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Connectivity Patterns Evoked by Fearful Faces Demonstrate Reduced Flexibility Across a Shared Dimension of Adolescent Anxiety and Depression

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Abstract

Adolescents experiencing anxiety or depression exhibit cognitive biases favoring the processing of negative emotional information. It remains unknown whether common neurobiological processes underlie these biases across anxiety and depression. Here, brain imaging was acquired from typical, anxious, and depressed adolescents during an emotional-interference task. Functional connectivity patterns were assessed while adolescents were cued to attend to or ignore faces. Results revealed a shared dimension of anxious and depressive symptoms was associated with reduced changes in connectivity patterns between conditions in which adolescents needed to ignore or attend to fearful faces. These findings were exclusive to fearful faces and observed only for functional connections with a primary face-representation area (fusiform gyrus). Results suggested a failure to flexibly adapt communication patterns with sensory-representation areas in the presence of negative emotional information, which may reflect a common neurobiological mechanism explaining biases favoring such information shared among adolescent anxiety and depression.

Keywords

adolescent development, anxiety, cognitive bias, depression

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Adolescence is a critical time for understanding the neurobiological processes involved in anxiety and depression given that nearly half of lifetime diagnoses of mental disorders emerge by age 14 (Kessler et al., 2005). Anxiety and depression often co-occur in adolescents (Brown et al., 2001; Kessler et al., 2005; Muris et al., 2004; Zavos et al., 2010), which suggests that similar factors may be involved in their etiology and maintenance (see Hofmann et al., 2012; Mathews &

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MacLeod, 2005; Watkins, 2008). Laboratory studies of anxiety and depression evidence impairments in the ability to disengage attention from or to inhibit ongoing cognitive processing of negative emotional information related to these disorders (Eysenck & Byrne, 1992; Ferneyhough et al., 2013; Fox et al., 2001, 2005; Goeleven et al., 2006; Heim-Dreger et al., 2006; Hubbard, Hutchison, Hambrick, & Rypma, 2016; Hubbard, Hutchison, Turner, et al., 2016; Joormann, 2004; Joormann & Gotlib, 2008; Klein et al., 2018; Koster et al., 2005; Ladouceur et al., 2005, 2009; Mathews & MacLeod, 1985; Richards et al., 2000; Yiend & Mathews, 2001). These findings highlight cognitive biases that favor the processing of negative emotional information, which may relate to core clinical phenomena observed across disorders (e.g., repetitive negative thinking [rumination and/or worry], sustained negative affect; see Hirsch & Mathews, 2012; Joormann & Vanderlind, 2014; Mathews & MacLeod, 2005). It remains unknown, however, whether common neurobiological processes underlie these biases across anxiety and depression.

Performance During Negative Emotional Conflict

Anxious and depressed persons exhibit performance impairments when negative emotional information precedes or is presented concurrently with goal-relevant information (i.e., negative emotional conflict), which evidences similar tendencies to prioritize the processing of negative information over goal-relevant information associated with these disorders. For example, supraliminal variants of the emotional Stroop task have revealed relationships among anxiety, depression, and slower naming of the ink color of negative emotional words or images (see Bar-Haim et al., 2007; Dudeney et al., 2015; Eysenck et al., 2007; Foland-Ross & Goblib, 2012; Williams et al., 1996). The goal of this task is to identify the superficial features of a word or image quickly and accurately (i.e., ink color). Additional (e.g., affective) processing of the stimulus is irrelevant and can impede goal-relevant performance. Although Stroop-interference effects are not always evidenced in anxiety and depression (see Yiend, 2010), a general trend of slowed identification of the ink color of negative emotional stimuli suggests greater processing of the affective features of these stimuli to the extent that this additional processing interferes with goal-relevant task performance.

Likewise, spatial-cuing paradigms have revealed that major depressive disorder (MDD), dysphoria (i.e., elevated depressive symptoms), and high state and trait anxiety are associated with slowed responses to goal-relevant targets when presented alongside goal-irrelevant, negative-emotion attention cues (Ferneyhough et al., 2013; Fox et al., 2001; Koster et al., 2005; Yiend & Mathews, 2001). These findings indicate prolonged attention to goal-irrelevant negative information associated with anxiety and depression. Studies employing working memory paradigms have additionally revealed anxiety- and depression-related impairments in inhibiting or disengaging ongoing cognitive processes from negative emotional information (Goeleven et al., 2006; Hubbard, Hutchison, Hambrick, & Rypma, 2016; Hubbard, Hutchison, Turner, et al., 2016; Joormann, 2004; Joormann & Gotlib, 2008; Ladouceur et al., 2005; see Schweizer et al., 2019).

Neurodevelopment and Emotional Conflict

Many of the findings discussed thus far have detailed adult anxiety- and depression-related performance impairments during negative emotional-conflict conditions. In general, adults exhibit faster and more accurate goal-relevant performance during emotional conflict relative to children and adolescents (hereafter referred to as "youths"; Cohen-Gilbert & Thomas, 2013; Cohen Kadosh et al., 2014; Grose-Fifer et al., 2013). However, anxious and depressed youths exhibit reduced performance during negative emotional conflict relative to their typically developing peers. For instance, studies employing emotional Stroop tasks have demonstrated positive associations between anxiety measures in youths and slowed color naming of negative emotional words or threatening facial expressions (Heim-Dreger et al., 2006; Richards et al., 2000; see Bar-Haim et al., 2007; Dudeney et al., 2015). Higher levels of both anxious and depressive symptoms are also positively associated with slower identification of happy faces in the presence of negative-emotional-face distractors (i.e., angry, fearful, or sad faces) relative to negative-emotional-face targets in the presence of happy distractors (Klein et al., 2018). Furthermore, relative to typically developing youths, youths with MDD, comorbid anxious and depressive disorders, or high trait anxiety are slower to verify goal-relevant working memory probes when these probes are accompanied by negative emotional scenes or fearful-face distractors (Ladouceur et al., 2005, 2009).

During the first 2 decades of life, age-related increases in goal-relevant performance during emotional conflict coincide with continuing development of brain regions and communication pathways involved in predicting the affective relevance (e.g., amygdalae) and goal relevance (e.g., prefrontal cortex) of stimuli (Frangou et al., 2022; Lebel & Beaulieu, 2011). Anxious and depressed youths exhibit alterations to these neural substrates relative to their typically developing peers.

For example, youths with anxiety or depression or who are at increased risk for these disorders (e.g., because of parental history of depression) show increased amygdala activation, principally in response to face images conveying negative emotional expressions (i.e., angry or fearful; Chai et al., 2015; Ferri et al., 2014; Lau et al., 2009; McClure et al., 2007; Monk et al., 2008; Thomas et al., 2001). These findings indicate elevated affective responses in anxious and depressed youths, especially when presented with potentially threating social cues. Furthermore, anxiety and depression in adolescence are characterized by reductions in the strength and density of prefrontal white-matter association tracts (Adluru et al., 2017; Cullen et al., 2010; Henderson et al., 2013; Sacchet et al., 2016). Such findings of reduced anatomical connectivity intimate a diminished capacity for communicating goal-related signals from prefrontal cortex in adolescent anxiety and depression.

Conflict and Selection Bias via Distributed Communication

Increased amygdala signaling in response to negative emotional stimuli or a diminished capacity to transmit goal-related signals via weaker prefrontal connections may contribute to anxious and depressed adolescents' cognitive biases favoring the processing of negative emotional information (for discussion on anxiety, see Bishop, 2007). However, it is important to underscore that amygdala and prefrontal cortex act within a larger network of brain regions to influence whether or the extent to which information is processed. Indeed, contemporary models of attention and cognitive control postulate that the selection of stimuli for continued or more elaborative information processing involves recurrent communication within a distributed network of brain regions (see Botvinick & Cohen, 2014; Buschman & Kastner, 2015; Desimone & Duncan, 1995; Miller & Cohen, 2001). Broadly, these models posit that amygdala, dorsolateral prefrontal cortex (DLPFC), and other regions are involved in predicting the relevance (e.g., affective relevance, goal relevance) of competing stimuli for ongoing behavior. This prediction is communicated to sensory-representation areas in which local neural representations of stimuli are enhanced or inhibited according to the prediction signals they receive. Ultimately, communication with these areas is thought to influence whether a stimulus's associated sensory representation is selected for continued or more elaborative processing (e.g., gaited into the focus of attention or working memory) among competing alternatives.

