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The emergence of top-down, sensory prediction during learning in infancy: A comparison of full-term and preterm infants

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Abstract

Prematurity alters developmental trajectories in preterm infants even in the absence of medical complications. Here, we use fNIRS and learning tasks to probe the nature of the developmental differences between preterm and full-term born infants. Our recent work has found that prematurity disrupts the ability to engage in top-down sensory prediction after learning. We now examine the neural changes during the learning that precede prediction. In full-terms, we found modulation of all cortical regions examined during learning (temporal, frontal, and occipital). By contrast, preterm infants had no evidence of neural changes in the occipital lobe selectively. This is striking as the learning task leads to the emergence of visual prediction. Moreover, the shape of individual infants' occipital lobe trajectories (regardless of prematurity) predicts subsequent visual prediction abilities. These results suggest that modulation of sensory cortices during learning is closely related to the emergence of top-down signals and further indicates that developmental differences in premature infants may be associated with deficits in top-down processing.

Keywords

fNIRS; infant; learning; prediction; premature

1 | INTRODUCTION

Prematurity, or birth before 37 weeks of a 40 week gestation, is emerging as one of the leading causes of neuro-developmental impairment. Advances in medical care have been increasing survival rates of infants born preterm, but the infants who survive exhibit a high rate of cognitive and behavioral problems. Globally, there are 15 million preterm births per year and rising (World Health Organization, 2014) with 400,000 preterm births in the United States alone, a rate of almost one in 10 (March of Dimes). Numerous studies have demonstrated that prematurity is associated with poor developmental outcomes: on average, preterm infants have significantly reduced IQ (Martinussen et al., 2009) and higher rates of learning disabilities (Morse, Zheng, Tang, & Roth, 2009; Orchinik et al., 2011), language

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delays (Gayraud & Kern, 2007; van Noort-van der Spek, Franken, & Weisglas-Kuperus, 2012),¹ and autism (Kuzniewicz et al., 2014; Wong, Huertas-Ceballos, Cowan, & Modi, 2014). With the large number of infants born preterm in the United States and abroad, prematurity constitutes a major public health risk.

While, historically, it was assumed that the poor developmental outcomes for preterm infants arose from medical complications,² even preterm infants without severe medical complications are at-risk. For example, late preterm infants (born 34–36 weeks gestation), who typically do not have severe medical complications, are at-risk for poor developmental outcomes (e.g., Kuzniewicz et al., 2014; Morse et al., 2009; van Noort-van der Spek et al., 2012). Moreover, studies that restrict their preterm population to those without serious medical complications continue to see differences between preterm and full-term infants both behaviorally and neurally (e.g., Mewes et al., 2006; Rose, Jankowski, Feldman, & Van Rossem, 2005; Smyser et al., 2010). Overall, these studies have revealed “effects of prematurity in the absence of detected brain injury” (Hüppi et al., 1996). Thus, the emerging view is that the risk for preterm infants is a combination of injury arising from medical complications as well as disturbances in their maturation or development resulting from having been born before their due date (Buser et al., 2012; Dudink, Kerr, Paterson, & Counsell, 2008; Ment, Hirtz, & Hüppi, 2009; Mento & Bisiacchi, 2012; Volpe, 2009). While it is clear that infants born preterm can exhibit disruptions to their development, the nature of this disruption is unknown.

Advances in neuroimaging technology have provided the means to delve deeper into the investigation of this developmental disruption by allowing exploration of the neural development of those born preterm (Mento & Bisiacchi, 2012; Miller & Ferriero, 2009). These studies have by and large revealed that those born preterm exhibit altered neural developmental trajectories and differing brain-behavior relationships. It has been established that effects of prematurity alter both the structure (Abernethy, Cooke, & Foulder-Hughes, 2004; Martinussen et al., 2009) and the function (Barde, Yeatman, Lee, Glover, & Feldman, 2012; Mullen et al., 2011; Schafer et al., 2009) of the brain and persist into adolescence. While these differences predict deficits in behavior, the neural differences between those born preterm or full-term are present even when participants have IQs and cognitive abilities in the normal range. Notably, Schafer et al. (2009) and Mullen et al. (2011) report altered connectivity, functional and structural respectively, in the brains of those born premature. These studies suggest that those who are born preterm traverse alternative developmental trajectories which likely result in higher risk for poor developmental outcomes.³ Looking much earlier in development, studies on connectivity of infants born preterm have found

In an interesting contrast to the large body of literature demonstrating language delays in preterm infants, work by Pena and colleagues has found that preterm infants have the same early developmental trajectories for speech perceptual as full-term infants. However, this work is intended to explore the question of whether maturational factors or experience support the development of speech perception as preterm infants have more extrauterine experience and not whether preterm infants have disrupted development. Similarly, in the field of visual development, Dobkins, Bosworth, and McCleery (2009) have found that across different aspects of visual development preterm infants either exhibit similar or sped up developmental trajectories (Bosworth & Dobkins, 2009).

Preterm infants often experience serious medical complications such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), which can cause permanent damage to white matter tracts in the brain, and retinopathy of prematurity (ROP), which can result in severe sensory deficits.

Due to the remarkable changes in neonatal medical care and outcome rates, Baron and Rey-Casserly (2010) caution that studies of preterm infants born from prior generations are less likely to accurately predict the outcome for preterm infants born today. However,

reductions in functional connectivity at 40 weeks or term age (Smyser et al., 2010). In other words, by the week that preterm infants should have been born, their brains already differ from infants who remained in utero. Numerous studies have found abnormalities in white and grey matter in preterm infants and have associated these differences with poor developmental outcomes years later (Ball et al., 2012; Beauchamp et al., 2008; Hüppi et al., 1996; Ment et al., 2009; Mewes et al., 2006). Importantly, these studies were restricted to infants without medical complications already associated with poor developmental outcomes and thus isolate the developmental disruptions preterm infants experience independent of brain injury.

