Report

Current Biology

Deficits in Top-Down Sensory Prediction in Infants At Risk due to Premature Birth

Highlights

- Prediction has been proposed to be essential for human development
- Infants at risk due to premature birth exhibit deficits in prediction
- Neural deficits were specific to prediction, and not to simple learning or perception
- Deficits were found early in development, suggesting a causal role for prediction

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In Brief

Emberson et al. compare the neural capacity to predict upcoming stimuli in 6-month-old infants at low and high risk for developmental delays (full-term and preterm infants). Infants at high risk exhibited selective deficits in top-down sensory prediction, providing evidence that neural prediction supports human development.

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Report

Deficits in Top-Down Sensory Prediction in Infants At Risk due to Premature Birth

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SUMMARY

A prominent theoretical view is that the brain is inherently predictive [1, 2] and that prediction helps drive the engine of development [3, 4]. Although infants exhibit neural signatures of top-down sensory prediction [5, 6], in order to establish that prediction supports development, it must be established that deficits in early prediction abilities alter trajectories. We investigated prediction in infants born prematurely, a leading cause of neuro-cognitive impairment worldwide [7]. Prematurity, independent of medical complications, leads to developmental disturbances [8–12] and a broad range of developmental delays [13–17]. Is an alteration in early prediction abilities the common cause? Using functional near-infrared spectroscopy (fNIRS), we measured top-down sensory prediction in preterm infants (born <33 weeks gestation) before infants exhibited clinically identifiable developmental delays (6 months corrected age). Whereas preterm infants had typical neural responses to presented visual stimuli, they exhibited altered neural responses to predicted visual stimuli. Importantly, a separate behavioral control confirmed that preterm infants detect pattern violations at the same rate as full-terms, establishing selectivity of this response to top-down predictions (e.g., not in learning an audiovisual association). These findings suggest that top-down sensory prediction plays a crucial role in development and that deficits in this ability may be the reason why preterm infants experience altered developmental trajectories and are at risk for poor developmental outcomes. Moreover, this work presents an opportunity for establishing a neuro-biomarker for early identification of infants at risk and could guide early intervention regimens.

RESULTS AND DISCUSSION

The goal of this study was to establish a direct link between the neuro-cognitive impairments associated with prematurity and an infant's ability to predict upcoming sensory input. To this end, we restricted our preterm population (born <33 weeks gestation) to those who did not experience severe medical complications or neurological insults and conducted the study at 6 months corrected age (i.e., matched to full-term infants based on time since conception, and not extra-uterine experience), before preterm infants missed any clinically identifiable developmental milestones. Testing at this young age allows us to circumvent the possibility that differences in prediction are arising from differences in developmental stage across the groups. Moreover, we employed a model task approach in which all infants receive equal experience with novel stimuli to control for possible differences in experience outside the lab.

Using functional near-infrared spectroscopy (fNIRS), a method for recording the hemodynamic response in the surface of the cortex using light [18–21], we recorded neural responses in 100 infants (50 preterm) to presented as well as predicted auditory and visual stimuli (see Figure 1). Following directly from findings in cognitive neuroscience (most closely [2, 22]), an important neural signature of top-down sensory prediction is responses to omitted information. If the developing brain is generating top-down predictions, an unexpected omission of visual information will result in activity in the same regions of the brain that process visual information. This has been observed in 6-month-old full-term infants: visually selective regions of the infant brain respond when visual input is unexpectedly omitted but exhibit no activity when the visual information was not expected to appear [5]. This paper extends this finding to infants at risk for poor developmental outcomes. To calculate the magnitude of the hemodynamic response, we averaged normalized changes in blood oxygenation from 5 to 9 s after stimulus onset within two neuroanatomically defined regions of interest (ROIs) (Figure 1; occipital: three NIRS channels; temporal: five NIRS channels; see Supplemental Experimental Procedures and [5, 23] for details on the MR-fNIRS coregistration method).

Prematurity Results in Differences for Predicted but Not Presented Sensory Input

Preterm and full-term infants exhibit the same pattern of response to presented auditory and visual stimuli. Building from [5], we examined the neural response of full-term infants during audiovisual trials in the temporal and occipital ROIs and confirmed the hypothesized perceptual cortex responses to auditory and visual stimuli: there was a significant increase

