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General anesthesia in early infancy accelerates visual cortical development

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How human brain function is established through protracted trajectories of development is not yet fully understood. Maturation of γ-aminobutyric acid (GABA) circuits drives critical periods of cortical development in animal models. Whether early functional inhibition similarly impacts the pace of human brain development remains unknown. Here, in a longitudinal study of 93 infants across a range of repeated exposures to general anesthesia shortly after birth, we observed a dramatically accelerated development of visual evoked potential (VEP) waveforms (but not their latency) consistent with a conserved biological mechanism across species. Such sequelae of prolonged GABA-active anesthesia in the first half year after birth may particularly impact those at-risk of altered excitatory–inhibitory circuit balance.

development | GABA | vision

Properly timed neuronal circuit maturation shapes healthy brain function and behavior lasting a lifetime (1). Shifted neurodevelopmental trajectories are implicated in a range of cognitive disorders and clinical etiologies (2). Seminal findings from animal models (3) reveal the late emergent balance of inhibitory γ-aminobutyric acid (GABA)–mediated transmission relative to excitatory signaling drives these windows of brain plasticity. Notably, premature GABA boosting accelerates cortical maturation across mouse sensory/associative areas (1). While GABAergic markers also undergo protracted changes after birth in humans (4, 5), whether the pace of infant brain function is similarly dictated by inhibition remains unknown.

Human visual cortex displays its greatest rate of maturation over the first year of life (6). Visual-evoked potentials (VEPs) derived from the electroencephalogram (EEG) (7) serve as a useful index of both underlying local V1 cortical circuit function via summed postsynaptic excitatory/inhibitory potentials (waveform amplitude) and structural integrity of the visual pathway (waveform latency), respectively (8). Specifically, VEP components include a magnocellular-generated positive deflection (P1) that is present from birth and largely sensitive to prenatal factors, surrounded by two parvocellular-generated negative deflections (N1, N2) that mature sequentially over the first 10 postnatal months (7, 9). General anesthetics (GA), like sevoflurane and propofol (10, 11), are potent $GABA_A$ receptor agonists commonly administered also to newborns. We hypothesized that early postnatal exposure to such drugs would lead to earlier N1 and N2 maturation within the first year of life, indicating accelerated neurodevelopment of the human visual cortex as observed previously in immature mice treated with benzodiazepines (3).

Results

A prospective longitudinal cohort of 93 infants was tested using a pattern-reversal VEP paradigm around 3, 5, and 10 mo of age (Fig. 1*A*). Thirty-seven had experienced early, prolonged sedation with sevoflurane and/or propofol for surgery during the first 3 mo of life (GA Group) for nonneurological issues (mean exposure: 5.28 h; range: 1 to 20.7 h; corrected mean first exposure age: 1.98 wk, range: −5.1 to 9.9 wk, *SI Appendix*, *Methods* and Table S3). Here, common surgeries treated abdominal, inguinal, or thoracic conditions. The remaining 56 infants served as a control (Comparison Group) without early GA. Groups did not differ significantly in key demographic factors, longitudinal parent-reported stress levels, rates of data contribution, data quality metrics, or infant characteristics ($P > 0.05$, *SI Appendix*, *Methods*).

Infants with GA exposure exhibited earlier maturation of N1 and N2 VEP amplitudes (Fig. 1*C*) relative to Comparison infants (linear mixed effect models' Age × GA interaction: N1, [$F(2, 52.49) = 4.6$, $P = 0.014$; N2, $F(2, 41.64) = 5.31$, $P = 0.009$; P1, $F(2, 42.85) = 3.18$, $P = 0.052$; n = 93, observations = 179, full models presented in *SI Appendix*, *Results*]. In Comparison infants, N1 deflections increased gradually between 3 to 5 mo [estimated

