female adolescents with a current diagnosis of depression. Contrary to predictions, average AI scores did not differ between participant groups when collapsed across emotions. This suggests the EIT may not be generally sensitive to attentional biases in depression, in contrast to prior studies which found attentional biases to emotion in adolescents with other diagnoses such as bipolar disorder and severe mood dysregulation (Rich et al., 2010). In addition, this study did not find estradiol levels differed between study groups defined by the presence or absence of MDD. However, because estradiol sampling was not standardized to menstrual phase this latter negative finding should not be viewed as conclusive, but rather suggestive of the likely lack of a relationship, at least within this age range. This highlights the need for future research to conclusively link absolute or relative levels of estradiol with risk factors for the onset and maintenance of mood disorders in adolescence.

Biased competition attention models for simultaneously presented visual information (Desimone, 1998; Desimone and Duncan, 1995) would suggest reaction time advantages or costs reflect neurobiologically-based priorities for processing certain types of material. Such theoretical explanations apply when stimuli are presented contemporaneously, as in commonly used attentional bias tasks such as the Emotional Stroop or Emotional Dot Probe. In contrast, the EIT task measures a comparable but distinct form of attentional bias whose effects are observed on stimuli which participants see after the ones that capture attention. While EIT attentional interference effects can be interpreted as most probably arising from attentional bias to emotionally relevant information, the interpretation takes on additional significance when one considers that this effect can only carry over to subsequent stimuli processing if there is some persistent trace effect of the emotional bias even when no emotional features are immediately competing for attentional prioritization. This suggests the current study's EIT results do not simply reflect a tendency for negative emotional features to become the focus of attentional resources when estradiol levels are relatively high, but rather to capture and briefly hold that focus at least several hundred milliseconds afterwards when processing non-emotional stimuli, as seen in the attentional blink task (McHugo et al., 2013). However, because the target stimulus is both preceded and followed by the emotional stimulus, the EIT cannot disentangle which emotional stimulus is producing the effects. Also, while longer reaction times most likely can be attributed to reduced availability of attentional resources, there are alternative explanations. They could be a result of the neutral stimulus obtaining a learned emotional relevance through repeated pairing of the positive or negative faces with the target stimulus as seen in reinforcement conditioning, additional cognitive processes to switch out of the emotion-congruent mental response set that was established, or perhaps a combination of these mechanisms.

Interestingly, AI scores on the EIT were associated with estradiol only for angry – but not happy – emotional face distractors in the remitted MDD adolescents. This indicates any influence of estradiol levels on attentional bias or capture is unlikely a general feature of emotional salience, but rather is selective to negative, perhaps specifically threateningly angry valence – at least, for the remitted MDD adolescents who showed this effect here. An interpretive caveat arises when recognizing study participants' mix of positive or negative AI scores. Although this study's non-MDD control group showed a small but significant angry AI facilitative effect on average, the participants in all study groups had a wide range of negative to positive AI scores, reflecting the presence of both emotional facilitation versus

interference. As such, emotional distractors either facilitated target engagement for some adolescents, or interfered with information processing as generally seen in prior EIT studies of adults (Mitchell et al., 2006; Mitchell et al., 2008). In light of this individual variability, perhaps the clearest interpretation of the main finding is that a small general tendency observed in the non-MDD adolescent control group for emotion to facilitate simple target identification clearly was reversed in the remitted-MDD group to become interference in those girls who had the highest estradiol levels.

Interesting questions are raised by the observation that the attentional interference effect was only observed in the remitted-MDD group and not the current-MDD group. Many other studies have similarly found that remitted depressed patients display attentional biases towards negative stimuli (Zvielli et al., 2016; Albert et al., 2017; Elgersma et al., 2018). One study even found that this attentional bias was exclusively seen in remitted, but not current, depressed individuals (Elgersma et al., 2018). This abnormal association may represent a selective cognitive vulnerability for MDD. However, this explanation is challenging to interpret in the context of a null finding for the current-MDD group. One potential explanation for the lack of effect in the current-MDD group could be that the estradiol/attentional bias relationship seen in the remitted-MDD group was masked by affective blunting often seen in current-MDD patients. Such well-described emotional blunting could have impacted the AI distribution of emotional interrupt performance in this group. Explanations for the lack of effect in the current-MDD group remain speculative at this stage and future research will be necessary to disentangle this or other possibilities. Another curious finding was the emotional facilitation effect seen in study controls is the opposite of what has been seen in prior EIT studies. Only one prior EIT study examined adolescents (Rich et al., 2010); it found an interference effect to both positive and negative pictures. While this might reflect sampling sex differences, our use of KDEF facial stimuli instead of IAPS emotional scenes also could have led to different interference effects. Control participants could have found the KDEF facial stimuli less arousing than the IAPs emotional scenes used in prior studies.

