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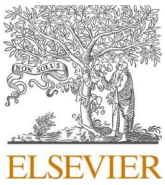

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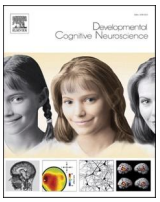

Prefrontal modulation of frustration-related physiology in preschool children ranging from low to severe irritability☆

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ABSTRACT

Limbic-prefrontal connectivity during negative emotional challenges underpins a wide range of psychiatric disorders, yet the early development of this system is largely unknown due to difficulties imaging young children. Functional Near-Infrared Spectroscopy (fNIRS) has advanced an understanding of early emotion-related prefrontal activation and psychopathology, but cannot detect activation below the outer cortex. Galvanic skin response (GSR) is a sensitive index of autonomic arousal strongly influenced by numerous limbic structures. We recorded simultaneous lateral prefrontal cortex (lPFC) activation via fNIRS and GSR in 73 3- to 5-year-old children, who ranged from low to severe levels of irritability, during a frustration task. The goal of the study was to test how frustration-related PFC activation modulated psychophysiology in preschool children, and whether associations were moderated by irritability severity. Results showed lPFC activation significantly increased, and GSR levels significantly decreased, as children moved from frustration to rest, such that preschoolers with the highest activation had the steepest recovery. Further, this relation was moderated by irritability such that children with severe irritability showed no association between lPFC activation and GSR. Results suggest functional connections between prefrontal and autonomic nervous systems are in place early in life, with evidence of lPFC down-regulation of frustration-based stress that is altered in early psychopathology. Combining fNIRS and GSR may be a promising novel approach for inferring limbic-PFC processes that drive early emotion regulation and psychopathology.

1. Introduction

Most common forms of early psychopathology are rooted in maladaptive responses to negative emotions such as frustration (Keenan, 2000). Problems tolerating negative emotions can emerge early in life and persist across the lifespan (Cicchetti et al., 1995), resulting in impairment in academics (Eisenberg et al., 2005), social skills (Eisenberg and Fabes, 1992), and daily functioning (Calkins and Marcovitch, 2010). Functional neuroimaging has produced major advances in elucidating how the brain responds to emotional challenges and how these neural mechanisms increase vulnerability to mental disorders (Monk, 2008). In particular, limbic-prefrontal connectivity during negative emotional challenges appears to be a critical neural system underpinning the adaptive emotion regulation response, with clear abnormalities seen across psychiatric disorders (Mayberg et al., 1999; Fitzgerald et al., 2017; Hafeman et al., 2017; Yoder et al., 2015). Yet limbic-prefrontal functional connectivity is almost entirely unexplored in children under five years of age, likely due to methodological challenges measuring cortical and sub-cortical activation during negative emotional challenges in very young children. The present study tested a novel approach of simultaneously recording Functional Near-Infrared Spectroscopy (fNIRS) and Galvanic Skin Response (GSR): a physiological correlate of amygdala activation, to elucidate prefrontal modulation of autonomic arousal in preschool-age children ranging from low to severe irritability.

Early work in primates revealed that the prefrontal cortex, an area implicated in planning and self-regulation (Rosenkilde, 1979) and the amygdala, an area implicated in threat and emotion processing (Sergerie

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et al., 2008) have robust connections to each other (Carmichael and Price, 1995). In particular, the lateral prefrontal cortex (lPFC) shares direct projections to and from the amygdala and indirect connections via the orbitofrontal and medial prefrontal cortices (Barbas, 2000). Subsequent functional neuroimaging studies in human adults demonstrated that onset of emotion-inducing stimuli, such as graphic photographs (Banks et al., 2007) was associated with amygdala and prefrontal cortex co-activation, and that the PFC activation appeared to attenuate the amygdala response. Amygdala-PFC connections are now widely accepted as crucial in executing emotion regulation strategies (Mayberg et al., 1999; Cheng et al., 2021) with obvious implications for the etiology of psychopathology. Studies have shown abnormalities in amygdala and PFC activation and amygdala-PFC functional connectivity in wide-ranging mental disorders, including depression and bipolar disorder (de Almeida et al., 2009; Perry et al., 2019), schizophrenia (Williams et al., 2004; Wang et al., 2020), and conduct disorders (Passamonti et al., 2012; Cupaioli et al., 2021). Across these disorder types, disruptions in emotion-related amygdala-PFC functional connectivity appeared to exhibit a common pattern such that non-diagnosed individuals exhibit the expected PFC attenuation of amygdala activation, whereas diagnosed individuals show weaker, or absent, PFC-amygdala connectivity.

Given that limbic-PFC functional connectivity during negative emotion induction appears abnormal in many disorders, its early development is likely crucial in the etiology of childhood-onset psychopathology. As the study of childhood psychopathology has shifted from a modular DSM-based framework to a dimensional framework focused on transdiagnostic symptoms (Insel, 2014), there has been particular interest in pediatric irritability (Leibenluft, 2017). Irritability is a predisposition to frustration, grumpiness, touchiness, etc. (Stringaris et al., 2017; Beauchaine and Tackett, 2020), is a symptom present in over a dozen DSM-5 disorders, and is the most common reason young children are referred for psychological services (Avenevoli et al., 2015). Pediatric irritability is also marked by abnormal neural activation during both reward (Dougherty et al., 2018) processing and frustration (Tseng et al., 2019). Given that irritability is a dimensional, transdiaganostic symptom defined by inadequate frustration regulation (Beauchaine and Tackett, 2020), it is an ideal candidate for investigating how early psychopathology may be driven by disrupted PFC modulation of amygdala activation during negative emotional challenges. However, almost nothing is known about early amygdala-PFC functional connectivity due to methodological limitations in neuroimaging young children using conventional fMRI.

