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The late positive potential (LPP): A neural marker of internalizing problems in early childhood

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ABSTRACT

Background: One potentially relevant neurophysiological marker of internalizing problems (anxiety/depressive symptoms) is the late positive potential (LPP), as it is related to processing of emotional stimuli. For the first time, to our knowledge, we investigated the value of the LPP as a neurophysiological marker for internalizing problems and specific anxiety and depressive symptoms, at preschool age.

Method: At age 4 years, children ($N = 84$) passively viewed a series of neutral, pleasant, and unpleasant pictures selected from the International Affective Pictures System. Affective picture processing was measured via the LPP (EEG recorded) and mothers reported on child behavior via the Child Behavior Checklist 1 ½ - 5 (internalizing, DSM-anxiety, DSM-affective/depression subscales). Difference scores between the neutral and affective pictures (i.e., neutral-pleasant and neutral-unpleasant) were computed for posterior, central and anterior brain locations for early (300-700 ms), middle (700-1200 ms) and late (1200-2000 ms) time windows.

Results: Greater LPP difference scores for pleasant images in the anterior recording site, in the middle time window, were associated with greater internalizing behaviors. Greater DSM-anxiety symptoms were associated with greater LPP difference scores for unpleasant and pleasant images. After correcting for multiple testing, only the association between greater DSM-affective/depression symptoms and greater LPP difference scores for unpleasant images in the anterior recording site (early time window) remained significant.

Discussion: Our study has identified a potential neural marker of preschool internalizing problems. Children with larger LPPs to unpleasant images may be at greater risk of internalizing problems, potentially due to an increased emotional reactivity.

Internalizing problems (e.g. anxiety, depressive symptoms) are the most common mental health problem reported by children. In preschool through early school years, approximately one-fifth of children experience internalizing problems and specific anxiety disorders (Beesdo et al., 2009; Dittman et al., 2011; Paulus et al., 2015; Whalen et al., 2017). At preschool age anxiety disorders are more prevalent, however, clinical depression is being more widely recognized and diagnosed at this age (Whalen et al., 2017). Child internalizing behaviors are characterized by greater behavioral expression of negative emotions (De Pauw and Mervielde, 2010) and altered neural processing of negative or threatening stimuli (Fu and Pérez-Edgar, 2019) such that those children excessively attend to negative or threatening information (Bar-Haim et al., 2007; Daleiden and Vasey, 1997). Research

investigating how neurophysiological measures relate to real-world functioning and behavior can help elucidate functional brain correlates associated with internalizing problems.

Event-related brain potentials (ERPs) recorded from the scalp through non-invasive electroencephalography (EEG) can be used to study engagement with emotional stimuli with excellent temporal resolution (on the order of milliseconds). They are therefore ideal for studying neural processes underlying dysfunctional emotional processing related to clinical and sub-clinical internalizing problems. The late positive potential (LPP) is an ERP component which provides a neural measure of emotional processing (Hajcak et al., 2012). It indexes sustained attention towards motivationally salient stimuli that can be reliably assessed across development, from early childhood (Hua et al.,

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2014), through adolescence (Kujawa et al., 2013) and adulthood (Moran et al., 2013). The LPP is a relative positivity in the ERP that begins as early as 200 ms after stimulus onset and is pronounced at centro-parietal recording sites. It is increased for emotional compared with neutral stimuli ranging from pictures, faces and words. Changes in amplitudes are evident throughout the duration of picture presentation.

As a temporal measure of emotional responsivity to stimuli, the LPP is a potentially useful neurophysiological correlate of internalizing problems. In adolescence through adulthood, altered LPP to emotional stimuli has been associated with internalizing disorders, including anxiety and depression (Bunford et al., 2017; Foti et al., 2010; Kujawa et al., 2015; MacNamara et al., 2016). Despite comorbidity (Kaufman and Charney, 2000) the literature to-date suggests that LPP responsivity may be related to anxious and depressive symptoms differentially, in adolescence and adulthood (MacNamara et al., 2016; Sandre et al., 2019; Weinberg and Sandre, 2018). Depressive symptoms have been linked to reduced reactions to pleasant versus neutral faces and images in adolescents and adults (MacNamara et al., 2016; Sandre et al., 2019; Weinberg et al., 2016). Other work in early adolescence suggests those with depression (Grunevald et al., 2019), as well as those at risk for depression based on temperamental traits (Speed et al., 2015) may be linked to reduced reactions to both pleasant and unpleasant faces, potentially reflecting a global disengagement from environmental stimuli (Rottenberg et al., 2005). Finally, some work suggests that depressive symptoms may be associated with *greater* LPP to emotional stimuli (Burkhouse et al., 2017) and specifically, negatively valenced self-referential words (Auerbach et al., 2015; Speed et al., 2016). Differences are likely due to the nature of the stimuli presented and age of participants. Considering anxiety, adolescents and adults consistently show increased engagement with negative environmental stimuli as indexed via greater LPP to unpleasant versus neutral images (Kujawa et al., 2015; MacNamara et al., 2016, 2019).

