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COMMENTARY

OF DREAMING AND WAKEFULNESS

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Abstract—Following a set of studies concerning the intrinsic electrophysiology of mammalian central neurons in relation to global brain function, we reach the following conclusions: (i) the main difference between wakefulness and paradoxical sleep lies in the weight given to sensory afferents in cognitive images; (ii) otherwise, wakefulness and paradoxical sleep are fundamentally equivalent brain states probably subserved by an intrinsic thalamo-cortical loop. From this assumption, we conclude that wakefulness is an intrinsic functional realm, modulated by sensory parameters. In support of this hypothesis, we review morphological studies of the thalamocortical system, which indicate that only a minor part of its connectivity is devoted to the transfer of direct sensory input. Rather, most of the connectivity is geared to the generation of internal functional modes, which may, in principle, operate in the presence or absence of sensory activation. These considerations lead us to challenge the traditional Jamesian view of brain function according to which consciousness is generated as an exclusive by-product of sensory input. Instead, we argue that consciousness is fundamentally a closed-loop property, in which the ability of cells to be intrinsically active plays a central role. We further discuss the importance of spatial and temporal mapping in the elaboration of cognitive and perceptual constructs.

CONTENTS

1. INTRODUCTION

Some of the truly important issues in neuroscience relate to the ability of the brain to generate global functional states that may significantly alter the relationship of the organism to its environment. Among these, the differences between the wakefulness and sleep states are perhaps the best known to everyone. Nevertheless, and in spite of considerable advances toward an understanding of the physiological and behavioral characterization of these states,[40] their functional meaning remains elusive.[106]

A point that we consider fundamental to understanding CNS function lies in the similarities and

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Abbreviations: AEP, averaged evoked potential; IO, inferior olive; LDT, laterodorsal tegmental; LGN, lateral geniculate nucleus; PGO, ponto-geniculo-occipital; PPT, pedunculopontine; RE, reticular thalamic nucleus; REM, rapid eye movement.

differences between wakefulness and paradoxical sleep. In fact, at the end of this essay, we will conclude that, from the standpoint of the thalamocortical system, *the overall functional states present during paradoxical sleep and wakefulness are fundamentally equivalent* although the handling of sensory information and cortical inhibition is different in the two states. The implications of this conclusion are far reaching since wakefulness may then be considered as nothing other than a highly coherent intrinsic functional state strongly modulated by sensory input. That is, paradoxical sleep and wakefulness are seen as almost identical intrinsic functional states in which subjective awareness is generated.[60]

1.1. *Paradoxical sleep*

Four major sleep stages (stages I–IV) have been distinguished on the basis of behavioral and physiological criteria and most of the functional variables examined fluctuate according to the stages. For example, the electrorhythmicity [electroencephalogram (EEG), electromyogram, electrooculogram][6,22] autonomic responsiveness[83] and sensory thresholds for awakening[89,117] vary in a well-defined manner with the sleep stages.

Aserinsky and Kleitman[6] and Dement and Kleitman[22] were the first to describe the cyclic variations of the human EEG during sleep. About every 90–100 min, the EEG cycles between the low-amplitude, high-frequency waves typical of stage I and the high-amplitude, low-frequency waves of stage IV. As sleep proceeds, the amount of time spent in the deeply synchronized stages (stages III and IV) progressively decreases while that spent in desynchronized sleep increases.[6,22] Finally, it was soon recognized by those authors that the EEG-desynchronization occurring during sleep (called paradoxical sleep) was, in fact, quite similar to the desynchronized activity that characterizes wakefulness.

Perhaps the most salient differences between wakefulness and rapid eye movement (REM) sleep are: (i) paradoxical sleep is characterized by the repeated occurrence of REMs,[7] from which the alternative designation "REM sleep" was derived: (ii) sensory input does not generate the expected cognitive consequences it does in the awake state; and (iii) from a motor point of view, complete muscular atonia is present during REM sleep.

With respect to other sleep states, REM sleep differs in that (i) sensory thresholds for awakening are the highest in REM sleep, except for stage IV[89,117] and (ii) subjects awakened during REM sleep often report having been dreaming.[6]

Studies in other mammalian forms extended these findings in several important respects. For instance, it was found by Jouvet and collaborators that REM sleep in felines is characterized by generalized muscular atonia,[49] which upon further investigation was found to be accompanied by a marked depression of motor reflexes.[87] These phenomena are probably due to the increased activity of the inhibitory medullary reticulospinal neurons.[30,77] A detailed study of the REMs that accompany REM sleep demonstrated that concurrent with their appearance were bursts of electrical activity in the pons, lateral geniculate nucleus (LGN), oculomotor nuclei, and occipital cortex. These transients were called ponto-geniculo-occipital (PGO) waves and occur just before[110] and during REM sleep.[50,74,80] More modern research has pinpointed the actual site of generation of this activity.[65,66]

2. RAPID EYE MOVEMENT SLEEP AND WAKEFULNESS ARE FUNDAMENTALLY EQUIVALENT FUNCTIONAL STATES

2.1. *Physiological comparison of the two states*

2.1.1. *Sensory evoked potentials and unit activities elicited by central electrical stimulation.*

Sensory stimuli. In general, the averaged evoked potentials (AEPs) recorded from the scalp in response to sensory stimulation during waking and REM sleep are very similar, but differ strikingly from those recorded during non-REM sleep. We will consider auditory and somatosensory human studies as well as animal studies in which the excitability of thalamic and cortical neurons was tested by means of direct electrical stimulation.