It is not known whether communication with sensory-representation areas bears influence on anxiety- and depression-related cognitive biases. However, considering abnormalities in anxious and depressed youths' amygdala and prefrontal cortex, there are multiple ways by which altered communication of relevance signals to sensory-representation areas may bias the selection of competing sensory representations in favor of those associated with negative emotional stimuli. For example, increased communication of affective-relevance signals to sensory-representation areas may bias the selection of representations associated with negative emotional stimuli over those associated with goal-relevant stimuli (Vuilleumier et al., 2004; see Bishop, 2007). In addition, weaker prefrontal connections may limit communication of goal-relevance signals to sensory-representation areas and thus limit the ability to bias the selection of representations associated with goal-relevant stimuli over competing stimulus representations (see Gregoriou et al., 2014; Hwang et al., 2019; Zanto et al., 2011). Furthermore, increased affective-relevance and decreased goal-relevance signaling may dually contribute to biased selection of sensory representations associated with negative emotional stimuli over those associated with competing goal-relevant stimuli (see Bishop, 2007).

Present Study

There is considerable evidence of impaired goal-relevant performance in the presence of negative emotional information cutting across traditional diagnostic boundaries and dimensional measures of anxiety and depression. This suggests shared cognitive biases favoring the processing of negative information over goal-relevant information across anxiety and depression. Anxious and depressed youths also demonstrate alterations to neural substrates that communicate with sensory-representation areas to influence whether sensory representations associated with emotional or goal-relevant stimuli are selected among competing alternatives. However, no research has examined whether communication with sensory-representation areas may be involved in cognitive biases favoring negative emotional information in youth anxiety or depression.

Here, we used functional MRI (fMRI) to investigate neural communication signatures with a sensory-representation area in a sample of typical, anxious, and depressed adolescents. In keeping with Research Domain Criteria (see Insel et al., 2010), adolescents with at least one anxious or depressive disorder and adolescents with no history of either were recruited. This approach emphasized sampling continua of adolescents' anxious and depressive symptoms and their natural co-occurrences. Accordingly, we were able to examine the extent to which individual differences in operationalized measures of neural communication and behavioral performance

varied across a shared dimension of adolescents' anxious and depressive symptoms. This approach was selected because of (a) high collinearity between adolescents' anxious and depressive symptoms (Muris et al., 2004; Zavos et al., 2010) and frequent comorbidity of these diagnoses (Brown et al., 2001; Kessler et al., 2005), (b) similar findings of impaired goal-relevant performance during negative emotional conflict across anxiety and depression, and (c) similar alterations to the neural substrates involved in predicting the affective relevance or goal relevance of stimuli across youth anxiety and depression.

During fMRI, adolescents completed a task to localize a sensory-representation area (i.e., fusiform face area [FFA]) that was active while they discriminated between images of actors' faces (Chai et al., 2015; Hariri et al., 2002). This task was also used to localize an extended network of regions active during face processing—including amygdala and DLPFC. A second task additionally required participants to discriminate between face images. However, in this emotional-interference task (EIT), participants were shown face images on one visuospatial axis and house images on an orthogonal axis (Fales et al., 2008; Wojciulik et al., 1998). The EIT manipulated the goal relevance of face images (i.e., appearing on goal-irrelevant or goal-relevant axis) and the valence of the actors' facial expressions (i.e., fearful or neutral). Combined, these manipulations permitted targeted examinations of neural and performance changes when fearful-face images were the goal-relevant targets compared with when these were the goal-irrelevant distractors.

Our primary analyses examined the extent to which neural communication patterns (operationalized using functional connectivity patterns) between FFA and other regions active during face discrimination (together referred to as the "face network") were modulated by changes to the goal relevance and valence of face images. FFA was targeted because it is the core sensory-representation area for high-level face information and is robustly active during face recognition and discrimination (Kanwisher et al., 1997; McCarthy et al., 1997; Rypma et al., 2015; see Haxby et al., 2000). FFA also responds to affective-relevant and goal-relevant task manipulations (Baldauf & Desimone, 2014; Banich et al., 2019; Furey et al., 2005; Gazzaley et al., 2005; Vuilleumier et al., 2004; Wojciulik et al., 1998); thus, it is poised to integrate signals communicated from amygdala and lateral prefrontal cortex (PFC; see Palermo & Rhodes, 2007; Vuilleumier, 2005). For instance, neural synchrony between FFA and lateral PFC is enhanced when face images are goal relevant (Baldauf & Desimone, 2014), and lesions within amygdala reduce FFA responses to fearful-face images (Vuilleumier et al., 2004).

As discussed previously, communication of signals from multiple sources may influence the selection of sensory representations for continued or more elaborative information processing. Therefore, we adopted a multivariate approach (i.e., pattern-stability analysis; Ezzyat & Davachi, 2014; Hubbard, Romeo, et al., 2020; Tambini & Davachi, 2013) to quantify aggregate changes in FFA functional connection patterns with all other nodes of the face network. Our analyses were guided by the assumption that a tendency to continuously bias the selection of face representations would result in fewer changes in the communication patterns between FFA and other face-network nodes because of changes in the goal relevance of face images (see Botvinick & Cohen, 2014; Miller & Cohen, 2001). Thus, functional connectivity patterns with this primary face sensory-representation area should remain relatively "stable" if adolescents continuously direct their attention or neural-processing resources toward face images regardless of the goal relevance of these images. We hypothesized that cognitive biases favoring the processing of negative emotional information would result in more stable FFA connectivity patterns for adolescents scoring higher on a shared dimension of anxious and depressive symptoms during the presentation of fearful-face images.

Method

Procedure and participants

This study was part of a larger, Human Connectome Project study undertaken by the Boston Adolescent Neuroimaging of Depression and Anxiety consortium. Deidentified data will be openly available through the National Institutes of Health Data Archive (https://nda.nih.gov; Collection ID 3037). Relevant procedures within this study are detailed here (for comprehensive descriptions, see Hubbard, Siless, et al., 2020; Siless et al., 2020). Parents provided informed consent, and adolescents assented to study procedures approved by Massachusetts General Brigham Institutional Review Board. Participants were administered an in-person clinical interview and symptom assessments, and eligible participants then underwent an MRI scanning session. Parents and adolescents were compensated for participation.

One hundred seventy adolescent participants were recruited from the greater Boston area. General inclusion criteria were adolescent age 14 to 17 at time of scanning and parent and adolescent English fluency. General exclusion criteria were adolescent magnetic resonance contraindicators, adolescent premature birth (< 37 weeks or < 34 weeks for twins or < 5 lb at birth), history of serious medical condition or head injury, hospitalization of more than 2 days for neurological or

cardiovascular disease, diagnosis of autism spectrum disorder, use of daily migraine medication, parent or adolescent estimated full-scale Intelligence Quotient (IQ) lower than 85.[1] For detailed participant selection criteria, see Table S1 in the Supplemental Material available online.

Clinical diagnoses

Adolescents were recruited who had at least one current diagnosis of an anxious or depressive disorder or no history of either type of disorder. Diagnoses were confirmed via the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS; Kaufman et al., 1997) adapted for the criteria in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association, 2013). The K-SADS was administered to the accompanying parent and adolescent, and diagnoses were confirmed by a licensed clinical psychologist. Stratified-random samples from an earlier report of the first 140 participants showed that interrater reliabilities of *DSM-5* anxious (κ = .55) and depressive (κ = .66) diagnoses were moderate to substantial (Hubbard, Siless, et al., 2020).

Adolescent self-report and parent-report measures

Adolescents completed seven self-report measures assessing anxious and depressive symptoms. Five measures were taken from the Revised Child Anxiety and Depression Scale (RCADS; de Ross et al., 2002), which included the Depression subscale, Generalized Anxiety subscale, Panic subscale, Separation Anxiety subscale, and Social Anxiety subscale. Two additional measures of anxious and depressive symptoms included the Mood and Feelings Questionnaire (MFQ; Angold et al., 1995) and the State subscale of the State-Trait Anxiety Inventory (STAI-State; Spielberger et al., 1970). These measures queried symptoms using multiple time frames that ranged from current (STAI-State) to within the previous 2 weeks (MFQ). The RCADS did not query a specific time frame. An earlier report showed that adolescents' responding on these measurements demonstrated acceptable to excellent levels of internal consistency (Cronbach's α range: = .78 [RCADS-Separation Anxiety]–.96 [MFQ]; Hubbard, Siless, et al., 2020).

