Part 10

Cognitive Neuroscience

Elementary CNS Arousal

71

Eugene M. Martin and Donald W. Pfaff

Brief History

Diffusely projecting, global controls over brain arousal have long been recognized in clinical neurology, as their damage leads to disorders of consciousness. In the first half of the twentieth century, brain arousal was thought to be triggered and maintained by the influx of sensory information. This viewpoint was superseded by two relevant lines of research that developed in relative isolation. One involved the "ascending reticular activating system," a system which comprises neuronal cell bodies in the brainstem reticular formation that have diffuse ascending axonal projections to the forebrain, including the central thalamus, and which play a key role in modulating levels of arousal and attention. The other system involves hypothalamic centers involved in controlling the expression of both sleep and motivated or goal-oriented behaviors essential for the survival of the individual (e.g., appetitive behaviors associated with hunger and thirst) and survival of the species as a whole (e.g., sexual and parental behaviors).

The first line of research gained traction through the classical experimental studies by both Bremer and the team of Moruzzi and Magoun who demonstrated that stimulation of the reticular activating system evoked changes in electroencephalogram (EEG) recordings from anesthetized cats. In these studies, electrical stimulation of the midbrain reticular core or the central thalamus changed EEG activity from a resting-state pattern to an awake-state pattern, with diffuse thalamocortical projections being implicated in the changes. Confirmation of this anatomical pathway from the midbrain reticular core to the central thalamus was later provided by detailed electrophysiological and anatomical studies. Subsequently, the thalamus, which was originally thought to play a simple role as a relay of information, has been shown to be critical to the state of an animal.

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The second line of research, which focused on the hypothalamus, linked stimulation of regions within the hypothalamus to basic survival behaviors (e.g., aggression, sex, and food intake), the CNS arousal necessary to support these behaviors, and to the control of the sympathetic and parasympathetic autonomic nervous system (ANS). Likewise, the experiments of Nauta showed that large lesions of the posterior hypothalamus resulted in a sleep-like behavioral state. Convergence of these two lines of research has since been established with the posterior hypothalamus having been shown to have important reciprocal projections with brainstem arousal-associated nuclei. Since these early lines of research, major technical and theoretical breakthroughs in almost all neuroscience domains have revealed much about the identity and structure-function organization of neural systems underlying (a) the sleep-wake cycle; (b) arousal, alertness, and attention; and (c) motivation and emotion.

Elementary CNS Arousal Refers to a Continuum of Behavioral States Marked by Increases in Motor, Emotional, and Sensory Responsiveness

Elementary CNS arousal serves to shift an animal between sleep and wakefulness, to orient an animal toward important stimuli, and to maintain wakefulness in the absence of important external stimuli. While specific motives and incentives explain why an animal does one thing rather than another, the likelihood of an animal performing any behavior at all is dependent on the animal's level of arousal (Fig. 71.1). Arousal is modulated by circadian, homeostatic, executive/cognitive, emotional, and environmental factors. Both conceptually and experimentally, we know that an animal's level of arousal can be variable across minutes, days, seasons, and years. These variations are associated with behavioral characteristics such as mood, feelings, temperament, and overall cognition. While arousal's role in promoting sleep or wakefulness is one of its most obvious, and well-studied, effects on behavior, the more subtle shifts between quiet waking, active waking, and attention are equally important, with potential clinical manifestations.

Although the concept of arousal seems obvious as an abstraction, it needs to be concretely defined in order to be tractable for experimental study. The definition should reflect that arousal is universal across vertebrates, that it incorporates multiple brain systems (sensory, motor, and executive), and is present continually throughout an animal's life. As such, the definition should be elementary and fundamental; it should be undifferentiated, not derived, from higher CNS functions; it should incorporate voluntary motor activity and muscle responses; and it cannot be limited by particular, temporary conditions or measures. For example, the definition cannot be confined to explaining responses to only one stimulus modality, nor should it be limited to reflex responses to environmental stimuli. Therefore, the following has been proposed as a definition that is intuitively satisfying and that leads to precise quantitative measurements:

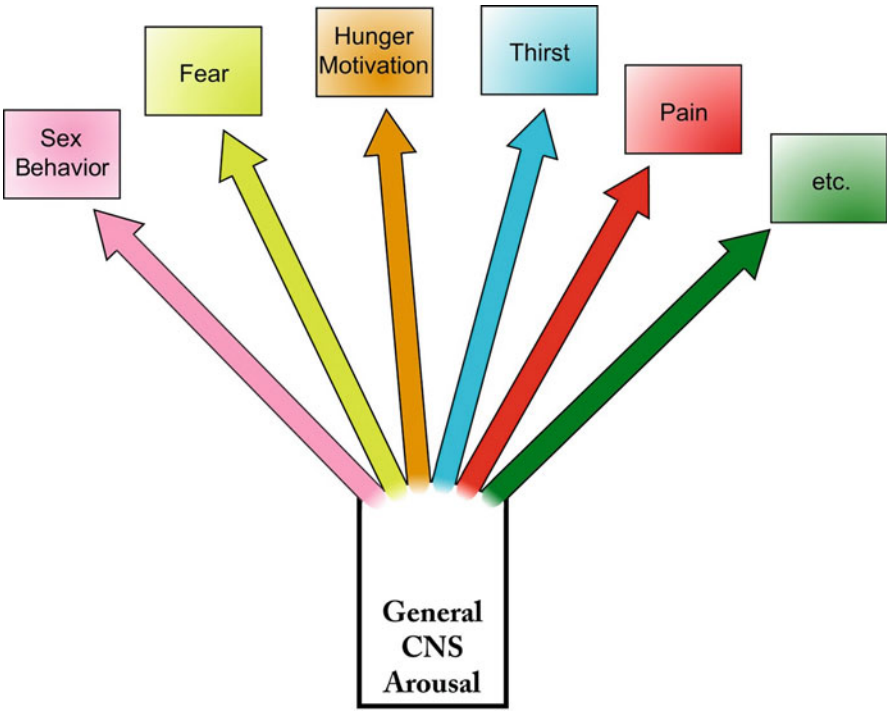

Fig. 71.1 Any given behavior that has a biological motivation depends both on generalized arousal and on a more specific kind of arousal (e.g., sexual arousal for sex). Without a sufficient level of generalized arousal, the specific arousals cannot be acted on (Adapted from Pfaff (2006))

Operational definition: "Generalized arousal" is higher in an animal that is
(S) More alert to sensory stimuli from all modalities
(M) More motorically active
(E) More reactive emotionally

All three components – sensory alertness, motor activity, and emotional reactivity – can be measured with precision and can therefore differentiate changes in arousal both within and between animals. This approach allows CNS arousal to be treated as a physical variable that can be explained with contemporary electrophysiological and genetic techniques (Fig. 71.2). Operational requirements for generalized CNS arousal systems are listed in Table 71.1.

Beyond observations from clinical neurology, three new lines of evidence indicate that a generalized arousal function operates in the vertebrate brain. First, factor analysis of behaviors by mice subjected to a variety of arousal-related assays revealed that a generalized arousal factor accounted for about one third of the variance. Secondly, generalized arousal is a function for which many of the brain mechanisms are, in fact, already understood (see below). Third, new results suggest that generalized arousal can be bred, producing high-arousal and low-arousal lines of mice. This last line of evidence also empirically shows that genetic

