ANESTHESIOLOGY

Changes in the Term Neonatal Electroencephalogram with General Anesthesia: A Systematic Review with Narrative Synthesis

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ABSTRACT

Background: Although effects of general anesthesia on neuronal activity in the human neonatal brain are incompletely understood, electroencephalography provides some insight and may identify age-dependent differences.

Methods: A systematic search (MEDLINE, Embase, PubMed, and Cochrane Library to November 2023) retrieved English language publications reporting electroencephalography during general anesthesia for cardiac or noncardiac surgery in term neonates (37 to 44 weeks postmenstrual age). Data were extracted, and risk of bias (ROBINS-I Cochrane tool) and quality of evidence (Grading of Recommendations Assessment, Development, and Evaluation [GRADE] checklist) were assessed.

Results: From 1,155 abstracts, 9 publications (140 neonates; 55% male) fulfilled eligibility criteria. Data were limited, and study quality was very low. The occurrence of discontinuity, a characteristic pattern of alternating higher and lower amplitude electroencephalography segments, was reported with general anesthesia (94 of 119 neonates, 6 publications) and with hypothermia (23 of 23 neonates, 2 publications). Decreased power in the delta (0.5 to 4 Hz) frequency range was also reported with increasing anesthetic dose (22 neonates; 3 publications).

Conclusion: Although evidence gaps were identified, both increasing sevoflurane concentration and decreasing temperature are associated with increasing discontinuity.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The effects of general anesthesia on neonatal electroencephalography patterns are quite different from those of adults
- There are no well-defined criteria to characterize these discontinuous patterns, including burst suppression

What This Article Tells Us That Is New

- There is an extreme paucity of unbiased information about the effects of general anesthesia on neonatal electroencephalography patterns
- A discontinuous electroencephalography pattern is common, but it is unclear how much is due to hypnotic drug concentrations and how much is due to hypothermia

Surface electroencephalography (EEG) noninvasively measures cortical brain electrical activity by the spatial summation of synchronous postsynaptic potentials from millions of aligned cortical neurons.[1–3] Components of the EEG can be used as biomarkers of brain activity or state, including

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amplitude, frequency, and pathologic features. Regional and global changes in brain activity can be identified by placing multiple electrodes across the scalp. An EEG output can consist of an unprocessed (raw) form consisting of voltage changes over time or a processed form that uses computer algorithms to generate an output from the raw EEG. Processed EEG monitors have been developed (*e.g.*, Bispectral Index [Aspect Medical Systems, USA], Narcotrend [MonitorTechnik, Germany], SEDline [Masimo, USA], and amplitude-integrated EEG [aEEG]) to generate outputs that correspond moderately to anesthetic dose and unconsciousness.[3–6] However, direct correlation between anesthesia-induced changes in EEG and the clinical effects of anesthesia measured with minimum alveolar concentration is yet to be shown. Processed outputs include spectrograms (*e.g.*, SEDline),[4,7] unitless integers (*e.g.*, Bispectral Index is 0 to 100),[8] and categorical read-outs (*e.g.*, aEEG).[9] Automated EEG decision-support tools are also becoming available (*e.g.*, seizure surveillance).[10–13]

Brain monitoring with EEG in anesthetized adults has been used to understand dose titration, perioperative outcomes, and the neurophysiologic basis of anesthesia.[4,7,14–16] In adults, typical EEG changes with inhalational anesthetics and propofol include global increases in amplitude with gradual slowing of oscillations during anesthesia induction, followed by frontal alpha (8 to 12 Hz) predominance during anesthesia maintenance. With further increasing dose, burst suppression—a profound form of discontinuity—develops.[17–20] Burst suppression is more likely in neurologically vulnerable adults such as those requiring surgery for epilepsy treatment,[21] those with neurodevelopmental disorders,[22] and the aging.[23]

EEG changes during general anesthesia have been reported throughout childhood.[8,24] Conclusions about specific age-related changes, particularly for neonates, are limited by the broad age ranges reported.[25–28] With general anesthesia, alpha oscillations emerge at around 3 months of age and become increasingly concentrated in the frontal cortex by 7 months of age.[29,30] Total frontal EEG power increases with age and anesthetic depth between 4 months and 6 to 8 yr of age; thereafter, it decreases with increasing age.[31–33] Other reproducible changes seen in EEG with general anesthesia (*e.g.*, alpha oscillation coherence) are not seen under 1 yr of age.[31–33] Development of a discontinuous trace with general anesthesia is more likely at younger ages, especially aged under 1 yr.[24,34–36]

Characterization of neonatal EEG with general anesthesia may improve our understanding of the effect of anesthesia on the developing brain. Neonatal surgeries are often gastrointestinal (61.8%) or cardiac (8.4%) and urgent or emergency cases (48%).[37,38] Newborns are all at least American Society of Anesthesiologists status III. When they are born prematurely (37%), they are more likely to require surgery and require intensive preoperative support (48.1%). Consequently, studying neonatal EEG during general anesthesia is logistically challenging, which results in small sample sizes or grouping with older children. This systematic review aims to summarize current literature reporting patterns of EEG during general anesthesia in term neonates aged 37 to 44 weeks postmenstrual age.