In children, as young as preschool age (Hua et al., 2014; van den Heuvel et al., 2018) the LPP has been found to be sensitive to emotional stimuli (Hua et al., 2014; Kujawa et al., 2013) with pleasant and unpleasant images eliciting significantly larger LPP amplitudes than neutral pictures. Emotional stimuli may be processed differently by young children compared to adults. Research suggests that children display a strong ‘negativity bias’, perceiving negativity or threat in ambiguous situations or neutral facial expressions (Marusak et al., 2016; Tottenham et al., 2013) with greater bias potentially linked to the development of internalizing behaviors. Yet, very little work has examined the relationships between observed behavior and neurophysiology with respect to the LPP in early development. This is surprising given the potential utility of non-invasive brain-behavior research for treatment intervention during early childhood, at symptom onset.

Studies in childhood that have examined the LPP in relation to internalizing behaviors have done so by comparing responses to neutral stimuli to either unpleasant or pleasant stimuli. Across studies (DeCicco et al., 2012; Dennis and Hajcak, 2009), greater LPP amplitudes for unpleasant in comparison to neutral stimuli showed small but significant associations with greater anxious-depressed symptoms (Dennis and Hajcak, 2009) and greater anxiety in children aged 5–10 years (DeCicco et al., 2012). Recently, Whalen et al. (2020) found that children with preschool-onset Major Depressive Disorder displayed reduced responding to pleasant stimuli. These studies further our understanding of the LPP as a correlate of internalizing behaviors, but are unable to assess the discriminative validity of the LPP. Of the studies that have examined LPP response in relation to both pleasant and unpleasant in comparison to neutral images during childhood, no associations between behavioral assessments and LPP response to pleasant versus neutral images were established. One study by Solomon et al., (2012) found that enhanced LPP response while passively viewing unpleasant compared to neutral images was associated with observed fearful behavior, but not maternal-reported fearfulness or anxiety at 5–7 years. Similarly, greater internalizing symptoms at age 10 years were

associated with greater LPP response to unpleasant images one year prior (Kujawa et al., 2016).

Kessel et al., 2017b were the first to examine the discriminative validity of LPP amplitudes for pleasant, unpleasant and neutral images in relation to child temperamental constructs associated with both depression and anxiety. The authors found that lower positive affectivity (a hallmark of depressive symptoms) at 6 years was associated with decreased LPP for pleasant but not unpleasant images at 9 years. Aspects of negative affectivity (fear, sadness) were more related to LPP response to unpleasant images. Interestingly, greater fear (a correlate of anxiety), was associated with greater LPP response to negative images while greater sadness (more akin to depression) was associated with decreased LPP amplitude to positive images. Relatedly, studies suggest that children and adolescents of depressed parents display a blunted LPP (Kessel et al., 2017a; Kujawa et al., 2012; Nelson et al., 2015) while children of anxious parents display greater LPP between neutral and unpleasant images only (Nelson et al., 2015). Yet, no study to date has examined associations between LPP responses to emotional stimuli (pleasant, unpleasant and neutral) and anxiety as well as specific depressive symptoms in preschool children.

To the best of our knowledge, research is yet to investigate whether neural processing of emotion, as measured by the LPP in response to both pleasant and unpleasant images, is associated with internalizing problem behaviors and importantly, specific sub-dimensions of internalizing behaviors in children at preschool age. As part of a longitudinal prospectively studied cohort, the current study examined neural reactivity to affective images (i.e. LPP) as a neurophysiological correlate of internalizing behaviors in a non-clinical population of preschool children. In line with our prior work in this cohort (van den Heuvel et al., 2018) we examined the LPP across three scalp regions (Anterior, Central, Posterior) at three time windows (Early, Middle, Late). We hypothesized that children with higher LPP values to negative stimuli relative to neutral, and lower response to pleasant stimuli have higher internalizing problems measured using the Child Behavior Checklist, CBCL 1 ½ - 5 (Achenbach and Rescorla, 2001). Given findings from the adolescent and adult literature as well as emerging research in children, we predicted that a lower response (lower LPP) to pleasant stimuli relative to neutral stimuli was associated with greater depressive symptoms as measured by the CBCL DSM-Oriented Affective problems subscale. Conversely, we expected a higher response (greater LPP) to unpleasant versus neutral stimuli to be associated with greater anxiety symptoms (scores on the CBCL DSM-Oriented Anxiety problems subscale). No specific hypotheses regarding brain-behavior associations by particular region and time windows were made, given the exploratory nature of our research.

1. Methods

1.1. Participants

The present study is part of the Prenatal Early Life Stress (PELS) study—a prospective pregnancy cohort study conducted at Tilburg University, the Netherlands. The study was approved by the medical ethical committee of the St Elisabeth Hospital, Tilburg, the Netherlands, and was conducted in full compliance with the Helsinki Declaration. All participating mothers and partners provided informed consent. For the current study, we analyzed the data of participants with complete child EEG data and maternal-report of child behavior at 4 years.

Data from 84 four-year-olds (mean age = 48 months, S.D. = 0.81, 40 boys) were included in the current study. Of the 103 four-year-olds that were assessed with EEG, 19 were excluded from analyses due missing questionnaire data ($N = 6$), technical problems ($N = 4$), fussiness/excessive movement ($N = 5$), low number of artifact free trials (< 20 trials; $N = 3$), and due to cortical visual impairment ($N = 1$). An earlier analysis of the EEG data from these children was previously published in van den Heuvel et al. (2018).