An accompanying parent completed the Child Behavior Checklist (CBCL; Achenbach, 1991). The CBCL queried parents about their adolescent's behavior currently or within 2 months before the study. Composite scores were generated from eight behavior syndrome subscales: Aggressive Behaviors, Anxious-Depressed Behaviors, Attention Problem Behaviors, Delinquent Behaviors, Social Problem Behaviors, Somatic Complaints, Thought Problem Behaviors, and Withdrawn-Depressed Behaviors. Composite scores were also computed from the Internalizing and Externalizing Problem Behaviors subscales of the CBCL.

Brain imaging

Acquisition. Imaging occurred on a 3-T Prisma MRI (Prisma; Siemens Medical Solutions USA, Malvern, PA) with a 64-channel head coil. Standardized training, foam padding, and regular reminders to remain still were used to minimize motion (see Siless et al., 2020). Tasks were practiced before entering the MRI environment. Responses were registered via finger pad placed in participants' dominant hand. Total scan protocol time was 1 hr 36 min. Procedures for T1-weighted structural (T1w) images and two task fMRI are described here. Task fMRI presentation code, stimuli, and participant instructions are available at https://github.com/BANDA-connect.

One magnetization-prepared rapid gradient-echo (MPRAGE) T1w image was acquired with volumetric navigators for prospective motion correction (Tisdall et al., 2012). T1w scans had 0.8-mm isotropic voxel size with 208 slices, field of view = 256 × 240 × 167 mm, acquired in the sagittal orientation, repetition time (TR) = 2,400 ms, and echo time (TE) = 2.18 ms. Task fMRI sequences were adapted from the Human Connectome Project (https://cmrr.umn.edu/multiband; see Siless et al., 2020), requiring sequences to be renewed semiannually and the possibility for minor updates to default sequences during the study. Task fMRI was acquired via two-dimensional multiband, gradient-recalled echo-planar imaging. Images had 2-mm isotropic voxel size with whole-brain coverage obtained from 72 oblique, axial slices; multiband acceleration factor = 8, TR = 800 ms, TE = 37 ms, flip angle = 52°. Task images were acquired using an even number of runs with two different phase-encoding directions (i.e., anterior-posterior, posterior-anterior).

Processing. Images were preprocessed using the open-source software *fmriprep* (Version 1.1.4; https://fmriprep.org/), which included T1 bias-field correction, brain extraction, normalization to the International Consortium for Brain Mapping 152 nonlinear template, tissue segmentation, and motion-correction and extraction procedures (Estaban et al., 2019). Normalized functional volumes were spatially smoothed (6-mm Gaussian kernel). Functional frames were censored via a Euclidean-norm approach (Cox, 1996) with a head-displacement threshold comparable with previous fMRI studies with youths (.7 mm; Church et al., 2017). Participant runs with fewer than 80%

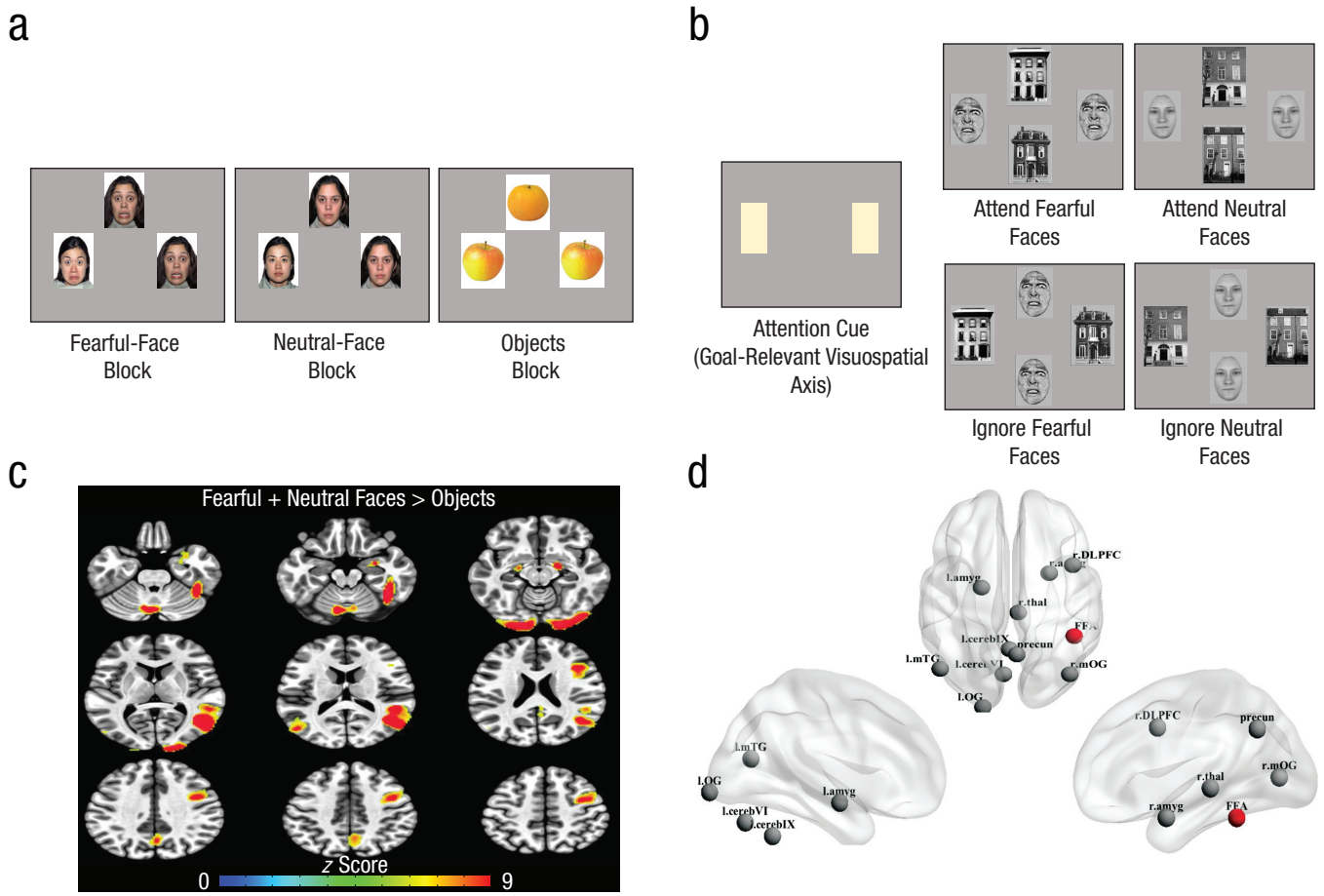

Fig. 1. Imaging tasks, localizer activation, and face-network nodes. Shown are examples of (a) fearful, neutral, and objects conditions from the localizer task (emotion-processing task [EPT]) and (b) goal-relevance and valence conditions from the emotion-interference task (EIT) when the horizontal visuospatial axis was goal relevant. The images in (c) show the average activation within clusters derived from the Faces > Objects contrast of the EPT. Clusters thresholded at $z \geq 6$; k-faces-touching voxels > 49; family-wise error rate (FWER) corrected $p <$ .001. The images in (d) show the 11 face-network nodes extracted from the EPT face-localizer analysis in (c). Red node = fusiform face area (FFA), the region of interest for our primary hypothesis tests. For cluster and node coordinates, see Table S6 in the Supplemental Material available online. Nodes in (d) inferior to cerebrum are within cerebellum, which is not featured in this three-dimensional viewing template.

of volumes after censoring were not included in analyses (Simmonds et al., 2017). Generalized linear models estimated task activations while also controlling for 6 degrees-of-freedom motion estimates, frame-wise displacement, and censored frames, and automatic (high-pass) polynomial filtering was applied to minimize other temporal trends.

Localizer task. The emotion-processing task (EPT; Chai et al., 2015; Hariri et al., 2002) was used to localize brain regions more active while participants discriminated between face images compared with when they discriminated between object images (Fig. 1a). One hundred sixty-eight adolescents completed the EPT. For both the EPT and EIT, a priori accuracy (≥ 60% accuracy) and response frequency (≥ 70% response rate) thresholds were set for including participants' imaging data in subsequent analyses (see Hubbard, Siless, et al., 2020). Regarding the EPT, no participants were excluded because of response accuracy, two participants were excluded for responding to fewer than 70% of trials, and six were excluded because of poor structural alignment.

