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Anesthesia-Induced Brain Oscillations

A Natural Experiment in Human Neurodevelopment

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Abstract

GABAergic inhibition mediates many crucial aspects of brain development, including the development of structural connections, critical period plasticity, and functional synchronization across large-scale networks via gamma-band oscillations. Disturbances in the development of GABAergic circuits are thought to underlie neurodevelopmental disorders such as schizophrenia and autism. Characterizing the developmental trajectory of these circuits in humans is a vitally important problem, but a challenging one. Current approaches in humans include postmortem studies and noninvasive imaging. These methods can provide highly specific information about GABA circuits in older children, and in-depth functional information in younger children, albeit with only indirect links to GABA circuit function. An ideal characterization in humans would map the continuous trajectory of GABA circuit function from infancy through adulthood with a common set of tools, alongside detailed measurements of sensory, cognitive, and language function. In this chapter it is proposed that studies of anesthesia-induced oscillations could be used to characterize and track the development of GABAergic oscillatory circuits from infancy through adulthood. The most commonly used anesthetic drugs in both pediatric and adult practice are powerful positive allosteric modulators of GABA receptors. These drugs induce large, stereotyped oscillations in the unconscious state that are likely generated by the same GABAergic circuits responsible for gamma oscillations in the conscious state. In the United States alone, these anesthetic drugs are administered to tens of millions of patients each year, under conditions of both neurotypical and atypical development. By harnessing this anesthetic experiment of nature, it may be possible to develop detailed developmental trajectories of GABAergic circuit function in humans.

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Introduction

Inhibitory signaling mediated by gamma-aminobutyric acid (GABA) plays a pivotal role in the maturation of the cerebral cortex (Le Magueresse and Monyer 2013). GABAergic interneurons contribute to the development of structural connections within cerebral cortex (Le Magueresse and Monyer 2013), mediate the regulation of critical period plasticity (Fagiolini and Hensch 2000; Takesian and Hensch 2013), and are thought to support functional synchronization of activity across large-scale networks via gamma-band oscillations (~30–70 Hz) (Uhlhaas and Singer 2013). In particular, fast-spiking parvalbumin-positive (PV+) GABA interneurons are required to generate gamma oscillations, as demonstrated in both computational models (Whittington et al. 2000; Börgers et al. 2005) and optogenetic studies (Cardin et al. 2009; Sohal et al. 2009; Cho et al. 2015). Given their essential role in brain maturation and in large-scale network function, disturbances in the development of GABAergic circuits are thought to underlie neurodevelopmental disorders such as schizophrenia and autism. Schizophrenic patients have reduced numbers of PV+ interneurons in the dorsolateral prefrontal cortex (Glausier et al. 2014; Enwright et al. 2016), and also show disrupted synchrony in gamma-band activity (Uhlhaas and Singer 2010). Autistic patients show reduced numbers of PV+ interneurons in medial prefrontal cortex (Hashemi et al. 2017), reduced GABAergic signaling during sensory processing tasks (Robertson et al. 2016), and altered resting-state functional connectivity across multiple oscillatory bands, including the gamma band (Kitzbichler et al. 2015; Vakorin et al. 2017).

Given the pivotal role that GABAergic circuits play in development and developmental disorders, characterization of these circuits in humans is vitally important. However, such characterizations are challenging. Postmortem studies can provide detailed anatomic information on inhibitory neuron circuits (Ariza et al. 2016; Hashemi et al. 2017), but this type of data is difficult to collect, and still more difficult to relate to covarying functional information. Magnetic resonance imaging (MRI) spectroscopy has been used to characterize GABA neurotransmitter levels noninvasively (Robertson et al. 2016), but such methods are challenging to apply in young children or infants. Electroencephalography (EEG) and magnetoencephalography (MEG) have been used to analyze oscillatory activity within large-scale functional networks (Uhlhaas and Singer 2013; Kitzbichler et al. 2015; Vakorin et al. 2017). At present, however, it is difficult to disambiguate gamma-band oscillations from gamma-band power that comes from the "1/f" spectrum generated inherently by neuronal and postsynaptic activity (Buzsáki et al. 2012). As a result, it is difficult to make clear inferences about GABAergic networks relating to gamma oscillations distinct from gamma-band power generated by overall neuronal activity. Event-related potentials have also been used to interrogate specific sensory (LeBlanc et al. 2015) and language (Ortiz-Mantilla et al. 2016) functions in children and infants, in some cases alongside information about gamma-band oscillations

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(Ortiz-Mantilla et al. 2016). Although highly plausible inferences can be made about inhibitory networks from these data, such inferences remain indirect in the absence of more specific information related more directly to GABAergic circuits.

Despite the rich information available from these studies, more direct assessments of GABAergic circuit function during human development are clearly needed. An ideal characterization would:

1. Map the continuous trajectory of circuit development from infancy through adulthood using a common set of tools.
2. Explicitly measure specific brain oscillations.
3. Conduct alongside measurements of covarying sensory, cognitive, and language function.

The question is: How could this be accomplished?

In this chapter I propose the idea that studies of anesthesia-induced oscillations could be used to characterize and track the development of GABAergic oscillatory circuits from infancy through adulthood. The most commonly used anesthetic drugs in both pediatric and adult practice are indeed powerful positive allosteric modulators of GABA receptors (Hemmings et al. 2005). These drugs induce large, stereotyped oscillations that coincide with unconsciousness (Purdon et al. 2013, 2015b)—oscillations which are very likely generated by the same GABAergic circuits responsible for gamma oscillations in the conscious state (Börgers et al. 2005; McCarthy et al. 2008; Ching et al. 2010). Moreover, in the United States alone, these anesthetic drugs are administered to tens of millions of patients each year, under conditions of both neurotypical and atypical development. By harnessing this anesthetic experiment of nature, I argue that it would be possible to develop detailed developmental trajectories of GABAergic circuit function in humans.