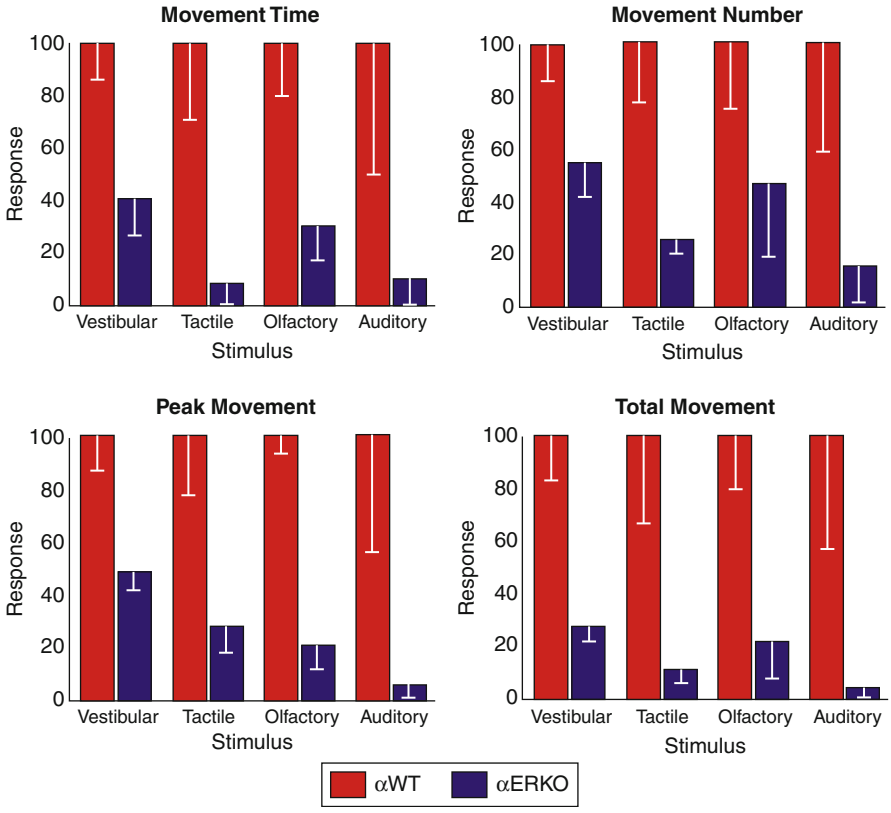

Fig. 71.2 The operational definition of arousal allows CNS arousal to be treated as a physical variable. Presented are data which, by measuring alertness to sensory stimuli and motor activity, show that knocking out the alpha estrogen receptor gene (αERKO) produces mice which have decreased arousal relative to wild-type mice (αWT) (Adapted from Pfaff (2006))

Table 71.1 Operational requirements for general arousal

Feature	Definition
Lability	"Hair triggered"; rapid, not sluggish
Sensitivity	The system can respond to small changes in input in a state-dependent manner
Convergence	All sensory stimuli activate the same set of arousal subsystems, which, in turn, activate each other
Divergence	Activation of cerebral cortex, autonomic nervous systems, and endocrine organs to initiate behavior
Robustness	The system does not fail; survival of the organism depends on adequate arousal

differences between individuals can account for some characteristics of an individual's arousal state.

While behavior is the most important physical manifestation of arousal, two other types of measurements are useful. Activation of electrical activity across the

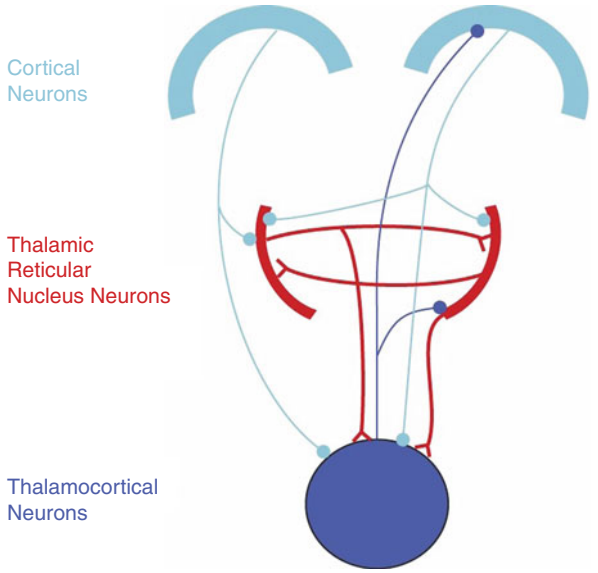

Fig. 71.3 Simplified diagram of the interconnections between neurons of the thalamus (*blue*), thalamic reticular nucleus (*red*), and cortex (*cyan*). Thalamic neurons send excitatory projections (*circles*) to both the thalamic reticular nucleus and the cortex. Neurons in the cortex send many more excitatory projections to both the thalamic reticular nucleus and the thalamus. Neurons in the thalamic reticular nucleus, in turn, send strongly inhibitory projections (*Forked endings*) to each other and to the thalamus. Not shown are local inhibitory interneurons which are present in both the thalamus and cortex

cerebral cortex, as measured by the electroencephalogram (EEG), correlates with – but is not identical to – behavioral activation. Likewise, increased activity in the sympathetic pathways of the autonomic nervous system (ANS), which leads to physiological changes such as increased heart rate, correlates with behavioral arousal but is not identical to it. While we know some of the biological mechanisms behind EEG and ANS changes, and they support our operational definition, behavior is the bottom line.

Elementary CNS Arousal is Marked by Electrophysiological and Behavioral Characteristics

The three primary categories of CNS arousal are slow-wave sleep (SWS), rapid eye movement sleep (REMS), and wakefulness. Slow-wave sleep and wakefulness are not unitary states, as SWS has multiple stages and wakefulness incorporates varying degrees of arousal (e.g., drowsiness and attention). These various behavioral states are associated with changes in muscle tone and specific CNS activity across the thalamus, reticular nucleus of the thalamus (RE), and cortex. The basic organization of the forebrain, with a recurrent thalamocortical network, can be

found in all mammals (Fig. 71.3). The thalamus and cortex both have excitatory projection neurons which project to both each other and the RE. In turn, the RE projects to the thalamus where its actions are solely inhibitory. Functionally, this network modulates how, and whether, information ascends to the cortex from the external world and the temporal dynamics by which it is processed.

Within the thalamus, the nonspecific nuclei play a dominant role in increasing an animal's level of arousal. Nonspecific refers to nuclei that do not correspond to a single modality and includes midline (rhomboid and reunions), medial (centromedial and ventromedial), and intralaminar (centrolateral and paracentral) thalamic nuclei. These nuclei receive cholinergic, noradrenergic, serotonergic, and glutamatergic inputs (see below) from the basal forebrain and brainstem; in essence, these nuclei are a link between the cortex and arousal-driving systems. Individual nuclei project diffusely to the cortex and/or striatum and hence have global influences on brain activity. Note that although the activity among the thalamus, RE, and cortex creates and maintains different arousal states, the brain regions that *drive* changes in an animal's arousal state are located in the brainstem, basal forebrain, and hypothalamus.

At the neuronal level, increased CNS arousal is equivalent to a shift toward a state of readiness in neurons of the forebrain. Electrophysiologically, this means that the average membrane potential of the neurons becomes more depolarized, such that incoming synaptic events are more likely to produce action potentials. This depolarization results in more reliable transmission of information and quicker responses. While depolarization occurs at the level of individual neurons, cognition of the external world requires *coordinated* activity between neurons, specifically between the thalamus and the cortex and among cortical regions. Without coordinated cortical electrophysiological activation, we are not alert and aware of our own acts.

The most common means by which cortical activation reflecting a change in arousal state can be measured is by recording an animal's EEG. The cortical EEG is recorded from the surface of the scalp and its waveforms result from large numbers of synchronous postsynaptic responses in local populations of neurons beneath the scalp electrode. When a large number of synaptic events happen concurrently, the EEG waveform has a large absolute amplitude at that instant. If the numbers of neurons involved in an event decrease, or if the timing of events becomes less correlated, the absolute EEG amplitude decreases. The fluctuations in amplitude over time have distinct characteristics, most notably in the periodicity of amplitude fluctuations, depending on the behavioral state of the animal. High-frequency (20–80 Hz; also called fast oscillations), low-amplitude activity is primarily associated with behavioral wakefulness and attention, whereas low-frequency (0.5–5 Hz), high-amplitude waveforms are associated with sleep and rest (Fig. 71.4). Current literature suggests that high-frequency oscillations facilitate the encoding and decoding of information during perceptual and cognitive processes, while low-frequency oscillations facilitate memory formation, plasticity, and restoring cell homeostasis.

