

RESEARCH ARTICLE

Emerging atypical connectivity networks for processing angry and fearful faces in very preterm born children

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Abstract

Very preterm born (VPT) children are those born before 32/40 weeks' gestational age and comprise 10% of the 15 million babies born prematurely worldwide each year. Due to advancements in neonatal medicine, the survival rate of VPT birth has increased, but few studies have investigated the nonmedical, social-cognitive morbidities that affect these children. In this study, we examined emotional face processing networks in VPT compared to age and sex matched full-term born (FT) children. Magnetoencephalography (MEG) was used to test VPT and FT born children at 6 years ($n = 78$) and 8 years ($n = 83$). Children were assessed using an implicit emotion face-processing task. Happy, fearful, and angry faces were presented for 150 ms, but children were asked to respond by button press to the location of a control pixelated image of the face displayed on the side of the screen opposite to the face. Children rated the valence of the images on a five-point scale. Group differences showed that VPT children rated angry faces more positively than their FT peers. VPT children had reduced connectivity for angry and fearful faces at 8 years in networks including regions such as the bilateral amygdala, superior temporal sulci, and anterior cingulate gyrus. Interventions should target both emotion recognition, as well as higher cognitive processes related to emotional control and thinking about one's own emotions.

KEYWORDS

emotion face processing, functional connectivity, magnetoencephalography, preterm birth

1 | INTRODUCTION

Over the last three decades, the number of babies born very preterm (VPT: ≤ 32 weeks' gestational age) who survive has been on the rise due to advancements in neonatal medicine (Chawanpaiboon et al., 2019). Despite increased survival rates, the majority of VPT children experience both medical and nonmedical morbidities following birth. The biggest challenges VPT children face throughout development are psychological rather than medical, with difficulties in behavioural, cognitive, academic, and social functioning (Anderson & Doyle, 2003; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Jones, Champion, & Woodward, 2013;

Winchester et al., 2009). While many have investigated the trajectories of cognitive development in VPT birth, the basis for social dysfunction is not well-understood (Fenoglio, Georgieff, & Elison, 2017). This lack of research is surprising given that social difficulties in this population persist with age and interfere with their ability to establish social bonds in adolescence and adulthood (Hille et al., 2008; Moster, Lie, & Markestad, 2008; Potharst et al., 2013; Ritchie, Bora, & Woodward, 2015). A classic model for social development suggests that social cognitive skills are a cornerstone for optimal social functioning (Cavell, 1990). Social cognition includes a host of cognitive processes used to understand, encode, and organize information about oneself and others,

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including processing others' emotions and thoughts (Van Overwalle, 2009). While VPT birth is associated with early exposure to the social world, several risk factors such as atypical structural maturation in brain regions underlying social-cognition (Montagna & Nosarti, 2016) as well as neonatal medical morbidities (Luu et al., 2009) could lead to abnormal brain development. In this study, we investigated the neural networks supporting emotion processing, a core social-cognitive skill, in VPT compared with matched full-term born (FT) controls, at a two-year interval, over an early school-age period when deficits in these skills often emerge in VPT children.

In our everyday interactions, emotional faces communicate important social information, allowing us to understand our social milieu and behave appropriately. It has been long hypothesized that facial expressions have significant biological value for survival (Darwin, 1872) and the advent of neuroimaging studies has supported this hypothesis showing that humans have developed distinct neural systems specialized in perceiving and responding to emotional faces (Adolphs, 2002; Haxby, Hoffman, & Gobbini, 2000). For example, faces elicit greater neural activity compared to objects in specific brain areas (Allison, McCarthy, Nobre, Puce, & Belger, 1994; McCarthy, Puce, Belger, & Allison, 1999; McCarthy, Puce, Gore, & Allison, 1997). These neural systems are so fine-tuned that responses to emotional faces can be measured even when the individual has not consciously perceived the face (Dimberg, Thunberg, & Elmehed, 2000; Whalen et al., 1998). The time course of emotion processing occurs very rapidly, with event related potentials occurring between 80 and 170 ms (P1, N170), then a late positive potential at around 250–300 ms (Eimer & Holmes, 2002; Williams et al., 2004). Differences between emotions can be observed as early as 100 ms (Esslen, Pascual-Marqui, Hell, Kochi, & Lehmann, 2004; Batty & Taylor, 2003, 2006). Regions implicated in emotional face processing include the inferior occipital, fusiform, and superior temporal gyri, insulae, amygdalae and orbital frontal gyri. The fusiform gyri (FG) are well established as core regions, which are reliably involved in processing invariant features of the face, with a strong right-hemisphere dominance, and are part of the ventral visual perceptual pathway. Multiple theories exist regarding how this region contributes to face processing (Gauthier, Skudlarski, Gore, & Anderson, 2000; Kanwisher, McDermott, & Chun, 1997; Tarr & Gauthier, 2000). The superior temporal gyri (STG) are also involved in the ventral visual perceptual pathway, in processing changing aspects of the face such as facial expressions (Allison, Puce, & McCarthy, 2000). The STG along with the FG process coarse information about the face, so that by 170 ms, a human face can be categorically processed based on identity or age (FG) and emotional expression (STG). More fine-tuned processing of the emotional face involves recruitment of the bilateral amygdalae and orbital frontal gyri. The amygdalae relay information to and from the thalamus and the superior colliculus and from the visual cortex. These two cortical and subcortical pathways allow the amygdalae to process positive and negative, explicit or implicit (Hariri, Bookheimer, & Mazziotta, 2000) emotional stimuli eliciting an automatic response and a top-down response to emotions (Adolphs, 2002; Davis & Whalen, 2001). The orbital frontal cortices (OFC) also receive information from the visual cortex, the FG and the STG, and are also connected through the uncinate fasciculus to

the temporal poles, which are also involved in processing emotions (Olson, Plotzker, & Ezzyat, 2007; Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Further processing involves reciprocal connections among these regions and others including the hippocampi, somatosensory cortices, basal ganglia, and insular cortices.

Structural brain differences have been reported in VPT children in areas overlapping with emotional face processing regions including the amygdalae (Peterson et al., 2000), insulae, fusiform gyri (Healy et al., 2013; Nosarti et al., 2008), and bilateral STG (Kesler et al., 2008). A handful of studies have focused on the functional correlates of emotional face processing in VPT infants (Carbajal-Valenzuela, Santiago-Rodríguez, Quirarte, & Harmony, 2017; Papini et al., 2016). To our knowledge, the present study is the first to assess task based functional connectivity in VPT children in two critical time points in development. We used magnetoencephalography (MEG), a neuroimaging modality that measures the magnetic fields produced by assemblies of pyramidal neurons. A direct measure of neuronal activity, MEG provides information on the timing and oscillatory features of these neural networks (Buzsaki & Draughn, 2004). Temporal information can help establish specific differences in early or late emotion face processing and information about the frequency of activity can further pin-point any functional atypicalities as different frequency bands play specific functional roles (Gross et al., 2013; Knyazev, 2007; Pulvermüller, Birbaumer, Lutzenberger, & Mohr, 1997; Von Stein & Sarnthein, 2000).

