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Evidence of Non-Linear Associations Between Frustration-Related Prefrontal Cortex Activation and the Normal:Abnormal Spectrum of Irritability in Young Children

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Abstract

Burgeoning interest in early childhood irritability has recently turned toward neuroimaging techniques to better understand normal versus abnormal irritability using dimensional methods. Current accounts largely assume a linear relationship between poor frustration management, an expression of irritability, and its underlying neural circuitry. However, the relationship between these constructs may not be linear (i.e., operate differently at varying points across the irritability spectrum), with implications for how early atypical irritability is identified and treated. Our goal was to examine how the association between frustration-related lateral prefrontal cortex (LPFC) activation and irritability differs across the dimensional spectrum of irritability by testing for non-linear associations. Children ($N = 92$; ages 3–7) ranging from virtually no irritability to the upper end of the clinical range completed a frustration induction task while we recorded LPFC hemoglobin levels using fNIRS. Children self-rated their emotions during the task and parents rated their child's level of irritability. Whereas a linear model showed no relationship between frustration-related LPFC activation and irritability, a quadratic model revealed frustration-related LPFC activation increased as parent-reported irritability scores increased within the normative range of irritability but decreased with increasing irritability in the severe range, with an apex at the 91st percentile. Complementarily, we found children's self-ratings of emotion during frustration related to concurrent LPFC activation as an inverted U function, such that children who reported mild distress had greater activation than peers reporting no or high distress. Results

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suggest children with relatively higher irritability who are unimpaired may possess well-developed LPFC support, a mechanism that drops out in the severe end of the irritability dimension. Findings suggest novel avenues for understanding the heterogeneity of early irritability and its clinical sequelae.

Irritability comprises annoyance, touchiness, angry mood, and temper outbursts (Stringaris, 2011), is a feature of both internalizing and externalizing disorders (Dougherty et al., 2013; Kim-Cohen et al., 2003; Nock, Kazdin, Hiripi, & Kessler, 2007; Wakschlag et al., 2015), and is one of the most common reasons young children are referred for clinical services (Avenevoli, Blader, & Leibenluft, 2015). In much of the clinical literature, irritability is described as a pathologic state, in which irritable mood and angry outbursts are pervasive and impairing (Leibenluft, Blair, Charney, & Pine, 2003). However, because irritable behaviors are common in early childhood, defining clinically salient irritability is particularly challenging (Wakschlag, Tolan, & Leventhal, 2010). When their increased goal-oriented drive collides with environmentally imposed limits, young children regularly experience frustration, defined as anger in response to a blocked goal or reward (Berkowitz, 1989). The result is the common occurrence of normative misbehaviors such as temper tantrums. Accordingly, many investigations of irritability in early childhood take a developmentally specified approach (Wakschlag et al., 2010), defining irritability along a dimensional spectrum present in all children ranging from low and normatively occurring to severe and atypical (Li, Grabell, Wakschlag, Huppert, & Perlman, 2016; Perlman, Luna, Hein, & Huppert, 2014). A major objective of the child irritability field is to identify the point along the dimension that marks when irritability crosses into the clinically significant range (Wakschlag et al., 2015). Dimensional ratings of behavioral irritability show significant heterogeneity in clinical and longitudinal outcomes of these children (Wakschlag et al., 2015). To more precisely characterize patterns of early abnormal irritability, the field has turned toward neuroimaging methods to better understand the normal:abnormal spectrum of irritability in early childhood (Avenevoli et al., 2015). Clinical descriptions of irritability throughout the DSM suggest a positive linear association between irritability and dysregulated response to frustration (American Psychiatric Association, 2013), implying higher irritability corresponds to weaker neural activation supporting frustration regulation across the irritability dimension. However, this assumption has yet to be tested in samples of young children comprising the full dimensional spectrum of irritability. In fact, early childhood irritability and frustration-related neural activation may follow a non-linear function with different implications for how typical versus atypical irritability is defined. For example, low and high irritable young children may vary in their capacity to recruit top down control in the face of frustration.