Functional Near-Infrared Spectroscopy (fNIRS) is a relatively newer neuroimaging technology that uses light to measure changes in oxygenated and deoxygenated hemoglobin in the outer cortex. fNIRS has become a popular technique in early childhood populations as it is much more tolerable to physical movement and easier for young children to comply with compared to fMRI (Strangman et al., 2002). Several fNIRS studies have shown that preschool-age children completing an emotional challenge, such as frustration, exhibit lPFC activation (Perlman et al., 2014), and that individual differences in activation during frustration predict parent-rated self-regulation (Grabell et al., 2019), concurrent facial expressions (Grabell et al., 2018), and psychopathology (Grabell et al., 2017). While fNIRS has good spatial and temporal resolution of the outer cortex, the near-infrared light only migrates a few centimeters of tissue and thus cannot penetrate sub-cortical areas. It is therefore unknown whether lPFC activation observed in extant pediatric fNIRS studies reflects attenuation of the amygdala response in preschool children during frustration and whether this pattern is disrupted, or weaker, in young children with elevated irritability. However, amygdala activation triggers a cascade of physiological changes that are integral to emotional arousal, experiencing frustration, and are easily measured via peripheral systems. GSR, the changes in electrodermal resistance of the skin due to sweat gland activity, is a well-known physiological byproduct of amygdala activation (Dawson et al., 2017). Several brain regions influence GSR, including a clear amygdala pathway that is activated during threat and emotional challenges as part of broader autonomic nervous system functioning. The amygdala is deeply connected to paraventricular and lateral hypothalamus, stria terminalis, and locus coeruleus, which in turn project to the intermediolateral spinal cord and postganglionic cells coiled around eccrine sweat glands (Critchley, 2002). Simultaneous fMRI/GSR studies in healthy adults have demonstrated that amygdala activation during fear (Furmark et al., 1997) and physical pain (Dube et al., 2009) strongly and positively correlate with GSR activity. Furthermore, different emotions (e.g., fear, anger) may be expected to elicit the same GSR activity (Boucsein, 1999), suggesting that frustration should also be measurable GSR is commonly used in young children (Fowles and Kochanska, 2000; Isen et al., 2010; Zahn-Waxler et al., 1995) as sticker sensors placed on palmar or plantar regions (where eccrine sweat glands are most densely populated) are easily tolerated. Simultaneous fNIRS-GSR recording may therefore be ideal for measuring real-time PFC modulation of emotional arousal in very young children.

The main goal of the present study was to test whether lPFC activation attenuates the GSR signal during frustration in preschool-age children, as a first step toward inferring PFC-amygdala dynamics in populations too young to tolerate fMRI. Eighty-two children between three and five years of age completed a frustration task while wearing both an fNIRS probe over the lPFC and GSR sensors on the palm of the non-dominant hand. Caregivers rated their child's irritability, and children with severe irritability were oversampled. We hypothesized that lPFC activation and GSR activity during frustration would be inversely associated with each other, such that children with stronger lPFC activation would exhibit low GSR reactivity and a stronger recovery to baseline levels. We also hypothesized that severely irritable children would exhibit weaker, or absent, lPFC attenuation of GSR compared to peers.

2. Methods

2.1. Participants

Eighty-two children between 3.5 and 5 years of age ($M = 4.6$ years, $SD = 0.74$) were recruited via Facebook advertisements and flyers distributed at local preschools and pediatricians' offices. The sample size was determined prior to data collection based on power analyses from pilot data and existing literature (e.g., Grabell et al., 2019). Nine participants had missing Galvanic Skin Response (GSR) data due to poor signals and children choosing not to wear electrodes. Four children were also missing neural data due to unusable signals and participants choosing not to wear the fNIRS cap. One subject was also removed from analyses due to poor fNIRS cap contact and data. Final analyses were completed with a total of 73 participants. An independent-samples t-test comparing children who were included vs. excluded in the final sample revealed no significant difference in age or level of irritability (p's $>$ 0.55). Race and ethnicity data are shown in Table 1. Exclusionary criteria were developmental disability or delay, or history of head trauma with loss of consciousness, and assessed via parent self-report during the phone screening. Specific flyers and advertisements targeted children with elevated irritability. The University of Massachusetts' Amherst Institutional Review Board (IRB) approved the study protocol. Data from the present study has not been previously published elsewhere.

2.2. Questionnaires

Parents rated their children's irritability using the Multidimensional Assessment profile of Disruptive Behavior (MAP-DB) Temper Loss scale (Wakschlag et al., 2010). The Temper Loss scales comprises 22 summed items (e.g., "Gets quite frustrated when prevented from doing something s/he wants to do") rated on a 6-point Likert scale (0 = *Never*, 6 = *Many*

Table 1
Sociodemographic data and study variable descriptive statistics and bivariate correlations.

