Biological Psychology 134 (2018) 9–19

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Convergence of BOLD and ERP measures of neural reactivity to emotional faces in children and adolescents with and without anxiety disorders

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ARTICLE INFO

Keywords:
Emotional face processing
BOLD
fMRI
LPP
Event-related potentials
Developmental neuroscience

ABSTRACT

The neural bases of emotion are commonly measured using blood-oxygen-level-dependent (BOLD) signal and the late positive potential (LPP) event-related potential (ERP) component, but rarely together in the same individuals. Despite evidence of developmental changes in processing socio-emotional signals (e.g., faces) as reflected by both BOLD and LPP indices of brain maturation, the literature on the correspondence between these measures is limited to healthy adults, leaving questions regarding such correspondence across development and in clinical populations unaddressed. We examined the relationship between BOLD and LPP during an emotional face processing task in a large sample of youth (N = 70; age 7–19 years) with and without anxiety disorders, and tested whether BOLD signal in regions corresponding to LPP may account for age-related decreases in LPP. Greater activation in bilateral inferior frontal gyrus (IFG)/orbitofrontal gyrus (OFG), left supplementary motor area, right superior parietal lobule, and bilateral amygdala correlated with enhanced LPP to emotional faces in both anxious and healthy youth. Older youth exhibited reduced activation in bilateral IFG/OFG and bilateral amygdala, as well as reduced LPP. Decreased right IFG/OFG activation mediated the association between age and LPP. These findings support correspondence between these measures and need for multi-method approaches and indicate that age-related decreases in LPP may be driven, in part, by decreased IFG/OFG activation.

1. Introduction

There has been an impetus, in the fields of neuroscience, psychiatry, and psychology to identify reliable, valid, and multi-method measures of behavior, cognition and emotion (Bunford, Kinney, Michael, & Klumpp, 2017; Mash & Hunsley, 2005). In the current study, the phenomenon of interest was emotional face processing; differences in emotional face processing are associated with variation in socio-emotional functioning, including a range of psychopathologies (Bunford, Kujawa, Fitzgerald et al., 2016; Bunford, Evans, & Wymbs, 2015; Kujawa, MacNamara, Fitzgerald, Monk, & Phan, 2015). Emotional face processing also lends itself well to study of multi-method measures as it is measurable across multiple levels of measurement (Sabatinelli, Keil, Frank, & Lang, 2013; Sabatinelli, Lang, Keil, & Bradley, 2007). Commonly used assessment methods of the neural correlates of emotional face processing include blood-oxygen-level-dependent (BOLD) signal, assessed via functional magnetic resonance imaging (fMRI), and event-related potentials (ERP), derived from the electroencephalograph (EEG).

The association between BOLD signal and ERPs is of specific interest, as BOLD signal and ERPs are complementary in that they reflect differential indices of neural activation to emotionally salient and arousing stimuli (see Sabatinelli et al., 2007 for review). fMRI provides better spatial resolution for brain structure-function localization, while ERPs provide better stimulus-locked temporal resolution. As such, understanding if (and where in brain) BOLD signal and ERPs converge is relevant as their combined use may provide a more comprehensive model of neural correlates of emotional face processing.

A few studies (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012; Sabatinelli et al., 2013, 2007; Wessing et al., 2015) have begun to address this question in adults, and findings suggest correspondence between BOLD signal and the late positive potential (LPP), an ERP component that is particularly relevant for examining BOLD-ERP correspondence given its sustained nature. In youth, the LPP is evident

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https://doi.org/10.1016/j.biopsycho.2018.02.006
Received 17 August 2017; Received in revised form 22 December 2017; Accepted 11 February 2018
Available online 17 February 2018
0301-0511/

at occipito-parietal electrode sites beginning approximately 500 ms after stimulus onset and persisting for at least several seconds, across stimulus presentation time and even beyond stimulus offset (Hajcak & Olvet, 2008; Kujawa, Klein, & Proudfit, 2013). LPP reflects sustained attention towards and processing of both negatively and positively valenced emotional stimuli, including emotional faces (Hajcak, Weinberg, Macnamara, & Foti, 2011; Schupp et al., 2000), and can be reliably assessed across development (Kujawa et al., 2013).

When BOLD and LPP were recorded during separate sessions in adults, the findings of Sabatinelli and colleagues (Sabatinelli et al., 2013, 2007) indicated that activation in lateral occipital, parietal, and inferotemporal cortices, amygdala, anterior cingulate cortex, anterior insula, and ventral striatum/nucleus accumbens is associated with LPP magnitude *across* individuals. The findings of MacNamara and colleagues (Macnamara, Rabinak, Kennedy, & Phan, 2017) indicated that activation in the amygdala is associated with LPP magnitude to fearful faces (> shapes), activation in the posterior fusiform gyrus and inferior temporal gyrus is associated with LPP magnitude to angry and happy faces (> shapes), respectively, *across* individuals. When BOLD and LPP was recorded during the same session with a trial by trial analysis, the findings of Liu et al. (Liu et al., 2012) indicated *within-individual* associations between activation in inferior, middle and superior temporal cortices, occipital cortex, insula, orbitofrontal cortex, amygdala/hippocampus, and temporal pole with LPP magnitude. To our knowledge, only one previous study has examined neural generators of LPP in youth. Using magnetoencephalography-based source localization in 8–14 year old children, Wessing et al. (2015) found reduced activity to reappraisal in the left dorsolateral prefrontal cortex (PFC) during emotion down-regulation and enhanced activity in the right parietal cortex during emotion up-regulation.

Although these studies have advanced our understanding of the correspondence between BOLD and LPP, the generalizability of their results could be expanded. First, these studies examined ERPs to emotional scenes (and not emotional faces but see Macnamara et al., 2017), and emotional scenes and faces may be processed differently at the neural level (Mavratzakis, Herbert, & Walla, 2016). Second, most studies were conducted with adults (and not youth). As there is extensive evidence of developmental differences in emotional face processing (e.g., Silk et al., 2009), both in the function and structure of brain regions related to emotional processing, and in LPP, extension to youth is needed. Specifically, the role of the amygdala in processing emotional stimuli changes across development, with evidence of age-related *decreases* in amygdala activation from childhood into young adulthood (Gee et al., 2013; also see Blackford and Pine 2012 for review). In addition, regions of PFC, which appraise and integrate responses to emotional stimuli, undergo considerable functional and structural changes throughout development, and are among the last regions to fully mature (see Pine 2007 for review). Prior findings also indicate age-related decreases in LPP to emotional images (Kujawa et al., 2013; MacNamara et al., 2016). However, the LPP has been linked to activation in a broad neural network and it is unclear which brain regions might underlie the observed developmental decrease in LPP. It stands to reason that age-related decreases in LPP to emotional images may be partly driven by decreased amygdala activation with age (Blackford & Pine, 2012), or decreased activation in visual processing regions which contribute to LPP (Moratti, Saugar, & Strange, 2011). Alternatively, developmental changes in PFC activation may underlie age-related changes in LPP, as suggested by evidence of both decreased (e.g., dorsolateral PFC; Durston et al., 2006) and increased (Blackford & Pine, 2012) PFC activation with age. Combining BOLD and ERP measures of emotional face processing has the potential to test these possibilities.

