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Introduction

This is a book written with a depth of literature review that should appeal to neurologists interested in the application of basic science to their profession. In addition, the text tries for a clarity that should invite a look by educated non-scientists.

To reverse engineer brain arousal mechanisms, I reframe a vital question with a formulation not previously used: "*Why does any animal or human do anything at all*"?

Beyond citing facts, I propose theoretical ideas about how brain arousal systems are organized. They must be reliable and they are. First, the nerve cell groups which support arousal are highly interconnected. In particular, some "master neurons" for arousal have such long axons sporting additional projections short, medium, and long that the neural net for what I call Generalized Arousal (GA) looks to me scale-free; that is, lots of neurons have few connections but these "master cells" have an extremely large number of connections. And the GA system can produce scale-free behavior. Thinking this way offers the opportunity of applying the rigor of physical and mathematical approaches to neurological and behavioral science. Because these master cells are supplying identical signals over their long axons up and down the neuraxis, they are, necessarily, producing "neuronal integration." Because these long axons run up (anterior) and down (posterior) the neuraxis, we therefore can talk about an anterior/posterior longitudinal integrated (A/P,L integrated) arousal system. As this system evolved from fishes to humans, it developed a high road (through the thalamus) as well as a low road (through the hypothalamus) from the brainstem to the forebrain. Both are important.

Chapters will follow this A/P, L integrated system from the hindmost brainstem cell groups – embryologically the myencephalon (medulla) – through the metencephalon (pons) and mesencephalon (midbrain) to see how arousing signals are sent through the "low road" (hypothalamus) and the "high road" (thalamus) to activate the forebrain.

This book is *not* a philosophical contemplation upon consciousness. It pits forth a theory which explains how all of us manage a phase transition from deep anesthesia, from deep sleep, or from traumatic brain injury into the dawn, the first light of consciousness.

Biological theorists who seek to explain consciousness have gotten stuck in the cerebral cortex, citing it as the *situs* of consciousness, i.e., where consciousness arises. I will challenge this notion and, accordingly, offer a new theory of how we become conscious during various natural or induced states in which we are unconscious. My approach will not limit activity bearing on consciousness to the cortex – or to any single element of the central nervous system (CNS) – but, rather, will take into account operations in an

Dedicated to the memory of the distinguished neurologist Fred Plum.

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array of neuronal structures. My purpose is to provide a better physical understanding of paths toward consciousness, and thereby enhance the ability of medical and neuroscience personnel to treat individuals whose physical consciousness is the desired goal.

Two leading theorists exemplify what I would call the cortico-centric tendency in the study of consciousness. The first, Giulio Tononi, a renowned neuroscientist in the Department of Psychiatry at the University of Wisconsin School of Medicine, has presented what he terms the "integrated information theory" of consciousness. The theory seems to offer unnecessary formalisms to explain the obvious, while failing to explain the causative routes of consciousness in the CNS. For example, he states that "a physical system in a state with high (integrated information) necessarily has many elements and specifies many causal relationships" (Marshall et al., 2016). The theory does not really provide mechanisms – it just pushes back the problem one step. When he experiments by tracking "changes in resting-state functional connectivity between wake and slow wave sleep," he does not need this theory at all (Deco et al., 2014). This "integrated" information theory does not provide a mechanism. It simply pushes the problem back one step – what kind of information? what exactly is integration? Professor Tononi simply names the goal; he does not get there.

In some of Tononi's theoretical work, he collaborates with a prominent researcher on the visual cortex, Christof Koch. When Koch was a professor at Caltech, he was stimulated to work on "the hard problem," consciousness, by the charismatic Nobel laureate Sir Francis Crick. While Koch and Tononi recognize that ever longer lists of "correlations between the behavioural and neuronal features of experience" (Tononi and Koch, 2015) will not suffice to explain causative routes to consciousness, they still feel the need to resort to "integrated information theory" with respect to cortical function and consciousness. This seems to beg the question, since it does not broach how the CNS, as a system, produces consciousness.