Panel A: Sociodemographic

Variable	Full Sample ($n = 73$)
% Male	53.7%
Race	
% White	75.8%
% African American	9.9%
% Multiracial	9.9%
% Asian American	1.1%
% Chose not to identify	3.3%
Ethnicity	
% Identified as Latinx	16.8%
% Did not identify as Latinx	83.2%

Panel B: Variable Descriptive Statistics and Bivariate Correlations

Variable	Mean	SD	1	2	3	4	5
1. Age (Months)	55.5	9.25					
2. MAPDB Temper Loss Score	36.10	21.01	-0.11				
3. Left PFC Activation	-6.60	20.83	-0.07	.02			
4. Right PFC Activation	-4.71	16.37	-0.12	-0.04	.48**		
5. GSR Reactivity	.07	.06	-0.19	.18	.12	.16	
6. GSR Recovery	-.06	.08	.22	.09	-0.24*	-0.25*	-0.64**

Abbreviations: SD, standard deviation; GSR, galvanic skin response.
* $p < .05$,
** $p < .00$.

times each day). The MAP-DB is now widely used in early childhood irritability research and exhibits good reliability and validity (Wakschlag et al., 2014). For the purposes of characterizing other dimensions of psychopathology within the sample, parents also rated their children's internalizing and externalizing behavior problems using the Child Behavior Checklist (Achenbach and Rescorla, 2000).

2.3. Frustration task

Children completed the Incredible Cake Kids (ICK) task, a touch-screen computer-based frustration task developed for young children (Grabell et al., 2019), while fNIRS and GSR data were simultaneously recorded. The premise of the game was that the child has taken over a bakery and must pick the "most delicious" cake, from an array of three cakes, for each customer. The game uses deception in that children are told selecting the most delicious cake is an objective skill that some children are better at than others are, and which they will be evaluated on. After a practice condition, children completed 30 trials of the Incredible Cake Kids task (See Fig. 1). For each trial, children first saw a cartoon avatar ("the customer") enter the screen, and three distinct cakes appear at the bottom of the screen. Children had 4 s to choose the "most delicious" cake by touching it, followed by 2 s of anticipation, and 2 s of predetermined positive or negative feedback. Positive feedback trials showed a smiling customer paired with a happy vocalization (e.g., "yum!") and negative feedback trials showed a scowling customer paired with a negative vocalization (e.g., "yuck!"). A 2-second inter-trial interval, showing the outside of the bakery at night, occurred after each trial. If children did not choose a cake during the 4-second window, they were shown a "warning" image of an empty cake tray (signifying that the customer did not receive a cake) for 2 s, and the experimenter then prompted the child to choose more quickly. Trials were grouped into three frustration and three reward blocks. Frustration blocks comprised four negative trials and one positive trial, and reward blocks comprised four positive trials and one negative trial.

After each block, the child was prompted to rate their current emotional state by choosing from seven cartoon faces ranging from negative to positive affect. Due to a technical issue, two-thirds of the self-rated emotion data were lost. However, a previous study using the Incredible Cake Kids task with a different sample found that children did not appear to reliably denote their emotional states (Grabell et al., 2019), consistent with other work documenting that emotion self-ratings are unreliable in preschool age children (Chambers and Johnston, 2002). Thus, we had not planned to use the self-rating data regardless of the technical problem.

A 20-second rest condition, designed to look like a loading screen, occurred before the first block and in between blocks. The ICK task was

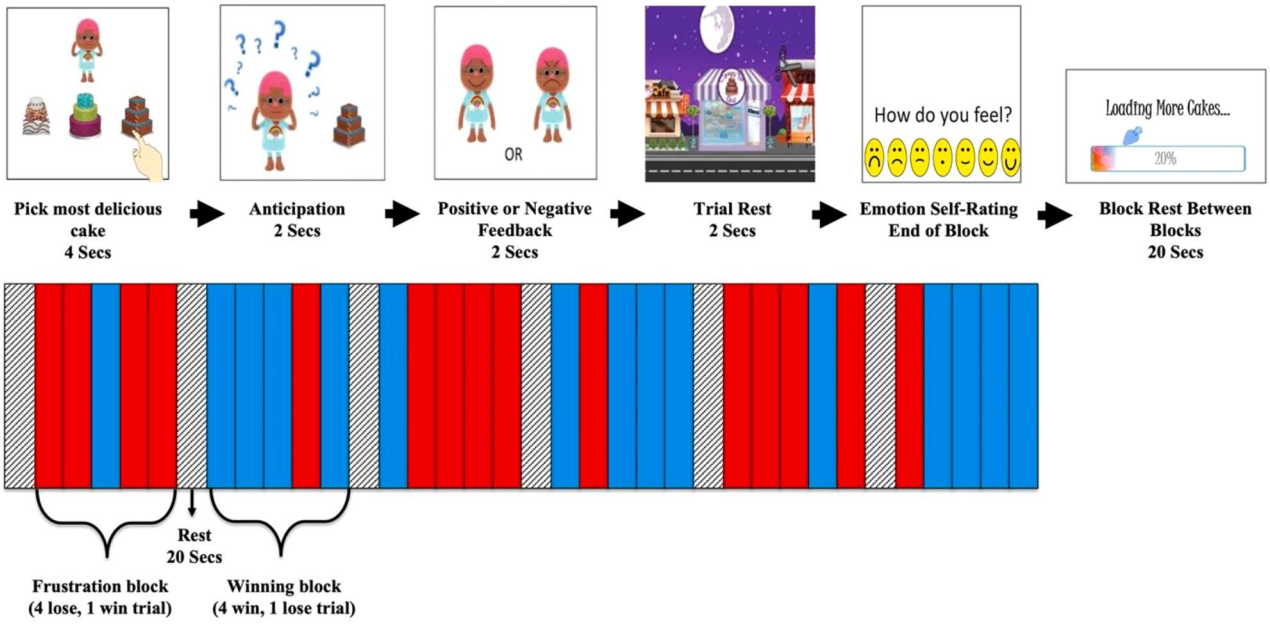

Fig. 1. Schematic of the Incredible Cake Kids Task. Children were instructed to select the "most delicious cake" and then given predetermined positive and negative feedback, which were organized into predominantly frustration and winning blocks.

designed and run using Eprime 3.0 and trigger events were simultaneously sent from the E-prime computer to fNIRS and GSR recording equipment (described below) using a parallel port and splitter cable.

