Neurosci Bull February 1, 2012, 28(1): 25–38. http://www.neurosci.cn
DOI: 10.1007/s12264-012-1062-8

·Review·

No phylogeny without ontogeny – a comparative and developmental search for the sources of sleep-like neural and behavioral rhythms

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Abstract: A comprehensive review is presented of reported aspects and putative mechanisms of sleep-like motility rhythms throughout the animal kingdom. It is proposed that 'rapid eye movement (REM) sleep' be regarded as a special case of a distinct but much broader category of behavior, 'rapid body movement (RBM) sleep', defined by intrinsically-generated and apparently non-purposive movements. Such a classification completes a 2 × 2 matrix defined by the axes sleep *versus* waking and active *versus* quiet. Although 'paradoxical' arousal of forebrain electrical activity is restricted to warm-blooded vertebrates, we urge that juvenile or even infantile stages of development be investigated in cold-blooded animals, in view of the many reports of REM-like spontaneous motility (RBMs) in a wide range of species during sleep. The neurophysiological bases for motorically active sleep at the brainstem level and for slow-wave sleep in the forebrain appear to be remarkably similar, and to be subserved in both cases by a primitive diffuse mode of neuronal organization. Thus, the spontaneous synchronous burst discharges which are characteristics of the sleeping brain can be readily simulated even by highly unstructured neural network models. Neuromotor discharges during active sleep appear to reflect a hierarchy of simple relaxation oscillation mechanisms, spanning a wide range of spike-dependent relaxation times, whereas the periodic alternation of active and quiet sleep states more likely results from the entrainment of intrinsic cellular rhythms and/or from activity-dependent homeostatic changes in network excitability.

Keywords: sleep; cortical arousal; development; evolution; neural network models; brain rhythms; spontaneous motility; neuroplasticity

"Life is not so much a struggle for survival as it is a struggle to stay awake."

–Michel Jouvet, personal communication

1 Introduction

It is rapidly becoming a consensus view that all (or practically all) multi-cellular animals 'sleep' in some sense of the word[1-3]. To be precise, intermittent periods of reduced motility and sensitivity to environmental stimuli, together with an evoked or spontaneous abrupt transition to the active, alert state that we call 'waking' behavior, have been reported in forms as evolutionarily primitive as free-swimming coelenterates[4,5]. Since these relatively simple and often miniscule animals possess only a diffuse, poorly differentiated nervous system (nerve net and ring), a periodic resting state with sleep-like characteristics might thus appear to be a universal property of organized nervous tis-

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Article ID: 1673-7067(2012)01-0025-14
Received date: 2011-11-01; Accepted date: 2011-11-28

sue in general. In addition, a compensatory 'rebound' when sleep has been prevented for any length of time has been observed in all classes of invertebrates and vertebrates that have so far been investigated[6,7], as well as in isolated neural networks cultured *in vitro*[8,9]. It thus appears to be a 'default' state to which the organism relaxes when the energetically more-demanding behaviors that we recognize as "being awake" become inactivated. What we have come to regard as being in a sleeping state may therefore represent the continuation and elaboration of fundamental neurophysiological processes that lie at the very root of behavioral and functional evolution[10-13].

Before launching into the relevant empirical material, however, it will be useful to confront several semantic issues. It may ultimately be futile to start from the kind of sleep that we are familiar with from mature specimens of highly evolved species, and then to project this concept 'downwards' neurologically, ontogenetically or phylogenetically. Should we regard, for instance, the sleep-generating regions of the brain as being 'asleep' if they are artificially maintained in an isolated condition? And what about the body organs – muscles, glands, *etcetera*, that drastically change their functional state during sleep – are they 'sleeping' too? The same conundrum applies with special force to early stages of development and evolution, where the physiological basis for what looks like behavioral 'sleep'[14,15] can be quite different from what we would expect on the basis of studies in adult mammals[16,17]. One might therefore be forgiven the temptation to speak only of "sleep-like behavioral or neurophysiological states", leaving it to the personal preference of each reader to define at what point of functional complexity or material composition s/he chooses to apply the S-word[18].

Nevertheless, an objectively-grounded broad categorization seems possible as well as desirable. Thus, just as wakefulness which, despite its myriad mechanisms and behavioral manifestations, can be subdivided into motorically active and 'resting' states, quiet sleep has its complementary active state[19-21]. This fourth category of behavior was first noticed in 1953 and, more or less arbitrarily as it turned out, designated rapid-eye-movement (REM) sleep[22]. It has since been found, by comparing the neural mechanisms and substrates operative at different ontogenetic and phylogenetic levels, that in fact there exist a number of qualitatively and/or quantitatively different physiological sub-groups which can be subsumed under this name, such as "paradoxical, REM, rapid-body-movement (RBM), or sleep-with-jerks". The obvious natural classification at the highest level of phenomenological generality, therefore, is to include all cases of spontaneous, non-purposive, movements while in a clearly non-waking state as representing sub-categories of 'active sleep' in the broadest sense of the term[18] (Fig. 1).

