Convergent behavioral and corticolimbic connectivity evidence of a negativity bias in children and adolescents

Hilary A. Marusak,1 Clara G. Zundel,2 Suzanne Brown,3 Christine A. Rabinak,1 and Moriah E. Thomason4,5,6

1Department of Pharmacy Practice, Wayne State University, Detroit, MI 48202, USA, 2Behavioral Neuroscience Program, Boston University School of Medicine, Boston, MA 02118, USA, 3School of Social Work, Wayne State University, Detroit, MI 48202, USA, 4Merrill Palmer Skillman Institute for Child and Family Development, Wayne State University, Detroit, MI 48202, USA, 5Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI 48202, USA and 6Perinatology Research Branch, NICHD/NIH/DHHS, Bethesda, MD 20892, USA

Correspondence should be addressed to Hilary A. Marusak, Department of Pharmacy Practice, Wayne State University, 259 Mack Ave, Suite 2190, Detroit, MI 48202, USA. E-mail: hmarusak@med.wayne.edu.

Abstract

Individuals differ in their tendency to perceive negativity in ambiguous situations or facial expressions. Prior research demonstrates that this so-called “negativity bias” is exaggerated in children; for instance, when they rate the emotional content of neutral facial expressions. However, neutral faces are frequently used as a baseline condition in pediatric emotion processing studies, as they are thought to be emotionally neutral. Here, we present data that challenge that notion. We demonstrate that children and adolescents rate neutral faces, particularly of adults, as negative, similar to ratings elicited by angry faces. In addition, we found a lack of age-related decrease in reaction time for neutral adult faces, suggesting that these stimuli remain salient across development. Demonstrating the relevance of individual differences, higher negativity bias was associated with lower self-reported reward sensitivity and increased functional connectivity of the amygdala. Together, these findings indicate that neutral faces are not perceived as emotionally neutral in children, thus discouraging their use as baseline condition in pediatric research. These data also offer a potential neurobiological substrate of the negativity bias in children. The link to corticolimbic emotion-processing circuitry and affective experience implies that exaggerations in these biases may be relevant for the development of emotional psychopathology.

Key words: amygdale; fMRI; emotion; affect; functional connectivity

Introduction

Facial displays of emotion are important nonverbal social signals. During interactions, we use observed facial displays to assess underlying emotional states, thereby setting the tone for subsequent interaction. Facial expressions therefore help us navigate a complex social landscape. The ability to detect emotion in facial expressions develops early in infancy (Adamson and Frick, 2003; Conradt and Ablow, 2010) and continues on
until early adulthood (Gao and Maurer, 2010). Facial expressions remain socially salient cues throughout the lifespan.

Neuroimaging studies of emotion processing frequently use neutral facial expressions as a baseline condition, as they are thought to be affectively neutral. However, emerging data, particularly in pediatric studies, are beginning to challenge this notion. For instance, children are likely to rate neutral faces as negative, similar to their ratings of fearful faces (Tottenham et al., 2013). In addition, neutral faces elicit similar amygdala responses in children as those observed for fearful and angry faces (Hoehl et al., 2010; Marusak et al., 2013). Moreover, neutral facial expressions of adults are the preferred approach for eliciting stress-related physiological responses in young children, the so-called “Still Face” paradigm (Adamson and Frick, 2003). Together, these findings suggest that children have a “negativity bias” for neutral facial expressions.

Some children may be more likely than others to perceive negativity from ambiguous expressions (e.g. neutral faces) or situations. Higher negativity bias is linked to increased susceptibility to emotional disorders, including anxiety and depression (Beck, 1976). Individual differences in negativity bias in early life may be important for understanding the developmental roots of these disorders.

Here, we test whether the previously identified negativity bias for neutral faces in children is exaggerated for neutral faces of adults relative to neutral faces of children, who represent their peers. This prediction is based on prior neuroimaging studies in children (Hoehl et al., 2010; Marusak et al., 2013) showing that the amygdala is more responsive to neutral faces of adults than neutral faces of children. The present study was designed to test whether this is due to the fact that children are more likely to interpret neutral facial expressions of adults as negative, relative to neutral expressions of their peers. Further, Nim Tottenham and colleagues (2013) found typical age-related decreases in reaction time (RT) for rating affective content of happy and angry adult faces, but not for neutral adult faces. We predict that lack of age-related decrease is specific for neutral adult faces, and will not be shown for neutral child faces. This prediction is based on the idea that adult facial expressions remain behaviorally and emotionally salient social signals to children across development. Moreover, adults represent authority figures to youth and prior research suggests that children engage more neural resources to decode their expressions (Hoehl et al., 2010; Marusak et al., 2013).