2.4. fNIRS recording and analysis

Non-invasive optical imaging was performed using a NIRx NIRScout system (NIRx Medical Technologies, LLC, Glen Head, NY). The fNIRS probe comprised 8 LED light source optodes emitting 690 nm (12 mW) and 930 nm (8mw) light and 4 detectors. Neighboring source and detector optodes were 3 cm apart. The probe was designed using NIRx NIRStar software to cover Brodmann areas 10 (ventrolateral prefrontal cortex) and 46 (dorsolateral prefrontal cortex) on each hemisphere. Thus, the probe was constructed, a priori, to examine only the lateral prefrontal cortex. fNIRS methodology has shown good test-retest reliability in emotion based studies (Huang et al., 2017).

Analyses were conducted using the NIRS Brain AnalyzIR Toolbox (Santosa et al., 2018). Data were collected at 7.81 Hz and down-sampled to 4 Hz. Changes in light saturation were converted to optical density and then changes in oxy- and de-oxy hemoglobin estimates via the modified Beer-Lambert Law. A general linear model was used to assess activation for each condition at the subject level with an auto-regressive whitened, weighted least-squares (AR-iRLS) model used to reduce effects of motion artifacts and systemic physiology (Barker et al., 2013). In order to reduce family-wise error, the 10 source-detector pair channels were averaged into two regions of interest (ROI) corresponding to left and right lateral PFC. Subject-level activation estimates for each ROI were used in group-level analyses.

2.5. Galvanic skin response recording and analysis

Continuous GSR was measured using a MindWare (Gahanna, OH) 8-slot BioNex Chassis with disposable foam electrodes. GSR methodology in emotion-based paradigms have shown good test-retest reliability, including in studies of youth (Schupak et al., 2016; Najafpour et al., 2017). GSR electrodes were applied to the palm of the child's non-dominant hand to minimize motion artifacts. Data were collected using a 1000 Hz with rolling filter. Children also wore a MindWare respiratory belt in order to better identify artifacts in the data reflecting sudden changes in breathing. Raw continuous GSR data were processed using MindWare proprietary analysis software. Raw data were viewed in time mode in order to first identify and correct motion and respiration artifacts. We used the pattern of participants' physiological responses in combination with video recordings to identify GSR artifacts within the segment. Motion artifacts were determined when participants made sudden movements with their non-dominant hand, causing a peak or trough that significantly varied from the rest of the segment, or were outside a normal microsiemens (uS) range (e.g., 2–45 uS) (Morgan, 2018). Respiration artifacts were identified when children coughed or sneezed, causing a drastic peak or trough in the data. Artifacts in the data were edited via splining or extending tools. The splining tool removed artifacts from the middle of a data segment by connecting the nearest neighboring points of usable data. The extending tool removed artifacts at the beginning or end of the data segment. Segments in which more than 50% of the data were edited were excluded.

In order to test how changes in PFC activation were associated with simultaneous changes in GSR, we examined *GSR reactivity*, defined as the increase in GSR activity as the child moved from rest to a frustration (or reward) block; and *GSR recovery*, defined as the decrease in GSR activity as the child moved from frustration (or reward) back to a rest block. Here, we operationalized changes in GSR activity as change in the frequency of skin conductance responses (SCRs), rather than change in mean microsiemen level, as microsiemen levels can be influenced by confounds such as individual differences in hydration (Cacioppo et al., 2007). An SCR is a discrete positive inflection or peak within the continuous GSR signal reflecting sympathetic neuronal activity (Venables and Christie, 1980). Consistent with extant literature, inflections were defined as SCRs if the electrodermal conductance increased by a minimum of 0.05 microsiemens. We exported the number of SCRs per subject for each frustration and rest block. Given that frustration or reward blocks could have different lengths depending on the child's responding pattern, we converted SCR scores to SCR rate per second. Next, we calculated GSR reactivity by subtracting the SCR rate during frustration (or reward) from the preceding rest block, and averaging across instances. Similarly, we calculated GSR recovery by subtracting the SCR rate during rest from the preceding frustration (or reward) block, and averaging across instances (see Fig. 2).

2.6. Analysis strategy

Zero-order correlations and multiple regression models were used to test the hypothesis that lPFC activation and GSR reactivity and recovery during frustration are inversely associated. PFC activation by irritability interaction terms were entered into the multiple regression models and graphically modeled for interpretation when significant. Two-tailed p-values were used for all statistical tests. The FDR correction was used to correct for family-wise error (Benjamini and Hochberg, 1995).

3. Results

3.1. Descriptive statistics

MAP-DB Temper Loss scores ranged from 0 to 95 ($M = 36.1$, $SD = 21$). Other studies have used a cut-off score of 42.5, 1.5 SD above the mean in the MAP validation sample, to denote severe irritability (Grabell et al., 2017, 2020), and 27% of the sample scored above this severity cut-off. Descriptive statistics for other study variables are shown in Table 1. CBCL scores revealed 7% of the sample scored above the clinical cutoff for internalizing behavior problems (16% above borderline cutoff), and 10% scored above the clinical cutoff for externalizing problems (13% above borderline cutoff).