Thus, we investigated functional networks related to happy, angry, and fearful child faces in a sample of VPT born and age and sex-matched FT born children at both 6 and 8 years of age. Based on the existing behavioural studies, it is clear that early exposure to the social environment does not offer advantages for VPT children who experience several social difficulties. We hypothesized that VPT birth would be associated with atypical emotional face processing network connectivity, lasting into middle childhood.

2 | METHODS

2.1 | Participants

Between 2008 and 2010, 105 babies who were born at or before 32 weeks of gestation were recruited for an 8-year longitudinal study. Babies were admitted to the Neonatal Intensive Care Unit at the Hospital for Sick Children, Toronto, Canada. Follow up assessments were carried out at 6 and 8 years, where all subjects from the initial ($n = 105$) cohort were contacted. Forty VPT children returned at the 6-year time point. At 8 years, three of those who participated at the 6-year time point did not return but three more from the initial cohort participated at 8 years. Therefore, a sample of 40 VPT children was assessed at each time point, and there were no differences between the two samples on any neonatal characteristics, (see Table S1). Neonatal characteristics of the returning cohort are reported in Table 1. A control group (GA ≥ 37 weeks) was recruited to match the VPT born group on age and sex by posted advertisements around the hospital and through flyers posted at schools and on social media. At 6 years, 38 children

TABLE 1 Neonatal characteristics of VPT participants at 8 years

	VPT (8 years)
N	40
Sex	24 M:16 F
Gestational age (weeks)	28.9 ± 1.9
Birth weight (grams)	1,212.7 ± 226.8
APGAR score at 5 min	7.3 ± 1.5
Neonatal therapeutic intervention scoring system (NTISS) at 3 min	16.0 ± 2.9
Clinical risk index for babies (CRIBII)	6.8 ± 2.4
Score for neonatal acute physiology-perinatal extension (SNAPPE-II)	15.4 ± 13.7
Continuous positive airway pressure (CPAP)	n = 35
Respiratory distress syndrome (RDS)	n = 35
Steroids	n = 26
Surfactant	n = 26
Sepsis	n = 23
Patent ductus arteriosus (PDA)	n = 18
Retinopathy of prematurity	n = 8
Congenital heart defect	n = 8
Intrauterine growth restriction (IUGR)	n = 5
Prolonged premature rupture of membranes (PPROM)	n = 5
Necrotizing enterocolitis	n = 4
Intraventricular hemorrhage	Grade 1: n = 4 Grade 2: n = 4 Grade 3: n = 7 Grade 4: n = 3
White matter lesions	n = 14
Cerebellar lesions	n = 4
Deep gray matter lesion	Globus Pallidi: n = 1 Putamen: n = 3 Caudate nucleus: n = 2 Lentiform nuclei: n = 1 Thalamus: 1

participated in the study. At 8 years, 43 participants took part in the study. Only 30/40 FT children returned at the 8-year time point so 13 more control subjects were recruited to match the VPT group. Group characteristics are found in Table 2. Given this difference in IQ between the groups, we examined whether IQ scores predicted any differences observed in neuroimaging findings by adding IQ x Group interactions as predictor variables for the observed network connectivity.

2.2 | Emotional faces task

Sixty child faces were taken from two databases: the NIMH (Egger et al., 2011) and the Radboud Faces Database (Langner et al., 2010). Faces presented were of 10 girls and 10 boys (Mean age = 11.7 ± 1.7, range: 8–15) who had a photo for each emotion of interest: happy, angry and fearful. We focused on this age group to measure processing

emotions of other children in an age range to which they would be exposed at school or other social situations. Images obtained from each database were altered in photoshop such that each image had a gray background and only the face was shown. A gray scarf was added to all images to cover the neck or any other exposed section of the body or clothing.

During the task, a white fixation cross was presented at the center of a black background with the emotional face presented randomly on one side of the screen and a jumbled version of the image presented on the opposite side. The jumbled image was made by dividing the emotional face into 28 smaller squares, randomly re-ordering these squares and blurring them to re-create a mosaicked image with the same dimensions, and features (brightness, contrast, etc.) but unrecognizable as a face (Figure 1).

Children were instructed to focus on the fixation cross and indicate by button press (using the left or right thumb) the side of presentation (left or right) of the jumbled, unidentifiable image. Responses were collected on a VPIXX 4 button pad (Visual Science Solutions, Saint-Bruno, Canada). Three hundred trials in total (100 Happy, 100 Angry, and 100 Fearful) were presented to each participant; stimulus duration was 150 ms followed by a 1,500 ± 100 ms inter-stimulus interval. The total task runtime was about 8 min long. Images were back projected through a set of mirrors onto a screen positioned at a viewing distance of 80 cm. The visual angle of the stimuli was 6.9°.

2.3 | Emotional faces task ratings

Following the MEG scan, participants were shown each face with a rating scale adapted from the Self-Assessment Manikin (Bradley & Lang, 1994) to indicate their subjective ratings of each face (1 = "Very Negative" to 5 = "Very Positive").

2.4 | MEG acquisition, preprocessing, and statistical analyses

2.4.1 | Acquisition

MEG data were obtained on a 151-channel CTF MEG system (CTF MEG International Service LP, Coquitlam, BC, Canada) in a magnetically shielded room with participants in supine position. Third order gradient noise cancelation was applied (600 Hz sampling rate, 250 Hz low pass filter). Head localization was performed continuously throughout the recording.

T1-weighted structural MRIs were collected using 3D MPRAGE protocols on a 3T Siemens MAGNETOM Trio scanner with a 12 channel head coil (TR/TE/TI: 2300/2.96/900 ms; FA: 9°; FOV: 240 × 256 mm; 192 slices; resolution: 1.0 mm isotropic) for the 6 year old subjects and a 3T Siemens MAGNETOM PrismaFIT with a 20 channel head and neck coil (TR/TE/TI: 1870/3.14/945 ms; FA: 9°; FOV: 240 × 256 mm; 192 slices; resolution: 0.8 mm isotropic) for the 8 year old subjects. All scanning took place at the Hospital for Sick Children (Toronto, Canada).