1.2. Measurements

1.2.1. Child behavior

Mothers reported on the child's behavior using the Child Behavior Checklist 1½ - 5 years (CBCL/1 ½-5; Achenbach and Rescorla, 2001). Data from the internalizing scale of the CBCL and the DSM-IV anxiety (anxiety symptoms) and affective disorder (depressive symptoms) subscales are reported here. Mothers rate how true statements regarding the child's behavior are from 0 = *Not True*, 1 = *Somewhat or Sometimes True*, to 2 = *Very True or Often True*. The CBCL-Internalizing total raw score is calculated as the sum of the responses to 36 statements, while the DSM anxiety and affective disorders sum responses to 10 statements for each subscale. The CBCL-Internalizing as well as DSM-IV disorder subscales demonstrate strong psychometric qualities including strong reliability and validity (Achenbach and Rescorla, 2001). The CBCL-internalizing subscale showed strong internal consistency (Cronbach's $\alpha = 0.82$). Internal consistencies for the CBCL-affective disorder (Cronbach's $\alpha = 0.58$) and CBCL-anxiety disorder subscales (Cronbach's $\alpha = 0.55$) were acceptable, considering the low number of items on each scale (10 items).

1.2.2. Affective picture processing

Ninety age-appropriate pictures were taken from the International Affective Picture System (IAPS; Lang et al., 2008). Thirty contained neutral household objects or nature scenes, 30 'pleasant' pictures depicted candy and happy scenes, and 30 'unpleasant' pictures depicted accidents and scary animals. All pictures were randomly displayed on a 19-in CRT monitor (2000 ms, full-screen mode: 1280 × 1024 px, ISI = 500 ms) via the E-Prime software (version 2.0.8.74, Psychology Software Tools, Pittsburgh, PA). The experimenter sat next to the children during the passive viewing task. During the experiment, EEG was recorded (see below for details), and after the experiment (which was embedded in a longer 2-h assessment), children received a small reward. Internal consistencies for LPP scores for neutral, pleasant and unpleasant stimuli were strong (all Cronbach α 's = 0.99).

1.2.3. EEG

The electroencephalogram was recorded with BioSemi ActiveTwo amplifiers (www.biosemi.com) at a sampling rate of 512 Hz, via 64-electrodes mounted in an elastic cap according to the extended International 10–20 system. The EEG was referenced on-line with the active Common Mode Sense electrode (CMS) and passive ground electrode (Driven Right Leg electrode; DRL). Two additional electrodes were placed on the mastoids, which were used for offline re-referencing. The data were (pre-)processed with the BrainVision Analyzer 2 (Brain Products, Munich, Germany) and the MATLAB (version R2012b, The Mathworks, Inc.) based EEGLAB package (version 13.0.1; Delorme and Makeig, 2004). After re-referencing the data (based on the average of the mastoids), independent component analysis (ICA) implemented in EEGLAB was used to identify and remove components that captured blinks and eye-movements. The data were filtered off-line with a zero-phase Butterworth bandpass 0.1–30 Hz (slope 24 dB) filter. Subsequently, the data were segmented into epochs of 2400 ms which included a 400 ms pre-stimulus period. Artifacts were identified as epochs in which there was a voltage change of $> 200 \mu\text{V}/200 \text{ ms}$, $> 75 \mu\text{V}/\text{ms}$, or $< 0.2 \mu\text{V}/100 \text{ ms}$, and those epochs were excluded from analyses. Children with < 20 artifact free trials for each condition (neutral, pleasant, unpleasant) were not included in the analysis, and the average number of trials per participant were 25 (neutral pictures), 26 (pleasant pictures), and 25 (unpleasant pictures). Epochs were averaged for each stimulus category, and the resulting ERPs were baseline-corrected to the average amplitude in the 400 ms pre-stimulus period. Following prior work examining ERPs in the current cohort (van den Heuvel et al., 2018) and others Solomon et al. (2012), mean LPP amplitudes were exported to SPSS for three time windows: early (300–700 ms), middle (700–1200 ms) and late (1200–2000 ms). We averaged the LPP over

three regions: posterior (PO4, PO8, O2, Oz, POz, PO3, PO7, and O1), central (C4, C6, CP6, Cz, CPz, C3, C5, and CP5), and anterior (FC4, F4, F6, Fpz, AFz, FC3, F3, and F5).

1.2.4. Statistical analyses

The ERPs in response to the Neutral stimuli were not correlated with the Internalizing problems, DSM-anxiety or DSM-affective symptoms at any of the three scalp regions (Anterior, Central, Posterior) at any of the time windows (Early, Middle, Late), all p 's $> .05$ (FDR-corrected; Benjamini and Hochberg, 1995), and were considered a within-subject base-line. We therefore subtracted the ERPs in response to the Neutral stimuli from the ERPs in response to the Pleasant and Unpleasant stimuli, and analyzed the relationship with Internalizing problems and the DSM-anxiety and DSM-affective symptoms subscales via Pearson's correlations. Analyses were corrected for multiple testing by using FDR-correction (Benjamini and Hochberg, 1995), controlling per hypotheses (Internalizing, DSM-anxiety, DSM-affective disorder), per region (Anterior, Central, Posterior), per stimulus (pleasant, unpleasant). Significant correlations were followed-up with linear regression models including all LPP windows (Early, Middle, Late). This allowed us to partial out the variance related to the voltage change over time within a scalp area and type of LPP difference wave. All analyses were performed in SPSS (IBM; version 24).

