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Consciousness and the brainstem

Josef Parvizi[1], Antonio Damasio*

Department of Neurology, Division of Behavioral Neurology and Cognitive Neuroscience, University of Iowa College of Medicine, 200 Hawkins Drive, Iowa city, Iowa 52242, USA

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Abstract

In the first part of this article we summarize a theoretical framework and a set of hypotheses aimed at accounting for consciousness in neurobiological terms. The basic form of consciousness, core consciousness is placed in the context of life regulation; it is seen as yet another level of biological processing aimed at ensuring the homeostatic balance of a living organism; and the representation of the current organism state within somato-sensing structures is seen as critical to its development. Core consciousness is conceived as the imaged relationship of the interaction between an object and the changed organism state it causes. In the second part of the article we discuss the functional neuroanatomy of nuclei in the brainstem reticular formation because they constitute the basic set of somato-sensing structures necessary for core consciousness and its core self to emerge. The close relationship between the mechanisms underlying cortical activation and the bioregulatory mechanisms outlined here is entirely compatible with the classical idea that the reticular formation modulates the electrophysiological activity of the cerebral cortex. However, in the perspective presented here, that modulation is placed in the setting of the organism's homeostatic regulation.

Keywords: Consciousness; Brainstem; Reticular formation; Cerebral cortex

1. Introduction

The terms consciousness and brainstem have long been associated on the basis of two lines of evidence. The first is the fact that damage to the upper brainstem is a known cause of coma and persistent vegetative state, the disease states in which

* Corresponding author. Fax: +1-319-353-6277.
E-mail address: josef-parvizi@uiowa.edu (J. Parvizi).
[1] Co-corresponding author.

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consciousness is most severely impaired. The second line of evidence originates from classical experiments which suggested, either through lesions or electrical stimulation, that a part of the brainstem, known as the reticular formation, is associated with the electrophysiological pattern commonly found in wakeful and attentive states. Such evidence supported a general account of the relationship between brainstem and consciousness that can be summarized as follows: (a) the brainstem contains the reticular formation which is the origin of the ascending reticular activating system; (b) the engagement of the ascending reticular activating system activates the cerebral cortex; (c) the process of activating the cortex underlies wakefulness and attention; and (d) wakefulness and attention are indispensable constituents of consciousness, or, as some might say, constitute consciousness.

While there is little doubt that cortical activation due to brainstem engagement is an indispensable part of the conscious state, we believe that the above account is incomplete for a number of reasons. For example, the account dates from a time in which the phenomena of consciousness were conceptualized in exclusively behavioral, third-person terms. Little consideration was given to the cognitive, first-person description of the experience of the subject who is conscious. Moreover, the neuroanatomical view of the brainstem that informs this traditional account does not include recent advances in the description of different nuclei within the reticular formation and of their distinct connections to other brain regions, nor does it include the consequent revision of the concept of reticular formation. No less importantly, the account does not address the functional context in which the brainstem plays its presumed activation role. For example, what drives the brainstem to activate the cerebral cortex in the manner in which it does? Why is the activation system based on brainstem structures as opposed to other structures?

Recently, we have proposed that the role of the brainstem in consciousness can be seen in a new perspective, that of life regulation, and that the new perspective may help explain why and how brainstem nuclei exert their varied influences on structures located rostrally, namely on the cerebral cortex (Damasio, 1998, 1999).

1.1. A brief summary of the new proposal

Some nuclei of the brainstem have long been linked to the regulation of life, along with nuclei in the nearby hypothalamus, but a link between nuclei that regulate life and the process of consciousness has not been proposed before. Likewise, the brainstem nuclei that have long been linked to consciousness, namely those of the reticular formation, have not been linked to the regulation of life. In terms of theoretical background, the critical feature of the proposal is the 3-way connection it proposes for consciousness, for the nuclei involved in homeostasis, and for the nuclei in the reticular formation.

The proposal specifies two closely related but separable problems in the investigation of consciousness. The first is the problem of understanding how the brain engenders the mental patterns we experience as the images of an object. By “object” we mean entities as diverse as a person, a place, a melody, or an emotional state; by “image” we mean a mental pattern in any of the sensory modalities, e.g. a sound

image, a tactile image, the image of an aspect of an emotional state as conveyed by visceral senses. Such images convey the physical characteristics of the object as well as the reaction of like or dislike one may have for an object and the plans one may formulate for it, or convey the web of relationships of the object among other objects. This first problem of consciousness is the problem of how we form a temporally and spatially unified "movie-in-the-brain", a metaphorical movie, of course, with as many sensory tracks as the brain's sensory systems. Solving this first problem in neuroscientific terms consists of discovering how the brain makes neural patterns in its neural circuits and turns those neural patterns into the explicit mental patterns of the whole range of possible sensory images, which stand for any object, any relationship, concrete or abstract, any word or any sign.

The second problem of consciousness concerns how, in parallel with creating mental patterns for an object, the brain also creates a sense of self in the act of knowing. The solution for this second problem requires the understanding of how each of us has a sense of "me"; of how we sense that the images in our minds are shaped in our particular perspective and belong to our individual organism. Solving the second problem of consciousness consists of discovering the biological underpinnings for the construction of the mental patterns which automatically convey the sense of a self. Importantly, the solution traditionally proposed for the problem, that of an homunculus creature who is in charge of knowing, is not acceptable. There is no homunculus.

The problem of how the movie in the brain is generated and the problem of how the brain also generates the sense that there is an owner and observer for that movie are so interrelated that the latter problem is nested within the former. The second problem is that of generating the *appearance* of an owner and observer for the movie, that materializes *within the movie*.

The new proposal specifies that we first become conscious when, in addition to being awake and capable of making sensory images of an object, our organisms internally construct and internally exhibit a specific kind of wordless knowledge – the knowledge that the organism has been changed by an object – and when such knowledge occurs along with the salient enhancement of the object image caused by attention being allocated to it.

The central question arising from this formulation is how this new knowledge begins to be gathered. The following hypothesis captures the solutions we propose to answer it*: core consciousness (the simplest form of consciousness) occurs when the brain*'s *representation devices generate an imaged, nonverbal account of how the organism*'s *own state is affected by the organism*'s *interaction with an object, and when this process leads to the enhancement of the image of the causative object, thus placing the object saliently in a spatial and temporal context. The protagonist of core consciousness is the core self, the simplest form of self.*

The hypothesis outlines two component mechanisms: the generation of an imaged nonverbal account of an object-organism relationship, and the enhancement of the images of an object. The hypothesis is grounded on the following premises:

1. That the organism, as a unit, is mapped in the organism's brain, within structures that regulate the organism's life and signal its internal states continuously; that

the object is also mapped within the brain, in the sensory and motor structures activated by the interaction of the organism with the object; that both organism and object are mapped as neural patterns, in first-order maps; and that all of these neural patterns can become mental images.
2. That the neural activity inherent in sensorimotor maps pertaining to the object cause changes in the neural activity of the maps pertaining to the organism.
3. That the activities described in (2) can in turn be conveyed to second-order maps which thus represent the overall relationship of object and organism.
4. That the neural patterns transiently formed in second-order maps can become mental images, just as is the case with the neural patterns in first-order maps, thus producing an image of the relationship between organism and object.

1.2. The proto-self

The organism referred to in the hypothesis is represented in the brain by a coherent collection of neural patterns which map, moment by moment, the state of the organism in its many dimensions. This ceaselessly maintained first-order collection of neural patterns is described in the proposal as the "proto-self". The proto-self occurs not in one brain region but in many, at a multiplicity of levels, from the brainstem and hypothalamus to the cerebral cortex, in structures that are interconnected by neural pathways. These structures are intimately involved in the processes of regulating and representing the state of the organism, two closely tied operations. In short, the *proto-self* is *a coherent collection of neural patterns which map, moment by moment, the state of the physical structure of the organism in its many dimensions*.

It should be noted at the outset that the proto-self is not the sense of self in the traditional sense, the sort of self on which our current knowing is centered, that is, the core self (the protagonist of core consciousness), and the autobiographical self (the extended form of self which includes one's identity and is anchored both in our past and anticipated future). The proto-self is the pre-conscious biological precedent of both core and autobiographical self.

The proto-self should also not be confused with the homunculus of classical neurology. The proto-self does not occur in one place only, and it emerges dynamically and continuously from interacting signals originating at multiple levels of the nervous system. The proto-self is not an interpreter; it is a reference.

The structures required to implement the proto-self are as follows:

1. Several brainstem nuclei which regulate body states and map body signals.
2. The hypothalamus and the basal forebrain.
3. The insular cortex, cortices known as S2, and the medial parietal cortices located behind the splenium of the corpus callosum, all of which are part of the somatosensory cortices.

The structures which are not required to implement the proto-self are as follows:

1. Several early sensory cortices, namely those of areas 17, 18, 19, which are

dedicated to vision; 41/42, 22, dedicated to hearing; area 37, which is partly dedicated to vision but is also a higher-order cortex, and the part of S1 concerned with fine touch. These cortices are involved in the making of modality-specific sensory patterns that support the mental images of diverse sensory modalities available in our mind. They play a role in consciousness inasmuch as the images of the object-to-be-known are assembled from these regions, but they play no role in the proto-self.

2. All the inferotemporal cortices, namely areas 20, 21, part of 36, 37, 38. These cortices support many of the autobiographical records on the basis of which the autobiographical self and extended consciousness can be realized, but they play no role in the proto-self.
3. The hippocampus.
4. The hippocampal-related cortices, namely areas 28 and 35.
5. The prefrontal cortices. Some of these cortices participate in high-level working-memory for spatial, temporal, and language functions. Because of their role in working memory, prefrontal cortices are critical for high levels of extended consciousness, but they play no role in proto-self.
6. The cerebellum.