In addition to understanding whether the negativity bias is specific to neutral faces of adults, it is as yet unclear whether the negativity bias is related to affective symptomology and/or neural variation in children. We will address this gap by testing initial relevance of individual differences in negativity bias for self-reported affective experience and functional neural connectivity (FC) of the amygdala, a region involved in detecting ambiguity and emotional salience of environmental cues (LeDoux, 1998).

### Materials and methods

#### Participants

Sixty-seven children and adolescents (34 females, ages 6–17) were recruited from the greater Detroit Area through advertisements on the Wayne State University (WSU) website, Craigslist (Metro Detroit), and printed flyers. All participants and their parents provided written consent or assent as approved by the WSU Institutional Review Board. Exclusion criteria consisted of a history of neurological injury, MRI indication, or significant learning disorder and all participants were fluent in English. Participants were shown a brief video about magnetic resonance imaging (MRI) experimental procedures to prepare them for their MRI scan session in advance (available at www.brainnexus.com/links). The study sample ranged in socioeconomic and demographic distribution (Table 1). Age was not associated with income, r_s(67) = 0.014, P = 0.9.

#### Negativity bias paradigm

Participants completed an adapted version of a brief forced-choice experimental paradigm previously used in adult (Neta et al., 2009; Neta and Whalen, 2010) and pediatric samples (Tottenham et al., 2013). During the paradigm, participants were instructed to indicate, as quickly and accurately as possible, whether an angry, happy, or neutral facial expressions “felt good or felt bad”, using a left or right hand (index finger) response. Response buttons for “good” and “bad” were counterbalanced across participants. Language used was consistent

### Table 1. Sample demographics (n = 67)

| Measure                              | Measure |
|--------------------------------------|---------|
| Age, m (SD)                          | 12.5 (3.1) |
| Gender, n females (%)                | 34 (51%) |
| Pubertal status                      |         |
| Tanner stages 1–2, n (%)             | 20 (30%) |
| Tanner stages 3–5, n (%)             | 30 (45%) |
| Not reported, n (%)                  | 17 (25%) |
| IQ, m (SD)                           | 104 (20.6) |
| Race/ethnicity, n (%)                |         |
| Caucasian                            | 29 (43%) |
| African American                     | 27 (40%) |
| Asian                                | 4 (6%)  |
| Hispanic                             | 2 (3%)  |
| Multiracial                          | 1 (2%)  |
| Not Reported                         | 4 (6%)  |
| Family annual income, n (%)          |         |
| Less than $10,000                    | 3 (4%)  |
| $10,000–$20,000                      | 7 (10%) |
| $20,000–$30,000                      | 10 (15%)|
| $30,000–$40,000                      | 8 (12%) |
| $40,000–$50,000                      | 7 (10%) |
| $50,000–$60,000                      | 9 (13%) |
| $60,000–$80,000                      | 6 (9%)  |
| $80,000–$100,000                     | 2 (3%)  |
| $100,000–$120,000                    | 3 (4%)  |
| $120,000–$140,000                    | 3 (4%)  |
| $140,000–$160,000                    | 2 (3%)  |
| $160,000–$180,000                    | 1 (1%)  |
| $180,000–$200,000                    | 2 (3%)  |
| Not reported                         | 4 (6%)  |
| Self-report measures of affective experience |         |
| Anxiety symptoms, m (SD)             | 30.4 (16.3) |
| Depressive symptoms, m (SD)          | 4.6 (4.5) |
| Reward sensitivity, m (SD)           | 37.8 (8.1) |

Abbreviations: n, number; m, mean; SD, standard deviation. Anxiety symptoms measured with the Screen for Child Anxiety Related Emotional Disorders. Depressive symptoms measured with the Children’s Depression Inventory, Short Form. Reward sensitivity measured with the Behavioral Inhibition and Activation Scales. IQ measured with the KBIT-2.
with a prior study using this task in children (Tottenham et al., 2013). An equal number of angry, happy, and neutral expressions were presented for 1500 ms, with each face followed by a 200 ms fixation. Rapid presentation was used to assess initial negativity biases. Face stimuli consisted of greyscale images of female and male adult actors of varied ethnicities, derived from the standardized NIMSTIM stimulus set (Tottenham et al., 2013). The task parameters were similar to those used in a previous pediatric study by Tottenham et al. (2013) with one modification: the additional use of child face stimuli. In particular, we added angry, happy and neutral face stimuli of children of varied ethnicities, derived from the standardized NIMH-ChEFS stimulus set (Egger et al., 2011). All images were matched on brightness and size. See (Figure 1) for example neutral adult and child face stimuli. A total of 72 trials were randomly presented in a single run, with a total of 16 actors (4 female child, 4 male child, 4 female adult, 4 male adult) displaying each emotion (angry, happy, neutral) and type-of-face (adult, child) combination 12 times. Total experiment time was 2 min 43 s. Before beginning the experiment, participants completed 20 practice trials, consisting of a separate set of actors. Study participants responded to a high number of trials (M = 97%, SD = 6%). The primary outcome measure was “negativity bias” for each face emotion (angry, happy, neutral) and type-of-face (adult, child). Negativity bias was calculated as the percent of stimuli rated as “bad”. For example, if a participant indicated that an angry adult face was “bad” on all trials, then his or her negativity bias for angry adult faces would be 100%. RT to each stimuli type was also calculated.

