·Review·

Call it sleep – what animals without backbones can tell us about the phylogeny of intrinsically generated neuromotor rhythms during early development

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A comprehensive overview is presented of the literature dealing with the development of sleep-like motility and neuronal activity patterns in non-vertebrate animals. It has been established that spontaneous, periodically modulated, neurogenic bursts of movement appear to be a universal feature of prenatal behavior. New empirical data are presented showing that such 'seismic sleep' or 'rapid-body-movement' bursts in cuttlefish persist for some time after birth. Extensive ontogenetic research in both vertebrates and non-vertebrates is thus essential before current hypotheses about the phylogeny of motorically active sleep-like states can be taken seriously.

Keywords: sleep phylogeny; behavior development; spontaneous motility; neuronal networks; cuttlefish

"In biological as well as physical-chemical sciences, one should reduce phenomena to as simple as possible experimental conditions": Claude Bernard, 'Un Introduction á l'Étude de la Medicine Expérimentale', Paris 1865.

Introduction

An earlier essay[1] charted the occurrence of sleep-like behavioral manifestations in species ranging from cnidarians to vertebrates. Although the mature, 'paradoxically' aroused, form of rapid-eye-movement (REM) sleep[2-6] appears to have evolved independently in birds and mammals[7-9], many cold-blooded animals — including a wide range of invertebrate species — are also on record as showing intermittent spontaneous, not evidently purposeful, muscular contractions while in an arguably sleep-like state[1]. The present essay pursues this enquiry into the earliest stages of development, and reviews the evidence that motorically active sleep (MAS), far from being a phylogenetic 'end point', may in fact be a relic of a primordial

physiological state that appeared at or close to the onset of neurally-generated behavior in multi-cellular animals[10,11].

Spontaneous Motility During Early Development in Invertebrates

Repetitive bursts of spontaneous body movements have been reported to occur embryonically in a wide spectrum of invertebrate species. These invariably consist of short episodes of non-purposive localized or generalized twitching, often at intervals of only a few seconds, the frequency of which is modulated by a nested hierarchy of cycles ranging from 'infra-slow' (i.e., every minute or so) to 'circa-horalian', i.e., approximately hourly[1,10,11]. In what might be the phylogenetically earliest reported behavior suggestive of what could be called 'seismic' sleep (*sommeil sismique*)[4], 'sleep-with-jerks'[6,12] or, more generally, just (motorically) 'active sleep' (Fig. 1), the nematode worm *Coenorhabitis elegans* displays trains of brief spontaneous motility bursts throughout larval development which alternate with movement-free

WAKING [behavior] SLEEPING

ACTIVE	Posture, orientate explore, approach consummate, avoid	Spontaneous, non-purposive motility bursts (phasic, periodic)
	[etc.]	Relaxed, immobile,
QUIET	Relaxed & immobile, alert to environment	relativey insensate, readily reversible

Fig. 1. A matrix representation of the four basic categories of normal animal behavior (adapted from Corner et al., Neurosci Bull, 2012[1]). The overlaps represent the possibility of occurrence of 'dissociated' states, normal as well as pathological[14].

episodes in a cycle of ~30 s–1 min[13]. This 'phasic' activity pattern apparently occurs about twice per day during hour-long 'lethargic' states which meet all of the currently-accepted general criteria for being asleep[7].

Leech embryos (Hirudinae, a class of annelids) spontaneously display variable "sets of pre-swimming contractions" (on the average at ~5-s intervals) which gradually mature into continuous swimming movements having a qualitatively different–putative waking–character[15,16]. Sessile cnidarians such as *Hydra*, on the other hand, seem to show nothing but stereotyped bursts of generalized neuromotor activity every few seconds for many minutes at a time[10,11], so that a state of quasi-wakefulness might not have been needed for survival at the very earliest stages of neural evolution.

Ascidians (Tunicates)

The larva of the 'sea squirt', *Ciona intestinalis* (a primitive chordate rather than a true invertebrate), displays episodic irregular movements after hatching, with 5–10 s bursts of swimming occurring 3 or 4 times per minute along with shorter bursts of rapid 'tail-flicks', in trains that repeat themselves at intervals of ~15–20 min[17]. Since the larva settles and attaches to the bottom within a few hours of hatching, however, any subsequent sleep-like states would be exceedingly difficult to demonstrate. The tunicate *Halocynthia roretzi* shows a discontinuous pattern of embryonic neuromotor electrical discharges that are associated with either

single twitches or "sustained rhythmic contractions", the latter consisting of concatenations of unitary twitches at <1-s intervals in recurrent bursts lasting up to 5 s[18]. These phasic spontaneous movements occur sporadically throughout the recording, either in isolation or at intervals of only a few seconds, but are mostly concentrated within peaks of activity at ~1–2 min intervals. It is noteworthy that newly-hatched larvae continue to exhibit essentially the same pattern of behavior, which thus strikingly mimics early spontaneous motility patterns in amphibians and other vertebrates[10,11,19].

