Anesthetic strategies for the management of compromised emergence

ESSAY SUBMITTED FOR THE PARTIAL FULLFILLMENT OF THE MASTER'S DEGREE IN ANESTHESIA

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AEP: Auditory Evoked Potential.
ASA: American Society of Anesthesia Scale.
BD: Brain Death.
BIS: Bispectral Index.
CABG: Coronary Artery Bypass Surgery.
CKD: Chronic Kidney Disease.
CPB: Cardiopulmonary Bypass.
DoA: Depth of Anesthesia.
ED: Emergence Delirium.
EEG: Electro-encephalogram.
EMG: Electro-myogram.
EOG: Electro-opthalmogram.
ETT: Endotracheal tube.
F_A: Alveolar Partial Pressure.
F_a: Arterial Partial Pressure.
FOUR scale: The Full Outline of UnResponsiveness scale.
GABA: Gamma-amino-butyric-acid.
GABA-A: Gamma-amino-butyric acid- type A receptor.
GCS: Glasgow Coma Scale.
GFR: Glomerular Filtration Rate.
LIS: Locked-in syndrome.
LMA: Laryngeal mask.
M3G: Morphine-3-glucuronide.
M6G: Morphine-6-glucuronide.
MAC: Minimum alveolar concentration.
MCS: Minimally Conscious State.
NMBA: Neuro-muscular blocking agents.
NMDA: N-methyl D-aspartate.
NREM: Non-Rapid Eye Movement Sleep.
PACU: Post-Anesthesia Care Unit.
PCO_2: Partial Pressure of Carbon Dioxide.
PET: Positron Emission Tomography.
POCD: Post-operative Cognitive Dysfunction.
POD: Post-operative Delirium.
RAS: Reticular-activating system.
REM: Rapid Eye Movement Sleep.
RF: Respiratory Failure.
TIVA: Total Intravenous Anesthesia.
TOFR: Train-of-four ratio.
VLPO: Ventro-lateral pre-optic nucleus.
VS: Vegetative State.
WHIM scale: The Wessex Head Injury Matrix.

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Chapter 1

The neural basis of consciousness and anesthesia

Part I: Consciousness and Sleep

Consciousness was defined by the American philosopher John Searle (2000) as "the inner qualitative, subjective states of awareness". In modern science, it can be defined as a continuous state of full awareness of the self and one's relationship to the external and internal environments, describing the degree of wakefulness in which an organism recognizes stimuli. ***(Jellinger, 2009).***

Consciousness can be described as having two main components: **wakefulness** (of the external environment) and **awareness** (of the inner self). Wakefulness permits open eyes and a degree of motor arousal (*i.e.* wakefulness defines the level of consciousness); awareness enables experience of thoughts, memories, and emotions (*i.e.* awareness defines the content of consciousness). Although wakefulness and awareness are intimately connected in general (one has to be awake to be aware), it is possible to identify circumstances under which they are dissociated: in complex partial seizures wakefulness can occur without awareness; in rapid eye movement sleep it is possible to be aware but not awake ***(Gawryluk et al., 2010).***

Wakefulness can be divided into **connectedness** to the environment and **responsiveness** to its stimuli. As we fall asleep, wakefulness **(connectedness** and **responsiveness** to the environment) fade, and only during early nonrapid eye movement (NREM) sleep do we become unawake. However, **awareness** (of the inner self) **is present** in NREM sleep later in the night and it becomes vivid during dreams in rapid eye movement (REM) sleep, although we remain disconnected from and largely unresponsive to our environment (unawake). During sleep, **connectedness** and **responsiveness** are tightly coupled so connection to the environment rapidly leads to responsiveness. However, that coupling is sometimes lost during anesthesia; hence unresponsiveness provides inconsistent and sometimes unreliable information about the consciousness under anesthesia. Table 1 shows the relations between consciousness, connectedness and responsiveness (***Sanders et al., 2012***).