This proposed terminological expansion does not entail a presumption that all such behavioral variants are necessarily homologous (i.e., having evolved from a common ancestor), although it would be premature to dismiss such a possibility. An alternative possibility, of course, is that, as in the well-known case of 'camera' eyes, several lines of evolution have converged onto a common solution to similar, as yet unknown, selective pressures. Indeed, the sufficient neurological bases for sleep-like behavior patterns appear to be so minimal that they could easily have emerged independently on several occasions[23,24]. This is not to say, of course, that neural mechanisms of greater complexity than a simple relaxation oscillation could not lie at the root of phenomenologically similar behaviors but,

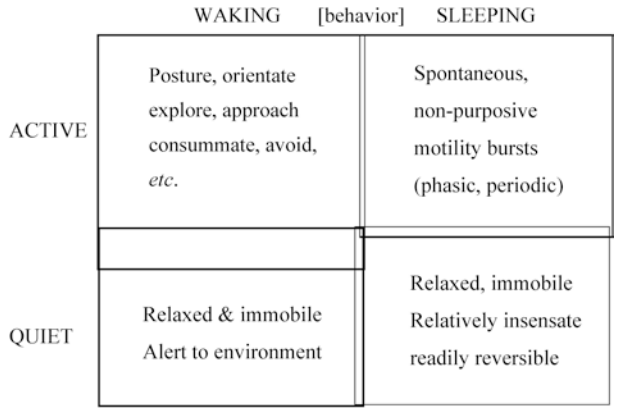

Fig. 1. 2 × 2 matrix representation of the four basic categories of normal animal behavior. The overlaps represent the possibility of occasional 'dissociated' states, normally as well as pathologically[25,26].

even then, nature might have proceeded in a stepwise manner rather than starting from a complicated basic design. A final conceivable explanation for the existence of strong similarities among sleep-like spontaneous motility patterns is that, as is the case with many parasites, originally complex mechanisms in certain highly-evolved organisms could have degenerated to a simpler state in mimicry of those characteristic for 'lower' forms of life.

In addition to terminological simplicity, conceptual clarity, and the short-circuiting of fruitless semantic debates, an advantage of considering the phenomenological and physiological differences among species or developmental stages to be variations on one of four basic themes (Fig. 1) would be to remind us of the possibility of homologies (and thus intimate phylogenetic relationships) among seemingly disparate neurophysiological mechanisms, and that even the simplest living 'model systems', regardless of their ancestry, might shed light on basic mechanisms operating in much more complex systems. In addition, puzzling borderline or 'dissociated' states of sleep and wakefulness involving pathological motor release[25,26], should become more easily recognizable as being derived from an overlap between two otherwise familiar broad behavioral categories.

2 Active sleep in adulthood

Roundworms, insects, crustaceans and molluscs have been the most studied invertebrates with regard to sleep[27-33], and in several of these suggestive indications have been reported in several of these of brief behavioral episodes corresponding to the activated phase of the cycle generally known as REM, or–but only in homeotherms (birds and mammals) after reaching a certain degree of maturation[19,20] as 'paradoxical' sleep (PS), i.e., the combination of an 'aroused', wake-like, electro-encephalogram (EEG) with a relatively motionless and unresponsive behavioral state. Neither has REM-like active sleep been reported unequivocally in fish, amphibians or reptiles, although some suggestive observations can be found in the literature[34,35]. Nor have recordings of spontaneous neuronal activity in the brainstem of turtles (an evolutionarily primitive reptile) detected any transient changes to a quasi-aroused firing pattern during quiet sleep[36], such as have been recorded in a primitive mammal (monotreme), the echidna, even in the absence (at least at some ambient temperatures[37]) of any overt motor manifestations of REM sleep[38].

Since the duckbill platypus, another monotreme, does show episodic muscular twitching during sleep in adulthood[39], active sleep in the behavioral sense could have been present in an ancestral reptile prior to divergence of the avian and mammalian lineages[40,41]. On the other hand, the failure of high-amplitude cortical slow-waves to change to a relatively desynchronized 'aroused' EEG pattern during REM sleep in either of the above-mentioned monotreme species[40] suggests that the evolution of PS *per se* (i.e., the mimicking of waking forebrain electrical activity during deep sleep) may have taken place independently in birds and mammals. High-amplitude cortical potentials ('sharp waves') appear throughout sleep in reptiles[42,43], so that a 'paradoxical' EEG arousal pattern may be a case of convergent avian and mammalian evolution secondary to the emergence of homeothermic temperature regulation[44]. This phylogenetic transformation of REM-like active sleep into 'PS' is brought about by the relatively late ontogenetic appearance[20] of a functional connection between a centralized 'sleep-motor' generator system, situated in the caudal brainstem[19,21,45], and the 'ascending reticular arousal system' that activates the cerebral hemispheres also during wakefulness[46,47].