TABLE 2 Between group characteristics at 6 and 8 years

6 year				
	VPT (n = 40)	FT (n = 38)	t(df)/ χ^2	p
Age (years)	6.6 ± 0.32	6.5 ± 0.54	t(60) = 1.1	.24
Sex	15F:25M	22F:16M	$\chi^2(1) = 2.4$.11
Birth weight (kg)	1.2 ± 0.24	3.5 ± 0.59	t(29) = 19	<.001
Gestational age (weeks)	29 ± 1.6	39 ± 1.6	t(64) = 26	<.001
IQ	103.5 ± 13.4	110.0 ± 13.02	t(75) = 2.1	.03
Mean neighborhood income (\$)	112,651	121,949	t(51) = 0.9	.33
Mother's education	n = 40 Grade school (n = 1) High school (n = 1) ^a Some post-secondary training (n = 12) University/college (n = 19) Post-graduate training (n = 7)	n = 33 Some post-secondary training (n = 5) University/college (n = 20) Post-graduate training (n = 8)	$\chi^2(4) = 4$.3
8 year				
	VPT (n = 40)	FT (n = 43)	t(df)/ χ^2	p
Age (years)	8.7 ± 0.51	8.6 ± 0.46	t(78) = 1	.27
Sex	16F:24M	21F:22M	$\chi^2(1) = 0.5$.47
Birth weight (kg)	1.2 ± 0.22	3.5 ± 0.60	t(54) = 24	<.001
Gestational age (weeks)	29 ± 1.41	39 ± 1.35	t(67) = 27	<.001
IQ	105.65 ± 14.5	119.7 ± 11	t(72) = 5	<.001
Mean neighborhood income (\$)	111,522	121,096	t(75) = 1	.32
Mother's education	n = 39 Grade school (n = 1) High school (n = 5) Some post-secondary training (n = 7) University/college (n = 18) Post-graduate training (n = 8)	n = 41 High school (n = 1) Some post-secondary training (n = 7) University/college (n = 18) Post-graduate training (n = 15)	$\chi^2(5) = 6.7$.24

^aSome post-secondary training: includes programs and diplomas that do not include formal education such as university or college.

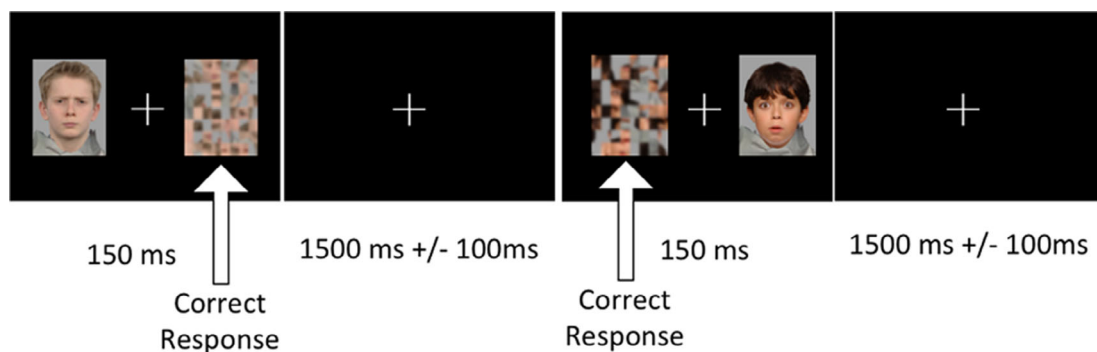


FIGURE 1 Emotion face processing task. Participants were instructed to attend to the fixation cross and press a button as quickly as possible indicating whether the scrambled image is on the left or right of the cross. They were also told to ignore the faces. Stimuli were presented for 150 ms followed by an inter-stimulus interval of 1,500 ± 100 ms

2.4.2 | Data processing and analyses

All MEG and MRI data processing, analysis, and statistics were conducted in MATLAB using custom scripts implementing functions from the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011), Network-Based Statistics (Zalesky, Fornito, & Bullmore, 2010),

BrainNetViewer (Xia, Wang, & He, 2013) and Marc's MEG Mart (MMM; <https://gitlab.com/moo.marc/MMM>).

MEG data were epoched at the onset of stimulus presentation from -500 ms pre-stimulus to 750 ms poststimulus. Independent component analysis was used to attenuate heartbeat and ocular artefacts. Components were rejected based on visual analysis from two

experienced reviewers. Trials were also rejected if the signal exceeded 2500 ft. Finally, each trial was also visually inspected to confirm the absence of artefacts. Trials with poor head motion were identified by fitting a rigid sphere to the average fiducial marker locations collected continuously during MEG acquisition, and by tracking the translation and rotation of the sphere at each recorded time point using HeadMotionTool from the MMM toolbox. The median head position during all trials was used as a reference. Trials with >10 mm head motion were rejected. To examine MEG power in each condition, grand-averaged data sets were computed, and then global field power (GFP) plots were generated for each group at each emotion at the 6 and 8-year time points to inform the temporal trajectory of the neural response to emotional faces.

MEG data were imported into MATLAB using FieldTrip and were mean-centred and filtered with a fourth order Butterworth band-pass filter at 1–150 Hz and a discrete Fourier transform notch filter at 60 and 120 Hz to remove line noise. Subject-specific single shell head models based on anatomical data from each subject's MRI were computed using SPM12 through FieldTrip. Template coordinates were nonlinearly transformed into subject-specific coordinates based on anatomical information from the MRI. Linearly constrained minimum variance (LCMV) beamforming with 5% regularization and projection of the activity to the dominant orientation was performed to estimate the neural activity index (NAI) at each source coordinate.

LCMV source estimation was performed at the centroid of each of the first 90 AAL regions (cortical and subcortical regions), and the timeseries were filtered into four canonical frequency bands: theta (4–7 Hz), alpha (8–12 Hz), beta (13–29 Hz), and gamma (30–55 Hz) using FIR filters (MATLAB's `fir1`). Instantaneous phase at the frequency bands was extracted using the Hilbert transform of the filtered source activity timeseries. Functional connectivity was estimated using the weighted phase lag index (wPLI) (Vinck, Oostenveld, Van Wingerden, Battaglia, & Pennartz, 2011) applied across trials to obtain an estimate of phase synchrony between each pair of nodes at each sample in the trial. The wPLI timeseries were baselined by computing the fractional change from the mean baseline wPLI from –400 to 0 ms, then compared between the VPT and FT groups within each emotion.

2.4.3 | Statistical analyses

Data were analyzed with R (R Development Core Team & R Core Team, 2018). Between group differences in sex and mother's education at each time point were analyzed with χ^2 tests. Between group differences in age, average neighbourhood income, gestational age, and birth weight were analyzed using independent samples *t*-tests. *p*-values were reported significant at $p < .05$.