Participants completed two runs (5 min 24 s per run) of a block-design EPT in which they were instructed to indicate via dominant hand, index- or middle-finger button press which of two images at the bottom of the screen matched a single image presented above (target). When the image to the left of the screen matched the target image, participants were instructed to respond with their index finger. When the image to the right of the screen matched the target image, participants were instructed to respond with their middle finger. Target responses (index or middle finger) were balanced across conditions and appeared pseudorandomly across runs.

Each trial displayed three images from a single condition. Each block consisted of six trials, lasted 18,000 ms,

and contained face images from the Radboud (Langner et al., 2010) and NimStim (Tottenham et al., 2009) databases or object images adapted from Chai and colleagues (2015). Six 18,000-ms blocks of trials for each condition were acquired across two task runs (36 trials per condition). Face images were of 72 actors portraying either fearful, happy, neutral, or sad expressions. An individual face image was presented only once during the experiment. Object images consisted of 72 fruit and vegetable images scaled and cropped to approximately the same size as the face images (Chai et al., 2015). Each object image was presented in a single trial. To remain consistent with the face images used in the EIT, only fearful and neutral facial expression blocks were used to localize the face-network regions.

EIT. An event-related EIT (Fales et al., 2008; Wojciulik et al., 1998) was used to examine functional connectivity patterns between regions of the localized face network. One hundred sixty-five adolescents completed the EIT. No participants were excluded on the basis of response frequency, 20 participants were excluded for less than 60% average response accuracy, and five were excluded because of excessive motion or poor structural alignment.

Participants completed four EIT runs (3 min 54 s per run). The EIT required participants to discriminate between two images on the same visuospatial axis while ignoring two images on the orthogonal axis. At the beginning of each run, a visuospatial cue indicated the axis that the goal-relevant images would appear on. Participants were instructed to attend to this axis and perform the discrimination task for these images and ignore images on the orthogonal axis. Participants indicated via button press using the dominant-hand index or middle finger whether the two images on the cued axis were identical or different. Thus, on each trial, one pair of images was goal relevant (participants cued to attend to and discriminate between images), and a simultaneously presented pair of different images was goal irrelevant (participants cued to ignore). There were two different classes of image pairs, faces and houses. Face-image pairs featured one of two possible facial expressions, fearful or neutral. Task design and stimuli were adapted from Fales and colleagues (2008). The four conditions were attend fearful faces (ignore houses), attend neutral faces (ignore houses), ignore fearful faces (attend houses), and ignore neutral faces (attend houses).

Each trial began with a 1,000-ms fixation cross, followed by a 250-ms presentation of images, and 2,200 ms allotted for each response. An equal number of presentations per condition occurred on each visuospatial axis and across each of the four runs (24 trials per condition across all runs). Intertrial intervals of 2,150, 4,660, 9,680, and 12,190 ms were randomly but equally distributed throughout each run. Performance accuracy was measured using the percentage of trials in which a participant correctly indicated whether the images on the cued axis were similar or different. Response time (RT) was also acquired for each button press within the allotted response period. Percentage accuracy and RT were averaged across trials for each of the four conditions.

Table 1. Quality-Assured Sample Characteristics ($N = 138$)

Characteristic	Value
Age	$M = 15.37$ ($SEM = 0.07$)
Reported sex	
Female	92 (66.67)
Male	46 (33.33)
Race	
African American	3 (2.17)
Asian	4 (2.90)
White	103 (74.64)
More than one race	18 (13.04)
Unknown or not reported	10 (7.25)
Ethnicity	
Hispanic	10 (7.46)
Non-Hispanic	124 (92.54)
Psychiatric medication reported	
Any	46 (33.33)
Antidepressant	39 (28.26)
Antiepileptic	2 (1.45)
Stimulant	9 (6.52)
Other	10 (7.46)

Note: Values are *n*s with percentages in parentheses unless otherwise specified.

Face-network localization. One hundred thirty-eight adolescents completed both the EPT and EIT with data of sufficient quality for second-level analyses according to the quality-assurance procedures described earlier (for demographics and clinical characteristics of the retained sample, see Tables 1 and 2; for extended demographics, see Table S2 in the Supplemental Material). EPT time series and task design were convolved with a boxcar function using the same nuisance covariates described in the "Processing" section. Beta weights from fearful- and neutral-face conditions were averaged and contrasted with betas from the object condition to create a Faces > Objects contrast. A high statistical threshold was set to enhance the reliability of these sample-wide localizer regions for use across subjects ($z \geq 6$; k-faces-touching voxels > 49; FWER corrected $p < .001$; Fig. 1c). Face-responsive clusters were transformed into 11 nonoverlapping regions of equal volume by placing a 7-mm sphere at each cluster's center of mass (hereafter referred to as the "nodes of the face network"; Fig. 1d).

Table 2. Quality-Assured Sample Clinical Characteristics ($N = 138$)

Clinical characteristic	Current	Lifetime[a]
DSM-5 anxiety and depression		
Any	85 (61.59)	42 (30.43)
Comorbid anxiety and depression	34 (24.64)	N/A
DSM-5 anxious		
Agoraphobia	3 (2.17)	0 (0.00)
Generalized anxiety	46 (33.33)	3 (2.17)
Panic	11 (7.97)	4 (2.89)
PTSD-single	3 (2.17)	0 (0.00)
Separation anxiety	4 (2.90)	17 (12.31)
Social anxiety	42 (30.43)	7 (5.07)
Specific phobia	14 (10.14)	5 (3.62)
DSM-5 depressive		
Adjustment disorder with depressed mood	0 (0.00)	3 (2.17)
Dysthymia	1 (0.72)	1 (0.72)
Depression NOS	4 (2.99)	1 (0.72)
Major depression	38 (27.54)	18 (13.04)

Note: Values are *n*s with percentages in parentheses unless otherwise specified. Parental educational attainment and household income are reported in Table S1 in the Supplemental Material available online. *DSM-5* = fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013); PTSD = posttraumatic stress disorder; NOS = not otherwise specified.
[a]Diagnostic criteria met for a lifetime disorder that was not present (i.e., subthreshold or absent) at the time of assessment.

Pattern-stability assessment. Trial-by-trial blood-oxygen-level-dependent (BOLD) activations during all trials of the four EIT conditions were modeled as separate regressors via convolution with the design matrix and double-gamma impulse response functions. The same nuisance covariates were used in this model as described in the Processing section. Trial-by-trial BOLD activations were extracted from the nodes of the face network for each EIT condition. Pearson correlations were applied to the trial-by-trial activations of face-network node pairs to produce functional connectivity weights (Rissman et al., 2004; Fig. 2a). Primary pattern-stability estimates included the functional connectivity weights between the right fusiform gyrus node (i.e., FFA) and other nodes in the face network.

Pattern stability quantified the magnitude of change in an individual's FFA functional connectivity with face-network nodes across goal-relevance conditions separately for each valence type (for a similar approach, see Ezzyat & Davachi, 2014; Hubbard, Romeo, et al., 2020; Tambini & Davachi, 2013). Specifically, this metric assessed the average inverse-Euclidean distance of FFA functional connectivity weights evoked during conditions in which face pairs of one valence type were on the goal-irrelevant axis versus when face pairs of this same valence type were on the goal-relevant axis (for a similar approach, see Hubbard. Romeo, et al., 2020). Estimates were Fisher transformed to approximate a normal distribution across participants. Greater pattern-stability scores indicated that FFA functional connectivity patterns evoked by face images of a specific valence on the goal-irrelevant axis were similar to those evoked when face images of the same valence were featured on the goal-relevant axis. Thus, a higher pattern-stability score indicated that an individual's FFA functional connectivity patterns were *less* influenced by the goal relevance of face images of a specific valence relative to individuals with lower pattern-stability scores.

Clinical and EIT behavior analyses

Latent anxious-depressive symptom dimension. A principal component analysis was used to extract factor scores from a single component based on linear combinations of the seven self-report measures of anxious and depressive symptoms. Factor scores were extracted from Component 1 ($\lambda_1 = 5.23$) via regression. Component 1 (hereafter referred to as "AD_L dimension") was the only component to feature an eigenvalue greater than 1. The convergent and discriminant validity of the AD_L dimension was assessed by evaluating relationships between adolescents' scores on this dimension and subscales of the CBCL ($N = 131$ available data sets). Partial correlations were used to test relationships between AD_L dimension scores and each behavior syndrome subscale of the CBCL, independent of all other subscales and their combined effects—which could reflect a more general individual-differences factor (e.g., p factor; Caspi et al., 2014). Partial correlations were also used to examine differential relationships between AD_L dimension scores and the Internalizing and Externalizing Problem Behaviors composite scales of the CBCL.