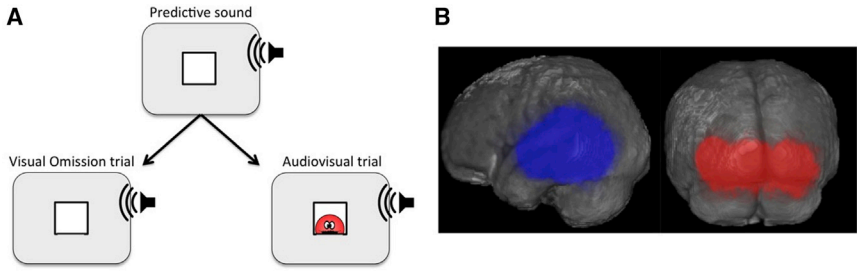

Figure 1. Task Structure and MR Coregistration of fNIRS Recordings

(A) Overview of task structure. All trials began with a predictive sound/auditory stimulus. In the majority of the trials, this was followed by the predicted visual stimulus (audiovisual trials, right branch). However, in a minority of the trials (20% of trials after initial familiarization), this predictive sound was followed by an unexpected omission of the visual stimulus (visual omission trial, left branch).

(B) MR coregistration of fNIRS recordings was used to create two neuro-anatomically defined regions of interest (ROIs): temporal and occipital lobe ROIs (left and right images, respectively).

from baseline in both the temporal ($t(35) = 4.18$, $p < 0.001$, $d = 0.70$) and occipital ($t(35) = 4.74$, $p < 0.001$, $d = 0.79$) ROIs. Importantly, we found the same pattern of perceptual cortex responses in preterm infants: they exhibited a robust response in temporal and occipital ROIs during audiovisual trials (temporal: $t(42) = 4.57$, $p < 0.001$, $d = 0.70$; occipital: $t(42) = 3.13$, $p < 0.003162$, $d = 0.48$; Figure 2).

However, preterm and full-term infants differed in their responses to visual omission trials, in which the predicted visual stimulus is unexpectedly omitted. Full-term infants exhibited a robust occipital lobe response to the unexpected omission of a visual stimulus ($t(35) = 3.63$, $p < 0.001$, $d = 0.61$; Figure 2, right panel) that was statistically indistinguishable from the response of this region to the presentation of the visual stimulus in the audiovisual trials ($t(35) = 1.51$, $p = 0.14$, $d = 0.22$). Thus, we found patterns consistent with previous work [5] showing occipital lobe responses in 6-month-olds to the unexpected absence of a visual event (see [22] for a detailed investigation of these effects in adults using fMRI). However, in contrast, preterm infants exhibited a significant difference in occipital response levels between audiovisual trials and visual omission trials ($t(42) = 6.31$, $p < 0.001$, $d = 0.86$). This difference between preterm and full-term infants is also highlighted by the fact that there appears to be a negative occipital response during visual omission trials among preterm infants ($t(42) = -2.44$, $p = 0.01878$, $d = 0.37$). Thus, although preterm infants exhibit a robust response to an unexpected visual omission, the response is negative and significantly reduced from the responses of the same region to the presentation of a visual stimulus.

Directly comparing occipital cortex responses between preterm and full-term infants across audiovisual and visual omission trials (mixed ANOVA) reveals a significant interaction of trial type and birth status, $F(1,77) = 4.61$, $p = 0.035$, $\eta^2 = 0.04$, which is driven by a difference between preterm and full-term infants in occipital lobe response levels during visual omission trials, $t(55.60) = -4.36$, $p < 0.001$, $d = 1.03$, and a significant difference across trial types in preterm but not full-term infants. There were additionally main effects for birth status, $F(1,77) = 13.92$, $p < 0.001$, $\eta^2 = 0.15$, and trial type, $F(1,77) = 24.98$, $p < 0.001$, $\eta^2 = 0.23$. There was also a significant difference in occipital response during visual present trials between the two groups, $t(62.40) = -2.23$, $p = 0.0295$, $d = 0.52$.

Importantly, these findings are specific to the occipital cortex: as both trial types are initiated by the presentation of an identical, predictive auditory cue, no differences in temporal lobe activation are predicted. Indeed, there were no main effects for birth status, $F(1,77) = 2.40$, $p = 0.162$, $\eta^2 = 0.03$, or trial type, $F(1,77) = 1.02$, $p = 0.316$, $\eta^2 = 0.01$, and no significant interaction, $F(1,77) = 0.88$, $p = 0.351$, $\eta^2 = 0.01$. Both groups of infants exhibited a strong, positive temporal cortex response to visual omission trials (full-terms: $t(35) = 4.73$, $p < 0.001$, $d = 0.79$; preterms: $t(42) = 4.29$, $p < 0.001$, $d = 0.65$; Figure 2, left panel).