Anesthetic Mechanisms

General anesthesia is a reversible drug-induced state consisting of unconsciousness, analgesia, amnesia, immobility, and autonomic stability (Brown et al. 2010). Each year, over 20 million patients (Brown et al. 2010), including 6 million children (Sun 2010), receive general anesthesia for surgical and medical procedures. Perhaps one of the most fascinating properties of anesthetic drugs is their ability to produce altered states of arousal and unconsciousness. Anesthetic drugs act by modulating neurotransmitter-gated ion channels in the central nervous system (Hemmings et al. 2005). Propofol, one of the most commonly used anesthetic drugs in both adult and pediatric practice, is a positive allosteric modulator of $GABA_A$ receptors, enhancing GABAergic inhibition (Hemmings et al. 2005; Brown et al. 2011). Sevoflurane, an inhaled ether-derived anesthetic frequently used in pediatric practice, also enhances

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inhibition via $GABA_A$ receptors (Hemmings et al. 2005). At low doses, both propofol and sevoflurane produce sedation, whereas at high doses they maintain a deep state of unconsciousness from which patients cannot be aroused (Purdon et al. 2015b). Other commonly used anesthetic drugs are known to act through distinct molecular mechanisms to produce other states of altered arousal. For instance, ketamine is an NMDA antagonist that produces analgesia, altered sensory perception, and hallucinations at low doses, and unconsciousness at high doses (Brown et al. 2011; Purdon et al. 2015b). Dexmedetomidine is an α2 adrenergic agonist that produces states of sedation which mimic nonrapid eye movement sleep, from which patients can be aroused with sufficiently strong stimuli (Brown et al. 2011; Purdon et al. 2015b).

Significant progress has been made in recent years to characterize how anesthetic drugs act at a systems level. A key insight has been that anesthetic drugs induce profound brain oscillations, visible in the EEG, whose structure corresponds to the drugs' underlying molecular mechanisms (e.g., GABA, NMDA, α2 adrenergic), as shown in Figure 10.1 (Purdon et al. 2015b). Moreover, for a given anesthetic drug, the structure of the oscillations varies with drug dose, in a way that correlates with a patient's state of altered arousal or unconsciousness (Purdon et al. 2013, 2015b). The neurophysiology and mechanisms of these drugs is becoming increasingly well understood,

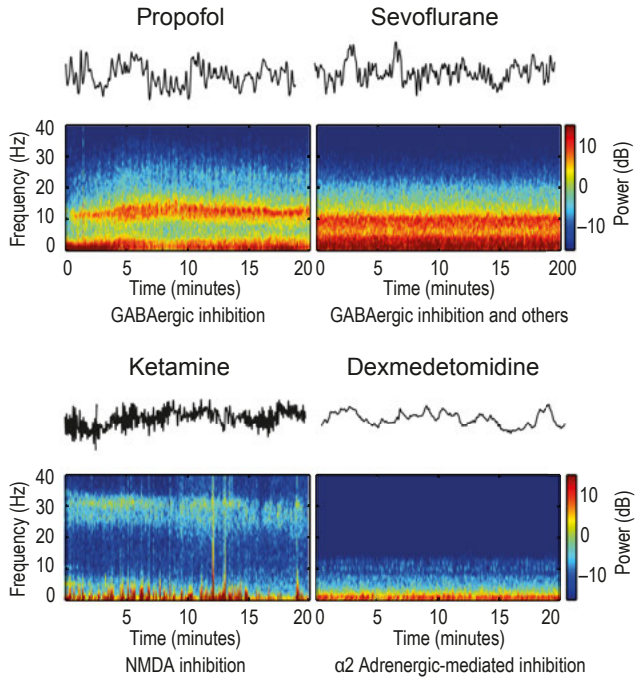

Figure 10.1 The structure of anesthesia-induced EEG oscillations varies by drug class and molecular mechanism (from Purdon et al. 2015b).

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making it possible, particularly in the case of the GABAergic drugs, to use the knowledge of anesthesia-induced brain oscillations to help characterize human brain development.

Slow and Alpha Oscillations: Markers of Propofol- and Sevoflurane-Induced Unconsciousness

Propofol-induced unconsciousness is characterized by the presence of large, stereotyped frontal alpha (8–12 Hz) and slow (0.1–1 Hz) oscillations (Figure 10.2; Lewis et al. 2012; Purdon et al. 2013, 2015b). When propofol is gradually administered, a combination of gamma and beta oscillations (~12–35 Hz) appears at a point in time that coincides with reduced responsiveness to external stimuli: a state of sedation (Purdon et al. 2013). At loss of consciousness, defined operationally as the point at which subjects stop responding to stimuli, large slow (0.1–1 Hz) and alpha (8–12 Hz) oscillations develop (Purdon et al. 2013). The propofol-induced alpha oscillations have a frontal predominance, whereas the slow oscillations are present across the scalp. The frontal alpha oscillations are coherent (i.e., spatially correlated at alpha frequencies), whereas the slow oscillations are not (Figure 10.3). General anesthesia maintained with sevoflurane is characterized by coherent frontal alpha oscillations (8–12 Hz), high-amplitude delta (1–4 Hz) and slow (0.1–1Hz) oscillations in the EEG (Akeju et al. 2014b). This pattern, observed when patients are sufficiently anesthetized to conduct surgery, is similar to what is observed during propofol-induced unconsciousness.