Emotional faces task behavioral outcomes

Between group differences at each time point were examined using a two-tailed *t*-test comparing means of behavioural outcomes of the emotion faces tasks: reaction time, accuracy, and emotion ratings.

Within group changes with age were computed using the two-tailed, paired *t*-tests in R.

Emotional faces task: MEG

Whole-brain network connectivity differences were tested using the Network Based Statistics (NBS) toolbox (Zalesky et al., 2010) to compute statistical contrasts between groups (FT > VPT) and (VPT > FT) within each emotion of interest. The data that support the findings of this study are openly available in Figshare at <https://doi.org/10.6084/m9.figshare.10314302.v1> (Mossad, 2020). Provided with the adjacency matrix of connectivity between the 190 nodes, NBS first tests the null hypothesis at each connection, a process known as mass univariate testing. Each connection is given a *t*-value. A *t*-statistic threshold is imposed such that only connections with a *t*-value exceeding that threshold can pass to a set of supra-threshold connections. In this study, a strict *t*-threshold of 2.5 was applied, allowing only connections with a *t*-value at or above 2.5 to be included in subsequent analyses. NBS does not assign statistical significance at this level. Rather, it examines the topology among the suprathreshold connections using cluster-based statistical methods. Each cluster therefore is composed of suprathreshold connections, where a path can be found across any two nodes. NBS thus assumes that an experimental effect is well represented by a main component or network rather than one single connection or several isolated connections. Since emotional face processing relies on a distributed network that includes several brain regions including frontal, temporal and subcortical structures, this method is appropriate to investigate the main network preferentially utilized between groups. Finally, a family-wise error rate (FWER) corrected *p*-value is computed for each component using permutation testing. Permutations were repeated 5,000 times. Permutation testing is a nonparametric test that assumes in this case, that if data points are shuffled between groups (ex. FT or VPT) that there would be no effect on the test-statistic. The corrected *p*-value for the component was determined by calculating the proportion of permutations (shuffled data) whose maximal component size exceeded that of the original (unshuffled) data. *p*-values for the resulting networks in each contrast (VPT vs. FT), time point and condition are reported after controlling for FDR (Benjamini & Hochberg, 1995) in R across the two time windows (0–250 ms and 250–500 ms). Networks with marginally significant FDR corrected *p*-values = .05–.06 are also reported here along with the corresponding significant uncorrected *p*-values.

In any graph or network, node degree describes the number of connections or edges connected to that node. Brain networks, weighted by degree, were then visualized using the BrainNet Viewer Connectivity Toolbox (Xia et al., 2013) to represent brain regions that were more highly connected to other nodes within that network compared to others. Centrality measures often correlate positively with brain network distributions and brain regions with high centrality measures (such as degree) represent a hub or core component of that brain network (Oldham et al., 2019). Since there were group differences in IQ, we investigated Group \times IQ interactions predicting mean node strength using generalized linear models in R (Model: $Y = \text{Group} + \text{IQ} + \text{Group} \times \text{IQ}$). Node strength was computed by summing the wPLI

connectivity values at each node of the observed networks. For each subject, mean strength of the observed network was derived by taking the average of all node strength values.

3 | RESULTS

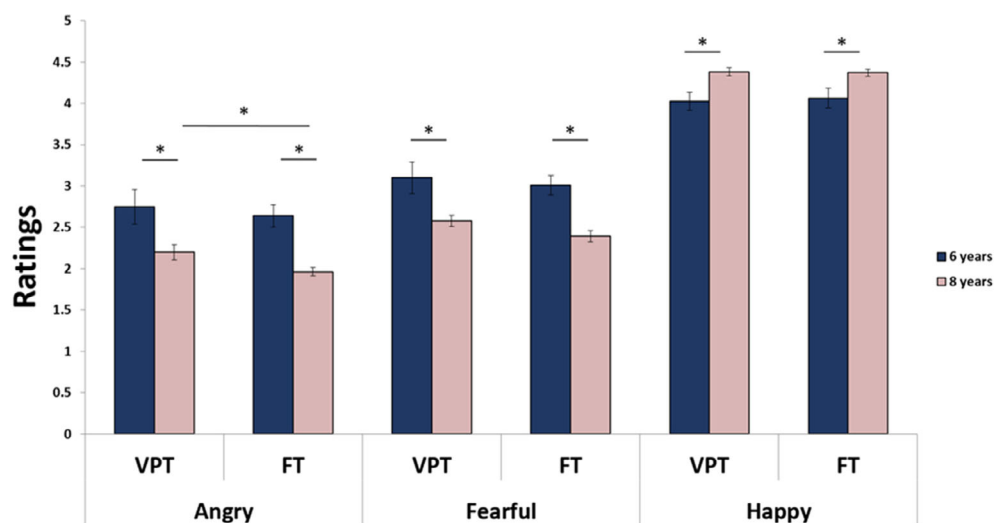
3.1 | Emotional faces task ratings

VPT and FT children rated all photos following the MEG scan on how positive (5) or negative (1) the face was, Figure 2. There was a significant age effect for each emotion within the VPT group (Angry: $t(39) = 4.7$, $p < .001$, Fear: $t(39) = 7.8$, $p < .001$, Happy: $t(39) = 37$, $p < .001$) and within the FT group (Angry: $t(60) = 4.2$, $p < .001$, Fear: $t(59) = 7.9$, $p < .001$, Happy: $t(59) = 41$, $p < .001$). Angry and fearful emotions were rated more negatively at the older age and happy faces were rated more positively at the older age. There were no group differences in emotion ratings at the 6 year time point (Angry: $t(21.8) = 0.42$, $p = .67$, Fearful: $t(20.9) = 0.39$, $p = .7$, Happy: $t(29.4) = 0.22$, $p = .82$) or at 8 years (Fearful: $t(62.7) = 1.99$, $p = .05$, Happy: $t(57.3) = 0.19$) except for Angry: $t(41.1) = 2.25$, $p = .02$). This group difference at 8 years showed that FT children rated the angry faces more negatively than VPT children.

3.2 | Emotional faces task reaction time and accuracy

Reaction times decreased with age across all emotions (Happy: $t(104) = 6.3$, $p < .01$, Fearful: $t(104) = 5.8$, $p < .01$, Angry: $t(105) = 6.12$, $p < .01$, Figure 3a). At 8 years, FT children were more accurate at performing the task during angry trials compared to VPT children ($t[48] = 2.19$, $p = .03$, Figure 3b); there were no other group or age differences in accuracy (Happy: $t(102) = 1.5$, $p = .13$, Fearful: $t(107) = 0.8$, $p = .4$, Angry: $t(104) = 1.5$, $p = .13$).