Third, there is evidence of alterations in both BOLD signal and LPP to emotional stimuli in anxiety and other psychiatric disorders (e.g., Etkin and Wager 2007; Kujawa et al., 2015). For example, anxiety in adults and youth has been consistently shown to be associated with fMRI-measured abnormalities in fear circuitry including amygdala hyperreactivity to threat (Brühl, Delsignore, Komossa, & Weidt, 2014) and alterations in the functional activity of frontal regions that are associated with the regulation of fear responses (Amir et al., 2005; Blair et al., 2008; Etkin, Egner, & Kalisch, 2011; Freitas-Ferrari et al., 2010; Goldin, Manber, Hakimi, Canli, & Gross, 2009; Phan, Fitzgerald, Nathan, & Tancer, 2006). Some evidence indicates association between the LPP and self-reported anxiety (Wessing et al., 2015) and emotion regulation (Dennis & Hajcak, 2011). Our group has found that children with anxiety disorders exhibit enhanced LPPs to angry and fearful faces relative to children without anxiety disorders (Kujawa et al., 2015), and that in children with anxiety disorders, pre-treatment differences in the LPP predict treatment response (Bunford, Kujawa, Fitzgerald et al., 2016). Despite these data indicating alterations in both BOLD signal and LPP to emotional stimuli in anxiety, the literature on the correspondence between BOLD and LPP is exclusive to healthy samples (but see Macnamara et al., 2017 whose sample comprised combat-exposed U. S. military veterans with varying levels of posttraumatic stress symptomatology). Thus, an essential question is whether correspondence between BOLD signal and LPP extends to more heterogeneous samples and clinical populations. Finally, the available evidence is based on relatively small (< 25 participants) samples, indicating the need for research with larger samples (Siegle, 2011).

1.1. The current study

With the goal of beginning to address these gaps, our primary aim was to (1) examine the correspondence between BOLD signal and LPP to emotional faces in a relatively large, clinically heterogeneous sample of children and adolescents (aged 7–19 years), roughly half of whom were free of any psychiatric diagnoses and half of whom had a primary anxiety disorder (i.e., an anxiety disorder was the disorder that was associated with greatest symptom severity and functional impairment, determined using a semi-structured clinical interview, see *Procedures*). Our aim was also to (2) examine whether the correspondence between BOLD signal and LPP to emotional faces differs between youth without and with anxiety disorders. Of note, although we aimed to test for differences in BOLD-LPP correspondence between youth with an without anxiety, our pertinent goal was not to address questions related to the pathophysiology of pediatric anxiety *per se*. Rather, our goals were to test the relation between measures of emotional face processing across youth with a range of anxiety disorders and healthy youth, which has been related to differences in BOLD signal and LPP, as well as to test whether the groups differ with regard to that relation. Given the low spatial resolution of EEG measures (Luck, 2014), our secondary aim was to examine whether fMRI-measured activation in regions corresponding to LPP may account for − or explains − developmental decreases in LPP (i.e., simple mediation). Specifically, our goal was to test whether BOLD signal in regions correlated with LPP activation mediates effects of age on LPP magnitude. The hypothesized direction of these effects is in accordance with the RDoC (Morris & Cuthbert, 2012) conceptualization of the measurement of micro-measurement level of circuits (often indexing neural activation via neuroimaging) preceding measurement of more macro-measurement level of physiology (often indexing neural activation via EEG) (see, e.g., Bunford, Kujawa, Swain et al., 2016; Merwood et al., 2014 as precedents and for pertinent argument and conceptualization).

2. Method

2.1. Procedures

Data were collected in the context of a single larger, two-site (University of Michigan [UM] and University of Illinois at Chicago [UIC]) research project. Youth between the ages of 7–19 years were recruited (see Kujawa et al., 2015 for additional information on study design). Youth taking psychotropic medications and with cognitive or

developmental disabilities, lifetime psychotic illness, and current severe depression or suicidal ideation were excluded. Data from this sample have been previously presented in separate examinations of the fMRI measures (Kujawa, Wu et al., 2016), the association between anxiety and the LPP (Kujawa et al., 2015) and rule-breaking and social problems (Bunford, Kujawa, Swain et al., 2016) as well as predictors of treatment response (Bunford, Kujawa, Fitzgerald et al., 2016; Bunford, Kujawa, Swain et al., 2016; Kujawa, Weinberg et al., 2016). The current study is the first to integrate both sets of data to evaluate correspondence between measures.

2.2. Participants

Eighty-five youth who had fMRI and LPP data (measured during separate sessions that were, on average, two weeks apart from one another) were included in this study. Two participants were excluded for technical errors preventing collection of analyzable data, five for excessive movement during the fMRI scan (> 3 mm movement), seven for noisy EEG data (i.e., fewer than 12 artifact-free trials per condition or visual inspection indicated noise remaining in the baseline period after averaging the LPP), and one for < 70% accuracy on the experimental task (of excluded, 60% were in the anxiety group), leaving a final sample of 70 participants (see Table 1 for Demographic data on the full sample and separately for the subsamples with and without anxiety). Youth who were excluded and youth who were retained did not differ on age, sex, or study site (all *ps* > 0.061). Among youth who were retained, study sites did not differ in age or sex (*ps* > 0.163). Participants were administered the Kiddie Schedule of Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997), by master's- or doctoral-level clinicians (see Kujawa et al., 2015 for additional details) to assess psychopathology (see Table 1 for Clinical data on the full sample and separately for the subsamples with and without anxiety).

Table 1
Demographic and clinical data for the full sample and subsamples.