In the context of explaining consciousness, the term "integrated information theory" presents a problem of transparency. In that theory, only "information" can be defined precisely in mathematical terms, as in Claude Shannon's well-known 1948 information equation (see Chapter 10). Tononi's approach amounts to a top-down theory. In a top-down theory the scientist deduces properties of a system from first, abstract principles, i.e., from an overview. Once in a while top-down works. For example, in 1943, MIT's Warren McCulloch and Walter Pitts proved what could be deduced about neural nets using only "the two-valued logic of propositions" (p. 133). But usually neuroscientists theorize from the bottom-up. A bottom-up system starts with experimental details and induces how they can be pieced together to form subsystems and (larger, more inclusive) systems.

Here I use the bottom-up approach, literally bottom up, starting in the lower brainstem (Pfaff et al., 2005, 2008), where large reticular neurons provide the essential driving force for elevated levels of CNS arousal. For this approach, we arrive at the cerebral cortex only after the operations of extended A/P signaling through several modules which will be explained in this book. Thus we strive to reframe thinking about CNS arousal and consciousness by conceiving *a long anterior/posterior longitudinal ladder-like (A/P,L) system that is vertically integrated,* by virtue of a scale-free network, with each module in the system coding for a different essential physiological property of the system. The long A/P connections serve to combine separate elements, to form a complete, coordinated entity – i.e., to achieve an integrated GA system.

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In this regard, the Nobel prize-winning physicist Richard Feynman once said that he could not really understand a physical phenomenon unless he could put it together himself, that is, reconstruct it from basic elements. An intellectually gratifying feature of studying CNS arousal systems is that we can, indeed, reconstruct, i.e., faithfully duplicate, the elementary steps of increased arousal by electrical and chemical manipulations of arousal pathways.

We not only know where those pathways are, we also know what they do.

Instead of being limited to individual neuronal regions, "centers" for CNS arousal, I focus on long, A/P systems of communication that support the initiation of behavioral acts and, indeed, consciousness. Such systems do not originate in the cerebral cortex. Electrical and metabolic activity in the cortex represent the ultimate expression of successful function of neuronal signaling systems that begin just above the spinal cord. Every bit of arousal and awareness, every thought, has an underlying cause resident in the function of these extended neuronal systems.

This book will offer a new view of how these systems work. Strung along the long A/P pathways are large modules, neuronal groups that process arousal-related signaling and add unique functions and features. These will be explained, chapter by chapter.

Consciousness. As I mentioned, the deepest roots of consciousness (e.g., the first onset of awareness as the brain moves from the null states of coma, deep anesthesia, or deep sleep) lie far posterior in the hindbrain, not just in the cerebral cortex where most people think they lie. In the hindbrain reticular formation, certain large neurons essential for initiating brain arousal and consciousness are found just above the spinal cord. These large neurons had their evolutionary origins in the fish brain and have their developmental origins on the surfaces of the embryonic brain.

Of course, as a neuroscientist I take a reductionist approach to the term "conscious," and address the *physical* elements of consciousness precedent to the fullest intellectual interpretations of the subject. For example, this book does not deal with states of deep contemplation, nor does it deal with philosophical speculations on the relationship between self and world.

Instead, I emphasize that neuroscientists are studying the most fundamental, elemental, primitive entries into consciousness. The writing here presents the physical realization of mechanisms which lay out in neurobiological and molecular detail how arousal pathways work, how they "wake up the brain" as from deep anesthesia, coma, or sleep.

Modules. The chapter order is linear, moving from hindbrain to forebrain and then from animal brain to human brain. Each chapter will take up an element of that idea, always building on the preceding chapter to produce a unified approach to our new understanding of brain arousal mechanisms necessary for consciousness.

Chapters

1. **Concept.** Some years ago, in *Brain Arousal and Information Theory*, *I* proposed the concept of Generalized CNS (central nervous system) Arousal (GA). The book presented an operational definition of GA and listed GA's operating requirements. Physicist Jayanth Banaver and I theorized that the passage from low GA to high GA had characteristics of a physical phase transition. Quantitative assays for measuring GA are available for experimental animals and patients. Many years of new data on arousal mechanisms have led us to focus on large reticular formation nerve cells,

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"Nucleus Giganto Cellularis" (NGC) as the most powerful and essential neurons for initiating GA.