Materials and Methods

Search Strategy and Information Sources

This review was registered at the PROSPERO international register of systematic reviews, registration number CRD42021290387, by Sebastian J. Corlette on December 10, 2021 (available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021290387, last accessed January 15, 2024). We searched MEDLINE, Embase, PubMed, and the Cochrane Library on February 22, 2022, and repeated on November 17, 2023, to capture any recent publications, using a predefined search strategy (see search terms in Supplemental Digital Content 1, https://links.lww.com/ALN/D582). The additional search on November 17, 2023, identified no additional eligible publications. We also searched PROSPERO for existing systematic reviews and published protocols and online trials registries for ongoing clinical trials or unpublished studies.

Data Extraction

Two reviewers (S.J.C., and C.B. or S.M.W.) independently screened titles and abstracts. No disagreements or uncertainties regarding screening criteria arose that required a third adjudicator. One reviewer (S.J.C.) then screened full-text articles. Data from the review of full-text articles was compiled using a template with specific criteria such as dependent and independent variables, the number of eligible patients for which data were reported, and descriptive findings. The data extraction template is included as Supplemental Digital Content 2 (https://links.lww.com/ALN/D583). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension checklist for reporting.[39]

Study Selection Criteria

We included randomized controlled trials, analytical cross-sectional studies, case control series, cohort studies, case series, and prospectively controlled single case studies that reported EEG in term neonates (defined as having postmenstrual age between 37 and 44 weeks) during general anesthesia administered by an anesthesiologist for surgery, procedural intervention, or investigation. Articles were excluded if they did not separately report data regarding term neonates. Data in the included publications that were not obtained from neonates were excluded. When multiple publications reported data related to the same patients, the patients were included in analysis only once.

Outcomes: EEG Features

Reported EEG features including amplitude, frequency, continuity, and seizures were extracted, including changes

over time during general anesthesia with varying dose. When reported, comparisons were made relating to the type and dose of anesthesia. Eligible EEG modalities included unprocessed EEG, processed EEG and derived indices, and modalities measured with any type of electrode, with any number of electrodes and with any electrode montage.

Data Quality

Risk of bias was assessed for each study using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool from the *Cochrane Handbook for Systematic Reviews of Interventions*.[40] The ROBINS-I tool systematically covers seven distinct domains through which bias might be introduced (*i.e.*, participant selection, missing data, measurement of outcomes) through comparison with a hypothetical randomized controlled trial that would produce similar results. The categories for risk-of-bias judgments are "low risk," "moderate risk," "serious risk," and "critical risk" of bias for each domain. The findings were summarized in tables and then collated for outcomes across the literature using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to determine the degree of certainty for each finding.[41] The level of certainty was rated as "very low," "low," "moderate," and "high." For example, evidence that includes observational data starts at low quality and thereafter is systematically upgraded to "moderate" or "high" or downgraded to "very low" depending on the following criteria: within-study risk of bias, indirectness, inconsistency, imprecision, and publication bias.

Results

Characteristics of Included Studies

Nine publications fulfilled the inclusion criteria (fig. 1) and reported results for 140 neonates (55% male).[35,42–49] The included publications were separated into noncardiac (seven publications; table 1) and cardiac surgery (two publications; table 2), because the latter included EEG effects associated with cardiac bypass and deep hypothermic cardiac arrest.

Two of the included studies were nonrandomized experimental studies, and seven were prospective cohort studies. No randomized controlled trials met the inclusion criteria. The risk of bias was moderate to serious for all publications (summarized in table 3, full details in Supplemental Digital Content 3, https://links.lww.com/ALN/D584). Because all included publications were either nonrandomized trials or prospective cohorts, all were initially rated as "low" quality of evidence and then adjusted accordingly using the GRADE method.