Self-report measures of affective experience
A subset of participants (n = 50) completed standardized self-report measures of anxiety (Screen for Child Anxiety-Related Emotional Disorders, SCR; Birmaher et al., 1997), depression (Children’s Depression Inventory—short form, CDI; Kovacs, 1992) and reward sensitivity (Behavioral Inhibition and Activation Scales, BIS/BAS; Carver and White, 1994). Of note, 37% of study participants exceed thresholds suggested for detecting pathological anxiety (SCR > 22; Desousa et al., 2013), 54% for depression (CDI-S ≥ 3; Allgaier et al., 2012), and 27% show significant reduction in reward sensitivity (BAS < 35; Kasch et al., 2002; Table 1). Thus, although diagnostic testing was not performed here, these standardized measures suggest a significant number of youth at risk for emotional psychopathology.

Neuroimaging procedures
MRI acquisition: Another subset of participants (n = 39, 19 females) underwent MR imaging. Six minutes of eyes closed resting-state functional MRI (fMRI) data were analyzed for each participant. T2*-weighted blood oxygenation level-dependent (BOLD) images were acquired (inter-leaved ascending acquisition) using echo-planar imaging (EPI). All MR scanning was conducted using the same 3.0 Tesla Siemens MAGNETOM Verio system (WSU MRI Research Facility), using one of two sets of imaging parameters. Data were combined across two fMRI sequences to achieve a larger sample size. Sixteen participants were scanned with the following EPI parameters: repetition time [TR] = 2000 ms; echo time [TE] = 25 ms; flip angle [FA] = 90°; voxel size = 3.44 x 3.44 x 4 mm; matrix = 220 x 200; 29 slices. Parameters for the remaining 13 participants

Fig. 1. Example neutral adult, A, and child, B face stimuli. Adult face stimuli were drawn from the NIMSTIM stimulus set (Tottenham et al., 2013); child face stimuli from the NIMH-ChEFS stimulus set (Egger et al., 2011).
were: TR = 1500 ms; TE = 31 ms; FA = 83°; voxel size = 2.9 x 2.9 x 2.9 mm; matrix = 186 x 186; 51 slices. Data processing steps accounted for scan parameters and follow-up analyses controlling for scan sequence yielded no changes to results reported.

**MRI preprocessing:** Image preprocessing steps were conducted with SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/) and DPARSF (Data Processing Assistant for Resting-State fMRI; http://fmril.org/DPARSF) software. After discarding the first 3 frames to allow for signal stabilization, images were slice-time corrected, realigned, spatially normalized to the Montreal Neurological Institute (MNI) template, and spatially smoothed using a 6 mm Gaussian kernel. To further control for the effects of motion-related artifact in the data, frames exceeding 0.5 mm motion were “scrubbed”, i.e. removed from analyses (Power et al., 2012). Participants that retained > 83% of frames under this threshold after scrubbing were included in the final analysis. Ten participants were excluded, leaving a sample of n = 29 for neuroimaging analyses. The MRI subsample was matched to the full sample on socioeconomic, demographic, self-reported affect measures, and negativity bias, p’ s > 0.08 (Table S1).