1.3. The basic mechanisms of core consciousness

As the brain forms images of an object and of the organism, and as the images of the object *affect* the state of the organism, yet another level of brain structure creates a nonverbal account of the events that are taking place in the varied brain regions activated as a consequence of the object-organism interaction. The mapping of the organism and the object occurs in first-order neural maps representing proto-self and object, respectively. On the other hand, the account of the *causal relationship* between object and organism occurs in second-order neural maps. Examples of second-order structures are the cingulate cortices, the thalamus, and the superior colliculi. The subsequent image enhancement is achieved via modulation from basal forebrain/brainstem nuclei, as well as thalamocortical modulation.

The hypothesis thus pivots on the relationship between the changing organism state and the sensorimotor maps of a given object that causes those changes. As the images of the object *affect* the state of the organism, another level of brain structures creates a nonverbal account of the events that are taking place as a consequence of the object-organism interaction.

In conclusion, the proposal specifies that the essence of consciousness is a continuously generated image of the act of knowing relative to the mental images of the object to be known. The image of knowing is accompanied by an enhancement of the images of the object. And because the image of knowing originates in neural structures fundamentally associated with the representation of body states, the image of knowing is a feeling.

In its normal and optimal operation, core consciousness is the process of achieving an all encompassing imagetic pattern which brings together the pattern for the

object, the pattern for the organism, and the pattern for the relationship between the two. The emergence of each of those patterns and their conjoining in time depends on the contributions of individual brain sites working in close cooperation, and the understanding of the mechanisms of consciousness depends on identifying those individual contributions. But the study of such contributions must be considered in the perspective of an important qualification regarding the relation between brain regions and functions: the functions hypothesized here are *not* located in one brain region or set of regions, but are, rather, a product of the interaction of neural and chemical signals among a set of regions.

Beyond the mechanisms responsible for core consciousness, there are mechanisms responsible for extended consciousness, the protagonist of which is the autobiographical self. Extended consciousness builds on core consciousness, requires memory, and is enhanced by language. The discussion of these mechanisms is outside the scope of this article (but see Damasio, 1999).

The role of brainstem structures in the generation of consciousness is thus a critical one. This article is dedicated to a review of some of the relevant evidence regarding the functional neuroanatomy of the brainstem, an understanding of which is indispensable to the above account of consciousness.

2. The brainstem and the reticular formation

The brainstem gray matter is organized in *nuclei*. A brainstem nucleus is a three-dimensional collection of neurons which is usually aligned in parallel to the long axis of the brainstem. Each nucleus has an idiosyncratic cytoarchitecture and tends to have a prevailing neurochemical identity that helps distinguish it from other nuclei; each nucleus has a unique location within the brainstem: each nucleus has connections with a distinct set of other neural structures; and each nucleus tends to have a prevailing function. Cranial nerve nuclei can be identified on the basis of the criteria and are prime examples of brainstem nuclei. For example, each cranial nerve nucleus can be distinguished from other brainstem nuclei based on the fact that it either receives primary afferents from, or sends out primary efferents to, a specific cranial nerve.

The fact that the brainstem has a nuclear organization was established more than a century ago (e.g. Kölliker, 1854; Ramón y Cajal, 1894; Jacobsohn, 1909). However, due to the lack of techniques such as immunohistochemical markers, tracing agents, and novel neurophysiological probes, many brainstem nuclei were defined on the basis of cytoarchitectural features, anatomical connections revealed only by the method of terminal degeneration, or mere appearance. For example, the substantia nigra was so labeled because of the pigmented appearance of its cells, and the periaqueductal gray matter was so named because it occupies the region surrounding the cerebral aqueduct. Similarly, the core region of the brainstem was labeled as the reticular formation because neurons in that region were surrounded by interlacing fibers, which gave the region the appearance of a "reticulum" that is a web. This region occupies most of the central and dorsal part of the brainstem extending from

the lower medulla to the level of the upper midbrain (Fig. 1A) (Olszewski & Baxter, 1982; Paxinos & Huang, 1995). It is anatomically continuous with the core regions of the spinal cord and extends rostrally into the thalamus (e.g. Martin, 1996). In short, the term reticular formation was assigned to a region of the brainstem when the nuclear heterogeneity of this region was not yet appreciated because of the limited methods of the time.

The term reticular formation became entrenched in the neuroscientific vocabulary largely because of the classical studies which suggested its involvement in consciousness. As early as the 19th century, there had been evidence that lesions in the brainstem core impair consciousness (e.g. von Economo, 1917), and in a series of classical experiments in the late 1940s, electrical stimulation within the reticular formation in lightly anesthetized non-human mammals, was associated with a desynchronization of the electroencephalogram (EEG) that hallmarks awake and attentive states (Moruzzi & Magoun, 1949; Lindsley, Schreiner, Knowles, Magoun, & Magoun, 1950; French & Magoun, 1952; Magoun, 1952a; Magoun, French, & Von Amerongen, 1952b; French, Verzeano, & Magoun, 1953). It was known by then that the reticular formation projects to the intralaminar nuclei of the thalamus, which are the origin of the so-called diffuse thalamocortical projections, since they are not connected in topographical fashion with specific sensory or motor regions (Morison & Dempsey, 1942). As a consequence, it was proposed that the brainstem reticular formation is the origin of the ascending reticular activating system that

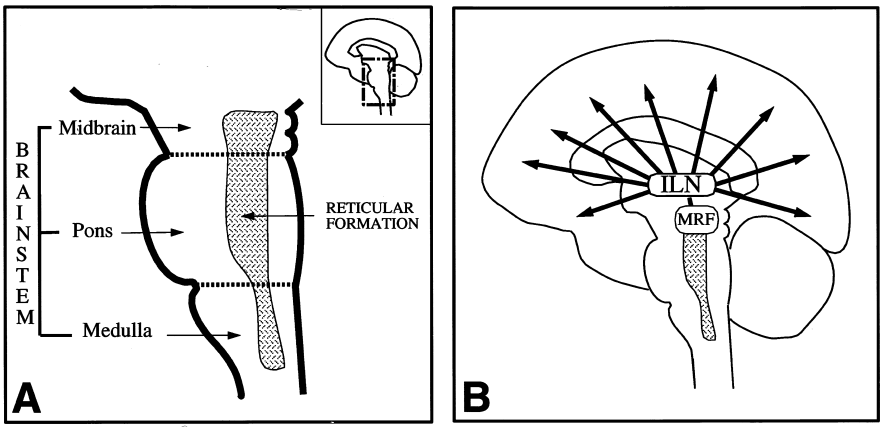

Fig. 1. The brainstem reticular formation and the conventional view of the ascending reticular activating system. (A) The brainstem is located between the spinal cord and the diencephalon. It encompasses the medulla oblongata, the pons, and the midbrain. Earlier histological studies indicated that the central and dorsal part of the brainstem extending from the lower medulla to the level of the upper midbrain had an appearance of a "reticulum". Therefore, this region was labeled as the reticular formation. (B) According to the conventional view, the mesencephalic reticular formation (MRF) is the origin of the ascending reticular activating system that operates through the intralaminar nuclei of the thalamus (ILN) and activates widespread regions of the cortex. As described in the text, this view is incomplete for several reasons.

would operate through the intralaminar nuclei of the thalamus and activate widespread regions of the cortex. Fig. 1B illustrates the conventional view of the brainstem reticular formation and the ascending reticular activating system. Subsequent neuropathological studies suggested that the brainstem areas whose lesions cause coma or persistent vegetative state in humans lie in the central and dorsal regions of the brainstem extending from about the level of the midpons to the level of the upper midbrain, a sizable part of the general region in which the reticular formation is located (Loeb & Stirling Meyer, 1965; Plum & Posner, 1980).

Since then, the conventional view of the reticular formation has been modified based on several lines of evidence. First, it is known that the reticular formation is not a homogeneous mesh of neurons but rather a collection of anatomically and functionally different nuclei (Fig. 2). Thus each component of the reticular formation may have a distinct role to play in modulating the electrophysiological activity of the cerebral cortex. It should be noted that as early as in the 1950s, Olszewski (1954) and Brodal (1959) suggested that the term reticular formation does not refer to a single anatomical unit and may be misleading. Blessing (1997a,b) has even suggested that the term should be avoided. Second, it is known that the heterogeneous collection of nuclei can modulate the activity of the cerebral cortex through routes other than the intralaminar nuclei of thalamus. Some nuclei can influence the entire cortex by making connections with basal forebrain nuclei, from which bilateral and widespread cortical projections originate. Other projections bypass both the thalamus and the basal forebrain and reach large expanses of both cerebral hemispheres directly, thereby inducing a modulatory effect. Moreover, some nuclei can modulate the electrophysiological activity of the cerebral cortex by changing the activity of the reticular nucleus of the thalamus. Jones (1998) has suggested that diffuse projecting thalamic neurons are not confined to the intralaminar nuclei and are present throughout the thalamus. Groenewegen and Berendse (1994) have suggested that each specific region of the intralaminar and midline nuclei of thalamus projects to specific parts of the cerebral cortex and striatum, and therefore, the term *diffuse* thalamic projections may be misleading. Third, with the advent of histochemical techniques, it has become known that different ascending channels from the reticular formation use different neurotransmitters, thus modulating the electrophysiological activity of the cerebral cortex through different mechanisms. Finally, new evidence suggests that the modulation of the cortex by the brainstem reticular formation is more complex than simply the desynchronization of its electrophysiological rhythm and leads, in effect, to local patterns of synchronization embedded in the global desynchronization (Munk, Roelfsema, König, Engel, & Singer, 1996; Herculano-Houzel, Munk, Neuenschwander, & Singer, 1999). Llinas (Llinas & Paré, 1991; Llinas, Ribary, Contreras, & Pedroarena, 1998) and colleagues have found that the non-specific projections from the thalamus are important for generating a thalamocortical resonance which they suggest is a necessary substrate for consciousness.