2. **NGC.** Experimentally elevating activity in these large reticular formation neurons activates the electrical activity of the cerebral cortex and initiates movements, even in deeply anesthetized animals. My lab have just discovered the entire transcriptome of one subclass of these neurons, among the "master cells" of CNS arousal, neurons whose axons project to the central thalamus (see Chapter 6). NGC neurons express genes for receptors of neurotransmitters and neuropeptides known to modulate GA.

   Since these neurons represent the origins of arousal, the physical location where arousal originates, I can, in this chapter, put forward the "origins of the origins of arousal" (i) in evolutionary terms, and (ii) during early brain development; and (iii) first awakenings just after birth.

   The next four chapters move up the neuraxis toward the forebrain, and will describe the physiology and genetic studies available at each of the four levels.
3. **Pons.** Just in front of NGC neurons are large neurons in the pons that regulate sleep. Their chemistry has been elucidated and their electrophysiology well described. Working on two nearby cell groups, Karolinska Institutet professor Ole Kiehn has discovered how chemically defined neurons at the anterior border of the pons regulate the initiation of locomotor behaviors.
4. **Midbrain.** Harvard professor Clifford Saper has laid out the neuroanatomy and physiology of opposing nerve cell groups in the pons and midbrain, one of which elevates arousal while the other decreases arousal.

   Pathways ascending from the midbrain will split into a "low road" and a "high road." The low road addresses the large cholinergic neurons of the basal forebrain. Those are the neurons that are helped by Alzheimers-delaying medications. The high road addresses the central thalamus, where electrical stimulation has caused a patient with a disorder of consciousness to regain consciousness.
5. **Hypothalamus.** Hypothalamic neurons receive signals from the low road. They include neuroendocrine neurons that regulate hormones associated with GA. Importantly, they also include the huge cholinergic neurons of the basal forebrain.

   A unique group of GA neurons express the gene for hypocretin/orexin (same gene, cloned and named by two labs). The gene product fosters higher GA especially when connected with hunger. Mutations in this gene or either of its two receptors leads to narcolepsy, a sudden and temporary loss of posture and consciousness.
6. **Central Thalamus.** These neurons receive signals from the high road. They participate with essential roles in a specific forebrain circuit named a "mesocircuit" by neurology professor Nicholas Schiff. High levels of activity in this circuit are required for purposeful movement. Electrical stimulation of central thalamic neurons by Schiff caused a high-end vegetative patient to regain consciousness.
7. **High arousal states.** This chapter will summarize succinctly what is known about mechanisms for sex behaviors, fear, and aggression and show how they are linked to and depend on GA.
8. **Low arousal states.** The chapter explores the medical analyses of coma, deep anesthesia, and deep sleep. Emergence from these "zero states" requires elevation of GA.

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9. **Aroused, conscious.** Neurophysiological and molecular biological supports for GA obviously feed into mechanisms underlying consciousness in the human brain. But how much farther can we go from a neuroscientific understanding of GA toward the elements of consciousness? As a skeptical scientist, I will argue that some philosophical approaches to the so-called "mind–brain problem" smack of the paradoxes of self-reference illustrated by Bertrand Russell (e.g., "This sentence is wrong").
10. **A vertically integrated system.** Obviously, some of the outstanding properties of GA systems are linked to each other. The length of axons in an A/P,L system with synaptic connections at several levels allows a high degree of connectivity and, because of these large neurons, raises the possibility of a scale-free system. The large NGC neurons – with widespread dendrites, lengthy projections, multimodal sensitivity, and high firing rates – exemplify neurons with incredibly large channel capacity, sending an integrated signal up and down the neuraxis.

    Visions for where work on GA in animal brains will go tend to concentrate on how new genetic and epigenetic knowledge will be integrated with the neural circuitry understanding which we already have. Regarding neurologists' work with human consciousness, I will concentrate on high-end vegetative states because patients in those states require the most attention and represent the greatest opportunities.