Intriguingly, REM-like behavior has been noticed in adult cephalopod molluscs, taking the form of intermittent brief flashes of color against a background of behavioral sleep[48,49]. More recently, juvenile cuttlefish (Sepia) have been observed to show stereotyped spontaneous bursts of motility that strongly resemble active sleep rhythms (Corner, unpublished observation). These preliminary reports urgently need to be followed up, since verification would provide the first unequivocal example of an active-sleep characteristic persisting at least partway into adulthood in an invertebrate species, perhaps in consequence of their exceptionally well-developed central nervous system[50]. This convergence would be all the more striking if it turns out

that generalized motor inhibition, driven by a neurologically circumscribed control system (a core feature of active sleep in mature mammals[21,51]) also takes place at such times in cephalopods. Distinct bioelectrical (EEG) changes from the waking pattern have been reported in quiescent octopi, although they do not take the form of vertebrate-like sequences of large-amplitude slow-wave complexes[52]. Insects, too, intermittently display sleep-like neuromotor activity. Rhythmic fluctuations of neuronal spiking within the slow 'delta' frequency band (0.4–1.2 Hz), for instance, have been reported in sleeping honey bees, and these are sometimes either accompanied or interrupted by minute-long trains of spontaneous antennal twitching[53]. These movements have a clearly 'phasic' character, consisting of brief bursts at what appear from the published records to be 5- to 10-s intervals on the average.

Cockroaches show short-lasting bursts of isolated antenna movements that are especially frequent during prolonged periods of immobility and reduced responsiveness[54]. Locust antennal motoneurons show irregular ongoing spontaneous firing throughout periods of nocturnal immobility, but also undergo periods of several minutes during which peaks of intensified firing lasting only a few seconds – and sometimes accompanied by short bursts of overt movements – can occur fairly regularly at ~15- to 20-s intervals[55]. Fruit flies display spontaneous movements not only during behavioral wakefulness but also during states of elevated arousal threshold in which brain electrical activity has a closer resemblance to that measured during quiet sleep than during active wakefulness[56]. In adult scorpions, another class of arthropod, brief periods (seldom longer than 1–2 min) of spontaneous twitching of the tail or extremities have been noticed during behavioral quiescence, and their incidence 'rebounds' to a higher level for a few days following several hours of rest deprivation[57]. Even flatworms, the most primitive bilaterally symmetrical animals, exhibit brief episodes of spontaneous neuromotor activity during prolonged quiescent periods[58] as well as, from time to time, 1- to 2-s bursts of neuronal activity at intervals of several seconds[59]. Should 'paradoxical' changes to quasi-waking neuronal activity, concurrent with muscular atonia and/or bursts of twitching, be found to occur during sleep in any of these animals, one would have to acknowledge the convergent evolution of a fully differentiated form of PS.

Since mammalian active sleep characteristically begins at a very high level, which by adulthood has declined to a species-variable low percentage of the total sleep time[19,20], physiological studies in this field of research need to be carried out also in immature specimens. For the same reason, species that show only quiet sleep in adulthood might, by means of appropriate neurological and behavioral experiments, be found to exhibit active (quasi-REM) sleep after all – with or without accompanying PS if early enough stages of development are investigated[61]. Adult crayfish brains have been reported to generate increased 'delta' EEG power during sleep[30] so that, in any case, a convergent evolution to some sort of 'slow-wave' sleep in crustaceans might be an unavoidable conclusion regardless of the presence or absence of active sleep in this group. Intermittent "respiratory and cardiovascular instability" has been claimed to be a universal characteristic of sleeping fish, amphibians and reptiles[34,35], and this suggestive indication for the persistence into adulthood of REM-like vestiges in all vertebrates could be put on a firmer footing if immature animals are investigated[60]. The neglect of ontogenetic studies of sleep in cold-blooded animals in general therefore renders inconclusive the mostly negative findings to date concerning the possible existence of active sleep early in phylogeny.

3 Neurophysiological basis of active sleep

The defining characteristic of 'active' sleep in all its forms is the periodic appearance of trains of brief ('phasic') bursts of chaotic, non-purposive twitching of the body musculature (Fig. 1), of which movements of the eyes just happen to be the first aspects to have attracted attention[22,47]. These spontaneous motility bursts are triggered from a 'pacemaker' center in the upper hindbrain[19,21,45,51] from where synchronized phasic neuronal discharges propagate throughout the rest of the central nervous system, including the forebrain in the form of 'ponto-geniculo-

occipital cortex (PGO)' and hippocampal 'theta' wave bursts[16,17]. Since decerebrate animals continue to show periodicities on the order of minutes in burst frequency as well as more prolonged periods of quiescence[19,45], it may be concluded that the entire hierarchy of vertebrate sleep rhythms – 'burst/pause' (seconds), 'phasic/tonic' (minutes), and 'activity/rest' (~hourly) – is a manifestation of an integrated caudal brainstem mechanism. Even the isolated frog medulla oblongata is characterized by spontaneous neuronal firing which, in most preparations, is clearly phasic in nature: variable trains of sometimes highly-regular short bursts appear periodically at intervals of up to 5 min[64]. Spontaneous muscle twitching is also rhythmically driven, in a region-specific manner, when innervated by explanted brainstem or spinal cord – but not forebrain – fragments taken from full-grown axolotls, a neotenic urodele species[65], and even from the neural plate of anurans[66].