**Connectivity analysis:** Preprocessed resting-state fMRI data were submitted to the CONN Functional Connectivity Toolbox (ver.15.h; www.nitrc.org/projects/conn). Prior to calculating functional connectivity (FC), component-based correction (CompCor; Behzadi et al., 2007) and temporal band-pass filtering (0.008–0.09 Hz) was applied to remove non-BOLD artifact from the data. Additionally, the six realignment parameters (with another six parameters representing their first order temporal derivatives) were removed with covariate regression analysis. Pearson bivariate correlation was used to compute seed to whole-brain FC. Bilateral amygdala (defined by FSL FIRST atlas; Patenaude et al., 2011) was used as the seed region of interest, based on the amygdala’s central role in emotion processing and salience detection (LeDoux, 1998). Resulting Fisher r-to-z-transformed correlation coefficients were submitted to SPM8 for regression analyses, with negativity bias to neutral adult faces as the variable of interest. Results were considered significant at an exploratory threshold of P < 0.005, 10 contiguous voxels, based on suggested standards for whole-brain analyses (Lieberman and Cunningham, 2009). Cytoarchitectonic areas for resulting peak coordinates were estimated using maps defined in SPM Anatomy toolbox, when available (Eickhoff et al., 2005).

### Results

#### Youth rate neutral faces of adults as more negative than neutral faces of children

Youth displayed a negativity bias for neutral adult and neutral child faces (Figure 2). The ratings differed significantly from chance level (t’ s > 19, P’ s < 0.001), suggesting that adult and child faces are rated as having negative valence across youth. Youth were more likely to rate neutral faces of adults as negative relative to neutral faces of children, t(66) = 3.28, P = 0.002. Consistent with prior work (Tottenham et al., 2013), youth consistently rate angry faces as negative, and happy faces as positive (Figure 2). A type-of-face (adult, child) x emotion (angry, happy, neutral) ANOVA showed a main effect of type-of-face, F(1,66) = 8.84, P = 0.004, such that adult faces were rated as more negative than child faces. The main effect of emotion was also significant, F(2,132) = 404.76, P < 0.001, such that angry faces were rated as more negative than happy and neutral faces. The main effect of type-of-face was driven by the difference within neutral expressions. However, the type-of-face x emotion interaction was not significant, P = 0.12.

Age of participant was not associated with negativity bias across all emotions, including neutral, F(1,65) = 0.001, P = 0.977. Nonetheless, we repeated analyses additionally controlling for age. Controlling for age, the main effect of emotion remained significant, F(2,130) = 17.3, P < 0.001, but the main effect of type-of-face was no longer significant, F(1,65) = 0.02, P = 0.89. The three-way interaction (age x emotion x type-of-face) did not reach significance, F(2,130) = 3.03, P = 0.052. We repeated the ANOVA in older and younger age groups (median split)
separately, to further explore potential age differences in ratings (Figure 2). The main effect of type-of-face was significant in the older age group, $F(1, 33) = 5.03, P = 0.032$, but did not reach significance in the younger age group, $F(1, 32) = 4.1, P = 0.051$. Similarly, the type-of-face x emotion interaction was significant in the older, $F(2, 66) = 3.49, P = 0.036$, but not younger age group, $F(2, 64) = 0.28, P = 0.76$. This effect appeared to be driven by neutral faces, such that neutral adult faces were more frequently rated as negative than neutral child faces, among older, $t(33) = 3.47, P = 0.001$, but not younger youth, $t(32) = 1, P = 0.32$ (Figure 2). Ratings for angry and happy faces did not differ between adult and child faces, in either age group, $P's > 0.07$.

**Age-related decreases in reaction time present for all but neutral adult faces**

Increasing age was associated with faster overall RT (all conditions), $r(67) = -0.304, P = 0.012$. Pearson bivariate correlation by emotion and type-of-face showed that this effect was significant for all but neutral adult faces, $r(67) = -0.07, P = 0.576$. Specifically, RT for neutral adult faces did not show the typical age-related decrease (Figure 3).

**Negativity bias is relevant for individual differences in self-reported affect in youth**

Across the sample and controlling for age, lower reward sensitivity, a risk factor for emotional psychopathology (McFarland et al., 2006), was associated with faster RT to neutral adult faces, $r(48) = 0.301, P = 0.034$ (Figure 4). There was a similar RT effect for neutral child faces, but it did not reach significance, $r(48) = 0.276, P = 0.052$. We also found an association between reward sensitivity and negativity bias to neutral child faces, such that lower reward sensitivity corresponded with higher negativity bias, $r(48) = -0.313, P = 0.027$. Anxiety and depressive symptoms were not related to RT or negativity bias to neutral faces, when controlling for age ($P's > 0.09$). When split by age group (and controlling for age), the observed associations between behavior and reward sensitivity appeared to be driven by the older, $P's 0.024$–$0.095$, rather than younger age group, $P's 0.2$–$0.5$.

Together, these findings support a link between self-reported affective experience and individual differences in behavioral response (i.e. RT, negativity bias) to neutral faces.