The auditory system. The auditory evoked potential comprises several components. In humans, the early components (< 10 ms, thought to reflect the responses of various brainstem and possibly thalamic nuclei)[76] do not display state-dependent fluctuations during the sleep–waking cycle[15,29,86] apart from small-latency variations related to changes in body temperature.[8] However, some middle-latency components (10–80 ms, thought to reflect early thalamocortical activity) decreased in amplitude from waking to stage IV but, returned to normal[16] or surpassed waking values in REM sleep.[20,72,73]

Few studies have dealt with the state-dependent fluctuations of the long-latency components which are relatively insensitive to the properties of the stimulus, but do change with attention level and task requirements.[76] In a study by Wesensten and Badia,[112] subjects learned to differentiate between target and non-target stimuli and auditory evoked responses were recorded for each type of stimulus during various stages of sleep. Although the evoked responses to targeted and non-targeted stimuli were most clearly distinguished when the subjects were awake, a slight difference between these two types of response was also seen during REM sleep. This indicates that the presence of a weak sensory specification may occur during REM sleep. In agreement with this finding is the common observation that occasionally sensory stimuli may be embedded into an ongoing dream or trigger a specific dream sequence, in which such stimulus is a nucleating point. Alternatively, these stimuli may be integrated

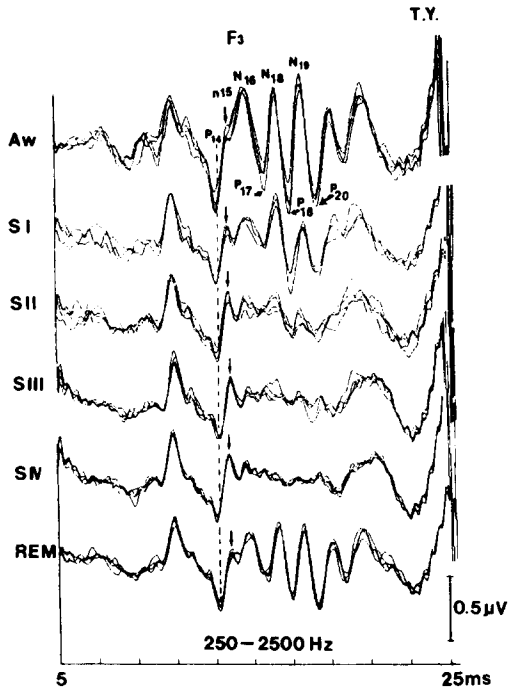

Fig. 1. State-dependent fluctuations of short-latency somatosensory evoked potentials in humans. Digitally filtered (250–2500-Hz) traces showing the potentials evoked by median nerve stimulation during different sleep stages (indicated on the left). Note that most components are attenuated during stages I–IV but recover in REM sleep (reproduced with permission from Yamada *et al.*[119]).

into cognitive constructs in which their significance may be quite different from that in the waking stage.

The somatosensory system. Short-, middle- and long-latency components are also distinguished in somatosensory evoked potentials. Although the latencies and anatomical correlations are the subject of some controversy, the early components (< 19 ms) are thought to reflect activity in the peripheral nerve (9 ms), spinal cord (11 ms), dorsal column nuclei and brainstem (12 ms), as well as in the cerebellum and thalamus (14–18 ms). The earliest activity in the cerebral cortex (19–20 ms) is followed by middle- and long-latency components which are highly dependent on task requirements and attentional level.[25]

Among the early components, only the positivity at 15 ms (P15) did not display state-dependent fluctuations.[119] The amplitude of the other components decreased markedly from waking to stage IV but partially recovered in REM sleep[119] (Fig. 1). The latency of the P20 component (which presumably reflects the primary cortical response) increased from waking to stage IV, but returned close to waking values in REM sleep.[119] However, the late components (P100, P200, P300) were abolished in REM sleep.[32,111]

Electrical stimuli

The visual system. The excitability of the visual pathways during REM sleep cannot be tested with photic stimulation due to miosis.[10] We must therefore turn our attention to experiments performed in chronically implanted, naturally sleeping animals. In this case the spontaneous and evoked activity of thalamocortical and corticofugal neurons were tested with central electrical stimulation. Single-unit recordings showed that the discharge rate of thalamocortical and corticofugal neurons is generally higher in REM sleep than in the waking state.[c.f.105] In addition, the ortho- and/or antidromic excitability of these cells was the same or higher in REM sleep than in awake animals[13,31,82,102,104] (Fig. 2). In particular, the probability of orthodromic activation of dorsal LGN neurons by optic tract stimulation increased above waking levels during REM sleep.[13]

At the cortical level, evoked potential studies of thalamic and cortical regions devoted to motor control suggest that their synaptic excitability diminishes from waking (W) to slow-wave sleep (S) but surpasses waking values in REM sleep[99,102] (Fig. 3). Finally, in contrast to wakefulness, REM sleep was shown to be accompanied by a reduction of inhibitory activity in cortical neurons.[95]

2.2. *Significance of the high sensory thresholds for awakening during rapid eye movement sleep*

Since the brain's response to sensory stimulation is very similar during REM sleep and wakefulness, the threshold for awakening should be lowest in REM sleep. Animal and human studies indicate that this in fact is not the case. In cats, Jouvet and collaborators[50] found that the auditory threshold for awakening was clearly higher in REM sleep than in deep slow-wave sleep while Dement[21] found that the auditory threshold was comparable or slightly lower in REM sleep than in deep slow-wave sleep.

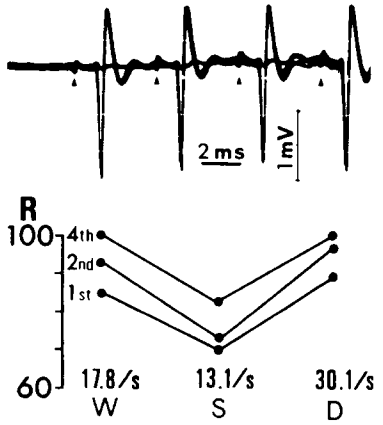

Fig. 2. Antidromic responsiveness of a corticothalamic neuron during the sleep–waking cycle. Area 5 neuron backfired from the nucleus centrum medianum of a cat. A four-shock train was applied periodically during a complete sleep cycle and the probability of antidromic invasion (R, bottom part) to the first, second and fourth shocks was computed in waking (W), slow-wave sleep (S) and REM sleep (D). Note that the responsiveness decreased from waking to slow-wave sleep but returned to waking levels in REM sleep (reproduced with permission from Steriade *et al.*[104]).

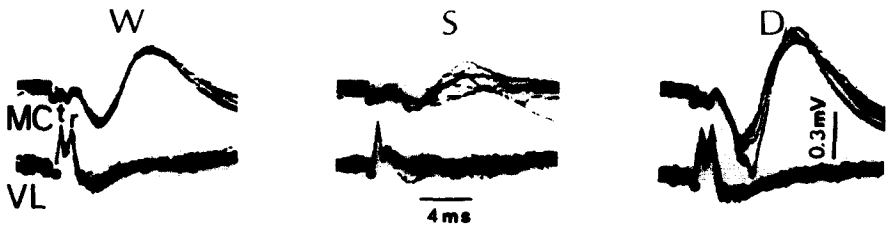

Fig. 3. Simultaneously recorded field potentials in the ventral lateral thalamic nucleus (VL) and motor cortex (MC) following stimulation of the superior cerebellar peduncle during waking (W), slow-wave sleep (S) and REM sleep (D). t, Presynaptic (tract) components; r, monosynaptic response. Note the almost complete abolition of thalamic and cortical responses in slow-wave sleep and their recovery above waking values in REM sleep. Reproduced with permission from Steriade *et al.*[102].