Further highlighting potential differences in brain development are findings from Emberson, Boldin, Riccio, Guillet, and Aslin (2017) comparing top-down predictions in infants born full-term versus prematurely. In work examining neural response to violations of learned top-down predictions, they found that premature birth impaired infants' ability to generate top-down predictions but, in a separate behavioral control, prematurity was not found to affect the formation of audiovisual association or the detection of test trials. This indicates a relatively selective impairment of top-down processing associated with learning and suggests that top-down processing plays an important role in development.

While previous work has suggested a potential link between top-down predictive ability and altered brain development observed in preterm infants, what, among infants in general, is the exact role and importance of top-down processing to learning? In fact, learning, the process by which experience changes internal representations, has often been thought of as a bottom-up weighting or encoding process, especially early in development. Specifically, this view proposes that increases in weight are given to the internal representations that have been experienced more frequently. In other words, these stimuli are better encoded through repeated exposure. After exposure, new sensory input that matches frequently encountered input is more easily processed, and sensory input that does not match these frequent experiences triggers a novelty preference.

However, a number of seminal findings from the field of cognitive neuroscience have suggested that the brain can also adjust to experience using top-down or feedback connections. In the theory of predictive coding, for example, perceptual cortices are an interplay of bottom-up or feed-forward sensory signals and top-down or feedback signals which convey the current expectations or predictions about the upcoming sensory input, and it is the match or mismatch of these responses that drives the cortical activity that we observe in neuroimaging experiments (Clark, 2013; Friston, 2005). Specifically, the better the prediction or expectation matches the sensory input, the less cortical activity will be observed in sensory input. The larger the mismatch between expectation and sensory input, the larger the cortical response. In this way, the brain is able to adapt to the structure or statistics in the environment in a top-down fashion through the feeding back of expectations.

we include these studies as they focus on those born preterm without major medical complications and who have IQ in the normal range. While cautious interpretation is needed, we believe these studies reveal something about the developmental differences associated with prematurity and not the medical complications that were more prevalent in earlier cohorts of preterm infants.

While learning has largely been considered as bottom-up in infancy, recent work has suggested that young infants are engaging in top-down modulation during learning as well. This work suggests that learning can indeed involve the interplay of top-down and bottom-up processes starting very early in life. Kouider et al. (2015) found evidence that a recently learned audiovisual association changes early stages of perception processing by 12-months. This is evidenced through changes in the ERP with augmentation of the early perceptual component when the visual event is consistent with the auditory cue. These components occur so soon after stimulus presentation that these changes in perceptual processing must arise from expectations or top-down predictions of that particular visual stimulus following the auditory cue. In a study that was later repeated with preterm infants (discussed briefly above), Emberson, Richards, and Aslin (2015) found that, after a short period of familiarization with a novel audiovisual association, 6-month-old infants were able to generate top-down predictions of their sensory input. These predictions are evidenced by activation of the visual system during the unexpected absence of the visual stimulus after the predictive auditory cue. Importantly, a separate control group confirms that learning the audiovisual association is necessary for activation of the visual system. This control group data suggests that these types of predictions are distinct from violations of expectation but, in general, the overlap of top-down predictions, as recorded neurally, and violations of expectation remains an important topic of future work. These findings suggest that learning produces top-down differences in processing starting early in infancy and after very little exposure. However, it is unknown when these top-down predictions come online during the learning process and whether the emergence of these top-down predictions are part of the neural changes seen over the time-course of learning.

Building from these existence proofs that young infants can generate top-down predictions, the central question for this paper is do these top-down predictions or processes shape learning in the developing brain? In the learning sciences, prediction has long been believed to be integral to learning (e.g., prediction errors support reinforcement learning, McClure, Berns, & Montague, 2003; Rescorla & Wagner, 1972), and, in developmental science, there is an increasing focus on top-down prediction as a key part of the “engine of change” in cognitive development (McClelland, 2002). However, despite both behavioral and neural findings that infants can generate prediction, there is no direct evidence that prediction supports learning early in development. Here, we tackle this question of whether predictions are shaping learning by examining the relationship between the emergence of top-down predictions and neural, learning trajectories.

Recent findings in the field of developmental cognitive neuroscience have started to characterize the neural signatures of learning and memory in young infants and move away from looking at outcome measures (e.g., novelty responses). While a number of studies have documented novelty responses after learning (i.e., increases for novel or unfamiliar stimuli after familiarization, e.g., Benavides-Varela et al., 2011; Gervain, Macagno, Cogoi, Pena, & Mehler, 2008; Nakano, Watanabe, Homae, & Taga, 2009), it is difficult to use offline novelty responses to gain direct information about the processes that support learning online (Karuza, Emberson, & Aslin, 2014). Specifically, while outcome measures or offline responses are clearly related to learning, they emerge after learning takes place, by definition and likely involve a large number of other cognitive processes such as memory retrieval. For

these reasons, looking at outcome measures reveals more about what is learned and are more limited in revealing how learning takes place to begin with. Instead, focus on neural changes during learning, or neural learning trajectories, is needed to learn about online processes supporting learning.

Broadly, examinations of learning trajectories in infants have suggested that neural responses in the infant brain follow the foundational Hunter and Ames (1988) model of infant looking times during habituation. Hunter and Ames proposed that, at early stages of learning, infants exhibit familiarity preferences and then, as learning or encoding proceeds, infants exhibit novelty preferences. An implication of this model is that with greater difficulty of learning, infants will tend toward familiarity preferences and, with greater ease of learning, infants will tend towards novelty preferences. Translating looking preferences to patterns of neural activation, the model would propose greater neural activation for familiar sequences early in learning and then an attenuation of this response with an increased response to novelty as learning increases. At large, findings of neural changes during learning support this view. While a number of studies have found no changes in the magnitude of neural activation during learning (e.g., Benavides-Varela et al., 2011), Nakano et al. (2009) found decreases in neural activation (i.e., repetition suppression) with repeated exposure to a single, auditory stimulus followed by a novelty response at test. There is also evidence that the degree of learning difficulty affects the direction of neural change: Gervain et al. (2008) examined auditory rule learning in neonates with two levels of difficulty, very difficult and extremely difficult, and examined neural responses over exposure. They found evidence of repetition enhancement for the very difficult rule and no change in activation during the extremely difficult rule in the temporal-frontal regions of the infant brain. Following this work, Bouchon, Nazzi, and Gervain (2015) examined more simple versions of these rules and found repetition suppression for one of the rules (now the more difficult of the two) and no change for the other. While these studies do not quantify the difficulty of learning these rules for neonates, the findings do broadly suggest that, with greater difficulty, infants exhibit increases in neural activation for the familiar with learning and, with less difficulty, infants exhibit decreases in neural activation for the familiar. Finally, Kersey and Emberson (2016) examined the neural trajectories during audiovisual learning and found that infants exhibited an increase in neural activation followed by a decrease over the course of learning (i.e., repetition enhancement followed by repetition suppression). This particular non-linear trajectory closely parallels the Hunter and Ames model where familiar stimuli are preferred, reflected in increases in neural activity for these stimuli, and then dispreferred, reflected in decreases in neural activity for these stimuli.