**Negativity bias is relevant for individual differences in corticolimbic connectivity in youth**

Finally, in preliminary analyses we tested whether negativity bias to neutral adult faces was associated with resting-state FC of the amygdala, a limbic region critical for detecting emotionally-charged and other salient environmental information. Youth with higher negativity bias showed increased amygdala FC with several interconnected regions involved in the rapid detection of emotional saliency, including the thalamus (THAL), ventrolateral prefrontal cortex (VLPFC) and visual cortex (Figure 5 and Table 2; Fan et al., 2011; Zikopoulos and Barbas, 2012; Kohno et al., 2015). Higher negativity bias was associated with decreased amygdala FC in several regions, including prefrontal and middle cingulate cortex (Table 2). Although age was not associated with negativity bias (see above), FC analyses were repeated with age as a nuisance covariate. Results were largely consistent with those reported here, with increased amygdala FC with THAL, VLPFC, and visual cortex in youth with higher negativity bias (see Table S2 for full summary).

**Discussion**

In this study, we demonstrate that the previously observed “negativity bias” for children rating neutral faces (see Tottenham et al., 2013) is exaggerated for neutral facial expressions of adults relative to neutral expressions of children. This difference appeared to be exacerbated by age, such that neutral adult faces were more frequently rated as negative than neutral child faces among older but not younger youth (median split). We found a similar effect for RT such that RT decreased with age for all facial expressions except neutral adult. Demonstrating the relevance of negativity bias in youth for the first time, we found that individual differences in negativity...
bias was associated with self-reported affective experience and altered FC of the amygdala. Together, our results challenge the notion that neutral faces are perceived as emotionally neutral, in children and adolescents. They also suggest that the ambiguity of neutral adult faces does not resolve with age.

We found that children and adolescents are likely to rate neutral facial expressions as negative, similar to ratings observed for angry faces. These results are fitting with prior pediatric studies showing that the amygdala is highly responsive to neutral faces, particularly of adults (Thomas et al., 2001; Hoehl et al., 2010; Marusak et al., 2013). These findings have critical implications for the use of neutral facial expressions as baseline in behavioral and neuroimaging research. This approach implicitly assumes that subtracting out responses to neutral faces removes signal associated with non-emotional processing (e.g., face processing, motor response). However, this is problematic if children perceive emotionality in these stimuli, and subtracting out this variance may diminish or bias effects.

Further, we observed individual differences in the degree to which children perceive neutral faces as negative. This variation further discourages the use of neutral faces as baseline, as baseline conditions should have little to no variability between participants (see Newman, 2001 for discussion of baseline conditions). Together, these findings support the notion that neutral faces are not an appropriate baseline condition for youth studies.

Our findings also suggest that the ambiguity associated with neutral adult facial expressions does not resolve with age within this sample (ages 6–17), as evidenced by lack of age-related decrease in RT. Further, results suggest that negativity ratings for neutral adult faces may even become more negative with age, as compared to neutral child faces. These findings could be due to the fact that neutral adult faces remain salient across development, as these stimuli may represent authority figures. Children may spend more cognitive or attentional resources attempting to disambiguate these cues, as they may...
predict subsequent disciplinary action or a negative interaction. Neutral faces of their peers, in contrast, are less likely to have negative behavioral consequences. An important question is whether adults demonstrate a negativity bias for neutral facial expressions of adults, who represent their peers. Although we did not include adults here, previous studies have tested adults with the negativity bias paradigm. While neutral facial expressions were not evaluated in these prior studies, adults demonstrated an initial “default” negativity bias for surprised faces, another ambiguous facial expression (Neta and Whalen, 2010). Notably, across adult participants, surprised faces were not consistently rated as positive or negative; there was considerable inter-individual variation (Neta et al., 2009). Future developmental research is needed to understand how the age of the face relative to the perceiver may influence these biases.

Supporting the notion that the observed individual differences in children are meaningful, we found that RT and negativity bias to neutral faces were associated with self-reported affective experience and amygdala FC. Specifically, we found that youth with faster responses to neutral adult faces and greater negativity bias to neutral child faces reported lower reward sensitivity, a risk factor for internalizing disorders (McFarland et al., 2006). This is consistent with prior research in children. For example, children reporting higher levels of internalizing symptomology were not only more likely to perceive negativity in ambiguous situations (Muris et al., 2003), but also submitted faster responses and required less information to conclude that ambiguous situations will have a threatening ending (Muris et al., 2000). Faster RTs and/or more frequent interpretations of threat in ambiguous stimuli are thought to reflect poorer regulatory control (potentially cortical control over amygdala responding), as higher control requires added processing time to override the default negative response (Neta and Whalen, 2010). Here, we found that youth with reduced reward sensitivity submitted faster responses and exhibited greater negativity bias to neutral faces. This may reflect poorer regulatory control, and contribute to the development or maintenance of emotional psychopathology.