	Consciousness	Connectedness	Responsiveness
Awake	Yes	Yes	Yes
NREM sleep	No	No	No
REM sleep	Yes	No	No

Table 1-1: Consciousness, Connectedness and Responsiveness in the Sleep-Wake States (*Sanders et al., 2012*).

In awake adults at rest, with unfocused attention and the eyes closed, the EEG shows an **alpha rhythm:** regular pattern of waves at a frequency of 8-13 Hz and amplitude of 50-100 μ V. When attention is focused on something (such as arithmetic problems), the alpha rhythm is replaced by a **beta rhythm:** irregular 13-30 Hz low-voltage activity (Fig. 1). This phenomenon is called an **alpha block**, or an **arousal response.** **Gamma oscillations** at 30-80 Hz are often seen when an individual is aroused and focuses attention on something. This is often replaced by irregular fast activity as the individual initiates motor activity in response to the stimulus ***(Barrett and Brooks, 2010)***.

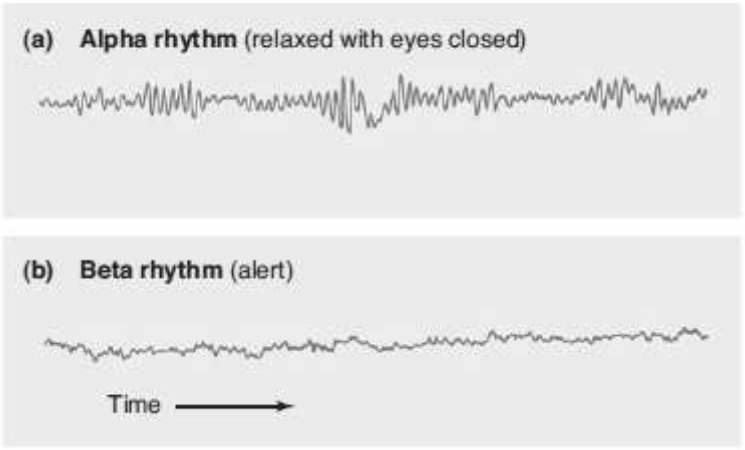

Figure 1-1: EEG records showing the alpha and beta rhythms. When attention is focused on something, the 8-13 Hz alpha rhythm is replaced by an irregular 13–30 Hz low-voltage activity, the beta rhythm *(Barrett and Brooks, 2010)*.

<u>Sleep</u> is actively generated by **hypothalamic**, **brain stem**, and **basal forebrain nuclei.** Normal sleep cycles between two states — rapid-eye-movement (REM) sleep and non-REM sleep — at approximately 90-minute intervals (Fig. 2) (***Kryger et al., 2010***).