Sample size ranged from 1 to 75 patients (see tables 1 and 2). Sex distribution ranged from 40 to 72% male. Four publications included either one or two term neonates only,[35,42,44,49] and two reported on the same patients with different analyses.[43,47] In total, 23 patients undergoing cardiac surgery were reported across two publications,[48,49] and 117 patients undergoing noncardiac surgery across seven publications.[35,42–47]

EEG Methodology

One publication (noncardiac) reported results from aEEG[45] in 75 patients, and the remainder reported unprocessed EEG[35,42–44,46–49] in 82 patients. Most publications used six or fewer electrodes. Bipolar electrode pairs positioned at C3–P3 and C4–P4 were used in three publications (95 patients).[43,45,47] One publication (two patients) reported the use of electrode positions F3, F4, CP3, and CP4, with a reference electrode on the nose.[42] In one publication (18 patients), a single electrode was positioned at FP1 with the left ear used as reference,[46] and in two publications (three patients), the electrode positions were unspecified.[44,49] One publication (one patient) reported using 34 electrodes,[35] and another publication (21 patients) reported using 16 electrodes,[48] both with a modified international 10/20 electrode placement system. The reference position was Fz in the former and unspecified in the latter.

Electrode types were silver/silver-chloride cup electrodes in three publications (21 patients),[35,42,46] gold-plated cup electrodes in one publication (21 patients),[48] and subdermal needle electrodes in one publication (1 patient).[44] Electrode type was not specified in the remaining four publications (97 patients).[43,45,47,49]

General Anesthesia

EEG changes during inhalational anesthesia with sevoflurane, isoflurane, or halothane were reported in 139 patients (99%) across nine publications.[35,42–49] In 116 patients (83%), anesthesia was maintained with sevoflurane, and in 22 patients (16%), anesthesia was fentanyl based with added isoflurane.[35,42,43,45–49] The data were insufficient to make comparisons among the agents. One publication (two patients) reported one patient receiving fentanyl-based general anesthesia without added isoflurane, with the other receiving both fentanyl and isoflurane.[49] The details of propofol administered in addition to inhalational anesthesia were not reported (dose, intermittent bolus *versus* continuous infusion, timing, or duration). Nitrous oxide use was permitted but not reported in one study of two cardiac patients.[49] In all other cases, nitrous oxide was not used during periods of anesthesia for which EEG was analyzed.[35,42–48]

Neuromuscular blocking agents were used in both cardiac surgery (23 patients),[48,49] and noncardiac surgery cases (42 patients).[35,42–44,46,47] The remaining publication reported use of neuromuscular blocking agents in 123 of 129 total patients (95%) but was not separately reported for the 75 term neonatal patients included in this review.[45]

EEG Properties

Discontinuity. Discontinuity was reported in four publications (71 of 96 patients) during noncardiac surgery[35,42,45,46]