These data also implicate a potential neurobiological basis of the negativity bias, for the first time. In particular, children with higher negativity bias showed increased FC of the amygdala with the THAL, VLPFC, and visual processing regions. These areas are highly interconnected with the amygdala and are involved in the coordinated rapid detection of threat and ambiguous information (Fan et al., 2011; Zikopoulos and Barbas, 2012; Kohno et al., 2015). Increased FC among these regions is

Table 2. Whole brain results of amygdala resting-state functional connectivity

| Contrast | Brain region | Cytoarchitectonic area [probability, if available] | Z-score | kE | x | y | z |
|----------|--------------|--------------------------------------------------|---------|-----|---|---|---|
| **Increasing connectivity with increasing negativity bias** | | | | | | | |
| R superior occipital lobe | thalamus, motor [66%] | 4.41 | 70 | 24 | -84 | 4 |
| L middle temporal lobe | area SL [28%] | 3.95 | 34 | -14 | -20 | -2 |
| L postcentral gyrus | hOc2 [27%] | 3.54 | 38 | 22 | -100 | 20 |
| R superior occipital lobe | thalamus, temporal [34%] | 3.40 | 68 | 6 | -14 | 20 |
| R middle temporal lobe | hOc5 [27%] | 3.36 | 68 | 50 | -66 | 8 |
| R inferior parietal lobe | area PFm [5%] | 3.34 | 22 | 60 | -58 | 42 |
| L middle temporal lobe | area PGp (IPL) [44%] | 3.33 | 15 | -48 | -82 | 20 |
| L ventrolateral prefrontal cortex | | 3.30 | 105 | -36 | 34 | -4 |
| R middle temporal lobe | | 3.22 | 36 | 38 | -64 | 6 |
| R postcentral gyrus | area 1 [69%] | 3.19 | 33 | 40 | -36 | 64 |
| R posterior cingulate/precuneus | | 3.16 | 40 | 22 | -46 | 28 |
| L cerebellum | lobule VIIa crus [63%] | 3.08 | 36 | -42 | -40 | -42 |
| R middle temporal lobe | | 3 | 41 | 42 | -44 | -2 |
| R orbitofrontal cortex | | 2.72 | 10 | 42 | 32 | -10 |
| **Decreasing connectivity with increasing negativity bias** | | | | | | | |
| R superior frontal gyrus | | 4.01 | 30 | 10 | 64 | 34 |
| R inferior temporal gyrus | | 3.89 | 25 | 36 | -20 | -48 |
| R cingulate gyrus | | 3.72 | 180 | 16 | -6 | 34 |
| L fusiform gyrus | | 3.35 | 55 | -20 | -6 | 38 |
| L middle cingulate gyrus | | 3.32 | 27 | -8 | 12 | 38 |
| L supplementary motor area | | 3.28 | 39 | -10 | 0 | 46 |
| R middle frontal gyrus | | 3.22 | 38 | 42 | 26 | 32 |
| L cerebellum | lobule VIIa crus [95%] | 3.12 | 10 | -54 | -64 | -40 |
| L insula | | 3.06 | 15 | -30 | 4 | 12 |
| R middle frontal gyrus | | 3.38 | 21 | 24 | -6 | 44 |
| L middle cingulate gyrus | | 3.06 | 26 | 12 | 26 | 32 |
| R caudate | | 2.91 | 19 | 10 | 22 | 8 |
| R brainstem | | 2.82 | 10 | 10 | -22 | -16 |

Abbreviations: R, right; L, left; BA, Brodmann area; kE, cluster extent. Exploratory whole brain threshold: $P = 0.005$, kE = 10 voxels. Cytoarchitectonic areas are assigned, when available, using SPM Anatomy toolbox v.2.1.
commonly reported in individuals with higher internalizing symptoms (e.g. Baur et al., 2013; Ousdal et al., 2014). These brain areas are also hyper-responsive to negative stimuli in depressed individuals (see meta-analysis by Hamilton, 2012). Altogether, these findings replicate the previously reported negativity bias for neutral facial expressions in children (Tottenham et al., 2013), suggesting a negativity default in youth. They also extend this prior work by suggesting that exaggeration in this bias may predict risk for the development of emotional disorders. This is evidenced by individual differences in self-reported affective tendencies, and variation within corticolimbic emotion-processing circuitry.