Similarly, studies in humans found that the percentage of awakenings evoked by auditory stimuli decreased from stage I to stage IV with REM sleep displaying intermediate values between stages III and IV.[89, 117]

These studies draw our attention to the central paradox of REM sleep. Namely, that stimuli which are perceived in the waking state do not awaken subjects in REM sleep, even though the amplitude of the primary evoked cortical responses is generally similar to, or higher than, in the waking state (see section 2.1). In other words, although the thalamocortical network appears to be at least as excitable during REM sleep as in the waking state, the input is mostly ignored.

Does the lack of behavioral response to suprathreshold sensory stimuli reflect the somatic paralysis characterizing REM sleep, or rather, a difference in the way the brain processes sensory input? The latter explanation seems to be more likely.

The first line of evidence comes from studies of the sensory responsiveness of sleeping cats in which the muscular atonia of REM sleep was suppressed by a small pontine lesion.[48]Although these animals can execute complex sequences of species-specific behavior during REM sleep, they were unresponsive to peripheral stimulation.[48] Similar events occur in humans with pontine lesions due to the lack of motor paralysis which normally accompanies REM sleep. These patients act their dreams out, endangering their lives and that of their bed-fellows.[90]

The second line of evidence is found in cases of sleep disturbances such as the cataplexy of narcoleptic patients,[51] or the postdormatory paralysis displayed by otherwise normal patients.[1] Indeed, about 70% of narcoleptics report cataplexy and are otherwise fully awake and conscious of their environment but cannot move.[51] Following the period of cataplexy, these subjects can provide a detailed description of events occurring during such periods.[1] Similarly, although subjects experiencing postdormatory paralysis are fully awake and oriented, they lack muscle tone and cannot make voluntary movements. These paralytic attacks generally occur at the end of a night of sleep and can be terminated by a slight stimulation such as a light touch.[1]

Therefore, if the high sensory thresholds to awakening do not reflect somatic paralysis during REM sleep, the resolution of the paradox probably lies in the nature of brain function, in a most fundamental sense. In particular, that the late potentials (P100, P200, P300) following sensory stimuli are abolished in REM sleep[32,111] suggests that the ongoing activity that generates cognition during dreaming prevents the early thalamocortical activation from being incorporated into the intrinsic cognitive world. Perhaps then, an altered state of attention is the most likely origin for the high awakening from REM sleep. This issue will be discussed further later on.

3. WAKEFULNESS AS AN INTRINSIC STATE FUNDAMENTALLY SIMILAR TO RAPID EYE MOVEMENT SLEEP, BUT SPECIFIED BY SENSORY INPUTS

The only tool available to study the functional state of the brain during REM sleep is a comparison of the dreams of control subjects with those of patients suffering from various central and peripheral dysfunctions.

Developmental studies by cognitive psychologists have led to the conclusion that dreaming is subjected to the constraints of general cognitive maturation.[28]

Moreover, the decline of higher cognitive abilities following circumscribed lesions of the temporal and parietal associative areas is also reflected in dream contents.[89a] For instance, patients afflicted with unilateral neglect resulting from right parietal lobe damage in which the opposite half of the visual field is not perceived, report a similar lack of perception in their dreams (M. Mesulam, personal communication). Similarly, people inhabiting the dreams of prosopagnosic subjects are faceless (A. Damasio, personal communication). Interestingly, when awake these patients perceive facial features but they cannot use such features to recognize individual faces. This fact suggests that dreaming operates on integrated symbolic structures and that sensory inputs which are not integrated in these structures during the waking state cannot be reproduced in the dreaming process. Furthermore, these observations indicate that mentation during dreaming operates on the same anatomical substrate as does perception during the waking state.

This view is supported by the analysis of the dream content of patients who acquire peripheral sensory neuropathologies late in life. In these patients, the dream scenes contain vivid sensations that incorporate the affected sensory modalities. For example, one subject who suffered total blindness due to bilateral retinal detachment in his adult life reported totally detailed visual imagery during dreaming but "returns to blindness" upon waking up.[41]

Thus, the evidence reviewed so far indicates that waking and REM sleep are similar in a number of respects. As far as we can tell from the studies on the state-dependent changes in sensory evoked potentials, the excitability of the thalamocortical system is essentially equivalent in the two states. Moreover, neuropsychological investigations indicate that even if dreams may seem irrational by waking standards, they still reflect the cognitive abilities present in the waking state.

Following upon what has been discussed, we may conclude that a possible approach to understanding the nature of wakefulness is to consider it as one element in a category of intrinsic brain functions, in which REM sleep is another element. The difference between these two states would be that in REM sleep, the sensory specification of the functionalities carried out by the brain is fundamentally altered. That is, *REM sleep can be considered as a modified attentive state in which attention is turned away from the sensory input, toward memories.* This hypothesis could, in principle, explain the total rejection of or, otherwise, the alteration of sensory input into our dreaming.[37,89]

Let us formally propose then *that wakefulness is nothing other than a dreamlike state modulated by the constraints produced by specific sensory inputs.*[60] Findings in support of this rather outrageous statement come from morphological and electrophysiological studies.

3.1. *Morphological evidence*

3.1.1. *Survey of quantitative studies of thalamocortical connectivity and its functional implications.* Quantitative morphological evidence suggests that only a minor part of the thalamocortical connectivity is devoted to the transfer of sensory input. Rather, the thalamocortical network appears to be a complex machine largely devoted to generating an internal representation of reality that may operate in the presence or absence of sensory input.

