Chapter 1

Arousal and normal conscious cognition

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Introduction

The knowledge of the neurophysiological processes that generates and maintains consciousness provides the clinician the foundations to understand its absence and alterations. Consciousness is probably the main feature of human wakefulness (W), which is lost in the falling asleep process. However, we have a hint that during our night sleep, our mind is very active and fly without control during our dreams. Dreams are a different type of cognitive state, with its own rules. Neurological syndromes such as comma or vegetative state suppress consciousness. Psychiatric conditions such as psychosis generate an alteration of consciousness. Furthermore, while general anesthetic drugs suppress consciousness, several drugs, such as hallucinogens, alter it.

Which are the neuronal networks involved in the generation consciousness? How do they work? What are the adjustments in these networks that determine that consciousness is not supported during sleep? In the present chapter, focusing on the information provided by the electroencephalogram (EEG), we reviewed the most relevant concepts of the electrocortical correlates of normal conscious cognition and the physiological and drug-induced network modification that are involved in its absence or alteration.

Arousal and consciousness

Arousal is the physiological and psychological state of being awoken from sleep and the increase in vigilance or alertness during W. It involves the function of the activating system (AS) in the brain; one of its main components is the reticular activating system (RAS) whose soma is located in the mesopontine brain stem. The RAS is a phylogenetically conserved system that modulates fight-or-flight responses (Yates and Garcia-Rill, 2015). An increase in the firing

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rate of the RAS neurons mediates the activation of the thalamocortical system (i.e., the main neuroanatomical structure associated with consciousness), the sympathetic autonomic nervous system, and the motor and the endocrine systems (Yates and Garcia-Rill, 2015). This increase in the firing rate of RAS neurons generates sensory alertness, mobility, and readiness to respond, that is, accompanied by an increase in heart rate and blood pressure, respiratory activity, and other phenomena related with fight-or-flight responses. Hence, during W, there are periods with low level of arousal (quiet or relaxed W) and periods with high level of arousal. A novel, painful, or motivational stimuli can induce high level of arousal; in any case, the result is alertness or full attention status. In humans (and supposedly in animals with high cognitive abilities), arousal is accompanied by consciousness.

"There is nothing we know more intimately than consciousness, but there is nothing harder to explain," stated the mind philosopher David Chalmers (Chalmers, 2005). Dictionaries usually define consciousness as the ability to be aware of surroundings and ourselves. Although this is a circular definition (because awareness and consciousness are synonyms), it captures the essence: consciousness allows us to know about ourselves and the existence of objects and events (Damasio and Meyer, 2009). In the present work, following the directives of Edelman and Tononi, we define consciousness in practical terms: "Everyone knows what consciousness is: it is what abandons you every evening when you fall asleep and reappears the next morning when you wake up" (Edelman and Tononi, 2000). This definition suggests that for normal W, consciousness is a sine qua non condition. However, we must keep in mind that dreams are considered a special (or altered) type of consciousness (see succeeding text).

The concept of "neural correlates of consciousness" (NCC) represents the smallest set of neural events and structures sufficient for a given conscious percept, explicit memory, or cognitive function. Where is the structural (neural) basis of consciousness? The thalamocortical system is the ultimate responsible for the generation of consciousness, and the associative cortices play a major role (Llinas and Pare, 1991; Tononi and Laureys, 2009).

Due to fact that the thalamocortical system is also the main responsible for the electric activity recorded in the EEG, in this chapter, we will focus in the EEG phenomena related to arousal and normal conscious condition and in its physiological and nonphysiological suppression or alteration.

Electroencephalogram

The EEG is produced by the summed electric activities of populations of neurons, with a modest contribution from glial cells (Lopes da Silva, 2010). Pyramidal neurons of the cortex are the main contributor of the EEG signal, since they are arranged in palisades with the apical dendrites aligned perpendicularly to the cortical surface. The electric fields generated by these neurons can be recorded by means of

electrodes located at a short distance from the source (local field potentials, LFPs), from the cortical surface (electrocorticogram or ECoG), or at longer distances such as from the scalp (standard EEG). In the standard EEG, oscillations higher than 30 Hz are difficult to observe because they are filtered out by the skull and scalp and there is more distance from the source and worse spatial resolution. On the contrary, oscillations up to 200 Hz can be recorded with LFPs or ECoG.

Several oscillatory rhythms can be observed in the EEG. These rhythms are generated in the thalamus and/or at cortical levels and are modified according to the behavioral state (W and sleep).

Wakefulness

In humans (and mammals in general), three behavioral states can be distinguished: W, nonrapid eye movement (NREM) sleep (also called slow-wave sleep), and rapid eye movement (REM) sleep. These behavioral states can be recognized by means of polysomnography, which consists of the simultaneous recording of various physiological parameters such as EEG, electromyogram (EMG), and electrooculogram.

The EEG recording during W is characterized by the presence of high-frequency and low-voltage oscillations (cortical activation). The EEG (ECoG in sensu stricto) during W (alert wakefulness, AW; quite wakefulness, QW) of a cat is shown in Fig. 1.1. EEG recordings during W show relatively low-amplitude and high-frequency oscillations (active EEG). As it is shown in Fig. 1.2, the analysis of the frequency content of the EEG signal (i.e., the power spectrum) shows that in comparison with other behavioral states the power of the low-frequency bands (delta, theta, and sigma bands) during AW is low, while there is an increment in high-frequency bands, especially the low gamma band (30–45 Hz).

High EEG gamma activity during W has been described in several species, including humans (Maloney et al., 1997; Cantero et al., 2004; Cavelli et al., 2017a). In the ECoG of the cat, gamma activity is readily observed in the raw recordings during W (indicated with "a" in Fig. 1.1). As is displayed in Fig. 1.3, low gamma (30–45 Hz) oscillations take place as "bursts" of approximately 25 μV of amplitude and 200–500 ms of duration; these "bursts" are enhanced (in frequency of appearance, amplitude, and duration) during arousal produced by a stimulus that produces alertness (sound and light) or motivation (smell of food). In Figs. 1.3 and 1.4A, AW was produced with random sound stimulation, and gamma bursts seem to be coupled among several cortices. As it is shown in Fig. 1.5, when this intercortical gamma coupling is analyzed by the magnitude square coherence function, gamma coherence increases during AW in comparison with QW and sleep (see Castro et al., 2013, 2014). Another clear example of gamma coherence increment during AW is exhibited in Fig. 1.6. In this case, a person unknown to the animal entered in the recording room, and there was a large increase in gamma power (Fig. 1.6A) and coherence (Fig. 1.6B). A large gamma coherence between two cortical areas strongly suggests that there is a