In the adult neuroimaging literature, evidence suggests frustration comprises the complex interaction of reward, reactive aggression, and regulatory systems (Blair, 2012; Coccaro, Sripada, Yanowitch, & Phan, 2011). Frustration may involve decreased ventral striatum activation, and increased amygdala, hypothalamus, anterior insula, and periaqueductal grey activation, coupled with increased activation of various prefrontal cortex regions (Abler, Walter, & Erk, 2005; Yu, Mobbs, Seymour, Rowe, & Calder, 2014). This prefrontal cortex activation, comprising dACC, orbitofrontal, and dorso and ventro medial and lateral areas,

among others, is hypothesized to reflect decision-making, processing, and regulation strategies to modulate salient frustration (Blair, 2015; Perlman, Jones, et al., 2015). Two regions within the prefrontal cortex hypothesized to support frustration regulation include the dorsolateral and ventrolateral prefrontal cortex (DLPFC, VLPFC, respectively; Blair, 2012; Coccato et al., 2011). The DLPFC is hypothesized to support frustration regulation via its role in myriad executive functions including reversal learning (Blair, 2012; Coccato et al., 2011; Ochsner et al., 2004), inhibition, attention shifting, and working memory (Carpenter, Just, & Reichle, 2000), that may be engaged to manage emotional challenges, including in early childhood (Zelazo & Carlson, 2012; Zelazo & Cunningham, 2007). The VLPFC is hypothesized to support frustration regulation via top down connections with subcortical structures, including the amygdala, that modulate the threat response (Wager et al., 2008). There is robust data showing DLPFC and VLPFC activation occurs during various emotional challenges, however, some studies have reported that this activation might be *positively* associated with irritability in healthy adults. For example, in a sample of healthy adults, higher self-ratings of susceptibility to frustration were related to *greater* DLPFC activation during a frustration task (Siegrist et al., 2005). The authors postulated that this seemingly counter-intuitive finding may reflect changes in DLPFC functioning that result from experiencing frustration more regularly in every day life. In clinical adult populations, however, evidence suggests that severe irritability may be associated with a *reduced* prefrontal response to frustration. Adults with extremely high trait aggression (phenotypically similar to irritability) showed less VLPFC activation during a frustration task compared to adults with low trait aggression (Pawliczek et al., 2013). Collectively, this literature suggests that, in adults, the association between irritability and LPFC activation during frustration may not be constant across the full irritability dimension.

Similar to adults, in early childhood the association between frustration-related DL and VLPFC activation and irritability appears to depend on level of irritability severity. Perlman and colleagues (2014) used functional near infrared spectroscopy (fNIRS), a neuroimaging technique that measures hemodynamic changes in the outer cortex and has less spatial sensitivity compared to fMRI (Boas, Elwell, Ferrari, & Taga, 2014) to probe the LPFC (comprising DL and VLPFC areas) during frustration in healthy preschoolers. Results showed that healthy preschoolers with higher levels of parent-rated irritability showed a greater LPFC response to frustration than peers with lower irritability. Like previous adult findings in healthy samples, a seemingly counter-intuitive positive association between LPFC activation and irritability may indicate that children with higher levels of normative irritability, and do not have psychopathology, may require greater LPFC activation to regulate frustration as well as peers. In other words, children in the sample with low irritability may have shown low frustration-related LPFC activation not because they were worse emotion regulators, but because they experienced frustration less saliently and required less down-regulation than peers. In contrast, we hypothesize that severe irritability will be associated with a reduced LPFC response to frustration in children, as shown in case studies of preschoolers sustaining lesions to regions including the LPFC (Marlowe, 1992) and in event related potential (ERP) investigations comparing children suffering from a severe form of clinically impairing irritability to healthy peers during a frustration task (Rich et al., 2007). If irritability and frustration-related LPFC activation are positively associated

in typically-developing children, and negatively associated in clinically irritable children, it suggests a potential inverted U association across the full normal to abnormal dimension. Specifically, children with low irritability may require less frustration-related LPFC activation, children with high but normative irritability may match salient frustration with an enhanced LPFC response, and children with clinically significant irritability may have an inadequate LPFC response to frustration.