The fact that periodically-modulated neuromotor bursts are generated spontaneously on a wide range of time-scales by rodent caudal brainstem networks cultured *in vitro*[62,63] implies that the underlying mechanisms need not be particularly complex. This supposition is strengthened by the strikingly similar spontaneous behavior exhibited by sessile coelenterates such as the hydra, in which not much more than a primitive nerve net is present throughout life[5]. Apparently, once having settled down, such animals do not require anything resembling 'waking' behavior in order to survive, but simply capture whatever floats by as they intermittently briefly stir up the water by means of phasic generalized contractions of the tentacles[10]. Freely motile coelenterates (cnidarians), on the other hand, can show environmentally-oriented swimming, including active predation[4], which could mean that something akin to wakefulness (in the strictly behavioral sense, see Fig. 1) appeared exceedingly early in the course of evolution. Nothing is currently known about either the ontogeny or the neurophysiology underlying this striking departure from the putative primordial oscillatory 'sleep' pattern[8,10]. Although these rudimentary organisms apparently undergo long episodes of behaviorally quiet sleep[4], no spontaneous twitching or other manifestations of 'REM'-like behavior during such periods have been reported.

4 Cortical activity patterns during sleep

Cerebral delta waves during quiet sleep in birds and mammals bear an unexpected similarity to the 'PGO' waves of the brainstem. During intermediate stages of non-REM sleep in humans, for instance, they occur in the form of discrete stereotyped waveforms ('K-complexes')[67] or brief trains of delta waves ('cyclic alternating pattern')[68] at intervals of several seconds, which are frequency-modulated in a 20- to 30-s cycle[69] and are accompanied by synchronous bursts of neuronal firing[17,20,67]. Only in deep slow-wave sleep do these appear superficially to adopt a continuous delta wave-like character, but at higher resolution they can be seen to retain their discrete characteristic morphology ('basic waveform') and the associated burst-pause discharges[20,23]. Human sleep-state hypnograms, moreover, exhibit frequent shifts at intervals of 10 min or less in the incidence of delta waves during quiet sleep[70]. Experiments with neuronally isolated cortical islands and organotypic cultures have revealed that under such conditions cerebral networks, just as their brainstem counterparts, typically generate variable short bursts of spikes ('UP-states') at intervals of several seconds or longer, interspersed with quiescent 'DOWN-states'[71-73]. Again as in the case of the brainstem REM-generating network, the incidence of such bursts is modulated in a hierarchical fashion, involving periodicities of several minutes and sometimes considerably longer[9,74].

Since these basic features are preserved in dissociated cortical cell cultures (Fig. 2), the columnar architecture of the mammalian neocortex – a structural specialization evolved to meet the needs of information processing during wakefulness – is evidently not a contributing factor in their generation. Underlying its columnar organization, then, cortical excitatory connections appear to retain a diffuse quasi-random reticular character[75,76], and this is presumably what underlies the sleep-like activity patterns seen whenever the cerebral cortex is permitted to return to its primordial 'default' mode of function[9,23]. In the intact avian or mammalian cerebral hemispheres during sleep,