EIT performance. Planned two-way repeated measures analyses of variance (ANOVAs) were used to test whether the AD_L dimension was related to EIT performance (accuracy or RT) while adolescents were cued to ignore versus attend to fearful-face images. The direction of significant Valence × AD_L interaction effects was evaluated by calculating performance differences when adolescents were cued to ignore fearful-face images versus when they were cued to attend to these images and correlating these differences with the AD_L dimension. These modeling procedures were also used to examine potential Goal Relevance × AD_L interaction effects during neutral-face conditions. Self-reported (binary) sex and age were also entered into the models to test whether they altered the significance of Goal Relevance × AD_L interaction effects on EIT performance.

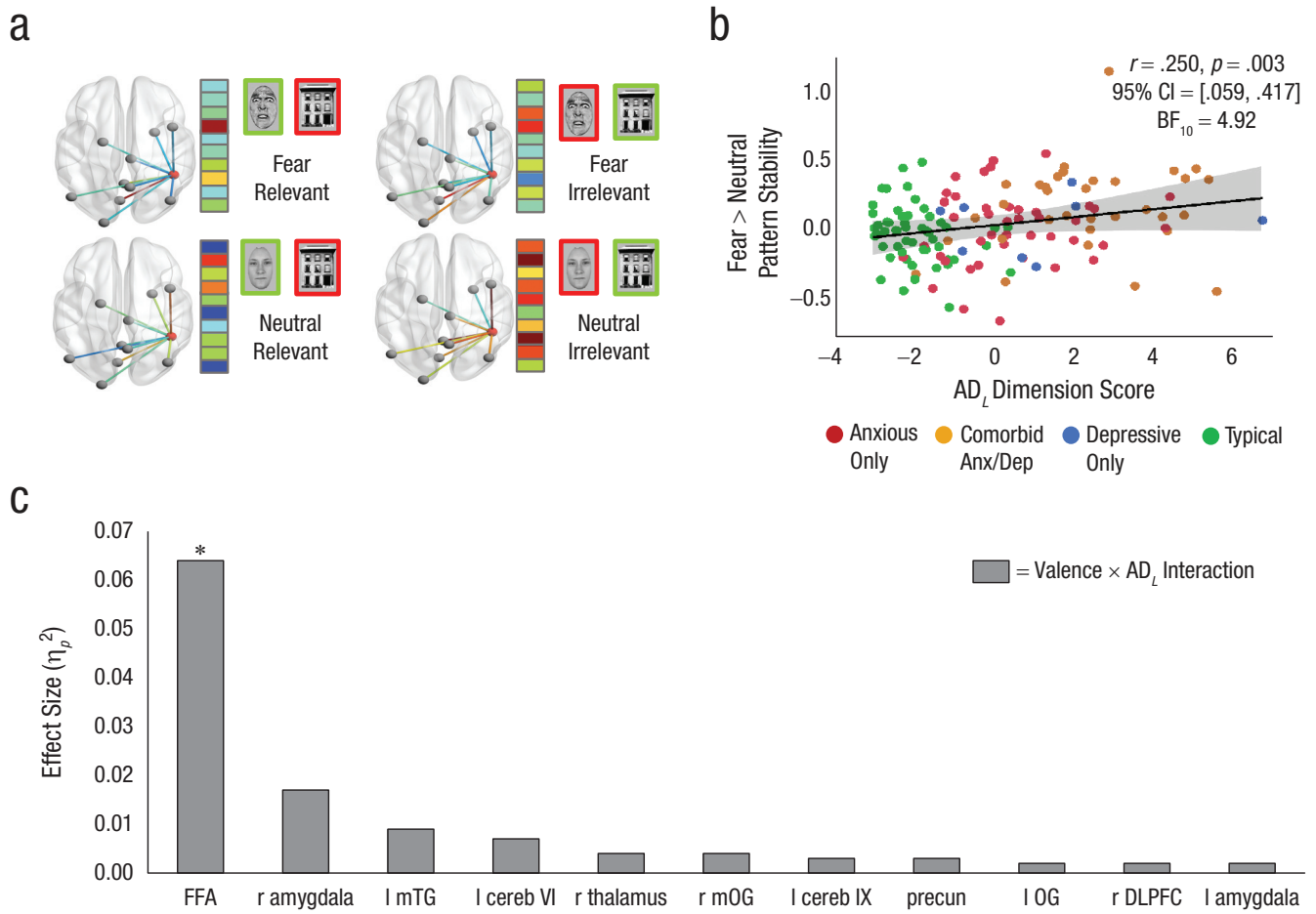

Fig. 2. Valence and latent anxious-depressive symptom dimension interaction on pattern stability. The images in (a) show an example participant's evoked fusiform face area (FFA) functional-connectivity patterns within the face network by goal-relevance and valence conditions during the emotional-interference task (EIT). Colors signify a node's correlation with FFA (color scale standardized across conditions). Green image frame = cued image class; red image frame = ignore image class. The graph in (b) shows the correlation between expression of the latent anxious-depressive dimension (AD_L) and valence-related changes in FFA pattern stability within the face network. Greater *y*-axis values reflect greater FFA pattern stability for fearful facial expressions compared with neutral facial expressions. Greater *x*-axis values reflect greater scores on the AD_L dimension. Shaded area reflects 99.9% confidence interval of regression line; data points are colored by diagnostic status. The graph in (c) shows the Valence × AD_L dimension interaction effects on pattern stability with each node in the localized face network used as the seed to derive pattern stability. Asterisk indicates significant Valence × AD_L dimension interaction (Bonferroni-corrected $p < .05$). Removal of the apparent outlier ("Comorbid Anx/Dep" participant data point with greatest *y* value) from the analysis in (b) did not alter the significance of this relationship ($r = .227$, $p = .008$). r, right; l, left; mTG, middle temporal gyrus; cereb VI, cerebellar lobule VI; mOG, middle occipital gyrus; cereb IX, cerebellar lobule IX; precun, precuneus; OG, occipital gyrus; DLPFC, dorsolateral prefrontal cortex.

Imaging analyses

Primary hypothesis tests examined whether greater scores on the AD_L dimension were associated with greater FFA pattern stability during the presentation of fearful images relative to the neutral-face images. Contrasts between goal-relevance conditions (i.e., attend vs. ignore face images) were incorporated into the calculation of pattern stability. A two-way repeated measures ANOVA was used in this and other pattern-stability tests. Covariates were subsequently entered into the original model to assess whether these altered the significance of the Valence × AD_L interaction effects on FFA pattern stability. Covariates included self-reported (binary) sex, age, adolescent medication status (reported vs. not reported use of antidepressants, antiepileptic, stimulant, or other psychiatric medication), individual differences in head motion estimated via average frame-wise displacement (Satterthwaite et al., 2012), and average percentage of motion-censored volumes across runs of the EIT. The direction of significant Valence × AD_L interaction effects was confirmed by calculating fearful minus neutral FFA pattern-stability scores and correlating these with scores on the AD_L dimension. We provide 95%

confidence intervals for these correlation coefficients on the basis of 1,000-iteration bias-corrected and accelerated bootstrapped resampling. The likelihood that these data occur under the alternative relative to null hypothesis is reported with BF_{10} estimated via the Jeffreys-Zellner-Siow (JZS) Bayes's factor procedure (Rouder et al., 2009). The effects of random subsampling on primary results were also examined (see the Supplemental Material).

The specificity of Valence × AD_L interaction effects on FFA pattern-stability scores was also evaluated. Two covariates were included into the repeated measures ANOVA to control for potential individual differences in broader pattern stability (e.g., Montez et al., 2017). Specifically, an average pattern-stability score was computed for all non-FFA nodes in the face network (n = 10) during each valence condition, and these two scores were entered into the repeated measures model. The specificity of the Valence × AD_L interaction effect on FFA pattern stability was also examined compared with the Valence × AD_L interaction effects on pattern stability derived from each node of the face network. The significance of these tests was evaluated after Bonferroni correction.

Repeated measures ANOVAs were used to determine Valence × AD_L interaction effects on pattern stability between FFA and individual nodes of the face network. Whereas our primary pattern-stability analyses relied on aggregated changes in FFA functional connections within the face network, these edgewise analyses permitted examining the Valence × AD_L interaction at the level of each individual FFA functional connection. The significance of edgewise tests was evaluated after Bonferroni correction for the 10 edgewise comparisons.