Recordings of intracranial neurophysiology in humans—spanning populations of single neurons, local field potentials, and intracranial EEG—show that propofol-induced slow oscillations reflect sustained periods of neuronal silence lasting 1 to 2 seconds, referred to as OFF states, interrupted by brief periods of firing, or ON states (Figure 10.4; Lewis et al. 2012). The slow oscillations become asynchronous or incoherent with increasing distance along the cortex, suggesting that the ON and OFF states in different areas of the cortex are likely to be misaligned in time. Thus, during this propofol-induced slow oscillation, both local cortical neuronal activity, as well as intracortical neuronal interactions are likely blocked, contributing to unconsciousness (Lewis et al. 2012).

Anesthesia-Induced Frontal Alpha: An Indicator of GABAergic Inhibitory Circuit Function

Computational models have been developed to study how propofol-induced oscillations might arise as a result of enhanced GABA inhibition within cortical and thalamocortical circuits. McCarthy et al. (2008) proposed a cortical model featuring inhibitory interneurons and excitatory pyramidal neurons with

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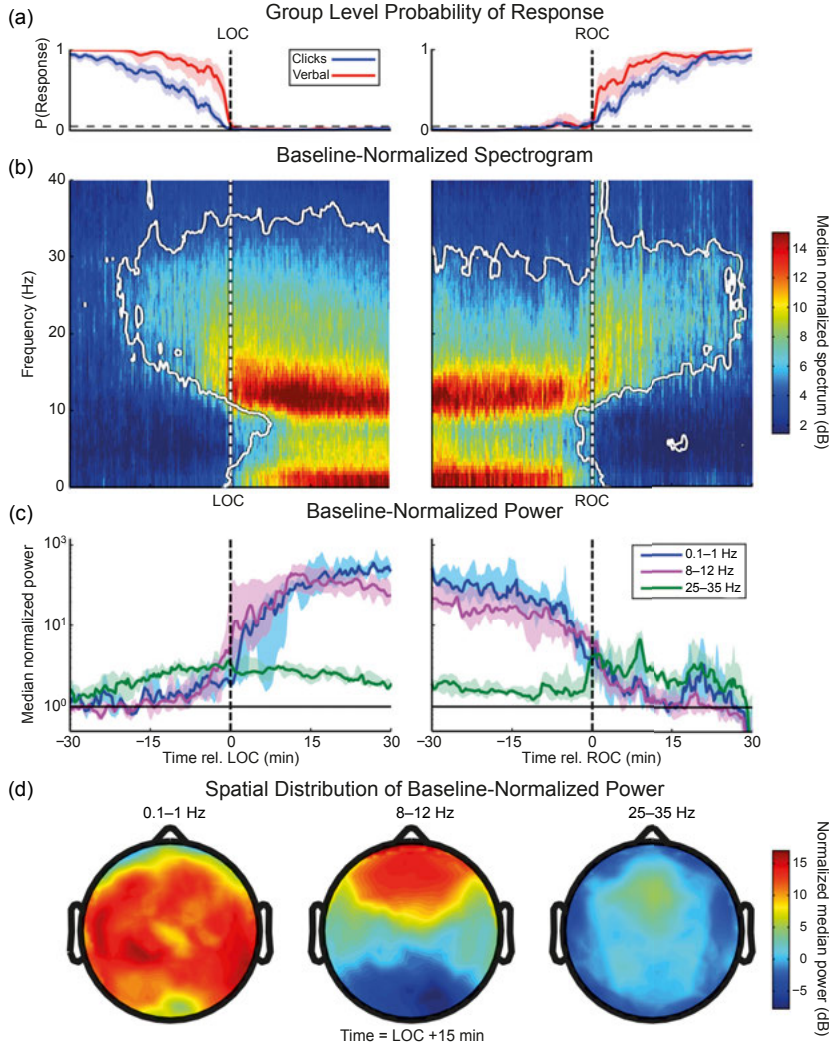

Figure 10.2 (a) Group-level probabilities of response to click (blue) and verbal stimuli (red) relative to loss of consciousness (LOC) and recovery of consciousness (ROC). (b) Group-level baseline-normalized spectrograms aligned with respect to LOC and ROC. (c) Group-level baseline-normalized power in the slow (0.1–1 Hz), alpha (8–12 Hz), and gamma (25–35 Hz) bands aligned with respect to LOC and ROC. (d) During profound unconsciousness with propofol, alpha power is concentrated in frontal channels, whereas the slow oscillations are distributed across the scalp. Reprinted with permission from Purdon et al. (2013).

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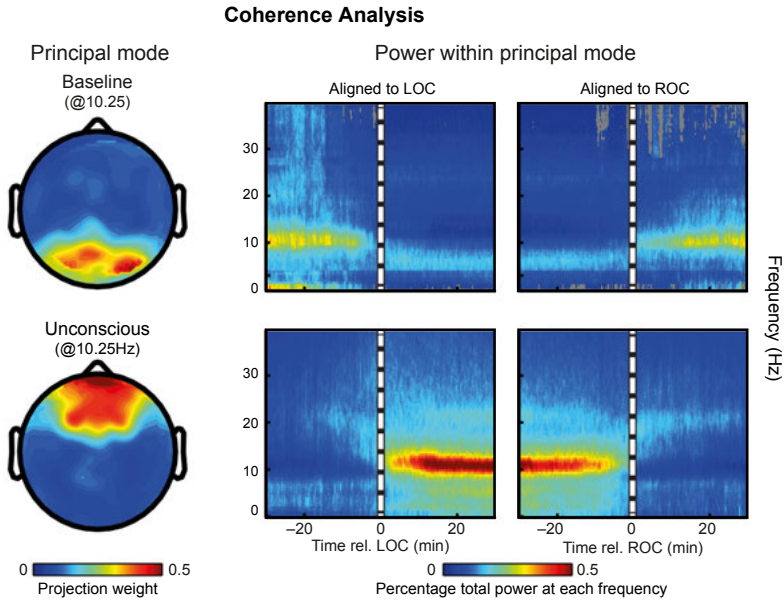