2. Results

2.1. Descriptive statistics

Overall, the current cohort represents a non-clinical, typically developing population. In total, 11 children scored in the borderline clinical range for internalizing problems (13.1%), with 5 of these children meeting clinical levels (6%). For depressive symptoms, 11 children scored within the borderline clinical range (13.1%) and four of them scored within the clinical range (4.8%). For DSM-anxiety problems, a total of six children scored within the borderline clinical range (7.1%) and none of the children met criteria for clinical anxiety symptoms. Scores on the CBCL-internalizing subscale were more highly correlated with DSM-anxiety disorder subscale ($r = 0.78$), than DSM-affective disorder subscale ($r = 0.60$). DSM-affective and anxiety disorder subscales were correlated $r = 0.56$, suggesting each subscale was assessing related but independent child symptoms. Independent t -tests showed no differences in CBCL-subscale scores for boys and girls (p 's $> .05$). Descriptive statistics are displayed in Tables 1 and 2.

2.2. Neural responses to affective pictures in four-year-olds

As demonstrated by van den Heuvel et al. (2018), in the same sample, four-year-olds are able to detect differences between affective and neutral pictures. The stimulus-locked ERPs in response to neutral, pleasant and unpleasant pictures in our sample of four-year-olds are presented in Fig. 1, with mean and standard deviations presented in Table 2. Fig. 2 shows the scalp distribution LPP waves for each stimulus type. Note that for the anterior and central regions the LPP is mirrored, resulting in negative-going waveforms for the LPP. As a result, higher LPP amplitudes for these areas are defined as more negative values (cf. van den Heuvel et al., 2018).¹ In the current paper, we examined whether individual differences in these LPP amplitudes, assessed as difference scores, predict internalizing behaviors.

¹ More specifically, as with our prior analysis of this data (van den Heuvel et al., 2018), four-year-olds showed higher LPP amplitudes to affective (pleasant and unpleasant) pictures compared to neutral stimuli at posterior electrode sites (Early, Middle, Late time windows, p 's $< .001$). The LPP amplitudes did not differ between affective and neutral pictures at anterior and central recording sites at the group level, as established in van den Heuvel et al. (2018).

Table 1
Descriptive statistics for outcome variables.

Variable	M (SD)
Internalizing behaviors ^a (raw score)	6.64 (5.32)
CBCL DSM-affective subscale ^a (raw score)	1.79 (1.87)
CBCL DSM-anxiety subscale ^a (raw score)	2.17 (1.93)

^a CBCL 1 ½ - 5 years.

Table 2
Means and standard deviations for LPP amplitudes for emotional and neutral stimuli for the three regions.

	Early		Middle		Late	
	M	SD	M	SD	M	SD
Anterior						
Pleasant	-23.84	9.56	-13.62	8.94	-6.84	9.37
Unpleasant	-22.16	8.90	-12.88	8.82	-8.06	6.45
Neutral	-23.12	8.56	-12.32	7.75	-8.21	8.19
Central						
Pleasant	-22.48	8.58	-10.95	8.22	-5.54	9.23
Unpleasant	-21.34	7.22	-11.28	7.53	-6.58	5.95
Neutral	-21.16	6.72	-9.36	6.57	-6.40	7.26
Posterior						
Pleasant	23.31	12.10	19.34	10.73	15.63	10.43
Unpleasant	21.82	11.94	17.54	11.35	15.65	9.94
Neutral	18.95	11.21	13.33	10.00	10.92	9.88

2.3. Internalizing behaviors

Results of correlation analyses between LPP values and child internalizing problems showed that the amplitude of the Middle Pleasant – Neutral LPP difference wave was significantly associated with Internalizing problems, such that greater difference scores were associated with greater Internalizing behaviors (Table 3). However, the correlation did not survive correction for multiple testing. No other significant associations were found.

2.4. DSM-IV anxiety subscale

As displayed in Table 4, when considering the DSM anxiety subscale, difference scores of the Pleasant – Neutral LPP in the anterior region were negatively associated with anxiety problems in the middle time-window. This association indicates that a larger difference in LPP response to neutral and pleasant pictures is related to more anxiety issues. In addition, greater difference scores in the Unpleasant – Neutral LPP condition were associated with greater anxiety problems, in the early time-window, anterior region. However, none of the significant associations remained significant after correction for multiple testing.

2.5. DSM-IV affective subscale

Analyses examining correlations with DSM-affective (depressive) symptoms showed two significant correlations in the early time window (Table 5). In both anterior and central regions during the early time window, the more negative the difference wave was (and thus, the more negative the Unpleasant ERP was relative to the Neutral ERP), the greater the depressive symptoms were. While the correlation in the central area did not survive FDR-corrections for multiple testing, the correlation in the anterior window did (Fig. 3).