While certain parts of the thalamus and cortex have been stressed here, other forebrain regions are involved in CNS arousal. For example, the intralaminar nuclei

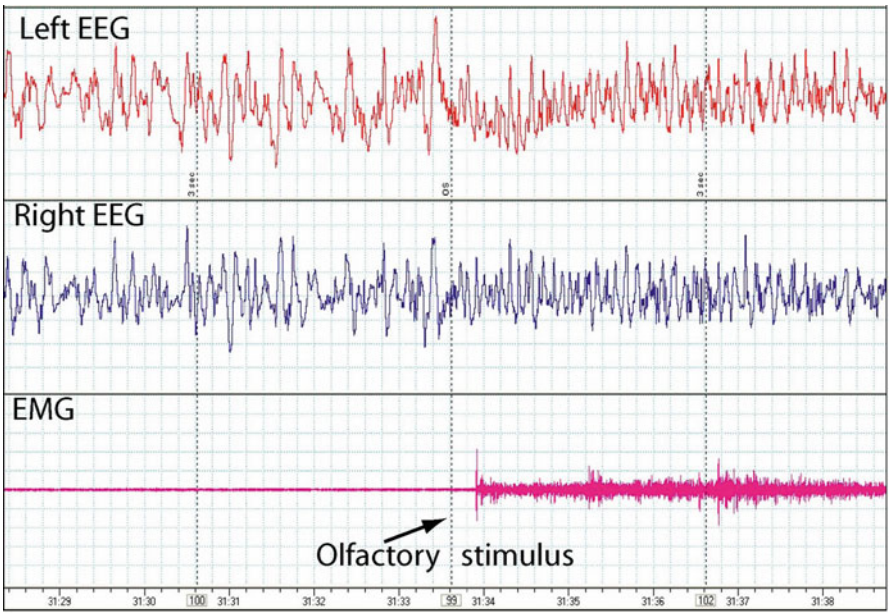

Fig. 71.4 Simultaneous electrophysiological recordings of the electroencephalogram (EEG) from the left and right cortices and neck muscle electromyogram (EMG) in a mouse. Experiments were conducted in the mouse's home cage during the light part of the daily cycle so that baseline activity would be steady and quiet. Upon presentation of a novel olfactory stimulus, the EEG changed from high-amplitude/low-frequency waves, which are associated with rest, to low-amplitude/high-frequency waves, which are associated with higher CNS arousal. Concurrently, the mouse contracted its neck muscles, consistent with increased axial muscle tone (Adapted from Pfaff (2006))

of the thalamus have substantial projections to the striatum, which, in concert with activation of the cortex, prepares an animal for motoric behavior. Although the striatum, which is a component of the basal ganglia, has historically been predominantly associated with motor function, recent studies have associated this region with behavioral arousal function. While the exact relationship between the striatum and behavioral arousal remains to be understood, the region forms a network with the frontal cortex and may be involved in shifting the cortical function toward an attentive state, directing attentional aspects of motor behavior, and modulation of an animal's sleep-wake cycle. The pattern of neural activity within the striatum changes with the state of the animal, with the striatum firing synchronously with the cortex during slow-wave sleep but nonsynchronously during wakefulness.

Likewise, the amygdala is involved in emotional activation of the brain, particularly with regard to the modulation of fear responses. The amygdala has access to sensory information from all modalities and projects widely throughout the nervous system. Neurons in the amygdala project to the cortex (more extensively in primates than in rodents and cats), striatum, nonspecific thalamic nuclei, hypothalamus, and the brainstem reticular core. Its activity may serve to bias attention toward emotionally relevant stimuli. The amygdala and other limbic-associated brain

regions are particularly active during REMS and likely contribute to the emotional valence of REMS dreams. As the precise relationship between behavioral arousal and both the basal ganglia and amygdala remains to be worked out, it will not be discussed in greater detail in this chapter.

Significant strides have been made in relating specific brain activity to particular behavioral states. Behavioral and neurophysiological characteristics of arousal states are discussed below:

Sleep. There are five stages of sleep that can be consolidated into two major groups: slow-wave sleep (SWS) and rapid eye movement sleep (REMS). Sleep is the product of both decreased firing of wake-promoting regions and increased firing of sleep-promoting regions – that is, it is generated by both passive and active neural mechanisms. Homeostatic mechanisms, which are related to how active the brain has been and the duration of wakefulness, influence the intensity and duration of sleep. The circadian system, which anticipates the timing of regularly occurring events, influences the timing of transitions to sleep and to wakefulness. The electrophysiological activity associated with sleep is conserved across most, if not all, vertebrates. Slow-wave sleep is associated with high-amplitude, low-frequency oscillations across the thalamus and cortex, and low muscle tone. In contrast, REMS is associated with low-amplitude, high-frequency oscillations; the complete absence of muscle tone; rapid movement of the eyes; and ponto-geniculo-occipital (PGO) waves. Both states are characterized by a significant attenuation of signals being communicated from the external world to the cortex.

Electrophysiologically, slow-wave sleep is defined by the presence of slow oscillations (0.5–1 Hz), delta activity (1–4 Hz), and spindles (7–15 Hz), with the latter two rhythms often superimposed on the slow oscillations. The different oscillations are the product of both intrinsic channel dynamics at the cellular level and synaptic interactions among the thalamus, RE, and cortex at the network level. While mechanistic details about the generation of each rhythm is beyond the scope of this chapter, each rhythm is associated with increased hyperpolarization at the thalamic level and long hyperpolarizations followed by long depolarizations (during the slow rhythm) at the cortical level. Hyperpolarization at the thalamus is secondary to cessation of activation from brainstem arousal systems and to prolonged bursting by afferent GABAergic RE neurons, with the latter mechanism being most pronounced during RE-generated spindle rhythms. This hyperpolarization largely prevents any sensory signals from relaying through the thalamus from the periphery. At the cortical level, neurons do not fire action potentials during the hyperpolarization phase of the slow oscillation. In contrast, during the depolarization phase, cortical neurons can fire at gamma frequencies (20–80 Hz) that have been more typically associated with wakefulness. Regionally, sleep differs from wakefulness in that multimodal cortices are less active while activity in the primary sensory cortices is relatively unchanged.

While SWS is universally considered a low-arousal state, REMS is sometimes considered to be a state of high brain arousal due to the depolarization, and fast oscillations, among cortical neurons. As it is deleterious for a healthy animal to show behavior during REMS, we categorize REMS as a low-arousal state as per the

operational definition at the beginning of this chapter. Rapid eye movement sleep is associated with vivid, surreal dreams. Activity within the thalamocortical network is associated with fast oscillations and PGO waves. Ponto-geniculo-occipital waves are phasic activity that is initiated by brainstem acetylcholine nuclei and then transmitted from the pontine reticular formation, through the lateral geniculate nucleus, into the occipital cortex. The percepts associated with this activity are independent of the external world. During REMS, the primary sensory cortices and limbic-associated brain regions have high activity, while frontal and association cortices show little activity. As such, thought processes during REMS lack logic and directed thought while they are highly emotional.

Wakefulness. Although wakefulness is not a unitary state, it is generally defined as the state when an animal can actively react to the environment. Wakefulness is electrophysiologically characterized as increased cortical activation (fast oscillations) and increased postural muscle tone. Intracellular recordings from chronically implanted cats demonstrate that the first sign of transition from SWS to either wakefulness or REMS is the abolition of the long-lasting hyperpolarizing potentials in the thalamus and cortex. Upon waking, experiments with humans have shown that the transition to an awake state is almost instantaneous, as determined by lack of disorientation, intact memory, and accuracy at performing tasks, while the transition to an attentive state, as determined by decreased reaction time, ranges in duration from minutes to hours (sleep inertia).

The abolition of long-lasting hyperpolarization at the cortex and thalamus is mediated, in part, by acetylcholine inputs from the brainstem and basal forebrain which decrease the hyperpolarizing potassium currents in the thalamus and cortex. This, in turn, changes the firing of thalamocortical neurons from slow rhythmic bursting activity to predominantly tonic firing, which is associated with fast oscillations and increased transmission of signals from the periphery. One of the consequences of the transition to tonic firing and fast oscillations is that it increases the rate by which the nervous system can sample the external world, thereby allowing quicker responses to a dynamic environment.

Attention. Attention refers to the moment-to-moment optimizing of CNS processing to fit the demands of a situation by focusing on one task and ignoring others. The adjustment of activity across cerebral structures is controlled by bottom-up brainstem reticular core activity and top-down signals from frontal regions involved in monitoring demands on effort and vigilance. Although there is no universal physiological signature of attention, it is associated with increases in high-frequency oscillatory activity in the 20–80 Hz range of the EEG. One of the basic foundations of attention is that an animal has only limited processing capacity at any one time. As such, the role of attentional systems is to modulate when the brain is at heightened activity and which processing systems are activated. Cognitive studies have shown that increasing activity within one processing system produces widespread interference with most other cognitive operations. Correspondingly, functional magnetic resonance imaging studies have shown that during tasks that require a high attentional load, unattended salient stimuli are not represented at higher cortical levels.

While it is known that attention is not a unitary phenomenon, the categorizing of attention mechanisms into different domains, and the biological processes supporting each domain, is still being debated. Here, we will divide attention into the three major domains proposed by Posner and Peterson: alerting, orientation, and executive control. Pharmacological and physiological studies in humans and other animals suggest that these domains are supported by distinct brain regions and predominant neurotransmitter signatures. Although each domain is independent, behavioral tasks often require coordinated activity among them.

Alerting is fundamentally a bottom-up attentional process by which stimuli in the environment activate brainstem arousal nuclei. An alert animal knows that an event has occurred, referred to as the "when" of attention, and the central nervous system is grossly primed to process stimuli. Activity at the locus coeruleus (LC) initiates an alerting response, which then releases noradrenaline (see below) at its target sites, including the frontal and parietal cortices. Often, an alerting response is followed by an orientation response to the alerting stimulus.