While investigations of neural activity during learning (i.e., the neural learning trajectories) reveal more information about how learning shapes the infant brain, it is unknown why and how these trajectories of neural activation occur. The Hunter and Ames model is descriptive and provides a clear frame-work with which to integrate these findings, but it does not provide a mechanistic explanation about why these neural changes occur during learning. Here, we investigate whether the emergence of top-down predictions shapes these neural learning trajectories. To this end, we compared neural learning trajectories between preterm and full-term infants. Specifically, since Emberson, Boldin, et al. (2017) established that premature infants are unable to generate top-down predictions after learning, examining

learning trajectories in this population provides an opportunity to investigate how top-down predictions shape the neural changes observed during learning. Crucially, Emberson, Boldin, et al. (2017) established that the basic ability to form the audiovisual association is intact in our cohort of premature infants so any differences are attributable to the differences the top-down predictions that are impaired in this population.

There is already some evidence that the emergence of top-down predictions are playing some role in neural learning trajectories. Kersey and Emberson (2016) found that full-term infants exhibit an inverted u-shaped learning trajectory (i.e., repetition enhancement followed by repetition suppression) during the audiovisual learning that supports the generation of top-down predictions. In exploratory analyses, Kersey and Emberson (2016) found that the shape of an individual infant's learning trajectory can predict an infant's individual top-down prediction abilities (i.e., their occipital lobe response during an unexpected visual omission). In other words, how much an infant's occipital lobe was modulated during learning, in this inverted u-shaped pattern, predicted how strongly an infant responded during unexpected omission trials which are designed to probe their top-down predictions. These findings suggest that neural learning trajectories are linked to top-down predictions.

Based on these findings, we hypothesized that premature infants, who exhibit deficits in top-down predictions, would exhibit robust alterations in the neural learning trajectories. Since it has been established that prematurity disrupts the emergence of top-down predictions after learning, if the emergence of top-down predictions shapes neural changes during learning, then we will observe disrupted neural learning trajectories in premature infants as well. This would provide convergent and more direct evidence that the emergence of top-down predictions contributes to neural learning trajectories. It is possible that differences in neural learning trajectories would be specific to the occipital lobe, as the task is designed to induce visual predictions (i.e., the auditory cue preceded and predicted the visual event) or it is possible that differences in neural learning trajectories would be observed more broadly in those born prematurely. To this end, we analyze the learning trajectories of a cohort of 100 infants (50 born prematurely) while they learn the audiovisual associations and characterize the neural changes they experience while they are learning. We are looking to uncover the same inverted u-shaped neural changes that were observed in Kersey and Emberson (2016) for this type of learning and contrast these trajectories across the two populations of infants. In addition to contrasting trajectories, we conduct an individual differences analysis (as in Kersey & Emberson, 2016) to investigate how variations in an infant's ability to generate top-down prediction relates to their individual learning trajectories. We expect to find a positive correspondence between the emergence of top-down predictions and the strength of U-shape neural trajectories during learning. Overall, this investigation allows the first direct test whether the neural capacities to predict are related to online learning trajectories.

2 | METHODS

2.1 | Participants

As in Emberson, Boldin, et al. (2017), fifty full-term infants (birth at 36 weeks gestation or later, as defined in database) were recruited from the database of interested families for the Rochester Baby Lab. Full-term infants had no major health problems or surgeries and had

normal vision and hearing. They participated in the study between 5 and 7 months of age. The first twenty-six of these infants are the same infants reported in Emberson et al. (2015). All fifty preterm infants were recruited from the University of Rochester Medical Center Neonatal Intensive Care Unit (NICU). In order to isolate the effects of prematurity and avoid effects related to other medically-based risk factors on neural and cognitive development, a number of strict exclusionary criteria were applied to the preterm population. Infants were excluded from the study if they met any of the following criteria: intraventricular hemorrhage (IVH, grade 3 or 4), periventricular leukomalacia, severe bronchopulmonary dysplasia (i.e., infants who required supplementary oxygen after discharge), major surgeries, seizures, failing hearing screening, chromosomal abnormalities, major malformations, congenital viral infections, retinopathy of prematurity requiring intervention, or weight and head circumference less than the 10th or greater than the 90th percentiles at birth. Preterm infants had gestational ages ranging from 23 to 32 weeks (mean = 30.01 weeks, median = 38.86 weeks), but only nine infants (21%) were born at less than 28 weeks gestation. Additionally, only one included infant had a gestational age <24 weeks (GA = 23 and 1 day), and this infant met all health-related criteria described above. This means that the majority of included infants were very, but not extremely premature. Preterm infants participated in the study when they were 5–7 months corrected gestational age.