Figure 10.3 Top: In the conscious eyes-closed state, coherent alpha-band oscillations with a posterior distribution are present. Bottom: In the propofol-induced unconscious state, spatially coherent alpha waves are concentrated in the frontal channels. Adapted after Purdon et al. (2013).

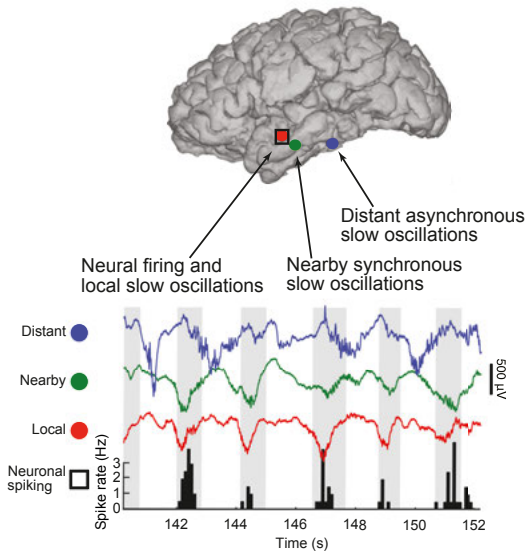

Figure 10.4 During propofol-induced unconsciousness in humans, neurons fire only in a specific phase interval defined by the local slow oscillations. Adapted after Lewis et al. (2012).

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Hodgkin–Huxley-style dynamics. The model included both putative PV+ fast-spiking interneurons and low-threshold spiking (LTS) interneurons (McCarthy et al. 2008). They found that enhanced GABA inhibition mimicking propofol, represented by increasing the $GABA_A$ conductance, could produce beta oscillations as well as alpha oscillations at higher levels of $GABA_A$ conductance, corresponding to higher propofol doses. A follow-up study by Ching et al. (2010) characterized thalamocortical loop dynamics in a similar fashion. This model included fast-spiking and LTS inhibitory interneurons and pyramidal excitatory neurons in the cortex as well as thalamic reticular interneurons and thalamocortical relay neurons in the thalamus. Here, propofol's actions were modeled by enhancing $GABA_A$ conductance by up to ~300% in both the cortex and thalamus. At baseline, this network showed gamma oscillations in the ~40 Hz range, driven by fast-spiking interneurons via a pyramidal interneuron mechanism, as described by Börgers et al. (2005). As the $GABA_A$ conductance was increased moderately by ~50% above baseline, corresponding to low propofol doses, oscillations formed in the low gamma (~30 Hz) and beta (13–25 Hz) frequency range (Figure 10.5). However, with increasing $GABA_A$ conductance, the oscillations decreased in frequency into the alpha range. Crucially, at some point the alpha oscillations became coherent (Figure 10.5). In the absence of the thalamic components of the model, the induced alpha oscillations

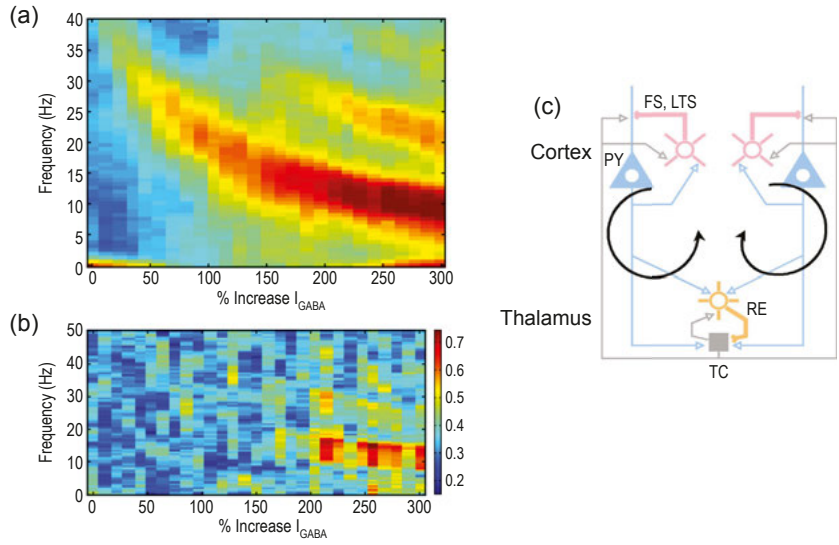

Figure 10.5 (a) Spectrogram and (b) coherence of cortical pyramidal postsynaptic currents from a (c) thalamocortical model as a function of increasing GABAergic inhibition. The dominant frequency decays monotonically, eventually settling into the 10 Hz alpha range at high GABA conductance levels (300% increase). At these levels, the cortical populations display high coherence, mediated by thalamocortical synchronization. Adapted after Ching et al. (2010).

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are not coherent (McCarthy et al. 2008). However, when the thalamus is part of the model, thalamic neuronal activity appears to entrain the cortical alpha oscillations, allowing them to become coherent (Ching et al. 2010).