	Full sample[a] (N = 70)	Subsample with anxiety[b] (n = 42, 60%)	Subsample without anxiety[c] (n = 28, 40%)
Age (*M, SD*)	15.01, 3.54	14.83, 3.33	15.281, 3.88
Sex (*n*/% female)	39/55.7%	22/52.4%	17/60.7%
Ethnicity/race	Caucasian: 64.3%, Asian: 12.9%, African American: 8.6%, biracial/ multiracial: 2.9%, Native Hawaiian/ Pacific Islander: 1.4%	Caucasian: 59.5%, Asian: 9.5%, African American: 9.5%, biracial/ multiracial: 4.8%, Native Hawaiian/ Pacific Islander: 2.4%	Caucasian: 71.4%, Asian: 17.9%, African American: 7.1%
Any diagnosis	–	SAD: 42.9%, GAD: 38.6%, specific phobia: 11.4%, SepAnx: 5.7%, OCD: 2.9%, PD: 2.9%, ADHD: 10.0%, depression: 2.9%	no current or past psychiatric disorders

Note. [a] = 9.9% did not provide ethnic/racial information; [b] = 14.3% did not provide ethnic/racial information; [c]3.6% did not provide ethnic/racial information; SAD = social anxiety disorder; generalized anxiety disorder = GAD; SepAnx = separation anxiety disorder; OCD = obsessive-compulsive disorder; PD = panic disorder; ADHD = attention-deficit/hyperactivity disorder;

2.3. Measures

2.3.1. Emotional face-matching task

Youth completed both an fMRI and EEG version of an emotional face-matching task (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002), previously used by our group to measure BOLD signal and LPP in youth (Kujawa, Wu et al., 2016; Kujawa et al., 2015; Wu et al., 2016). Youth were presented with three images in a triangular arrangement and selected which one of two images at the bottom of the screen matched the image at the top of the screen. In face-matching trials, an angry, fearful, or happy face was presented at the top of the screen and a different angry, fearful, or happy face as well as a neutral face were presented at the bottom of the screen. Shape-matching trials, wherein youth matched geometric shapes, were included to measure activation and LPP in a neutral condition.

Consistent with conventions in the respective fields, the EEG version used an event-related design, whereas the fMRI version used a block design (Hariri, Tessitore et al., 2002). Specifically, in the EEG version, youth completed two blocks with 12 trials for each condition presented in a random order within each block, for a total of 24 trials per condition. On each trial, the stimulus was presented for 3000 msec, with the interval between trials between 1000–3000 msec. The fMRI version of the task was completed across two runs and consisted of 18face blocks (6 each for fearful, angry, and happy faces) interspersed with 18 shape matching blocks. Each block lasted 20 s, containing 4 matching trials (5 s each) (Hariri, Tessitore et al., 2002). Prior findings indicate effectiveness of the experimental manipulation (i.e., faces elicit both greater BOLD signal and LPP to emotional faces vs. shapes) (Bunford, Kujawa, Fitzgerald et al., 2016; Bunford, Kujawa, Swain et al., 2016; Hariri, Mattay et al., 2002; Hariri, Tessitore et al., 2002; Kujawa, Swain et al., 2016; Kujawa et al., 2015).

2.3.2. ERP data collection and processing

Continuous EEG was recorded using a BioSemi (Amsterdam, Netherlands) 34-channel cap (32 channel cap plus FCz and Iz). Electrodes were placed on the left and right mastoids, and electrooculogram was recorded from four facial electrodes placed approximately 1 cm above and below the right eye and beyond the outer edge of each eye. Data were digitized at 24-bit resolution with a sampling rate of 1024 Hz. Data were processed offline using Brain Vision Analyzer software (Brain Products, Gilching, Germany), converted to a linked mastoid reference, and filtered with high-pass and low-pass filters of 0.01 and 30 Hz, respectively. Data for correct trials were segmented beginning 200 msec before stimulus onset and continuing for the 3000 msec stimulus duration. Eyeblinks were corrected using the method by Gratton, Coles, and Donchin, (1983), and semi-automated artifact rejection procedures removed artifacts with voltage step of more than 50 μV between sample points, voltage difference of 300 μV within a trial, and maximum voltage difference of less than 0.5 μV within 100 msec intervals. Visual inspection (performed by A.K.) was then used to remove additional artifacts not detected by the automated procedures.

ERPs were averaged across each condition and baseline corrected to the 200 msec prior to stimulus onset. LPP was scored at a pooling of O1, O2, Oz, PO3, PO4, P3, P4, and Pz, where the emotion minus shapes difference was maximal in the complete sample (Kujawa et al., 2015). The LPP to faces vs. shapes emerged around 500 msec after stimulus onset, and given our aims to examine the relation between the relatively slower BOLD with LPP, we scored the LPP from 500 msec after stimulus onset through the 3000 msec stimulus duration (Kujawa et al., 2015). Analyses were conducted on the emotional face minus shapes difference score to isolate ERPs specific to emotional face processing and correspond with contrasts in fMRI. Analyses were conducted on this difference score given that the LPP is primarily sensitive to arousal (regardless of valence). As such, we expected activation in similar regions to correspond with LPP magnitude across emotional face type and

collapsed across those to reduce the number of analyses.

2.3.3. fMRI data collection and processing

MRI data were collected on 3 T GE scanners with 8-channel head coils at both sites. At UM, functional data were collected with a gradient-echo reverse spiral acquisition with the following parameters: repetition time (TR) = 2s, echo time (TE) = 30 ms, flip angle = 90°, = field of view (FOV) = 22 × 22 cm, acquisition matrix 64 × 64, 3-mm slice thickness, 43 axial slices, 180 vols per run. At UIC, functional data were acquired using gradient-echo echoplanar imaging (EPI) sequence with the following parameters: TR = 2 s, TE = minFull [~25 ms], flip angle = 90°, FOV = 22 × 22 cm, acquisition matrix 64 × 64, 3-mm slice thickness, 44 axial slices, 180 vols per run. Functional images were preprocessed in SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) for slice timing correction, image normalization, resampling at a 2 × 2 x 2 mm^3 voxel size, and 8-mm Gaussian smoothing kernel. First-level within-subject analysis was performed with a general linear model (GLM) with 4 regressors of interest: angry, fearful, and happy face and shape matching. Additional nuisance regressors for 6 motion parameters were included to correct for motion artifacts. For each participant, contrast images of brain activity were generated for second-level analysis. As our interest was in emotional face processing and we did not have any *a priori* hypotheses that BOLD-LPP correspondence would be moderated by emotional expression (angry, fearful, vs. happy), for primary and secondary aims we collapsed across angry, fearful, and happy face types to evaluate BOLD and LPP reactivity to emotional faces vs. shapes. Additional exploratory analyses tested whether correspondence between BOLD and LPP differed by face type (see Supplementary Results).