Limitations of this work warrant mention. First, this study was cross-sectional, which limits us from drawing strong conclusions about developmental effects. Additionally, MRI scanning was performed only on a subset of youth, and may thus be considered preliminary. Second, this study used static facial expressions, which are thought to be less life-like (Katsyri and Sams, 2008; Widen and Russell, 2015). Future studies should replicate these findings with dynamic facial expressions. A third limitation was that eye gaze was not monitored during the negativity bias task. However, participants responded to a large portion of trials (97%), suggesting that attention was maintained throughout the task. There may nonetheless be individual differences in patterns of eye gaze that are associated with variation in negativity bias (e.g. threat avoidance, fixation on eye area). Future research should explore these possibilities.

Conclusions

Research investigating facial processing in children has largely relied on neutral facial expressions as a baseline, as they are thought to be emotionally neutral. Here, we present data that challenge this notion. We found that children and adolescents consistently rate neutral faces, particularly of adults, as negative. We also found a lack of age-related decrease in RT for neutral adult faces, suggesting that these stimuli remain salient across development. Supporting the relevance of individual differences, faster RT and higher negativity bias to neutral faces were associated with individual differences in self-reported affect, and variation within corticolimbic emotion-processing circuitry. Together, our findings demonstrate that neutral faces are not perceived as emotionally neutral to children and adolescents, and thus may not be an appropriate baseline in pediatric research. In addition, exaggerated negativity bias among some youth may presage the development of emotional psychopathology.

Acknowledgements

The authors thank Laura Crespo, Kelsey Sala-Hamrick, Farah Sheikh, Aneesh Hehr, Klararama Gelci, Joshua Hatfield, Sajah Parkhouri, Limi Sharif, Shelley Paulisin, Allesandra Iadipaolo, Kassem Soufan, Craig Peters, Brian Silverstein and Farrah Elrahal of Wayne State University for assistance in participant recruitment and data collection, and the children and families who generously shared their time. Development of the NIMSTIM Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development. Please contact Nim Tottenham at nlt7@columbia.edu for more information concerning the stimulus set.

Funding

Research reported in this publication was supported, in part, by the Merrill Palmer Skillman Institute, Department of Pharmacy Practice, and Department of Pediatrics of Wayne State University (WSU), NIH National Institute of Environmental Health Sciences awards P30 ES020957 and R21 ES026022 (MET), NIH National Institute of Mental Health award R01 MH110793 (MET), and a NARSAD Young Investigator Award (MET). Dr. Marusak is supported by American Cancer Society award 129368-PF-16-057-01-PCSM. Dr. Rabinak is supported by NIH National Institute of Mental Health grant K01 MH101123. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest: None declared

References

Adamson, L.B., Frick, J.E. (2003). The still face: a history of a shared experimental paradigm. Infancy, 4(4), 451–73.
Allgaier, A.K., Fruehe, B., Pietsch, K., Saravo, B., Baethmann, M., Schulte-Korne, G. (2012). Is the Children’s Depression Inventory Short version a valid screening tool in pediatric care? A comparison to its full-length version. Journal of Psychosomatic Research, 73(5), 369–74.
Baur, V., Hanggi, J., Langer, N., Jancke, L. (2013). Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. Biological Psychiatry, 73(1), 85–92.
Beck, A.T. (1976). Cognitive Therapy and the Emotional Disorder. New York: Meridian.
Behzadi, Y., Restom, K., Liau, J., Liu, T.T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage, 37(1), 90–101.
Birmaher, B., Khetarpal, S., Brent, D., et al. (1997). The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. Journal of American Academy Child Adolescent Psychiatry, 36(4), 545–53.
Carver, C.S., White, T.L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. Journal of Personality and Social Psychology, 67(2), 319.
Conradt, E., Ablow, J. (2010). Infant physiological response to the still-face paradigm: contributions of maternal sensitivity and infants’ early regulatory behavior. Infant Behavior Development, 33(3), 251–65.
Desousa, D.A., Salum, G.A., Isolan, L.R., Manfro, G.G. (2013). Sensitivity and specificity of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a community-based study. Child Psychiatry and Human Development, 44(3), 391–9.
Egger, H.L., Pine, D.S., Nelson, E., et al. (2011). The NIMH Child Emotional Faces Picture Set (NIMH-ChEFPS): a new set of children’s facial emotion stimuli. International Journal of Methods and Psychiatric Research, 20(3), 145–56.
Eickhoff, S.B., Stephan, K.E., Mohlberg, H., et al. (2005). A new SPM toolbox for combining probabilistic cytoarchitec tonic maps and functional imaging data. Neuroimage, 25(4), 1325–35.
Fan, J., Gu, X., Liu, X., et al. (2011). Involvement of the anterior cingulate and frontoinsular cortices in rapid processing of salient facial emotional information. *Neuroimage, 54*(3), 2539–46.