    There emerges the picture of a bilaterally symmetric A/P,L integrated long-axon scale-free system in which its high degree of connectivity enforces its physiological power.

For the first time, neuroscientists are closing in on a comprehensive understanding of brain arousal pathways and mechanisms that are essential for consciousness. Hopefully these neuroscientific efforts will augment the progress already made on the crushingly severe problems of disorders of consciousness by pioneering neurologists (Laureys and Schiff, 2012; Laureys, 2016a,b; Bodart et al., 2017; Chennu et al., 2017). This book considers the physical manifestation of how traditional neuroanatomical results with regard to this topic are now complemented by neurophysiological and molecular genetic work. From those large reticular neurons mentioned above, a "low road" ascends deeper in the brain, through the hypothalamus and a "high road" through the thalamus ascends to the forebrain to support brain arousal. All of these basic neuroscience results support a new understanding of the deepest elements of human consciousness.

Here, then, the idea is to take a hard problem, consciousness, and in the interest of precisely determining brain mechanisms, to restate and reduce part of that problem to a smaller piece, that is, to ask "how do animals and human beings initiate behavior?" What are the physical paths toward consciousness? The general principles that I propose in response to that question will likely hold true universally for all vertebrates.

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Chapter 1

Concept

Why does a human or any vertebrate animal do anything at all? In the central nervous system (CNS), what accounts for the initiation of behavior – any behavior, from the simplest to the most complex? And how universal an answer to these questions can we achieve?

Of course, some behavioral responses are reflexes triggered automatically by compelling stimuli – for example, in response to touching fire a person will quickly withdraw his hand. This book does not concern reflexes, or similar automatic actions that are not indicia of emerging consciousness.

Among non-reflexive behavior patterns, virtually all are motivated, directly or indirectly, by some state of body or mind. In many cases, these are obvious: hunger, thirst, fear, sex, anger. Equally obvious are states of mind such as motivations to achieve, compete, look good, or help others. If we think of these as "forces," neuronal modulations that increase the probabilities of certain kinds of behavioral patterns, then it is easy to understand that entire fields of neuroscience are devoted to how these motivational systems work – specific forces, specific behaviors.

But now we get to the issue that drives this book. Does there exist, at a level deeper than these specific motivational forces and prior to them in the causal chains for behavior, a powerful nonspecific influence? Yes. It is a concept, an influence that I have named "generalized CNS arousal" (GA) (Pfaff, 2006). Theoretically, GA would be very important to understand and regulate because it would contribute to the excitation of a wide range of behaviors. Correspondingly, its dysregulation would cause tremendous cognitive and emotional dysfunction.

Suppose, as argued below, GA does indeed exist. In this context, and inspired by the considerations outlined above, I want to reframe our thinking, and conceive a vertically integrated, ladder-like anterior/posterior longitudinal (A/P, L) network that produces GA. The integration likely comes about from a scale-free network – many neurons with small numbers of connections, as well as a few neurons, including those highlighted in these chapters, with very large numbers of connections.

I am thinking about GA differently from what has for a long time been the conventional approach to arousal, i.e., its *situs* is in the cortex. However, while GA is exciting to contemplate, it was also initially scary to conjecture, since up until not too long ago my scientific efforts were devoted to understanding very specific, simple behaviors such as sex and maternal behaviors (Pfaff, 2017). The most encouraging thing that happened along the way to my initial conjecture was that I could cross the street to learn about consciousness from a world authority on the disorders of consciousness, Professor Fred

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Plum, Chief of Neurology at Cornell Medical School. This book is dedicated to Dr. Plum. But even so, understanding of arousal systems at that time was still couched in pure neurology and pure neurophysiology. That is, neurologists would consider the effects of certain kinds of damage – strokes, cardiac events, traumatic brain injuries – on the cognitive capacities of patients. Neurophysiologists knew that certain kinds of electrical stimuli in the brainstem could cause the appearance of higher frequencies of electrical wave activity recorded at the cerebral cortex and that major brainstem damage would have the opposite effect (Dempsey and Morison, 1942a, b; Lindsley et al., 1949; Moruzzi and Magoun, 1949; Magoun book, 1958). But I wanted to think differently about brain arousal mechanisms.