2.4. Analytic plan

In second-level whole-brain voxel-wise analyses, we entered individual-specific regressors of LPP magnitude to test associations with BOLD signal to emotional faces vs. shapes. In cases where our aim was to examine the correspondence between BOLD signal and LPP in a heterogeneous sample of youth, regardless of diagnostic status, we controlled for clinical (healthy vs. anxious youth) and methodological (scanner/site; i.e., UM or UIC) variables by including them as covariates of non-interest (i.e., in all cases except when testing whether correspondence between BOLD signal and LPP differed between youth without and with anxiety disorders). To constrain the search area to task-related brain activity, we employed an anatomically-based mask based on the *meta*-analytic findings of Fusar-Poli et al. (Fusar-Poli et al., 2009) on brain activation during emotional face processing. This large mask (volume = 1,279,304 mm^3) included bilateral fusiform gyrus, insula, medial and middle frontal gyri, inferior and middle occipital gyri, middle temporal gyrus, parahippocampal gyrus/amygdala, parietal lobule, posterior cingulate, and lingual gyrus but excluded cerebellum due to limited coverage (created with MARINA; Walter et al., 2003). To correct for multiple comparisons, joint height and extent thresholds were determined within the mask via Monte Carlo simulations (10,000 iterations) and applied to second-level statistical results (AlphaSim, AFNI; Cox 1996). Minimum cluster size for corrected $p < 0.05$ was set at 236 contiguous voxels.

We first regressed LPP onto activation within the mask to examine which regions that are activated to emotional faces correspond to LPP magnitude. Second, to interpret direction and range of significant effects, beta weights from a 5-mm sphere around peak voxels were extracted from individual activity maps using MarsBar (Brett et al., 2002). Next, in SPSS, data were checked for extreme values (cases with values more than 3 times the interquartile range [IQR]) using a step of 1.5 × IQR and such values were removed from further analysis.

Next, differences were tested between groups (healthy vs. anxious youth) with regard to correspondence between BOLD signal in these regions and LPP, first, by conducting bivariate correlational analyses (with 95% confidence intervals [CIs] around the *r* values obtained with 1000 bootstrap resamples) and then by transforming the *r* values into z scores (i.e., Fisher's r to z transformation) and comparing z scores for statistical significance.

For our secondary aim, we first conducted bivariate correlational analyses (with 95% confidence intervals [CIs] around the *r* values obtained with 1000 bootstrap resamples) to identify which brain regions that are correlated with LPP magnitude also correspond to age. Finally, with age as the predictor, LPP as the outcome, and regions corresponding to both age and LPP as the mediator, we tested mediational models. To test for mediation, we used PROCESS (Hayes, 2013) to calculate 95% CIs with 1000 bootstrap resamples around the indirect effect.[1] For significant mediational models, we also tested the reversed model (i.e., wherein the roles of the predictor and mediator variables were reversed) so as to ensure that only models in the hypothesized direction were supported and clarify the direction between predictor and mediator.

Finally, we conducted exploratory analyses with the amygdala as an *a priori* region of interest (ROI) in light of prior findings indicating an association between amygdala activation and primary variables of interest, including both LPP (Liu et al., 2012; Sabatinelli et al., 2013) and age (Blackford & Pine, 2012; Gee et al., 2013). For analyses with the amygdala, we used a bilateral anatomically derived MARINA-based amygdala mask and applied small volume correction but otherwise followed the same analytic procedures as described above (i.e., regressed LPP onto activation within the amygdala mask, extracted beta weights, conducted bivariate correlational analyses, and tested mediational models).

In line with Vul and Pashler (Vul & Pashler, 2012), so as to not report correlations for BOLD activation in regions we extracted precisely for having high correlations with LPP, we are not reporting ROI-specific *r* or *p* values corresponding to relationships between BOLD and LPP, but are reporting such values for relationships among BOLD signal with age and LPP with age as well as for relationships among regions of activation.

Table 2
Whole-brain voxel-wise regression between LPP onto BOLD response to Emotional Faces.

Brain Region	Z-score	Volume (mm^3)	Coordinates[a]
right inferior frontal/orbitofrontal gyrus	4.45	5840	30,32, − 18
left supplementary motor area	4.08	10136	− 6,34,62
left inferior frontal/orbitofrontal gyrus	3.86	2440	− 26,30, − 22
right superior parietal lobule	3.56	2864	36, − 62,30
right amygdala	3.02	392	− 26, − 6, − 12
left amygdala	2.93	376	28, − 8, − 12

Note. Significance set at $p < 0.05$ corrected for multiple comparisons, except for amygdala (corrected within an anatomically-based amygdala mask)
[a] = Montreal Neurological Institute (MNI) coordinates for fMRI clusters.

3. Results

3.1. Whole-brain voxel-wise analyses within emotion face processing brain areas

3.1.1. fMRI and LPP

Positive associations were observed between activation in right inferior frontal gyrus (IFG)/orbitofrontal gyrus (OFG), left IFG/OFG, left supplementary motor area, and right superior parietal lobule and LPP

[1] The macros provide a 95% confidence interval around the indirect effect. When zero is not in the 95% confidence interval (i.e., both numbers fall on the same side of 0), it can be concluded that the indirect effect is significantly different from zero at $p < 0.05$ (two tailed).