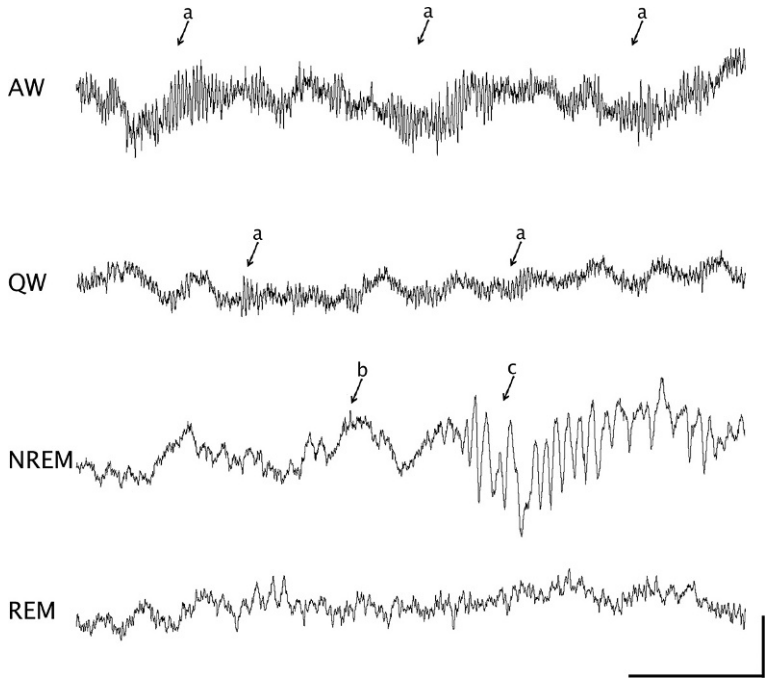

FIG. 1.1 EEG raw recordings of the dorsolateral prefrontal cortex of the cat during alert wakefulness (AW), quiet wakefulness (QW), and NREM and REM sleep. *a*, gamma (30–45 Hz) oscillations; *b*, slow waves; *c*, sleep spindles. Calibration bars, 1 s and 200 µV.

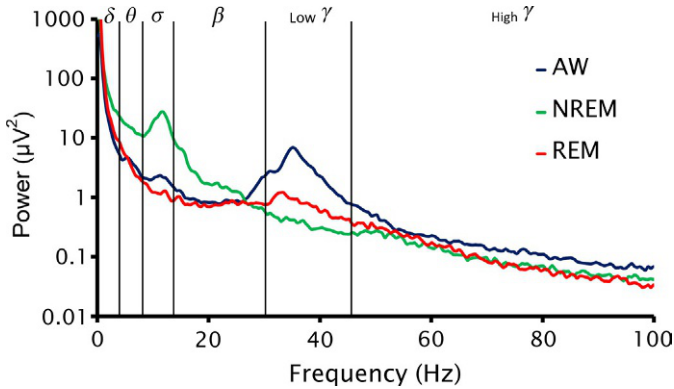

FIG. 1.2 Power spectrum (0.5–100 Hz) during wakefulness and sleep. The figure shows the average profile of 10,100 s' windows from the prefrontal cortex EEG of a cat during alert wakefulness (AW), NREM sleep, and REM sleep. Delta (0.5–4 Hz), theta (5–9 Hz), sigma (10–15 Hz), beta (16–30 Hz), and low (31–45 Hz) and high gamma (46–100 Hz) bands are shown between vertical lines.

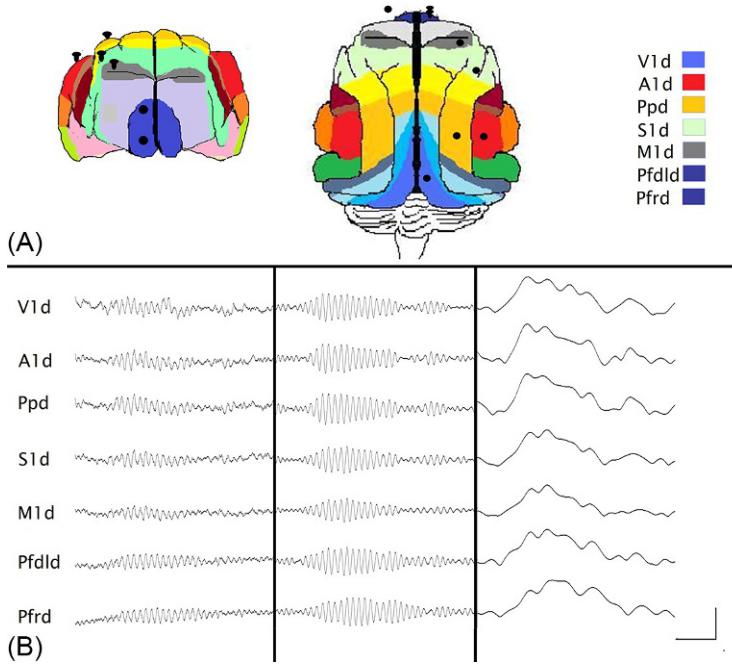

FIG. 1.3 Gamma oscillations during alert wakefulness. (A) Anterior and top view of the cat brain. The position of the cortical recording electrodes on the right cerebral hemisphere is displayed. The recordings were monopolar and referenced to an electrode located in the left frontal sinus. (B) The simultaneous recordings of the cortical gamma oscillation are exhibited. Raw recordings are shown on the left, filtered recordings (band pass 30–45 Hz) are on the middle, and the envelope of the gamma oscillations is displayed on the right. There is a large coupling in the gamma oscillations among cortical areas. Horizontal calibration bar, 200 ms. Vertical calibration bar: raw recording, 200 μV; filtered recording, 100 μV; envelopes, 50 μV. *Pfrd*, right rostral prefrontal cortex; *Pfdld*, right dorsolateral prefrontal cortex; *M1d*, right primary motor cortex; *S1d*, right primary somatosensory cortex; *Ppd*, right posterior parietal cortex; *A1d*, right auditory cortex; *V1d*, right visual cortex.

high degree of communication between these areas at the gamma band. This gamma coupling during aroused W has been also observed in rodents and humans (Llinas and Ribary, 1993; Cantero et al., 2004; Voss et al., 2009; Cavelli et al., 2015, 2017a).

During relaxed or QW, gamma activity decrease, and oscillations at lower frequencies begin to appear. This fact is readily observed in humans; during relaxed W with eyes closed, a high-amplitude alpha (8–12 Hz) oscillation appears mainly in the occipital (visual) cortex. The frequency of these oscillations is considered the basic idle (resting) speed of the brain during W (Garcia-Rill, 2015a).