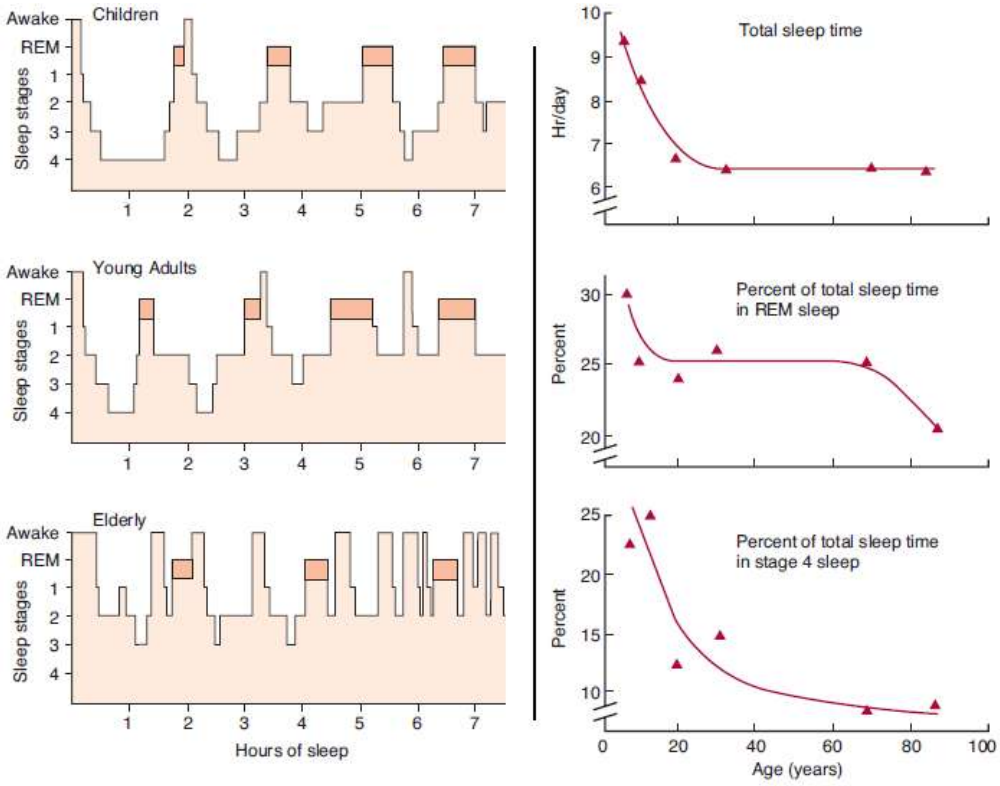

Fig. 1-2: Normal sleep cycles at various ages. REM sleep is indicated by the dark colored areas (left panel), and changes in human sleep patterns with age (right panel) (*Barret and Brooks 2010*).

During non-REM sleep, wakefulness is absent, and the eyes are closed. Muscle tone is normal, and spontaneous movements occur. The reversibility of consciousness by external stimulation depends on sleep depth. Awareness of the environment and ability to respond to command fall off. There is no awareness of self and mental imagery, despite occurrence of dreams. **Electroencephalographic (EEG)** modifications include waxing and waning oscillations of 12-15 Hz frequency lasting for at least a half second (spindle oscillations) and K-complexes (high voltage negative peak immediately followed by a slower positive complex) at sleep onset, and widespread increased power in lower frequencies (delta waves or slow oscillations, 0.5-4 Hz) at deeper stages. Slow oscillations originate in frontal regions and propagate to posterior regions of the cortex following a reproducible track. NREM sleep has 3 stages. Stage 1 is characterized by a slight slowing of the EEG. Stage 2 has high-amplitude K complexes and spindles. Stages 3 shows slow, high-amplitude delta waves, as shown in Figure 4 (***Barash et al., 2006***).

REM sleep is more frequently associated with dreaming, and hence mental imagery, with virtual self perception. Due to muscle atonia, no movements occur, except for specific movements of the eyes. Awareness of the environment is altered, as well as response to command. REM sleep is easily reversed by external stimulation. **EEG patterns** are close, but not identical, to those observed during the wake state, including low voltage desynchronized fast activity, and increased power in the theta range (4-10 Hz). The differences between REM and non-REM sleep are shown in table 2 (***Bonhomme et al., 2011***).

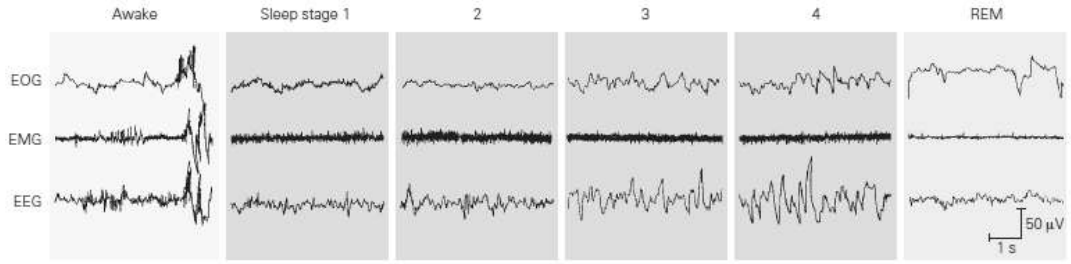

Figure 1- 3: EEG and muscle activity during various stages of the sleep–wake cycle. The higher voltage activity in the EOG tracings during stages 2 and 3 reflect high amplitude EEG activity in the prefrontal areas rather than eye movements. EOG, electrooculogram registering eye movements; EMG, electromyogram registering skeletal muscle activity *(Barrett and Brooks, 2010)*.