In order to "think differently," one can ask whether it is possible to construct a set of ideas about CNS arousal that would have a degree of precision and generality – even universality – that is more typical of physical than biological science. That is, physicists have been able to refer to physical principles that hold true under wide varieties of circumstances, and they could say to biologists "you guys don't have principles, but only Latin names and long lists of phenomena to memorize." In this vein, this book offers a precise and universal *operating definition* of CNS arousal, discussed as follows:

Operational definition: A more aroused animal or human, with higher GA, is more alert to sensory stimuli in many sensory modalities (S), more active motorically (M), and more reactive emotionally (E).

What about *operating requirements*? To start, at least four requirements can be justified on a theoretical basis: (i) GA mechanisms must work fast enough to allow the individual to escape danger, (ii) there must be great convergence of inputs onto GA mechanisms so that a wide variety of incoming signals can trigger adequate behavioral responses, (iii) there must be great divergence of signals emanating from GA mechanisms so that a wide variety of behavioral responses can be initiated, and (iv) GA mechanisms must be robust enough so that they will not fail (Pfaff et al., 2012).

As conceived, GA mechanisms work in all vertebrate brains including, of course, the human brain.

Within this definition and set of operating requirements, GA is fundamental to all cognitive functions. For example, you can be aroused without being alert, but not alert without being aroused. You can be alert without paying attention, but not the reverse. This holds true on up the chain of more complex cognitive states, all dependent on GA.

Likewise, GA is essential for all emotional expression. Whether a person is exhibiting a certain range of emotions momentarily (feelings), over hours (moods), or over a lifetime (temperament), the nature of the emotion depends on the situation, but the *strength* of expression depends on GA. If you think of emotional expression as a vector, the angle of the vector depends on the exact feeling but the length of the vector is determined, in part, by the level of GA.

Of course, since GA is so basic to cognitive and emotional functions, when something goes wrong with its mechanisms the organism can be thrown into chaos. Some of the maladies that can result are discussed below.

Other properties of CNS arousal systems have become evident over decades of research (Pfaff, 2006). Five of them are discussed in the following:

Bilaterality. In contrast to sensory and motor systems, for which directionalities of stimuli and responses are, essentially, the "name of the game," there is no need for

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sidedness in CNS arousal. In fact, it would be hard to imagine a life in which one half of a brain is more capable of arousal than the other.

Unilateral damage to the brain is unlikely to cause coma. Unilateral damage can cause asymmetry in the electrical activity of the cerebral cortex, as displayed in the electroencephalogram (EEG), but it does not cause coma (Kushida ref 660 in 2006).

In the words of Steven Laureys (2016a, b), absence of arousal and awareness results from "diffuse bihemispheric cortical damage or from focal but extensive brain stem lesions" (3346). See also the work of Bartolomeo and Chokron (2002), a neurologist at INSERM Unit 324 in Paris, dealing with patients who are conscious but who have received unilateral damage to their posterior cerebral cortex. If the damage was on the right side of the cerebral cortex, they would tend to ignore objects on their left, objects that would otherwise be seen. However, the situation is not entirely symmetric. If the damage was on the left side, attentional processes "seem to be relatively preserved, if slowed, in left unilateral neglect." The reason for the difference is not known. In any case, the idea of a bilateral arousal system is clearly accurate.

There are many unanswered questions about how the two sides of an arousal system work together. The next chapter focuses on what can be called the "master cells" for arousal deep in the hindbrain reticular formation. What will happen if we do new experiments in which only the left or only the right side of these cell populations are selectively stimulated or inhibited by specially designed viral vectors? Will behavioral responses be one-sided, or will they be bilaterally symmetrical? New studies of gait control by Veronique VanderHorst at Harvard Medical School, presented at the annual meeting of the Society for Neuroscience, suggest specific one-sided and nuanced contributions by medullary reticular neurons, but many neuroanatomical studies predict bilateral symmetry. By the way, up and down the long anterior/posterior longitudinal (A/P, L) systems emphasized in the book, many neurons project from the left side of the brainstem to the right, and *vice versa*. A first guess regarding their function is that they add stability to arousal systems. Particularly, if one side is damaged, signals from the other could compensate. But that is not known. These are open questions.