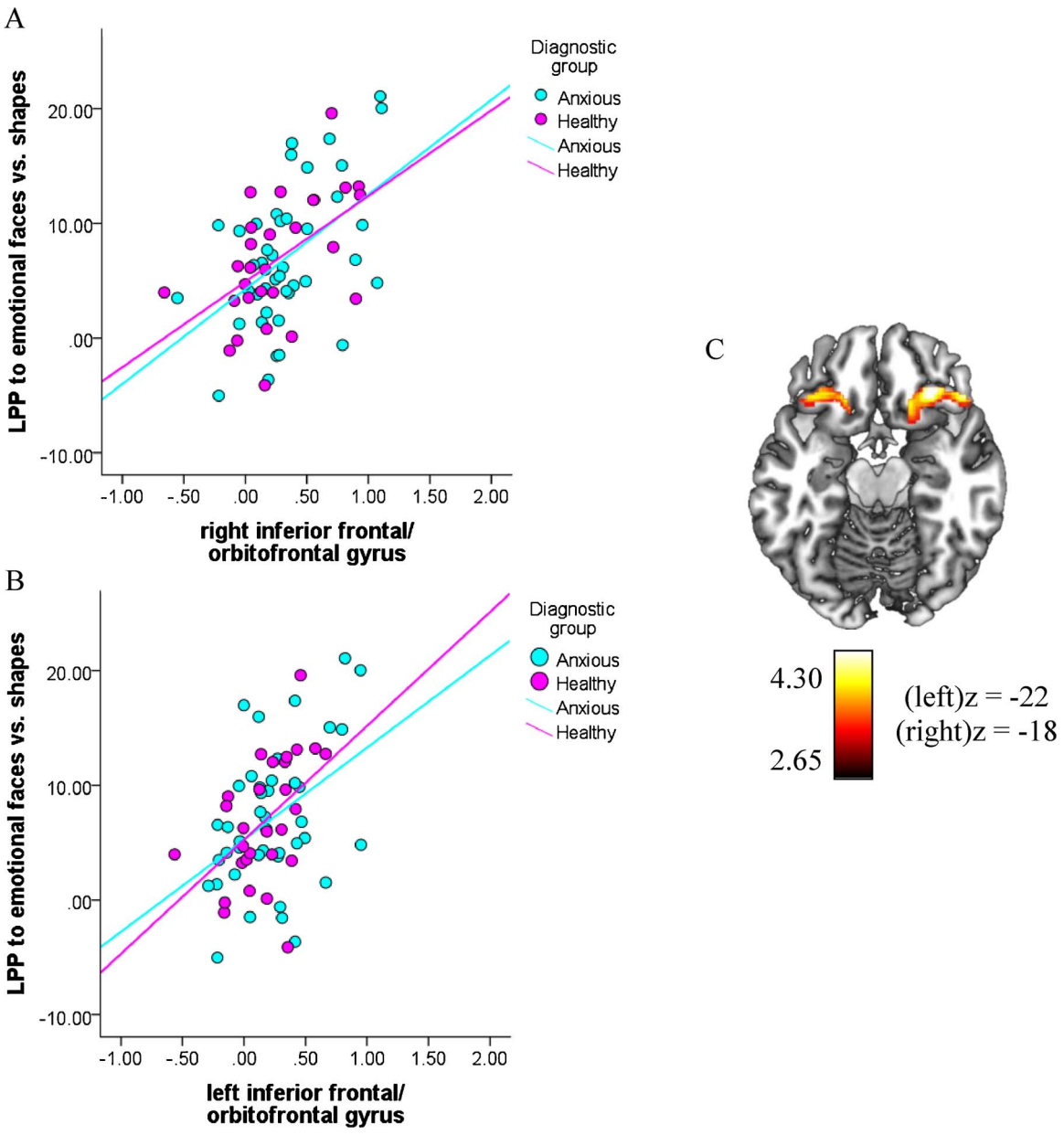

Fig. 1. Scatterplots depicting the relationship between right (A) and left (B) inferior frontal/orbitofrontal gyrus activation and LPPs to emotional faces for youth with and without an anxiety disorder. (C) Regression-based brain t-map showing that LPP magnitude is related to activation in the right and left inferior frontal gyri to emotional faces.

magnitude (see Table 2 for Montreal Neurological Institute [MNI] coordinates and Figs. 1 and 2). Relationships between BOLD and LPP were comparable across groups (see Figs. 1 and 2), with no significant differences in the correlations for healthy vs. anxious youth (Fisher *r* to *z* transformations to test the difference between correlations for the healthy relative to the anxious portion of the sample ranged from $p = 0.240$ to 0.860). Comparable (whole-brain analyzed) results were observed with *and* without anxiety diagnosis as a covariate. In addition, in *post hoc* analyses, similar patterns were observed for each emotional face (i.e., angry, fearful, happy; see Supplementary Results).

3.1.2. Age-related correlations

The results of simple bivariate correlations indicated, as expected, an association between LPP to emotional faces and age, $r = -0.343$, $p = 0.004$ (bias = −0.002, SE = 0.118, 95% CI[−0.546; −0.080]), as well as activation in right IFG/OFG with age and left IFG/OFG with age (Table 3).

3.1.3. Age-related mediation

The parallel mediational model (PROCESS Model 4) with age as a predictor, left and right IFG/OFG as parallel mediators, and LPP to emotional faces was significant ($R^2 = 0.290$, $F[3,66] = 8.974$, $p < 0.001$), and indicated that, jointly, age and left and right IFG/OFG activation accounted for 28% of the variance in LPP. This effect was driven by significant mediation by right IFG/OFG, point estimate = −0.183; SE = 0.125; 95% CIs [−0.556, −0.012]) (but not left IFG/OFG, point estimate = −0.060; SE = 0.096; 95% CIs [-0.325, 0.084]). The relationship between age and right IFG/OFG activation was negative ($b^2 = -0.023$, $p = 0.020$), between right IFG/OFG activation and LPP was positive ($b = 5.204$, $p = 0.053$) and between age and LPP was negative ($b = -0.319$, $p = 0.082$). The reversed right IFG/OFG model (wherein the predictor and mediator were reversed) indicated nonsignificant mediation (point estimate = 1.048;

[2] Unstandardized coefficients, as recommended for mediation/PROCESS (http://afhayes.com/macrofaq.html).