A primary inference from these studies has been that the thalamus plays a key role in generating propofol-induced coherent frontal alpha oscillations. However, these computational studies also suggest that inhibitory cortical circuit components that normally mediate gamma oscillations, namely fast-spiking interneurons within a pyramidal-interneuron network (Börgers et al. 2005), produce beta and alpha oscillations under the enhanced inhibitory influence of propofol (Ching et al. 2010). These computational results suggest that propofol-induced frontal alpha oscillations could be used to quantify cortical inhibitory circuit function, and that coherence in these frontal alpha oscillations could be an indicator of related thalamocortical functional interactions.

Experimental evidence from both human and rodent studies is consistent with the predictions of these computational studies. The model behaviors correspond closely to the EEG dynamics seen in the propofol human volunteer studies described earlier (Purdon et al. 2013). These data have also been corroborated by hundreds of operating room recordings of propofol and other GABAergic anesthetic drugs, such as sevoflurane (Akeju et al. 2014b; Purdon et al. 2015b). Multisite invasive rodent neurophysiological recordings show that propofol-induced alpha oscillations are present in both the thalamus and cortex (Baker et al. 2014; Flores et al. 2017), and that those oscillations are coherent in the alpha band after loss of consciousness (Flores et al. 2017). The specific circuit-level contributions of different cell types (e.g., PV+ fast-spiking interneurons versus LTS interneurons) remain to be studied in detail. Nonetheless, the experimental and computational evidence to date is consistent with the notion that propofol- and sevoflurane-induced frontal alpha oscillations are generated by cortical and thalamocortical GABAergic inhibitory circuits.

Age-Dependent Anesthesia-Induced EEG Oscillations from Infancy to Adulthood

Through studies on human volunteer subjects we have learned a great deal about the clinical neurophysiology of anesthetic drugs (Purdon et al. 2013; Akeju et al. 2014a). Our ability to perform studies on humans safely is a direct consequence of improvements in anesthesia patient safety, developed over several decades, punctuated by the introduction of physiological monitoring standards in 1984, which ensured that electrocardiogram, end-tidal CO_2, blood pressure, and pulse oxygenation were monitored in every patient (Cooper et al. 1984). This allowed anesthesiologists to monitor and precisely manage the cardiovascular and respiratory side effects of anesthetic drugs. These safety improvements address the major concerns that might arise in

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volunteer studies in adults, but the situation is more complicated in children. First, there are concerns that anesthetic exposure may have lasting neurodevelopmental effects in children (Jevtovic-Todorovic et al. 2013). Moreover, clinical management in children is far more challenging. As a result, anesthesia studies in children are only conducted when surgical or medical procedures require general anesthesia.

Early studies of anesthesia-induced EEG changes in children focused on characterizing (a) quantitative EEG features as a function of age (Schultz et al. 2004), and (b) the behavior of commercial proprietary processed EEG "depth of anesthesia" parameters (Davidson et al. 2005). These studies found that EEG spectral parameters varied with age (Schultz et al. 2004) and that "depth of anesthesia" parameters developed for adults worked differently when applied to children (Davidson et al. 2005). These findings were of value clinically, because they made clear that anesthesia-induced EEG patterns in children differed from those in adults (Schultz et al. 2004), and that existing processed EEG monitors developed for adults could not be reasonably applied to children (Davidson et al. 2005). Their scientific utility, however, was limited by the absence of neural mechanisms that could link drug mechanisms to EEG features. Fortunately, significant progress has been made in recent years to work out the relationships between drug actions, neural circuits, and anesthesia-induced EEG oscillations (Brown et al. 2011; Purdon et al. 2015b). Moreover, as described earlier, there is a plausible and specific link between inhibitory circuits crucial in development and anesthesia-induced oscillations: the putative PV+ fast-spiking interneuron circuits that mediate gamma oscillations slow to beta and alpha frequencies under the influence of GABAergic anesthetic drugs. This new perspective, coupled with improved data analysis methods (Prerau et al. 2017), allows us to gain new insights by analyzing EEG oscillations recorded in children receiving general anesthesia.

A recent study by Lee et al. (2017b) analyzed age-dependent changes in frontal EEG power and coherence in 97 patients, between 0 and 21 years of age, who received propofol to maintain general anesthesia. They found that total power (0–40 Hz) increased from infancy through approximately 7 years of age, subsequently declining to a plateau at approximately 21 years (Figure 10.6). The top panels in Figure 10.6 show EEG spectrograms from representative subjects across the age range. The three older patients, aged approximately 4, 10, and 20 years, show the same combination of slow and alpha oscillations described above for adults. The EEG for the youngest patient, less than 1 year of age, however, has a different structure that lacks a distinct alpha peak. Lee et al. (2017b) also performed a more detailed analysis of alpha (8–13 Hz) and slow oscillation (0.1–1 Hz) power as a function of age (Figure 10.7). They found that alpha power peaked at approximately 7.3 years of age, whereas slow oscillation power peaked at approximately 11.6 years of age. Earlier studies by Akeju et al. (2015) showed similar results for the anesthetic drug sevoflurane. Given the putative GABAergic mechanism for propofol- and