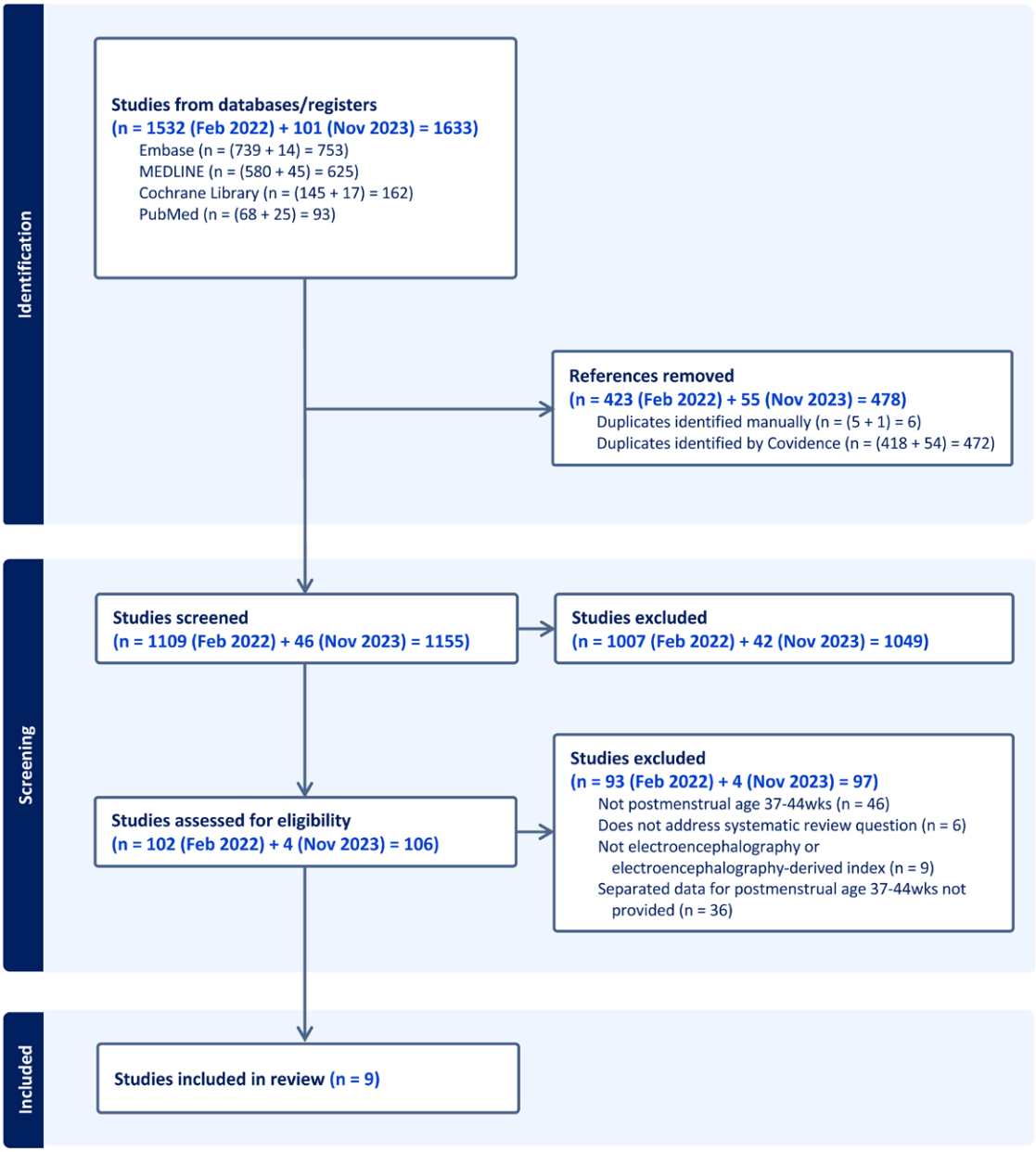

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

and in two publication (23 of 23 patients) during cardiac.[48,49] During noncardiac surgery, one publication (75 patients) reported discontinuity in 4 term neonates before anesthesia and in 69 term neonates during sevoflurane anesthesia.[45] Concomitant propofol administration was associated with most cases of profound discontinuity.[45] In another study (18 patients), there was no difference in burst suppression ratio between end-tidal sevoflurane concentrations of 0.5 and 2%.[46] One publication (two patients) reported intermittent periods of low-frequency oscillations (0.5 to 2 Hz) with amplitudes between 25 and 100 μV that merged to become continuous oscillations during washout from mean end-tidal concentration of sevoflurane of 2.3% (SD, 0.5; range, 1.5 to 3.5). This is suggestive of discontinuity, albeit not explicitly defined by the authors.[42] In a fourth publication (one patient), the incidence of discontinuity with general anesthesia was the primary outcome measure, and it was reported to not have occurred.[35]

During cardiac surgery, in one publication (21 patients), both the number of patients developing discontinuity and the degree of discontinuity progressively increased in response to decreasing temperature both before and during