3.2. Changes in galvanic skin response and PFC activation

As a validity check that frustration blocks were associated with expected changes in GSR reactivity and recovery, we conducted a series of paired-sample t-tests to test how GSR rates changed between task conditions. As shown in Fig. 2, SCR rates were significantly higher during reward and frustration compared to rest. SCR rates significantly increased between rest and the next frustration or reward blocks (reactivity), and significantly decreased between each frustration or reward block and the subsequent rest (recovery). A paired-sample t-test revealed no significant difference in reactivity and recovery between frustration and winning (p's > 0.38). Fig. 3.

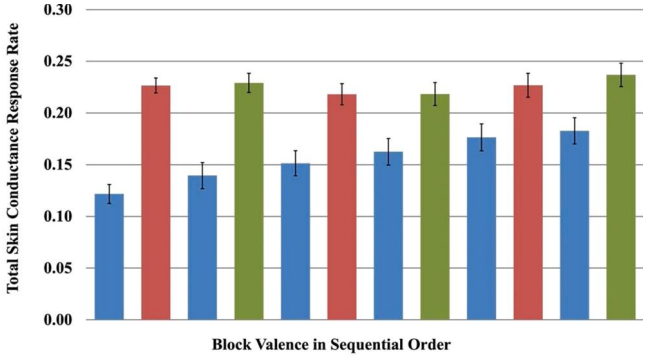

Fig. 2. Changes in Skin Conductance Levels Over the Course of the Task. Rest (blue), negative (red), and positive (green) blocks of the task in sequential order.

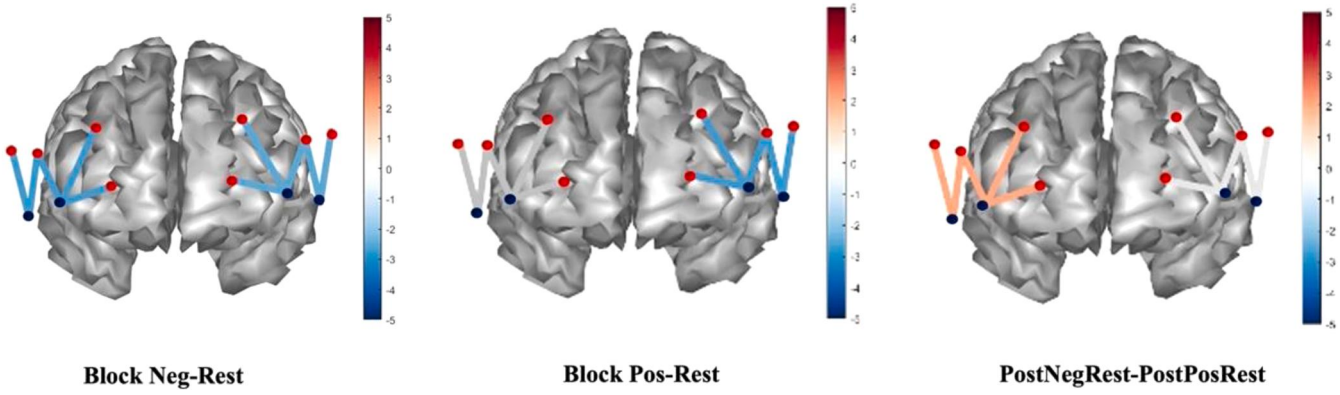

Fig. 3. fNIRS contrasts. (rest-frust and post-frust rest vs. post-reward rest). Abbreviations: fNIRS, functional Near-Infrared Spectroscopy; Frust, frustration; Pos, positive; Neg, negative. Lateral prefrontal cortex activation following frustration (far left) and winning blocks (middle) compared to rest. The far right panel shows lateral prefrontal cortex activation during rest following a frustration block relative to following a winning block.

The NIRS AnalyzIR generalized mixed effects model (Santosa et al., 2018) was used to examine activation differences between frustration, reward, and rest conditions. Activation was significantly higher during rest than frustration in both the left ($t(144) = -2.99$, $p < .01$, $q < 0.05$) and right ($t(144) = -2.33$, $p = .05$, $q = 0.05$) lPFC. Activation was also higher during rest than during reward in both the left ($t(144) = -2.81$, $p < .01$, $q < 0.05$) and right ($t(144) = -2.23$, $p < .05$, $q < 0.05$) hemisphere. Frustration and reward blocks did not have significant differences in activation in either hemisphere ($p > .56$), however, post-hoc analyses revealed that activation during rest conditions immediately following frustration had higher activation than rest conditions following reward, although the trend was only significant at the $p < .08$ level, ($t(81) = 1.32$, $p = .10$, $q = 0.41$) in the right lPFC. Subject-level PFC activation data for the frustration-rest contrast, at each ROI, were exported to SPSS. To test whether effects were specific to frustration, comparison analyses were run with reward block PFC activation.

3.3. Associations between fNIRS, GSR, and Irritability

Bivariate correlations between study variables (See Table 1) revealed activation in the left and right lPFC was significantly positively correlated with each other. Left and right lPFC activation was also significantly correlated with GSR recovery, such that higher activation was associated with a steeper recovery slope. GSR reactivity and recovery were significantly correlated with each other, such that steeper GSR reactivity was associated with steeper GSR recovery. Age and irritability were not significantly correlated ($p = .36$), and were not correlated with any other study variable.

3.4. Regression models

We conducted multiple linear regression models to examine the main effects of left and right lPFC activation, as well as irritability on GSR reactivity and recovery. Results revealed that there was a negative effect of right lPFC activation on GSR recovery when controlling for irritability, such that increased right lPFC activation predicted steeper GSR recovery ($b = -0.001$, $SE = 0.001$, $p = .03$; note that steeper recovery was represented with more negative values). There was also a negative effect of left lPFC activation on GSR recovery when controlling for irritability, such that increases in left lPFC activation predicted steeper GSR recovery ($b = -0.001$, $SE < 0.001$, $p = .04$). All other model coefficients were not significant (p's > 0.15).