In short, although the precise contribution of each reticular nucleus and ascending pathway still remains unclear, it has become apparent that several nuclei and several pathways may be involved in modulating the electrophysiological activity of the

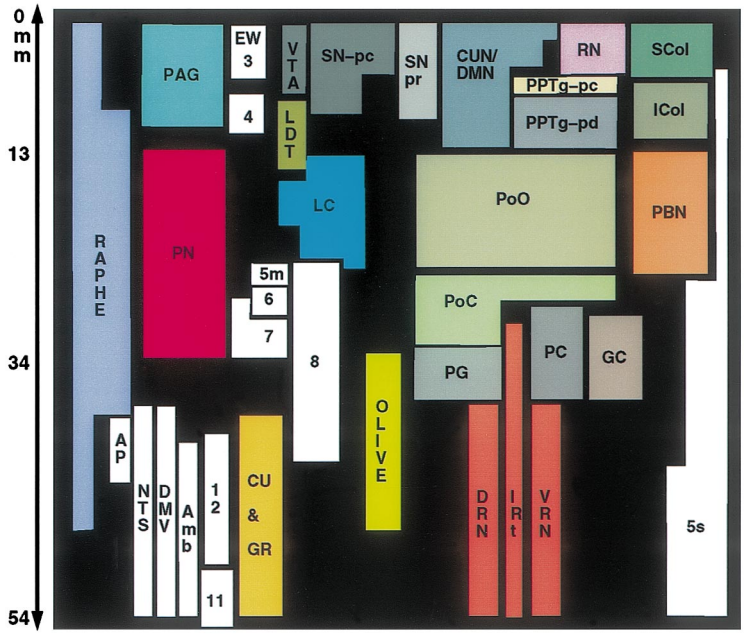

Fig. 2. The heterogeneous collection of brainstem nuclei. The brainstem gray matter, including the region traditionally known as the reticular formation, is organized in nuclei. There are two sets of nuclei, one on each side of the brainstem. Here only the collection of nuclei on one side of the brainstem is shown. A nucleus is a three dimensional collection of neurons which is usually aligned in parallel to the long axis of the brainstem. As this figure illustrates, each nucleus has its own idiosyncratic position within the brainstem. Some extend throughout the entire brainstem (such as the trigeminal nucleus, 5s) whereas some others (such as the area postrema, AP) occupy a small region and extend only a few millimeters or less. The size and the shape of the columns, as shown here, reflect the relative area of the brainstem occupied by the nucleus. Abbreviations: 3: oculomotor; 4: trochlear; 5m: trigeminal motor; 5s: trigeminal sensory; 6: abducens; 7: facial; 8:vestibulochoclear; 12:hypoglossus; Amb: ambiguus; AP: area postrema; CU and GR: cuneate and gracile; CUN/ DMN: cuneiforme and the deep mesencephalic; DMV: dorsal motor nucleus of vagus; DRN: dorsal medullary reticular complex including the region of the subnucleus reticularis dorsalis; EW: Edinger–Westphal; GC: gigantocellularis; ICol: inferior colliculus; IRt: Intermediate reticular zone; LC: locus coeruleus; LDT: laterodorsal tegmental nucleus; NTS: nucleus tractus solitarius; OLIVE: olivary complex; PAG: periaqueductal gray matter; PBN: parabrachial nucleus; PC: parvocellular; PG: paragigantocellular; PoC: pontis caudalis; PoO: pontis oralis; PPTg-pc: pedunculopontine tegmental nucleus pars compacta; PPTg-pd: pedunculopontine tegmental nucleus pars dissipatus; RN: red nucleus; SCol: superior colliculus; SNpc: substantia nigra pars compacta, SN-pr: substantia nigra pars reticulata; and VRN: ventral reticular complex.

cerebral cortex. In the paragraphs ahead, we provide an outline of the anatomical heterogeneity of the reticular formation and of the multiplicity of channels through which the reticular formation influences the activity of the cerebral cortex. We only discuss those components that are, to the best of our knowledge, anatomically capable of modulating the global activity of the cerebral cortex or functionally known to do so. As will be noted, the majority of these components lie in the upper brainstem, and only a few lower brainstem components are mentioned, on

the basis of evidence suggesting that they too may influence the activity of the cerebral cortex either directly or via the upper brainstem nuclei. Based on their histochemical features, functional properties, and anatomical connections, we group these components within four families of nuclei:

1. The *classical reticular nuclei* which include the nucleus cuneiforme, the deep mesencephalic nucleus, the non-cholinergic portion of the pedunculopontine tegmental nucleus, and the pontis oralis nucleus. These nuclei are located in the core of the brainstem in a relatively cell-poor but interlaced region, which first suggested the term reticular formation. They send presumably glutamatergic ascending projections to the basal ganglia and the intralaminar thalamic nuclei which in turn project to various cortical regions (Brodal, 1959; Jones & Leavitt, 1974; Edwards & de Olmos, 1976; Jackson & Crossman, 1983; Kaufman & Rosenquist, 1985; Steriade, Pare, Parent, & Smith, 1988; Lavoie & Parent, 1994; Groenewegen & Berendse, 1994; Newman & Ginsberg, 1994). The deep mesencephalic nucleus and, to a lesser extent, the nucleus pontis oralis project to the basal forebrain, from which widespread cholinergic projections arise aimed at the cerebral cortex (Jones & Yang, 1985).

The classical reticular nuclei mentioned above are located in the upper brainstem. However, some structures in the lower brainstem, well below midbrain and upper pons, may also have the anatomical means to modulate the cerebral cortex either directly or indirectly. Several anatomical tracing studies suggest that there are also neurons projecting to the intralaminar nuclei of the thalamus from classical reticular nuclei located in the lower pons and the medulla, such as the pontis caudalis, paragigantocellularis, parvocellularis, and subnucleus reticular dorsalis (Bernard, Villanueva, Carroué, & Le Bars, 1990b; Royce, Bromley, & Gracco, 1991; Newman & Ginsberg, 1994; Villanueva, Desbois, Le Bars, & Bernard (1998). Yet it should be noted that, as Royce (1991) and colleagues have found, the brainstem afferents to the intralaminar nuclei are most numerous in the upper brainstem and decline gradually at successively caudal levels through the pons and medulla. Finally, there is evidence suggesting that classical reticular nuclei in the lower brainstem can also modulate the activity of the upper brainstem nuclei and thus affect the cerebral cortex indirectly. One such nucleus is the nucleus paragigantocellularis which provides excitatory afferents to the noradrenergic locus coeruleus (Aston-Jones, Ennis, Pieribone, Nickell, & Shipley, 1986; Van Bockstaele & Aston-Jones, 1992, 1995).

2. The *monoaminergic nuclei* of the brainstem which encompass noradrenergic, serotonergic, and dopaminergic nuclei (Moore, 1980). There are direct noradrenergic and serotonergic projections from the locus coeruleus and the rostral raphe complex, respectively, to most of the cortical mantle (Moore & Bloom, 1979). The dopaminergic projections from the substantia nigra and the

ventral tegmental area project extensively to the putamen, caudate nucleus, nucleus accumbens, and the thalamus (van Domburg & Ten Donkelaar, 1991). There are also direct dopaminergic projections from the brainstem to many cortical areas with a predominance towards the prefrontal, the cingulate, and the insular cortex (Porrino & Goldman-Rakic, 1982). Moreover, there are projections from brainstem dopaminergic, noradrenergic, and probably serotonergic nuclei to the basal forebrain where, as noted, widespread cortical projections originate (Smiley, Subramanian, & Mesulam, 1999). The physiological involvement of the serotonergic and noradrenergic systems in modulating the global activity of cortex, and in supporting increased attentiveness and behavioral response to environmental stimuli, is well documented (Clark, Geffen, & Geffen, 1987; Jacobs, Wilkinson, & Fornal, 1990; Azmitia & Whitaker-Azmitia, 1991; Aston-Jones, Chiang, & Alexinsky, 1991; Berridge, Arnsten, & Foote, 1993; Geyer, 1996; Bloom, 1997; Cahill & McGaugh, 1998; Rico & Cavada, 1998). The role of dopaminergic nuclei in the same processes is less well understood although their central role in motor control and reward mechanisms underlying motivation is widely accepted (Dunnett & Robbins, 1992; Brown & Gershon, 1993; Schultz, Dayan, & Montague, 1997; Schultz, 1998). The above-mentioned monoaminergic nuclei are located within the upper reticular formation. Monoaminergic nuclei in the lower brainstem reticular formation such as the nuclei in the caudal raphe complex are known to have largely descending rather than ascending projections (Moore, 1980).

3. The *cholinergic nuclei* which include the laterodorsal tegmental nucleus and the cholinergic portion of the pedunculopontine tegmental nucleus (Mesulam, Geula, Bothwell, & Hersh, 1989). These cholinergic nuclei are also located in the upper brainstem. They project to several thalamic nuclei including the reticular nucleus of the thalamus (Pare, Smith, Parent, & Steriade, 1988; Steriade, McCormick, & Sejnowski, 1993), and to basal forebrain regions such as the substantia innominata (Muller, Lewandowski, & Singer, 1993). The reticular nucleus of the thalamus projects to other thalamic nuclei (Scheibel & Scheibel, 1966), and inhibits their activity (Steriade & Deschenes, 1984; Barth & MacDonald, 1996), thereby functioning as a pacemaker for the thalamic spindle oscillations which hallmark deep sleep (Steriade & Deschenes, 1984; Steriade, McCormick, & Sejnowski, 1993). The activity of the brainstem cholinergic system blocks the generation of these spindles and thereby initiates the wakeful state (Steriade, 1993).