Table 1. Summary of Findings for Noncardiac Surgery Using GRADE Method

Outcomes	Studies	Neonates	Main findings	Quality
Discontinuity	4	96	(i) EEG was classified as discontinuous in 6% before anesthesia and in 98% during surgery. Discontinuity during surgery was burst suppression in 51% of patients and the grade of discontinuity classification regressed by two classes compared to preoperatively in 49% of patients. Concomitant propofol administration was associated with most cases of profound changes in discontinuity classification (n = 75 of 111).[45] (ii) Discontinuity did not occur during anesthesia (n = 1 of 68).[35] (iii) Low-frequency oscillations (0.5–2 Hz) resembling regular transients (spontaneous activity transients) observed to gradually merge to become continuous oscillations in neonates during early phase of washout from sevoflurane anesthesia (n = 2 of 20).[42] (iv) Burst suppression ratio showed little anesthesia-dependent change under sevoflurane concentrations between 0.5 and 2% (n = 18 of 62).[46]	Very low
Power spectrum	3	22	(i) Absolute EEG power in 0.5–2, 2–4, and 30–100 Hz bands were compared. Median power decreased from baseline in 0.5–2 and 2–4 Hz in the sevoflurane group, analyzed across whole intraoperative period (n = 20 of 37).[43] (ii) Averaged EEG power in the 0.5–4 Hz (delta) band was reduced during sevoflurane anesthesia (n = 19 of 36).[47] (iii) Infants with < 52 weeks postmenstrual age demonstrate little change in P5–20 Hz and P8–13 (alpha) with anesthesia. Total P5–20 Hz and P8–13 (alpha) is under 100 μV^2 and is monotonically (maybe linearly) related to age in infants < 52 weeks postmenstrual age (n = 2 of 20).[42]	Very low
EEG-derived indices	1	18	Calculated 90% spectral edge frequency, relative beta ratio, and approximate entropy showed little anesthesia-dependent change under sevoflurane concentrations between 0.5 and 2% (n = 18 of 62).[46]	Very low
Time-series analysis	2	3	(i) During maintenance halothane anesthesia, neonatal EEG "consisted of a mixture of irregular delta, theta and alpha waves which were different from those of older patients who had waves of 10–12 Hz" (n = 1 of 62).[44] (ii) Low-frequency oscillations (0.5–2 Hz) resembling regular transients (spontaneous activity transients) observed to gradually merge to become continuous oscillations in neonates during early phase of washout from sevoflurane anesthesia (n = 2 of 20).[42]	Very low
Seizures	1	75	Seizures may occur in up to 4% neonates during surgery. However, the distribution between term (n = 75 of 111) and preterm (n = 36 of 111) was not reported.[45]	Very low
aEEG	1	75	Propofol during sevoflurane anesthesia was associated with most cases of profound changes in aEEG patterns (n = 75 of 111).[45]	Very low

The findings were determined with a population of 37- to 44-week postmenstrual age humans during noncardiac surgery. Anesthesia condition was the intervention and the comparator.

aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

cardiac bypass.[48] In this study, the EEG became isoelectric in all patients cooled less than 32°C,[48] whereas in another (two patients), all patients were cooled to less than 20°C, and isoelectric EEG only developed after additional administration of thiopental.[49] These data suggest an association between lower body temperature and the development of discontinuity during cardiac surgery; however, anesthetic management during these periods were not reported in detail.[48,49]

Power Spectrum and EEG-derived Indices. Four publications (40 patients) with noncardiac surgery reported details of the power spectrum or EEG-derived indices. Two publications (20 patients) reported a decrease in spectral power in the frequency range 0.5 to 4 Hz during volatile anesthesia compared with 3 to 6 h preanesthesia and 3 to 6 h postanesthesia, although the data were not adequately detailed to show a graded dose–response relationship.[43,47] One publication (two patients) reported no change in spectral power in the frequency range 5 to 20 Hz,[42] and another (20 patients) showed no meaningful change in the frequency range 30 to 100 Hz with washout of volatile anesthesia.[43] Spectral power in the frequency range 20 to 30 Hz was not reported. In 18 patients, 90% spectral edge frequency, relative beta ratio, and approximate entropy showed little change between end-tidal sevoflurane concentrations of 0.5 and 2%.[46]

Seizures. In a study of 111 neonates (36 preterm and 75 full-term) requiring noncardiac surgery, none were known to have seizures preoperatively, but 11 had electrographic seizure activity identified by aEEG in the perioperative period. Intraoperative electrographic seizure activity occurred in four patients (two single occurrences, two repetitive occurrences), with onset during induction (end tidal sevoflurane concentration, 2.5 to 5%) in one case.[45] In the first 24 postoperative hours, electrographic seizure activity was identified in eight neonates (six single seizures, two repetitive seizures), and one had electroclinical seizures.[45] Data relating intraoperative electrographic seizure activity to postoperative seizures, preterm or full-term birth, or suspected genetic syndromes (in four patients) were not reported.

Table 2. Summary of Findings for Cardiac Surgery Using GRADE Method

Outcomes	Total studies	Total neonates	Findings	Quality (GRADE)
Discontinuity	2	23	(i) Moderate burst suppression occurred in all neonates during cardiopulmonary bypass. In neonates with CPB but not DHCA, moderate burst suppression (an interburst interval under 30 s) was the maximum effect. All neonates who cooled to < 32°C developed severe burst and subsequence isoelectric EEG (n = 21 of 21).[48] (ii) Neonates with profound hypothermia (17.9 ± 1.6°C) in addition to fentanyl/neuromuscular blocker anesthesia exhibit ongoing EEG activity. A thiopental bolus of 8 mg/kg in addition to hypothermia before DHCA rendered EEG isoelectric during DHCA (n = 2 of 15).[49]	Very low
Time-series analysis	1	21	With the induction of general anesthesia, neonatal EEG changed from typical for age to slow and continuous (n = 21 of 21).[48]	Very low
Seizures	1	2	During DHCA, there were no patterns consistent with seizure activity, focal ischemia, or global hypoperfusion (n = 2 of 15).[49]	Very low

The findings were determined with a population of 37- to 44-week postmenstrual age humans during cardiac surgery. Anesthesia condition was the intervention and the comparator. CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; EEG, electroencephalography.