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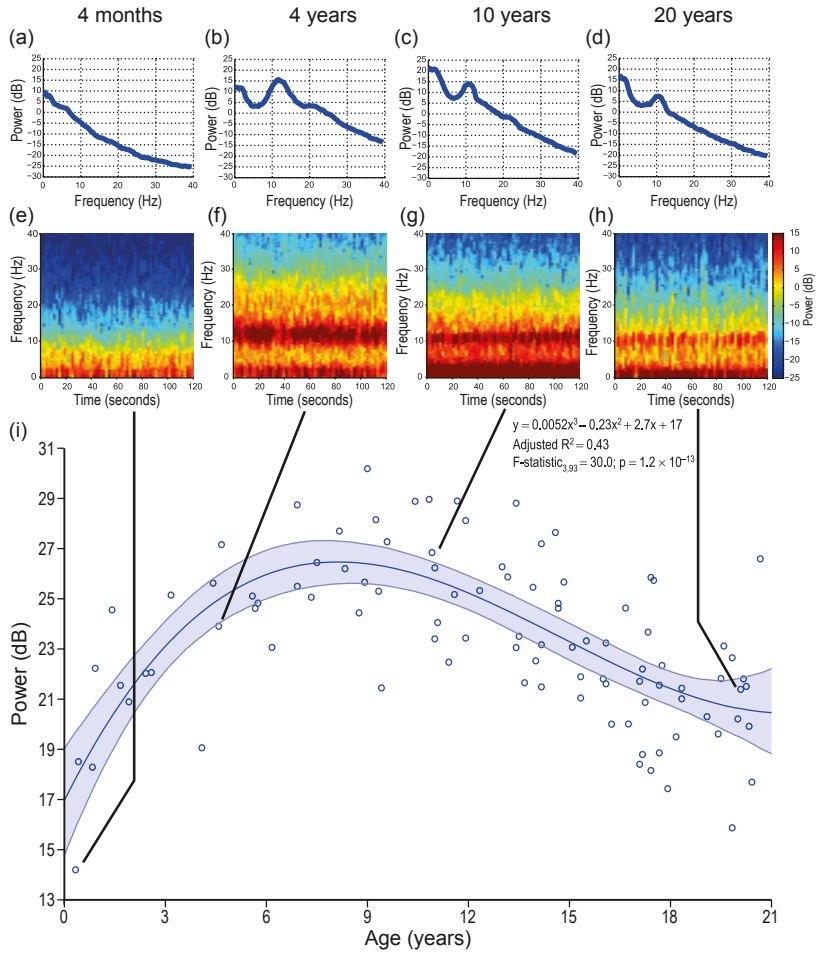

Figure 10.6 Representative frontal EEG spectrograms (a–h) illustrating that slow (0.1–1 Hz) and delta (1–4 Hz) oscillations are present during general anesthesia maintained with propofol. Alpha (8–13 Hz) oscillations appear to emerge after 1 year of age. Total EEG power (1–40 Hz) for each patient is plotted in (i) as a function of age. From Lee et al. (2017b).

sevoflurane-induced frontal alpha oscillations, and the evidence for a medial prefrontal cortical generator (Flores et al. 2017), these results imply that GABAergic inhibition in the medial prefrontal cortex increases in extent from infancy through approximately 7 years of age, declining gradually thereafter into early adulthood. This interpretation is consistent with postmortem studies of age-dependent human (Petanjek et al. 2011) and nonhuman primate synaptic density (Cruz et al. 2003). Human prefrontal cortical pyramidal neuron dendritic spine density peaks at approximately the same age, ~ 7 years (Petanjek et

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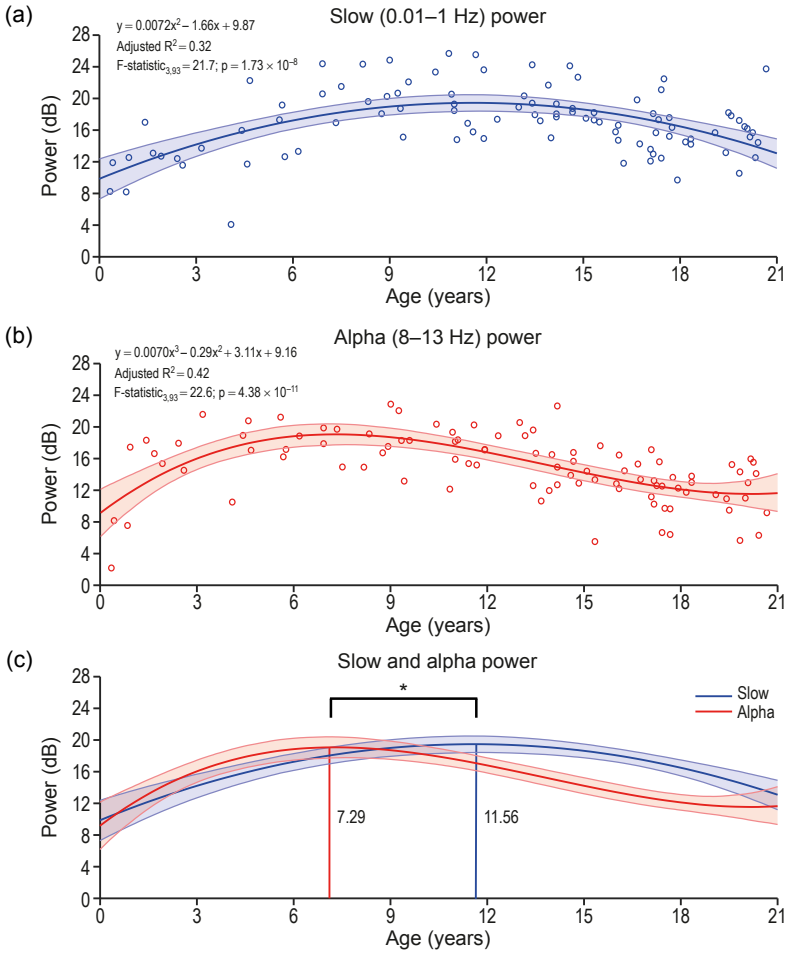