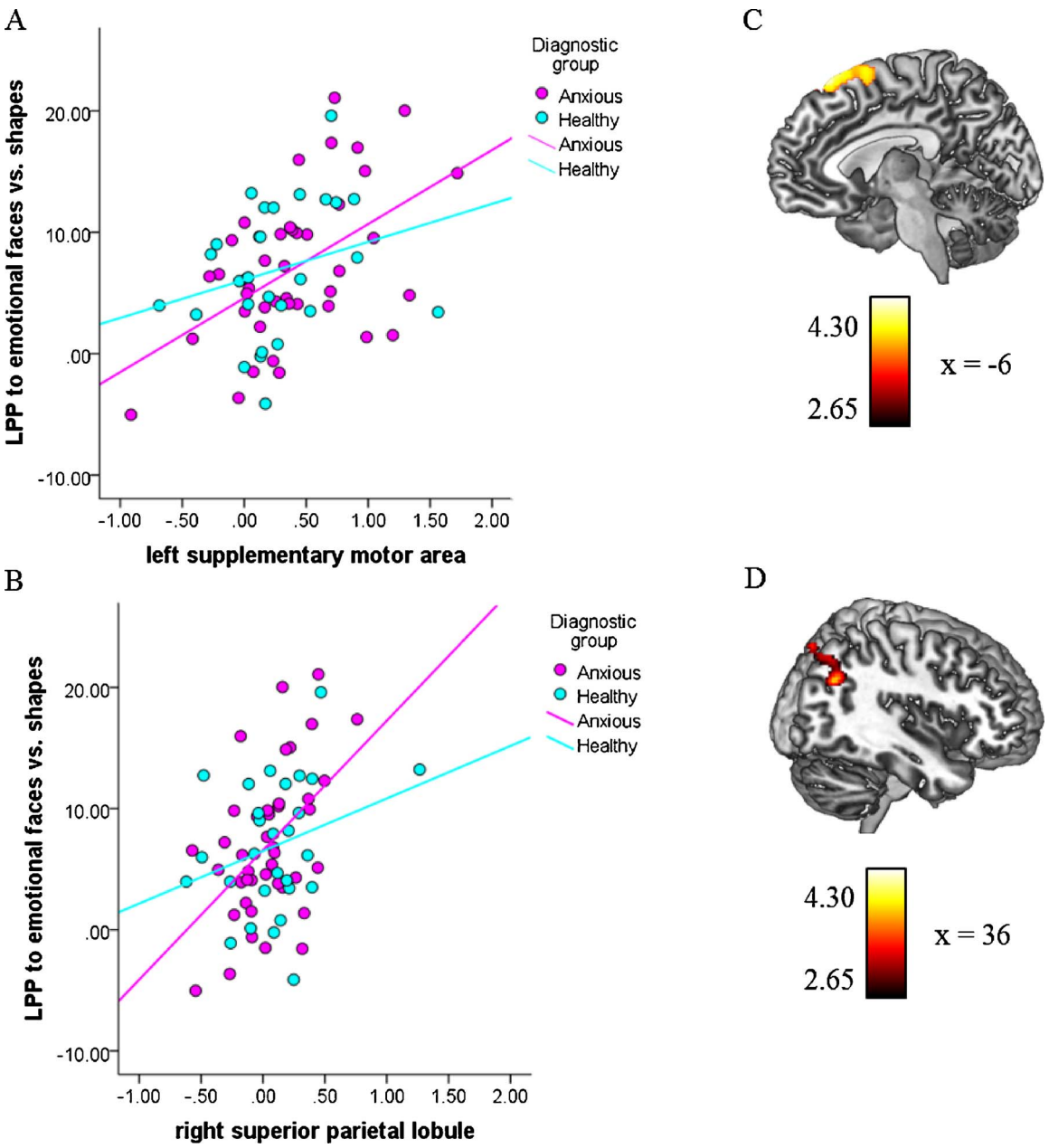

Fig. 2. Scatterplots depicting the relationship between left supplementary motor area (A) and right superior parietal lobule (B) activation and LPPs to emotional faces for youth with and without an anxiety disorder. Regression-based brain t-map showing that LPP magnitude is related to activation in left supplementary motor area (C) and in right superior parietal lobule (D) to emotional faces.

SE = 0.754; 95% CIs [-0.115, 3.085]), supporting a unidirectional effect between age as a predictor and right IFG/OFG activation as a mediator.

3.2. Exploratory analyses with amygdala as an a priori region of interest

3.2.1. fMRI and LPP

Although it did not survive AlphaSim correction, we conducted exploratory analyses with the amygdala as an *a priori* ROI. Regressing LPP onto amygdala activation, effects were significant at the peak-level for both right and left amygdala (family-wise error [FWE]-corrected right peak $p = 0.05$, left peak $p = 0.04$, and FWE-corrected right and left cluster *p*s = 0.07) (see Table 2 for MNI coordinates and Fig. 3). All LPP-BOLD relationships were positive. Relationships between BOLD and LPP were comparable across groups (see Fig. 3), with no significant differences in the correlations for healthy vs. anxious youth (Fisher *r* to *z* transformations to test the difference between correlations for the healthy relative to the anxious portion of the sample ranged from $p = 0.342$ to 0.363).

3.2.2. Age-related correlations

The results of simple bivariate correlations indicated an association between activation in right and left amygdala with age (see Table 4).

3.2.3. Age-related mediation

Although the parallel mediational model with age as a predictor, left and right amygdala as parallel mediators, and LPP to emotional faces was significant ($R^2 = 0.178$, $F[3,66] = 4.761$, $p = 0.005$) and indicated that, jointly, age and left and right amygdala activation accounted for 18% of the variance in LPP, neither the mediation by right nor the mediation by left amygdala was significant (point estimate = −0.105; SE = 0.135; 95% CIs [−0.475, 0.091] and point estimate = 0.003;

Table 3
Bivariate Correlations Among Age and fMRI-Measured Activation.

				1	2	3	4
1. Age.	*r*			–			
	p			–			
	Bootstrap	Bias		–			
		Std. Error		–			
		95% CI	Lower	–			
			Upper	–			
2. left IFG/OFG	*r*			−0.276			
	p			0.021			
	Bootstrap	Bias		0.000			
		Std. Error		0.123			
		95% CI	Lower	−0.510			
			Upper	−0.034			
3. right IFG/OFG	*r*			−0.338	0.773		
	p			0.004	0.000		
	Bootstrap	Bias		0.000	−0.004		
		Std. Error		0.106	0.051		
		95% CI	Lower	−0.539	0.658		
			Upper	−0.121	0.856		
4. right superior parietal lobule	*r*			−0.042	0.254	0.371	
	p			0.727	0.034	0.002	
	Bootstrap	Bias		−0.006	−0.006	−0.009	
		Std. Error		0.128	0.121	0.103	
		95% CI	Lower	−0.304	−0.012	0.146	
			Upper	0.190	0.477	0.542	
5. left supplementary motor area	*r*			−0.175	0.644	0.606	0.337
	p			0.147	0.000	0.000	0.004
	Bootstrap	Bias		−0.005	−0.013	−0.006	0.001
		Std. Error		0.111	0.091	0.076	0.119
		95% CI	Lower	−0.400	0.432	0.438	0.099
			Upper	0.042	0.780	0.736	0.562

Note. fMRI = functional magnetic resonance imaging; IFG = inferior frontal gyrus; 95% CI = 95% bootstrapped confidence interval using 1000 resamples.

SE = 0.153; 95% CIs [−0.389, 0.249], respectively).

Note that we also tested the unique effects of LPP to emotional faces and LPP to shapes in predicting extracted betas and only the effects of the former (all *ps* < 0.009) but not of the latter (all *ps* > 0.334) were significant.

4. Discussion

Our primary aim in the current study was to examine the correspondence between fMRI-measured whole-brain BOLD signal and EEG-measured LPP to emotional faces in children and adolescents with and without anxiety disorders. Related, we conducted exploratory analyses with the amygdala as an *a priori* region of interest, to examine the correspondence between fMRI-measured BOLD signal in the amygdala and LPP to emotional faces.

Similar to Sabatinelli et al. (2013, 2007) and Wessing et al. (2015), we found that enhanced activation in parietal regions, related to the integration of sensory information, was associated with an enhanced LPP. Similar to Liu et al.'s (2012) finding of an association between activation in the orbitofrontal cortex (OFC) and the LPP, we found activation in the bilateral IFG/OFG, regions very close to those Liu et al. report and associated with relevant functions such as the assessment of facial emotion (Nakamura et al., 1999), to be associated with LPP. In addition, we found an association between LPP and activation in the left supplementary motor area, related primarily to the control of movement but also to fear conditioning (Etkin et al., 2011) and emotion regulation (Kohn et al., 2014). Thus, although we observed the LPP to be correlated with some similar regions as those identified in the adult literature, some differences emerged. These differences between prior and the current findings may reflect differences in developmental stages of interest (adults vs. youth; Liu et al. vs. Wessing et al. and the current findings), differences in type of emotional stimuli (scenes vs. faces; Liu et al. vs. Wessing et al. and the current findings) and/or differences in type of paradigm (passive viewing vs. task-based; Liu et al. and the current findings vs. Wessing et al.).