To partial out the variance related to the voltage change over time within the anterior scalp area, a regression model was run with unpleasant-neutral LPP difference scores in each time window (Early, Middle, Late). In line with the correlation analyses, only the amplitude of the Early difference wave ($\beta = -0.45, p = .006$) was significantly

related to the DSM-affective sub-scale. Larger differences between LPP amplitude of neutral and unpleasant stimuli are associated with higher scores on the DSM-affective sub-scale.

3. Discussion

In the current study we set out to examine the Late Positive Potential (LPP) as a potential neurophysiological marker for internalizing behaviors in children at preschool age. Considering internalizing behaviors, we observed that children with greater internalizing behaviors attend more to pleasant stimuli. Interestingly, when examining LPP responses separately for anxiety and depressive symptoms, we observed that children high in anxiety display higher neural responses to both pleasant and unpleasant images relative to neutral images, while children high in depressive symptoms displayed only higher responses to unpleasant images. Importantly, when correcting for multiple testing, only the association between child depressive symptoms and unpleasant images remained significant. Findings suggest that a pattern of emotional reactivity to unpleasant images may be associated with depressive symptoms in young children.

3.1. Depressive symptoms

When considering maternal-rated child depressive symptoms, greater LPP to unpleasant relative to neutral images, early in processing in the anterior scalp region, showed a small association with greater symptom severity. DSM-affective symptoms were not associated with greater LPP difference between pleasant and neutral stimuli. Taken together, our findings contrast Rottenberg's (2005) emotional insensitivity context hypothesis which has been supported by much literature – showing reduced reactions to both pleasant and unpleasant stimuli in depressive adolescents and adults (Hill et al., 2019; Sandre et al., 2019; Weinberg et al., 2016). Findings also differ to recent empirical assessments in children that suggest blunted LPP to positive images to be related to lower positive affectivity and greater sadness at age 6–9 years (Kessel et al., 2017a), as well as preschool-onset major depressive disorder assessed at 4–7 years (Whalen et al., 2020). Inconsistencies could have also been introduced due to differences in outcomes assessed (temperament, symptoms, clinical diagnoses).

It is difficult to directly compare our research to much research in children, given that the majority of studies in children have only examined depressive symptoms and LPP amplitude in relation to positive but not negative images. Our finding is, however, consistent with the few studies that have examined LPP difference waves considering both positive and negative relative to neutral stimuli in children. This research has established associations between larger LPPs in relation to unpleasant but not pleasant images during early processing, and anxious-depressed symptoms at 10 years (Dennis and Hajcak, 2009), as well as in adolescents when presented with emotional self-referential words (Auerbach et al., 2015). Children of depressed mothers similarly show enhanced LPP response to negative stimuli (Speed et al., 2016). Collectively, these findings support the negative potentiation hypothesis, where by negative mood evokes enhanced responses to negatively-valenced cues in the environment (Beck, 1976). Children who display depressive symptoms may excessively attend to negative or threatening information, with negative mood potentially leading one to be hypersensitive or primed to react more so to negative stimuli in their environment (Scher et al., 2005). As reviewed by Platt et al. (2017), behavioral studies suggest that depression in childhood and adolescence is characterized by an attention and interpretation bias for negative stimuli. From early childhood onwards, attention towards negative stimuli for those displaying depressive symptoms is evident.

Interestingly, as with our previous work in this cohort (van den Heuvel et al., 2018) our finding was specific to LPP difference waves in the anterior region. Other work in children and adults has established LPP-behavior associations primarily in posterior scalp regions (e.g.,