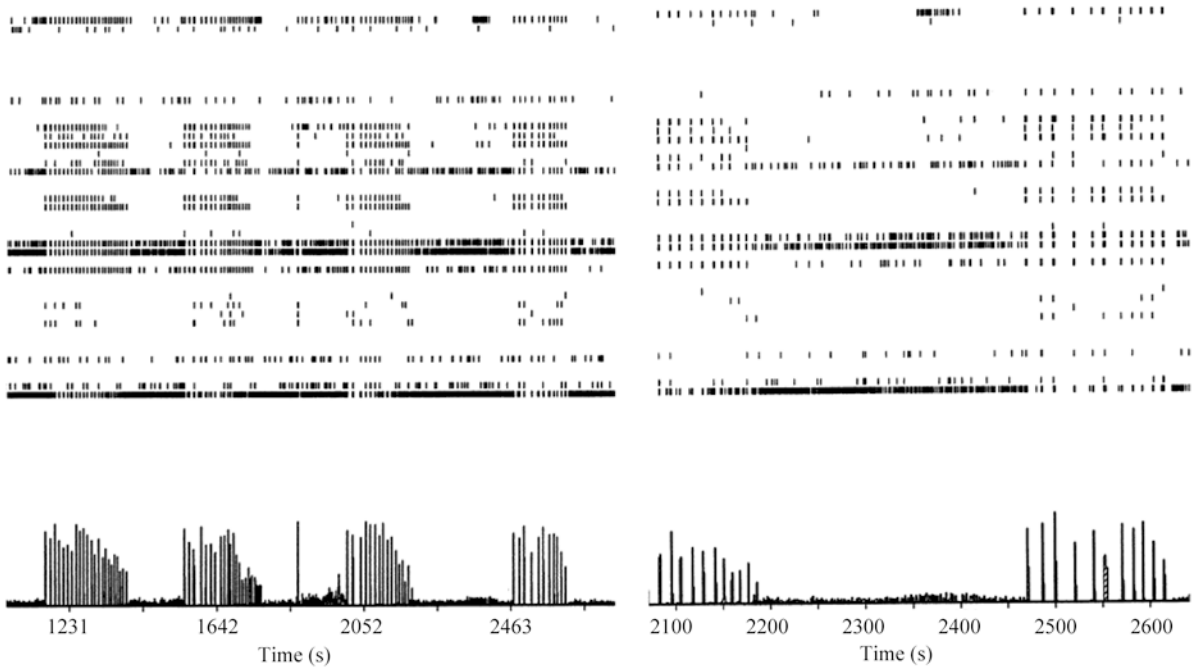

Fig. 2. Reaggregated rat neocortex cell culture (3 weeks *in vitro*) on a multi-electrode recording plate, showing a continuously regular (~8 min) cycle between 'phasic' and 'tonic' spontaneous firing over a period of at least 3 h (van Pelt and Corner, unpublished observations). Upper: time stamps of events (action potentials) recorded at 64 locations on a multi-electrode matrix; Lower: tachograms of the relative number of events occurring in consecutive 1-s time bins.

synchronized firing and the associated summated synaptic potentials are organized into a matrix of more or less discrete netlets such that differential bipolar EEG recordings do not generally cancel out, but rather give rise to a picture that is essentially identical to EEGs recorded from a single site[68,77]. There is sufficient interaction, probably mediated to some extent via extracellular field potentials[78,79] in addition to synaptic activation, that coherent slow-wave activity is possible over a considerable distance[80]. The spatial dimensions and stability of such islands of relatively synchronous neural activity, as well as their developmental origins, are a fundamental challenge for future research[81-83]. In view of the fact that inhibitory synaptogenesis and function are enhanced by spontaneous burst discharges during cortical maturation[9,84], it follows that competing strong foci of excitation could determine their respective boundaries in an activity-dependent manner.

This fluctuating poly-rhythmic pattern of bursts of electrical activity can be maintained even when the cerebral cortex (in mammals; pallium in birds[85]) or the entire forebrain is functionally deafferented from the rest of the brain[20,23,86,87]. Intermittent unbroken trains of slow-wave bursts at a given location must therefore result from interactions among cerebral nerve nets so that, in addition to their own intrinsic activity, they are continuously being re-excited in a non-epileptiform manner by excitation propagating from adjacent and distant sources[80,81,88]. Indeed, in organotypic bilateral neocortical 'mega-cultures', bursts of activity in all regions last considerably longer and occur more frequently than those in isolated small fragments[9,72]. The chief evolutionary difference between the neocortex (or neo-pallium) and the hindbrain, as well as between the neocortex and the archicortex (i.e., hippocampus) or the 'general' cortex of reptiles[86], thus appears, as far as quiet (slow-wave) sleep is concerned, to lie mainly in the considerably expanded size of the former structure in the phylogenetically most recent mammals, such as primates[85].

We arrive, then, at a picture of the intact sleeping

brain wherein, at both the rostral and the caudal ends of the neuraxis, primordial mechanisms are operating which may have persisted throughout the eons since neuronal networks first appeared in multicellular organisms, and which resurface as a unit whenever the evolutionary constraints imposed during wakefulness are removed[10]. At such times the forebrain and hindbrain largely go their separate rhythmic ways, interacting only insofar as the latter (relatively late in both ontogeny and phylogeny) becomes capable of activating ascending arousal mechanisms – and thus 'desynchronizing' the ongoing forebrain neuronal firing patterns – without arousing the organism from its sleeping state. This change from 'phasic' to 'tonic' firing is basically a matter of cholinergic receptor stimulation causing an attenuation of the activity-dependent outward membrane currents and synaptic depression that terminate stereotyped burst discharges[71,89,90], while at the same time weakening local excitatory connectivity so as to impede focal activation from initiating a propagating chain reaction[91-93]. In a cholinergically 'aroused' neocortical network, widespread stereotyped bursts thus become transformed to a variable extent into irregular, longer-lasting and less tightly synchronized spike trains[94] (Figs. 3, 4).

