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.

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.

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,

"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.

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.