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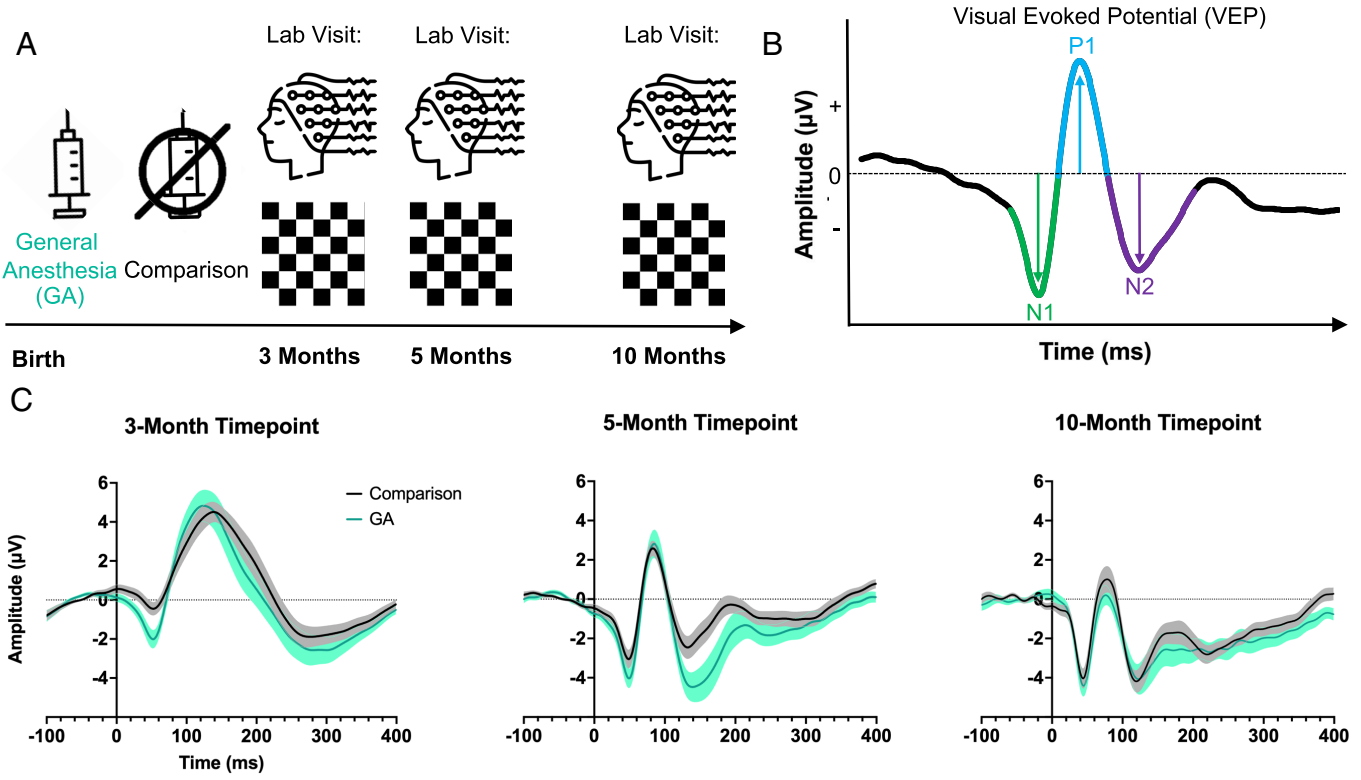

Fig. 1. Accelerated VEP Morphology Across Infancy Following GA. (*A*) Longitudinal study design for general anesthesia (GA) and Comparison Group tested at 3, 5, 10 mo after birth by repeated electroencephalography (EEG) recordings using a pattern-reversal VEP paradigm. (*B*) Component VEP morphology extracted from EEG signal: initial (N1) downward followed by upward (P1) and later downward (N2) deflections, characterized by peak amplitude (μV in color) and latency (ms). (*C*) Changes in VEP morphology across the three study timepoints for GA (green) and age-matched comparison (gray) groups. Visual stimulus onset (at time 0 ms). Group-mean VEP amplitude and SEM (shading).

difference (SE) −2.40 μV (0.5), P = 0.000008]. Instead, N1 was already present in 3-mo GA infants comparable to later 5-month control N1 amplitudes [t(70) = −1.78, P =0.08, n = 72]. Longer exposure to prior GA resulted in deeper N1 amplitudes by 3 mo [b(SE) −0.282 (0.064), t(62) = −4.41, P = 0.000045, n = 63], indicating a dose–response for early GABA boosting and the rate of neurodevelopmental acceleration. Beyond 5 mo, N1 amplitudes did not change further, aligning all infants at the same level [5 mo: b(SE) −0.084 (0.072), t(67) = −1.16, P = 0.25, n = 67; 10 mo: b(SE) 0.005 (0.077), t(48) = 0.059, P = 0.95, n = 49].