There are numerous explanations for negative hemodynamic responses in the fMRI literature. First, it may be that the negative response we observe when preterm infants experience an unexpected visual omission reflects a suppression of neural activity below spontaneous or baseline levels [24]. This interpretation of the negative BOLD response would result in the conclusion that preterm infants exhibit a neural pattern distinct from that of full-term infants when no expectation is present (control study [5]). However, an alternative explanation for negative BOLD responses is that these differences arise from changes in baseline (e.g., [25]). In this case, a response to baseline stimuli in preterm infants could be elevated when compared to the full-term baseline. As all responses were recorded relative to baseline, an elevated baseline response would explain the smaller visually evoked response to the audiovisual trials and could also explain a significant reduction to the unexpected visual omission trials. In the Supplemental Information, we conducted a baseline correction that equates the level of neural response in the occipital ROI to the audiovisual trials across preterm and full-term infants and found the same effects across trial type and group.

There Are No Differences across Levels of Prematurity

Preterm infants in this study were born from 23 to 32 weeks gestation. While all of these infants were born before the third trimester, the level of neural maturity at birth varied widely across this sample. Moreover, many risk factors for prematurity are much more severe in, or are restricted to, infants born extremely premature (<28 weeks gestation, [26, 27]). We investigated whether the deficits we observed are modulated by gestational age at birth: is there evidence for gradation in these deficits of top-down prediction across gestational age, or are these deficits uniform across infants born before the third trimester? First, removing early preterm infants from our sample (gestational age < 28 weeks) did not change the significance of any relevant statistical analysis. The remaining preterm infants showed significant occipital response during both audiovisual trials, $t(33) = 2.56$, $p = 0.01519$, $d = 0.02$, and visual omission trials, $t(33) = -2.57$, $p = 0.01487$, $d = 0.44$, with a significantly

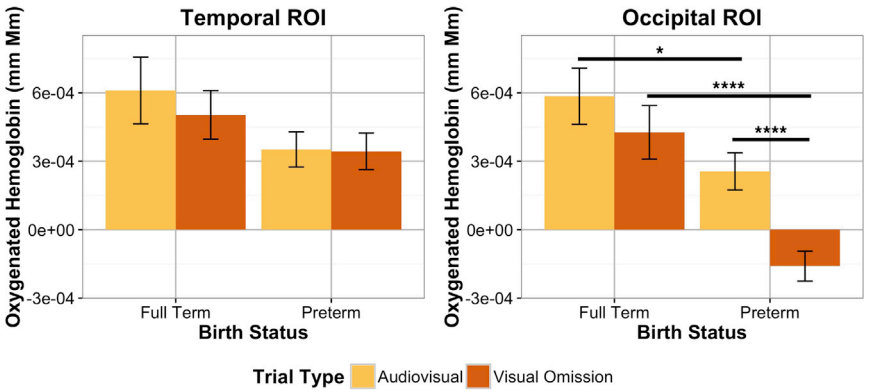

Figure 2. Neural Activation in Temporal and Occipital Lobes

Mean levels of oxygenated hemoglobin (relative to baseline) during audiovisual and visual omission trials in temporal lobe (left) and occipital lobe (right). Error bars represent SEM. $0.01 < *p \leq 0.05$; $****p \leq 0.0001$. See Figure S1 for histograms of the key effects, Figures S2 and S3 for baseline corrections of the premature infant neural responses, and Figure S5 for the spatial distribution of this effect across channels in the occipital lobe.

negative response to the visual omission trials. There was still a significant difference in preterm occipital response between both trial types, $t(33) = 5.46$, $p < 0.001$, $d = 0.87$, and a significant difference in occipital response during visual omission trials between preterm and full-term infants, $t(55.34) = -4.43$, $p < 0.001$, $d = 1.04$. The fact that our results withstood the exclusion of this group indicates that the effects observed are not driven by infants born very early, but rather are effects that may distinguish preterm infants in general from full-term infants. Since relatively few ($n = 9$) infants fell into this early category, we do not have the statistical power to determine the specific influence of these extremely premature infants on our analysis. We also considered whether gestational age has a more subtle but graded effect on differences of responses to unexpected visual omissions. As Figure 3 illustrates, gestational age, within the preterm sample, does not account for variation in the neural response to visual omissions, $R^2 = 0.01$, $F(1,41) = 0.47$, $p = 0.4949$. Importantly, we also did not find that gestational age within the preterm sample explains occipital lobe responses to audiovisual trials when a visual stimulus is presented, $R^2 = 0.01$, $F(1,41) = 0.56$, $p = 0.4581$. Future work will address this surprising finding: is there is a categorical shift in early top-down prediction abilities after the first trimester, as the current data suggest, or would a sample including more infants born extremely premature reveal gradations in this ability?