An inverted U association between early irritability and frustration-related neural activation has the potential to shift how we consider the normative vs. maladaptive tipping point of irritability across the child population. Thus, the goal of the present study was to examine the association between frustration-related LPFC activation and irritability by testing for non-linear patterns. We examined 92 children (ages 3–7), 24% ($n=22$) of whom were seeking clinical services. All children completed a developmentally sensitive and well-validated frustration task (Perlman, Jones, et al., 2015; Perlman et al., 2014) while we recorded LPFC hemoglobin levels using fNIRS and parents rated their child's level of irritability. We hypothesized that frustration-related LPFC activation would be positively associated with irritability at the low to normative end of the dimension, and negatively associated at the impairing end of the dimension.

Methods

Subjects

We recruited young children from the community and from psychiatric outpatient clinics to examine the full range of low to high irritability. Children from the community were recruited via paper and internet advertisements. Community-recruited subjects were reported by their parents to have no psychiatric diagnoses and no lifetime history of severe psychiatric diagnoses (e.g., psychosis) in any first-degree relative. Level of irritability was allowed to vary. Based on prior work in community samples of preschoolers, we expected the non-referred children to exhibit the full spectrum of irritability (Copeland, Brotman, & Costello, 2015). Children seeking assessment or intervention services at an outpatient clinic were recruited via flyers and by clinic staff, as well as through an online registry. Exclusionary criteria were diagnosis or history of autism spectrum disorder, mental retardation, psychotic disorder, or history of head trauma with loss of consciousness. Although we recruited from clinics for the purposes of sampling at the high end of the irritability spectrum, clinically recruited children were included in the study regardless of their level of irritability or diagnostic status.

Four children were excluded from analyses due to poor quality fNIRS data (1), technical error (2), and experimenter error (1). The final sample included 92 children between 3 and 7 years ($M=5.3$ years, $SD=1.3$ years), 71 community-recruited and 22 clinic-recruited. Clinic and community-recruited children did not differ in Verbal IQ score on the Peabody Picture Vocabulary Test, Fourth Edition (Dunn & Dunn, 2012). Clinic-recruited children were more likely to be older, male, and African American compared to community-recruited children (see Table 1). The goal of the study, however, was not to compare discrete groups, but examine a dimensional sample of children from a diverse range of backgrounds. Referral

status, age, gender, and verbal IQ were added as covariates in all analyses. Experimental procedures were approved by the local Institutional Review Board.

fNIRS instrument and analysis

Set up—As described in previous reports (Perlman et al., 2014), non-invasive optical imaging was performed using a CW6 real-time fNIRS system (Techen, Inc, Milford, MA). The fNIRS probe comprised four light-source emitter positions containing 690nm (12mW) and 830nm (8mW) laser light, and eight detectors, mounted within a child-friendly elastic cap. The average inter-optode distance was 3cm. The probe was positioned according to international 10–20 coordinates such that the interior medial corner of the probe was aligned with FpZ. The probe was designed to extended over Brodmann areas 10, the ventrolateral prefrontal cortex, and 46, the dorsolateral prefrontal cortex, on each hemisphere using AtlasViewer software (Aasted et al., 2015). Given the reduced spatial sensitivity of fNIRS compared to fMRI, we describe this region as the “LPFC”, consistent with our prior studies (Perlman, Huppert, & Luna, 2015; Perlman et al., 2014). As described in Okamoto et al. (2004), individual differences in head circumference have a negligible effect on how the probe is positioned over the cortical region of interest for each subject. Children were seated in front of a touch-screen computer that recorded their responses.