Next, we used two regression models using the PROCESS macro (Hayes, 2012) to test how PFC activation in the left and right lPFC, irritability, and the PFC activation*irritability interaction, predicted GSR recovery. There was a significant, positive interaction between right lPFC activation and irritability on GSR recovery ($b = 0.0001$, $SE < 0.001$, $p = .006$). There was also a negative effect of right lPFC activation on GSR recovery when controlling for irritability, such that as lPFC activation on the right hemisphere increased, GSR recovery became steeper ($b = -0.0033$, $SE < 0.001$, $p < .001$). As shown in Fig. 4, for illustrative purposes, we visualized the lPFC*irritability interaction using groups with + /- 1 SD from the mean as cutoff points. Children with low ($b = -0.0024$, $SE < 0.001$, $p < .001$) levels of irritability showed a significant increase in GSR recovery steepness as right lPFC activation increased in comparison to peers with moderate and severe levels of irritability. Children with moderate irritability showed the same significant association direction ($b = -0.0012$, $SE < 0.001$, $p = .029$) and children with severe irritability did not show a significant change in GSR recovery as lPFC activation increased ($b = -0.0001$, $SE < 0.001$, $p = .92$). There was a marginally, negative significant effect of left lPFC activation on GSR recovery when controlling for irritability, such that as lPFC activation increased, GSR recovery became steeper, ($b = -0.0016$, $SE < 0.001$, $p = .08$). There was no significant interaction between activation of the left lPFC and irritability on GSR recovery ($b < 0.001$, $SE < 0.001$, $p = .38$). All other model coefficients were also non-significant (p's > 0.31).

For comparison purposes, two additional regression models using the PROCESS macro were conducted to test how lPFC activation, irritability, and the lPFC activation*irritability interaction, predicted GSR recovery during the reward blocks. There were no significant interactions between right activation and irritability on GSR recovery ($b < 0.001$, $SE < 0.001$, $p = .89$) with all other model coefficients also showing non-significant associations (p's $> .20$). Similarly, there were no significant interactions between left lPFC activation and irritability on GSR recovery ($b < 0.001$, $SE < 0.001$, $p = .48$) with all other model coefficients remaining non-significant as well (p's > 0.20).

4. Discussion

The goal of the present study was to examine how frustration-related lPFC activation attenuates simultaneous physiological arousal, and how this association may be disrupted in the presence of early irritability. We found that preschool-age children, even those with severe irritability, tolerated simultaneous fNIRS and GSR recording while being frustrated. Results showed that as children moved from periods of frustration to periods of rest, lPFC activation increased as physiological arousal decreased, or recovered. These two signal changes correlated with each other such that preschool children who exhibited greater lPFC activation had steeper GSR recovery slopes relative to peers with lower lPFC activation, suggesting lPFC activation attenuates physiological arousal. This attenuation pattern was strongest in children with low to moderate irritability, while children with severe irritability showed no association between lPFC and GSR reactivity or recovery during frustration.

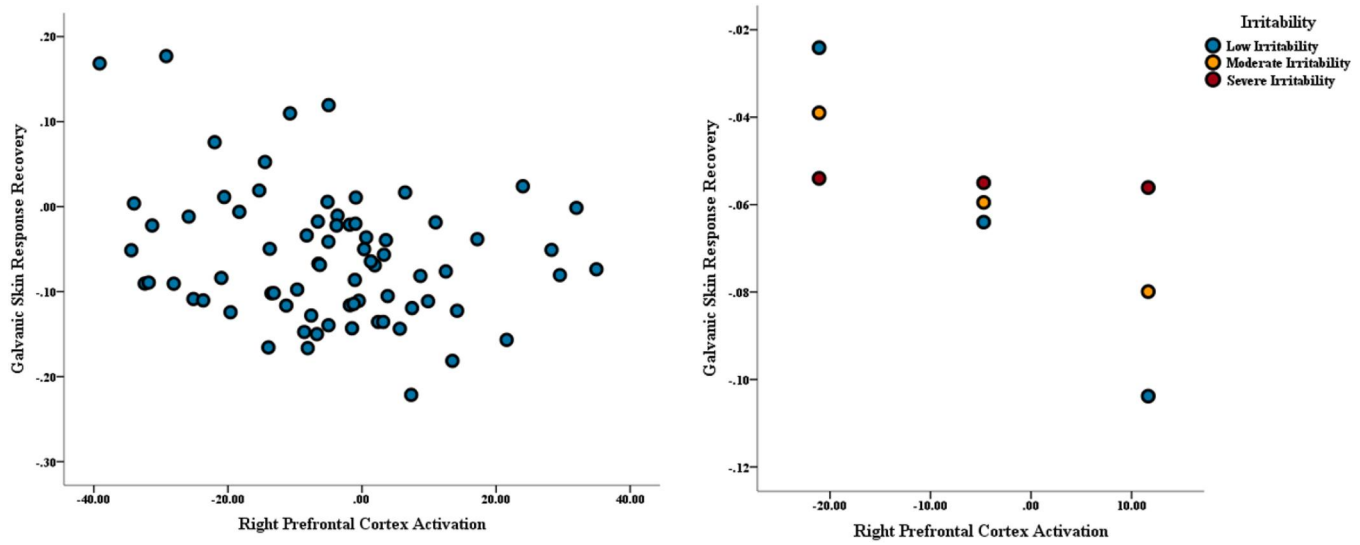

Fig. 4. Right PFC Activation and GSR Recovery at Different Levels of Irritability. Abbreviations: PFC, prefrontal cortex activation; GSR, galvanic skin response, Prefrontal cortex activation in the right hemisphere and galvanic skin response recovery in children with low (blue), moderate (yellow), and severe (red) levels of irritability.