Table 3. Risk of Bias Summary Determined Using the ROBINS-I Tool

Study ID	Bias due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations from Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall Bias
Stolwijk *et al.* (2017)[45]	Serious risk	Low risk	Serious risk	Serious risk	Low risk	Low risk	Moderate risk	Serious risk
Costerus *et al.* (2021)[43]	Serious risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk	Serious risk
Hendrikx *et al.* (2022)[47]	Serious risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk	Serious risk
Seltzer *et al.* (2016)[48]	Moderate risk	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk	Moderate risk
Hayashi *et al.* (2012)[46]	Serious risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Serious risk
Rung *et al.* (1991)[49]	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Sury *et al.* (2014)[42]	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Cornelissen *et al.* (2017)[35]	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk
Oshima *et al.* (1981)[44]	Serious risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk

Discussion

Despite many publications meeting the search criteria, only nine publications including a total of 140 patients addressed the review question. Sample sizes were small, and there was significant heterogeneity in the types of surgeries, electrode montages, and EEG analysis methods. The quality of the evidence was very low when assessed using the GRADE system. Four publications reported data from just one or two patients, and there was significant heterogeneity of outcomes. Although the predominance of observational study designs introduces risk of bias, it is consistent with the ethical imperative to provide general anesthesia to neonates only when clinically necessary and to always provide standard-of-care anesthesia when doing so.

Many publications did not report the postmenstrual ages of individual subjects. Despite reaching out to investigators directly, these data had either not been collected or could not be retrospectively accessed. Knowledge about this population could be improved through standardized reporting of postmenstrual age in clinical studies and better public availability of data.

Most studies included in this review used six or fewer electrodes, and scalp positions were heterogenous. As a result, the evidence does not support any interpretation of spatial patterns of activity. Because the neuroanatomical associations between anesthesia and EEG are still uncertain[25,28] and the neonatal cortex is still developing,[50] there is much to be gained from exploring the spatial patterns. If loss of consciousness with general anesthesia is indeed a direct drug effect on the cortex,[51] then a more nuanced understanding might consider where, as well as what, changes are best measured in the term neonatal EEG.

Although not observed in all patients, some form of discontinuity was reported in 94 of 119 neonates across both cardiac[48,49] and noncardiac[35,42,45,46] groups. Discontinuity increased with increasing dose of anesthesia; however, there was heterogeneity between the definitions used for discontinuity, and these definitions were not clearly referenced. Cornelissen *et al.*[35] defined discontinuity as a period of

greater than 2 s with an amplitude of less than 25 μV across most electrodes. Seltzer *et al.*[48] defined discontinuity as burst suppression graded according to duration of the interburst intervals (less than or equal to 30 s, greater than 30 s and less than 180 s, and greater than or equal to 180 s), without any amplitude criteria. Sury *et al.*[42] described "regular transients that later merged to become continuous oscillations" with washout of sevoflurane, which suggests discontinuity albeit not systematically defined.

Interestingly, definitions of burst suppression are also heterogenous across the entire neonatal literature.[52] This is despite discontinuity being typical in the developing brain[50] and burst suppression being a key feature used to grade severity of neonatal encephalopathies and guide clinical treatment.[53] Neonatal burst suppression is considered an ominous sign, yet discontinuity with neonatal general anesthesia is reversible and has no known associated harm.[54] It remains unclear whether the discontinuity observed in term neonates with general anesthesia is the same phenomenon as burst suppression seen with general anesthesia in older patients.

EEG-derived depth-of-anesthesia indices, which often incorporate discontinuity detection in their algorithms, perform poorly in children under 5 yr of age, particularly in those under 1 yr.[25,55–58] It is unclear whether this represents a fundamental difference in general anesthetic effects on the developing brain or age-related changes in pharmacodynamic potencies. In other words, are the mechanisms of anesthesia effect fundamentally different in neonates, or are the unique effects that anesthesia has on neonatal EEG independent of the effect on clinical stage of anesthesia? This question presupposes the possibility that the EEG does not directly measure anesthetic state.[28]

aEEG was reported for 75 patients (54%). It classifies filtered and compressed EEG by relatively simple pattern recognition of background activity.[59] aEEG was originally developed to enhance EEG monitoring in adult patients after cardiopulmonary resuscitation.[60] In neonates, aEEG is used to grade the degree of discontinuity and screen for seizures.[61,62]