Acquisition and data pre-processing—Data were collected at 20Hz and down sampled to 4Hz using a custom-built Matlab-based (Mathworks, Natick, MA) acquisition software program (Barker, Aarabi, & Huppert, 2013). fNIRS data is recorded as changes in the light from a source position incident on a detector position as a function of time. Signals are first converted to changes in optical density (OD) over time as given by $OD(t) = -\log(I(t)/I_0)$ where $I(t)$ is the intensity of the signal recorded and I_0 is the reference signal intensity at baseline. The optical density signals are converted to oxy- and deoxy-hemoglobin estimates via the modified Beer-Lambert law with a partial pathlength correction of 0.1 for both wavelengths (e.g., DPF=6 and partial volume factor=60). The time-course of hemoglobin changes for each source-detector pair was analyzed using a general linear model $[HbX] = X * \beta + \epsilon$ where X is the design matrix encoding the timing of stimulus events and is the coefficient (weight) of that stimulus condition for that source-detector channel. The design matrix (X) was constructed from the convolution of the stimulus timing and duration with a canonical response model.

To reduce effects of motion artifacts and systemic physiology, we used an iteratively auto-regressively whitened, weighted least-squares (AR-iRLS) model to solve the general linear equation. This regression model uses an n th order auto-regressive (AR) filter determined by an Akaike model-order (AIC) selection to whiten both sides of the GLM expression. Using this model, the regression coefficients (β) and their error-covariance (Cov) is estimated, which is used to define statistical tests between task conditions or baseline. The regression model is solved sequentially for each data file for each subject. All source-detector pairs within a file are solved concurrently yielding a full covariance model of the noise, which is used in group-level analysis.

Questionnaires

Parents rated their child's irritability using the Temper Loss subscale of the Multidimensional Assessment Profile for Disruptive Behavior (MAP-DB; Wakschlag et al., 2012). This subscale was developed to differentiate normative from clinically salient irritability, has shown good reliability and validity, and has been shown to predict children's brain activation following frustration (Perlman, Jones, et al., 2015; Wakschlag et al., 2014; Wakschlag et al., 2012). The Temper Loss scale provides coverage of both irritable mood (e.g., "Act irritable") and tantrums (e.g., "Have hot or explosive temper") features of irritability rated on an objective frequency 6-point Likert scale (1 = *Never in the past month*; 6 = *Many times each day*). Temper Loss summary scores were used in all analyses. A summary score of 42.5 corresponds to a 1.5 SD clinical cutoff based on the MAP DB community sample (Wakschlag, unpublished data). Reliability of the Temper Loss scale was excellent ($\alpha = .96$).

The Frustration Emotion Task for Children (FETCH)

The Frustration Emotion Task for Children (FETCH; Perlman, Huppert, et al., 2015; Perlman, Jones, et al., 2015) is a frustration induction task tolerable to young children and stimulates frustration-related neural activation. Prior to the task, children were shown three boxes: a blue box containing attractive toys, a red box containing small stickers, and a yellow box containing a broken crayon (Cole, Zahn-Waxler, & Smith, 1994). Children were told that how well they did in the game would determine from which box they would choose their final prize at the end. During the task (see Figure 1) children competed with Sparky, "a very sneaky dog", to fetch bones by touching the bone as it appeared on the screen. Trials were fixed where sometimes the child could fetch the bone before Sparky (win trials), but sometimes Sparky would fetch the bone before the child's possible reaction time (frustration trials). After win trials, an animated drawing depicted the child grabbing the bone and placing it within one of five boxes indicating progression towards the most desired reward (the blue box). Frustration trials showed Sparky grabbing the bone and removing it out of the previously won box. Five bones had to be accumulated to win the game. Trials were grouped into three win and two frustration blocks. Win blocks comprised five win and one frustration trial, with the exception of the final win block, which had an extra win trial so the child would beat the game. Frustration blocks comprised five frustration and one win trial. After each block, children completed an online emotion rating by choosing from seven cartoon faces ranging from negative to positive mood.