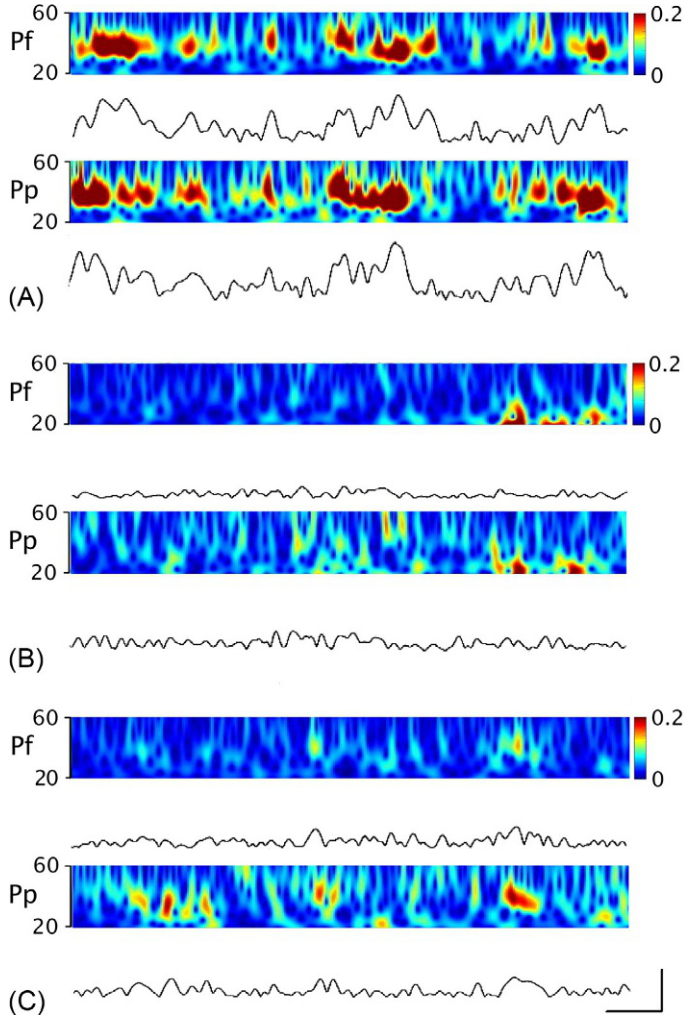

FIG. 1.4 Spectrograms (by means of wavelet function) and rectified gamma band (30–45 Hz) or gamma envelopes, during alert (A) wakefulness (AW) and (B and C) NREM and REM sleep. Calibration bars, 30 μV and 400 ms. The color code of the spectrograms shows a wavelet coefficient that represents in relative units the energy of the signal.

In summary, during W, the EEG activity transits from slower EEG rhythms such as alpha during relaxed W to higher-frequency rhythms during aroused W (especially at frequencies around 40 Hz in humans and cats). Both cortical gamma power (associated with synchronized neuronal oscillations within a cortical area) and long-range gamma coherence (associated with gamma coupling between distant cortical areas) tend to increase in correlation with the level of arousal.

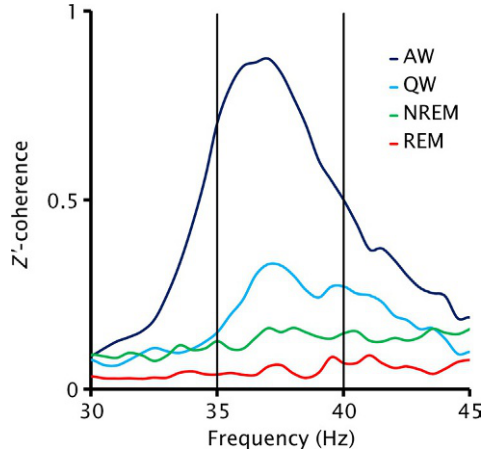

FIG. 1.5 Gamma coherence. Average EEG gamma z'-coherence profiles (between prefrontal and posterior parietal cortices) of 12,100 s' windows during alert (AW) and quiet wakefulness (QW) and NREM and REM sleep. The gamma coherence peak is between 35 and 40 Hz and is shown between vertical lines.

EEG correlates of wakefulness and arousal

As previously mentioned, consciousness (awareness) is the cognitive counterpart of normal W. It is considered that two "components" are needed to support consciousness (Posner et al., 2007; Garcia-Rill, 2015b). One is the "content" of consciousness. In spite of the fact that several neural networks contribute to the cognitive well-being (such as the basal ganglia, neocerebellum, hippocampus, and reticular formation), the thalamocortical system constitutes its main anatomical site where the "content" is processed; the associative cortical areas and related thalamic nuclei are considered to play the major role. These areas are fed with information provided by sensory pathways. The other component that supports consciousness is activation or arousal, which is also supposed to provide the "context" of sensory experience. This function is supported by the AS, in which the RAS and nonspecific thalamic nuclei play a critical role. A disturbance in the "content" of W is characteristic of diffuse cortical lesions and metabolic or toxic disorders that affect the cortex or thalamic nuclei; these injuries may produce what it is known as vegetative state. On the other hand, subtle injuries or deficits of the AS may produce comma, usually accompanied by an increase in the EEG slow activity (Posner et al., 2007).

Which are the electrocortical correlates of waking consciousness? In a very schematic way, the main EEG correlates of W consciousness are listed in Table 1.1. As commented before, an active EEG is needed to support W. In other words, widespread slow waves (delta waves) and sleep spindles that are features of NREM sleep do not support W.