FIGURE 2 Emotions were rated on a scale from (1 = most negative to 5 = most positive) using the valence picture scale adapted from the Self-Assessment Manikin (Bradley & Lang, 1994) to indicate their subjective ratings of each face. Bars represent mean ratings and error bars represent the SD, * $p < .05$



3.3 | Global field power plots

Visual examination of the GFPs showed that for both groups, peak activations occurred around 150, 250, then at 400 ms poststimulus. Functional connectivity time windows were therefore established based on these evoked fields with an early window: 0–250 ms and a later window: 250–500 ms (Figure 4).

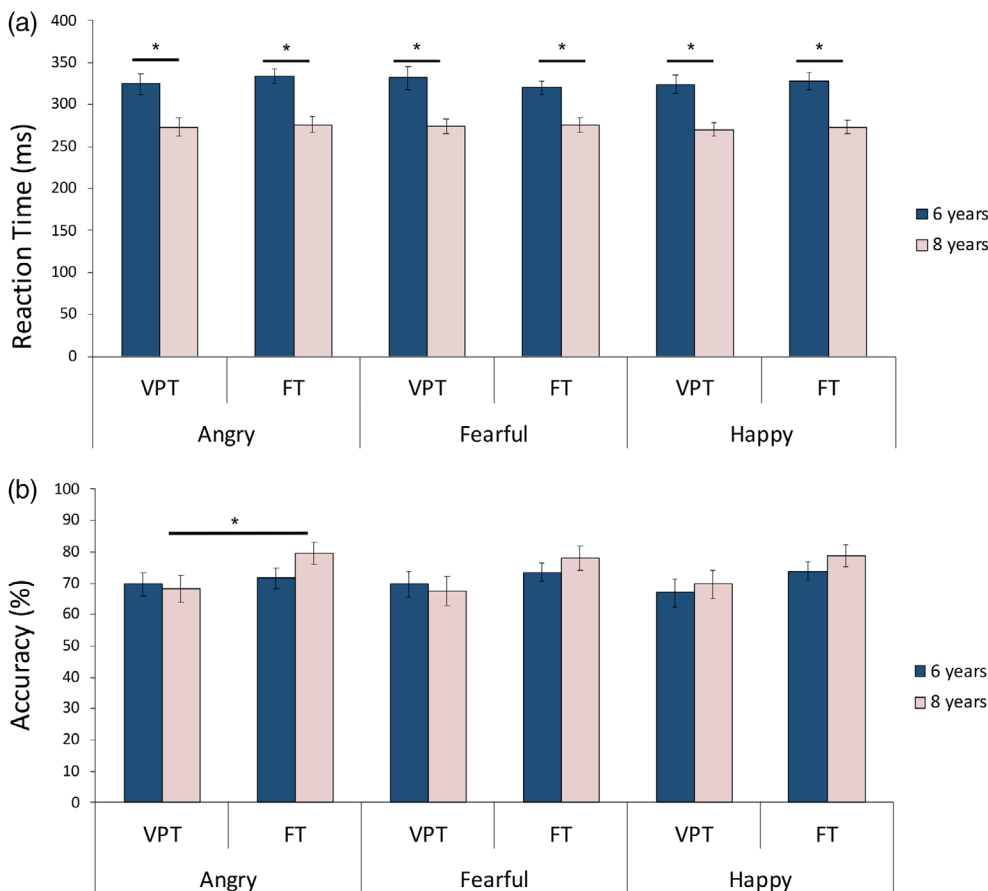
3.4 | Whole brain connectivity

We generally found reduced connectivity in VPT children across all emotions studied apart from one network of increased connectivity at 6 years in response to angry faces (See Table S2–S7 for a full list of all of the nodes). We did not find that $IQ \times Group$ interactions predicted differences in mean node strength in these networks, all $ps > .05$. As described previously, the networks presented are corrected for multiple comparisons in NBS at $p_{FWE} < .05$ and then corrected in R for the number of time windows tested using FDR.

3.4.1 | Angry faces

At 6 years, increased network connectivity in the VPT group was found in beta band (13–29 Hz) from 0 to 250 ms ($p_{FDR} = .01$) in a network with hubs in the right orbital and middle frontal gyri, bilateral superior parietal gyri and the right temporal pole, Figure 5a.

At 8 years, reduced functional connectivity was seen in VPT compared with FT children from 0 to 500 ms in networks across theta (0–250 ms: $p_{FDR} = .0016$, 250–500 ms: $p_{FDR} = .038$), alpha (0–250 ms: $p_{FDR} = .02$), and gamma (35–55 Hz, 0–250 ms: $p_{FDR} = .02$, 250–500 ms: $p_{FDR} = .02$), Figure 5b. In theta, the network in the first time window was right hemisphere dominant, including hubs in the bilateral orbital frontal cortices, right inferior frontal gyrus, bilateral hippocampal gyri,



right amygdala, right fusiform gyrus, right pallidum, right thalamus and left temporal pole. From 250 to 500 ms, reduced connectivity in theta included hubs in frontal regions such as the left middle and inferior frontal gyri, which were connected to a hub in the right inferior temporal gyrus. In alpha (8–12 Hz), we found reduced synchrony in the VPT group, in a right dominant network, including the superior frontal and left middle frontal gyri, anterior cingulate, right precuneus, left temporal pole, and right inferior temporal gyrus.

In gamma, we found reduced phase synchrony in the VPT group in the first time window (0–250 ms) in a network involving the right temporal pole, with an even distribution of connections involving the bilateral orbital frontal, inferior frontal and supramarginal gyri, right inferior occipital gyrus, left posterior cingulate and subcortical hubs. In the second time window (250–500 ms), reduced connectivity was found in a network with frontal-temporal hubs including the medial prefrontal cortex and the right fusiform gyrus and right inferior temporal gyrus.

Fearful faces

At 8 years, decreased functional connectivity in the VPT group was found from 0 to 250 ms in gamma band ($p_{FDR} = .06$, $p_{uncorrected} = .03$). Decreased connectivity from 0 to 250 ms involved a network with hubs in the bilateral orbital frontal gyri, left calcarine, left lingual, right caudate, right putamen, right pallidum, and left inferior temporal gyrus. Other regions also included the bilateral insulae and left amygdala, Figure 6a.

Happy faces

We also found reduced connectivity in VPT compared to FT children at 6 but not 8 years during happy trials from 0 to 250 ms. Reduced connectivity was found ($p_{FDR} = .05$, $p_{uncorrected} = .02$) in theta band and included a number of largely left-lateralized frontal and orbital frontal regions, with connections to subcortical structures, the angular gyri and temporal poles, Figure 6b.