Of the 100 overall infants recruited for the study, 20 were excluded (6 preterm, 14 full-term) from analysis. As each infant exhibited different levels of interest in the experiment, the experiment was ended when the subject became fussy or noncompliant. This meant that some recruited infants (1 preterm infant and 3 full-term infants) did not sit through enough trials to be included in the final analysis, a minimum of 4 complete learning blocks (described in detail below) and 2 of each single trial (4 single trials total). An additional 5 preterm infants and 10 full-term infants were excluded for poor signal quality. One full-term infant was excluded for too many missing channels (>50% of the channels in any of the three ROIs). One preterm infant was excluded after it was found that they failed to meet initial exclusionary criteria (head size <10th percentile). Overall, 79 infants were included in the final sample for the study (36 full-term and 43 preterm). Testing for racial ($\chi^2(8, N = 79) = 11.73, p = 0.164$) and sex ($\chi^2(1, N = 79) = 0.11, p = 0.742$) differences between the preterm and full-term infants yielded no significant population distinctions. Overall, there were 62 white, 5 black, 10 other, and two unreported infants with four reported as Hispanic and 75 as non-Hispanic. There were 39 female (20 preterm, 19 full-term) and 40 male (23 preterm, 17 full-term) infants.

2.2 | Stimuli and experimental design

Auditory and visual stimuli were presented while the monitor displayed a monochromatic gray screen with a white box (black bordered) in the middle. Auditory stimuli were novel, non-speech sounds that included an unusual rattle sound and a honk like that of a clown horn. The visual stimulus was a red cartoon smiley face that entered the white box from either the top or bottom of the box. Each of the two sounds was consistently and uniquely paired with one direction of movement for the visual stimulus and this pairing was counterbalanced across infants. After entering the box, the stimulus moved into the box to touch the opposite side in 500 ms and then exited the box from the same side it had entered

in 500 ms. The total duration of the visual stimulus presentation was 1 s, which was the same as the length of the auditory stimuli. This audiovisual sequence was repeated six times to form a block of audiovisual stimuli. These blocks had three of each of the two types of audiovisual pairing presented in random order and separated by a jittered ISI (1–1.5 s). As these blocks form the basis of audiovisual learning, they will be referred to as learning blocks throughout the paper. In addition to learning blocks, infants also viewed individual trials. In each individual trial, one of the two auditory stimuli was presented. In half of these trials, the corresponding visual stimulus appeared 750 ms after the onset of the auditory stimulus (consistent with the audiovisual events contained in the learning blocks). The other half of trials were unexpected visual omissions designed to reveal top-down sensory predictions: the visual stimulus did not appear and infants instead saw only the presentation of the white square. After the initial presentation of three learning blocks, blocks and single trials were presented in “chunks” that included one learning block, two single audiovisual trials, and two single visual omission trials. The order of the presentation of the block and single trials within each chunk was randomized and each event was separated by baseline stimuli (dimmed fireworks video, Watanabe, Homae, Nakano, & Taga, 2008, and instrumental version of “Campdown Races,” Baby Music 2010) that lasted from 4 to 9 s. Figure 1 details the experimental procedure. The main analyses here focus on neural activity across the learning blocks. Each infant viewed a different number of learning blocks, depending on how long they maintained interest in the experiment. Included infants saw at least five learning blocks and at most eight. The single trials, not used in the primary analyses of this paper, are analyzed fully in Emberson, Boldin, et al. (2017).

The experiment was conducted in a darkened room with floor-to-ceiling curtains surrounding the infant and their caregiver such that only the monitor was visible to the infant. Infants sat on their caregiver’s laps, facing the screen. Caregivers were instructed not to interfere with the infant’s watching the video but to prevent them from grabbing the cap on their head or in any way moving the cap. Caregivers were also asked to keep the infants still as possible, but to allow them to stand or move in order to keep them contentedly watching the video. Stimuli were presented on a Tobii 1750 eye tracker, screen measuring 33.7 by 27 cm and computer speakers placed directly below the screen but behind the black curtain. Sounds were presented between 64 and 67 dB using MATLAB for Mac (R2007b) and Psychtoolbox (3.0.8 Beta, SVN revision 1245).

2.3 | FNIRS recordings

FNIRS recordings were conducted using a Hitachi ETG-4000 with a total of twenty-four channels: 12 over the back of the head to record bilaterally from the occipital lobe, and 12 over the left side of the head to record from the left temporal lobe and prefrontal cortex. Channels were organized into two 3×3 arrays, and the cap was placed so that, for the lateral array, the central optode on the most ventral row was centered over the left ear and, for the rear array, the central optode on the most ventral row was centered between the ears and over the inion. The cap positioning was selected based on which NIRS channels were most likely to record from the occipital and temporal cortices in infants (Fillmore, Richards, Phillips-Meek, Cryer, & Stevens, 2015). Because of the curvature of the infant head, a number of channels (the most dorsal channels for each pad) did not provide consistently

good optical contact across all infants. Thus, we only considered a subset of the channels (seven on the lateral pad over the ear and five on the pad at the rear array) in subsequent analyses, excluding those with inconsistent optical contact. Locations of each channel were determined using a strict MRI coregistration procedure. Only the channels that provided consistently good optical contact across infants and had the highest proportion of localization to each of the three relevant neuroanatomical regions were included in analysis and each infant contributed all included channels in each ROI. In total, five channels were localized to the temporal lobe, three to the occipital lobe, and two to the frontal lobe (see Figure 2). fNIRS recordings were collected at 10 Hz (every 100 ms). Using a serial port, marks were presented from MATLAB on the stimulus presentation computer to the Hitachi ETG-4000 using standard methods. Marks were sent for the start and end of each presentation type for the given experiment.

2.4 | Data analysis

The raw data were exported from the Hitachi ETG-4000 to MATLAB (version R2015a for Mac) and were subsequently analyzed with HomER 2 (Hemodynamic Evoked Response NIRS data analysis GUI, version 1.5) using the default preprocessing pipeline of the NIRS data. First, raw intensity data were converted to optical density. Next, motion artifacts were identified and removed using a PCA filter and other techniques. Finally, the data was low-pass filtered (3 Hz cutoff frequency) to remove noise and the modified Beer-Lambert Law was used to determine levels of hemoglobin concentration for each channel (all subsequent analyses used the oxyHb values outputted by HomER). The HomER 1 users guide contains a more detailed description and further information (Huppert, Diamond, Franceschini, & Boas, 2009). Timing information (mark identity and time received by the ETG-4000 relative to the fNIRS recordings) was also extracted from the ETG-4000 data using custom scripts run in MATLAB R2015a.