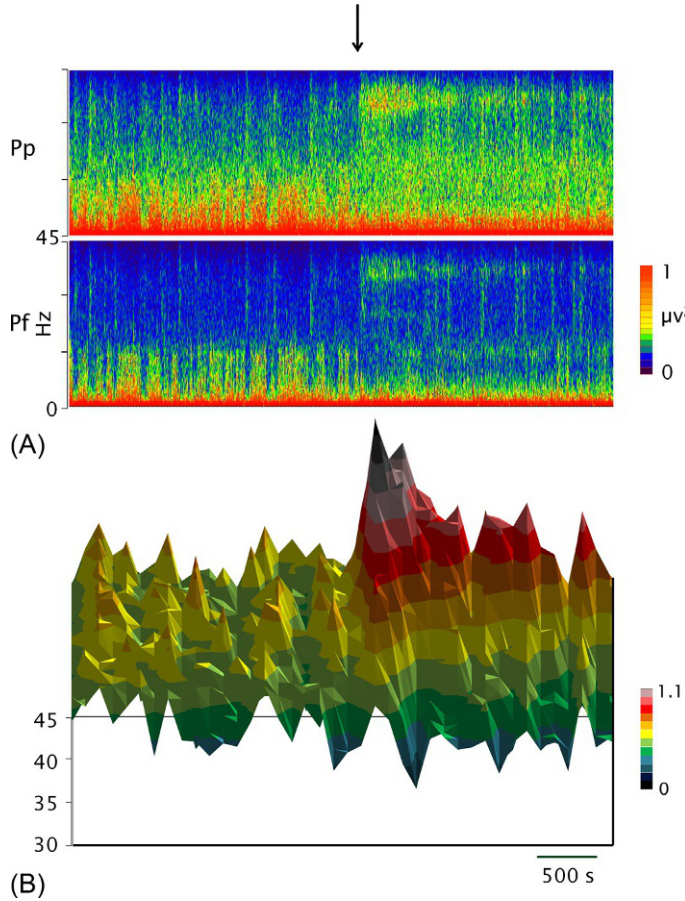

FIG. 1.6 Dynamic evolution of the EEG gamma z'-coherence when the animal is aroused. (A) Gamma power spectrograms of prefrontal (Pf) and posterior parietal (Pp) cortices when the animal is alerted by a stimulus that consisted on unknown people entering to the recording room *(arrow)*. (B) Three-dimensional spectrogram of the gamma z'-coherence between Pf and Pp cortices (same recordings as in A). Time and frequency are displayed on the horizontal and vertical axes (depth), respectively; the z'-coherence is represented in a color code.

For unified perceptual experiences, the brain integrates fragmentary neural events that occur at different times and locations. Synchronization of neuronal activity by phase locking of network oscillations has been proposed for integration or binding mechanism ("binding by synchrony") (Singer, 1999). Gamma activity, especially gamma coherence, has been involved in the explanation of this "binding problem" (Varela et al., 2001; Uhlhaas et al., 2009; Buzsaki et al., 2013; Buzsaki and Schomburg, 2015) and is one of the most studied neural correlates of consciousness (Noreika, 2015). In this regard, gamma coherence is lost during general anesthesia (see succeeding text). Higher-frequency

TABLE 1.1 Main EEG features across physiological and nonphysiological states

	W	NREM	REM	Isoflurane	Ketamine	S/A
Slow waves	–	+	–	+	–	+
Sleep spindles	–	+	–	+	–	+
Gamma power	+	–	+	–	+	+
Gamma coherence	+	–	–	–	–	+

Main electrographic features during wakefulness (W), NREM sleep, REM sleep, isoflurane general anesthesia, ketamine (subanesthetic dose), and scopolamine or atropine treatment (S/A). These profiles could explain the cognitive differences between these physiological and pharmacological conditions. Positive symbols indicate the presence of these features in the EEG; negative signs indicate absence.

oscillations, known as HFO (up to 160 Hz), may also play a role in this function (Cavelli et al., 2017b).

Wakefulness-promoting neuronal networks

Thalamocortical, premotor/motor, autonomic, and hypothalamic neuroendocrine neuronal networks modify their function during the waking-sleep cycle. However, the "primary engine" that determines changes in these neuronal networks during W is the AS. This system is composed of neurons that utilize different neurotransmitters (such as acetylcholine, noradrenaline, serotonin, dopamine, histamine, and hypocretins) and have widespread projections (Torterolo and Vanini, 2010; Torterolo et al., 2016b). The firing rate of the W-promoting neurons and the release of their neurotransmitters into the synaptic cleft tend to be maximal during W and decrease during NREM sleep.

NREM sleep

In the falling asleep process, adults enter into NREM sleep. In addition to the quiescent behavior and deep modification of autonomic and endocrine activity that regulate visceral functions, NREM sleep is associated with impressive cognitive alterations. The manifestation of the changes in thalamocortical activity on passing from W to NREM sleep can be partially appreciated in the EEG.

In humans, three NREM sleep phases are recognized: N1, N2, and N3, according to the depth of the state. N1 is the transitional stage from W, where hypnagogic imaginary (dreamlike activity) is common. This transition into NREM sleep is complex and heterogeneous from the EEG point of view. In fact, Tanaka et al. (1996) divided the transition in nine "hypnagogic states" (from relaxed W with alpha activity to N2). N2 is characterized by the presence of sleep spindles (11–15 Hz oscillatory events with a duration

of 0.5–2 s) and K-complexes. K-complex, which is often associated with sleep spindles, consists of a brief negative sharp high-voltage peak (usually greater than 100 μV), followed by a slower positive complex and a final negative peak.

The presence of high-amplitude (approximately 70 μV), low-frequency (0.5–4 Hz, delta) oscillations characterizes N3 (Carskadon and Dement, 2011). Fig. 1.1 shows the EEG activity during NREM sleep in the cat; slow-wave oscillations and sleep spindles are indicated (indicated with "b" and "c," respectively). Fig. 1.2 depicts the power spectrum during NREM sleep. Large values of delta and sigma power produced by slow waves and spindles, respectively, are distinctive features of NREM sleep. Also, the decrease in the gamma band power and coherence is another remarkable feature of NREM sleep (Figs. 1.2, 1.4B, and 1.5).

Somnambulism or sleepwalking is an NREM sleep parasomnia that can be explained as a dissociated state, with both waking and NREM sleep features (Mahowald and Schneck, 2011; Canclini et al., 2018). In other words, part of the brain is active (i.e., as in waking state, with probable activation of motor cortical and subcortical regions), while other cortical regions present slow waves (as in NREM sleep) in the EEG. As a result, the individual is awake enough to carry out complex motor acts but is unconscious and irresponsible for these actions (because is partially asleep). It is likely that slow waves during these events are mainly present in associative cortical areas that are critical for awareness (Tononi and Laureys, 2009). The slow cortical activity during somnambulism is a pathological manifestation of what is known as local sleep. Nowadays, it is accepted that during W, part of the cortical columns behaves as they were asleep, especially when there is high sleep pressure, that is, during sleep deprivation or prolonged W (Vyazovskiy et al., 2011).