Anterior/posterior longitudinal (A/P, L) bidirectionality. Long A/P, L, ladder-like signaling forms the backbone of CNS arousal signaling. Its features are easiest to think about in that they comprise activation of neurons in more posterior ("lower") neuronal groups projecting ("ascending") to more anterior ("higher") neuronal groups. Consequently, signals will reach the hypothalamus, the thalamus, and the cerebral cortex. This is the textbook view of arousal systems neurophysiology (Kandel, 2000; Squire et al., 2008).

Arousal levels depend on the state of excitation of this long A/P, L network. Just think of one example: the long and widely distributed axons ascending from a noradrenergic cell group, locus coeruleus, in the pons, comprises cells that release noradrenalin (also known as norepinephrine) in the forebrain (e.g., Aston-Jones et al., 2001).

The reverse scenario is equally interesting. Clif Saper, now professor of neurology at Harvard Medical School, demonstrated axonal projections from the anterior hypothalamus all the way to the spinal cord (Saper et al., 1976). In my lab, graduate student Lily Conrad used radioactively labeled amino acids microinjected into the hypothalamus or into neuronal groups just in front of the hypothalamus to make radioactive proteins that could be followed as they traveled down axons descending to the lower brainstem (Conrad and Pfaff, 1975; Conrad et al., 1976a, b). Most startling, scientists in Arthur Loewy's lab at Washington University in Saint Louis used special viruses that are transported across

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synapses to demonstrate connections from preoptic neurons in the basal forebrain all the way to sympathetic autonomic ganglia in the abdomen.

The great Spanish neuroanatomist Valverde (1961) used the silver stain, discovered by Camillo Golgi, and exploited brilliantly by Ramon and Cajal, to study the morphology and explore the logic of long A/P, L systems of the brainstem (see Figure 2.2). While his (and my) most intense focus is on the human brain, his basic conclusions would hold true for all mammals. Valverde charted both long axonal systems that run up and down the A/P, L axis of the brainstem and short connections, i.e., short collaterals at right angles to the long axons. He pictures the operation of a "multiple chain system" (Valverde, 1961, 1962), by which he means that parallel A/P, L running axons start at different points in the neuraxis, end at different points, and probably overlap in their functions but are not identical. In this system, specificity of signaling would seem impossible.

Another leading group that used the Golgi stain concurs (Scheibel and Scheibel, 1961; Hobson and Scheibel, 1980; Jasper, 1958). They also emphasized long A/P, L connectivity in what they called "the reticular core" of the brainstem, coupled with extensive collateral protrusions perpendicular to the A/P, L axis where there would be contact with local dendrites. My neuroanatomy professor at MIT, Walle J. H. Nauta, taught us that the phylogenetically primitive reticular core extended from the intermediate nerve cell groups of the posterior spinal cord, through the upper spinal cord, through the lower brainstem, forward to the hypothalamus and central thalamus. Connections with local nerve cells would be intense because the very broad dendritic spreads are shaped in a so-called "isodendritic" tree (Ramon-Moliner and Nauta, 1966). In such a tree, the first dendritic segment sticking out from the nerve cell body would be shorter than the second, which is shorter in turn than the third segment (opposite to the so-called "allodendritic" tree, typical specific sensory relay pathways).

This situation can give rise to the network structure highlighted by physicist Albert-Laszlo Barabási (2002, 2009). In this type of network, large numbers of neurons have small numbers of connections, close by, whereas just a few neurons have large numbers of connections, in our case with arousal systems, distributed along the A/P, L axis of the brainstem. Chapter 2 discusses these latter neurons, with large numbers of A/P, L connections.