Socioeconomic Status and other Demographic Differences Do Not Explain the Effects of Prematurity

In addition to prematurity, there were a number of demographic differences between our groups. Notably, our preterm sample had a lower socioeconomic status and were much more likely to have come from multiple births (e.g., twins, triplets). Importantly, additional analyses confirmed that the deficits in top-down sensory prediction observed across these groups were not explained by these other demographic differences. See Supplemental Experimental Procedures for more details.

Preterm and Full-Term Infants Equally Detect Visual Omissions

We found that infants born prematurely exhibit a significant reduction in the neural signature of top-down prediction. An alternate explanation of this result is simply that the unexpected visual omission is less unexpected to preterm infants. This could arise, for example, from reductions in cross-modal associative learning [28]. If preterm infants are slower to learn the cross-modal association between the sound and the visual event, that could explain the lack of occipital response to the visual omission trials. The current study was carefully designed to avoid this possibility (i.e., by providing infants with an equal amount of exposure to the stimuli in a paradigm that reduces learning demands through temporal overlap between audio and visual stimuli). Moreover, we previously examined neural responses to visual omissions for a control group of full-term infants who did not learn the audiovisual association and found that the occipital lobe did not respond differently from baseline, in contrast to the strong negative response observed in the occipital lobe for preterm infants [5]. Although predictive processes are well established as being involved in reinforcement learning, the nature of these signals is distinct from the type of prediction being studied here. Specifically, prediction errors involved in reinforcement learning are found in the basal ganglia and other subcortical circuitry [29–31]. This type of prediction is well reflective of a feedforward system in which this subcortical circuitry modulates expectations based on sensory input that continues on to modulate motor responses. By contrast, the current study investigates top-down prediction of sensory input that modulates perceptual cortices [22, 32]. Top-down sensory prediction is a distinct but complementary type of prediction that relies on the formation of an association (in the case of the current study) as an origin for a feedback signal that affects the perceptual cortices. Thus, while associative or reinforcement learning is likely involved in the current study, we aimed to isolate the effects of prematurity to top-down prediction signals, and not differences in associative learning, which can rely on a largely feedforward network architecture.

To confirm that preterm and full-term infants detect visual omissions similarly, we conducted a behavioral control experiment. A new sample of 50 full-term and 50 preterm infants were recruited using the same methods and populations as the fNIRS study. Specifically, we asked whether the exposure that infants received in the fNIRS study would result in similar looking preferences (i.e., length of looks) to visual omissions for preterm and full-term infants. Systematic looking preferences are canonically interpreted in relation to the strength of internal representations [33]. Thus, similar looking-time preferences would suggest that preterm and full-term infants detect the visual omission equally. After exposure to audiovisual pairs in an exposure similar to the fNIRS experiment, infants were presented with sequences of

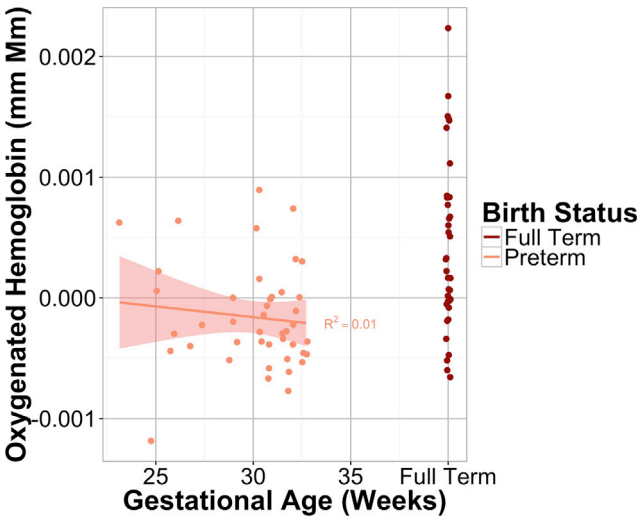

Figure 3. Gestational Age versus Top-Down Sensory Prediction

Oxygenated hemoglobin is not an absolute measure but is relative to changes from baseline. Linear fit to preterm data is shown. See Figure S4 for relationship of gestational age and occipital lobe responses in audiovisual trials. See also Table S1.