		Sleep		General anesthesia			
		n-REM	REM	Inhib. neurotrans.	Ketamine	Xenon	α_2 agonists
Wakefulness		Absent	Absent	Absent	Present	Absent	Reduced
Movements	Spontaneous	Present	Absent	Absent	Present	Absent	Reduced
	Evoked	Present	Absent	Absent	Absent	Absent	Reduced
	Purposeful	Present	Absent	Absent	Absent	Absent	Reduced
Muscle tone		Normal	Atonia	Reduced	Normal	Few effects	Normal
Environment awareness		Absent	Absent	Absent	Absent	Absent	Reduced
Response to command		Absent	Absent	Absent	Absent	Absent	Altered
Self perception		Absent	Virtual	Absent	Absent/Virtual	Absent	Altered
Mental imagery		Dreaming possible	Present	Absent Dreaming during emergence	Present	?	Altered
Reversibility		stage-dependent	Yes	No	No	No	Yes
EEG features		Spindles K-complex Delta	desynchronized fast activity Theta	Beta activation Theta, Delta Burst suppression Isoeletricity Spindles	Reduced alpha Rhythmic theta Polymorphic delta Scattered beta	Similar to halogenated vapors	Spindles Delta and theta activity

Table 1-2: Behavioral and surface electroencephalogram (EEG) characteristics of sleep and general anesthesia (*Bonhomme et al., 2011*).