The presence of slow waves and/or sleep spindles during NREM sleep is against the generation of consciousness (Table 1.1). The high-amplitude slow waves of NREM sleep are widespread throughout the cortex and are produced by the synchronization of a large number of pyramidal neurons. This electrocortical condition suggests that large groups of neurons are doing quite the same at the same time; this reduction in the degree of freedom would wane consciousness. On the contrary, a feature of cortical activity during W is regional "functional differentiation," and according to Tononi's information integration theory, functional differentiation between different areas is critical for consciousness (Tononi, 2010). This feature is lost during NREM sleep. A similar circumstance occurs in generalized seizures such as "petit mal," where unconsciousness of the event is associated with widespread stereotyped slow waves. In addition, functions such as cortical lateral inhibition that is critical for perception are lost when pyramidal neurons behave in an homogeneous manner such as in deep NREM sleep (Garcia-Rill, 2015c).

Oneiric activity is scarce or absent during deep NREM sleep (N3) (Dement and Kleitman, 1957; Pace-Schott, 2011; Siclari et al., 2017). As previously

mentioned, widespread slow waves and spindles, as well as low gamma power and coherence in the EEG, do not support cognitive activity (neither W consciousness nor dreams) (Table 1.1). However, oneiric activity may appear by local REM sleep–like activation of critical areas in a background of light NREM sleep (N1 and N2 at the end of a nocturnal sleep period). In fact, both during NREM and REM sleep, dream reports were associated with local decrease in low-frequency activity in posterior cortical regions, while an increase in high-frequency activity within these regions is correlated with specific dream contents (Siclari et al., 2017).

NREM sleep-promoting system

Cognitive activity (waking consciousness and dreams) and the different EEG rhythms that support these functions are mainly generated by the activity of cortical and thalamic neuronal networks, which are mutually interconnected. Thalamic neurons have a complex electrophysiology that allows them to operate differently according to their level of polarization (Steriade et al., 1993). When hyperpolarized, the thalamic neurons that project to the cortex (thalamocortical neurons) oscillate at low frequency (0.5–4 Hz) and tend to block the sensory information that travels toward the cortex. This "oscillatory mode" of function synchronizes cortical neurons and, accompanied by other phenomena of cortical origin, generates the slow waves of NREM sleep (Huguenard and McCormick, 2007; Crunelli et al., 2015). Moreover, the reticular nucleus of the thalamus is the site of generation of the sleep spindles that characterize N2 (Fuentealba and Steriade, 2005; Huguenard and McCormick, 2007). On the contrary, when thalamic neurons are relatively depolarized, they enter in the "tonic mode" of function. In this condition, the thalamocortical neurons transmit sensory information toward the cortex in a reliable way. This mode of function occurs during W and REM sleep because the AS maintains a depolarized membrane potential in these neurons.

Neurons from the preoptic area (POA) of the hypothalamus are critical in the generation and maintenance of NREM sleep (Torterolo and Vanini, 2010; Torterolo et al., 2016b). Most of these neurons are GABAergic; these inhibitory neurons project in monosynaptic form toward the activating nuclei. On the other hand, experimental evidence suggests that W-promoting neurons inhibit NREM sleep–promoting POA neurons (Gallopin et al., 2000; Williams et al., 2014). This reciprocal inhibition between activating and hypnogenic neurons is critical for the transition between sleep and W and the basis of the flip-flop state switch model (Saper et al., 2010).

Other neuronal networks also seem to play a role in NREM sleep generation, such as neurons located in the medullary reticular formation (Anaclet et al., 2012) and the melanin-concentrating hormone (MCH)-containing neurons of the lateral hypothalamus and incertohypothalamic area (Torterolo et al., 2011; Monti et al., 2013).

REM sleep

REM sleep (also called stage R) is a deep sleep stage even though it exhibits similar electrographic characteristics to that of W, that is, has an active EEG. Hence it is also called "paradoxical" sleep. REM sleep is also characterized by REM, muscle atony, and phasic changes in autonomic activity.

REM sleep EEG in rodents and cats is similar to W (Fig. 1.1) (Torterolo et al., 2016b). However, the EEG during REM sleep in humans has more similarities to N1; in both states, the EEG is described as low-voltage, mixed-frequency activity (Keenan and Hirshkowitz, 2011).

In humans, during nighttime sleep, REM sleep episodes occur with a period of approximately 90 min; in fact, there are four to five "sleep cycles" per night. The "sleep cycles" are the period between the onset of sleep until the end of the first episode of REM sleep or the period from the end of an episode of REM sleep to the end of the subsequent REM sleep episode (Carskadon and Dement, 2011).

Dreams occur mainly during REM sleep and are considered a special kind of cognitive activity or protoconsciousness (Hobson, 2009). REM sleep dreams are characterized by their vividness, single-mindedness, bizarreness, and the loss of voluntary control over the plot. Attention is unstable and rigidly focused, facts and reality are not checked, violation of physical laws and bizarreness are passively accepted, contextual congruence is distorted, time is altered, and memories become labile (Rechtschaffen, 1978; Hobson, 2009; Nir and Tononi, 2010). Interestingly, some authors have suggested that cognition during REM sleep resembles psychosis (Gottesmann and Gottesman, 2007). In fact, Hobson stands that "dreaming is, by definition, a psychosis" (Hobson, 1997).

High local cortical gamma activity (and hence relatively large gamma power) is present during REM sleep (Fig. 1.2), both in humans and animals (Maloney et al., 1997; Cantero et al., 2004; Cavelli et al., 2017a). However, long-range gamma coherence is almost absent during REM sleep (Figs. 1.4C and 1.5). High gamma power accompanied by minimal gamma coherence is a trait that characterizes REM sleep (Fig. 1.7 and Table 1.1), which is conserved in rodents, felines, and humans (Cantero et al., 2004; Voss et al., 2009; Castro et al., 2013, 2014; Cavelli et al., 2015, 2017a; Torterolo et al., 2016a).

Coherent EEG gamma activity has been observed during REM sleep solely during lucid REM sleep dreaming; the level of gamma coherence during lucid dreaming is intermediate between W and nonlucid REM sleep (Voss et al., 2009). Lucid dreams are a relatively infrequent phenomenon, whereby the "sleeper" reports being aware that he/she is dreaming and, in some cases, is able to deliberately modify the events of the ongoing dream. Interestingly, externally imposed resonance at 40 Hz by means of electric stimulation produces self-awareness (lucidity) during REM sleep (Voss et al., 2014). From the electrocortical point of view, lucid dreams share features for both W and REM sleep; hence it could be considered a type of dissociate state.