Orienting is usually thought of in the spatial domain and involves an animal focusing on a restricted area while relatively attenuating everything outside of that area. Functionally, orienting increases the signal-to-noise ratio of the attended target. Events that occur within an oriented location are responded to more rapidly, are associated with greater neural activity, and can be reported at lower thresholds. The process of orienting requires disengagement from what the animal was attending to, changing the target, and maintenance on the new target. This activity is associated with the parietal lobe, prefrontal cortical regions, and the pulvinar nucleus, and the response is modulated by acetylcholine from the basal forebrain. The cholinergic projections of the basal forebrain inhibit the thalamic reticular nucleus via muscarinic receptors, which, in turn, regionally disinhibit the thalamus. Likewise, axons projecting from the basal forebrain may also synapse at muscarinic receptors on inhibitory cortical interneurons, thereby regionally disinhibiting cortical projection neurons.

Finally, executive control resolves conflicts among attentional and motoric action systems. While this system has been the least studied, it appears to be mediated by prefrontal and anterior cingulate cortical systems and is predominantly affected by dopamine. The anterior cingulate cortex may also be involved in a diverse range of cognitive demands and has reciprocal connections with the thalamus and provides diffuse projections to the prefrontal cortex, suggesting it may widely activate the prefrontal cortex. The anterior cingulate cortex is recruited by a diverse range of cognitive demands and is activated with increasing cognitive load across a wide variety of tasks.

Drowsiness/Somnolence. The state of drowsiness reflects decreased transmission of peripheral signals from the thalamus to the cortex. It is associated with increases in bursting activity, and the associated prolonged hyperpolarization, in isolated thalamocortical neuron populations. As such, drowsiness can be considered a sleep-like state within local neuronal assemblies.

Disorders of Consciousness

Coma/Vegetative State. Coma is characterized by a persistent lack of awareness and lack of arousal that is secondary to thalamocortical dysfunction. Persistent vegetative state differs from coma in that while there is still an absence of awareness, a patient in a vegetative state cycles through eyes open and eyes closed states that are crude representations of arousal, and their EEG is often monotonously slow. During wakefulness, the individual in a vegetative state shows no awareness of self or the environment and shows no evidence of sustained, purposeful, or voluntary behavior. Likewise, the EEG is markedly slowed. Coma is often caused by ischemic or traumatic events and is typified by bilateral thalamic damage, diffuse cortical or cortical tract damage, damage to the brainstem superior to the medulla, or a combination of these injuries.

The Brainstem Core, Hypothalamus, and Basal Forebrain Serve as Modulators and Effectors for Changes in Elementary CNS Arousal States

While thalamic and cortical nuclei play an essential role in supporting the state changes of the forebrain arousal systems, and, indeed, manifesting awareness and motivated behaviors, these nuclei are not sufficient to act as effectors of state changes. The nuclei which cause, and also help maintain, changes in state are predominantly located in the brainstem, basal forebrain, and hypothalamus. These regions may have an activating effect (i.e., evoke depolarization) or a sleep-producing effect on the subcortical relays, thalamus, cortex, striatum, amygdala, and related subsystems. Neurons in these regions tend to have broad dendritic fields, which facilitates the integration of information from multiple sources, and they transmit nonspecific information. Additionally, the systems tend to have mutually excitatory actions on each other. It is important to understand that there is no single activating center, or sleep center, but multiple functionally overlapping systems.

Brainstem systems that control CNS arousal and behavior tend to ascend toward the forebrain following either a "low road" or a "high road" (Fig. 71.5). The low-road system comprises the ventral pathways – which are the evolutionarily older of the two pathways – that impact (at least) the cholinergic neurons of the basal forebrain. Basal forebrain neurons, in turn, release acetylcholine in the cerebral cortex. The "high-road" system comprises the dorsal pathways – which are more recently evolved among vertebrates and especially well developed among primates – that impact the nonspecific thalamic nuclei. Brainstem systems can be distinguished by their efferent targets, although they show significant overlap (Fig. 71.6). The systems that drive changes in arousal are also organized according to the predominant neurotransmitter synthesized in each nucleus. Although these systems are treated individually, they are highly interconnected both anatomically and functionally.

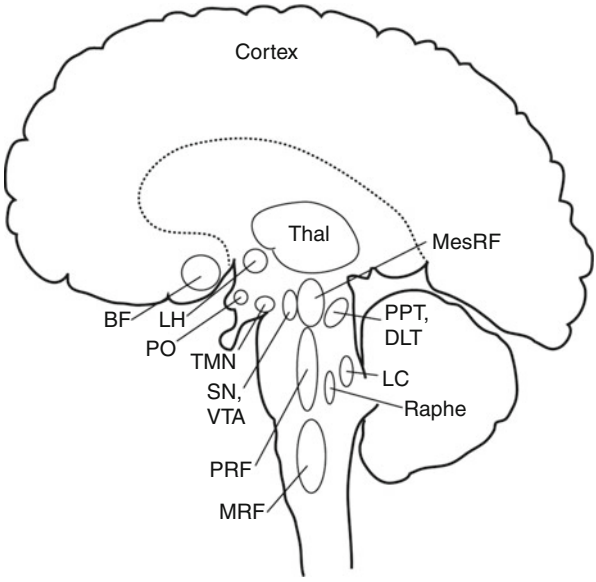

Fig. 71.5 The nuclei which predominantly drive changes in arousal state are clustered in the brainstem. Their projections tend to ascend toward the forebrain following either a low road to the basal forebrain (BF) or a high road toward the thalamus. Ultimately, both pathways modulate the activation of the cerebral cortex (Adapted from Jones (2008))

Serotonin (5-HT). The raphe nuclei of the brainstem are the principal source of 5-HT in the CNS. Serotonin, in addition to modulating social behaviors, is associated with quiet wakefulness (which includes behavior such as grooming) and may promote the transition to SWS. Neurons that produce serotonin are most active during wakefulness, have low activity during SWS, and are quiet during REM (Fig. 71.7). These serotonergic neurons project to the hypothalamus and to several regions of the limbic system, including the hippocampus, septum, and amygdala; serotonergic projections to the thalamus are also strongest in thalamic nuclei that are associated with the limbic system. Serotonergic connections to the cortex are widespread and include the olfactory cortex, the olfactory bulb, and the neocortex.

Nerve cells in the raphe nuclei receive significant ascending afferents from adrenergic neurons in the lower brainstem as well as from neurons expressing peptides related to arousal, such as orexin. The raphe nuclei also receive descending inputs from the forebrain, including influences from the limbic system and hypothalamus, and even from the pineal gland, which imposes a daily rhythm on serotonin production. Despite being associated with wakefulness, serotonin attenuates cortical activation through inhibitory actions on brainstem arousal systems, including the acetylcholine system. Increased 5-HT concentrations in the CNS are associated with decreases in reactivity to sensory stimulation and with decreased motivation, for example, for sex. Stimulation of the raphe nuclei causes the cessation of active waking behaviors, such as eating or sexual activity. According to the operational definition of arousal, serotonin potentiates a low-arousal state.

The diversity of molecular structures and expression of the 14 genes coding for serotonin receptors tells us that the logic of their cellular functions will be quite

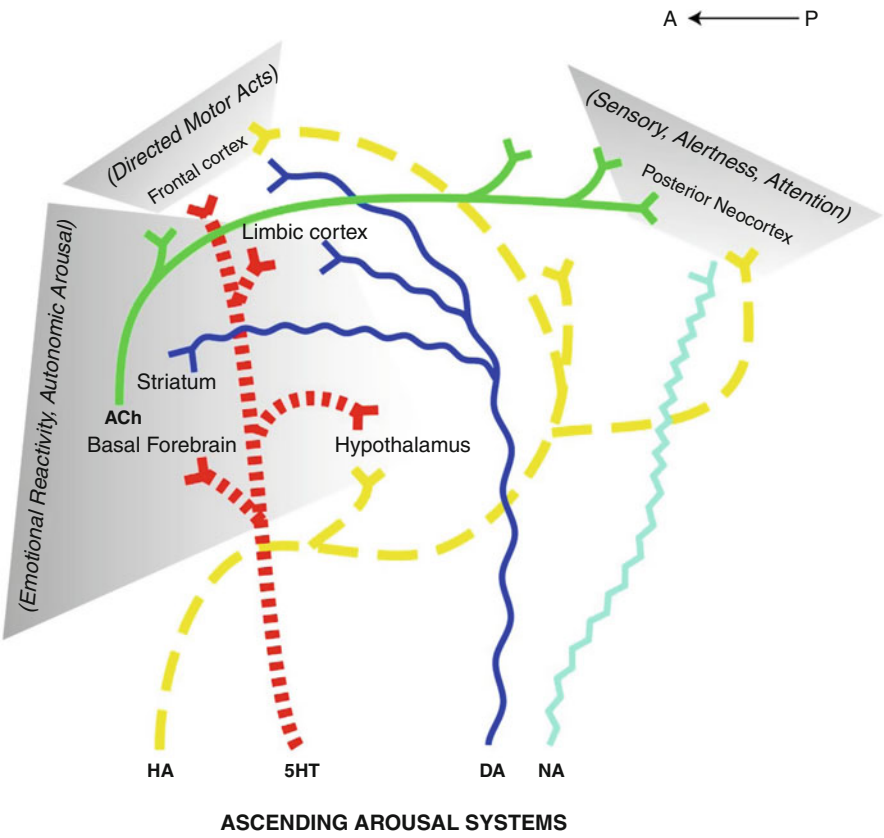

Fig. 71.6 Each brainstem system is biased toward unique efferent targets, which is functionally associated with that system impacting one aspect of arousal. Despite this, there is wide overlap among the targets, which emphasizes the redundancy among these critical brainstem systems (Adapted from Pfaff (2006))