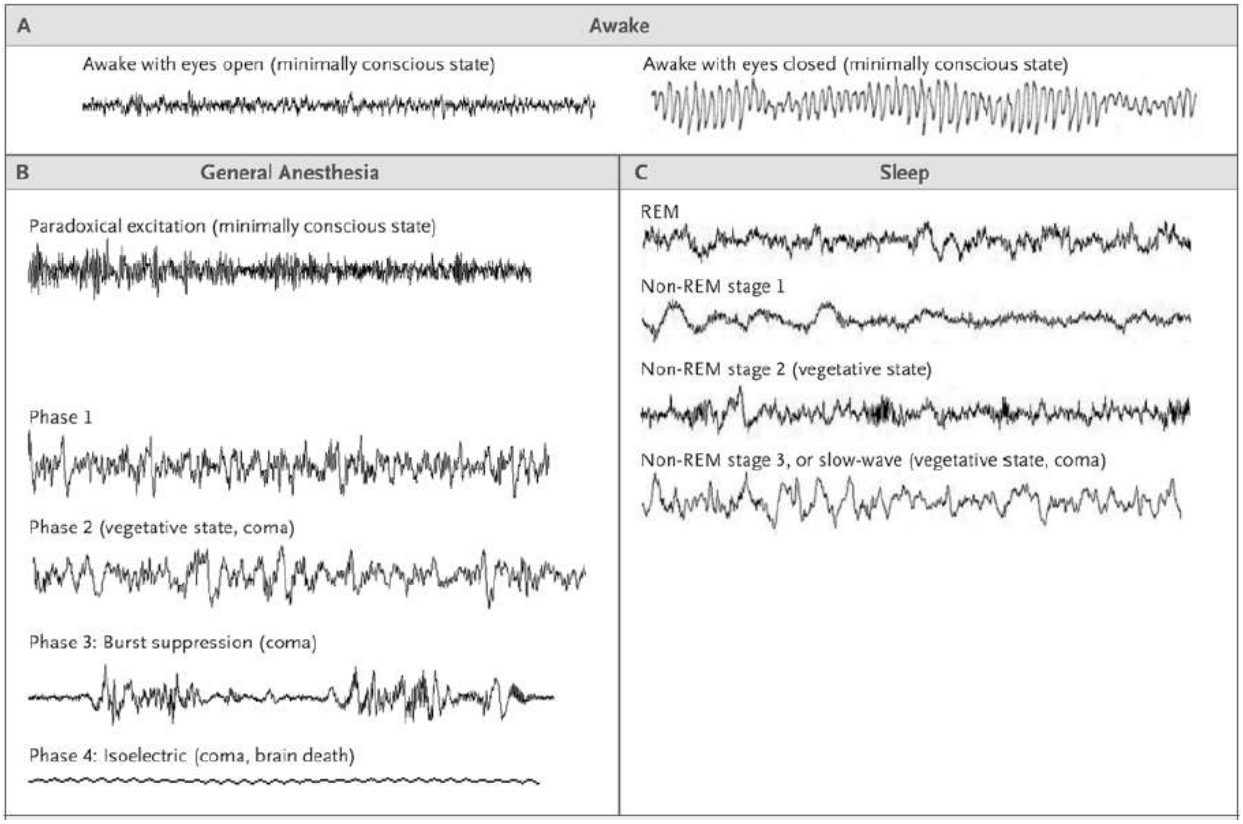

Figure 1-4: EEG Patterns in sleep, awake, general anesthesia states. Panel A shows the EEG patterns when the patient is awake, with eyes open (left) and the alpha rhythm (10 Hz) with eyes closed (right). Panel B shows the EEG patterns during the states of general anesthesia: paradoxical excitation, phases 1 and 2, burst suppression, and the isoelectric tracing. Panel C shows the EEG patterns during the stages of sleep: rapid-eye-movement (REM) sleep; stage 1 non-REM sleep; stage 2 non-REM sleep, and stage 3 non-REM (slow-wave) sleep. The EEG patterns during recovery from coma — coma, vegetative state, and minimally conscious state — resemble the patterns during general anesthesia, sleep, and the awake state (*Brown et al., 2010*).

Part II: Diseased States of Unconsciousness

Several diagnostic levels are used to describe the spectrum of diseased unconsciousness: **coma**, **brain death, vegetative state**, **minimally conscious state**, and **locked-in syndrome (Fig. 5)**. While these terms do not completely describe all patients, they provide a useful classification starting point that is widely used in literature ***(Gawryluk et al., 2010).***

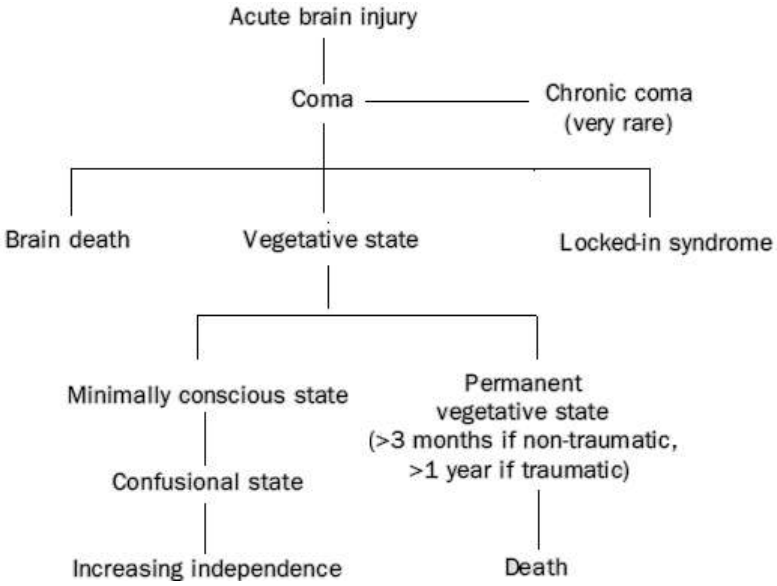

Fig. 1-5: Flowchart of cerebral insult and coma (*Laureys et al., 2004*)