The aEEG algorithm defines burst suppression within a continuum of discontinuity, a point at which background activity has low amplitude and no variability (0 to 1 μV) and bursts have amplitude greater than 25 μV. It is quantified by the density of bursts per hour.[59] In contrast, consensus guidelines define burst suppression as atypically composed EEG bursts separated by prolonged and atypically low voltage interburst periods (less than 5 μV), with no spontaneous variability or reactivity to external noxious stimulation. Burst suppression is distinguished from excess discontinuity by the absence of typical patterns within the bursts.[19]

The potential association between body temperature and discontinuity may be a significant confounder for the interpretation of EEG as a biomarker of anesthetic state. In adults undergoing controlled hypothermia during cardiac surgery, the degree of burst suppression systematically depends on the degree of hypothermia. In the setting of 1% isoflurane administration, the average interburst interval increases with decreasing temperature and returns toward baseline with rewarming.[63] This is relevant because hypothermia is likely in neonates undergoing general anesthesia, both therapeutic during cardiac bypass and iatrogenic. Therapeutic hypothermia is also routinely used in neonatal encephalopathy.[64] Although there are no data reporting the effects of mild hypothermia on neonatal EEG, the direct effect of temperature has potential to make EEG-guided therapeutic decisions more difficult.[65] One study (14 patients) of children aged less than 2 yr during deep hypothermic arrest for cardiac surgery reported decreased EEG voltages without spectral change with decreasing temperature alone; however, there were internal inconsistencies, and the anesthesia data were not reported in detail. This suggests further targeted investigation may be worthwhile.[66]

With increasing interburst interval, a neonatal EEG contains fewer low-frequency oscillations in any given data window being analyzed. This is mathematically consistent with a power spectrum containing less absolute power in these lower frequencies. In turn, neonatal EEG is dominated by the frequency range 0.5 to 4 Hz, the spectral power of which is observed to decrease with increasing volatile anesthesia.[43,47] Detailed characteristics of discontinuity associated with hypothermia are not reported. Thus, it is plausible that a common underlying mechanism (or family of mechanisms) is being observed, relating both increasing anesthesia dose and decreasing body temperature with increasing discontinuity in a dose-related way. One might speculate receptor-mediated mechanisms that are dependent on the rate of adenosine triphosphate production. This is presented visually in figure 2.

Although the quality of evidence is very low, the results herein may suggest two divergent interpretations regarding the measurement of hypnosis with general anesthesia. We set aside the conundrum of defining consciousness itself, let alone consciousness in a neonate, other than to acknowledge that the lack of a clear definition makes it a difficult phenomenon to measure. Nonetheless, if we assume that inhalational anesthetics do have a hypnotic effect in neonates, then the challenge lies in measuring the effect size using EEG. Based on the evidence above, doing so by quantifying changes in EEG activity in the 5- to 100-Hz frequency band is unlikely to be successful. This is consistent with familiar EEG-based indices being unreliable in these patients. However, examining patterns that might occur in activity below 5 Hz or patterns observed with discontinuity may hold promise. Unfortunately, low-frequency signals are notoriously vulnerable to artifact.

Alternatively, one might consider that the typical changes observed in EEG with inhalational anesthesia represent a direct neurologic correlate of hypnosis. In this case, their absence in neonates might suggest the confronting idea that when neonates go limp and unresponsive on administered