Notably, these effects were specific to frustration onset, as reward blocks were unrelated to GSR and irritability.

The present study is, to our knowledge, the first to demonstrate that lPFC activation may attenuate physiological stress, in children as young as three years, during a frustration challenge. This attenuation pattern is similar to reports of PFC activation attenuating the amygdala response during negative emotional challenges in older children and adolescents (Silvers et al., 2015), and adults (Lee et al., 2012). However, this attenuation pattern during frustration had not been replicated in younger samples (though see Gee et al., discussed below) due to difficulties getting children to remain still while experiencing strong negative emotions in an fMRI scanner. While more recent work with fNIRS has confirmed that negative emotional challenges, such as frustration, are associated with greater lPFC activation in children as young as preschool-age (Perlman et al., 2014), these studies were unable to test whether lPFC activation was down-regulating amygdala-related psychophysiology. Because the lPFC is implicated in myriad cognitive and self-regulation-related processes, the fNIRS literature to date has been ambiguous in terms of whether lPFC activation is proximally or distally integrated with emotion modulation (Grabell et al., 2019). To our knowledge, the present findings that greater lPFC activation predicted a stronger, simultaneous, GSR recovery from frustration, is the first to suggest this critical neural mechanism of frustration response may become established within a few years after birth.

Results of the present study also replicate adolescent and adult fMRI work showing PFC-amygdala functional connectivity during emotion is weaker, or absent, in participants with certain types of psychopathology relative to healthy controls (Mayberg et al., 1999; Fitzgerald et al., 2017). Here, children with severe irritability lacked an association between lPFC and simultaneous GSR reactivity and recovery during frustration. Previous work, largely with fNIRS, showed that lPFC activation during frustration correlated with irritability, and was weaker in children with more severe levels of irritability (Grabell et al., 2017). Although we did not detect an association between lPFC activation and irritability, the present results suggest this lPFC activity may be, similar to older populations, part of a system integrated with autonomic nervous system functioning. The present findings suggest weak lPFC activation reported in other studies may indicate a specific deficit in modulation of the cascade of physiological responses that occur downstream of amygdala activation. The present study therefore raises the possibility that combining fNIRS and GSR may allow the field to move beyond studying single neural markers that differentiate levels of irritability to more integrated systems of emotion regulation.

Our findings also have implications for the "when to worry" problem of pediatric irritability, in which early clinical irritability prodromal to chronic mental health problems is difficult to differentiate from normative misbehaviors common in toddlers and preschoolers (Wiggins et al., 2017). Longitudinal work using parent-ratings of irritability found that only 50% of the variance in irritability ratings predicted future scores, and a third of children with elevated irritability had no psychopathology 6 months later (Wakschlag et al., 2010). This ambiguity over the meaning of early irritability scores has pushed the field to examine neural markers that can elucidate the early development of "clinical" irritability. Work in early childhood populations, largely done with fNIRS, has linked lPFC activation during frustration to the full spectrum of irritability and where within that spectrum abnormalities occur (Grabell et al., 2017). The present study suggests "clinical" irritability may be driven by weak lPFC activation that results in elevated and prolonged physiological arousal following frustration.

The present findings may suggest a seemingly straightforward downward replication of adult regulatory patterns to early childhood, however, other studies of PFC-amygdala functional connectivity in preschoolers, though extremely sparse, offer a complicated picture. Most notably, Gee and colleagues (2013) conducted, to our knowledge, the only study of emotion-related PFC-amygdala functional connectivity in a sample that included preschool children. Forty-five 4–22-year-olds viewed happy, fearful, and neutral faces during fMRI imaging. Results showed that medial prefrontal cortex (mPFC) activation during fearful faces was *positively* associated with amygdala activation in 4–9-year-olds, before shifting to the expected inverse association around age 10. The positive-to-negative switch was also associated with age-related decreases in both amygdala activation, and normative separation anxiety. The authors contended that positive associations between the amygdala and mPFC may reflect stronger bottom-up regulatory processes that may be more prevalent in earlier ages, with top-down regulation becoming more common as children mature. While these findings, when contrasted against the present findings, appear to present a mixed picture of early childhood emotion regulation, there are numerous crucial differences between the studies. First, the Gee et al. study examined 12 children between 4 and 9, and fewer than 4 children under age 6, who did not meet criteria for any mental disorder, whereas the present study comprised 82 3–5-year-olds, with an oversampling of

children with severe irritability. The Gee et al. study also found connections with the mPFC and directly measured amygdala activation occurring at the same instant, whereas the present study focused on the lPFC and examined a physiological proxy for amygdala activation with a delayed onset of several seconds (Dawson et al., 2017). Most notably, the Gee et al. protocol focused on fear processing whereas the present study examined frustration, raising the possibility that fear and anger regulation may develop differently in early childhood. Indeed, very early neural development supports infant reflexes designed to survive danger, such as the moro and swimming reflexes (Capute, 1986), that children age out of. In contrast, there are no known unique early reflexes related to tolerating anger. It is therefore conceivable that there are early evolutionary-based reasons why young children would process fear differently than other emotions, such as anger, although extensive additional research is clearly needed to explore this further.