1. **Coma:** is a state of profound unresponsiveness, usually the result of a severe brain injury. A comatose patient may grimace, move limbs, and have stereotypical withdrawal responses to painful stimuli yet make no localizing responses or discrete defensive movements. As the coma deepens, the patient's responsiveness even to painful stimuli may diminish or disappear (***Posner et al., 2007***). Outcome is known to be bad if, after 3 days of observation, there are no pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, isoelectrical or burst suppression pattern EEG. Prognosis in traumatic coma survivors is better than in anoxic cases ***(Tshibanda et al., 2010).***
2. **Brain Death (BD):** is an irreversible loss of all functions of the brain, including the brainstem. The essential findings in brain death are coma, absence of brainstem reflexes, and apnoea (***Goila and Pawar, 2009***). It is classically caused by a brain lesion as massive traumatic injury, intracranial haemorrhage or anoxia, which result in an intracranial pressure higher than the mean arterial blood pressure. After excluding the impact of pharmacological (or toxic) treatments or hypothermia, the diagnosis can be done within 6-24 hours ***(Powner, 2009).***

3. **The Vegetative State (VS):** is **a state of wakefulness without awareness**. It implies the preservation of autonomic functions (e.g., cardio-vascular regulation, thermoregulation) and the sleep-wake cycle, with the absence of awareness (Fig. 6). Patients open their eyes spontaneously or in response to stimulation, but they only show reflex behaviors, unrelated to the environment. External stimulation, such as a painful stimulus, still activates 'primary' sensory cortices in these patients but these areas are functionally disconnected from 'higher order' associative areas needed for awareness (***Laureys, 2005***).
4. **Minimally conscious state (MCS):** is **a state of wakefulness with fluctuating signs of awareness**. These patients can manifest emotional and oriented behavioral responses such as response to verbal order, object manipulation, oriented responses to noxious stimulation, visual pursuit or fixation. However, these behaviors can fluctuate in time, which makes challenging the detection of awareness. Recovery from MCS is defined by the emergence of a functional communication and/or functional objects use (***Giacino et al., 2002***). Even if prognosis is better as compared to the VS, some patients can remain in a MCS without fully recovering consciousness for a prolonged period of time (***Fins et al., 2007***).
5. **Locked-in syndrome (LIS):** LIS patients cannot move or talk but are able to use vertical eye movements and blinking to communicate with their surroundings. This syndrome is often due to a selective supra-nuclear motor de-efferentation producing a paralysis of all four limbs and the last cranial nerves without interfering with consciousness or cognition. **Classical LIS** consists of a total immobility, but preserved vertical eye movements and blinking. **Incomplete LIS** is characterized by remnant non-ocular voluntary motions (e.g., head or fingers movements). **Total LIS** patients are completely immobile, unable to control any eye movements. Even if it is not an altered state of consciousness, it may present the same behavioral pattern than what is observed in VS, and thus the distinction has to be made (***Shnackers and Laureys, 2012***).

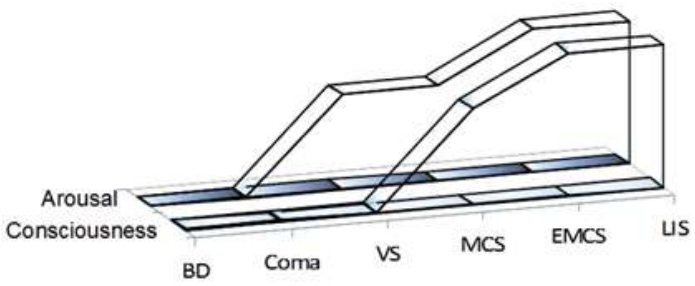

Fig. 1-6. – Diseased states of consciousness: brain death – BD, coma – C, vegetative state – VS, minimally conscious state – MCS), emergence from minimally conscious state – EMCS and locked-in syndrome – LIS *(Schnakers and Laureys, 2012).*