4. The *autonomic nuclei* which include in the upper brainstem the parabrachial nucleus (PBN) and the periaqueductal gray matter (PAG). The PBN and the PAG are known for their involvement in the control of visceral functions, and there is evidence suggesting that they are also involved in modulating the global activity of the cerebral cortex. For instance, both PAG (Jones & Yang, 1985; Kaufman & Rosenquist, 1985; Pare et al., 1988) and the internal lateral

subregion of the PBN (Bester, Bourgeais, Villanueva, Besson, & Bernard, 1999), project to the intralaminar thalamic nuclei. Moreover, there are projections from the PBN (Fulwiler & Saper, 1984; Alden, Besson, & Bernard, 1994) and the PAG (Mantyh, 1983; Beitz, 1990; Parent & Steriade, 1981) to the basal forebrain and other brainstem nuclei such as the classical reticular nuclei involved in activating the cerebral cortex. Thus the PBN and the PAG have the anatomical means to modulate the activity of the cerebral cortex either through the thalamus or the basal forebrain, or through the classical reticular nuclei or monoaminergic and cholinergic nuclei. Interestingly, in a recent study by Munk (1996) and colleagues, the stimulation of the PBN was found to induce maximal changes in the electrophysiological activity of cortex.

In a series of studies by Moruzzi (Moruzzi, Magni, Rossi, & Zanchetti, 1959; Moruzzi, 1963) and others (Batini, Moruzzi, Palestini, Rossi, & Zanchetti, 1959) it was found that another component of the brainstem autonomic system, the nucleus tractus solitarius (NTS) in the medulla, can strongly modulate the global activity of the cerebral cortex. In these experiments, both synchronized and desynchronized states of the EEG were elicited depending on the frequency and the power of electrical stimulation in the NTS. Recently, the stimulation of the vagus nerve, which is the major source of afferents to the NTS, has been shown to be effective in the treatment of epilepsy by changing the pathologically synchronized electrophysiological activity of the cortex (Schachter & Saper, 1998).

Altogether, the above discussion indicates that first, the principal nuclei involved in modulating the electrophysiological activity of the cerebral cortex lie in the upper pons and in the midbrain, but this does not exclude the possible involvement of some lower brainstem structures. Second, it indicates that cortical activation is not likely to depend on one single brainstem nucleus or one single family of nuclei, but rather on a network formed by several families of nuclei (Fig. 3). Accordingly, several studies have confirmed that bilateral single lesions to some of the brainstem nuclei mentioned above are not sufficient to cause coma (Jones et al., 1973; Kitsikis & Steriade, 1981; Webster & Jones, 1988; Lai, Shalita, Hajnik, Wu, Kuo, Chia, & Siegel, 1999). Third, it also indicates that the notion of "mesencephalic" reticular formation as the sole platform for modulating the global activity of the cerebral cortex is incorrect because many of the relevant nuclei are located in the pons rather than in the midbrain (Fig. 2). Bremer's (1935) discovery that transecting the brainstem of cats at the pontomesencephalic junction, which he referred to as *cerveau isolé* preparation led to irreversible synchronization of the EEG is in keeping with this view. In a recent study, it was shown that a cell specific lesion in the core of the midbrain – that spared both ascending pathways originated below the midbrain and local connections within the midbrain – did not cause alterations in the EEG pattern (Denoyer, Sallanon, Kitahama, & Jouvet, 1991).

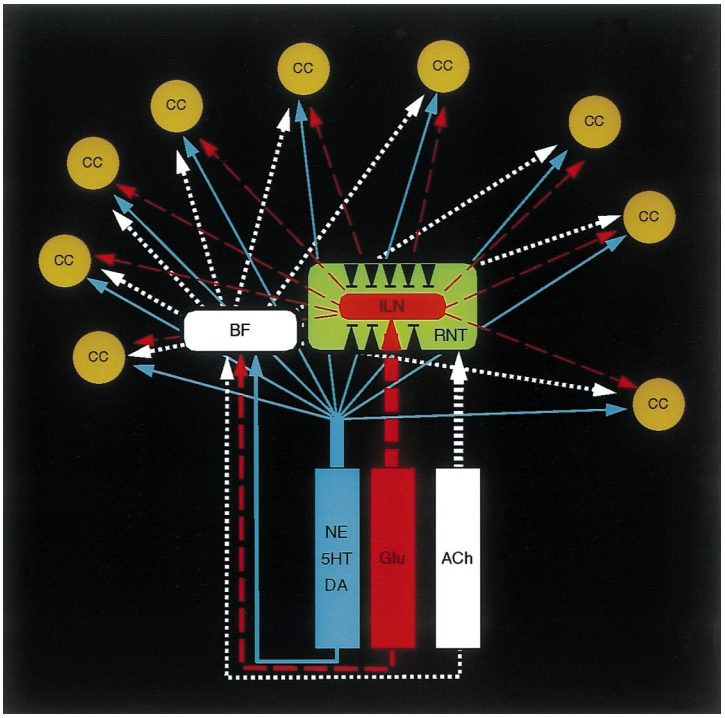

Fig. 3. The modern view of the ascending reticular activating system. There is evidence that the activation of the cerebral cortex (CC) by the brainstem is mediated through several channels, each of which originates from a different set of nuclei. Each set is distinguished on the basis of neurotransmitter of its component nuclei or the neural structures they target. Some nuclei send glutamatergic projections (Glu, dashed red lines) to the intralaminar nuclei of the thalamus (ILN) or to the basal forebrain (BF), from which widespread projections to the cerebral cortex originate. Other nuclei serve as the source of cholinergic (Ach, dotted white lines) projections to the BF or to the reticular nucleus of the thalamus (RNT). The RNT inhibits (black arrows) the activity of the other thalamic nuclei. There are also direct monoaminergic projections (solid blue lines) from noradrenergic (NE), serotonergic (5HT), and dopaminergic (DA) nuclei to the BF or to the cerebral cortex.

3. A functional context for the ascending reticular activating system

In the introduction to this article, we noted that it is important to understand the context in which the ascending reticular activating system operates, an issue which includes, among others, the consideration of why the system is located in the brainstem, and of which functional influences drive its operation. A possible answer to such questions can be gleaned in part from the pattern of afferent connections of the brainstem nuclei discussed above. These afferents are grouped based on the source of the signals they carry (Fig. 4).

1. One of the major sources of afferents originates from (a) the lamina I of the superficial dorsal horn of the spinal cord located continuously throughout

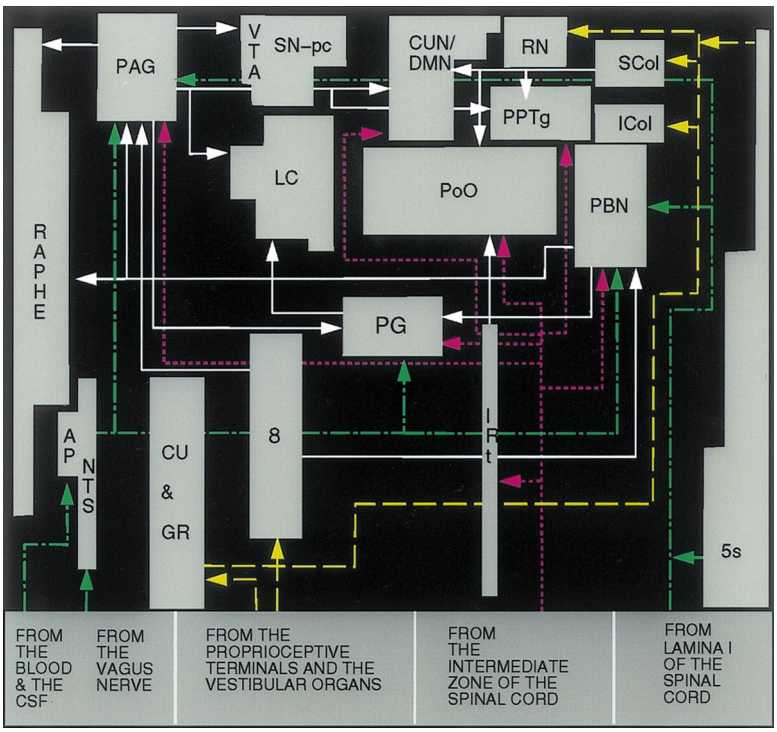

Fig. 4. The afferents to brainstem reticular nuclei. The brainstem reticular nuclei receive afferents from various sources. The state of the organism is portrayed in its multiple dimensions via incoming afferents each of which signals the current state of the internal milieu and the viscera – including the afferents to the vagal complex, and the introceptive afferents from the lamina I of the spinal cord (green dashed and dotted lines). There are also afferents from the vestibular organs and the musculoskeletal frame (yellow dashed lines); The deeper zones of the spinal cord convey signals about ongoing changes in the state of the organism as it interacts with an object (purple dotted lines). White solid lines represent the local connections within the brainstem nuclei. For abbreviations see Fig. 2.

the vertical extent of the cord, at the level of all its segments, and (b) the caudal spinal trigeminal subnucleus of the medulla, which is the rostral extension of the superficial dorsal horn. Both the superficial dorsal horn and the caudal spinal trigeminal subnucleus receive primary afferents through unmyelinated C-fibers and lightly myelinated Aδ fibers which convey signals related to pain and temperature. The phylogenetically old C- and Aδ fibers have free endings, unlike other sensory fibers which have specialized sensory receptors (Cervero & Iggo, 1980; Brown, 1982; Willis & Coggeshall, 1991: pp. 13–45).