It has been theorized that estradiol can act as a potential modulator to rapidly mediate a number of behaviors, cognitive processes, and neurobiological systems by altering neuronal function, including brain regions related to emotional attention and depression (Srivastava and Penzes, 2011). Using fMRI, Mitchell and colleagues showed EIT emotional distractors increased amygdala activity and reduced prefrontal and parietal lobe activity in regions engaged for attentional control (Mitchell et al., 2008). This raises the possibility that any direct effect of estradiol on EIT behavior might be measurable as altered activity in these particular brain regions. It is plausible that estradiol levels might influence the exchange of information among these cortical regions when they are engaged in direct attention. Review of human fMRI studies of estrogen-brain function relationships find that sex hormone levels affect prefrontal cortex activity levels on tasks that require emotional information processing, albeit in different ways depending on menstrual cycle phase (Toffoletto et al., 2014). High estradiol levels versus low levels predict amygdala activation to negatively-valenced stimuli (Andreano and Cahill, 2009; Gingnell et al., 2012) and dorsolateral prefrontal activity during regulation of negative emotions (Chung et al., 2019). However, an fMRI EIT study that examines how high versus low estradiol levels would be needed to determine if this hormone influence brain activity that underlies attentional biases to emotional information.

Additional research will be needed to disentangle these complicated mechanistic possibilities or to extend the current study's main finding in meaningful ways. In particular, the credibility of this EIT association with estradiol as a mood disorder risk marker would be bolstered if future studies find AI scores are heritable, or by finding the estradiol/AI association is developmentally influenced or has a specific genetic risk profile. Attentional bias in MDD itself already has met similar criteria. For instance, studies have strong heritability estimates of 0.40–0.55 for modulation of the P300 in response to emotional stimuli and for neural regions thought to underlie attentional biases (Gibb et al., 2016). Even in the current absence of such empirical reassurance, the possibility that estradiol levels might accentuate a known MDD risk factor should prompt some speculation on how such knowledge might be leveraged for any therapeutic benefit to mitigate MDD recurrence. For instance, it has been shown attentional bias modification (ABM) treatment in individuals with previous depression can reduce activation in the amygdala when viewing negative images (Hilland et al., 2020). Similarly, training attentional bias with positive faces using computerized attentional bias modification tasks also has been shown to reduce the score of two separate scales that measure risk of depressive recurrence (Browning et al., 2012). It might be that such preventative treatment can be optimized to best prevent MDD relapse if administered when girls undergo training when they presumably are most susceptible to the negative effects of attentional bias, i.e., when estradiol levels are high.

There are several study limitations to acknowledge. First, while all prior EIT studies used IAPS pictures as stimuli, this study used the KDEF database. Although utilizing the KDEF database provides useful new information, the choice also limits direct comparability to previous EIT studies. Second, small samples and the differences in sample size of each group – while arguably appropriate for an initial study – raise the possibility that this was an isolated effect. Moreover, false negative findings are possible for small or medium effect sizes. As such, replication studies with larger samples are necessary both for representativeness and for more confident control over Type II error rates. Third, estradiol values exist in a milieu of other sex hormones (e.g., progesterone, testosterone, and other estrogens). Although a focus on estradiol can be justified given the initial, exploratory nature of the study, any larger future study ideally would assess if these other hormones or menstrual phases influence emotion-related attentional bias. In addition, replication studies utilizing LC-MS/MS salivary assays or serum estradiol measurement methods could be conducted to corroborate the findings of this study and provide comparative continuity with prior serum estradiol-based research. Fourth, while other studies have found elevated estradiol is associated with elevated depression scores in adolescent boys (Chronister et al., 2021), this study did not include adolescent boys in its analysis. Future studies could examine whether similar relationships between estradiol, attentional interference, and diagnosis exist in adolescent boys. Finally, the cross-sectional nature of this study prevents any inferences about possible causality in the relationship found between EIT score, estradiol, and mood disorder risk. Future studies should consider an exogenous estradiol challenge or a within-subjects retest design throughout the menstrual cycle to begin to differentiate cause from consequence in this association. Conversely, study strengths include the novelty of measuring attentional inference with the EIT to study depression, estradiol levels and their interaction, the use of robust statistics to maximize the small sample size, and attention to statistical covariates and analysis alternatives to ensure rigor. These strengths bolster the link found between estradiol and attentional bias for remitted MDD adolescent girls.

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Declaration of competing interest

All authors have confirmed they have no financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yhbeh.2023.105450.

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