The thalamus is considered to be the functional and morphological gate to the forebrain.[103] Indeed, with the exception of the olfactory system, all sensory messages reach the cerebral cortex through the thalamus.[47] Yet, synapses established by specific thalamocortical fibers comprise a minority of cortical contacts. For example, in the primary somatosensory and visual cortices, the axons of ventroposterior thalamic and dorsal LGN neurons account for, respectively, 28% and 20% of the synapses in layer IV and adjacent parts of layer III[55,113] (where most thalamocortical axons project). Even in primary sensory cortical areas, most of the connectivity does not represent sensory input transmitted by the thalamus, but input from cortical and non-thalamic CNS nuclei. Indeed, corticostriatal, corticocortical and corticothalamic pyramidal neurons receive, respectively, 0.3–0.9, 1.5–6.8 and 6.7–20% of their synapses from specific thalamocortical fibers, while less than 4% of the synaptic contacts on multipolar aspiny neurons in layer IV originate in the thalamus.[113 116]

Equally important is the fact that the connectivity between the thalamus and the cortex is bidirectional. Indeed, layer VI pyramidal cells project back to that area of the thalamus where their specific input arises.[46] The number of corticothalamic fibers is about one order of magnitude larger than the number of thalamocortical axons.[118] Moreover, the number of optic nerve axons projecting to the LGN is smaller than the number of corticothalamic axons projecting to the same nucleus.[118]

Clearly, the sensory input arising from the thalamus is necessary for perception as in the absence of specific inputs, there is no externally guided sensory function. However, the specific thalamocortical input accounts for a minority of the synaptic contacts in the cortex.

What are the implications of these morphological data for brain function? Specifically, what is the function of the majority of inputs to the cortex and how is their activity related to sensory input? One conclusion seems inescapable. The ability to see, i.e. to place sensory input into the context of consciousness or a state resembling consciousness, requires an enormous computational machine. This is not surprising since the essence of brain function seems, to us, to be that of generating the functional scaffolding required to create an internal image consistent with external reality. And more importantly, such a consistent image of reality, requires that inputs from different sensory modalities coalesce into a singular perceptual event. Interestingly, most of the connectivity necessary for this amalgamation is present at birth,[38] i.e. the connectivity allows a cognitive capacity that is truly *a priori.* By this, we do not mean, however, that the total content of consciousness is innate. Even though the mechanisms necessary for its generation are present at birth, the emergence of consciousness arises out of interactions between the brain and its environment. Yet, the internalization of sensory events and the elaboration of memories require an intrinsic mechanism different from that which is primarily responsible for the acquisition and central conduction of sensory inputs.

3.2. *The relation between brain states and external reality*

Let us briefly discuss the nature of the interaction between this set of innate mechanisms and the sensory world. At the outset, it must be recognized that sensory events are nothing other than simplifications

determined by the physical properties of our sensory organs. Similarly, the internal representation derived from the sensory specification is constrained by the computational capabilities of the brain. In our opinion, the model of the world emerging during ontogeny is governed by innate predispositions of the brain to categorize and integrate the sensory world in certain ways. Although the particular computational world model derived by a given individual is a function of the sensory exposure he is subjected to, the resulting functional accommodation is genetically determined. As a result, sensory inputs presented during adult life would only convey the parameters required to specify the dimensions relevant to the cognitive templates which stemmed from this accommodative process. Finally, these cognitive templates could be used to recreate world-analogs during dreaming or, once specified by sensory inputs, to generate an adaptive representation of the environment.

Thus, we may consider a closely related problem, that of the open (extrinsic) or closed (intrinsic) nature of nervous system function. One view stipulates that the brain states which represent the external world are nothing other than point-to-point representations having as the basic coinage for functioning the elaboration of reflexes. This view may be traced back, in modern times, to William James,[44] who suggested that as sensory inputs proceed through the nervous system they generate functional states which serve as representations of external reality. James referred to this flow of activity as a "stream of consciousness". His assumption that consciousness is generated solely as a by-product of sensory input was for many years a most pervasive view of how the brain works. Indeed, most physiological thinking in the first two-thirds of this century was dominated by the idea that the nervous system is essentially organized as an extrinsic, open device.

An opposite point of view is that the nervous system is basically a closed device. Support for this proposal comes from electrophysiological studies indicating that the intrinsic membrane properties of neurons allow them to oscillate or resonate at different frequencies and that such intrinsic activity may play a fundamental role in CNS function.[61] We will argue that the insertion of such elements into complex synaptic networks allows the brain to generate dynamic oscillatory states which deeply influence the brain activity evoked by sensory stimuli.

Graham Brown[12] was among the first to propose that physiological states, such as locomotion, are products of oscillatory events intrinsic to the spinal cord. These oscillatory states are synaptically transferred to motor neurons, into a well-defined set of muscle movements, resulting in locomotion. Recent evidence indicates that intrinsic neuronal activity in the spinal cord is at the foundation of locomotion.[36] In this context, the function of sensory input in locomotion is to modulate the intrinsic oscillatory properties of the spinal cord network in order to adapt it to the irregularities of the terrain on which the animal moves. This view of spinal cord function may be extended to the brainstem and forebrain.

3.2.1. *Intrinsic oscillations in the brainstem and the forebrain*

Inferior olive. In structures such as the inferior olive (IO), electrophysiological studies have shown that the function of a neuronal system is not determined only by its connectivity, but is also directly related to the intrinsic membrane properties of the constitutive elements. Conductances which endow nerve cells with the ability to act as single-cell oscillators were first described in the IO.[58,59] Recent studies have demonstrated the importance of oscillations of IO neuronal ensembles in the accurate timing of motor neuron activity that is required to generate co-ordinated movements.[63]

Thalamus. Similar experiments in the thalamus were performed both under *in vitro* and *in vivo* conditions. The *in vitro* experiments characterized the electroresponsiveness and intrinsic membrane properties of thalamic cells.[42,43] The *in vivo* studies explored the functional consequences of the incorporation of these cells into complex synaptic circuits.[24,98-101]

A new view of thalamic operations emerged from these studies. Indeed, the thalamus appeared to be capable not only of controlling the transfer of sensory input to the cerebral cortex, but of expressing its own electrical activity, these two aspects of thalamic functions being intimately related.[103]

Other brain areas. Other systems capable of demonstrating autorhythmicity are discovered daily in studies of the mammalian nervous system. Examples of the richness of the intrinsic electrical activity of central neurons are found in the neocortex,[56] hypothalamus,[3] entorhinal cortex[4] and brainstem.[54]

3.2.2. *The brain as a closed system.* Several factors suggest that the brain is essentially a closed system. In addition, this system is capable of self-generated oscillatory activity which determines the functional events specified by the sensory stimuli. First, as stated above, only a minor part of the thalamocortical connectivity is devoted to the reception and transfer of sensory input (see section 3.1.1). Second, the number of cortical fibers projecting to the specific thalamic nuclei is larger than the number of fibers conveying the sensory information to the thalamus.[118] Thus, a large part of the thalamocortical connectivity is devoted to re-entrant[27] or to reverberating activity.[64] Third, the insertion of neurons with intrinsic oscillatory capabilities into this complex synaptic network allows the brain to generate global oscillatory states which shape the computational events evoked by sensory stimuli. In this context, functional states such as wakefulness (or REM sleep and other sleep stages) appear to be particular examples of the

multiple variations provided by the self-generated brain activity.