Analysis strategy

A mixed-effects group level model was used for secondary analysis to examine associations between parent-rated irritability/child-rated emotion and hemoglobin levels during FETCH win and frustration blocks. A modified version of the Matlab function fitLME (linear mixed effects model estimator) was used to solve the weighted maximum likelihood estimate of the parameters. The model was weighted by the covariance of the GLM model parameter estimated from the subject level analysis by applying a whitening matrix (W) applied to both sides of the expression and given by $W * \beta = W * A * \Gamma + W * B * \Theta$ where the whitening matrix is defined as $W^T * W = Cov_{\beta}^{-1}$ and Cov is the noise covariance matrix which was

estimated from the temporal general linear model for each subject. The weighted model is used since the noise in fNIRS across channels and subjects is not normally distributed as it is partially determined by the sensor contact of the probe on the head. For each model, parent-rated irritability or child-rated emotion was entered as a fixed factor, and age, gender, clinical status (0 = community-recruited, 1 = clinic-recruited), and verbal IQ were entered as covariates. Subject ID was entered as a random-effects term in the model. As an initial step, we regressed FETCH win and frustration hemoglobin levels onto parent-rated irritability/child-rated emotion as a linear term. Next, to determine whether associations fit a quadratic function, we ran models entering linear and quadratic irritability terms simultaneously. Independent variables were not centered given that reducing non-essential collinearity and re-scaling to include a true zero point were not needed to interpret the results and test hypotheses (Dalal & Zickar, 2012).

Some studies in adults have shown that LPFC activation is greater in either the left or right hemisphere depending on whether the adult was prompted to use an emotion regulation strategy, and which strategy was prompted (e.g., reappraisal versus suppression; Ochsner et al., 2004). Evidence of LPFC laterality is less established in the child literature (but see Fox & Davidson, 1988), and moreover, in the present study, children were not prompted to use a specific emotion regulation strategy. We therefore did not have an a priori hypothesis about hemisphere laterality and, to limit the number of comparisons, reduced the original 12 channels into six bi-lateral regions of interest by combining each channel with its corresponding channel on the opposite hemisphere, similar to techniques used in the fMRI literature (e.g., Dolcos, LeBar, & Cabeza, 2004). Although it is not currently the standard in the field to correct for multiple comparisons, as fNIRS is a region-of-interest and hypothesis driven method, we employed the False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995) to provide a more conservative estimate of effects.

Results

Distribution of parent-reported irritability

MAP-DB Temper Loss scores ranged from 0 to 107 ($M = 22$, $SD = 18.5$; maximum possible score was 110). Based on scores of 42.5, representing 1.5 SD above the mean in the MAP-DB community sample (Wakschlag, unpublished data) 12% of the sample was in the clinically significant range. Clinic-recruited children had significantly higher Temper Loss scores (~2x higher) than community-recruited children (See Table 1). However, there was overlap in the distribution of Temper Loss scores in community and clinic-recruited children, and the total sample comprised the full dimensional spectrum of irritability (See Figure 2).

Child Self-Report of Frustration

On average, children selected negative faces following frustration blocks ($M = 3.62$ on a 1–7 scale with 1 being most negative and 7 being most positive), and positive faces following win blocks ($M = 6.21$). A paired-sample t-test revealed that emotion ratings following frustration and win blocks were significantly different, $t(91) = -10.44$, $p < .001$, $d = 2.19$. Step-wise multiple regression revealed irritability was unrelated to children's emotion