complex. For example, while serotonin can depolarize neocortical cells and enhance their excitability consistent with neocortical arousal, the effects of serotonin at the single neuron level are varied, depending upon the receiving cell. Recording from dissociated prefrontal cortical pyramidal neurons, Carr and Surmeier found that serotonin could inhibit a sodium current in a manner dependent on phospholipase C and protein kinase C, which would reduce excitability.

Noradrenaline/Norepinephrine. There are seven distinct nuclei that synthesize NA (A1–A7), with the locus coeruleus (A6) being the largest and groups A1, A2, A5, and A7 being positioned in the lateral tegmental area of the medulla. Noradrenergic (NA) neurons are most active during wakefulness, especially during active wakefulness, show low activity during SWS, and cease firing during REM sleep. Activity of NA neurons serves to depolarize systems involved in waking and to hyperpolarize systems involved in promoting sleep. Likewise, drugs that inhibit NA

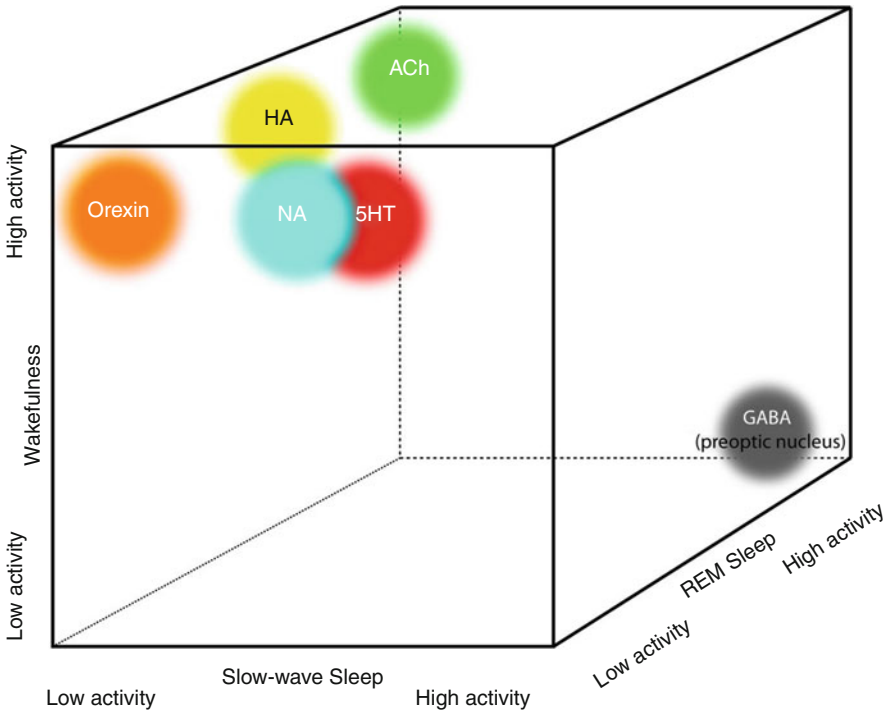

Fig. 71.7 Each neurotransmitter system tends to have unique normalized rates of firing across the states of wakefulness, slow-wave sleep, and rapid eye movement sleep. For example, orexin neurons fire maximally during wakefulness and are silent during both slow-wave and rapid eye movement sleep. Note that although dopamine does not significantly change its firing rate across states, it tends to fire in bursts during wakefulness

action facilitate sleep onset. Noradrenergic neurons send substantial projections to the frontal and parietal cortices, and are widely interpreted as supporting sensory alertness, while projections to the other forebrain structures, including the amygdala, help control cardiovascular, visceral, and neuroendocrine functions. Furthermore, NA neurons send diffuse projections to the spinal cord, where they can modulate motoric processes. This fact feeds the idea that hindbrain cell groups supporting arousal are not simply divided into those that just ascend and those that just descend – some cell groups project to both forebrain and spinal cord nuclei. Returning to our operational definition of general CNS arousal, NA can influence sensory, motor, and emotional responsiveness. Amphetamines, which act at noradrenergic and dopaminergic synapses, likely have their arousing effects via the noradrenergic and dopaminergic systems' diffuse stimulation of the frontal cortex; in contrast, the rewarding effects of amphetamines are likely linked to noradrenergic synapses in the nucleus accumbens. Despite the clear links between arousal and the LC, chemical lesioning of the LC does not result in coma; there are redundant arousal systems.

By and large, sensory afferents do not project directly to the LC. The inputs which best account for the LC's integrative powers are those from the medullary and pontine reticular formation in the hindbrain. These regions integrate inputs from a variety of sensory modalities in a generalized fashion and feed the LC as a nodal point in ascending arousal circuitry. Among them, stress-related and autonomic-related inputs must be of special importance. Transmitters involved include noradrenaline itself, serotonin, and excitatory amino acids such as glutamate. Importantly, not all of the inputs ascend from the periphery toward the forebrain. The LC also receives descending inputs from regions involved in sleep and other circadian behaviors, including a small preoptic area devoted to sleep, the dorsomedial hypothalamus, and the suprachiasmatic nucleus. It also receives descending inputs from limbic-associated regions including the amygdala and the bed nucleus of the stria terminalis.

Neurons of the primate LC have been shown to fire to novel, unexpected, important, or salient stimuli. Likewise, phasic activation of LC neurons is associated with network-wide enhancement of sensory processing of salient environmental stimuli. Maximal discharge of LC neurons is associated with highly aroused conditions, including stress. Correspondingly, genetic ablation of the LC showed a decrease in anxiety in mice.

Examples of how arousal mechanisms can have valences assigned to their eventual behavioral impacts come from the actions of adrenergic transmitters in the forebrain. Adrenaline and noradrenaline participate in generalized arousal of the CNS. However, as Stone et al. have pointed out, alpha-1 adrenoreceptors function both in positively motivated approach activities and in behavioral inhibition. The ability for adrenergic transmitters to evoke seemingly opposite behaviors is based on the regional activity of the transmitter. Adrenoreceptors mediating adrenergic effects at neuroanatomic sites such as the lateral hypothalamic area, the nucleus accumbens, and the piriform cortex activate positive-approach behavioral explorations. However, those receptors in sites such as the paraventricular hypothalamus and the central nucleus of the amygdala are associated with fear, stress, immobility, and signs of depression.

Histamine (HA). Histamine is synthesized in the tuberomammillary nucleus of the posterior thalamus and influences arousal and the sleep-wake cycle. Histaminergic neurons are likely most active during waking, quiet during SWS, and cease their firing during REM; inhibition of these neurons leads to decreases in wakefulness. The tuberomammillary nucleus receives multiple inputs from brainstem arousal systems. It sends diffuse, widespread projections to many brain areas, including the cortex, basal forebrain, and brainstem arousal systems. By acting through the H1 and H2 receptors, HA neurons excite cholinergic neurons of the basal forebrain, which, in turn, activates the cortex. Additionally, the reciprocal innervation between HA neurons and the sleep-associated ventrolateral preoptic area should help to enforce rapid and powerful state changes between sleep and wakefulness.

Behaviorally, decreasing activity at the H1 receptor has been shown to reduce responsivity of female mice to external stimuli. Electrophysiologically, the

histaminergic system strengthens CNS transmission of afferent, sensory signaling. Despite the above relationships between histamine signaling and general CNS arousal, our understanding of the mechanisms involved in HA's behavioral effects is still quite incomplete. We know that HA can depolarize neurons, making them more able to respond to afferent information, but, compared to the large amount of data on H1 receptors, we know little about H2 and H3 receptor actions. Finally, wiping out HA by itself does not put an animal to sleep. This underlines a main point of this section: redundancy among neurochemical mechanisms serving arousal prevents system failure.