Results

Latent dimension of anxious and depressive symptoms

The first principal component accounted for approximately three-quarters of the variance (74.7%) in adolescents' responses across the seven measures of anxious and depressive symptoms; single-component solution, $\chi^2(14) = 61.19$, $p < .001$. As expected, correlations between these seven measures were positive and statistically significant (r: range = .57–.91; $ps < .001$), and all measures showed positive and significant factor loadings on the extracted AD_L dimension (r: range = .78–.92; $ps < .001$; see Table S3 in the Supplemental Material). Positive and large-effect size loadings on this component demonstrated that AD_L adequately captured variance in all seven measures of anxiety and depression, which supported the use of AD_L as a shared dimension of adolescents' anxious and depressive symptoms.

Partial correlations indicated that the AD_L dimension was differentially related to anxious and depressive subscales of the CBCL: Anxious-Depressed Behaviors subscale ($r_{X.Y|Z} = .325$, $p < .001$) and Withdrawn-Depressed Behaviors subscale ($r_{X.Y|Z} = .212$, $p = .018$). These were the only subscales that showed independent, positive, and significant relationships with AD_L (see Table S5 in the Supplemental Material). Partial correlations also demonstrated a differential relationship between the AD_L dimension and the Internalizing Problem Behaviors composite scale ($r_{X.Y|Z} = .623$, $p < .001$), whereas a negative but nonsignificant relationship was observed between AD_L and the Externalizing Problem Behaviors composite scale ($r_{X.Y|Z} = -.164$, $p = .063$; see Table S5 in the Supplemental Material). The AD_L dimension was strongly and independently related to parent reports of adolescents' anxious and depressive behaviors and their broader internalizing problem behaviors—which are the primary behaviors observed across anxiety and depression (Fergusson et al., 2006; Krueger et al., 1998; Zahn-Waxler et al., 2000). Findings supported the validity of our interpretation that AD_L scores reflected a shared dimension of adolescents' anxious and depressive symptoms. For Additional correlations with AD_L (e.g., sex, age), see Table S4 in the Supplemental Material.

EIT performance and latent symptom dimension

A significant Goal Relevance × AD_L interaction was observed on performance accuracy during fearful-face conditions, $F(1, 134) = 4.44$, $p = .037$, $\eta_p^2 = .032$. Goal relevance was also a significant factor in the model, $p < .001$, $\eta_p^2 = .089$. Sex and age were included as a covariate into this model, and neither altered the significance of the Goal Relevance × AD_L interaction effects (p: range = .028–.054). A follow-up correlation indicated that adolescents who expressed greater scores on the AD_L dimension showed reduced accuracy when cued to ignore fearful-face images versus when cued to attend to these images ($r = .179$, $p = .037$).

No significant main effect of goal relevance ($p = .089$, $\eta_p^2 = .021$) or significant Goal Relevance × AD_L interaction effect was observed on RT during fearful-face conditions ($p = .215$, $\eta_p^2 = .011$). No significant Goal Relevance × AD_L interaction effects were observed on accuracy ($p = .285$, $\eta_p^2 = .009$) or RT ($p = .640$, $\eta_p^2 = .002$) during the neutral-face conditions. No significant goal-relevance main effects were observed on accuracy ($p = .773$, $\eta_p^2 = .001$) or RT ($p = .106$, $\eta_p^2 = .019$) during the neutral-face conditions.

Face network localizer

Figure 1c demonstrates suprathreshold voxel clusters and average *z* scores from the Faces > Objects contrast of the EPT (FWER-corrected $p < .001$). For Montreal Neurological Institute (MNI) coordinates for the 11 suprathreshold cluster centers and anatomical labels for nodes within the localized face network, see Table S6 in the Supplemental Material. Consistent with extant studies of face processing, we found that the network of nodes determined using the EPT included right fusiform gyrus (FFA), bilateral amygdalae, and DLPFC (see Haxby et al., 2000; Palermo & Rhodes, 2007). Additional analyses did not indicate relationships between individual differences in activation within these nodes and AD_L (see the Supplemental Material).

FFA pattern stability and latent symptom dimension

FFA pattern stability. The hypothesized interaction effect between valence and AD_L on FFA pattern stability was significant, $F(1, 134) = 8.91$, $p = .003$, $\eta_p^2 = .062$. There was also a significant main effect of valence within the model, $p = .031$, $\eta_p^2 = .034$. A follow-up correlation supported our hypothesis that adolescents who expressed greater scores on the AD_L dimension exhibited greater FFA pattern stability within the face network during the presentation of fearful-face images relative to the neutral-face images (Fig. 2b).

The Valence × AD_L interaction effect on FFA pattern stability remained significant after including age, sex, and individual differences in head-motion metrics into the original model (*p*: range = .003–.006). None of these covariates showed significant interactions with valence (*p*s > .05). The Valence × AD_L interaction also retained significance after including antiepileptic, stimulant, or other psychiatric medication statuses into the original model (*p*: range = .003–.006), and none of these covariates showed significant interactions with valence (*p*s > .05). Antidepressant status showed a significant interaction with valence, $F(1, 133) = 4.03$, $p = .047$, $\eta_p^2 = .029$. However, the Valence × AD_L interaction effect also retained significant in this model, $F(1, 133) = 4.38$, $p = .038$, $\eta_p^2 = .032$, which indicates that the hypothesized interaction accounted for unique variance in FFA pattern stability beyond the variance accounted for by antidepressant status. Covarying for adolescents' average number of incorrect responses on the EIT did not alter the significance of the Valence × AD_L interaction effects (see the Supplemental Material). In addition, age alone was entered into a new repeated measures model as a predictor of FFA pattern stability. No significant Valence × Age interactions were observed, $F(1, 136) = 0.075$, $p = .785$, $\eta_p^2 = .001$.

Specificity of Valence × AD_L interaction effects on FFA connectivity patterns. When we added average pattern stability from each valence condition into the original model, the significant Valence × AD_L interaction effect on FFA pattern stability remained, $F(1, 133) = 9.00$, $p = .003$, $\eta_p^2 = .064$. Figure 2c demonstrates the specificity of the Valence × AD_L interaction effects on FFA pattern stability. The Valence × AD_L interaction effect on FFA pattern stability within the face network also retained significance after Bonferroni correction for these 10 additional node comparisons (corrected $p = .03$; Fig. 2c).

FFA edgewise pattern stability and latent symptom dimension

Edgewise analyses explored the Valence × AD_L interaction effect at the level of individual FFA functional connections. After Bonferroni correction for 10 edgewise tests, a single significant interaction was observed for the Valence × AD_L interaction on pattern stability between right DLPFC and FFA, $F(1, 134) = 9.72$, $p = .002$ (corrected $p = .02$), $\eta_p^2 = .068$ (Fig. 3a). A follow-up correlation demonstrated that adolescents who expressed greater scores on the AD_L dimension exhibited greater pattern stability between right DLPFC and FFA for the fearful-face condition relative to the neutral-face condition (Fig. 3b). The Valence × AD_L interaction effect on pattern stability between right DLPFC and FFA remained significant after including age, sex, and head-motion covariates and antidepressant, antiepileptic, stimulant, or other psychiatric medication status into the original model (*p*: range = .002–.014); none of these covariates showed significant interactions with valence (*p*s > .05). Covarying for adolescents' average number of incorrect responses on the EIT did not alter the significance of the Valence × AD_L interaction effects (see the Supplemental Material). In addition, age alone was entered into a new repeated measures model as a predictor of right DLPFC and FFA pattern stability; no significant Valence × Age interactions were observed, $F(1, 136) = 1.27$, $p = .262$, $\eta_p^2 = .009$.