ratings following frustration blocks linearly, $\beta = -.16$, $p = .13$ or quadratically, linear irritability term: $\beta = .02$, $p = .93$; quadratic irritability term: $\beta = -.19$, $p = .50$. Next, linear and quadratic mixed effects models were used to test for associations between frustration-related LPFC activation and child self-ratings of frustration, controlling for age, gender, verbal IQ, and clinical status. A linear mixed-effects model revealed that children's emotion ratings following frustration blocks were positively associated with LPFC activation during frustration blocks at two bi-lateral regions of interest in the LPFC, $t(356) = 2.97$, $p < .01$, $d = 0.31$; $t(356) = 3.19$, $p < .01$, $d = 0.34$, such that children who rated themselves as less negative following frustration had higher LPFC activation. These associations remained significant after FDR correction for multiple comparisons. In addition, the quadratic model revealed children's emotion ratings following frustration blocks were associated with LPFC activation at three bi-lateral regions of interest such that the linear terms were positive, $t(354) = 2.81$, $p < .01$, $d = 0.30$; $t(354) = 2.46$, $p < .05$, $d = 0.26$; $t(354) = 2.01$, $p < .05$, $d = 0.21$, and the quadratic terms were negative, $t(354) = -3.02$, $p < .01$, $d = 0.32$; $t(356) = -2.79$, $p < .01$, $d = 0.30$; $t(356) = -2.02$, $p < .01$, $d = 0.21$, respectively; See Figure 3. After FDR correction for multiple comparisons, the inverted U association remained significant at two channels. As shown in Figure 4, the emotion rating associated with the inverted U apex, for the most robust channel, was 3.7 suggesting that children who rated themselves as mildly distressed had greater frustration-related LPFC activation than peers who rated themselves as happy or very upset.

Parent reported irritability

Linear and quadratic mixed effects models were used to test for associations between frustration-related LPFC activation and parent-rated irritability, controlling for age, gender, verbal IQ, and clinical status. When irritability was included as a linear term only, a mixed-effects model revealed no association with LPFC activation during frustration (all p-values $> .09$) or winning (all p-values $> .10$). Next, we simultaneously entered linear and quadratic terms into the model. As shown in Figure 5, the linear and quadratic irritability terms were both associated with one region of interest in the middle LPFC, such that the linear term was positive, $t(356) = 2.69$, $p < .01$, $d = 0.29$, and the quadratic term was negative, $t(356) = -2.74$, $p < .01$, $d = 0.29$, indicating an inverted U function. The inverted U finding remained significant after FDR correction for multiple comparisons. As shown in Figure 6, at the low to moderate end of the irritability dimension, frustration-related LPFC activation increased with irritability, but at the high end of the irritability dimension, frustration-related LPFC decreased with irritability. A MAP-DB Temper Loss score of 32, the 91st percentile in the sample, corresponded to the inverted U apex. In comparison, the MAP DB clinical cutoff score, 42.5, corresponded to the 96th percentile the current sample. There were no associations between irritability and LPFC activation during win blocks in the quadratic model (all p-values $> .50$).

Discussion

We found evidence that an inverted U function characterized the association between young children's hemodynamic response to frustration and level of irritability. Whereas a linear model showed no association between frustration-related LPFC activation and irritability, a

quadratic model revealed that frustration-related LPFC activation was positively associated with irritability at the low to moderate end of the dimension, and negatively associated with irritability at the high end of the dimension. Strikingly, the LPFC activation apex was nearly identical to the behaviorally identified clinical threshold on the MAP-DB. We similarly found an inverted U association between frustration-related LPFC activation and children's self-ratings of emotion, such that children who endorsed mild negative emotion following frustration had greater activation than peers who endorsed either no or high negative emotion.