Clinical Assessment of Consciousness

1- **The Glasgow Coma Scale (GCS):** remains the most widely used scale in trauma and acute care settings. The GCS was the first validated rating scale developed to monitor level of consciousness in the intensive care unit**.** It includes three subscales that address arousal level, motor function and verbal abilities, to yield a total score from 3 to 15. Despite its widespread use, the GCS has been criticized for variable inter-rater agreement and problems deriving scores in patients with ocular trauma, tracheostomy or ventilatory support ***(Schnakers and Laureys, 2012).***

2- **The Full Outline of UnResponsiveness (FOUR) scale**: was recently developed to replace the GCS to assess **severely brain-injured patients in intensive care** (Table 3). The scale includes four subscales assessing motor and ocular responses, brainstem reflexes and breathing. The total score ranges from 0 to 16. Unlike the GCS, the FOUR does not assess verbal functions to accommodate the high number of intubated patients in intensive care. A score of 0 on the FOUR assumes the absence of brainstem reflexes and breathing and, therefore, helps to diagnose brain death. The scale also monitors recovery of autonomic functions and tracks emergence from VS. The FOUR is specifically designed to detect patients with locked-in syndrome as it uses oculomotor commands that detect vertical eye movements and eye blinks, both being preserved in LIS ***(Wijdicks et al., 2005).***

3- **The Wessex Head Injury Matrix (WHIM):** was developed to capture changes in patients in VS through emergence from post-traumatic amnesia. This tool is particularly sensitive to detecting changes in patients in MCS not captured by traditional scales such as the GCS ***(Majerus et al., 2000)***.

Glasgow Coma Scale	FOUR Score
Eye response	Eye response
4 = eyes open spontaneously	4 = eyelids open or opened, tracking, or blinking to command
3 = eye opening to verbal command	3 = eyelids open but not tracking
2 = eye opening to pain	2 = eyelids closed but open to loud voice
1 = no eye opening	1 = eyelids closed but open to pain
	0 = eyelids remain closed with pain
Motor response	Motor response
6 = obeys commands	4 = thumbs-up, fist, or peace sign
5 = localizing pain	3 = localizing to pain
4 = withdrawal from pain	2 = flexion response to pain
3 = flexion response to pain	1 = extension response to pain
2 = extension response to pain	0 = no response to pain or generalized myoclonus status
1 = no motor response	
Verbal response	Brainstem reflexes
5 = oriented	4 = pupil and corneal reflexes present
4 = confused	3 = one pupil wide and fixed
3 = inappropriate words	2 = pupil or corneal reflexes absent
2 = incomprehensible sounds	1 = pupil and corneal reflexes absent
1 = no verbal response	0 = absent pupil, corneal, and cough reflex
	Respiration
	4 = not intubated, regular breathing pattern
	3 = not intubated, Cheyne–Stokes breathing pattern
	2 = not intubated, irregular breathing
	1 = breathes above ventilator rate
	0 = breathes at ventilator rate or apnea

Table 1-3: Comparison between the GCS and the FOUR scale (*Bruno et al., 2011*).

Part III: Neural Mechanisms of Sleep and Arousal

The ability to be 'properly awake' or 'properly asleep' is achieved by neuronal mechanisms that interact over a variety of different scales of size. The **cerebral cortex** is awakened by inter-linked **sub-cortical systems** acting via a number of different chemical substances such as glutamate, acetylcholine, amines, and orexin. Perhaps only a few thousand neurons in the brain-stem influence huge areas of the neocortex by wide projection (Fig. 7) (***Sleigh et al., 2011***).