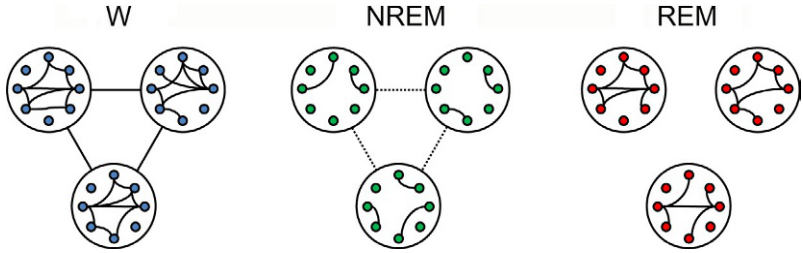

FIG. 1.7 Schematic representation of the short- and long-range gamma synchronization during wakefulness (W), NREM sleep, and REM sleep. The *small circles* represent neurons, while *large circles* represent the areas of the cortex where these neurons are located. Colors in neurons represent the behavioral states (*blue*, W; *green*, NREM sleep; *red*, REM sleep) and connecting lines between the circles represent the gamma synchronization between distant cortical areas. Short-range (local) and long-range (distant) gamma synchronization occurs during W. During NREM sleep, both short- and long-range gamma synchronization decrease. During REM sleep, while gamma synchronization is present at local level, distant gamma coupling is absent.

Neural systems that promote the generation of REM sleep

The neural networks necessary and sufficient for the generation and maintenance of REM sleep are found in the mesopontine reticular formation (Siegel, 2011). In fact, most of the mesopontine neurons that play a role in the maintenance of W coincide with the neurons that are responsible for the generation of REM sleep.

Within these areas, monoaminergic (noradrenergic and serotonergic) neurons that are active during W turn off during REM sleep (REM-off neurons). On the other hand, cholinergic neurons increase their firing rate both during W and REM sleep (REM-ON neurons) (McCarley, 2007). Mesopontine GABAergic and glutamatergic neurons (Luppi et al., 2007) and hypothalamic MCH-containing neurons also play a critical role in REM sleep generation (Torterolo et al., 2011, 2015; Monti et al., 2013).

Drug-induced loss of consciousness: General anesthesia

Comma, vegetative state, and seizures are the more salient conditions related to pathological loss of consciousness. Since the variety and complexity of these conditions, they will not be analyzed in the present report. However, we will focus in drug-induced loss and alteration of consciousness.

General anesthesia is a drug-induced state, characterized by a relatively safe and reversible loss of consciousness. The ability to render a patient unconscious (hypnosis) and insensible to pain made modern surgery possible, and general anesthetics have become one of the most widely used class of drug (Franks, 2006). Sleep and anesthesia share many behavioral and electroencephalographic characteristics (Vanini et al., 2011). In addition, several authors suggest that sleep and anesthesia (induced by most anesthetic) share an underlying mechanism. In fact, several studies showed that most anesthetics suppress consciousness by recruiting or inhibiting regions that regulate sleep and W (Vanini et al., 2011).

When the anesthetic plane is reached, NREM sleep–like slow waves are present during this drug-induced state (Lydic and Baghdoyan, 2005). In addition, as it is shown in Fig. 1.8, isoflurane decreases EEG gamma power and coherence activity in the cat. Similar effects were observed for long-range gamma coherence in humans and rats (John, 2002; Mashour, 2006; Pal et al., 2016). Hence both the presence of slow waves and the decrease in gamma power and coherence are associated with the absence of consciousness induced by anesthesia (Table 1.1).

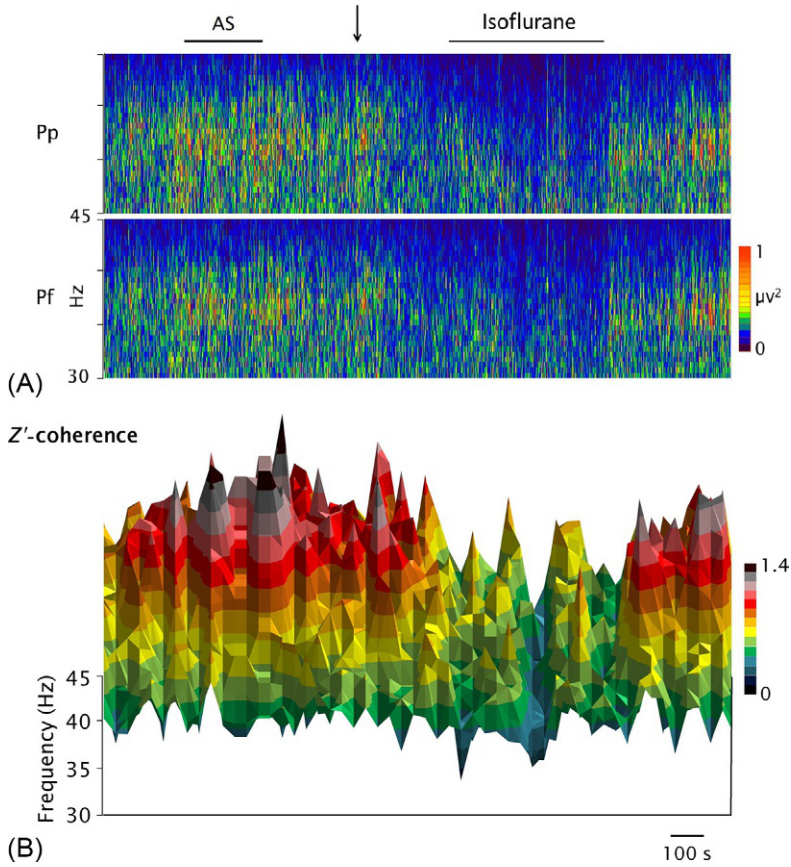

FIG. 1.8 Dynamic evolution of the EEG gamma z'-coherence following isoflurane administration (bar). (A) Gamma power spectrograms of prefrontal (Pf) and posterior parietal (Pp) cortices. The first bar (AS) shows when the animal is alerted by a stimulus that consisted of unknown people entering the recording room during wakefulness. The *arrow* indicates an auditory stimulus. The time during the administration of an anesthetic dose of isoflurane is also displayed. (B) Three-dimensional spectrogram of the gamma z'-coherence between Pf and Pp cortices (same recordings as in A). Time and frequency are displayed on the horizontal and vertical axes (depth), respectively; the z'-coherence is represented in a color code. The decrease in gamma power and coherence is readily observed.

Drug-induced alteration of consciousness

Ketamine, a pharmacological model of psychosis

The word psychosis (from Greek "disorder of the mind") is used in psychiatry to define a mental state in which there is a loss of contact with reality. The *Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th Edition (2013)* classifies psychotic disorders in a chapter entitled "Schizophrenia Spectrum and Other Psychotic Disorders," highlighting among them schizophrenia (Bhati, 2013). This pathology is characterized by the presence of positive or psychotic (visual and auditory hallucinations, delusions, and paranoia) and negatives symptoms (apathy, the loss of motivation, and serious social isolation) and memory and executive function disorders.