4 | DISCUSSION

Transitioning from preschool to school age is a time of important social development that requires automatic integration of social cues including positive and negative emotions. By 8 years, VPT children show typical neural processing of happy faces but reduced connectivity was found in networks recruited for the two negative emotions: anger and fear. VPT children also had lower accuracy compared to FT children at 8 years on trials where angry faces were presented implicitly. While over-activation in response to negative emotions has been reported in mood disorders (Noll, Mayes, & Rutherford, 2012), reduced connectivity is also maladaptive, since it may index inadequate processing of these emotions which are critical in dangerous or urgent situations, and to understand social transgressions, in the case of processing angry faces.

From 6 to 8 years, both VPT and FT children rated angry and fearful emotions more negatively and happy faces more positively

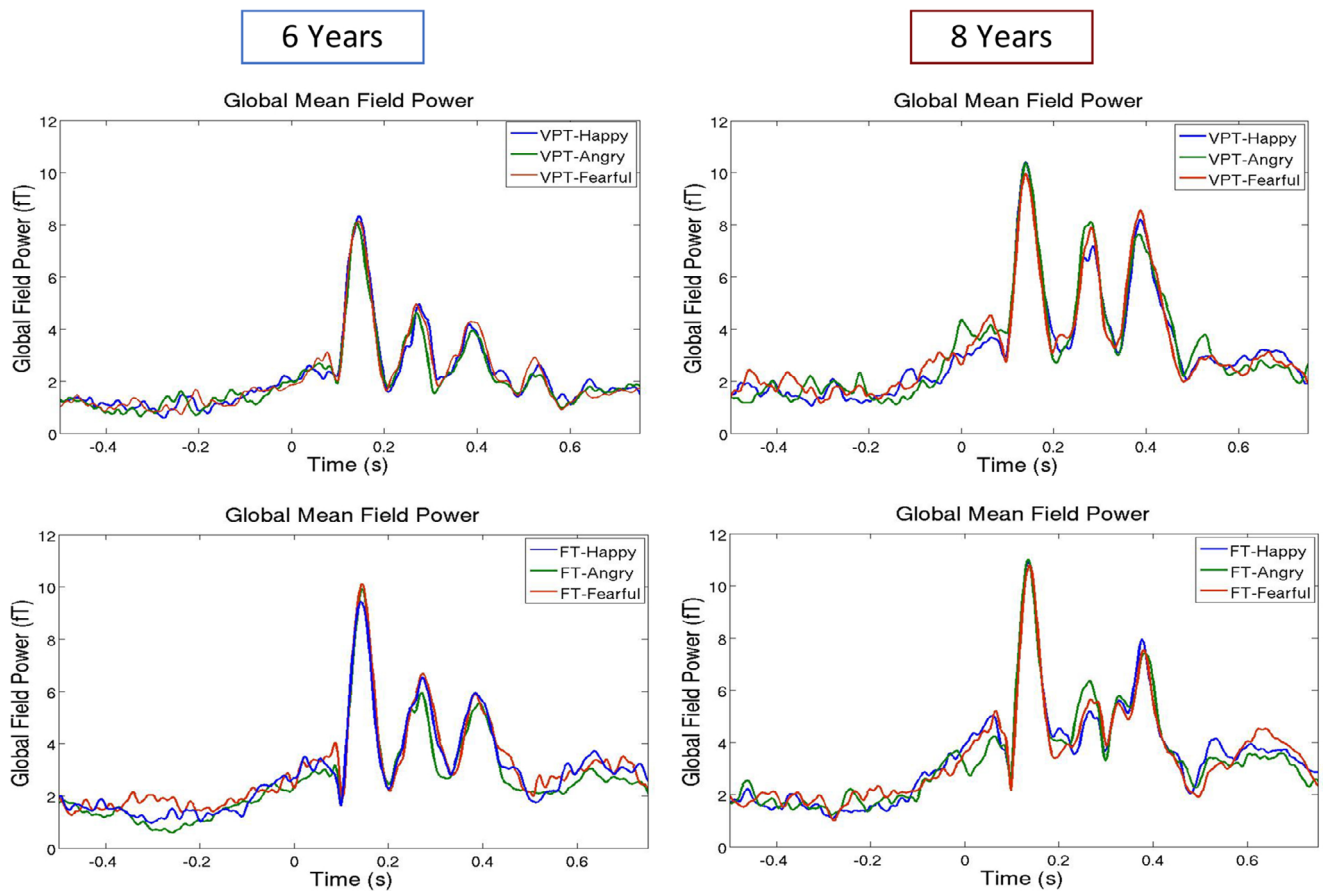


FIGURE 4 Global field power plots for the 6-year-old (left) and 8-year-old (right) children. Both VPT children (top panel) and FT (bottom panel) children show a similar trajectory of mean power over time with three distinct peaks before and after 200 ms and third at 400 ms

with age. However, at 8 years, FT children rated angry faces more negatively compared to VPT children. Task behavioural results also pointed to group differences during angry trials, where 8-year old FT children had significantly higher accuracy compared to VPT children. Response times were not different across group or emotion, and decreased with age. It is not surprising that negative expressions like anger, though processed implicitly, are still more salient with age, a finding corroborated by others (Eastwood, Smilek, & Merikle, 2003) but we extend this by showing that FT children may allocate more attentional resources to processing anger than VPT children.

Global field power plots over time showed a similar pattern of emotional processing for both VPT and FT children. The timing of the peaks replicated what is classically found in neurophysiological studies; peaks at 170–200 ms and a peak at 400 ms (Ashley, Vuilleumier, & Swick, 2004; Batty & Taylor, 2003). Event-related potentials (ERPs) have been linked to distinct stages of face processing, where early peaks (P1 and N170) reflect rapid visual processing sensitive to faces, while later components (e.g., N240) reflect semantic categorization, recognition and storage into memory (Eimer & Holmes, 2002; Maupin, Hayes, Mayes, & Rutherford, 2015; Schweinberger, Pfütze, & Sommer, 1995). Group differences in network connectivity occurred predominantly in the earlier time window, from 0 to 250 ms.