The neuropsychological evidence discussed in section 2.2 also supports this view of the brain as a closed system in which sensory input plays an extraordinarily important but, nevertheless, a mainly modulatory role. The cases of prosopagnosic patients dreaming of faceless characters indicate that the significance of sensory cues is largely dependent on their incorporation into larger cognitive entities and upon the functional state of the brain. In other words, sensory cues gain their significance by virtue of triggering a pre-existing disposition of the brain to be active in a particular way.

4. SPATIAL AND TEMPORAL MAPPING

A discussion of how the brain might use space and time to elaborate cognitive and perceptual constructs will be used in formulating a hypothesis to account for the difference between waking and REM sleep.

That general connectivities present at birth in humans are not fundamentally modified during normal maturation has been known from the inception of neurological research.[14,38] The localization of function in the brain began with the identification of a cortical speech center by Broca in 1861[11] and was followed by the discovery of point-to-point somatotopic maps in the motor and sensory cortices[85] in the thalamus[78,79] and more recently in the superior colliculus.[33,52,91]

A totally different type of functional geometry[84] has emerged in which that of temporal mapping, in addition to its spatial counterpart, are important variables. Temporal mapping has been far more difficult to understand and to study than spatial mapping since its study requires an understanding of natural computation and the importance of simultaneity in brain function.

4.1. *Synchronous activation in the face of spatial disparity*

The question of temporal simultaneity with spatial disparity had been addressed in studies of the discharge of electrical organs in teleosts. Maximal current density is achieved when the electroplaques at different distances from the command nucleus are activated synchronously.[9] The solution to the problem is elegant. The conductance time from the command nucleus to the individual electroplaques is uniform because the conduction velocity of the motor axons varies directly with the distance of the individual electroplaques from the motoneurons; axons of the closest electroplaques have the slowest conduction velocity.

Recent studies of the olivocerebellar system have shown that a similar mechanism is used to achieve isochronic activation of Purkinje cells following direct IO activation.[109] Similarly, the volley entering the optic nerve following activation of the entire ganglion cell population is close to synchronous.[94] Thus, activity from peripheral and centrally located ganglion cells reaches the optic nerve at the same time.[94]

4.2. *Forty-Hertz activity and cognitive conjunction*

Synchronous activation has recently been seen in the mammalian cerebral cortex. Visual stimulation with light bars of optimal dimensions, orientation and velocity may synchronously activate cells in a given column of the visual cortex.[26,34,35] Moreover, the components of a visual stimulus which relate to a singular cognitive object (such as a line in a visual field) produce coherent 40-Hz oscillations in regions of the cortex that may be separated by as much as 7 mm.[34,35] Also a high correlation coefficient has been found for 40-Hz oscillatory activity between related cortical columns.

These findings have inspired a number of theoretical papers with the view that temporal mapping is very important in nervous system function (e.g. Refs 26, 92). The central tenet can be summarized simply. Spatial mapping allows a limited number of possible representations. However, the addition of a second component (serving to form transient functional states by means of simultaneity) generates an indefinitely large number of functional states, as the categorization is accomplished by the conjunction of spatial and temporal mapping.

Magnetoencephalographic recordings performed in awake humans[57] have revealed the presence of continuous 40-Hz oscillations over the entire cortical mantle. The presentation of auditory stimuli having random frequency components produced a clear synchronization of this 40-Hz activity (Fig. 4). Phase comparison between the oscillatory activity recorded from different cortical regions revealed the presence of a close to 12-ms phase shift between the rostral and caudal pole of the brain (Fig. 5). What could be the mechanisms underlying this well-organized 40-Hz activity and what function might it serve?

The high level of organization displayed by this 40-Hz oscillation suggests that the candidate mechanisms must: (i) be able to produce and maintain a synchronized pattern of activity in very distant groups of neurons; and (ii) have extensive projections to the cerebral cortex. Furthermore, if this oscillatory activity were to play a significant role in providing a context for sensory events transmitted by specific thalamocortical systems, return projections from the cerebral cortex would be necessary.

Few prosencephalic structures have extensive reciprocal connections with the cerebral cortex: the thalamus[47] and the amygdala[5] probably constitute the best-known examples. It has already been hypothesized that the thalamus is involved in 40-Hz activity.[62] Specifically, it was proposed that sparsely spiny layer IV neurons which are able to generate intrinsic 40-Hz oscillations[56] would produce an inhibition-rebound sequence (probably sodium depen-