Several hypotheses that attempt to explain the pathophysiology of psychotic disorders have been postulated. Among them, it is widely accepted that glutamatergic hypofunction mediated by the *N*-methyl-D-aspartate receptor (NMDA-R) is a key mechanism contributing to the positive, negative, and cognitive symptoms observed in this condition (Krystal et al., 1994; Pomarol-Clotet et al., 2006; Javitt, 2010). This is based on clinical reports showing that the consumption of noncompetitive antagonists of NMDA-R, such as ketamine, induces in healthy individuals the characteristic alterations of the psychotic disorders and exacerbates the symptoms in schizophrenic patients (Krystal et al., 2003; Pomarol-Clotet et al., 2006). Therefore models involving NMDA-R hypofunction is considered a valid pharmacological approach for the study of the psychotic disorders (Corlett et al., 2007; Scorza et al., 2008; Javitt, 2010).

Ketamine in subanesthetic doses produces an activated state, with relatively high gamma power (Fig. 1.9); however, it also produces a deep decrease in gamma (30–45 Hz) band coherence (Fig. 1.10). This decrease was similar to that occurring during REM sleep, which is considered a natural model of psychosis (Hobson, 1997; Gottesmann, 2006; Gottesmann and Gottesman, 2007). Furthermore, under ketamine, the gamma coherence was not affected by novel stimuli (Fig. 1.10), which in basal conditions alert the animal causing a large increase in gamma coherence (Castro-Zaballa et al., 2019b).

Disruptions in gamma activity similar to the induced by ketamine, have been described in psychosis (Lee et al., 2003; Light et al., 2006; Yeragani et al., 2006; Uhlhaas and Singer, 2010; Sun et al., 2011; White and Siegel, 2016).

In summary, it is possible that an active state with high local gamma band synchronization (i.e., high gamma power), accompanied with low long-range gamma coherence, is associated to the cognitive features shared by REM sleep and psychosis (Table 1.1).

Dissociative state induced by atropine and scopolamine

Mesopontine and basal forebrain cholinergic neurons are critically involved in the EEG activation during W and REM sleep (Torterolo and Vanini, 2010;

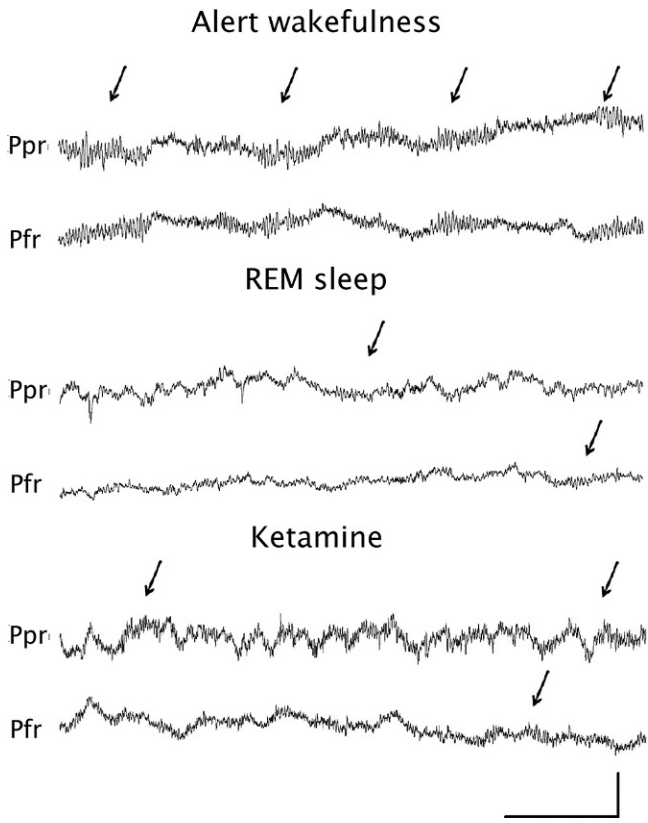

FIG. 1.9 Simultaneous raw recordings of the prefrontal (Pf) and parietal posterior (Pp) cortices during alert wakefulness and REM sleep and under the administration of ketamine (15 mg/kg). The *arrows* indicate the gamma "bursts." Calibration bars, 1 s and 200 μV. Gamma activity is present under ketamine; however, this gamma activity is not coupled between cortical areas.

Torterolo et al., 2016b). In this regard, animals treated with muscarinic antagonists (atropine or scopolamine) display high-voltage slow waves and spindles in EEG that resembles NREM sleep; however, they remain behaviorally awake and active (Wikler, 1952). Furthermore, these drugs decrease the electrocortical arousal response elicited by either sensory or midbrain reticular formation stimulation, but the gross behavior in response to such stimuli is not affected (Rinaldi and Himwich, 1955; Bradley and Key, 1958). This "dissociation" in which waking behavior coexists with NREM sleep–like EEG was observed in different animals and humans (Wikler, 1952; Longo, 1956; Chow and John, 1959; Lindsley et al., 1968; Yamamoto, 1988).

Classic pharmacological studies have also shown cognitive disturbances in humans treated with muscarinic antagonists (Ostfeld et al., 1960). They produce