Acetylcholine (ACh). Brainstem cholinergic neurons are most active during REMS and strongly active during wakefulness, particularly during attentional behaviors. Acetylcholine has differential effects on state depending on the physiological context: in the presence of monoamines (DA, NA, 5-HT) and orexin, it leads to attention; in the absence of monoamines, it facilitates REMS. Functionally, ACh is associated with cortical activation, heightened attention, and heightened sensory-motor processing, particularly during taxing conditions (attentional effort). Compared to monoaminergic compounds, acetylcholine has very strong effects on thalamocortical neurons and hence is critical in effecting CNS arousal state. Nerve cells which synthesize acetylcholine are found in three major regions: (a) the pedunculopontine and (b) dorsolateral nuclei of the tegmentum (PPT and DLT), which are located in the brainstem at the border between the pons and midbrain, and (c) in the basal forebrain. Through the combined actions of the PPT, DLT, and basal forebrain, ACh affects behaviors associated with arousal through both cortical and limbic activation. In the basal forebrain area, they are spread out across the magnocellular preoptic nucleus, the diagonal bands, and the septum. Acetylcholine neurons receive substantial inputs from glutamatergic, cholinergic, noradrenergic, dopaminergic, and histaminergic ascending arousal system neurons.

Acetylcholine-producing neurons in the PPT and DLT project to the thalamus and, to a lesser extent, to the lateral hypothalamus and basal forebrain. Activation of these neurons makes thalamic neurons more sensitive to sensory information and activates the cortical EEG. Bilateral destruction of the PPT and DLT in humans, with large amounts of neighboring areas around them also damaged following mechanical or vascular accidents, produces a vegetative or comatose state. The functional significance of having two widely separated cell groups producing ACh – the PPT/DLT and the basal forebrain, both of which are crucial for arousal – is still unknown.

Hypocretin (Orexin). Hypocretin (also known as orexin) refers to a recently discovered set of gene products that are associated with modulating locomotor activity, feeding, and energy homeostasis and have dramatic modulatory effects on behavioral arousal, including CNS arousal and increased muscle tone. Neurons which produce hypocretin are located in the perifornical region of the lateral hypothalamus and in the dorsomedial hypothalamus. While the inputs to the perifornical region of the lateral hypothalamus and dorsomedial hypothalamus have not been fully worked out, these regions receive projections from other hypothalamic nuclei, the dorsal raphe nuclei, the cholinergic A2 group, and the

solitary tract nucleus. Both circadian (SCN) and homeostatic factors regulate the release of hypocretin. Hypocretin neurons project broadly through the nervous system, including projections to the cortex, spinal cord, VTA, dorsal raphe nuclei, substantia nigra, LC, amygdala, and medullary reticular formation. Hypocretin has solely excitatory influences, and hypocretin neurons are most active during an animal's waking state. Indeed, the firing of orexin-producing neurons may anticipate wakefulness in a sleeping animal by a few seconds. Likewise, delivery of orexin into an animal's nervous system, either intravenously or intraventricularly, increases behaviors associated with wakefulness; in contrast, knocking out orexin in mice leads to narcolepsy.

In vitro studies show that hypocretin-producing neurons can have sustained activity in the absence of synaptic inputs – that is, they would need to be inhibited to cease firing – which can provide these neurons with the ability to maintain an animal's waking state. Hypocretin also interacts with ACh at the cellular level in the brainstem to potentially maintain the integrity of behavioral state. As such, combined ACh and hypocretin activity leads to attention with muscle tone, while ACh alone leads to cortical activation with atonia (muscle paralysis).

Dopamine (DA). Neurons that produce dopamine do not show changes in *mean* firing rate across SWS, wakefulness, and REMS, although they do show peak, burst firing to rewarding conditions and salient stimuli during wakefulness. While the mean firing rates of DA neurons are stable across states, the patterns of firing of DA neurons are important: tonic activity preferentially activates D2 receptors and phasic activity activates D1 receptors. As the biophysical effects of these receptors at the cellular level can oppose each other, bursting of DA neurons during wakefulness may be critical to active waking behaviors. Dopaminergic axons course from the brainstem toward the forebrain via two predominant routes: From the substantia nigra, they ascend to innervate the striatum, a noncortical motor control region of the forebrain that also has a broader role in general arousal. A second DA system arises in a loosely formed cell group in the midbrain called the ventral tegmental area (VTA). These DA neurons innervate the phylogenetically ancient cortex called the limbic system, which is known to be important for controls over motivational states and moods.

While the DA system has historically been linked to the phenomenon of reward, recent studies suggest that the system may have broader functionality. A strong line of research from Jon Horvitz at Boston College demonstrated that the salience of stimuli would be the critical requirement for activating DA neurons rather than reward. Put another way, the reward value of a stimulus is just one way for that stimulus to gain salience. Destroying DA systems markedly slows responses to salient stimuli and leads to the omissions of responses. Continuing on this theme, DA neurons are not necessarily sensitive to reward itself but instead seem to signal anticipations and predictions of future rewarding events. Fluctuations of dopamine levels in nucleus accumbens during rewarded acts are consistent with the following new point of view: DA projections to nucleus accumbens signal excitement and arousal, not simply reward. When DA is virtually obliterated in mice, these mice show profound changes in behavior. They do not explore either new environments

or other mice, and they rarely initiate behaviors. Dramatically, these mice, despite being able to move and having palatable food available, will starve due to decreased feeding behavior. This effect has been localized to DA inputs to the striatum, where it is thought to facilitate glutamatergic signaling from the cortex. In contrast, when the concentration of DA in the synaptic cleft is experimentally elevated, the affected animals have remarkable behavioral hyperactivity in novel environments, making them act similarly to animals on psychostimulants.

The axonal trajectories of DA neurons can be distinguished functionally from those of NA neurons by DA neuron's tendency to synapse in more anterior regions of the cerebral cortex, which are cortical regions that are associated with motor activity. This can be contrasted to more posterior (except for occipital cortex) trajectories of NA axons, which are associated with sensory processing. Notably, some of these DA axons reach the prefrontal cortex where they synapse on neurons which coordinate the left and right sides of the frontal cortex. This is important, in part, because the two sides the frontal cortex have opposite effects on arousal and mood: heightened activity on the right side is associated with unpleasant feelings in humans, while heightened activity on the left side is associated with positive feelings. Some of these prefrontal cortical neurons project back to the VTA, emphasizing the bipolar, bidirectional feature of arousal systems.

Glutamate and GABA: Glutamate and gamma-aminobutyric acid (GABA) are, respectively, the predominant excitatory and inhibitory neurotransmitters in the nervous system, and each neurotransmitter has receptors distributed throughout the CNS. As depolarization and hyperpolarization are critical features of CNS arousal, these neurotransmitters play important roles in determining an animal's state of arousal and could be considered the backbone of the entire arousal system. For example, one of the mechanisms by which general anesthetics induce unconsciousness is by decreasing activity at glutamatergic receptors (e.g., ketamine) or increasing activity at GABAergic receptors (e.g., barbiturates).

The midbrain reticular core is the most effective activating system. Large lesions of this area lead to coma. It is, in turn, driven by the pontine and medullary reticular cores. All of these areas predominantly have their excitatory effects mediated by glutamate. One important group of these glutamatergic neurons, the medullary gigantocellular reticular nucleus (mGi), is currently under investigation as possible "master cells" of general arousal. The mGi is in a position to integrate both ascending sensory information from the periphery and descending information from the forebrain. Electrophysiologically, these neurons increase their firing rate to inputs from multiple sensory modalities (Fig. 71.8) and, with regard to tactual inputs, from multiple body regions. In turn, mGi neurons project to arousal-related targets including the basal forebrain, locus coeruleus, midbrain reticular core, and intralaminar nuclei of the thalamus (Fig. 71.9). Their activity has been associated with increased muscle tone and with changes in EEG from slow to fast oscillations.