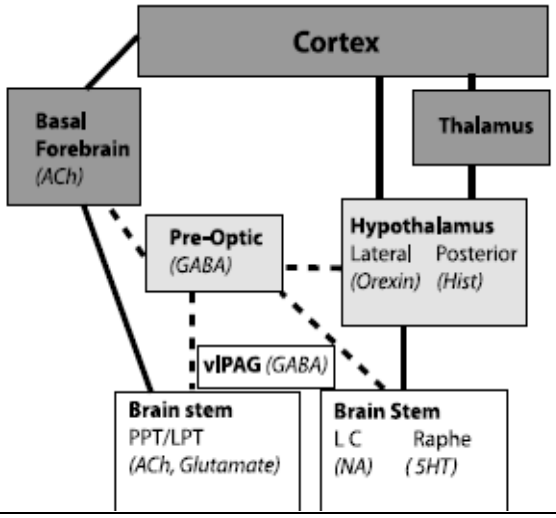

Fig. 1-7: Brain Components of the Sleep-Wake Process (*Sleigh et al., 2011*)

Sleepiness can arise from at least two sources; from circadian inputs of the suprachiasmatic nucleus of the hypothalamus (***Fuller et al., 2006***), or from homeostatically derived neuromodulator somnogens (such as adenosine), which can be generated from prolonged neuronal activity, or from pathological origins (such as in septic encephalopathy). Sleep is then further classified into rapid-eye- movement (REM) or paradoxical sleep; and non-REM (NREM) or slow-wave sleep states. REM sleep is associated with relatively high levels of activity in cholinergic and glutamatergic neurons, whereas NREM sleep is predominantly a GABAergic state (Fig. 8) (***Krueger et al., 2008***).

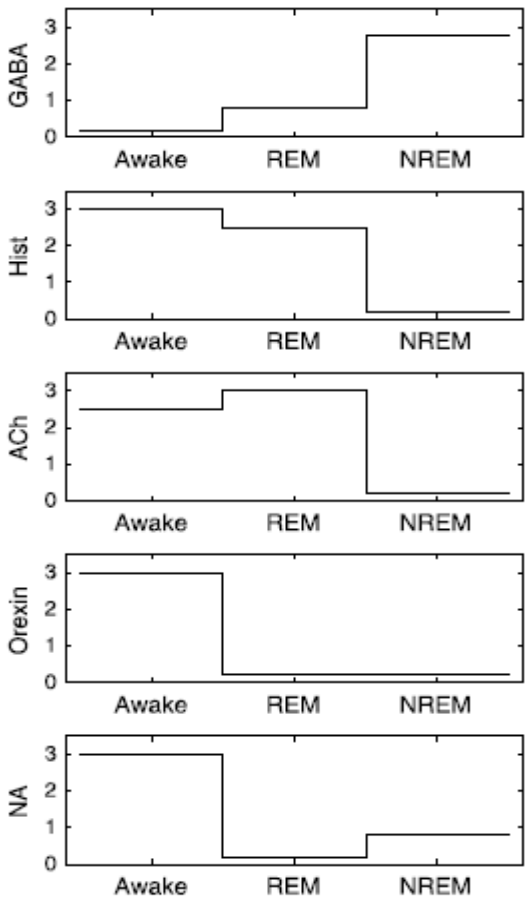

Fig 1-8: The neuromodulator changes in different states of sleep and wakefulness. The main Awake–Sleep differentiators are orexin and noradrenaline, whereas acetylcholine and histamine differentiate active (= REM and Awake) from inactive (NREM) states (*Sleigh et al., 2011*).

In the awake state, the gamma-amino-butyric-acid (GABA)-ergic neurons of the ventro-lateral preoptic nucleus (VLPO) of the hypothalamus (***Winsky, 2009***) are suppressed by many excitatory arousal substances (amines, glutamate, acetylcholine, orexin). If the somnogen levels—or the suprachiasmatic circadian input—are sufficient to reduce the effect of these arousal neuromodulators, the sleep-active GABAergic neurons in the VLPO become active and these cells then further suppress the activity in the excitatory arousal systems. Thus a positive feedback is set up leading to rapid and almost complete suppression of activity in the arousal systems (***Verret et al., 2006***).