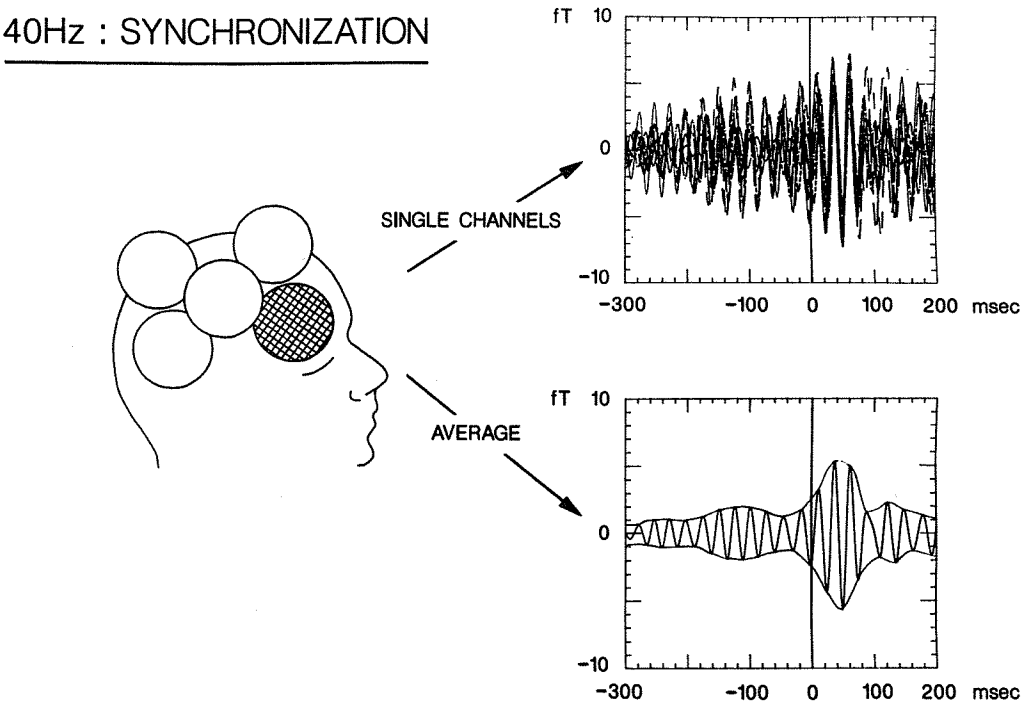

Fig. 4. Synchronization of human magnetic 40-Hz oscillatory activity during auditory processing within seven single channels of one probe placed over lower frontal areas. The graph on the top right indicates a superimposition of 40-Hz activities, time locked to the stimulus onset, recorded from the seven channels. The graph on the lower right indicates an average of the seven individual channels, demonstrating synchronization over a large area (around 25 cm^2). Reproduced from Llinás and Ribary.[57]

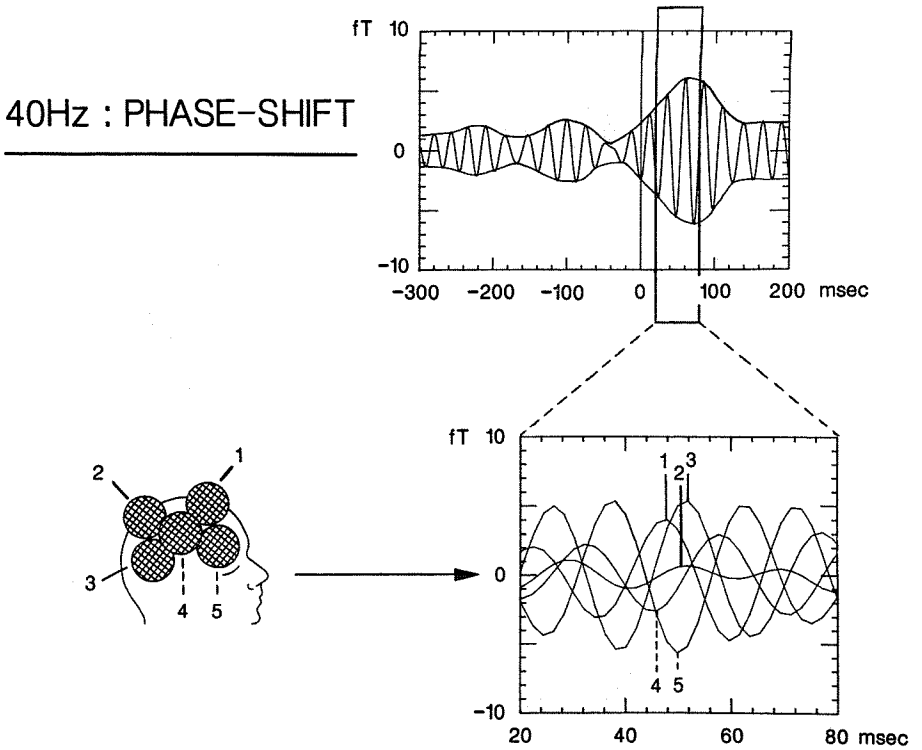

Fig. 5. Phase shift of human magnetic 40-Hz oscillatory activity during auditory processing. The time period between 20 and 80 ms after the onset of the auditory stimuli is enlarged in the lower panel. The lowest panel shows the superposition of averaged responses from all sensors in each of the five probe positions (hatched and numbered at left). Note the large, consistent phase shifts from region to region, indicating a continuous rostrocaudal phase shift over the hemisphere. Reproduced from Llinás and Ribary.[57]

dent) in thalamically projecting pyramidal neurons. These cells would then generate a 40-Hz inhibitory rebound oscillation in cells of the reticular thalamic nucleus (RE), a group of GABAergic neurons projecting to most relay nuclei of the thalamus.[45,108] More recently, it has been demonstrated that thalamic neurons *in vivo* can also oscillate intrinsically at the same frequency using a similar ionic mechanism.[96] Consequently, cortico-thalamo-cortical pathways could be led to resonant oscillation at 40 Hz (Fig. 6). According to this hypothesis, RE cells would be responsible for the synchronization of the 40-Hz oscillations in distant thalamic and cortical territories. Indeed, it has been shown that neighboring RE cells are linked by dendrodendritic and intranuclear axon collaterals.[23,120]

The amygdala may also play an important role in the generation of 40-Hz activity. Golgi and immunohistochemical studies indicate that, like the thalamus, most amygdaloid nuclei contain two populations of cells: projection cells and GABAergic interneurons.[71,81] In addition, the amygdala is endowed with a group of GABAergic cells,[81] the intercalated cells, which appear to play a role analogous to the RE nucleus in the thalamus: they are contacted by projection cell axon collaterals and seem to project within the amygdaloid nuclei.[75] However, in contrast with the thalamus, the projection cells have intranuclear recurrent collaterals which probably contact neighboring projection and local-circuit cells.[71] In addition, there is an important system of connections linking various amygdaloid nuclei.[2] Because projection cells are believed to use glutamate as a neurotransmitter,[17] these intra- and internuclear links could constitute a means to synchronize projection cells rapidly through excitatory connections. Such a mechanism seems more potent than the subtler influence produced by the aforementioned inhibitory rebound mechanism.[56]

Another reason to favor the amygdala as a candidate for the synchronization of the 40-Hz oscillations lies in the role it is believed to play in memory.[5,93] If we assume that a function of this 40-Hz activity is to maintain a general, continuous neuronal humming against which intra- or externally generated "irregularities" can stand out, the importance of a