Still another property of the primitive reticular core has just been discovered by Inna Tabansky in my lab at Rockefeller (Tabansky et al., 2018). As discussed in Chapter 2, she listed the genes expressed by certain large reticular neurons in the posterior hindbrain, i.e., the medulla just above the spinal cord, and found a gene with a product that can operate on blood vessels. Further, these same neurons are right next to blood vessels with no intervening cells. A small amount of preliminary evidence also suggests that some of these medullary reticular neurons can sense chemicals in the blood; thus, they may be called "chemosensors." Exactly what this discovery means for the regulation of CNS arousal remains to be worked out.

Response potentiation. Most of the time, higher generalized arousal prepares the animals or human beings to initiate a behavioral response to stimuli of all sensory modalities, initiate voluntary locomotion, and react with feeling to emotional challenges. The trickiest interpretation of this idea is when a vertebrate is responding to a stimulus that indicates danger and "freezes." Under such circumstances, when for example a person is walking along, relaxed, and then freezes because of a danger ahead, the ostensible nonreaction would be considered an active behavioral response.

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Sensitivity combined with stability. It is clear that changes in CNS arousal systems must, under some circumstances, cause the brain and body to rapidly achieve change of states. Yet they must also function within defined limits, and have the capacity to return to baseline. These two properties would seem to oppose each other, and we do not know yet how the balance between them is achieved. What are the critical arousal network features that shape the performance of the CNS through time? To address this question, we (Bubnys et al., in press) are trying to simulate such systems to ask the "what-if" questions imaginatively and rapidly.

Some aspects of arousal system stability may derive from opposing actions both at the electrophysiological level and at the transcriptional level. As to the former, in parts of the A/P, L extended CNS arousal system, excitatory glutamatergic neurons are surrounded by inhibitory GABA neurons. In the latter, not all transcriptional systems pull in the same direction. For example, while gene expression associated with adrenergic and dopaminergic actions would clearly heighten arousal, expression of the gene for prostaglandin-D synthase (promoting sleep) or opioid receptors would have the opposite effect. All control systems – biologic, electronic, or digital – face similar requirements for balance among activating and suppressive subsystems, within the limitations of the overall system.

Wide ranges of temporal and spatial properties. Different neurons within arousal systems have different time constants with respect to the regulation of their electrical activity. Consider the fastest mechanisms for spreading electrical excitation – gap junctions, also called "electrical synapses." Some neurons in the hindbrain reticular formation express the gene that codes for Connexin-36, the protein through which electrically charged molecules can travel rapidly from one nerve cell to an adjacent nerve cell (Martin et al., 2011). Then, of course, there are regular, chemical synapses, operating on time scales of milliseconds. But some hindbrain reticular neurons likely respond to very slow-changing signals, since we have preliminary evidence that a few of such neurons lie outside the blood–brain barrier and, indeed, as mentioned above and detailed in Chapter 2, Inna Tabansky et al. (2018) has discovered large medullary reticular ("Nucleus GigantoCellularis," NGC) neurons with molecular and morphologic properties that support intimate relations with blood vessels, potential "chemosensors." Chemical signals from the blood certainly will fluctuate with much slower time courses than electrical signals among neurons.

How this wide range of temporal properties is used in the CNS in an adaptive fashion is not clear. Do arousal-related neuronal changes have to occur in certain order? I think of the NGC neurons in the medullary reticular formation as "first responders," but that supposition simply is inferred from what we know about them (Chapter 2). Is there a hierarchy amongst different components of arousal responses? If so, to what extent do different aspects of brain arousal have to be synchronized? Or are there ideal delays amongst subsystems? With respect to the human brain, are subsystem parameters optimized in the normal case, or is there room for improvement? Are alterations in timing a potential cause of the types of maladies listed below? All of these questions need answers.

This uncertainty also prevails for the range of spatial properties of arousal-related neurons. Again, are they optimized in the normal human brain, or could they be improved? Chapters 2 through 6 present the idea of modularity within the overall A/P, L system that governs arousal, with different modules theoretically contributing different properties and characteristics to the overall system. Classically, non-neuroscientists theorizing the nervous system began with random systems, but that approach almost certainly is wrong. Instead, considering the medullary reticular formation, for example, we have very large

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