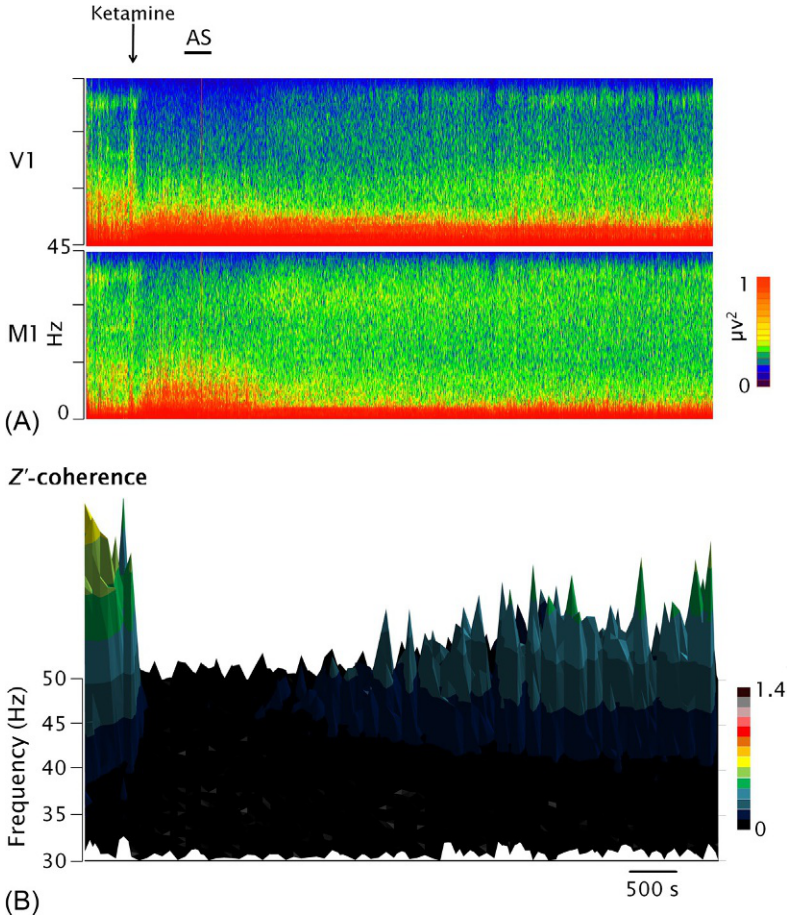

FIG. 1.10 Dynamic evolution of EEG gamma power and z'-coherence following the administration of subanesthetic dose of ketamine. (A) Gamma power spectrograms of primary motor (M1) and primary visual (V1) cortices following ketamine administration (*arrow*). The horizontal bar represents at random sound stimulation (AS) in order to arouse the animal. (B) Three-dimensional spectrogram of the gamma z'-coherence between M1 and V1 cortices (same recordings as in A). Time and frequency are displayed on the horizontal and vertical axes (depth), respectively; the z'-coherence is represented in a color code. Ketamine produced a large decrement in gamma coherence that was not affected by sensory stimulation.

a decrease in spontaneous speech and movement, impairment in memory and attention, and drowsiness. However, subjects are able to answer simple questions and perform tasks without the requirement of prolonged attention or memory. They can sit, stand, open or close their eyes, or extend their extremities on request, although they move more slowly than in the predrug period. In addition, muscarinic antagonists produce sedation, impairment of coordinative and reactive skills, visual disturbances, and diminution of short-term memory (Nuotto, 1983).

Furthermore, these drugs affect simple and choice reaction time, number matching, and memory scanning tasks (Ebert et al., 1998). It is considered that the most prominent effects of scopolamine involve discrimination processes, vigilance, selective attention, and consolidation and retrieval of memories (Sahakian, 1988).

Anticholinergic drugs have been used for recreational or ritualistic purposes. One of the most widely described religious or magical experiences dating back to ancient times is the alteration of consciousness with the induction of hallucinations by a member of the Solanaceae family of plants (belladonna, henbane, or datura), which contain scopolamine, atropine, and other closely related alkaloids (Perry and Perry, 1995). Perhaps the most extraordinary example of cognitive dysfunction is the criminal use of anticholinergic substances that are present in datura extracts (called "burundanga"), to induce amnesia and submissive behavior or "obedience" in victims (Ardila and Moreno, 1991; Ardila-Ardila et al., 2006).

We recently demonstrated that under the effect of atropine or scopolamine, coherent gamma (≈40 Hz) oscillations are conspicuous (Castro-Zaballa et al., 2019a) (Fig. 1.11). This "dissociated" EEG not only with slow waves and sleep

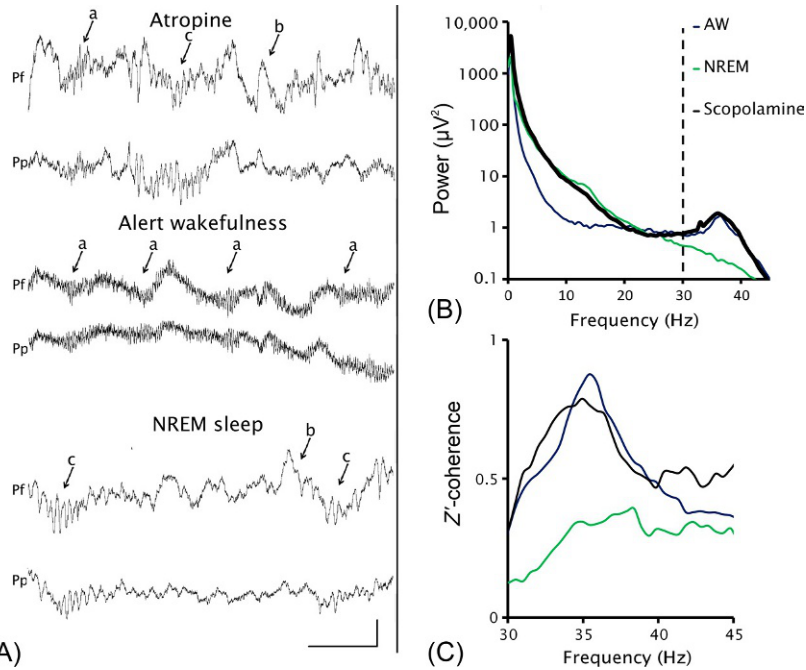

FIG. 1.11 (A) Simultaneous raw recordings of the prefrontal (Pf) and parietal posterior (Pp) cortices. Raw recordings during alert wakefulness and REM sleep and following the administration of atropine. *a*, gamma (30–45 Hz) oscillations; *b*, slow waves; *c*, sleep spindles. Calibration bars, 1 s and 200 μV. (B) Power spectrum (0–45 Hz) of the posterior parietal cortex during alert wakefulness (AW), NREM sleep, and scopolamine administration. (C) Average gamma *z*′-coherence profiles (30–45 Hz) in the same conditions as in B. The coherence profile during AW and scopolamine is similar.

spindles but also with coherent 40 Hz oscillations (a trait of AW) may be the neurophysiological basis of the "classic" EEG and behavior dissociation that is produced by these drugs. Hence the alteration of consciousness produced by antimuscarinic drugs is associated with slow waves and spindles (NREM sleep feature), combined with high gamma power and coherence, a trait of AW (Table 1.1).

Conclusions

Consciousness is the cognitive counterpart of normal W, at least for animals with higher cognitive abilities. W is characterized by an EEG with the absence of slow-wave (delta) activity and the presence of coherent high-frequency waves, mainly at about 40 Hz. These coherent gamma oscillations are highly dependent of the level of arousal. On the other hand, important adjustments of the delta waves and/or gamma activity (power and coherence) are associated with physiological absence or alteration of consciousness (NREM and REM sleep, respectively). An important modulation of gamma and delta activity is also associated with either the loss or alteration of consciousness induced by drugs.

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