Two examples of important GABAergic neurons are the projection neurons of the preoptic nucleus and the basal forebrain. The preoptic nucleus receives information about an animal's circadian rhythm from the suprachiasmatic nucleus

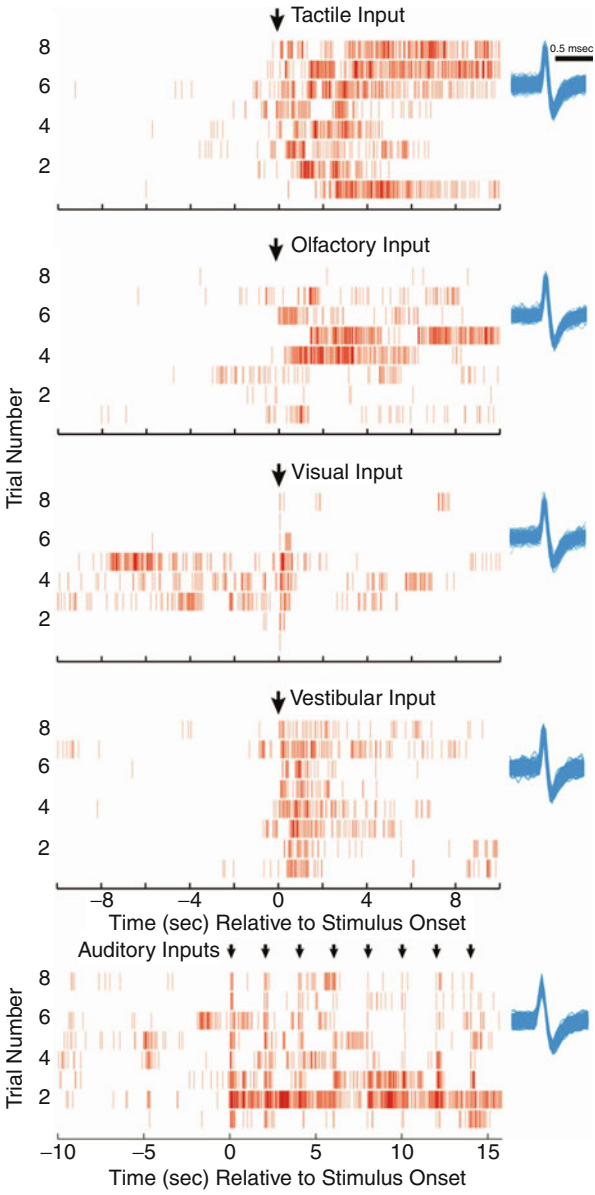

Fig. 71.8 Neurons in the medullary gigantocellular nucleus are hypothesized to be powerful drivers of state change in general arousal. A recording electrode was placed in the medullary gigantocellular nucleus of a rat and, after the rat had been motionless and resting (negative time values), the rat was presented with stimuli from five different sensory modalities. Stimuli from each sensory modality were presented eight times (eight rows in each raster plot), and the stimulus was presented at approximately Time 0 (*black downward arrows*); in the auditory domain, stimuli were presented eight times in each of the eight rows (*black arrows*). Each hash mark (*red*) represents the occurrence of an action potential. Responses of this single neuron to tactile, olfactory, vestibular, and auditory stimuli were obvious. Responses to the visual stimulus were present, although the middle rows show some of the intrinsic firing variability of these neurons. An overlay all of action potentials (*cyan*) for a given raster plot are shown to the right of each figure, showing that all action potentials were from the same neuron (Adapted from Martin et al. (2010))

(whose activity has a wake-promoting effect) and is activated by homeostatic factors, including adenosine (see below). It is a sleep-promoting nucleus that uses GABA to inhibit wake-promoting nuclei, specifically the locus coeruleus, tuberomammillary nucleus, and raphe nuclei. In turn, the preoptic nucleus is inhibited by NA and ACh.

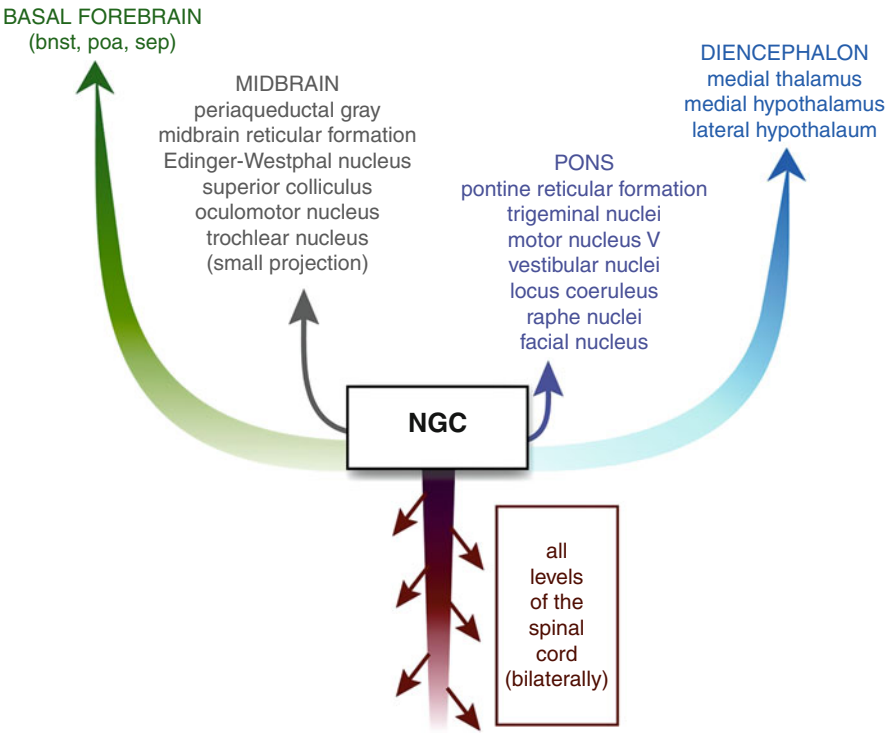

Fig. 71.9 Medullary reticular nucleus neurons have significant ascending and descending projections to arousal-related nuclei. These ascending projections reach regions of the midbrain reticular formation that are essential to consciousness, portions of the nonspecific thalamus, and basal forebrain sites important for modulating neocortical activity (Adapted from Pfaff et al. (2011))

In the basal forebrain, GABAergic neurons are interleaved with ACh neurons, which are hypothesized to have opposing effects. While NA depolarizes the ACh population, it hyperpolarizes the GABAergic population. Interestingly, while the basal forebrain GABAergic neurons are sleep active, and can promote sleep, they also receive strong excitatory input from the cortex – this circuitry is hypothesized to mediate top-down attentional mechanisms during taxing situations.

Adenosine. Adenosine is a metabolite of ATP use and serves as a homeostatic regulator of cell function. As it is related to cell function, it is globally present throughout the brain, and increased concentrations of adenosine have been shown to have sleep-promoting effects. Caffeine, in part, has its wake-promoting effects by inhibiting adenosine 2A receptors. While infusion of adenosine into the basal ganglia results in the onset of sleep, it may also be able to invoke sleep at the level of the hypothalamus and cortex. New theories in neuroscience suggest that adenosine may work at the local level to put isolated populations of neurons into a sleep-like state, as may be apparent during drowsiness.

Genetic Support of and Influences on Elementary CNS Arousal

A great multiplicity of genes is involved in producing CNS arousal signals. Likewise, these are genes through which CNS arousal can be regulated, by influencing their transcription rate and efficiency. How is the large number of genes arrived at? Consider all of the neurochemicals mentioned in the last few pages. Each of them has (a) gene products necessary for their synthesis, (b) gene products encoding their receptors, (c) gene products encoding their transporters, and (d) gene products responsible for their regulated chemical breakdown. Therefore, the numbers of all of the neurotransmitters and neuropeptides we have identified here (plus the others we did not mention for sake of simplicity and brevity) must be multiplied by at least 4, to begin to estimate the variety of genetic influences.

Redundancy Prevents System Failure

The diversity of arousal-related nuclei may serve multiple purposes. First, the separate origins and neurochemistries of the different pathways should allow some pathways to survive and function even when others are compromised. The fact that all these systems can respond to many forms of stimuli, and distribute their excitation widely, is consistent with each of them serving the common goal of brain arousal.

Second, even as these pathways have generalized features, they are not identical. Their dominant regions of termination in the forebrain, and their greatest points of functional impact, provide opportunities for separate manipulation. Noradrenergic terminals are somewhat denser in the posterior regions of the cerebral cortex (except occipital) than in the anterior regions. Correspondingly, as the posterior cortical regions are more devoted to sensory processing than to motor acts, noradrenergic pharmacology has been tied most closely to alertness. In contrast, DA pathways travel more anteriorly toward the forebrain, terminating in regions convincingly tied to motor control. Correspondingly, their neuropharmacology shows them crucial for motor acts directed toward salient stimuli. The emotional valences of different ascending systems may also differ: For example, the NA system tends to signal stressful stimuli, the DA system tends to signal positive rewards, and 5-HT function has been implicated in the control of mood.