Although correlations between amygdala activation and LPP did not survive correction for multiple comparisons within our large mask, indicating pertinent results should be interpreted with caution, the results of exploratory analyses with the amygdala as an *a priori* region of interest and small volume correction indicated that activation in bilateral amygdala was associated with LPP, consistent with Liu et al. (2012), Macnamara et al. (2017), and Sabatinelli et al. (2013). As such, in combination with our parietal and IFG/OFG findings, these results extend prior evidence indicating that subcortical structures such as the amygdala, along with sensory processing and frontal regions, contribute to the generation and modulation of LPP.

Importantly, none of the associations differed between youth with and without anxiety diagnoses, indicating that the observed relationships – and thus neural circuitry that may underlie the LPP – are comparable across clinical and non-clinical groups, broadly conceptualized. Of note, the absence of between-group differences reflects there being no difference between youth with and without anxiety in the *correspondence* between BOLD signal and the LPP. As such, even if youth with anxiety disorders have been shown to be more reactive to threat than youth without (as indicated by group differences both in BOLD and in the LPP when examined separately), the relative correspondence between different measures of such reactivity does not necessarily have to differ between groups. In fact, the observed absence of a group difference in correspondence is validation of the BOLD signal and the LPP as indices of emotional processing across a range of functioning from healthy to psychiatric populations. This type of validation fulfills an important RDoC task (Morris & Cuthbert, 2012).

Our second aim was to examine whether BOLD activation in regions corresponding to LPP accounts for developmental differences in LPP (i.e., age-related decreases). The results of our mediation models indicate that previously observed age-related decreases in LPP magnitude (Kujawa et al., 2013; MacNamara et al., 2016) are related, in part, to age-related decreased right IFG/OFG activation, consistent with prior

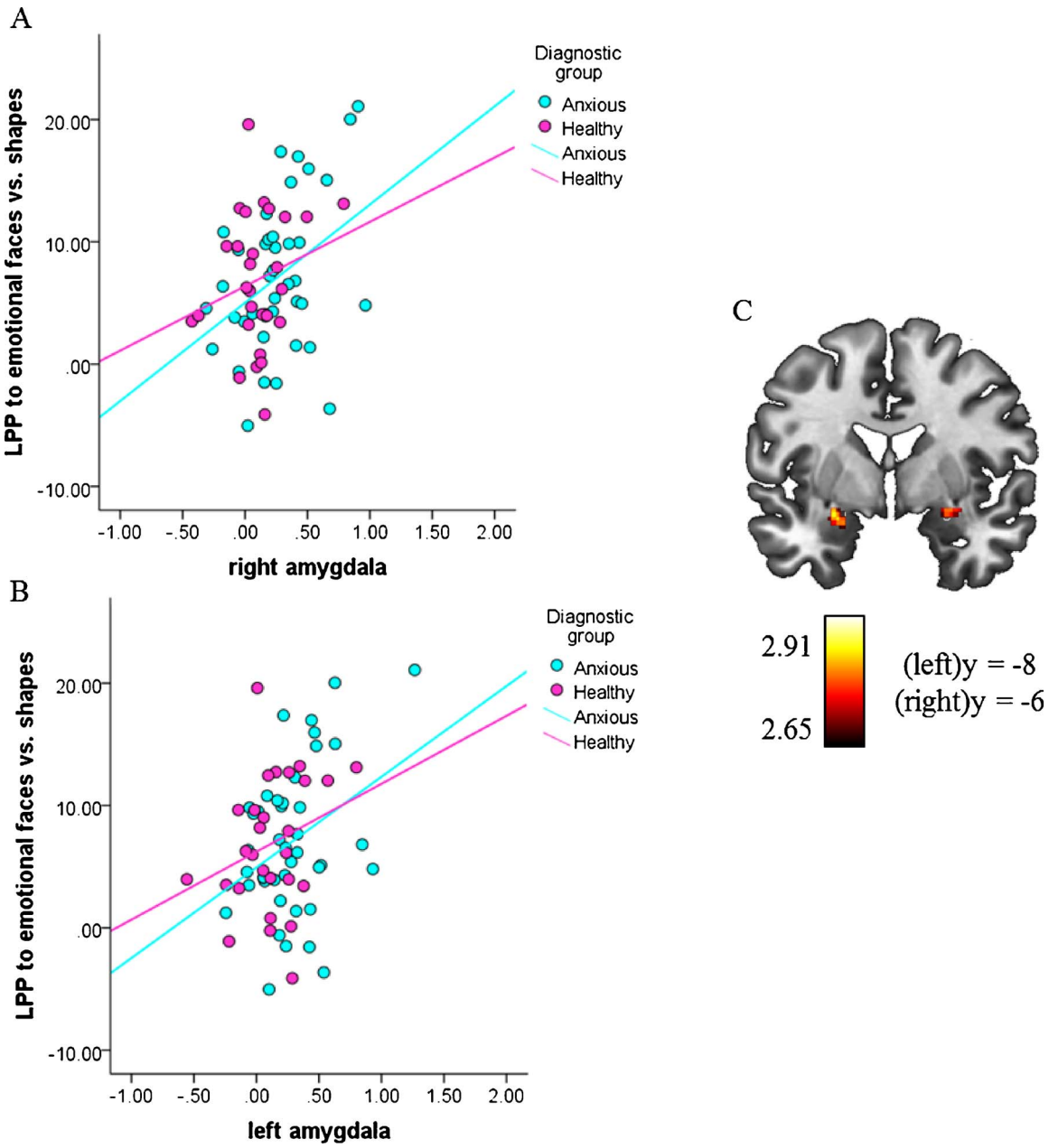

Fig. 3. Scatterplots depicting the relationship between right (A) and left (B) amygdala activation to emotional faces and LPPs to emotional faces for youth with and without an anxiety disorder. (C) Regression-based brain t-map showing that LPP magnitude is related to activation in the right and left amygdala to emotional faces.