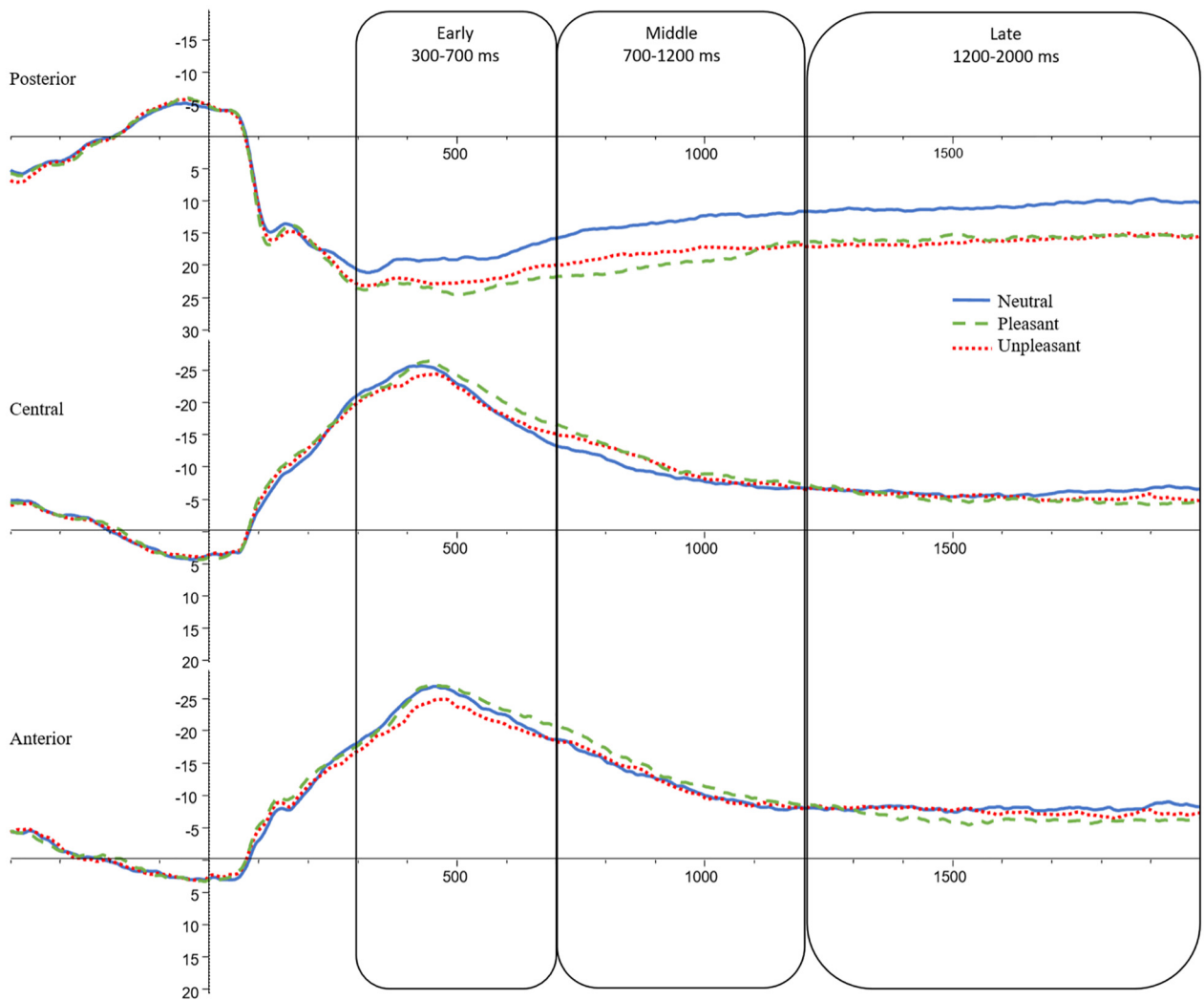


Fig. 1. ERP responses to neutral (blue/solid lines), pleasant (green/dashed lines) and unpleasant (red/dotted lines) pictures for posterior, central and anterior electrode sides. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

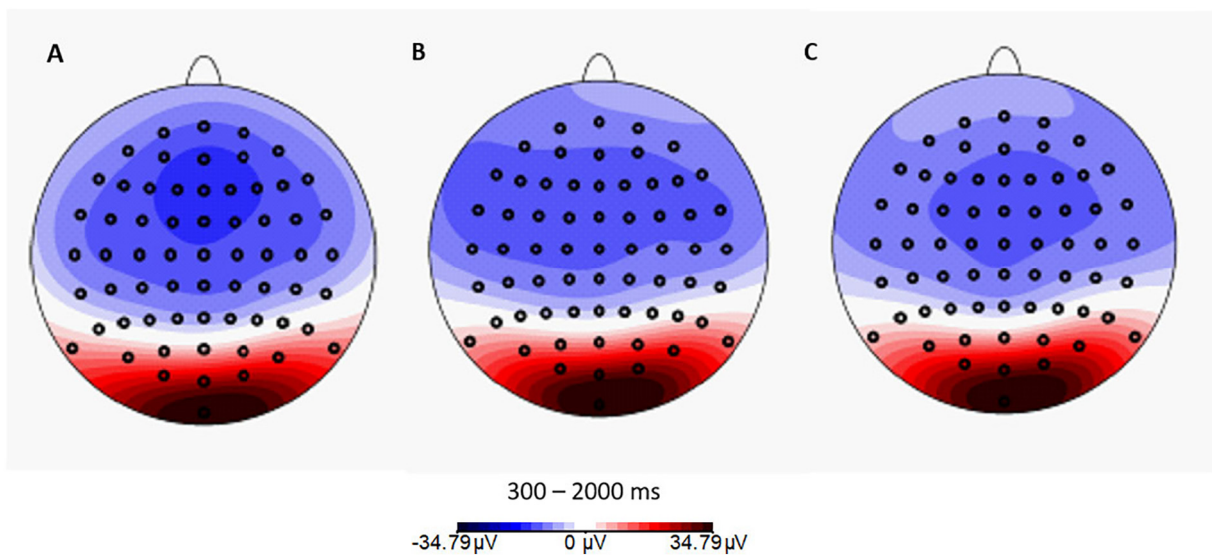


Fig. 2. Scalp distribution of neutral (A), pleasant (B) and unpleasant (C) LPP waveforms across early, middle and late time windows.

Table 3
Correlations between LPP difference waves and internalizing problems.

Time-window	Pleasant – Neutral LPP						Unpleasant – Neutral LPP					
	Region						Region					
	Anterior		Central		Posterior		Anterior		Central		Posterior	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Early	–0.211	.054	–0.138	.212	–0.024	.828	–0.163	.137	–0.191	.081	–0.114	.301
Middle	–0.241 ^a	.027	–0.179	.103	0.046	.680	–0.157	.155	–0.178	.106	–0.024	.827
Late	–0.003	.977	0.022	.844	0.115	.299	–0.012	.915	–0.037	.742	–0.001	.995

Note.