The N2 component also matured earlier following GA exposure (Fig. 1*C*). Typically increasing in Comparison infants between 5 and 10 mo [estimated difference (SE) at 3 to 5 mo: −0.93 μV (0.67), P = 0.17; at 5 to 10 mo: −1.77 μV, P = 0.007], the N2 amplitude was already present between 3 and 5 mo of age after increasing GA exposure [3 to 5 mo estimated difference (SE) −1.44 μV (0.64), P = 0.026; 5 to 10 mo estimated difference (SE) −0.45 μV (0.60), P = 0.46]. Once again, 5-month GA group N2 amplitudes were no different from twice as old control N2 peaks at 10 mo [t(51) = 0.73, P = 0.47, n = 53], consistent with earlier VEP maturation of GA-exposed infants. Longer GA exposures yielded deeper N2 amplitudes at the 5-mo visit [b(SE) −0.298 (0.102), t(67) = −2.91, P = 0.005, n = 67], suggesting a dose–response relation as for N1. By 10 mo of age, groups no longer differed in N2 amplitude [GA b(SE) = 0.016 (0.088), t(48) = 0.186, P = 0.85, n = 49], indicating similar endpoints of maturation.

Developmental changes in N1 and N2 VEP amplitudes as a function of GA exposure are shown in Fig. 2 *A* and *B*. To assess potential confounding factors, post hoc exploratory analyses in the models predicting N1 and N2 amplitudes included 1) cumulative days as hospital in-patient; or 2) stays in the intensive care unit (ICU). In all cases, GA-related effects remained significant regardless of hospitalization variables (*SI Appendix*, *Results*). We further examined whether GA affected structural pathway integrity [i.e., myelination (8)] by exploratory models predicting N1, P1, and N2 latency (Fig. 2*C*). No significant GA or GA x Age interactions were observed for any VEP peak latencies (all P > 0.05, *SI Appendix*, *Results*).

Discussion

We found that precocious GABA boosting by early sevoflurane/propofol anesthetic exposure accelerates visual cortical maturation in human infants. Hours of GA exposure shortly after birth are consistent with a substantial boost of inhibition above baseline in infancy to trigger these effects as reported for animal models (3). General cortical disruptions related to GA or medical complexities and alternative non-GABA-dependent mechanisms (e.g., cortical structure, tissue resistance) are unlikely explanations. First, no significant impact of GA was observed in our cohort on resting-state brain networks over the first year (12) or on multiple neurodevelopmental outcomes over the first 2-3 years (13). Second, indistinguishable visual cortical function was attained by 10 mo of age, consistent with developmental timing of GABA-dependent V1 orientation-selectivity (14). Third, dose-related effects of GA were observed, even when controlling for other medical parameters, like hospital/ICU length of stay. Finally, acceleration was limited to VEP components normally emerging during this postnatal window (i.e., N1/N2 but not P1), and not observed for VEP latencies reflecting structural maturation like myelination. These other VEP components are