At 8 years, we found reduced connectivity in VPT children to angry faces in theta, alpha and gamma from 0 to 500 ms. In theta band, network hubs included the bilateral orbital frontal cortex, right amygdala, right FG, right thalamus. These results suggest that the core emotional face processing regions in the FT group are part of a theta band network (4–7 Hz), a frequency band associated with longer-range communication in the brain (Von Stein & Sarnthein, 2000). Theta oscillations have also been associated with various cognitive functions including emotional processing, via thalamocortical interaction with the limbic system, sustained attention and working memory. The right lateralization of this network is consistent with negative emotions being preferentially processed in the right hemisphere, suggesting that this lateralization of function is already present in school age children. Reduced theta connectivity has been previously reported in VPT children (Ye, Aucoin-Power, Taylor, & Doesburg, 2015) and other pediatric populations such as ASD (Doesburg, Vidal, & Taylor, 2013); further investigation into the relationship between theta band network connectivity and behaviour in the VPT population is warranted.

In alpha and gamma, network hubs included the frontal regions, anterior cingulate cortex, right precuneus, temporal poles and right FG and cuneus. These regions are implicated in emotion face processing in fMRI, transcranial magnetic stimulation, and lesion

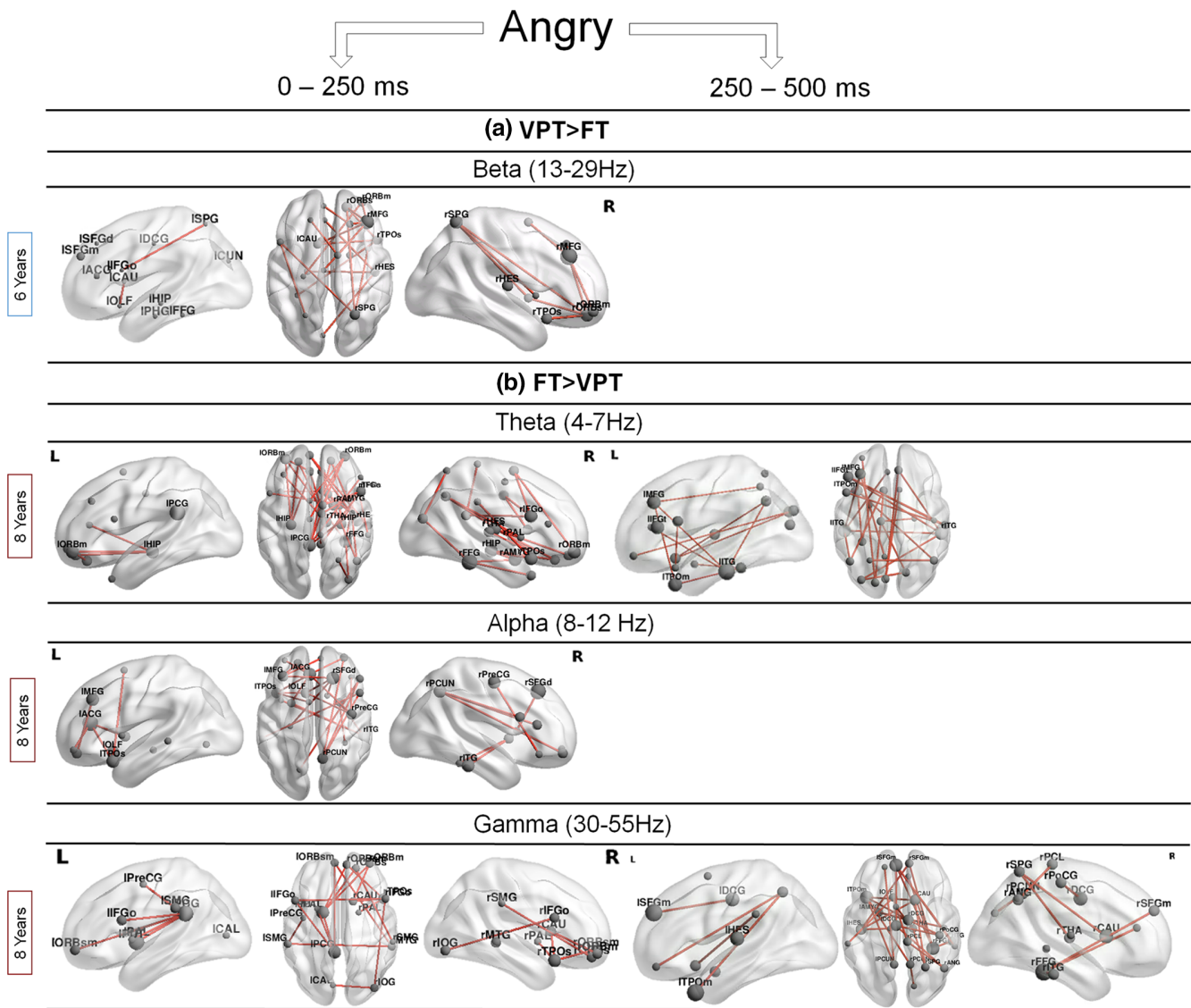
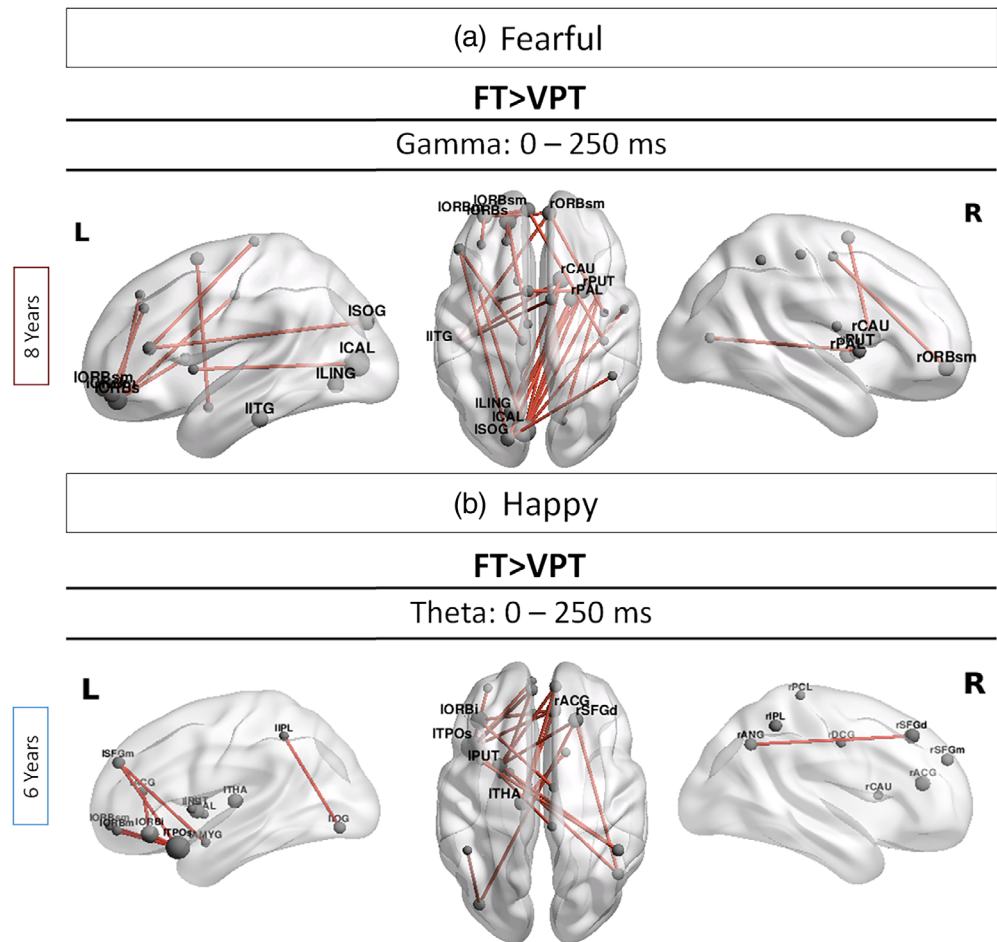