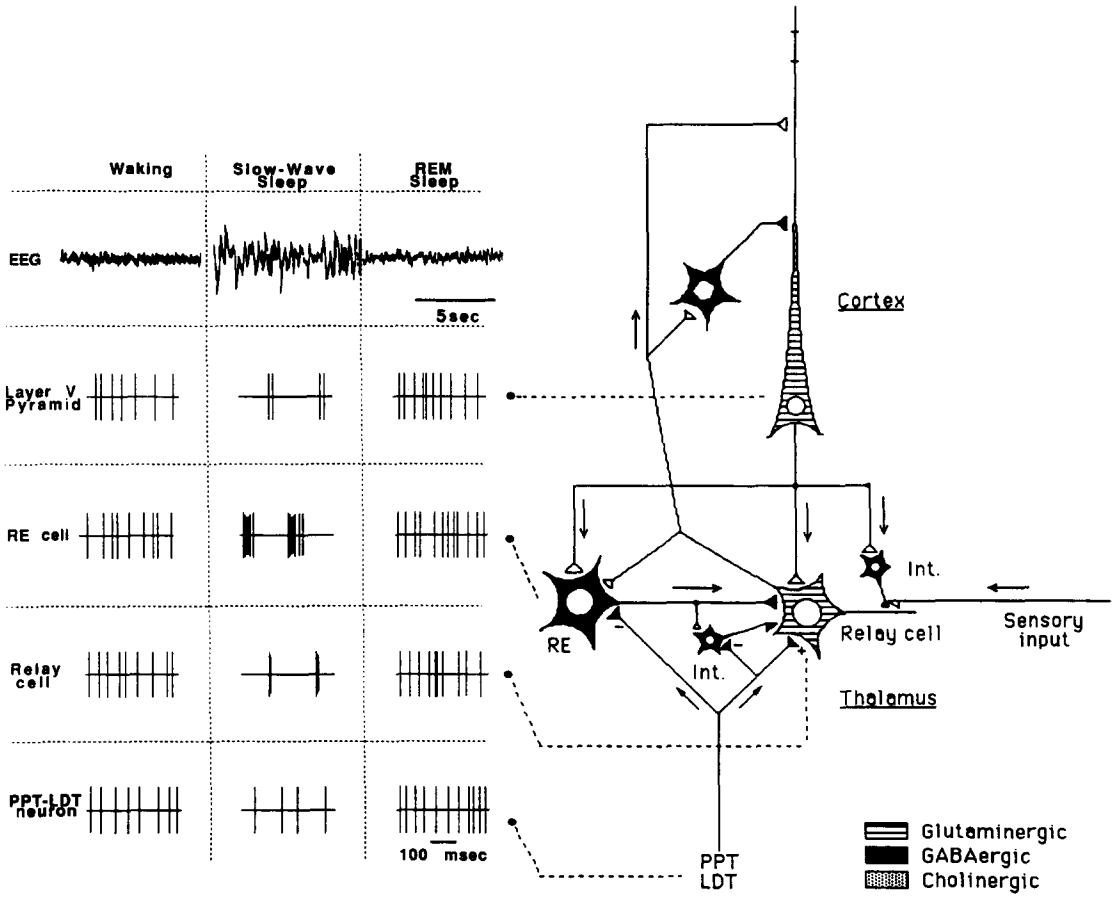

Fig. 6. Schematic diagram showing the interconnections of the basic cellular components of the thalamocortical system (right). The left panel illustrates simulated spike trains of these various cell types in waking, slow-wave sleep and REM sleep (first to third column, respectively). Note the sharp contrast between the activity of thalamic and cortical cells in slow-wave sleep and EEG-desynchronized states. The spike trains were derived from publications by Steriade *et al.*[97,103]

structure which could communicate this "irregularity" to other neuronal groups becomes self-evident. Indeed, through preferential intra-amygdaloid connections reinforced by previous experiences, neuronal groups which are relevant to the computations required by the irregularity in question could be led to oscillate in phase with each other, thereby maximizing the effectiveness of synaptic interactions between them.

However, a variety of neuronal types are endowed with intrinsic membrane properties which allow them to generate voltage-dependent 40-Hz oscillations, as in the cerebral cortex,[56] and thalamus.[96] These observations suggest that it might be a mistake to search for a single site for the generation and synchronization of this oscillation.

5. THE NATURE OF THE DIFFERENCES BETWEEN WAKEFULNESS AND RAPID EYE MOVEMENT SLEEP: A HYPOTHESIS

5.1. *Electrophysiological properties of the thalamocortical cells and circuit*

It is well known that the thalamus has two basic operating modes: a relay mode characterizing EEG-desynchronized states, such as waking and REM sleep; and an oscillatory mode characterizing EEG-synchronized states such as drowsiness and slow-wave sleep.[98] In the relay mode, thalamocortical cells show an increased synaptic responsiveness, tonic discharge and short periods of inhibition. In contrast, the oscillatory mode is characterized by a decreased ability to transfer incoming sensory inputs and by long-lasting periods of inhibition interrupted by burst discharges.

These two functional states arise from interactions between the intrinsic membrane properties of thalamocortical cells and the properties of the complex synaptic network in which they are embedded. Indeed, the firing mode of thalamocortical cells varies with their membrane potential.[42,43] From a depolarized level, a suprathreshold depolarizing pulse evokes a tonic discharge during the pulse, whereas from a hyperpolarized level it evokes a brief (30-ms), high-frequency (250–400-Hz) burst of fast sodium-dependent action potentials riding on a slow calcium-mediated spike.[42,43] Single-unit recordings throughout the dorsal thalamus in naturally sleeping cats[104] have shown that thalamocortical cells display a burst discharge in slow-wave sleep (when their membrane potential is relatively hyperpolarized), and a tonic discharge during EEG-desynchronization (when their membrane potential is relatively depolarized[39]).