Subsequent analyses were conducted in MATLAB (R2015a) with custom analysis scripts. First, the continuous data was segmented and sorted into individual trial types based on the timing of marks. Because the experiment was stopped when the infant became inattentive, trials at the end of the experiment that were not presented past the mean duration of the baseline (duration of stimulus presentation + 6.5 s) were excluded. The number of complete trials was determined for each trial type and it was evaluated whether the infant met the inclusion criteria of watching a minimum of two single trials of both types (e.g., two audiovisual trials and two visual omission trials, see Participants for the number of infants excluded for insufficient number of trials watched). Additionally, infants who watched fewer than four block trials were excluded. This minimum is consistent with previous work done by Emberson, Cannon, Palmeri, Richards, and Aslin (2017) (Kersey & Emberson, 2016) as well as with other groups of researchers (e.g., Lloyd-Fox, Széplaki-Köll d, Yin, & Csibra, 2015). Full-term infants included in analysis looked on average for 6.34 block trials (SD = 0.97, range = 5–8) while preterm infants looked on average for 6.63 blocks (SD = 0.93, range = 5–8). As response levels to single trial events are not analyzed in detail here, see Emberson, Boldin et al. (2017) for information on the average number of single trials (both audiovisual and visual omission) watched by included infants.

Next, for each infant, the average concentration of oxygenated and deoxygenated hemoglobin per channel was determined for each condition. In this paper, we focus on average activation during the learning blocks. If the data collected was still noisy at this point (determined through a combination of visual inspection, experimental notes on optical contact and the presence of hair, and output from the `otparex.m` script, which provided a measure of the number of “bad” channels) infants were excluded. Critically, the decision to include or exclude infants was made before group averages were determined and was not revisited, thus minimizing experimenter bias. Next, the mean and variance of responses for oxygenated hemoglobin were determined within each ROI for each infant. An analysis time window of 26 s (5 s after stimulus onset to 31 s after stimulus onset) was used for all learning blocks. This window was defined to start with the initial stimulus presentation (adjusted to account for delay in hemodynamic response) and continue into the jittered ISI to capture the hemodynamic response to the learning block. Subsequent analyses on the mean hemodynamic responses were conducted in RStudio (version 0.99.484, R version 3.2.2) using the `lme4` (Bates, Maechler, Bolker, & Walker, 2015) and `Imertest` (Kuznetsova, Brockhoff, & Christensen, 2016) packages.

2.5 | Statistical analyses

We calculated the average magnitude of the hemodynamic response for each infant during each learning block and used mixed effects modeling to uncover the overall patterns in response over the course of these blocks (i.e., the time-course of learning). We conducted this analysis separately for three neuroanatomically defined regions of interest (ROIs): the temporal, frontal and occipital cortices. Here, we briefly outline the general analysis approach. We first modeled the response data from the full-term and preterm infants separately. For each group, we performed our analysis in three steps. First, we fit a linear model to the data to examine overall linear trends. Next, we fit a model that included both a linear and square term in order to examine any non-linear (quadratic) fits. Finally, we evaluated the difference between these models to determine whether a non-linear, inverted u-shaped fit was superior to a linear fit (as previously reported in Kersey and Emberson [2016]). After examining each group separately, we used the same methods to model both the preterm and full-term infants. In the combined analysis, we included effects related to birth status (premature or full-term) to examine the role that prematurity plays in the formation of these learning trajectories. Finally, we employed a method of analysis initially reported in Kersey and Emberson (2016) to examine the relationship between individual infant’s learning trajectories and infants’ signature of top-down prediction (occipital responses to unexpected visual omission trials). Because each infant watched a different number of trials, we recognize the possibility that some of the results of the analyses described may be affected by these differences. To account for this, we performed all analyses using proportion of blocks completed (in addition to these analyses using absolute block number). These results are reported in the supplementary materials.

3 | RESULTS

First, we show that full-term infants exhibit significant non-linear (inverted u-shaped) changes in neural activity over learning (Figure 3a). To start, we fit linear models to the full-

term neural response in each of the three ROIs. These models showed that the temporal and frontal ROIs exhibit significant linear increases in activation over the course of learning (temporal: $t(26.78) = 2.89, p = 0.008$; frontal: $t(27.18) = 3.45, p = 0.002$). The occipital ROI showed only a marginal linear increase in activation in this model ($t(26.99) = 1.81, p = 0.082$). Next, we added a square term to each model to examine non-linear neural changes during learning. In all ROIs, we see a significant linear increase in activation over the course of learning ($ts > 5.39, ps < 0.001$) as well as a significant square term ($ts < -5.29, ps < 0.001$). Full report of these statistics are shown in Table 1. The negative sign of the square terms confirmed that we find an inverted u-shaped pattern of activation across learning blocks. Model comparisons show that each of the three non-linear models explain significantly more of the variance in response levels than the linear only models ($\chi^2s > 25.77, ps < 0.001$, also summarized in Table 3, rows 1,2, and 3). These results confirm and extend previous findings from Kersey and Emberson (2016) that audiovisual learning in infancy is associated with non-linear, inverted u-shaped learning trajectories.

Next, we applied the same analytical approach to the learning trajectories of preterm infants. We find that patterns of activation in the occipital ROI deviate from the patterns exhibited in the other ROIs and all ROIs in the full-terms (Figure 3b). In the linear only model, there is no significant pattern of activation in the occipital ROI among the preterm infants ($t(43.64) = 1.13, p = 0.264$). This is in contrast to the other two ROIs, both of which show significant linear increases in activation over the course of learning ($ts > 2.38, ps < 0.023$). In the non-linear models (i.e., a squared term is added to each model), preterm infants exhibited the same pattern of activation in the temporal and frontal ROIs (linear term: $ts > 6.45, ps < 0.001$; square term: $ts < -5.45, ps < 0.001$). In contrast, the occipital ROI showed no significant patterns in response over the course of learning (linear term: $t(266.55) = 0.64, p = 0.526$; square term: $t(249.48) = -0.15, p = 0.878$). Full report of these statistics are shown in Table 2. Comparing the linear and non-linear models shows that the non-linear models are a significant improvement over the linear models in the temporal and frontal ROIs (Table 3, rows 5 and 6). In the occipital region, however, the addition of the non-linear term does not significantly improve the model (Table 3, row 5). This is expected as both the linear and non-linear occipital models show no significant patterns. These results provide strong evidence of differences in neural changes during learning between full-term and preterm infants and suggests that these differences are not found broadly but, for the three cortical regions investigated here, are specific to the occipital lobe.