FIGURE 5 Group differences in response to angry faces at 6 and 8 years. Panel (a) Increased network connectivity in VPT compared to FT children in beta band at 6 years from 0 to 250 ms. Panel (b) Reduced network connectivity in VPT compared to FT children across time and frequencies at 8 years

studies (Blair et al., 1999; Harmer et al., 2001; Marinkovic et al., 2000; Nakamura et al., 1999; Schmolck & Squire, 2001). While VPT children had increased connectivity in response to angry faces at 6 years of age, the regions recruited in this network were limited and the network was anchored in the right middle frontal gyrus, a region that is not classically recruited in emotional face processing tasks. This change from increased to reduced connectivity from 6 to 8 years points to a dynamic period of brain network development in VPT children. It is likely that atypical structural architecture and structural connectivity in VPT children also contribute to these changes in functional connectivity. For example, reduced fractional anisotropy in the uncinate fasciculus, a white matter tract that connects the orbital frontal cortex to the temporal poles has been found in school age children born very preterm, aged 7–9 (Lax et al., 2013; Von Der Heide et al., 2013) and delayed development in this white matter tract (Kelly et al., 2016) may lead to the observed

changes in functional connectivity. The relationship between fractional anisotropy in the uncinate fasciculus and emotion processing has not been directly tested in preterm birth. However, this relationship was tested in individuals with ASD where lower fractional anisotropy in the bilateral uncinate fasciculi was related to social and emotion regulation difficulties, but not repetitive behaviours (Samson et al., 2016). The relationship between the structure of the uncinate fasciculus and emotion processing is an important future direction. In the early time window (0–250 ms), a network with hubs involving subcortical structures with connections to orbitofrontal and temporal areas was found in the gamma band. In FT compared with VPT children, fear elicited more automatic subcortical connectivity than hubs in frontal regions. Oscillations in the gamma band are thought to involve local cortical synchrony (Von Stein & Samthein, 2000), which likely support communication between these subcortical structures.

FIGURE 6 (a) Reduced connectivity in VPT compared to FT children to fearful faces in gamma at 8 years. (b) Reduced phase synchrony in theta during happy trials in 6-year-old VPT children



We only found differences between VPT and FT children for happy faces at the 6-year time point in theta band. We found reduced connectivity in the VPT group, between the amygdala and frontal regions (superior frontal gyrus) and between the orbital frontal cortex and the anterior cingulate cortex. Adolphs (2002) proposed that the amygdala and the orbital frontal cortex fine-tune the categorization of facial expressions by allocating attention to a specific facial feature. Here we found reduced connectivity to happy faces between the amygdala and the prefrontal cortex in VPT children, which may affect top-down processes of emotional control. The anterior cingulate cortex has been implicated in assessing the salience of emotional information and emotion regulation (Bush, Luu, & Posner, 2000). By 8 years, there were no differences, suggesting catch up in emotion face processing neural networks but only in response to happy faces.

Our results provide new insight into the neural bases for atypical social cognitive networks supporting emotion face processing in VPT children. These group differences were found in response to happy faces at 6 years and to both fearful and angry faces at 8 years. While FT children allocated neural networks to prioritize emotional faces of peers displaying fearful and angry faces, VPT children did not. This less intense negativity bias in VPT children, along with less negative ratings of the angry faces can have implications in daily life. Reduced awareness to the presence and/or intensity of anger or fear may put VPT children at a disadvantage during social situations. Psychiatric

disorders and especially anxiety disorders are more prevalent in VPT than in typically developing individuals (Johnson & Marlow, 2011, 2014; Johnson & Wolke, 2013; Mathewson et al., 2017) and a recent study of the developmental trajectory of mood and anxiety symptoms in VPT born individuals from 6 to 26 years of age showed that these disorders presented differently over time (Jaekel, Baumann, Bartmann, & Wolke, 2018). At 6 years, there were no group differences between VPT and FT children on anxiety or depression. However, at 8 years, VPT children were more likely to be diagnosed with anxiety disorders compared to FT controls. We speculate that anxiety of social situations may emerge in middle childhood and become exacerbated during adolescence due to difficulties in efficiently and automatically processing negative emotions. Considering our findings of emerging of abnormal processing of negative emotional faces at 8 years in addition to the increase of anxiety disorder diagnosis at this time point, we suggest that an optimal window for intervention is middle childhood rather than later in adolescence or young adulthood.

As we found reduced connectivity in VPT children in both early and later time windows along with differences in behaviour to angry faces, interventions could target both emotion recognition, as well as less automatic processing of emotion such as thinking about others' emotions. Since children with ASD often experience similar difficulties in emotion processing (Ashwin, Chapman, Colle, & Baron-Cohen, 2006;

Uljarevic & Hamilton, 2013), the effectiveness of existing evidence-based interventions should be assessed in the VPT population with some consideration that some of the reported interventions have limited generalizability (see Berggren et al., 2018 for a review of interventions). The "Emotional Trainer" (Silver & Oakes, 2001) is an example of an intervention used in ASD populations that could be implemented in VPT children. This multistep approach to emotional training begins with emotion intensity ratings similar to those used in the current study and eventually trains more advanced processes such as understanding the emotions of others during social scenarios. Given that networks of atypical processing of negative emotions emerged in a group of high functioning (average IQ) VPT born individuals at 8 but not 6 years, our findings highlight the importance of follow-up assessment into school age as these differences are likely to be amplified in adolescence.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Figshare at <https://doi.org/10.6084/m9.figshare.10314302.v1>.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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