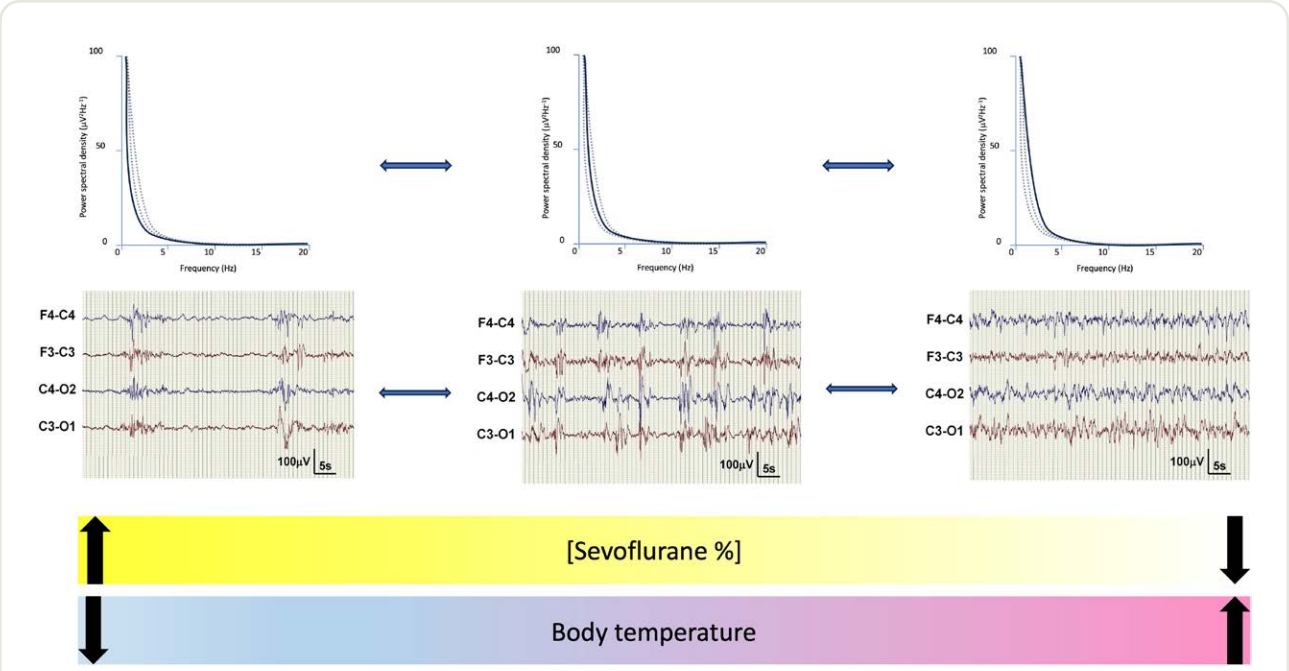

Fig. 2. Possible common underlying mechanism. With increasing sevoflurane concentration and/or with decreasing body temperature, the low-frequency oscillations of neonatal electroencephalography (EEG) become increasingly discontinuous and *vice versa*.

inhalational agents, it is not due to hypnosis at all. It could simply reflect a direct drug effect at the spinal cord level. An exploration of pharmacologic plausibility for anesthesia-induced immobility mediated primarily at the spinal cord without hypnosis mediated in the brain follows.[67,68]

Inhalational agents act in the brain to inhibit synaptic transmission, albeit with limited receptor selectivity. They are active at γ-aminobutyric acid type A ($GABA_A$), glutamate, glycine, and nicotinic receptors, as well as nitric oxide pathways.[69–71] Although it remains unclear how their actions translate into clinical effects, it is thought that augmentation of $GABA_A$-mediated postsynaptic hyperpolarization predominates.[3,4,17,70]

In the neonatal brain, higher postsynaptic intracellular chloride concentrations mean that when $GABA_A$ receptors are activated and open chloride channels, postsynaptic membranes depolarize rather than hyperpolarize. This leads to excitatory rather than inhibitory signaling.[4,72–76] In the neonatal brain, the role of $GABA_A$ receptors is thought to be primarily involved in signaling for neuronal proliferation.[77,78] The neonatal brain also undergoes massive proliferation of astrocytes, which reuptake and recycle GABA from the synaptic cleft, further modifying the synaptic environment.[79]

In contrast, in the neonatal spinal cord, $GABA_A$-mediated signaling does not provide excitatory drive.[80] A balance between excitation and inhibition is preserved due to concurrent increases in GABAergic and glutamatergic pathways and immature descending inhibitory signaling.[81,82] Therefore, it may be that anesthesia-induced GABAergic signaling remains inhibitory in the spinal cord but not in the brain.

If this is true and if one considers it plausible that anesthesia-induced hypnosis might not occur at all in neonates, alternative measurement strategies are needed that better reflect the clinical goals of anesthesia. Such strategies might include characterizing changes that occur with general anesthesia to evoked response potentials from noxious stimuli. In conclusion, both increasing sevoflurane concentration and decreasing temperature appear to be associated with increased discontinuity measured in neonatal EEG, and there is scope for more detailed characterization of these relationships.

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Competing Interests

Dr. Corlette is the founder and CEO of a prerevenue medical device company developing a novel pediatric EEG sensor, of which they are the inventor. The other authors declare no competing interests.

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Supplemental Digital Content

Supplement 1. Literature search terms, https://links.lww.com/ALN/D582
Supplement 2. Data extraction template, https://links.lww.com/ALN/D583
Supplement 3. Extracted data tables, https://links.lww.com/ALN/D584

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