findings indicating developmental shifts in neural activation. These include age-related attenuation of activation in dorsolateral prefrontal cortex and enhancement of focal activation in ventral prefrontal regions during performance of a cognitive control task (Durston et al., 2006). Further, while in children greater amygdala activation has been observed to both aversive and neutral stimuli, at the transition from childhood to adolescence, there is a ventral-to-dorsal shift in medial prefrontal responses to aversive, but not neutral, stimuli (Silvers et al., 2016). There are also linear age-related increases in activation in the left ventrolateral prefrontal cortex and quadratic age-related differences in activation in medial prefrontal, posterior cingulate, and anterior temporal cortices (with relatively lower reactivity-related but higher reappraisal-related activation in adolescents) (McRae et al., 2012). Our findings thus help further elucidate the neural mechanisms underlying developmental changes in LPP. Certainly, developmental changes in cortical folding may also underlie age-related changes in LPP (or even BOLD signal). As the brain's cortical folding undergoes developmental changes, with increased gyrification into the first postpartum year (Caviness, 1975) followed by a reduction in cortical folding until adulthood (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Hogstrom, Westlye, Walhovd, & Fjell, 2013; Mutlu et al., 2013; Raznahan et al., 2011; Su, White, Schmidt, Kao, & Sapiro, 2013), changes in cortical folding are associated with differences in cerebral electrical activity indexed via continuous EEG (Biagioni et al., 2007). Whether developmental changes in cortical folding underlie age-related changes in LPP could be examined in future studies given that although the idiosyncratic pattern of cortical folding is one potential source of observed inter-individual differences in ERP waveforms across individuals, there is no formal study on the relationship between individual differences in cortical folding patterns and ERP waveforms (Luck, 2014). Nevertheless, it is important to note that we focused on difference scores analyses to isolate the variance in measures attributed to emotional processing and to reduce potential effects of structural changes.

Table 4
Bivariate Correlations Among Age and fMRI − Measured Amygdala Activation.

				1	2
1. Age	*r*				
	p				
	Bootstrap	Bias			
		Std. Error			
		95% CI	Lower		
			Upper		
2. right amygdala	*r*			−0.246	
	p			0.040	
	Bootstrap	Bias		0.004	
		Std. Error		0.137	
		95% CI	Lower	−0.489	
			Upper	0.035	
3. left amygdala	*r*			−0.326	0.887
	p			0.006	0.000
	Bootstrap	Bias		0.012	−0.002
		Std. Error		0.127	0.027
		95% CI	Lower	−0.541	0.825
			Upper	−0.053	0.929

Note. fMRI = functional magnetic resonance imaging; LPP = late positive potential to emotional faces vs. shapes; 95% CI = 95% bootstrapped confidence interval using 1000 resamples.

To our knowledge, the current study is the first examination of the correspondence between BOLD signal and ERPs in youth, and our results provide insight both into the neural structures associated with the LPP and into developmental changes in neural systems underlying emotional face processing. As noted, the importance of identifying reliable and valid predictors has been underscored, in part so that research on normative development, developmental psychopathology, and preventions and treatments may advance. The current findings are particularly significant, as neural predictors have been emerging as promising predictors of the development of psychopathology and responses to treatment (see Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015 for review). Understanding the degree to which measures of such predictors provide shared vs. unique information is paramount, including for understanding developmental changes in characteristics that are key to the functioning of youth, such as emotional processing.

4.1. Limitations and future directions

There are limitations to this study that warrant consideration. First, although we mathematically/statistically established mediation, what we established is atemporal mediation (i.e., without a definitively established temporal sequence of the predictor preceding the mediator and both preceding the outcome); experimental and prospective designs are needed to establish temporal mediation (i.e., with a temporal sequence) and thus causation (Shadish et al., 2002). Nonetheless, given that we reversed our models as recommended in cases where temporal precedence is not definitively established, such as in cross-sectional designs (Agler & De Boeck, 2017; Danner, Hagemann, & Fiedler, 2015), our findings are encouraging and indicate further studies should be undertaken to replicate and extend our results.

Second, following conventions established in the separate BOLD and ERP literatures, fMRI data were collected using a block design and ERP data were collected using an event-related design and we measured BOLD signal and LPP in separate sessions. This method has potential shortcomings: 1) although it allows for conclusions about the correspondence between BOLD signal and LPP at the group level (i.e., those with enhanced BOLD signal also exhibited enhanced LPP), it does not allow for conclusions about that correspondence at the individual level (i.e., within any given individual, enhanced BOLD signal co-occurs with enhanced LPP); and 2) the comparison of the hemodynamic and electrocortical data recorded here is predicated on the assumption that the effects of the emotional faces are consistent from one session to the next. The findings of prior studies support this assumption as those indicate that LPP (Codispoti, Ferrari, & Bradley, 2006) exhibits consistent modulation by emotion across multiple sessions, suggesting that the impact of emotional stimuli is comparable across presentations (see Sabatinelli et al., 2007 for review). Collecting simultaneous BOLD signal and EEG data in an MR scanner and/or trial by trial analyses could ameliorate these shortcomings though it should be noted that measuring simultaneous BOLD signal and EEG data is with technical challenges, including compromising signal quality in both measurements (see Sabatinelli et al., 2007 for review). In addition, the relatively slower BOLD signal can be measured less quickly compared to the LPP. This does not necessarily mean that activation in observed brain regions cannot underlie age-related decreases in LPP, but simultaneous BOLD-EEG work could provide greater clarity. The work of Liu et al. (Liu et al., 2012) is a notable precedent and these considerations underscore the need for continued improvement in these technologies. Third, our design was cross-sectional and studies with longitudinal designs (i.e., following children as they age) will be important to further our understanding of the development of various neural systems related to emotional face processing. Fourth, although the average time between fMRI and EEG assessments was relatively short, the order of the measurements was not counterbalanced. Fifth, we did not assess and thus could not statistically account for pubertal status, which might influence emotional processing (Silk et al., 2009). Sixth, the number of runs and trials was low relative to the number of conditions and between-group analyses conducted. Nevertheless, although we may have only had two runs for fMRI, we have six, 20-s blocks for each condition. Further, there is evidence that there are stable LPP difference waves after 12 trials (Moran, Jendrusina, & Moser, 2013) and all of our participants had at least that many trials.

Individual differences in right IFG/OFG activation play a unique role in developmental changes in LPP. We anticipate that a model that adequately explains the relationships among age and BOLD signal and LPP to emotional faces is actually far more complex than the models we tested in that it likely includes additional variables relevant to one or more of these characteristics and measures, such as type of function indexed by BOLD signal and the LPP (e.g., emotion recognition, emotion regulation) or the population examined (e.g., the LPP is enhanced to threatening stimuli in anxiety but blunted in depression; Kujawa et al., 2015). Thus, there is need for continued research on these constructs, including by identifying and examining the role of such additional variables, so as to increase our understanding of the way in which they interact to impact neural reactivity to emotional faces among youth over time.

4.2. Conclusion

This is the first study on the correspondence between BOLD and LPP in youth and findings both support and extend upon previous ones, with implications for understanding the neural structures involved in generating the LPP as well as for developmental neuroscience and developmental psychopathology.

Funding

This work was supported by NIMH R01MH086517 awarded to Drs. Christopher S. Monk and K. Luan Phan.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.biopsycho.2018.02.006.

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