^{*} $p < .05$.

^a Correlation no longer significant after FDR-correction for multiple testing.

Whalen et al., 2020), based on prior literature, or as is often the case, where LPP difference waves are maximal. Considering our finding, it may be important that in future research, central and anterior scalp-regions, in addition to posterior regions, are also examined, even if differences are not maximal in these regions. Finally, findings were established in the early time window, suggesting this process of sustained engagement to emotional content of stimuli is likely automatic in nature, in service of basic survival by motivational systems (Lang et al., 1997).

Differences in the association between neural responses to affective images and depression may exist, dependent upon developmental stage. It is important to consider the possibility that both disengagement from as well as sensitivity towards one's environment in the form of alterations to LPP responses to emotional stimuli, may be associated with the development of depressive symptoms across childhood through adolescence. While we find evidence to support a tendency to attend to negative stimuli as associated with depressive symptomatology from an early age in our study, heterogeneity in the long-term function of this neural correlate may be dependent upon early temperamental biases (Kessel et al., 2017a), early life experiences (van den Heuvel et al., 2018), parenting environment (Liu and Pérez-Edgar, 2018), and those continually exposed to negative experiences (Kindt, 2001). It is also possible that the LPP develops in conjunction with other dysregulation processes such as neuroendocrine disruptions (Alomari et al., 2015; Ursache and Blair, 2015). Given the dearth of longitudinal studies examining development of multiple neurophysiological dysregulated processes in conjunction with environmental exposures within individuals, it is difficult to situate our findings within developmental theoretical frameworks of cognitive biases and threat perception in at-risk and depressive populations. This is an exciting avenue for future research.

Table 4
Correlations between LPP difference waves and the anxiety symptoms sub-scale.

Time-window	Pleasant – Neutral LPP						Unpleasant – Neutral LPP					
	Region						Region					
	Anterior		Central		Posterior		Anterior		Central		Posterior	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Early	–0.187	.088	–0.137	.215	–0.024	.826	–0.233	.033 ^a	–0.212	.053	–0.107	.331
Middle	–0.216	.048 ^a	–0.186	.091	0.010	.927	–0.187	.089	–0.212	.053	–0.084	.445
Late	0.098	.375	0.085	.440	0.132	.231	0.035	.750	–0.038	.734	–0.045	.682

Note.

^{*} $p < 0.05$.

^a Correlation no longer significant after FDR-correction for multiple testing.

3.2. Anxiety and internalizing behaviors

We failed to find brain-behavior links between LPP amplitudes to emotional stimuli and anxiety symptoms as well as internalizing behaviors. Findings of no association between LPP responses to pleasant images and these behavioral outcomes, are in line with previous studies in children (Kujawa et al., 2016; Solomon et al., 2012) and adults (MacNamara et al., 2019; Weinberg et al., 2016). It is, however, surprising that we did not establish an association between LPP difference waves for negative relative to neutral images, and preschool-age internalizing behaviors, nor anxiety symptoms given this is a consistent finding in the literature across development (Auerbach et al., 2015; Kujawa et al., 2016; Speed et al., 2016). Findings are also inconsistent with research examining the nature of attentional biases (Fu and Pérez-Edgar, 2019; Liu and Pérez-Edgar, 2018), neurophysiological correlates of anxiety symptoms (DeCicco et al., 2012; Kujawa et al., 2015), and temperamental fearfulness (Kessel et al., 2017b; Solomon et al., 2012) in anxiety and internalizing behaviors, which suggest that children exert greater attentional resources towards negative stimuli. Still, as is the case in our study, no associations between broad internalizing behaviors in relation to LPP difference waves have been established in children aged 6–9 years (Dennis and Hajcak, 2009). Together with our findings for depressive symptoms, it is clear that ongoing research is needed to determine the utility and specificity of the LPP as a neural marker of internalizing behaviors as well as clinical symptoms of anxiety and depressive symptoms across childhood.

3.3. Strengths, limitations and future research

There are multiple strengths of this study. Building on prior work (van den Heuvel et al., 2018), we have examined LPP in relation to pleasant, unpleasant and neutral stimuli, in a comparatively large cohort of children. Furthermore, in line with adult literature, we examined not only overall internalizing behaviors but the specific DSM-IV

Table 5
Correlations between LPP difference waves and the affective (depressive) symptoms sub-scale.

Time-window	Pleasant – Neutral LPP						Unpleasant – Neutral LPP					
	Region						Region					
	Anterior		Central		Posterior		Anterior		Central		Posterior	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Early	−0.114	.300	−0.119	.281	0.000	.997	−0.277 ^a	.011	−0.238 ^a	.029	−0.121	.274
Middle	−0.032	.772	−0.093	.398	0.113	.306	−0.115	.299	−0.151	.169	−0.003	.982
Late	0.134	.225	0.100	.364	0.166	.131	0.006	.960	0.000	.997	0.024	.827

Note.

^a *p* < .05.