Third, even though pathways which ascend toward the forebrain have been emphasized here, some very important controls over arousal begin in the basal forebrain and descend. An excellent example is the small group of GABA neurons in the ventrolateral preoptic area (vlPOA). Clifford Saper and his lab at Harvard Medical School have used a wide variety of experimental approaches to demonstrate that these neurons are important for normal sleep to occur. Another example is the suprachiasmatic nucleus (SCN) of the hypothalamus, discovered as a "biological clock" in mammals by lesion studies. Now, the "non-image-forming visual system" emanating from the SCN is understood to influence many biological rhythms, including daily changes in arousal.

Specific Example: Elementary Arousal and Sex Behavior

In the literature on mechanisms of motivation, it is clear that the occurrence and forcefulness of any motivated behavior depends on arousal. This section relates how elementary CNS arousal is related to a specific behavior, mating. Using the genomic and biophysical mechanisms of mating as background, we will explore potential "trading relations" between a specific form of arousal (sexual) and generalized arousal.

To approach this issue conceptually, suppose you have an animal that lacks sex hormones situated in a well-controlled experimental environment. You supply the experimental animal with a stimulus animal of the opposite sex for mating and nothing happens. The test animal does not mate. Then, suppose you inject the test animal with an appropriate sex steroid hormone and retest using the same controlled environment, the same time of day, the same age of test animal, and the same stimulus animal. This time, the test animal mates. In the logical equations which describe behavior, the stimulus and the response have been held constant. Therefore, the sex steroid hormone must have altered another variable term in the equation. That variable is called "sexual motivation."

Even in relatively simple mammals such as mice, motivation to mate plays out in a series of courtship responses. Given an adequate environment, the female will initiate unusually fast and directed locomotion to orchestrate her contact with the male. In fact, an entire series of communicative and locomotor behaviors culminate in approach responses. Social investigation and affiliative behaviors are increased, while aggression is decreased. In the female mammal, these courtship and locomotor behaviors depend very much on circulating estrogen levels working through the ER alpha receptor. More generally, a wide variety of behavioral assays shows that a female animal's sexual motivation is estrogen-dependent. In reference to locomotion, estradiol (which is the predominant molecular form of estrogen) enters the brain and is bound by neurons in the preoptic area, where it excites electrical activity in neurons associated with locomotor circuits and the initiation of courtship behaviors by female animals.

Effects of Elevated Generalized Arousal on Sexual Arousal. In both female and male experimental animals, neurochemical manipulations which mimic ascending arousal systems increase sexual behavior. Administering NA to female rats increases the primary female sex behavior, lordosis, and also mediates the ovulatory surge of luteinizing hormone (LH) from the pituitary. Thus it helps to synchronize the female's sexual arousal with her endocrine preparations for reproduction. Conversely, depleting hypothalamic NA abolishes lordosis behavior and disrupts the LH surge. Noradrenaline's effects in the hypothalamus work through adrenergic alpha 1b receptors. They originate with NA cell bodies in the lower brainstem, following the low road (e.g., from locus coeruleus), and increase activity of both ventromedial hypothalamic cells that control lordosis and preoptic cells which control the locomotion associated with courtship behaviors. Reducing ventromedial hypothalamic neuronal electrical activity, for example, by using a high dose of a selective mu opioid receptor agonist, correspondingly reduces lordosis.

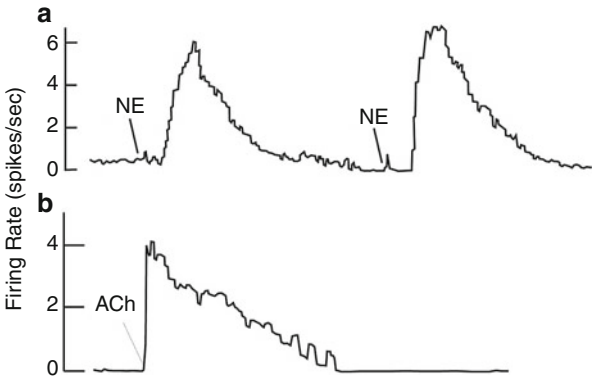

Fig. 71.10 Neurotransmitters which signal general arousal can elevate electrical activity in ventromedial hypothalamic neurons responsible for sexual arousal and sexual behavior. Recordings here are from ventromedial hypothalamic neurons in female rats in response to noradrenaline (**a**) and acetylcholine (**b**) (Adapted from Pfaff (2006))

Other arousal-related transmitters that influence sex behavior are HA and NA. These neurotransmitters act by increasing activity in the hypothalamic cells that control the lordosis behavior circuit (Fig. 71.10). Additionally, acetylcholine biochemistry ties into the mechanisms by which estrogens facilitate female sex behavior. Estradiol treatment increases the activity of the enzymes required for ACh biosynthesis and also upregulates the expression of ACh receptors. Thus, in females, neurotransmitters that increase generalized arousal also increase sex behavior.

For male sex behavior, the focus shifts from the ventromedial hypothalamus to the medial preoptic area and the neurotransmitter DA. Dopamine increases male sex behavior through at least three functional roles: it increases sexual arousal and the courtship behavior; it potentiates the motor acts of mounting behavior; and it facilitates genital responses to stimulation. Testosterone promotes DA release in the forebrain, and this release, in turn, is timed to coincide with actual mating behavior of the male. The impact of generalized arousal on sexual arousal is underscored when considering that erections and ejaculations require complex activation of both the parasympathetic nervous system and the sympathetic nervous system, also intimately involved in CNS arousal. In fact, the paraventricular nucleus, which is a hypothalamic cell group crucial for autonomic nervous system control, shows increased DA concentrations during male sexual activity. Other arousal-related neurotransmitters also tied to male sexual performance include NA, glutamate, and orexin. For example, microinjecting orexin into the preoptic area of male rats potentiates their sex behavior. These close relations between generalized arousal and sexual arousal are not limited to experimental animals. In heterosexual men, sexual interest is strongly suppressed during depressed mood states. Further, in women and men, drugs used to treat decreased libido include those which operate on generalized mood and arousal states.

Effects of Elevated Sexual Arousal on Generalized Arousal. Sex hormones can modulate gene transcription, membrane biochemistry, and electrophysiology. These hormones bind in regions associated with generalized CNS arousal and modulate general arousal states. Estrogenic hormones accumulate in NA cell groups in the lower brainstem that give rise to major ascending arousal systems. The novel estrogen receptor gene product, ER beta, is found in the midbrain raphe nuclei, which gives rise to serotonin pathways, as well as in midbrain cells that give rise to DA pathways.

A completely different mechanism for sexual behavior to impact generalized arousal depends on sensory physiology. Sexually significant stimuli from the genitalia, coming into the body over the pelvic and pudendal nerves, send strong signals to the lower brainstem reticular formation's gigantocellular reticular nucleus, which in turn increases activity in the locus coeruleus and the midbrain reticular core, which then activates the entire forebrain.

The molecular biology of sex hormone action at regions associated with generalized arousal further shows how sex hormones contribute to generalized arousal. Prominent among the molecular routes of influence are the ways in which sex steroids increase NA synthesis and effectiveness. Estradiol stimulates gene expression for the enzymes which synthesize NA in the locus coeruleus. In the hypothalamus, estrogens stimulate gene expression for a specific NA receptor subtype, the alpha 1b receptor, and foster interactions between these receptors and signal transduction pathways in hypothalamic neurons. Likewise, sexual interactions by female rats with males evoke NA release in specific parts of the hypothalamus. It appears that sex hormones increase the signal-to-noise ratio in arousal-related pathways by acting at an entire train of mechanisms – from synthesis through release through receptors through postsynaptic action.

Estrogens work through several other arousal-chemical systems as well. For example, Ingrid Reisert at the University of Ulm, Germany, has found that sex steroids can promote neurite outgrowth in midbrain DA neurons. Estrogens have been shown to affect the amount of time DA can reside in a synapse, increasing the effectiveness of DA at the postsynaptic neuron. Estrogen receptors are also found in many histaminergic neurons. Indeed, estrogen administration can amplify neuronal responses to HA. Estrogen also increases gene expression for the rate-limiting synthetic enzyme tryptophan hydroxylase and modulates serotonin receptors. Sex hormones desensitize the 5-HT1A autoreceptor, thus facilitating serotonin's synaptic functioning and, probably, heightening mood. Sex hormones also heighten cholinergic function, not only in the hypothalamus but also, importantly, in the basal forebrain.

In summary, sex hormones are able to increase generalized arousal through several molecular and neurochemical routes. While sexual behavior and sexual arousal were used as a specific example to highlight the interaction between generalized arousal and a specific arousal, note that other specific arousals, such as fear, likely both modulate, and are modulated by, generalized arousal systems.

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