Among the brainstem nuclei that receive the majority of these C- and Aδ fiber-related inputs are the PBN and the PAG (Wiberg & Blomqvist, 1984; Bernard & Besson, 1990a; Blomqvist & Berkley, 1992; Barnett et al., 1995; Craig,

1995; Willis and Westlund, 1997). In fact it is estimated that the lamina I projects three times more densely to the PAG than to the thalamus (Mouton & Holstege, 1998). The noradrenergic nuclei such as the locus coeruleus, and the classical reticular nuclei such as the nucleus cuneiforme are examples of other nuclei that receive this kind of spinal afferents (Wiberg & Blomqvist, 1984; Blomqvist & Berkley, 1992; Barnett et al., 1995; Craig, 1995; Willis and Westlund, 1997). Projections from the superficial dorsal horn of the spinal cord and the caudal spinal trigeminal subnucleus provide the anatomical means for relaying to the upper brainstem information about potentially harmful stimuli. In addition to their role in detecting noxious stimuli, recent evidence suggests that C-fibers are also involved in detecting changes in pH, pCO2, pO2, glucose concentration, osmolarity and in signaling the presence of inflammatory agents (Moskowitz, 1991; MacIver & Tanelian, 1992; Burnstock & Wood, 1996; see Craig, 1997, for more references). Thus these fibers carry signals related to the internal state of the organism. Contrary to the traditional view, not all C-fibers are silent in the absence of noxious stimuli (e.g. Schaible and Schmidt, 1983). Moreover, only a portion of cells in the superficial dorsal horn of the spinal cord are specific to noxious stimuli (Zhang, Han, & Craig, 1993; Han, Zhang, & Craig, 1998). Other studies have confirmed that there are both nociceptive and non-nociceptive C-fibers (e.g. Vallbo et al., 1993; or see Lawson, 1996, for more references). As Craig has suggested, the ascending pathways from lamina I and the caudal spinal trigeminal subnucleus should be considered *introceptive* rather than only nociceptive (Craig, 1996, 1997).

Interestingly, the PAG and the PBN are also major endpoints for projections from the NTS and the area postrema (Beckstead, Morse, & Norgren, 1980; Mantyh, 1982; Fulwiler & Saper, 1984; Herbert, Moga, & Saper, 1990; Ito & Seki, 1998). As mentioned, the NTS receives afferents through cranial nerves such as the vagus, which carry signals pertaining to the visceral state. While the NTS constructs a neural map of the viscera, the area postrema, which is one of the periventricular organs lacking a blood brain barrier and is located in the vicinity of the NTS, receives signals pertaining to the chemical profile of the organism (Ito & Seki, 1998).

2. The brainstem also receives major projections from the intermediate zone of the spinal cord. Many neurons in this part of the spinal cord, such as the so-called “wide dynamic range” neurons, receive convergent input from several sensory laminae and thus function as an integrative pool for several somatosensory submodalities (Willis & Coggeshall, 1991). Some neurons in the intermediate zone are also able to act as interneurons, coupling sensory and motor neurons. The intermediate zone is a major recipient of descending projections from the motor regions of the brainstem, cerebellum, and cerebral cortex. Thus the projections from the intermediate zone to the brainstem are well suited to signal the presence of interactions between an object and the

organism without signaling the sort of specific information about the object. Interestingly, the nuclei that receive most of the projections from the intermediate zone are many classical reticular nuclei such as the subnucleus reticularis dorsalis (Villanueva, Cliffer, Sorkin, Le, & Willis, 1990), the nucleus paragigantocellularis, the nuclei pontis caudalis and oralis (Willis & Westlund, 1997), which together constitute, in anatomical terms, the rostral extension of the intermediate zone.

3. The brainstem also receives signals from the vestibular system. The vestibular nuclei are located at the level of the upper medulla and lower pons, and receive their afferents from the vestibular organs in the inner ear which are involved in detecting changes in the position and the movement of the head in space. There are major projections from the vestibular nuclei to other brainstem nuclei such as the PBN in the upper brainstem (Balaban, 1996; Balaban & Porter, 1998). These projections are involved in mediating adjustments in cardiovascular, respiratory, and gastroenteric functions needed when the position of the body is changed in space.

4. The state of the musculoskeletal frame is also represented in the brainstem. The proprioceptive afferents from muscles and tendons ascend in the dorsal column of the spinal cord along with afferents conveying signals from primary cutaneous receptors or some visceral nociceptors (Willis & Coggeshall, 1991: pp. 265–295; Willis & Westlund, 1997). They terminate in the gracile and cuneate nuclei of the medulla (known as the dorsal column nuclei). There is evidence that different modalities of afferents terminate in distinct groups of neurons within these nuclei. Anatomical and physiological studies indicate that some clusters of neurons receive ascending input almost exclusively via primary afferent fibers from cutaneous origin whereas other regions within these nuclei receive primary muscle afferents and non-primary afferents from deep structures or cutaneous receptors with large receptive fields (see Willis and Coggeshall, 1991: pp. 265–306). In turn, there are distinct projections from the dorsal column nuclei to rostral regions such as in the midbrain, thalamus, zona incerta, and cerebellum (Berkley, Budell, Blomqvist, & Bull, 1986). Interestingly, the regions that receive primary cutaneous afferents project, in somatotopical order, to the thalamic relay nuclei whereas the upper brainstem receives projections from neurons that receive non-primary or muscle afferents (Berkley et al., 1986; Wiberg, Westman, & Blomqvist, 1987). In the midbrain, the tectum is among the recipients of these projections (Berkley & Hand, 1978; Berkley et al., 1986; Wiberg & Blomqvist, 1984; Wiberg et al., 1987). In turn the tectum projects to the nuclei of the pons and midbrain (Shammah-Lagnado, Negrao, Silva, & Ricardo, 1987; Cornwall, Cooper, & Phillipson, 1990). Another motor-related channel to the upper brainstem is via the cerebellum (Brodal, 1959; Boivie, 1988; Rathelot & Padel, 1997). Some other nuclei in the brainstem, such as the

lateral reticular nucleus, also receive motor related projections directly from the spinal cord (Brodal, 1959).

The picture we are drawing of a context for the operation of brainstem nuclei is completed by evidence that the brainstem nuclei receive major afferents from rostral brain structures. For instance, the classical reticular nuclei receive major afferents from the zona incerta, the hypothalamus, and the medial thalamic nuclei (Parent & Steriade, 1981; Steriade, Parent, Ropert, & Kitsikis, 1982; Shammah-Lagnado et al., 1987; Cornwall et al., 1990). These rostral structures and the extended amygdala, cingulate gyrus, insula, and prefrontal cortex are also known to project to the PAG and the PBN (Hardy & Leichnetz, 1981a,b; Holstege, Meiners, & Tan, 1985; Moga, Herbert, Hurley, Yasui, Gray, & Saper, 1990; Beitz, 1990; Buchanan, Thompson, Maxwell, & Well, 1994; An, Bandler, Ongur, & Price, 1998; Moga et al., 1990). In a recent study, R.J. Morecraft has traced direct projections from the cingulate cortex to the locus coeruleus (personal communication).

In conclusion, the state of the organism is continuously portrayed in its multiple dimensions by incoming afferents to several brainstem nuclei. These diverse afferents relay signals related to the current state of the internal milieu, the viscera, the vestibular system, and the musculoskeletal frame. There are also afferents relaying signals which describe ongoing changes in the state of the organism as it interacts with an object. There is little doubt that the fundamental function of these brainstem nuclei is the regulation of the state of the organism based on the representation of its current state along several dimensions. It is reasonable to suggest, however, that there are other closely related functions, namely (a) the modulation of the electrophysiological state of the cerebral cortex as influenced by the current state of the organism with the goal of supporting mental processes and behaviors conducive to further homeostatic regulation; and (b) the generation of a composite representation of organism states available to rostral brain structures.

In effect, evidence that the nuclei within the brainstem reticular formation are involved in functions other than modulating the electrophysiological activity of the cerebral cortex is already available. For instance, the serotonergic system is involved in the modulation of autonomic activities, hunger and body weight regulation, neuroendocrine functions, reproductive behavior, aggression and suicidality (for extensive review see Feldman, Meyer, & Quenzer, 1997: Chapter 9, pp. 380–9); the noradrenergic system is involved in mechanisms underlying attention and learning (Aston-Jones & Bloom, 1981a,Aston-Jones and Bloom, 1981b; Aston-Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996; Cahill and McGaugh, 1998); the dopaminergic system is involved in motor control and reward mechanisms underlying motivation (Dunnett & Robbins, 1992; Brown & Gershon, 1993; Schultz et al., 1997; Schultz, 1998). Furthermore, classical reticular nuclei such as the nucleus cuneiforme and the pedunculopontine tegmental nucleus are also involved in locomotion (Allen, Inglis, & Winn, 1996). The pedunculopontine tegmental nucleus also plays an important role in mechanisms underlying attention and learning (Allen et al., 1996), and in subserving the rewarding effect of opiates (Bechara & van der Kooy, 1989). As already noted, the PBN and the PAG are essential for homeostatic

control. The PBN and the PAG have extensive reciprocal connections with rostral and caudal regions involved in cardiovascular, respiratory and gastroenteric control. These are structures appropriate for integrating signals related to the body proper and coordinating distinct innate behavioral strategies for coping with environmental demands. In keeping with this view, it has been shown that the stimulation of the lateral column of the PAG brings about an active coping strategy with vocalization, confrontation, hypertension, tachycardia, and aggression, whereas stimulation of ventrolateral columns of the PAG, on the other hand, produces a passive coping strategy with hyporeactivity, hypotension, bradycardia, freezing, and immobility (Bandler & Shipley, 1994).