To directly compare learning trajectories between preterm and full-term infants, we combined preterm and full-term infants into a single model. In these models, we included a linear and square term, as with the previous individual models, as well as a main effect of birth status (preterm or full-term) and interaction terms between birth status and the linear term and between birth status and the non-linear term. To provide further evidence of a distinction between preterm and full-term audiovisual response we used model comparisons to test if the models were significantly improved by the inclusion of the birth status related terms (main effect and interactions). Figure 3c overlays fits to response in each of the individual populations, enabling direct visual comparison between the two groups.

In the temporal ROI model, as in each individual group, there was a significant linear term ($t(437) = 9.84, p < 0.001$) and a significant square term ($t(408.13) = -9.43, p < 0.001$). However, there was no main effect of prematurity ($t(164.24) = 1.19, p = 0.235$) and no interaction between prematurity and the linear term ($t(434.94) = -1.67, p = 0.095$) or the square term ($t(404.1) = 1.73, p = 0.085$). Model comparisons showed no significant differences between this model and its counterpart that did not include any effects related to birth status ($\chi^2 = 3.08, p = 0.380$) indicating that preterm and full-term infants are responding similarly in this ROI. Similarly, in the frontal ROI model, there was also a significant linear term ($t(452.11) = 7.68, p < 0.001$) and a significant square term ($t(435.12) = -6.91, p < 0.001$) but no significant main effect of prematurity ($t(189) = 1.24, p = 0.218$). There were also no significant interactions between prematurity and either the linear ($t(450.45) = -1.57, p = 0.117$) or the square ($t(431.69) = 1.85, p = 0.065$) terms. Again, model comparisons revealed no significant difference between the two model types in the frontal lobe ($\chi^2 = 4.95, p = 0.176$), indicating again that the addition of birth status does not significantly improve the model.

The occipital ROI shows markedly different patterns across groups. There were significant interactions between prematurity and the linear term ($t(441.27) = -3.91, p < 0.001$) as well as between prematurity and the square term ($t(413.95) = 4.09, p < 0.001$). These significant interaction terms indicate that the preterm infants show a distinct trajectory of activation in the occipital lobe compared to full-term infants (see second panel, Figure 3c). However, there was no main effect of prematurity ($t(146.34) = 1.93, p = 0.055$). Like the other two ROIs, there was a significant linear term ($t(444.71) = 5.72, p < 0.001$) and a significant square term ($t(420.06) = -5.45, p < 0.001$).⁴ These group differences are further supported by the model comparison which indicates that the inclusion of factors related to prematurity improved the model ($\chi^2 = 25.24, p < 0.001$).

The effects of prematurity on learning trajectories in the occipital lobe are particularly interesting in the context of previous results showing that preterm infants show significantly reduced occipital lobe response during trials that probe top-down visual prediction (unexpected visual omissions). Finally, we more directly probed the relationship between these neural trajectories during learning and top-down prediction. In exploratory analyses, previous work found that infants who have learned the audiovisual associations presented in the learning blocks exhibit stronger signatures of top-down prediction (i.e., occipital responses to unexpected visual omissions Kersey and Emberson [2016]). Following these exact methods, we examined whether the learning trajectories that were modeled above would predict response to the visual omissions in any ROI. Visual omission response was calculated by averaging overall response data within a 5–9 s time window after stimulus onset, followed by averaging over the total number of visual omission trials. This process was performed for each of the three ROIs. We used the coefficients for linear and square terms in each infant's learning model (described above) to index the shape of individual

Note that the degrees of freedom of the statistics vary greatly between the different models reported here. This variation is largely due to different numbers of subject being included in a given model (e.g., preterms, full-terms or both groups combined) as well as the types of models or estimator being predicted. Additionally, the same model and the same dataset can give rise to slightly different degrees of freedom because an estimating procedure is employed (using R packages lme4 and lmerTest Bates et al., 2015; Kuznetsova et al., 2016) to determine the degrees of freedom of these mixed effects models.

infants' learning trajectories. We then used a multiple regression to determine if these terms could predict the visual omission response. We included all infants (preterm and full-term) in this analysis with no factors related to prematurity. This result confirms that, considering both preterm and full-term infants, the shape of an infant's learning trajectory in the occipital ROI significantly predicts visual omission response in the occipital lobe ($F(2, 75) = 10.71$, $p < 0.001$, $R^2 = 0.20$, Table 4, rows 1 and 2 shows more statistics for this model).

Additionally and inconsistent with Kersey and Emberson (2016), we also found that learning trajectories in both the temporal ($F(2, 74) = 8.70$, $p < 0.001$, $R^2 = 0.17$ and Table 4, rows 3 and 4) and frontal ($F(2, 75) = 4.22$, $p = 0.018$, $R^2 = 0.08$ and Table 4, rows 5 and 6). ROIs significantly predicted occipital lobe omission response. Given that there is no difference in learning trajectories across birth status in the temporal or frontal lobes and the relationship between learning trajectories and visual omission response was exclusive to the occipital lobe in Kersey and Emberson (2016), we hypothesized that there might be more subtle relationships between learning in the temporal and frontal lobes and the visual omission response. If these effects are weaker than in the occipital lobe, this would explain both why these differences are not revealed at the group level (e.g., when mixed effects for subject are included in the model) and why they were not found with a much smaller sample size Kersey and Emberson (2016). To this end, we compared the goodness of fit of these models (R^2 or the amount of variance explained). We see that the occipital model has the highest R^2 value (0.22). The frontal model has a comparatively low R^2 value (0.10) and the temporal model has an R^2 value that is slightly reduced from the occipital model (0.19). This pattern is matched by another measure of goodness of fit, the coefficients of the square terms (see Figure S2, which is included in the supplementary materials). These patterns indicate that while all models are significant overall, the model relating occipital learning trajectories to occipital omission response is a better predictor than the models predicting the occipital omission response from either temporal or frontal learning trajectories. This analysis is repeated using visual present trials in the supplementary materials (Ludlow & Klein, 2014).