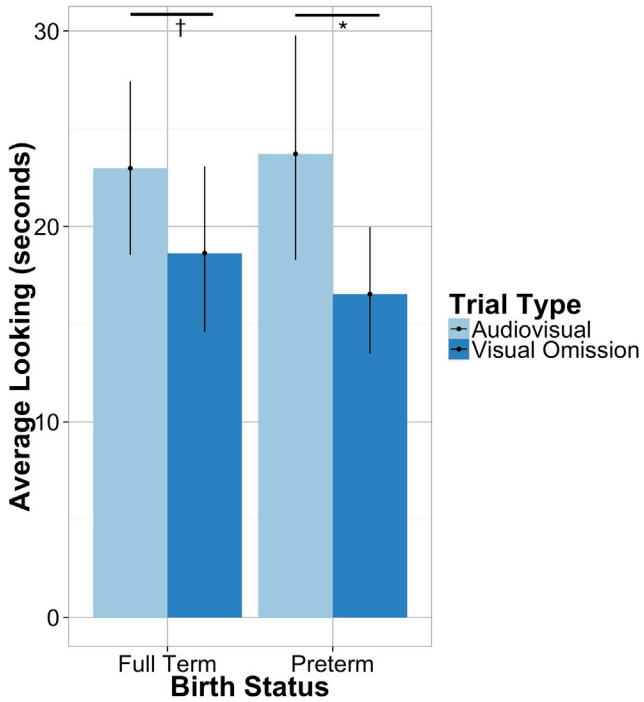

Figure 4. Detection of Visual Omissions for Full-Term and Preterm Infants

Looking times in response to test trials presenting only audiovisual events versus test trials containing 50% visual omissions for full-term and preterm infants. Error bars represent SEM. $0.05 < \dagger p \leq 0.1$; $0.01 < {}^{*}p \leq 0.05$.

familiar audiovisual trials in counterbalanced order with sequences that contained 50% visual omission trials. We found strikingly similar looking-time preferences across the two groups. Indeed, direct comparisons between the groups yielded no significant difference (see Figure 4 and Supplemental Experimental Procedures for full experimental details). This control experiment confirmed that there were no differences in detection of the visual omission trials across the two groups. This finding suggests that the differences between preterm and full-term infants are specific to top-down sensory prediction and do not arise from differences in foundations necessary to this task.

Why does being born prematurely disrupt the underlying neural mechanisms of top-down prediction? Having established that detecting visual omissions, medical complications, and socioeconomic status do not explain these deficits, one possibility is that preterm infants' early extrauterine experience negatively affects the development of this ability. Specifically, extrauterine experience is richly endowed with a myriad of patterns and statistical information that preterm infants receive well before full-term infants, during the third trimester, which is crucial for neural development (e.g., the development of long-range functional connectivity [34]). Receiving this experience too early may be detrimental because the developing brain is not ready for the input (e.g., neural connectivity is limited, which could prevent or bias learning). Another possibility, which is not mutually exclusive, is that the type of extrauterine experience that preterm infants receive is importantly different from that of full-term infants (e.g., due to necessary medical interventions). Numerous studies have investigated preterm infants with the goal of determining whether development of different abilities is supported by experience or neural maturation. In contrast to the present study and the large literature documenting the developmental difficulties associated with prematurity, many of these studies have concluded that preterm infants are relatively unimpaired or even accelerated in their development (e.g., [35–37]). It may be that relatively low-level early-developing abilities are not disrupted by premature birth, but that the disruption of foundational developmental mechanisms, as reported here, has developmental consequences that emerge later in life or in different domains.

In summary, we investigated neural signatures of top-down sensory prediction in young infants who are at risk for poor developmental outcomes due to premature birth. In comparison to their full-term peers, preterm infants exhibited typical neural responses to presented auditory and visual stimuli but showed substantially reduced neural responses to predicted visual stimuli. Moreover, these neural differences were present before infants missed any clinically apparent developmental milestones, suggesting that alterations in top-down sensory prediction could give rise to the developmental impairments that preterm infants experience but that are revealed months or years later (e.g., language delays, learning disabilities). This result dovetails with the finding that premature birth affects information processing and memory that predict cognitive outcomes later in life [38–40]. Overall, this work provides evidence that top-down prediction is part of the engine driving development and an important component of how the infant brain uses experience to mature. If being born prematurely affects the mechanisms by which development proceeds, as this work suggests, this would explain why the effects of prematurity are ongoing and compounding [14]. Moreover, this discovery presents an opportunity for establishing a neuro-biomarker to identify infants at risk and

to guide early intervention attempts once it has been established that these early life deficits predict poor developmental outcomes.

SUPPLEMENTAL INFORMATION

Supplemental Information includes five figures, one table, and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.12.028.

AUTHOR CONTRIBUTIONS

Experimental idea: L.L.E; experimental design: L.L.E., R.G., and R.N.A.; data collection and analysis: L.L.E., A.M.B., R.G., and J.E.R.; manuscript drafting and editing: L.L.E., A.M.B., R.G., J.E.R., and R.N.A.

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