Evidence from functional imaging studies also supports the notion that the upper brainstem nuclei are involved in a broad range of functions. For instance, Maquet and colleagues (Maquet, Dive, Salmon, Sadzot, Franco, Poirrier, von Frenckell, & Franck, 1990; Maquet, Peters, Aerts, Delfiore, Degueldre, Luxen, & Franck, 1996) found that the regional blood flow in pontine tegmentum was increased during rapid-eye-movement sleep and decreased during deep sleep; Kinomura, Larsson, Gulyás, and Roland (1996) found a significant blood flow increase in mesencephalic nuclei when subjects performed tests requiring attention; and recently, we found a significant blood flow increase in the upper pons and midbrain when subjects reenacted past emotional events (Damasio, Grabowski, Bechara, Damasio, Parvizi, Ponto, & Hichwa, 2000).

The remarkable overlap of functions thus revealed might be a fortuitous combination of anatomical units, but we see it instead as indicative of a meaningful anatomical and functional integration engendered by evolution. In fact, these functions – wakefulness, basic attention, and emotion – are interrelated and all aim, in one way or another, at achieving homeostatic balance. The close proximity of structures governing wakefulness and attention and structures involved in processing emotion would enhance their functional and anatomical interdependence.

The close relationship between the mechanisms underlying cortical activation and bioregulatory mechanisms, as outlined here, is entirely compatible with the classical idea about the role of the reticular formation in modulating the electrophysiological activity of the cerebral cortex. But it places that modulation in the setting of the organism's homeostatic regulation.

4. Concluding remarks

The multiple dimensions which describe the overall current state of the organism are mapped in several groups of brainstem nuclei. We believe that this comprehensive and continually changing map of the organism state creates a functional context for the brainstem nuclei whose activity can modulate the operation of rostral brain structures, namely those in the cerebral cortex. In addition, the map of the organism state, along with the fact that such a state is being changed as a result of an interaction with an object, can be signaled to rostrally located structures and be *remapped*. We see the remapping of the changing organism state in relation to a

causative object as the basis for the experience of knowing, the very core of the process of consciousness and self.

The brainstem is the source of several ascending neural pathways, each of which originates in distinct sets of nuclei. These pathways, which reach widespread regions of the cortex either directly or via the thalamus and the basal forebrain, affect the operations of the cerebral cortex both by modulating aspects of its overall activity (and leading to wakefulness and attention) and by conveying to specific regions the contents with which a subjective sense can be created.

In the framework outlined at the outset of this article, consciousness is grounded in both of these brainstem roles: providing an organism-based context for the modulation of rostral brain structures; and conveying signals necessary to represent the "caused changed state" of the organism within rostral structures.

The intriguing overlap of functions attributable to the several families of brainstem nuclei – emotion, wakefulness and sleep, basic attention, and of course consciousness itself – becomes less intriguing when it is seen in the perspective of homeostasis, the ultimate physiological role of all the operations in which these nuclei are involved.

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References

Alden, M., Besson, J. M., & Bernard, J. F. (1994). Organizations of the efferent projections from the pontine parabrachial area to the bed nucleus of the stria terminalis and neighboring regions: a PHA-L study in the rat. *The Journal of Comparative Neurology*, *341*, 289–314.

Allen, L., Inglis, W. L., & Winn, P. (1996). Is the cuneiform nucleus a critical component of the mesencephalic locomotor region? *Brain Research Bulletin*, *41* (4), 201–210.

An, X., Bandler, R., Ongur, D., & Price, J. L. (1998). Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. *Journal of Comparative Neurology*, *401* (4), 455–479.

Aston-Jones, G., & Bloom, F. E. (1981a). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *Journal of Neuroscience*, *1* (8), 876–886.

Aston-Jones, G., & Bloom, F. E. (1981b). Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *Journal of Neuroscience*, *1* (8), 887–900.

Aston-Jones, G., Ennis, M., Pieribone, V. A., Nickell, W. T., & Shipley, M. T. (1986). The brain nucleus locus coeruleus: restricted afferent control of a broad efferent network. *Science*, *234* (4777), 734–737.

Aston-Jones, G., Chiang, C., & Alexinsky, T. (1991). Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. *Progress in Brain Research*, *88*, 501–520.

Aston-Jones, G., Rajkowski, J., Kubiak, P., Valentino, R. J., & Shipley, M. T. (1996). Role of the locus coeruleus in emotional activation. *Progress in Brain Research*, *107*, 379–402.

Azmitia, E. C., & Whitaker-Azmitia, P. M. (1991). Awakening the sleeping giant: anatomy and plasticity of the brain serotonergic system. *Journal of Clinical Psychiatry*, *52*, 4–16.

Balaban, C. D. (1996). Vestibular nucleus projections to the parabrachial nucleus in rabbits: implications

for vestibular influences on the autonomic nervous system. *Experimental Brain Research*, *108* (3), 367–381.

Balaban, C. D., & Porter, J. D. (1998). Neuroanatomic substrates for vestibulo-autonomic interactions. *Journal of Vestibular Research*, *8* (1), 7–16.

Bandler, R., & Shipley, M. T. (1994). Columnar organization in the rat midbrain periaqueductal gray: modules for emotional expression? *Trends in Neurosciences*, *17* (9), 379–389.

Batini, C., Moruzzi, G., Palestini, M., Rossi, G. F., & Zanchetti, A. (1959). Effects of complete pontine transections on the sleep-wakefulness rhythm: the midpontine pretrigeminal preparation. *Archives Italiennes de Biologie*, *97*, 1–12.

Barnett, E. M., Evans, G. D., Sun, N., Perlman, S., & Cassell, M. D. (1995). Anterograde tracing of trigeminal afferent pathways from the murine tooth pulp to cortex using herpes simplex virus type 1. *Journal of Neuroscience*, *15* (4), 2972–2984.

Barth, D. S., & MacDonald, K. D. (1996). Thalamic modulation of high-frequency oscillating potentials in auditory cortex. *Nature*, *383*, 78–81.

Bechara, A., & van der Kooy, D. (1989). The tegmental pedunculopontine nucleus: a brain-stem output of the limbic system critical for the conditioned place preferences produced by morphine and amphetamine. *Journal of Neuroscience*, *9* (10), 3400–3409.

Beckstead, R. M., Morse, J. R., & Norgren, R. (1980). The nucleus of the solitary tract in the monkey: projections to the thalamus and brainstem nuclei. *The Journal of Comparative Neurology*, *190*, 259–282.

Beitz, A. J. (1990). Central gray. In G. Paxinos (Ed.), *The human nervous system* (pp. 307–320). New York: Academic Press.

Berkley, K. J., & Hand, P. J. (1978). Efferent projections of the gracile nucleus in the cat. *Brain Research*, *153* (2), 263–283.

Berkley, K. J., Budell, R. J., Blomqvist, A., & Bull, M. (1986). Output systems of the dorsal column nuclei in the cat. *Brain Research*, *396* (3), 199–225.

Bernard, J. F., & Besson, J. M. (1990a). The spino(trigemino)pontoamygdaloid pathway: electrophysiological evidence for an involvement in pain processes. *Journal of Neurophysiology*, *63* (3), 473–490.

Bernard, J. F., Villanueva, L., Carroué, J., & Le Bars, D. (1990b). Efferent projections from the subnucleus reticularis dorsalis (SRD): a phaseolus vulgaris leucoagglutinin study in the rat. *Neuroscience Letters*, *116*, 257–262.

Berridge, C. W., Arnsten, A. F., & Foote, S. L. (1993). Noradrenergic modulation of cognitive function: clinical implications of anatomical, electrophysiological and behavioural studies in animal models. *Psychological Medicine*, *23* (3), 557–564.

Bester, H., Bourgeais, L., Villanueva, L., Besson, J. M., & Bernard, J. F. (1999). Differential projections to the intralaminar and gustatory thalamus from the parabrachial area: a PHA-L study in the rat. *Journal of Comparative Neurology*, *405* (4), 421–449.

Blessing, W. W. (1997a). Inadequate frameworks for understanding bodily homeostasis. *Trends in Neurosciences*, *20* (6), 235–239.

Blessing, W. W. (1997b). *The lower brainstem and bodily homeostasis* (1st ed.) New York: Oxford University Press.

Blomqvist, A., & Berkley, K. J. (1992). A re-examination of the spino-reticulo-diencephalic pathway in the cat. *Brain Research*, *579* (1), 17–31.

Bloom, F. E. (1997). What is the role of general activating systems in cortical function? In P. Rakic, & W. Singer (Eds.), *Neurobiology of neocortex* (pp. 407–421). New York: Wiley.

Boivie, J. (1988). Projections from the dorsal column nuclei and the spinal cord to the red nucleus in cat. *Behavioural Brain Research*, *28* (1-2), 75–79.

Bremer, F. (1935). Cerveau "isolé" et physiologie du sommeil. *Comptes Rendus de la Societé Biologie*, *118*, 1235–1241.

Brodal, A. (1959). *The reticular formation of the brainstem: anatomical aspect and functional correlation*. Edinburgh: The William Ramsay Henderon Trust.

Brown, A. G. (1982). The dorsal horn of the spinal cord. *Quarterly Journal of Experimental Physiology*, *67*, 193–212.

Brown, A. S., & Gershon, S. (1993). Dopamine and depression. *Journal of Neural Transmission – General Section*, *91* (2-3), 75–109.