5 Reduced neuronal networks can display sleep-like activity

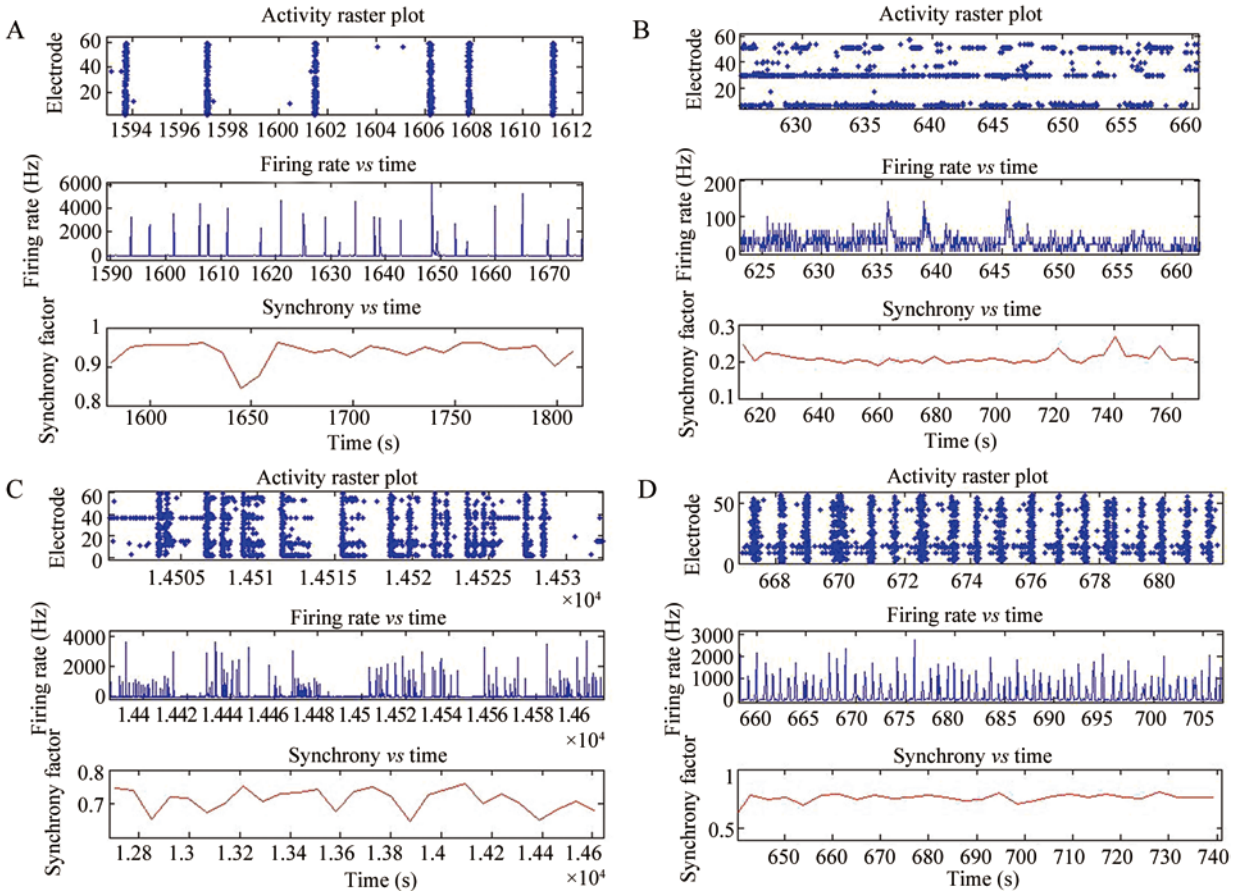

Fig. 3. Spontaneous action potentials in dissociated rat neocortical neurons cultured on a multi-electrode plate, showing the change from brief synchronous discharges (A) ~3 min after start of control recording: 2, 10 and 50 s/div from top to bottom; to a chaotic, desynchronized, firing pattern upon cholinomimetic activation (B) after 10 min in carbachol: 5, 5 and 20 s/div; with a partial restoration of synchronized bursting starting after a few hours of carbachol exposure (C) after ~4 h in carbachol: 5, 20 and 200 s/div; and enhanced bursting after return to control medium (D) ~1 h post-carbachol: 2, 5 and 10 s/div (Corner, unpublished observations).