It is important to note that the observed differences between the populations (full-term and preterm) in the occipital ROI, as compared to the other two ROIs, may be modulated by a general difference in activation between these three regions. Indeed, looking at the average-time course through a single learning block does reveal qualitative differences in patterns of activation between the ROIs. However, it is also clear from these plots that there are stronger differences in pattern between the full-term and preterm infants in the occipital ROI (Figure S3) than in either of the other two regions (Figures S4 and S5). This suggests that, while there may be differences in learning in general between the occipital lobe and other regions of the brain, there is evidence of differences between the populations beyond this general, regional distinction.

4 | DISCUSSION

This study is the first to investigate the relationship between neural changes during learning and the top-down prediction signals enabled by learning. To this end, we compared learning trajectories in two groups of infants: typically developing full-term infants and infants at-risk for developmental impairment due to premature birth. Importantly, previous work has found

that premature birth gives rise to impairments in top-down prediction abilities (Emberson, Boldin, et al., 2017). Here, we asked whether these differences in the ability to generate top-down predictions also have an impact on the online learning trajectories that the infant brain experiences. By comparing learning trajectories across these groups, we find that the nature and degree of modulation of the infant brain activity during learning is closely related to the emergence of top-down prediction.

Specifically, we examined neural changes while infants learned that an auditory event predicts a visual event. Extending Kersey and Emberson (2016), we find that learning in full-term infants is characterized by robust inverted u-shaped patterns of activation in three regions of the brain (temporal, occipital, and frontal). In all of these regions, we find a highly significant fit of a non-linear model to the neural data indicating no substantial differences between the ROIs. However, direct comparisons between the ROIs were not conducted for three reasons: 1) we have no specific hypotheses for differences in learning across these regions; 2) regions of the brain differ in their skull thickness and space available for fNIRS recordings; 3) our focus is on a comparison within regions and across groups. Indeed, the group comparison revealed both striking similarities and differences between full-term and preterm infants. Overall, this inverted u-shaped pattern is closely matched in the temporal and frontal lobes of the preterm infants, but neural activation in the occipital lobe is strikingly different. Here, we see no significant changes in activation during learning over the course of the experiment. In other words, activity in the visual system is not modulated during learning in those born prematurely while they are given the opportunity to learn to predict a visual event. Moreover, in models including infants in both groups, we find that neural changes during learning significantly interact with prematurity. Again, these interactions are not found in the other ROIs. The specificity of this difference to the visual system is notable because the learning task is designed to induce visual prediction. Overall, the results present a tight link between neural changes observed during learning and top-down signals.

Importantly, these differences in occipital learning trajectories are directly related to the signatures of top-down prediction that have been found to differ in those born prematurely.

Previous work has shown that full-term infants exhibit evidence of visual prediction as a result of this learning (i.e., occipital response during unexpected visual omission trials Emberson et al., 2015) while preterm infants show deficits in these visual prediction abilities after being given the same learning opportunities (Emberson, Boldin, et al., 2017). Following analysis techniques established in Kersey and Emberson (2016), we used linear modeling to determine whether the shape of the learning trajectory of an individual infant would predict their individual visual prediction abilities (indexed through their level of neural response to an unexpected visual omission event). The linking hypothesis here is that the shape of the learning trajectory arises from the emergence of top-down predictions and thus, this shape will be predictive of the level of response to a violation to these learned associations. Specifically, because we observe that differences in learning trajectories are specific to the occipital lobe, these predictive relationships may also be specific to the occipital lobe, as was found in Kersey and Emberson (2016). We do find that the shape of the learning trajectory in the occipital lobe significantly predicts occipital response to

unexpected visual omission trials. This result provides an additional, convergent link between the neural changes that co-occur with learning and the emergence of prediction from learning.

While the majority of our results demonstrate specificity in this link between learning and top-down prediction in the occipital lobe, we also find that individual learning trajectories in the temporal and frontal regions significantly predict occipital omission response. This is a surprising result considering that there are no differences in learning trajectories across groups. A comparison of two different measures of model fit revealed that while all of these relationships are significant, they are strongest for the occipital lobe. Thus, while our main analyses indicate that overall there are distinctions between groups only in the occipital region, there may be differences in learning trajectories that relate to the emergence of top-down prediction between individual subjects, possibly regardless of birth status, that allow for these predictions even in the temporal and frontal ROIs.

One important area for future investigation is the nature of the deficits in learning and top-down signals in the occipital lobe. For example, is the lack of modulation in the occipital lobe during learning because visual information is being predicted and prediction is impaired in prematurity, or are the deficits in top-down prediction specific to the occipital lobe and the intact learning dynamics in the temporal and frontal lobes evidence that learning is exerting a top-down influence on these regions? The current data is unable to disentangle these two possibilities, and it is an important topic for future investigation. Moreover, it is also beyond the scope of the current study to uncover which regions of the infant brain are initiating these feedback signals, den Ouden, Friston, Daw, McIntosh, and Stephan (2009) investigated modulation of the occipital lobe during visual prediction using fMRI in adults and found evidence that the basal ganglia (an important learning and memory system likely available early in life) was involved in modulating top-down connections to the visual system based on associative learning. While recording neural activity in the basal ganglia is not currently possible with fNIRS and fMRI with awake infants is extremely difficult (Aslin, Shukla, & Emberson, 2015), understanding the broader network of regions underlying these learning and prediction dynamics is an important topic for future investigation.