Discussion

In this study, we sought evidence for a potential neurobiological link among adolescent anxiety, depression, and cognitive biases for negative emotional information. We hypothesized that cognitive biases favoring the processing of negative emotional information would result in more stable FFA connectivity patterns for adolescents who scored higher on a shared dimension of anxious and depressive symptoms in the presence of fearful-face images. Our findings supported this hypothesis. That is, relative to neutral-face images, greater

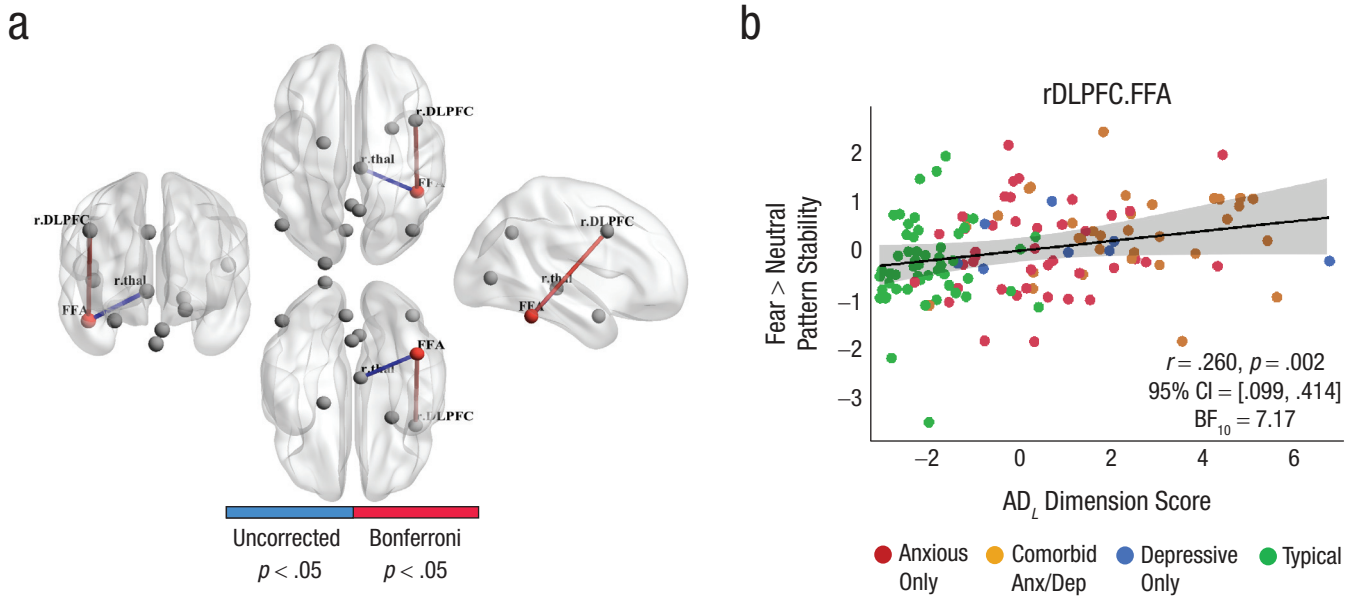

Fig. 3. Fusiform face area (FFA) edgewise pattern stability and correlation with latent anxious-depressive symptom dimension (AD_L). In the images shown in (a), edges shown reflect significant Valence × AD_L interaction effect on pattern stability between a given node in the face network and FFA. The graph in (b) shows the correlation between expression of the AD_L and valence-related changes in pattern stability between right DLPFC and FFA. Greater *y*-axis values reflect greater pattern stability between right dorsolateral prefrontal cortex (DLPFC) and FFA for fearful facial expressions compared with neutral facial expressions. Greater *x*-axis values reflect greater scores on the AD_L dimension. The shaded area reflects 99.9% confidence interval of regression line; data points are colored by diagnostic status. Removal of the apparent outlier ("Typical" participant data point with the lowest *y*-value) from the analysis in (b) did not alter the significance of this relationship ($r = .250$, $p = .003$).

expression of the latent anxious-depressive symptom dimension was associated with fewer changes in FFA connectivity patterns (i.e., greater pattern stability) within the face network as a function of the goal relevance of fearful-face images. These effects on pattern stability were demonstrated exclusively for functional connections with FFA, as opposed to connections between other regions shown via the localizer to be active while participants discriminated between face images.

FFA represents high-level sensory information necessary for determining facial identity (see Haxby et al., 2000). When adolescents were cued to attend to and discriminate between actors' faces during the EIT, selection of FFA representations was necessary to perform this task. However, when they were cued to attend to and discriminate between house images (i.e., faces on the goal-irrelevant axis), FFA needed to be inhibited or, at least, no longer required enhancement via top-down signaling (Baldauf & Desimone, 2014; Banich et al., 2019; Furey et al., 2005; Gazzaley et al., 2005). Thus, changes in communication patterns with FFA were expected if attention or neural processing resources were directed toward house images versus when these resources were directed toward face images. For example, when typical participants are cued to selectively attend to and discriminate between face images and ignore superimposed house images, FFA increases neural synchrony with DLPFC (Baldauf & Desimone, 2014). Conversely, when participants are cued to discriminate between house images and ignore superimposed faces, FFA decreases neural synchrony with DLPFC (Baldauf & Desimone, 2014). Likewise, functional connectivity between FFA and primary visual cortex increases according to cues to attend to and discriminate between faces versus simultaneously presented images of buildings (Hwang et al., 2019). Findings in typical participants also suggest that amygdalae adopt an inhibitory relationship with FFA when fearful-face images are goal-irrelevant distractors (Schulte Holthausen et al., 2016). In sum, typical participants flexibly adapt communication patterns with FFA according to the goal relevance of face stimuli, and this flexibility may serve to facilitate or inhibit the continued processing of face representations, depending on their relevance (see Botvinick & Cohen, 2014; Miller & Cohen, 2001).

Our primary results demonstrated that goal-related changes in FFA functional-connectivity patterns were significantly smaller in the presence of fearful-face images relative to neutral-face images for adolescents who expressed greater scores on the latent anxious-depressive symptom dimension. We interpret these

findings to reflect an inflexibility in neural communication that favors the selection of sensory representations associated with negative emotional information regardless of their goal relevance, common across adolescent anxiety and depression. However, pattern stability assessed relative changes in connectivity patterns between goal conditions. Thus, a possible alternative explanation for the observed increase in FFA pattern stability is that adolescents who expressed higher scores on the latent anxious-depressive symptom dimension continuously avoided attending to fearful faces regardless of their goal relevance (Monk et al., 2006). Yet this interpretation is difficult to reconcile with our behavioral findings. If adolescents higher on the latent symptom dimension avoided attending to fearful faces across goal conditions, it would be expected that they show reduced accuracy in discriminating between fearful faces when these images were cued as goal relevant versus their accuracy in discriminating between house images when fearful faces were irrelevant. Our behavioral findings demonstrated the opposite effect. Increased expression of the latent symptom dimension was associated with reduced accuracy in discriminating between goal-relevant house images in the presence of irrelevant fearful-face images compared with the accuracy in discriminating between goal-relevant fearful faces in the presence of irrelevant house images. No such effects emerged for neutral-face images. In sum, behavioral results are not consistent with the notion that adolescents higher on the latent dimension continuously avoided attending to fearful faces. Rather, these findings suggest that adolescents higher on this dimension favored attending to or otherwise engaged in additional processing of fearful faces regardless of their goal relevance.

The edgewise analyses revealed that adolescents who expressed greater scores on the latent anxious-depressive symptom dimension exhibited greater pattern stability between right DLPFC and FFA during fearful-face conditions. This effect was observed relative to neutral-face conditions, which limits the likelihood that it arose from basal decreases in prefrontal anatomical connectivity associated with youths' anxiety and depression (Adluru et al., 2017; Cullen et al., 2010; Henderson et al., 2013; Sacchet et al., 2016). This effect was exclusive to DLPFC-FFA functional connections, as opposed to other functional connections within the face network (e.g., amygdala-FFA; occipital-FFA). Thus, the edgewise results illustrated that the most and only significantly stable individual FFA functional connectivity patterns were with DLPFC. We emphasize here that pattern-stability analyses were not designed to assess whether DLPFC directly influenced FFA or vice versa. The edgewise findings do, however, intimate a failure to flexibly adapt communication patterns between these key cognitive-control and sensory-representation regions in the presence of negative emotional information.

Lateral PFCs are critical for suppressing goal-irrelevant behaviors and limiting interference from irrelevant information (Burman & Bruce, 1997; Chao & Knight, 1995; Gregoriou et al., 2014; Suzuki & Gottleib, 2013). These regions modulate information processing in sensory-representation areas according to task goals (Baldauf & Desimone, 2014; Coste et al., 2011; Lee & D'Esposito, 2012; Zanto et al., 2011), which evidences their involvement in biasing the selection of goal-relevant sensory representations. In typical participants, DLPFC increases activation during emotional conflict, which suggests the orchestration of cognitive-control processes to overcome this conflict (Fales et al., 2008; Ochsner et al., 2008). In anxiety and depression, alterations in DLPFC activation have been observed during negative emotional conflict. However, it is unclear how DLPFC-mediated cognitive-control processes may relate to such activation changes given that some studies have reported decreased DLPFC activations (Bishop et al., 2004; Fales et al., 2008) and others have reported increased DLPFC activations (Colich et al., 2017; Stout et al., 2017) related to anxiety or depression.