^a Correlation no longer significant after FDR-correction for multiple testing.

anxiety and affective disorder subscales. The use of a well validated and widely used maternal report of behavior, enabled us to compare our results to that of prior work in older children.

It is important to acknowledge limitations of the current study. In line with prior work in this cohort (van den Heuvel et al., 2018), the LPP amplitudes did not differ between affective and neutral pictures at anterior and central recording sites at the group level; differences were only established at the posterior recording sites. However, as shown in the current paper, individual differences in LPP difference waves across regions, are potentially useful markers of child behavior. Because we used a validated picture set of scenes including negative, positive and neutral stimuli, a potential limitation is the wide variety of unique stimuli the children were presented with. The unpleasant stimuli included “fearful” as well as “sad” stimuli, and some pictures may therefore represent a bias to “threat”, while others may be more saliently depicting “sad” stimuli. It is possible that sub-group analyses of these scenes may yield different results given that anxiety symptoms may be more strongly related to threat biases. We did not collect valence and arousal of stimuli information. Such information would have assisted in validating the stimuli, in line with prior work in this field (Dennis and Hajak, 2009). Future studies should look to replicate and

extend our findings. Our ability to determine relationships at clinical levels of symptoms is limited, due to the largely non-clinical sample of children and relatively small range in scores across CBCL subscales. Finally, maternal report of child behavior and EEG assessments were collected at the same age. Longitudinal studies collecting both EEG and behavioral data (maternal report or objective assessment) at multiple points across early childhood are warranted, in order to determine the direction of effects. This work will also help determine the utility of the LPP as a marker of internalizing behaviors across early childhood.

4. Conclusions

This study examined the value of the LPP in response to affective images in young children as a neural marker for internalizing problem behaviors. Our study demonstrated that greater early LPP responses to negative images were associated with depressive symptoms in preschoolers. Overall, the predictive value of the LPP in young children is likely not sufficient for clinical purposes. However, given our findings differ to that of work in middle childhood and adolescents, our study highlights the importance of examining the nature of neurophysiological markers of behavior across development. We therefore encourage

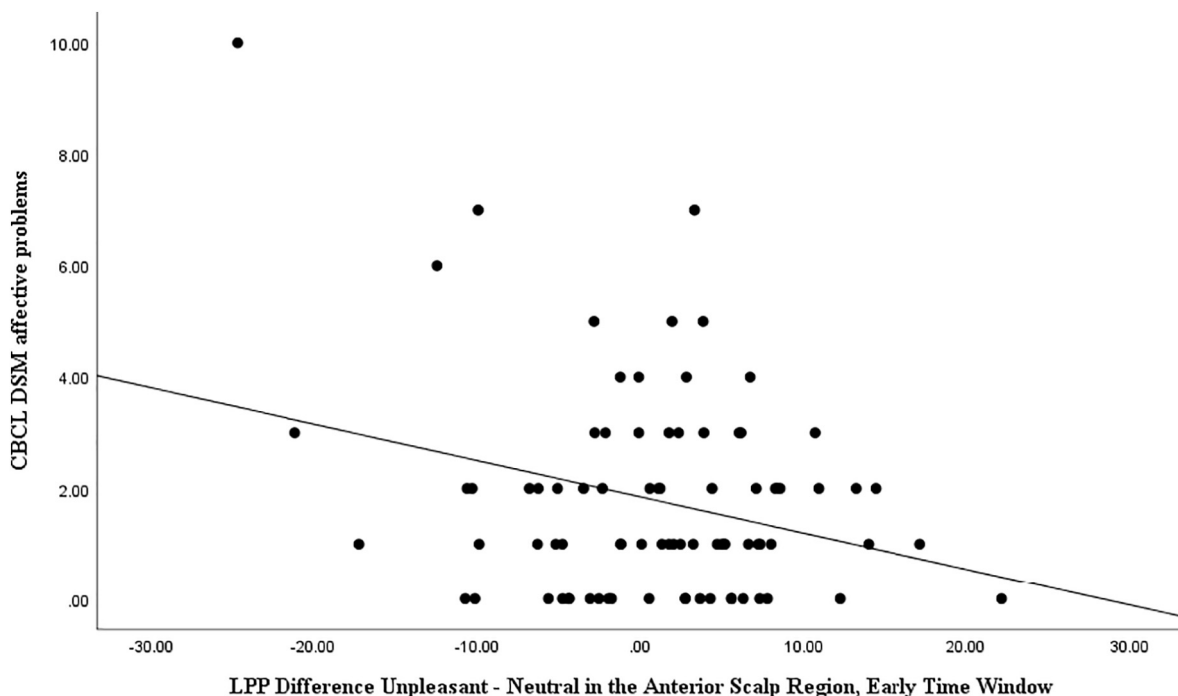


Fig. 3. Correlation between the Anterior Early LPP Unpleasant – Neutral ERP difference waves and affective (depressive) symptoms. Note: the association was still significant when the extreme value on the CBCL affective problems was winzorized (*r* = −0.248, *p* = .023).

replication and extension of our study. Ultimately, research into childhood neural markers for psychopathology can help improve long-term outcomes, through the improvement of diagnostic tools and development of novel mechanistic interventions that impact these neurophysiological correlates and behavioral processes.

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