Overall, this work helps us more deeply understand the learning trajectories seen in infant brain. Specifically, we provide evidence that these neural changes during learning could arise, at least in part, through the emergence of top-down predictions. More generally, we believe these findings indicate that learning, even starting very early in life, arises from an interplay of feedforward and feedback (e.g., prediction) processes (see Figure 4 for a visual depiction of our model of this relationship). Previous work has found that preterm infants exhibit deficits in top-down prediction that arise as a result of learning (i.e., no occipital lobe response to an unexpected omission of visual information). However, they do have an intact ability to detect unexpected visual omissions that likely arises from feedforward associative learning processes (Emberson, Boldin, et al., 2017). In other words, previous work established that this population is able to form the audiovisual association but is not able to capitalize on this knowledge to initiate top-down visual predictions. Here, we find that the visual system (occipital lobe) exhibits no changes in neural activity during learning: This

relationship provides evidence that the non-linear neural dynamics found during learning are arising from top-down predictions. Specifically, we propose that even in infancy, learning is supported by both feedforward processes (e.g., to form the initial association or statistical learning in learning and memory systems beyond perceptual systems, e.g., the basal ganglia, hippocampus, amygdala, frontal lobe) and feedback processes which modulate perceptual systems. This feedback can take the form of prediction for future sensory input which can either facilitate better perception or processing of correctly predicted information or can create signals (e.g., a prediction error) that can guide future learning if these predictions are incorrect. In this way, the infant brain is able to use the interplay between learning and memory and perception to tune their developing brains to the structure of their environment.

In addition to providing crucial insight into the relationship between learning trajectories and top-down prediction early in life, these results bear on the nature of deficits associated with prematurity. Specifically, these results provide convergent evidence that prematurity is associated with deficits in top-down processes that are available to young infants and come online with learning. We find that deficits in top-down prediction likely arise from a broader lack of modulation of the visual system (in a context that allows visual prediction) throughout the entire time-course of learning. We propose that this feedback, prediction process is a crucial part of a dynamic learning system that not only modifies developing perceptual systems but can also support future learning. In addition, impairment in feedback or top-down modulation might be intimately related to impairments in neural connectivity associated with prematurity (Back, 2014; Ball et al., 2012; Hüppi et al., 1996; Ment et al., 2009; Smyser et al., 2010). Specifically, these top-down signals have been suggested in adults to be important for guiding and supporting the development of long-range connectivity (den Ouden, Daunizeau, Roiser, Friston, & Stephan, 2010; den Ouden et al., 2009). Thus, deficits in the initiation of these top-down signals might initiate a disruptive cycle where reductions in connectivity result in poorer connections available to provide feedback and in turn reduce the developing brain's ability to form these long-range connections based on co-activation, learning or effective information transfer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Breakdown of experimental design. Top panel shows step-by-step experimental procedure. In the second portion of the experiment (after the first three learning blocks), remaining stimuli are presented in groups of five trials, shuffled within each group. In each group, one learning block and four single trials (only one is depicted here) are presented, separated by baseline stimuli. Inset depicts an audio-visual trial. Six repeated audio-visual trials (of two types) make up a single learning block

FIGURE 2.

Left panel shows the three regions of interest on a template infant brain. Right panel shows representative example pictures used to determine the location of the NIRS optodes and anatomical markers for each individual infant

FIGURE 3.

Changes in neural activation with learning in full-term (a) and preterm (b) infants across multiple regions of the brain. The black lines represent the quadratic fit of the model and the colored lines are individual data points for each infant. Overlaid fits are included (c) to enable direct comparison. Note that the most striking visible difference between full-term and preterm fits occurs in the occipital lobe

FIGURE 4.

Schematic of bottom-up/feedforward and top-down/feedback processes during learning in infancy

TABLE 1

Results of linear models of full-term neural response across blocks

ROI	Term	<i>t</i>	Df	<i>p</i>
Temporal	Linear	9.80	181.2	<0.001
	Square	−9.54	169.6	<0.001
Occipital	Linear	5.39	172.3	<0.001
	Square	−5.29	169.4	<0.001
Frontal	Linear	8.82	251.3	<0.001
	Square	−7.02	234.1	<0.001

Each model includes both a linear and square term.

TABLE 2

Results of linear models of preterm neural response across blocks

ROI	Term	<i>t</i>	df	<i>p</i>
Temporal	Linear	8.93	251.3	<0.001
	Square	−8.64	234.1	<0.001
Occipital	Linear	0.64	266.6	0.526
	Square	−0.15	249.5	0.878
Frontal	Linear	6.45	258.4	<0.001
	Square	−5.23	244.3	<0.001

Each model includes both a linear and square term.

TABLE 3

Results of analysis showing that quadratic models give a better fit to the learning timecourse than models with only a linear term

ROI	Birth Status	χ^2	<i>p</i> -value
Temporal	Full-term	72.51	<0.001
Occipital	Full-term	25.77	<0.001
Frontal	Full-term	42.89	<0.001
Temporal	Preterm	64.32	<0.001
Occipital	Preterm	0.02	0.878
Frontal	Preterm	27.44	<0.001

Output of ANOVA model comparisons quantifying difference between linear only models and models including both a linear and a square term are shown. Degrees of freedom for all results are equal to 1 as there is a difference of only one term between the models.

TABLE 4
Results of models exploring relationship between learning trajectory shape and visual omission response in combined set of infants

Model	Term	Coefficient	t	p
Occipital omission ~ Occipital trajectory	Block	0.88	4.60	<0.001
	Block ²	5.96	4.13	<0.001
Occipital omission ~ Temporal trajectory	Block	0.81	4.15	<0.001
	Block ²	5.51	3.78	<0.001
Occipital omission ~ Frontal trajectory	Block	0.59	2.52	0.014
	Block ²	3.48	2.04	0.045
Temporal omission ~ Temporal trajectory	Block	0.93	5.72	<0.001
	Block ²	6.03	4.94	<0.001
Frontal omission ~ Frontal trajectory	Block	0.51	2.63	0.010
	Block ²	3.13	2.24	0.028

Significance of individual model terms are included here, overall model significance is included within the main text.