5.2. *Brainstem influence on thalamic firing mode*

While the firing mode of thalamocortical cells is related to the expression of intrinsic membrane properties, the state-dependent fluctuations in membrane potential result from extrinsic synaptic influences. Morphological and electrophysiological data suggest that cholinergic cells of the pedunculopontine and laterodorsal tegmental nuclei are largely responsible for modulating the operating mode of thalamocortical cells during the transition from EEG-synchronized to EEG-desynchronized states.[105] *In vitro* studies in the dorsal LGN suggest that the cholinergic effects result from: (i) the hyperpolarization of somata of thalamic interneurons[67] and reticularis thalamic cells,[68] and (ii) the increased input resistance of thalamocortical cells[69,70] (by closing various types of potassium channels), thereby increasing their sensitivity to incoming synaptic volleys. These findings are consistent with the results of *in vivo* intracellular studies performed in a variety of thalamic nuclei.[18,19]

During REM sleep, the tonic discharge rate of most thalamically projecting pedunculopontine (PPT) and laterodorsal tegmental (LDT) neurons increases above waking levels (on average from 24 to 34 Hz[97]), thereby activating thalamocortical neurons. A large proportion of PPT and LDT neurons increase phasically their discharge rate before and during PGO waves.[107] These tonic and phasic increases in the discharge rate of PPT and LDT neurons during REM sleep could be largely responsible for the corresponding tonic and PGO-related phasic augmentations in firing displayed by thalamocortical cells during REM sleep.[103] Since most humans sleep in a relatively stimulation-free environment, the activity of thalamocortical neurons has no immediate external meaning. Therefore, although the ongoing neuronal events reflect normal thalamocortical interactions, the activity generated has a totally different nature than the same activity would have during the waking state.

5.3. *Hypothesis*

We propose that wakefulness and REM sleep are fundamentally the same type of functional state and that the main difference between them lies in what particular input is most prevalent. But both are most probably related to coherent thalamocortical activity. As mentioned above, recent results from EEG and magneto-encephalography studies suggest that during the waking state, there are organized 40-Hz oscillations throughout the cortex.[57] Sensory stimuli in this case will reset this intrinsic rhythmicity in a way similar to that described in single cells.[26,34,35] During REM sleep, the brain would be turned away from the sensory world because sensory stimuli would not be able to take hold of the consciousness-generating apparatus, i.e. the thalamocortical system.

Thus, during REM sleep, temporal associations which generate subjectivity do not coincide with the temporal maps, and only strong sensory inputs are capable of resetting such temporal conditions. In short, if the sensory input coming to the brain is not put in the context of thalamocortical reality by being correlated temporally with ongoing activity, the

stimulus does not exist as a functionally meaningful event.

5.4. *Consciousness and subjectivity are intrinsic properties of the brain*

The most fundamental conclusion to be drawn from the states described above is that consciousness is an intrinsic property arising from the expression of existing dispositions of the brain to be active in certain ways. It is a close kin to dreaming, where sensory input by constraining the intrinsic functional states specifies, rather than informs, the brain of those properties of external reality that are important for survival.

If this is the case, we may conclude that the perception of external reality is an *a priori* cognitive ability of the CNS developed and honed by the same evolutionary pressures that generated other biological specializations. Moreover, this implies that secondary qualities of our senses such as colors, identified smells, tastes and sounds, are inventions of our CNS which allow the brain to interact with the external world in a predictive manner.[60] The degree to which our perception of reality and "actual" reality overlap is inconsequential as long as the predictive properties of the computational states generated by the brain meet the requirements of successful interaction with the external world.

Indeed, that one person sees red as having the same subjective quality as another person is unimportant. The important variable is that of distinguishing red from green or blue, as colors are intrinsic functional events that do not necessarily correspond to any reality in the external world. Rather, they are a means for the brain to distinguish between rather small differences in surface spectral reflectances.

That consciousness is generated intrinsically is not difficult to understand when one considers the completeness of the sensory representations in our dreams or in the hallucinations of the mentally impaired or the pharmacologically challenged.

6. RAPID EYE MOVEMENT SLEEP, HALLUCINATIONS AND DAYDREAMING

The possible intrinsic nature of consciousness has serious implications for our understanding of psychiatric conditions characterized by illusional states in which the intrinsic view of reality and the emotional states generated by them are in discord with the perception of other individuals in the same social setting.

What would happen if the differences between intrinsically generated REM sleep and extrinsically modulated dream imagery were to go awry? According to the views expressed above, the thalamocortical system is ultimately responsible for the generation of consciousness. Thus, individuals who experience certain forms of hallucinatory states may be convinced that their hallucination indeed corresponds to events in the external world.

Finally, when one considers that attentiveness is selective, i.e. paying attention to certain external events while not paying attention to others, the lack of responsiveness of a person dreaming, hallucinating or deep in thought (daydreaming) becomes clear. In all three cases, intrinsically generated activity similar to that observed in REM is rampant and does not necessarily heed the vicissitudes of external reality.

The above statement addresses the two important issues of the nature of consciousness and the nature of attention. Of interest here is the fact that electrophysiological studies indicate that REM responsiveness resembles non-attentive responsiveness rather than responsiveness to attended stimuli (see section 2.1). Thus the possibility arises, as proposed above, that dreaming is basically a hyperattentive state in many ways similar to full wakefulness. If we assume this is the case, what follows?

7. CONSCIOUSNESS AS A THALAMOCORTICAL TEMPORALLY DEPENDENT CONJUNCTIVE STATE

As stated in the previous section, those aspects of brain function which form part of our consciousness must occur at the same time, most probably with 40-Hz activity recently described in animals and humans (see section 4.2). This may be taken to indicate that attentive states are those that fall within neuronal circuits displaying 40 Hz at any particular time. Indeed, recent experiments indicate the existence of coherent 40-Hz activity in the human brain which demonstrates a phase shift in the rostrocaudal direction with a conductance time near 12 ms (Figs 4, 5). This rostral-to-caudal 12-ms phase shift of 40-Hz activity suggests that synchronous events may be occurring within our head with a frequency close to 80 Hz.[57]

If we assume that the phase shift observed in these preliminary studies is related to the presence of simultaneity waves which scan our brain at 80 Hz, we can conclude that consciousness is not a continuous event. Rather, it is determined by the simultaneity of activity in the thalamocortical system, modulated by the brainstem, and fed when one is awake by sensory input, and when one is asleep by circuits that support memories.

7.1. *Thalamocortical activity as the functional basis for consciousness*

From the above, it follows that the major development in the evolution of the brain of higher primates, including man, is the enrichment of the corticothalamic system. This is supported by evolutionary studies if one considers the increase in corticalization in mammals. The increase in the surface area of the neocortex in man is approximately three times that of higher apes.[53]

How can this thalamo-cortico-thalamic functional state generate the unique experience we all recognize as existence of self or existence of the here and now? In principle, the activity generated via thalamocortical interactions may mimic the responsiveness generated during the waking state (i.e. reality-emulating states, such as hallucinations, may be generated). The implications of this proposal are of some consequence, for this means that if consciousness is a product of thalamocortical activity, *it is the dialogue between the thalamus and the cortex that generates subjectivity*.

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