Notably, the Gee et al. study also included participants who did not meet criteria for a mental disorder, whereas the present study recruited a sample enriched for irritability. This difference raises a broader issue over the specificity of the present findings to other disorder types. It has been proposed that the vast majority of DSM 5 disorders involve some disruption of prefrontal-amygdala connectivity (Kovner et al., 2019). However, this does not mean weak or absent prefrontal-GSR associations would necessarily be observed for all youth enriched for psychopathology, and for all types of emotional challenges. Disorders in which irritability and poor frustration tolerance are a core component of the diagnostic criteria, such as Oppositional Defiant Disorder (ODD) and Disruptive Mood Dysregulation Disorder (DMDD) (Burke et al., 2014; Roy et al., 2014), or a common associated feature, such as in Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) (Karalunas et al., 2019; Lecavalier et al., 2009) could plausibly exhibit weak PFC-GSR connections in early childhood. Less clear are what PFC-GSR disruptions might look like for young children with internalizing or trauma-based disorders. Although irritability is common in anxiety and depression, several event-related potential studies have shown that internalizing disorders are often characterized by hyper-reactive self-regulation neural processes, such as an exaggerated error-related negativity component, whereas externalizing disorders are linked to blunted, hypo-reactive processes (Meyer and Klein, 2018). Moreover, fMRI and animal work suggests that early adverse experiences are linked to early abnormal maturation of PFC-limbic connectivity marked by an earlier developmental shift to top-down PFC-modulation of limbic activation (Tottenham and Gabard-Durnam, 2017). Certain clinical pediatric populations may therefore show heterogeneous patterns of abnormality, with some phenotypes potentially exhibiting exaggerated PFC modulation of psychophysiology.

While the magnitude of lPFC activation during frustration predicted steeper GSR recovery, lPFC activation was unrelated to GSR reactivity across the entire sample or at any level of irritability severity. This was contrary to our hypotheses and particularly surprising given that the sample showed a clear GSR reactivity response as they moved from rest into a frustration block. It is possible that associations between lPFC activation and GSR as children move into the onset of a stressor reflects a more bottom-up emotion regulation process, whereas associations moving off of a stressor reflect more top-down modulation of negative emotion (Gross, 2014). Indeed, top-down emotion regulation processes, such as reappraisal, are associated with a more robust prefrontal response (Ochsner and Gross, 2008), including in early childhood samples (Grabell et al., 2019), raising the possibility that lPFC-GSR associations were more easily detectable during the recovery phase. However, this possibility is also highly speculative at present as there is little to no empirical base on the cognitive processes driving GSR reactivity and recovery. fMRI methodology in studies of self-regulation lack the temporal sensitivity needed to tease apart distinct phases of limbic activation, and, to the best of our knowledge, there are no GSR studies exploring cognitive processes underlying emotion-related reactivity and recovery phases. Future studies using a simultaneous fNIRS-GSR multimodal design may be able to elucidate GSR reactivity and recovery phenomena by manipulating the valence, intensity, and context of emotional stimuli.

As previously stated, results were specific to task frustration blocks, and activation during reward blocks was unrelated to GSR changes or irritability. Although some fMRI studies have found lateral PFC activation during reward processing, many of these studies simulated the purchase of high value items (Knutson et al., 2007). Other reward-processing studies, particularly studies in youth oversampled for psychopathology, have found reward effects in more medial frontal and orbitofrontal areas, which are outside the reach of fNIRS light migration (Kamkar et al., 2017; Sauder et al., 2016).

4.1. Strengths, limitations, and future directions

Strengths of the present study include a large pediatric sample, including a significant proportion of severely irritable children, and the use of a multi-modal approach that, to our knowledge, was the first to examine simultaneous fNIRS and GSR in children this young. The present study also provides guidance for future research to further examine how different components of an integrated prefrontal-physiological system interact early in life, and the role this system plays in both normative and pathological emotion regulation. Although the premise of the study was to better understand early prefrontal-amygdala functional connectivity, it is important to note that the amygdala was not measured directly, due to the same methodological constraints that make fMRI work in young children difficult. Given extensive research showing strong amygdala-GSR signal correlations during negative emotions (Furmark et al., 1997; Dube et al., 2009), based on detailed physiological mapping in animal models (Rosenkilde, 1979), it appears unlikely the connection between the amygdala and GSR activity differs substantially in early childhood. However, there is a notable paucity of studies examining fMRI and GSR during frustration, and in pediatric populations. The present findings suggests the feasibility of future longitudinal work in which children are measured with fNIRS and GSR when they are young, and fMRI when they are older, to robustly test if early fNIRS-GSR connections forecasts later PFC-amygdala functional connectivity. In addition, the present study deliberately oversampled children with severe irritability given the importance of this transdiagnostic symptom in early disorders (Avenevoli et al., 2015), yet the present findings do not necessarily generalize to other forms of psychopathology. That preschool children with severe irritability tolerated simultaneous fNIRS and GSR recording is an encouraging sign for future studies to examine prefrontal attenuation of physiological arousal in other pediatric clinical populations. Moreover, the present findings have potential implications for future early intervention work. In older populations, changes in limbic-prefrontal connectivity reflect post-intervention symptom improvement (Santamarina-Perez et al., 2019; Schmitt et al., 2016), suggesting fNIRS-GSR methodology may elucidate intervention effects in early childhood. Finally, while the present study focused on the preschool period as a logical extension of prior research on functional connectivity (i.e., Gee et al., 2013), there is substantial neural and behavioral growth between birth and age 3 years. The present findings raise the exciting possibility of examining prefrontal-physiological associations at even earlier ages to further explore the complex neurobiology of emotion regulation in its most nascent stages of development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

All data, tasks, and analysis code will be shared upon request.

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