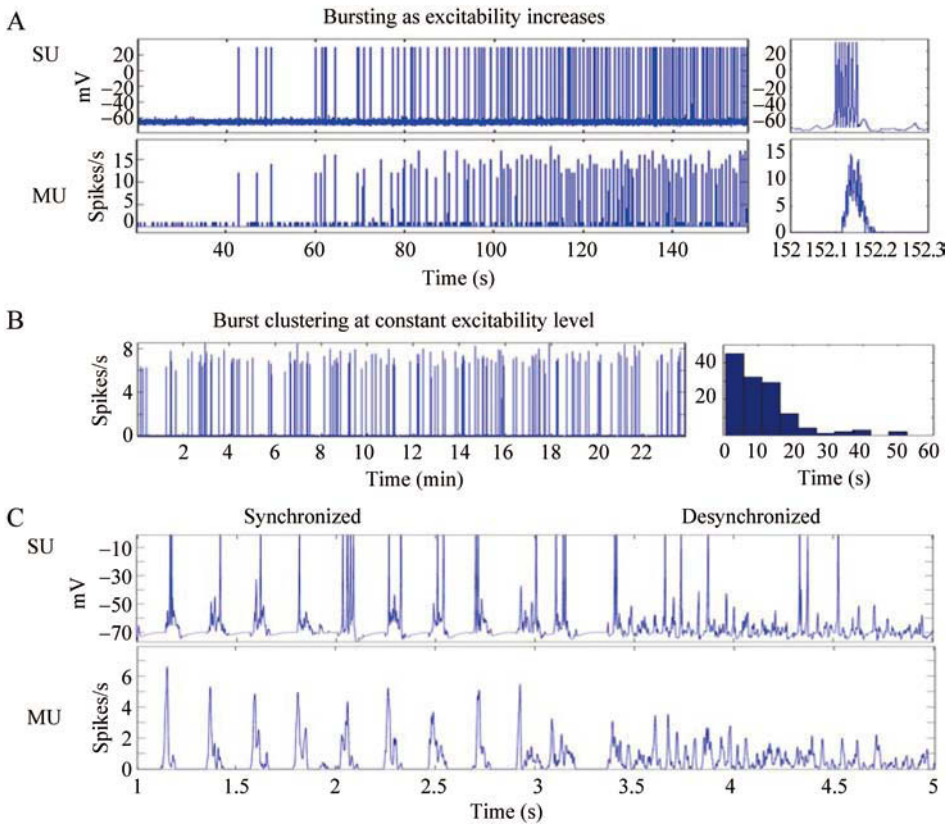

Fig. 4. A: Relaxation oscillation model simulating the intrinsic homeostatic acceleration of stereotyped 'phasic' network burst discharges, against a steady background of sporadic local neuronal spiking, as excitatory synaptic interactions are selectively enhanced; the two panels show a single neuron (intracellular: SU) and local regional group discharges (MU) [N.B., in a cultured rodent brainstem network this development would take place over ~2 days rather than 2 min]. Right-hand panel: expanded 300-ms sweep showing an individual network burst. B: A stretch of ~15 min of spontaneous bursting activity at a steady intermediate excitability level and a suprathreshold intensity of miniature synaptic potentials, illustrating the tendency for clusters of short bursts to form irregular 'super-clusters' on a scale of several minutes. Right-hand panel: histogram of intervals between successive bursts. C: Simulation of the abrupt transformation of synchronized 'phasic' into desynchronized 'tonic' firing when activity-dependent spike frequency adaptation is suppressed (van der Togt, unpublished observations).

So what are the essential features of the putative primitive circuitry which could lie at the root of behavioral and neurophysiological evolution? Tissue culture 'model systems' have demonstrated that excitatory synaptic drive exists within cerebral cortical networks in the form of widespread stochastic leakage of neurotransmitter[90,95], independent of sodium action potentials and possibly facilitated by endogenous 'pacemaker' potentials[97], thus eliciting miniature post-synaptic potentials in target neurons that can sum up to reach the threshold for triggering an action potential[69,90,96] (Fig. 4). This leads to 'avalanches' of clustered spike events following a power law (i.e., a log-linear decline in the incidence of 'events' of progressively greater length) that falls to a negligible value within 15–20 ms[98,99]. The resulting chaotic background of single and grouped action potentials is a necessary but not sufficient condition for the spontaneous occurrence of stereotyped bursts of generalized network firing: they can be triggered only when the effective density of excitatory interactions attains a critical level at which, emanating from an active focus, a chain reaction of reverberatory neuronal firing can spread over at least part of the network[90,100,101]. In a large enough network with multiple active foci, inhibitory synaptic opposition to the spread of excitatory discharg-

es[102-104] results in the formation of interacting shifting 'small-world' neuronal groupings[72,83,105] rather than a single tightly-integrated mega-network.

Thus, stereotyped all-or-none network bursts appear spontaneously in development only following the appearance of stochastic 'background' spiking, but not before the threshold for evoking a spreading all-or-none burst by applied local stimulation of the network has declined from its original high level[62,63]. Spontaneous inhibitory miniature post-synaptic potentials help to regulate this threshold[103,106], while feed-forward synaptic inhibition limits the recruitment of neurons into the bursts without qualitatively altering the pattern of activity[62,63,102]. Activity-dependent refractoriness (or 'spike frequency adaptation') (Fig. 4) then causes the recurrent network discharges to either terminate stereotypically within several hundred milliseconds[23,96,107,108] or to recur in rapid succession for up to a second or two[8,67,109], not to be triggered again for a variable period (from a few seconds to several minutes) depending on the degree of activity-dependent depression, the kinetics of its 'relaxation' to the baseline value, and the mean level of ongoing background firing[59,62,110,111]. An especially remarkable example of this relaxation oscillation mechanism is furnished by microculture experiments in which even one or two isolated excitatory neurons, by forming 'autapses', so extensively innervate themselves that they repetitively generate spike bursts resembling those recorded from neurons embedded within large networks[112]. The mechanisms underlying intrinsic bioelectric activity patterns at different levels of neuronal organization are summarized in Table 1.