Gao, X., Maurer, D. (2010). A happy story: developmental changes in children’s sensitivity to facial expressions of varying intensities. *Journal of Experimental Child Psychology, 107*(2), 67–86.

Hamilton, J.P. (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. *American Journal of Psychiatry, 169*, 693–703.

Hoehl, S., Brauer, J., Brasse, G., Striano, T., Friederici, A.D. (2010). Children’s processing of emotions expressed by peers and adults: an fMRI study. *Society Neuroscience, 5*(5–6), 543–59.

Kasch, K.L., Rottenberg, J., Arnow, B.A., Gotlib, I.H. (2002). Behavioral activation and inhibition systems and the severity and course of depression. *Journal of Abnormal Psychology, 111*(4), 589–97.

Katsyri, J., Sams, M. (2008). The effect of dynamics on identifying basic emotions from synthetic and natural faces. *International Journal of Human-Computer Studies, 66*(4), 233–42.

Kohno, S., Noriuchi, M., Iguchi, Y., Kikuchi, Y., Hoshi, Y. (2015). Emotional discrimination during viewing unpleasant pictures: timing in human anterior ventrolateral prefrontal cortex and amygdala. *Frontiers in Human Neuroscience, 9*, 51.

Kovacs, M. (1992). Children’s Depression Inventory. North Tonawanda, NY, USA: Multi-Health Systems, Incorporated.

LeDoux, J. (1998). Fear and the brain: where have we been, and where are we going? *Biological Psychiatry, 44*(12), 1229–38.

Lieberman, M.D., Cunningham, W.A. (2009). Type I and Type II error concerns in fMRI research: re-balancing the scale. *Social Cognitive and Affective Neuroscience, 4*(4), 423–8.

Marusak, H.A., Carre, J.M., Thomason, M.E. (2013). The stimuli drive the response: an fMRI study of youth processing adult or child emotional face stimuli. *Neuroimage, 83*C, 679–89.

McFarland, B.R., Shankman, S.A., Tenke, C.E., Bruder, G.E., Klein, D.N. (2006). Behavioral activation system deficits predict the six-month course of depression. *Journal of Affective Disorder, 91*(2–3), 229–34.

Muris, P., Merckelbach, H., Damsma, E. (2000). Threat perception bias in nonreferred, socially anxious children. *Journal of Clinical and Child Psychology, 29*(3), 348–59.

Muris, P., Rapee, R., Meesters, C., Schouten, E., Geers, M. (2003). Threat perception abnormalities in children: the role of anxiety disorders symptoms, chronic anxiety, and state anxiety. *Journal of Anxiety Disorders, 17*(3), 271–87.

Neta, M., Norris, C.J., Whalen, P.J. (2009). Corrugator muscle responses are associated with individual differences in positivity-negativity bias. *Emotion, 9*(5), 640–8.

Neta, M., Whalen, P.J. (2010). The primacy of negative interpretations when resolving the valence of ambiguous facial expressions. *Psychological Science, 21*(7), 901–7.

Newman, S.D. (2001). Baseline conditions and subtractive logic in neuroimaging. *Human Brain Mapping, 14*, 228–35.

Ousdal, O.T., Andreassen, O.A., Server, A., Jensen, J. (2014). Increased amygdala and visual cortex activity and functional connectivity towards stimulus novelty is associated with state anxiety. *PloS One, 9*(4), e96146.

Patenaude, B., Smith, S.M., Kennedy, D.N., Jenkinson, M. (2011). A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage, 56*(3), 907–22.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage, 59*(3), 2142–54.

Thomas, K.M., Drevets, W.C., Dahl, R.E., et al. (2003). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry, 58*(11), 1057–63.

Tottenham, N., Phuong, J., Flannery, J., Gabard-Durnam, L., Goff, B. (2013). A negativity bias for facial emotion-expression valence during childhood: converging evidence from behavior and facial corrugator muscle responses. *Emotion, 13*(1), 92–103.

Widen, S.C., Russell, J.A. (2015). Do dynamic facial expressions convey emotions to children better than do static ones?. *Journal of Cognition and Development, 16*(5), 802–11.

Zikopoulos, B., Barbas, H. (2012). Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. *Journal of Neuroscience, 32*(15), 5338–50.