Figure 10.7 (a) Age-dependence of propofol-induced slow (0.1–1 Hz) power. (b) Age-dependence of propofol-induced frontal alpha power (8–13 Hz). (c) The putative GABA-mediated alpha power peaks at 7.3 years of age, distinct from the slow oscillation, whose power peaks at 11.6 years of age. From Lee et al. (2017b).

al. 2011), in accordance with the peak in propofol-induced alpha wave power (Lee et al. 2017b). The dendritic spines correspond to excitatory synapses, but based on studies of nonhuman primate prefrontal cortex, GABAergic inhibitory synapses are thought to develop in parallel with excitatory synapses in early life (Anderson et al. 1995), consistent with the interpretation that the anesthesia-induced frontal alpha power reflects inhibitory signaling.

The EEG spectrogram shown for the youngest representative patient in Figure 10.6 (upper left corner) lacks a distinct alpha wave, suggesting that

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different circuit dynamics may be active in children less than 1 year of age. Cornelissen et al. (2015) conducted a series of multichannel EEG recordings in infants less than 6 months of age during general anesthesia for surgery maintained with sevoflurane. Their findings reveal that sevoflurane-induced frontal alpha power was absent in children between 0 to 3 months of age (Figure 10.8). At 4 to 6 months of age, sevoflurane induced broad-band power spanning alpha (8–12 Hz) and beta (12–30 Hz) frequencies, albeit without the pronounced peak at alpha frequencies observed in adults (Figure 10.8). The studies by Lee et al. (2017b) showed a similar effect under propofol: patients between 4 months and 1 year of age showed increased power at beta frequencies, but not at alpha frequencies (Figure 10.9). This would suggest that inhibitory networks are still developing in prefrontal cortex in the first year of life. In particular, modeling studies by McCarthy et al. (2008) and Ching et al. (2010) suggest that the capacity for inhibitory signaling is lower in infants compared to adults and older children, such that propofol- and sevoflurane-induced actions are only able to slow cortical pyramidal-interneuron circuits into the beta-frequency range, short of the alpha range as in older children and adults.

Cornelissen et al. (2015) performed a coherence analysis, similar to that depicted in Figure 10.3 for adults (Purdon et al. 2013), which characterized the spatial distribution of coherent activity. Cornelissen et al. (2015) found that, in contrast to adults (Purdon et al. 2013; Akeju et al. 2015; Purdon et al. 2015a), children 6 months of age or younger do not have coherent frontal alpha waves (Figure 10.10). Coherence analysis in children less than 1.5 years old, who received sevoflurane (Akeju et al. 2015), showed that frontal

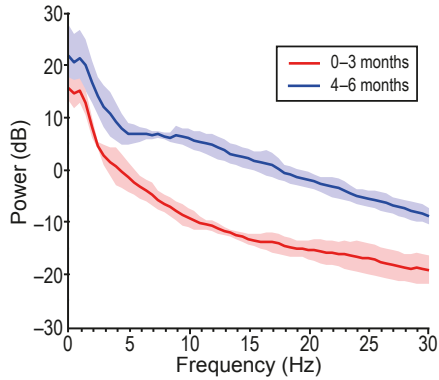

Figure 10.8 Spectra during maintenance of sevoflurane-induced general anesthesia in patients 0–3 months (red) and 4–6 months of age (blue). Unlike adults, infants in both age groups lack a distinct alpha peak. The older infants show increased broad band power spanning alpha (8–12 Hz), beta (12–25 Hz), and gamma bands (>25 Hz). From Cornelissen et al. (2015).

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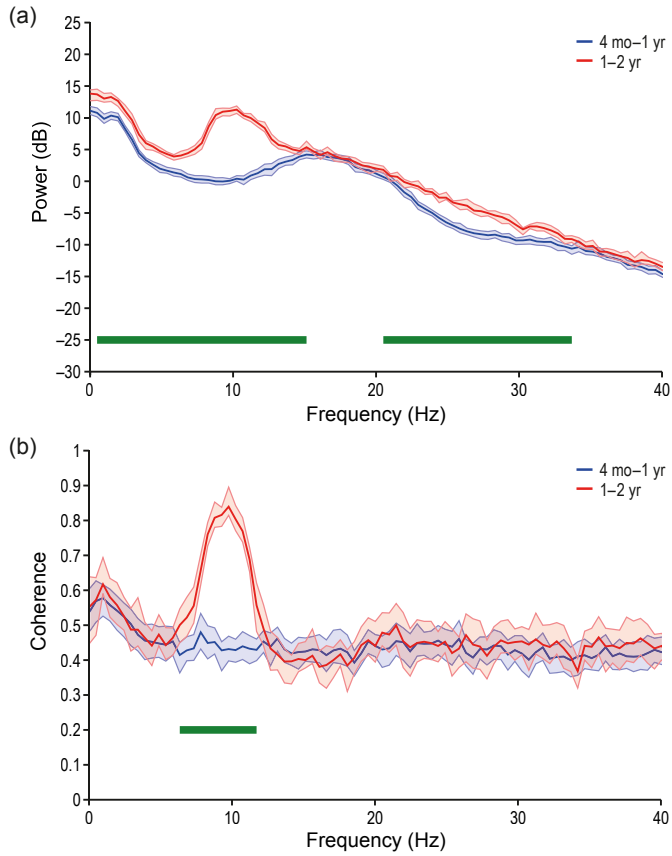