The small number of parameters in such a network means that its behavior can be readily simulated by a simple computer model. A rising level of sporadic spontaneous activity in a weakly connected, purely excitatory, network leads to a widespread stochastic background of action potential discharges which, at a critical net excitatory connectivity level[71,95] (Fig. 4), triggers repetitive bursts of runaway firing which terminate due to the combined effect of spike-dependent membrane adaptation and synaptic

Table 1. Mechanisms underlying spontaneous neuronal discharges at different levels of organization

Levels of organization	Mechanisms
Cellular	(a) Stochastic 'leakage' of excitatory synaptic transmitters → irregular miniature membrane potential fluctuations, occasionally reaching threshold for triggering an action potential; (b) Inward calcium ion fluxes may trigger brief (a few milliseconds) intrinsic spike bursts.
Intercellular	Supra-threshold driving of downstream neurons by intrinsically bursting neurons → 'avalanches' of background firing following a declining power-law distribution, ranging from highly frequent single spikes to increasingly rare clusters of up to ~20 ms in duration.
'Small world' network	Exceptionally active neurons form foci for triggering all-or-none chain reactions of recurrent, spreading, burst discharges which are spatially constrained to a few millimeters by feed-forward inhibition, and which typically terminate within several hundred milliseconds due to a minute-long activity-dependent depression of synaptic and membrane excitability.
Intergroup	Except under 'epileptogenic' conditions, synaptic inhibition prevents spontaneously bursting netlets within a given brain structure from discharging in strict synchrony, but without preventing a certain degree of coherence among their respective bursts.
Inter-regional	Spontaneously active brain regions interact with one another to generate the dynamic architecture characteristic of sleep, such as thalamo-cortical 'spindle' bursts and reciprocal epochs of 'phasic' activity in the reticular formation and neocortex.

depression[82,113]. The incidence of such bursts thus reflects a complex interaction among (i) the two refractory mechanisms, (ii) local levels of background firing and (iii) the distributed excitability spectrum of the network. Inhibitory neurons are crucially important in this last aspect, and the ratio of inhibitory to excitatory synaptic drive controls not only the burst threshold at a given site within the network, but also the number of recruited neurons and thus the burst's recorded amplitude and intensity, as the chain reaction of spiking activity spreads out from its source (Table 1).

A striking aspect of the active phase of the sleep cycle is that it is itself periodic, with increased clustering of phasic discharges occurring every few minutes[10,16,17,20]. Since post-burst refractoriness can last for a minute or more[58,62,82,110], whereas interburst intervals are usually much shorter than this, quiescent epochs during active sleep (tonic REM) could result from a buildup of refractoriness in the course of successive bursts of neuronal firing (phasic REM), eventually leading to a distinct set of relatively prolonged silent periods. Being considerably longer than the reported post-burst relaxation times, the circa-hourly alternation between active and quiet sleep, on the other hand, is likely to involve considerably slower oscillatory mechanisms. The entrainment of intrinsic cellular biochemical oscillations in this frequency range[114] is one possibility, while another probable contributing factor is the homeostatic buildup of network excitability during periods of overall reduction or strong desynchronization of neuronal firing[6-9,18,84,115,116]. Such 'desynchronization' of spontaneous neuronal firing can be achieved simply by simultaneously weakening activity-dependent neuronal refractoriness and short-distance excitatory interactions[90-92], thus mimicking the effect of cholinergic arousal in suppressing intrinsic cortical burst synchronization and stereotypy (Figs. 3, 4).

A model such as this can thus be regarded (at least to a first approximation, since slower fluctuations of burst parameters have not been included) as essentially simulating a 'coelenteroid' or early embryonic nerve net[4,5,10,117,118]. The simplicity and ubiquity of relaxation oscillation mechanisms for generating sleep-like bursts of activity indicate that, despite the myriad differences in biochemical, cytological and biophysical details, there could conceivably have been a high degree of convergent physiological evolution with subsequent conservation over the eons. The concatenation of a variable number of tightly connected neuronal sub-groups would constitute, on widely differing anatomical scales, a pervasive set of primitive underlying neuronal systems capable of functioning independently of the organizational constraints imposed upon them during wakefulness by the differentiated structure of which they are part[76,119]. Indeed, recent evidence suggests that such constraints are capable of being locally suspended to allow occurrence of sleep-like physiological activity in restricted brain areas even during global waking[120,121]. This would mean that sleep on the whole is a 'default' mode to which organisms revert whenever waking behavior can afford to be suspended. It survives to the present day because it presumably conferred a survival advantage at some time in the distant past, and either there was never any subsequent evolutionary pressure to eliminate it or it later assumed some useful function. Given the neurological simplicity of this putative 'universal sleep circuitry', most of the complexity of sleep mechanisms in such highly evolved animals as homeothermic vertebrates is more likely to be concerned with regulating the environmental and physiological conditions under which this default state is released from inhibition than with dictating its overt manifestations.

"It's not enough to use the brain of your experimental animal, it's also necessary to use your own."

–Michel Jouvet

(pioneering 'somnophysiologist' *extra-ordinaire*, to whom this review is admiringly and gratefully dedicated)

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