Buchanan, S. L., Thompson, R. H., Maxwell, B. L., & Well, D. A. (1994). Efferent connections of the medial prefrontal cortex in the rabbit. *Experimental Brain Research*, *100* (3), 469–483.

Burnstock, G., & Wood, J. N. (1996). Purinergic receptors: their role in nociception and primary afferent neurotransmission. *Current Opinion in Neurobiology*, *6* (4), 526–532.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neurosciences*, *21* (7), 294–299.

Cervero, F., & Iggo, A. (1980). The substantia gelatinosa of the spinal cord. *Brain*, *103*, 717–772.

Clark, C. R., Geffen, G. M., & Geffen, L. B. (1987). Catecholamines and attention. I: Animal and clinical studies. *Neuroscience and Biobehavioral Reviews*, *11* (4), 341–352.

Cornwall, J., Cooper, J. D., & Phillipson, O. T. (1990). Afferent and efferent connections of the laterodorsal tegmental nucleus in the rat. *Brain Research Bulletin*, *25* (2), 271–284.

Craig, A. D. (1995). Distribution of brainstem projections from spinal lamina I neurons in the cat and the monkey. *Journal of Comparative Neurology*, *361* (2), 225–248.

Craig, A. D. (1996). An ascending general homeostatic afferent pathway originating in lamina I. *Progress in Brain Research*, *107*, 225–242.

Craig, A. D. (1997). Pain, temperature and the sense of the body. In O. Franzen, R. Johansson, & L. Terenius (Eds.), *Proceedings of the 1994 Wenner-Gren Symposium on somatosensation* Birkhauser: Basel.

Damasio, A. R. (1998). Investigating the biology of consciousness. *Philosophical Transactions of the Royal Society of London – Series B: Biological Sciences*, *353* (1377), 1879–1882.

Damasio, A. R. (1999). *The feeling of what happens: body and emotion in the making of consciousness*, New York: Harcourt Brace.

Damasio, A. R., Grabowski, T. J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., & Hichwa, R. D. (2000). Distinctive patterns of subcortical and cortical brain activation associated with self-generated emotions and feelings. *Nature Neuroscience*, *3* (10), 1049–1056.

Denoyer, M., Sallanon, M., Kitahama, K., & Jouvet, M. (1991). Neurotoxic lesion of the mesencephalic reticular formation and/or the posterior hypothalamus does not alter waking n the cat. *Brain Research*, *539* (2), 287–303.

Dunnett, S. B., & Robbins, T. W. (1992). The functional role of mesotelencephalic dopamine systems. *Biological Reviews of the Cambridge Philosophical Society*, *67* (4), 491–518.

Edwards, S. B., & de Olmos, J. S. (1976). Autoradiographic studies of the projections of the midbrain reticular formation: ascending projections of nucleus cuneiformis. *Journal of Comparative Neurology*, *165* (4), 417–431.

Feldman, R. S., Meyer, J. S., & Quenzer, L. F. (1997). *Principles of neuropsychopharmacology* (1st ed.). Sunderland, MA: Sinauer Associates.

French, J. D., & Magoun, H. W. (1952). Effect of chronic lesions in central cephalic brainstem of monkeys. *Archives of Neurology and Psychiatry*, *68*, 591–604.

French, J. D., Verzeano, M., & Magoun, H. W. (1953). An extralemniscal sensory system in the brain. *Archives of Neurology and Psychiatry*, *69*, 505–519.

Fulwiler, C., & Saper, C. B. (1984). Subnuclear organization of the efferent connections of the parabrachial nucleus in the rat. *Brain Research Reviews*, *7*, 229–259.

Geyer, M. A. (1996). Serotonergic functions in arousal and motor activity. *Behavioural Brain Research*, *73* (1–2), 31–35.

Groenewegen, H. J., & Berendse, H. W. (1994). The specificity of the 'nonspecific' midline and intralaminar thalamic nuclei. *Trends in Neurosciences*, *17* (2), 52–57.

Han, Z. S., Zhang, E.-T., & Craig, A. D. (1998). Nociceptive and thermoceptive lamina I neurons are anatomically distinct. *Nature Neuroscience*, *1* (3), 218–225.

Hardy, S. G. P., & Leichnetz, G. R. (1981a). Cortical projections to the periaqueductal gray in the monkey: a retrograde and orthograde horseradish peroxidase study. *Neuroscience Letters*, *22*, 97–101.

Hardy, S. G. P., & Leichnetz, G. R. (1981b). Frontal cortical projections to the periaqueductal gray in the rat: a retrograde and orthograde horseradish peroxidase study. *Neuroscience Letters*, *23*, 13–17.

Herbert, H., Moga, M. M., & Saper, C. B. (1990). Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat. *The Journal of Comparative Neurology*, *293*, 540–580.

Herculano-Houzel, S., Munk, M. H., Neuenschwander, S., & Singer, W. (1999). Precisely synchronized oscillatory firing patterns require electroencephalographic activation. *Journal of Neuroscience*, *19* (10), 3992–4010.

Holstege, G., Meiners, L., & Tan, K. (1985). Projections of the bed nucleus of the stria terminalis to the mesencephalon, pons, and medulla oblongata in the cat. *Experimental Brain Research*, *58* (2), 379–391.

Ito, H., & Seki, M. (1998). Ascending projections from the area postrema and the nucleus of the solitary tract of Suncus murinus: anterograde tracing study using Phaseolus vulgaris leucoagglutinin. *Okajimas Folia Anatomica Japonica*, *75* (1), 9–31.

Jackson, A., & Crossman, A. R. (1983). Nucleus tegmenti pedunculopontinus: efferent connections with special reference to the basal ganglia, studied in the rat by anterograde and retrograde transport of horseradish peroxidase. *Neuroscience*, *10* (3), 725–765.

Jacobsohn, L. (1909). Über die Kerne des menschlichen Hirnstammes (der medulla oblongata, des pons und des pedunculus). *Vorlautige Mitteilung Neurol Centralblad*, *xxviii*, 674–679.

Jacobs, B. L., Wilkinson, L. O., & Fornal, C. A. (1990). The role of brain serotonin. A neurophysiologic perspective. *Neuropsychopharmacology*, *3* (5–6), 473–479.

Jones, E. G. (1998). Viewpoint-the core and matrix of thalamic organization. *Neuroscience*, *85* (2), 331–345.

Jones, B. E., Bobillier, P., Pin, C., & Jouvet, M. (1973). The effect of lesions of catecholamine-containing neurons upon monoamine content of the brain and EEG and behavioral waking in the cat. *Brain Research*, *58* (1), 157–177.

Jones, E. G., & Leavitt, R. Y. (1974). Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. *Journal of Comparative Neurology*, *154* (4), 349–377.

Jones, B. E., & Yang, T. Z. (1985). The efferent projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat. *Journal of Comparative Neurology*, *242* (1), 56–92.

Kaufman, E. F., & Rosenquist, A. C. (1985). Afferent connections of the thalamic intralaminar nuclei in the cat. *Brain Research*, *335* (2), 281–296.

Kinomura, S., Larsson, J., Gulyás, B., & Roland, P. (1996). Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science*, *271*, 512–515.

Kitsikis, A., & Steriade, M. (1981). Immediate behavioral effects of kainic acid injections into the midbrain reticular core. *Behavioural Brain Research*, *3* (3), 361–380.

Kölliker, A. (1854). *Manual of human histology*. London: Sydenham Society.

Lai, Y. Y., Shalita, T., Hajnik, T., Wu, J. P., Kuo, J. S., Chia, L. G., & Siegel, J. M. (1999). Neurotoxic N-methyl-D-aspartate lesion of the ventral midbrain and mesopontine junction alters sleep-wake organization. *Neuroscience*, *90* (2), 469–483.

Lavoie, B., & Parent, A. (1994). Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. *Journal of Comparative Neurology*, *344* (2), 210–231.

Lawson, S. N. (1996). Neurochemistry of cutaneous nociceptors. In C. Belmonte, & F. Cervero (Eds.), *Neurobiology of nociceptors* (p. 85). New York: Oxford University Press.

Llinas, R. R., & Paré, D. (1991). Of dreaming and wakefulness. *Neuroscience*, *44* (3), 521–535.

Llinas, R., Ribary, U., Contreras, D., & Pedroarena, C. (1998). The neuronal basis for consciousness. *Philosophical Transactions of the Royal Society of London – Series B: Biological Sciences*, *353* (1377), 1841–1849.

Lindsley, D. B., Schreiner, L. H., Knowles, W. B., Magoun, M. S., & Magoun, H. W. (1950). Behavorial and EEG changes following chronic brainstem lesions in the cat. *Electroencephalography and Clinical Neurophysiology*, *2*, 483–498.

Loeb, C., & Stirling Meyer, J. (1965). *Strokes due to vertebro-basilar disease: infarction, vascular insufficiency and hemorrhage of the brainstem and cerebellum*. Springfield, IL: Charles C. Thomas.

MacIver, M. B., & Tanelian, D. L. (1992). Activation of C fibers by metabolic perturbations associated with tourniquet ischemia. *Anesthesiology*, *76*, 617–623.

Magoun, H. W. (1952a). Ascending reticular activating system in the brainstem. *Archives of Neurology and Psychiatry*, *67* (145), 154.

Magoun, H. W., French, J. D., & Von Amerongen, F. K. (1952b). An activating system in brainstem of monkey. *Archives of Neurology and Psychiatry*, *68* (5), 577–590.

Mantyh, P. W. (1982). The ascending input to the midbrain periaqueductal gray of the primate. *Journal of Comparative Neurology*, *211* (1), 50–64.

Mantyh, P. W. (1983). Connections of midbrain periaqueductal gray in the monkey. I. Ascending efferent projections. *Journal of Neurophysiology*, *49* (3), 567–581.