Our finding that irritability and frustration-related LPFC activation relate as an inverted U function, as opposed to a linear function, represents a potential shift in how early irritability and its underlying neurophysiology might be conceptualized in this burgeoning field of research. Assuming a linear versus non-linear association between early irritability and frustration regulation generates different assumptions about the role of emotion regulation, and its underlying neural systems, in clinical versus non-clinical early irritability. If we assume irritability and frustration-related hemodynamic activation correlate as a linear function, it follows that more irritability is worse and linked to greater dysregulation, and that children with the lowest irritability levels should show the strongest frustration-related LPFC activation. However, this assumption is incongruent with studies showing that higher irritability was associated with a stronger, not weaker, frustration-related LPFC response in non-impaired children and adults (Perlman et al., 2014; Siegrist et al., 2005). In contrast, the present study suggests that LPFC activation during frustration is greatest at the inverted U apex, corresponding to moderate irritability levels. Among non-impaired children, being a relatively more irritable child may be associated with well-developed LPFC support for managing anger and frustration. Moreover, an inverted U association between self-reported emotion and frustration-related LPFC, such that children who rated themselves as experiencing moderate negative emotion had the highest activation, further supports this contention. The inverted U apex may therefore mark the point along the irritability dimension when higher levels of severe irritability become associated with increasing *decrements* in frustration-related LPFC activation, a combination with potential to predict mental disorder (Lewis, Granic, & Lamm, 2006). Specifically, young children with high irritability paired with an underactive LPFC response to frustration may be most at risk for a chronic course. The Temper Loss score corresponding to the apex, 32, the 91st percentile, approximated the clinical cutoff reported in the MAP DB community sample, 42.5, which was the 96th percentile in our sample. To our knowledge, this finding represents the first pathophysiologic validation of a dimensional irritability scale, suggesting that high irritability scores on the MAP-DB are indicators of underlying atypical hemodynamic activation. The present study may therefore facilitate future research using an inverted U framework to more accurately identify the normal:abnormal irritability tipping point in early childhood. Further, the present findings set the stage for future work to explicate, in greater detail, the etiology of clinically impairing irritability and associated psychopathology. For example, children populating the descending arm of the inverted U function may lack an LPFC "buffer" against impairing irritability that peers closer to the apex possess, or, alternatively, it may be that irritability levels exceeding a certain threshold interfere with LPFC activation during frustration.

An inverted U association between early irritability and frustration-related LPFC activation has potential implications for a more precision medicine-based approach to treating early irritability (Insel, 2014). Children referred to clinics for irritability fall across a wide swath of the dimension (Drabick & Gadow, 2012) and may be routed to myriad treatments that interact with the developing LPFC. Controversial medications to treat severe irritability in early childhood, such as Risperidone (Biederman et al., 2005), affect mood and behavior, in part, by changing brain metabolism in the LPFC (Lane, Ngan, Yatham, Ruth, & Liddle, 2004). Interventions for young children, such as cognitive behavioral therapy (CBT), require implementing meta-cognitive and emotion regulation skills that may only benefit irritable children with competent LPFC functioning (Grave & Blissett, 2004; but note studies showing the reverse may be true in adulthood, e.g., Siegle, Carter, & Thase, 2006). Other interventions, such as parent-child interaction therapy (PCIT), are efficacious in cognitively delayed children and may benefit irritable children with poor LPFC functioning (Eyberg, 2005). Finally, more recently developed interventions that attempt to strengthen regulatory neural networks through executive function training have shown mixed success (Morris et al., 2014). Our findings suggest that children referred to treatment for irritability may exhibit substantial variability in their LPFC activation during frustration. Future work that further elucidates links between early irritability and LPFC functioning has the potential to impact clinical decision making.

Limitations, Future Directions, and Conclusions

Although this study provides insight into the heterogeneity of early of irritability that could challenge the manner in which irritability and its neural underpinnings are conceptualized, some limitations must be acknowledged. Scatterplots revealed a skewed association between frustration-related LPFC activation and irritability scores, such that a smaller subset of participants populated the descending arm of the inverted U. However, studies using larger samples suggest that irritability is similarly skewed in the general child population (Wakschlag et al., 2015). Thus, the inverted U association and irritability score associated with the apex may have clinical utility in identifying a subset of irritable children who are most at risk. A strategy to oversample severely irritable children to create more evenly distributed samples may have adversely affected the ecological validity of the findings. Relatedly, distribution of self-ratings following frustration blocks showed that nearly half the sample chose either the most negative or most positive rating every time, suggesting largely bimodal responding consistent with previous studies in this age range (Chambers & Johnston, 2002). This bimodal distribution of self-reported emotion may explain why we failed to find an association between children's self-ratings of emotion and parent-rated irritability. Further, our interpretation of the inverted U function suggests the apex may discriminate children with elevated irritability that do and do not exhibit functional impairment in everyday life. Although we were unable to directly test if children populating the descending arm of the inverted U curve showed greater functional impairment than peers, prior work has shown that the MAP-DB Temper Loss scale is significantly positively associated with measures of functional impairment (Wakschlag et al., 2015). An additional limitation is that fNIRS is a technique capable only of measurement within the outer cortex and only on focused regions of interest (the LPFC in our study). However, the neural network underlying frustration regulation comprises many structures projecting to and from