Figure 10.9 (a) The frontal EEG spectrum in infants (blue, 4 months to 1 year of age) and toddlers (red, 1–2 years of age). (b) The frontal EEG coherence in these same groups. The green bars indicate a statistically significant difference (95% bootstrap confidence intervals for the difference do not intersect zero). These data illustrate how propofol-induced coherent frontal alpha oscillations do not fully develop until 1 year of age. From Lee et al. (2017b).

coherence, though absent at 6 months of age, appears at approximately 1 year of age (Figure 10.10). Lee et al. (2017b) showed a similar result for propofol: coherent alpha waves were absent in children less than 1 year of age but appear thereafter (Figure 10.9). These results suggest that in infancy, the functional and/or structural connections required to generate and maintain coherent frontal alpha waves are absent, and only develop later, at approximately 1 year of age. This interpretation is consistent with studies of thalamocortical functional connectivity in infants using functional MRI, which show an absence of frontal thalamocortical connectivity in newborn children that subsequently develops by 1 year of age (Alcauter et al. 2014).

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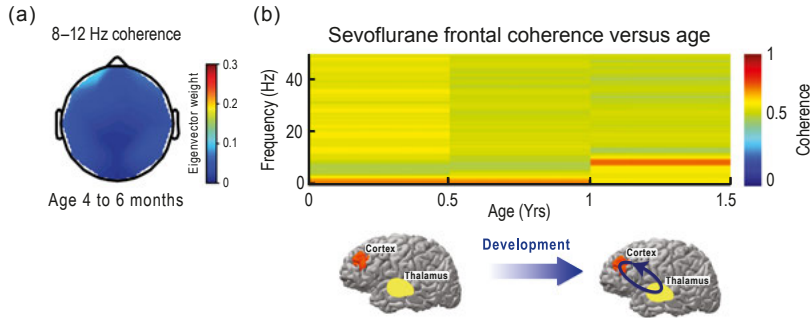

Figure 10.10 (a) Studies of sevoflurane-induced EEG in infants less than 6 months old show that they do not have coherent frontal alpha waves (adapted after Cornelissen et al. 2015). (b) Analysis of sevoflurane-induced EEG in children from 0–1.5 years shows that frontal alpha waves become coherent at approximately 1 year of age (adapted after Akeju et al. (2015).

Discussion

Age-related changes in the EEG of children have been described during both wakefulness and sleep, and show similar trends throughout childhood (Gaudreau et al. 2001; Feinberg and Campbell 2010; Segalowitz et al. 2010; Miskovic et al. 2015). However, age-related anesthesia-induced changes are perhaps unique in that they appear to reflect GABA interneuron-dependent frontal cortical and thalamic function (McCarthy et al. 2008; Ching et al. 2010; Flores et al. 2017). The changes in anesthesia-induced frontal alpha power from infancy through childhood, adolescence, and adulthood might therefore be interpreted as a marker of GABA interneuron circuit development. Our current understanding of the mechanisms for the anesthesia-induced frontal alpha wave has specific implications for the development of fast-spiking PV+ interneuron circuits within the prefrontal cortex. The age-dependent time course for propofol-induced slow oscillations, the other major feature of the EEG under propofol, differs significantly from that of the frontal alpha wave (Figure 10.7). In the future, as we learn more about the mechanisms for the propofol-induced slow oscillations, it may be possible to make inferences about other developing brain circuits. The age-related changes in EEG power shown in Figure 10.6 might also reflect a more general process of development that includes synaptogenesis in early childhood, followed by neural pruning during maturation. Given the putative frontal thalamocortical mechanism for the propofol- and sevoflurane-induced frontal alpha oscillations, the absence of coherent frontal alpha waves during infancy and subsequent appearance at approximately 1 year of age (Figures 10.9, 10.10) likely reflect an underlying development within the thalamus and cortex.

The age dependence of anesthesia-induced EEG oscillations in children has a number of clinical implications. The differences in EEG power across all

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frequency bands as a function of age suggest that "depth of anesthesia" monitors developed for adult patients are not accurate for use in children. However, the form of the anesthesia-induced EEG oscillations—namely, large, slow, and frontal alpha oscillations—is similar in patients above 1 year of age. Monitoring strategies based on these features might therefore apply equally well in children as they do in adults. In the simplest of forms, this could consist of direct interpretation of the unprocessed EEG and spectrogram during general anesthesia (Bennett et al. 2009; Purdon et al. 2015b). The options for anesthetic drugs are limited, with a limited pipeline of drugs in development. If concerns persist that anesthetic exposure may have neurodevelopmental effects, a strategy to minimize exposure could help mitigate potential harm. EEG monitoring in children might help establish in individual patients an appropriate level of sedation or unconsciousness using the smallest possible anesthetic dose.

The age-dependent features of the propofol- and sevoflurane-induced EEG patterns raise interesting possibilities for future studies: clinical anesthetics could be used to assess cortical inhibitory circuit function in relation to developing sensory or cognitive function, or in relation to developmental neurocognitive disorders. The insights gained from analyses of age-dependent effects in GABAergic anesthetic drugs suggest that similar insights might be gained by analyzing oscillations induced by anesthetic drugs that act at other sites, such as NMDA, α2 adrenergic, or μ-opioid receptors. Ketamine is being studied extensively as a model for schizophrenia (Rivolta et al. 2015); studies of the age-dependent effects of ketamine might lead to additional insights from this model. Further investigation of the neural circuit mechanisms for anesthetic drugs could make it possible to gain deeper insights into human brain development viewed through the lens of this clinical anesthetic experiment of nature.

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