More research is needed examining functional connectivity patterns with other sensory-representation areas and during other negative-emotion conditions and employing experimental or computational approaches to characterize the precise role of DLPFC influence during negative emotional conflict. However, an inability to use top-down signaling to flexibly alter communication patterns with sensory regions may reflect one common neurobiological mechanism influencing anxiety- and depression-related impairments in goal-relevant performance during negative emotional conflict. For instance, distributed processing models resolve conflict and produce goal-relevant responses by flexibly adapting their communication between sensory-representation areas and other task-relevant regions in accordance with task goals (see Botvinick & Cohen, 2014; Miller & Cohen, 2001). Specifically, these models implement top-down signals via control nodes (e.g., lateral PFC) to alter the communication pathways with content-specific processing nodes (e.g., sensory-representation areas), which acts to bias the selection of goal-relevant stimulus representations over competing goal-irrelevant representations. Consistent with our findings of increased FFA pattern stability and impaired goal-relevant performance related to the latent symptom dimension, distributed processing models demonstrate that if communication pathways are not altered with content-specific processing nodes according to task goals, a

goal-relevant stimulus representation is less likely to be selected, and the model is less likely to produce a goal-relevant response.

Limitations and future directions

Several limitations should be considered alongside the present findings. First, the latent dimension provided a quantitative measure of the extent to which an adolescent expressed a broad characteristic shared among anxious and depressive symptoms. A limitation of this approach is that it cannot precisely qualify what that characteristic may be. Indeed, anxiety and depression are linked to similar traits, such as behavioral inhibition and neuroticism (Brown, 2007; Brown & Naragon-Gainey, 2013), and similar tendencies for repetitive negative thinking (McLaughlin, Nolen-Hoeksema, 2011). Measures of behavioral inhibition and repetitive negative thinking also correlate with neural and behavioral phenomena observed during negative emotional information processing (Fu et al., 2017; Kaiser et al., 2018; Morales et al., 2017). Furthermore, there is evidence linking serotonergic transporter allele expression in anxious and depressed adolescents to increased affective responses to negative emotional information (Lau et al., 2009). One important direction for future research is to determine whether such personality or genetic factors mediate relationships between adolescents' anxious and depressive symptoms and the neurobiological processes involved in cognitive biases favoring the processing of negative emotional information.

A second limitation to consider alongside our findings is that the EIT did not feature an additional emotion condition. Because fearful-face conditions were not examined along with a separate emotion condition (e.g., happy faces), it is difficult to definitively conclude that these findings were specific to anxiety- and depression-related cognitive biases favoring the processing of negative emotional information, as opposed to general biases favoring emotional information. In anxiety, some findings support the specificity of cognitive biases favoring the processing of negative emotional information in the form of increased Stroop task interference from threatening or more general negative words (e.g., "weak," "despair," "coffin") compared with nonthreatening, mostly positively valanced words (e.g., "overjoyed," "playful," "merriment") or specifically curated positive words (Mathews & MacLeod, 1985; Richards et al., 1992; see also Mogg et al., 1989). In depression, a meta-analysis of dot-probe findings also supports the specificity of depression-related cognitive biases favoring the processing of negative emotional information as opposed to other (i.e., positive) emotional information (see Peckham et al., 2010). However, there are conflicting meta-analytic results from studies using emotional Stroop-task paradigms that suggest depression-related cognitive biases may extend to multiple classes of emotional information (e.g., negative and positive; see Epp et al., 2012). Although, this meta-analysis also demonstrated that depression-related, Stroop-task interference effects from negative emotional information were significant when contrasting with those induced from positive information (see Epp et al., 2012). Future research employing multiple classes of emotional stimuli could aid in verifying the specificity of negative emotional information-processing biases across adolescent anxiety and depression.

A third limitation regards the unknown potential of our findings for clinical translation. This study took a first step toward uncovering a common neurobiological link among adolescent anxiety, depression, and cognitive biases favoring negative emotional information. Rigorous prospective testing is still needed to evaluate the clinical utility of this link. Moreover, to our knowledge, this was one of the largest fMRI studies to date examining common neural phenomena across adolescent anxiety and depression. However, a lack of a dedicated validation sample places the burden on future research to examine the extent to which the present effects are applicable to the broader population (see Gabrieli et al., 2015).

Conclusion

The neural functions and structures involved in controlling attention and directing information-processing resources in emotional contexts continue development into one's early 20s (e.g., Cohen-Gilbert & Thomas, 2013; Lebel & Beaulieu, 2011). Accordingly, adolescence may be a crucial and final period for working with natural developmental plasticity to mitigate cognitive biases for negative emotional information that afflict persons with or at risk for anxious or depressive disorders. Our primary findings suggested reduced flexibility in neural communication patterns that may favor the selection of sensory representations associated with negative emotional information regardless of its goal relevance across a shared dimension of adolescent anxiety and depression. The edgewise findings further suggested that DLPFC communication was central in this inflexibility, which indicates the potential involvement of top-down, cognitive-control processes in these effects. Future experimental or computational approaches are still needed to determine the precise upstream signals contributing to inflexible communication with FFA or other sensory-representation areas. However, an inability to flexibly adapt communication

with sensory-representation areas reflects a potential common neurobiological mechanism explaining cognitive biases favoring the processing of negative emotional information shared across adolescent anxiety and depression.

Transparency

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Author Contributions

N. A. Hubbard developed and performed hypothesis tests and drafted the manuscript with R. P. Auerbach and J. D. E. Gabrieli. A. Yendiki and S. Whitfield-Gabrieli developed the concept of the parent study in collaboration with R. P. Auerbach, S. S. Ghosh, A. Henin, S. G. Hofmann, D. A. Pizzagalli, and J. D. E. Gabrieli. V. Siless, S. S. Ghosh, A. Henin, S. G. Hofmann, D. A. Pizzagalli, I. M. Rosso, A. Yendiki, and S. Whitfield-Gabrieli supplied critical revisions. N. A. Hubbard, N. Lo, I. R. Frosch, D. E. Clark, R. Jones, and I. M. Rosso implemented descriptive analyses or data curation. V. Siless, R. Jones, R. Kremens, M. Pinaire, F. Vaz-DeSouza, A. Henin, and A. Yendiki collected the data. All of the authors approved the final manuscript for submission.

Declaration of Conflicting Interests

D. A. Pizzagalli has received consulting fees from Albright Stonebridge Group, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathways, Concert Pharmaceuticals, Engrail Pharmaceuticals, Neurocrine Biosciences, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; an honorarium from Alkermes; stock options from Blackthorn Therapeutics; and compensation for his work as editor from the Psychonomic Society. S. G. Hofmann receives compensation for his work as editor from SpringerNature and the Association for Psychological Science; compensation for his role as an advisor from Otsuka Pharmaceutical, Jazz Pharmaceutical, and the Palo Alto Health Sciences; and compensation for his work as a subject-matter expert from John Wiley & Sons, Inc., and SilverCloud Health, Inc. V. Siless received consulting fees from BioMakers and salary and stock from Quipu Market. The author(s) declared that there were no other potential conflicts of interest with respect to the authorship or the publication of this article.

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Open Practices

At the time the manuscript was accepted, curation of brain imaging data was ongoing for inclusion into the National Institute of Mental Health Data Archives (NDA) repository. We anticipate that the data used in this manuscript and additional data that were collected during the broader Connectomes Related to Anxiety and Depression in Adolescence project will eventually be publicly accessible via the NDA at https://nda.nih.gov/edit_collection.html?id=3037. More information about the Open Practices badges can be found at https://www.psychologicalscience.org/publications/badges.

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Supplemental Material

Additional supporting information can be found at http://journals.sagepub.com/doi/suppl/10.1177/21677026221079628

Note

1. The exclusion criterion of parent and adolescent Wechsler Abbreviated Scale of Intelligence estimated full-scale IQ lower than 85 was instituted at study onset. This criterion was relaxed during study progression, and participants were allowed to matriculate into the study on the basis of an experimenter's clinical judgment. Two adolescents (IQs = 78 and 84) and three parents (IQs = 80, 83, 84) who did not meet the preliminary IQ exclusion criterion matriculated into the study.

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