the LPFC that may play a role in early irritability (Blair, 2012; Perlman, Jones, et al., 2015). Irritability also has many environmental determinants (e.g., neighborhood and family characteristics) that were not measured but nonetheless shape early brain development (Hackman & Farah, 2009). Future work is needed to understand how neural response to frustration corresponds with other biological systems, environmental factors, and different clinical endpoints later in development. Finally, the present findings suggest that at the lowest point on the irritability spectrum irritability is coupled with low frustration-related LPFC activation, which may be clinically meaningful and warrant future investigation. Increasing interest in the clinical significance of early irritability, and defining clinical phenotypes, carries a risk of mislabeling irritability as a ubiquitously negative trait. The present study suggests rethinking this view. How irritability, and underlying regulatory systems, contributes to early psychopathology may be more complex than disorder-based criteria suggest and unpacking this complexity may lead to major strides in addressing childhood-onset mental illness.

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Figure 1.
Depiction of the Frustration Emotion Task for Children (FETCH).

Figure 2.
Distribution of Temper Loss scores in community and clinic-recruited children.

Association between Emotion Self-Ratings and Oxygenated-hemoglobin Levels during Frustration

Figure 3. Channel-space probe super-imposed over 3D mesh brain showing the association between linear and quadratic self-rated emotion following frustration and oxygenated-hemoglobin levels during frustration. The original 12 channels were combined into 6 bi-lateral regions of interest.

Figure 4.

Scatterplot showing the inverted U fit between frustration-related activation at the significant left hemisphere channel and self-rated emotion following frustration, with vertical line denoting the apex. The fit line appears in black with 95% confidence interval denoted with light gray lines.

Linear and Quadratic Association between Irritability and Oxygenated-hemoglobin Levels during Frustration

Figure 5. Channel-space probe super-imposed over 3D mesh brain showing the association between linear and quadratic MAP-D Temper Loss scores and oxygenated-hemoglobin levels during frustration. The original 12 channels were combined into 6 bi-lateral regions of interest.

Figure 6.

Scatterplot showing the inverted U fit between frustration-related activation at the significant left hemisphere channel and MAP-DB Temper Loss scores. Vertical lines denote the inverted U apex score (blue) and the 1.5 SD clinical cutoff score from the MAP DB norming sample (green). The fit line appears in black with 95% confidence interval denoted with light gray lines.

Table 1

Demographic data describing the study sample, children referred from the community, and children referred from clinics.

	Full Sample (n = 92)	Community-Recruited (n = 70)	Clinic-Recruited (n = 22)	t/χ^2
Age (Years)				
Mean (SD)	5.22(1.3)	5.01(1.3)	5.86(1.2)	-2.66 [*]
Range	3–7	3–7	3–7	
% Male	61%	55%	82%	5.11 [*]
Race				
% Caucasian	63.4%	69%	45.5%	6.28 [*]
% African American	33.3%	26.8%	54.5%	
% Other	3.2%	4.2%	0%	
Family Income				
Median	\$55,000	\$60,000	\$20,000	<i>ns</i>
Range	\$6000–\$1.2M	\$6000–\$1.2M	\$10,000–\$150,000	
Temper Loss Score				
Mean (SD)	22.19(18.6)	18.48(16.2)	34.18(22.1)	-3.64(27.17) ^{**a}
Range	0–107	0–107	1–85	

^{*}
 $p < .05$,

^{**}
 $p < .01$.

^a Adjusted for unequal variances