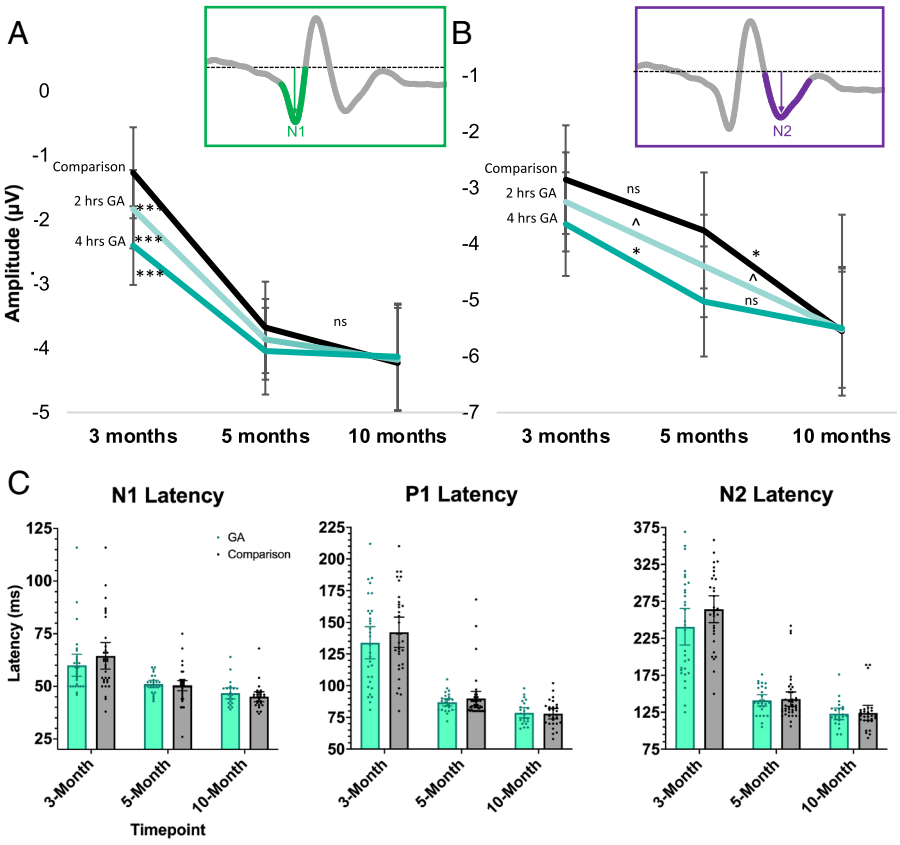

Fig. 2. Early Strengthening of VEP Peaks as a Function of GABAergic Anesthesia. Linear mixed-effect model estimates for VEP as a function of GA exposure duration before 3-mo (*A*), for N1 peak amplitude (*Inset*) [GA × Age interaction $F(2, 52.49) = 4.6$, $P = 0.014$]. Comparison (0 h of GA), 2 h (sample mean) and 4 h of exposure (~1 SD from mean). (*B*) for N2 peak amplitude (*Inset*) [GA × Age interaction $F(2, 41.64) = 5.31$, $P = 0.009$]. ns, $P > 0.1$, ^$0.05 < P < 0.1$, *$P < 0.05$, ***$P < 0.001$. (*C*) No changes in VEP latency to N1, P1, N2 peak across Groups and study visits (all $P > 0.05$). Error bars reflect 95% CI.

instead sensitive to different complex medical conditions or drug exposures that are not $GABA_A$ receptor agonists (7).

Our findings support a general mechanism governing neurodevelopmental timing across species, namely GABAergic inhibition as a potent driver of trajectories of cortical functional maturation in humans as in mouse models. The shift from depolarizing to hyperpolarizing GABA signaling (due to conserved upregulation of chloride transporter (KCC2) occurs by birth in humans compared to the second postnatal week in rodents (15). Alternative non-GABA active anesthetic classes and ventilation exposures for the neonatal age range merit further investigation. Also, the downstream cumulative impact of early GA on cascading critical periods underlying higher cognitive function remains to be determined (1). Patients already on a spectrum of neurodevelopmental disorders linked to excitatory-inhibitory circuit imbalance (2) may be particularly at risk.

Materials and Methods

Infants were recruited to participate in a prospective, longitudinal, observational study. The Institutional Review Board of Boston Children's Hospital approved all methods and procedures used in this study (IRB protocol number P00028129). All parents gave informed consent prior to enrollment and received remuneration and a travel stipend for every visit completed over the study course. Protocol registered with Open Science Framework, https://osf.io/2bmvg). *Materials and Methods* are provided in *SI Appendix*. All relevant data and materials will be made publicly available at https://osf.io/xs6mj.

Data, Materials, and Software Availability. Anonymized study data have been deposited in GABA OSF Repository (https://osf.io/xs6mj) (16).

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