Maquet, P., Dive, D., Salmon, E., Sadzot, B., Franco, G., Poirrier, R., von Frenckell, R., & Franck, G. (1990). Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method. *Brain Research*, *513* (1), 136–143.

Maquet, P., Peters, J., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., & Franck, G. (1996). Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature*, *383* (6596), 163–166.

Martin, J. H. (1996). *Neuroanatomy, Text and Atlas*. New York: A Simon and Schuster Company.

Mesulam, M. M., Geula, C., Bothwell, M. A., & Hersh, L. B. (1989). Human reticular formation: cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and some cytochemical comparisons to forebrain cholinergic neurons. *The Journal of Comparative Neurology*, *283* (4), 611–633.

Moga, M. M., Herbert, H., Hurley, K., Yasui, Y., Gray, T. S., & Saper, C. B. (1990). Organizations of cortical, basal forebrain, and hypothalamic afferents to the parabrachial nucleus in the rat. *The Journal of Comparative Neurology*, *295*, 624–661.

Moore, R. Y., & Bloom, F. E. (1979). Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. *Annual Review of Neuroscience*, *2*, 113–168.

Moore, R. Y. (1980). The reticular formation: monoamine neuron systems. In J. A. Hobson, & M. A. B. Brazier (Eds.), *The reticular formation revisited* (pp. 67–81). New York: Raven Press.

Morison, R. S., & Dempsey, E. W. (1942). A study of thalamo-cortical relations. *American Journal of Physiology*, *135*, 281–292.

Moruzzi, G. (1963). Active process in the brainstem during sleep. *Harvey Lectures* (pp. 233–297). .

Moruzzi, G., Magni, F., Rossi, G. F., & Zanchetti, A. (1959). EEG arousal following inactivation of the lower brainstem by selective injection of barbiturate into the vertebral circulation. *Archives Italiennes de Biologie*, *97*, 33–46.

Moruzzi, G., & Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology*, *1*, 455–473.

Moskowitz, M. A. (1991). The visceral organ brain: implications for the pathophysiology of vascular head pain. *Neurology*, *41*, 182–196.

Mouton, L. J., & Holstege, G. (1998). Three times as many lamina I neurons project to the periaqueductal gray than to the thalamus – a retrograde tracing study in the cat. *Neuroscience Letters*, *255* (2), 107–110.

Muller, C. M., Lewandowski, M. H., & Singer, W. (1993). Structures mediating cholinergic reticular facilitation of cortical responses in the cat: effects of lesions in immunocytochemically characterized projections. *Experimental Brain Research*, *96* (1), 8–18.

Munk, M. H. J., Roelfsema, P. R., König, P., Engel, A., & Singer, W. (1996). Role of reticular activation in the modulation of intracortical synchronization. *Science*, *272*, 271–274.

Newman, D. B., & Ginsberg, C. Y. (1994). Brainstem reticular nuclei that project to the thalamus in rats: a retrograde tracer study. *Brain, Behavior and Evolution*, *44* (1), 1–39.

Olszewski, J. (1954). Cytoarchitecture of the human reticular formation. In J. F. Delafresnaye (Ed.), *Brain mechanisms and consciousness* (pp. 54–80). Springfield, Il: Charles C. Thomas.

Olszewski, J., & Baxter, D. (1982). *Cytoarchitecture of the human brainstem* (2nd ed.). New York: Karger.

Pare, D., Smith, Y., Parent, A., & Steriade, M. (1988). Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience*, *25* (1), 69–86.

Parent, A., & Steriade, M. (1981). Afferents from the periaqueductal gray, medial hypothalamus and medial thalamus to the midbrain reticular core. *Brain Research Bulletin*, *7* (4), 411–418.

Paxinos, G., & Huang, X. F. (1995). *Atlas of the human brainstem* (1st ed.). New York: Academic Press.

Plum, F., & Posner, J. B. (1980). *The Diagnosis of Stupor and Coma* (3rd ed.). Philadelphia, PA: F.A. Davis Company.

Porrino, L. J., & Goldman-Rakic, P. S. (1982). Brainstem innervation of prefrontal and anterior cingulate cortex in the rhesus monkey revealed by retrograde transport of HRP. *Journal of Comparative Neurology*, *205* (1), 63–76.

Ramón y Cajal, S. (1894). *Estructura del ganglio habénula de los mamÍferos*. Anales de la Sociedad Española de Historia Natural (Tomo 23).

Rathelot, J. A., & Padel, Y. (1997). Ascending spinal influences on rubrospinal cells in the cat. *Experimental Brain Research*, *116* (2), 326–340.

Rico, B., & Cavada, C. (1998). Adrenergic innervation of the monkey thalamus: an immunohistochemical study. *Neuroscience*, *84* (3), 839–847.

Royce, G. J., Bromley, S., & Gracco, C. (1991). Subcortical projections to the centromedian and parafascicular thalamic nuclei in the cat. *Journal of Comparative Neurology*, *306* (1), 129–155.

Schachter, S. C., & Saper, C. B. (1998). Vagus nerve stimulation. *Epilepsia*, *39* (7), 677–686.

Schaible, H. G., & Schmidt, R. F. (1983). Activation of groups III and IV sensory units in medial articular nerve by local mechanical stimulation of knee joint. *Journal of Neurophysiology*, *49* (1), 35–45.

Scheibel, M. E., & Scheibel, A. B. (1966). The organization of the nucleus reticularis thalami: a Golgi study. *Brain Research*, *1* (1), 43–62.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, *275* (5306), 1593–1599.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80* (1), 1–27.

Shammah-Lagnado, S. J., Negrao, N., Silva, B. A., & Ricardo, J. A. (1987). Afferent connections of the nuclei reticularis pontis oralis and caudalis: a horseradish peroxidase study in the rat. *Neuroscience*, *20* (3), 961–989.

Smiley, J. F., Subramanian, M., & Mesulam, A. M. (1999). Monoaminergic-cholinergic interactions in the primate basal forebrain. *Neuroscience*, *93* (3), 817–829.

Steriade, M. (1993). Central core modulation of spontaneous oscillations and sensory transmission in thalamocortical systems. *Current Opinion in Neurobiology*, *3* (4), 619–625.

Steriade, M., & Deschenes, M. (1984). The thalamus as a neuronal oscillator. *Brain Research*, *320* (1), 1–63.

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, *262* (5134), 679–685.

Steriade, M., Pare, D., Parent, A., & Smith, Y. (1988). Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. *Neuroscience*, *25* (1), 47–67.

Steriade, M., Parent, A., Ropert, N., & Kitsikis, A. (1982). Zona incerta and lateral hypothalamic afferents to the midbrain reticular core of cat–HRP and electrophysiological study. *Brain Research*, *238* (1), 13–28.

Vallbo, A., Olausson, H., Wessberg, J., & Norrsell, U. (1993). A system of unmyelinated afferents for innocuous mechanoreception in the human skin. *Brain Research*, *628* (1–2), 301–304.

Van Bockstaele, E. J., & Aston-Jones, G. (1992). Collateralized projectionis from neurons in the rostral medulla to the nucleus locus coeruleus, the nucleus of the solitary tract and the periaqueductal gray. *Neuroscience*, *49* (3), 653–668.

Van Bockstaele, E. J., & Aston-Jones, G. (1995). Integration in the ventral medulla and coordination of sympathetic, pain and arousal functions. *Clinical and Experimental Hypertension*, *17* (1-2), 153–165.

van Domburg, P. H., & Ten Donkelaar, H. J. (1991). The human substantia nigra and ventral tegmental area. A neuroanatomical study with notes on aging and aging diseases. *Advances in Anatomy, Embryology and Cell Biology*, *121*, 1–132.

Villanueva, L., Cliffer, K. D., Sorkin, L. S., Le, B. D., & Willis Jr. W. D. (1990). Convergence of

heterotopic nociceptive information onto neurons of caudal medullary reticular formation in monkey (Macaca fascicularis). *Journal of Neurophysiology*, *63* (5), 1118–1127.

Villanueva, L., Desbois, C., Le Bars, D., & Bernard, J. F. (1998). Organization of diencephalic projections from the medullary subnucleus reticularis dorsalis and the adjacent cuneate nucleus: a retrograde and anterograde tracer study in the rat. *Journal of Comparative Neurology*, *390* (1), 133–160.

Von Economo, C. F. (1917). *Encephalitis lethargica*. Wien: W. Braumuller.

Webster, H. H., & Jones, B. E. (1988). Neurotoxic lesions of the dorsolateral pontomesencephalic tegmentum-cholinergic cell area in the cat. II. Effects upon sleep-waking states. *Brain Research*, *458* (2), 285–302.

Wiberg, M., & Blomqvist, A. (1984). The spinomesencephalic tract in the cat: its cells of origin and termination pattern as demonstrated by the intra-axonal transport method. *Brain Research*, *291* (1), 1–18.

Wiberg, M., Westman, J., & Blomqvist, A. (1987). Somatosensory projection to the mesencephalon: an anatomical study in the monkey. *Journal of Comparative Neurology*, *264* (1), 92–117.

Willis, W. D., & Coggeshall, R. E. (1991). Peripheral nerves and sensory receptors. *Sensory Mechanisms of the spinal cord*. New York: Plenum Press.

Willis, W. D., & Westlund, K. N. (1997). Neuroanatomy of the pain system and the pathways that modulate pain. *Journal of Clinical Neurophysiology*, *14* (1), 2–31.

Zhang, E. -T., Han, Z. S., & Craig, A. D. (1993). Morphological classes of spinothalamic lamina I neurons in the cat. *Journal of Comparative Neurology*, *367* (4), 537–549.