Crustaceans (A Class of Arthropods)

Although viscero-motor activity might not seem to qualify as 'behavior' in the strictest sense, it bears mentioning at this point that spontaneous phasic discharges have been reported to typify neuronal activity in the embryonic lobster stomatogastric ganglion, taking the form of a highly regular train of 0.5–1 s bursts every 2–3 s[20]. A subset of neurons displays irregular interruptions or slowing of this primitive rhythm, with forward reference to the stable slower cycle that characterizes the behavior of these cells in adulthood[21,22]. The existence of phasic discharges such as these in an invertebrate visceral ganglion is in keeping with the proposition that this pattern of spontaneous activity is a well-nigh universal property of primitive neural networks, subserving smooth muscle visceromotor as well as striated muscle somatic motor systems, and is based upon a small number of identified basic mechanisms[1,10,23,24].

Insects (Another Class of Arthropods)

Spontaneous bursting also characterizes neurogenic movements in fruit-fly embryos, at first consisting of infrequent localized twitches of the body wall, which gradually become transformed into short bursts of increasingly well-coordinated interneuron-driven contractions involving several segments[25]. From the outset, bursts occur at ~1–10-s intervals independent of sensory input and inhibitory feedback, in trains lasting 2–3 min on average, which repeat themselves 4 or 5 times/h[26]. Just before eclosion (the insect equivalent of 'hatching') these bursts give way to sustained forward crawling and feeding movements which then continue as the larvae search for food while in a primitive 'quasi-waking' state. A paradoxical "intermediate state between sleep and waking", characterized (as in mammals and birds during REM sleep) by a waking level of tonic neuronal firing together with a reduced incidence of spontaneous move-

ments and an elevated arousal threshold, has been described in post-metamorphic fruit flies[27]. Such movements appear to have the complex phasic and cyclical character that defines 'MAS' (Fig. 1), with burst trains lasting up to 10 recurring every ~20 s for a minute or two at a time. These hierarchically-organized clusters repeat themselves several times at 3–5 min intervals before being interrupted by a quiescent gap of 15–20 min[24].

The only invertebrate species in which the postnatal development of sleep/wake behavior appears to have been systematically followed is the honey bee, *Apis mellifera,* the youngest specimens of which show highly fragmented sleep throughout the day and night[28]. Sleep episodes become fewer but longer as a clear-cut circadian rhythm develops, while the behavior pattern of worker bees changes from cleaning the hive to foraging for nectar. Intriguingly, during periods of rest, immature bees often exhibit isolated twitches and short bursts of coordinated movements of the antennae, wings and other body parts (Fig. 2).

Cephalopod Molluscs

In squid, cuttlefish and octopus, prenatal motility begins as irregular local twitching of tentacle, eye and chromatophore musculature, sometimes together with coordinated short-lasting pumping movements of the mantle accompanied by fluttering of the lateral fins[11,29-32]. As these bursts become more and more frequent (Fig. 3; Suppl. movie 1), a hierarchy of apparently non-random fluctuations ranging from one every few seconds to an hour or more can be dem-

onstrated[1,11]. In the pelagic larvae of squid and octopus, hatching triggers a dramatic shift to continuous pumping in order not to sink to the bottom[29]; intermittent resting behavior, with or without spontaneous movement bursts, has not been reported in very young specimens although the mature octopus has been reported to sleep[33,34].

Newly-hatched cuttlefish larvae, in contrast, continue to episodically display a typically late prenatal motility pattern after emerging from the egg capsule, viz., variable trains of short bursts of coordinated mantle, fin and head movements along with frequent twitching of the tentacles (Fig. 4; Suppl. movie 2) . On rare occasions, at least up to several weeks after hatching, these spontaneous 'rapid-body-movements' can take the form of well-organized 'oneiric' behavioral displays (i.e., dream-like acting out of feeding, fighting, fleeing or other characteristically waking motor patterns) (Fig. 4; Suppl. movies 2 and 3). In addition, qualitatively and quantitatively distinct wake-like behavior can make its appearance immediately upon hatching, viz., variable episodes of swimming gracefully about the tank (Fig. 5; Suppl. movie 3). These increase progressively in frequency on the following days as the incidence of sleep-like motility bursts declines sharply: in eight 3-day-old specimens, only thirty such bursts occurred during several hours of observation. It is striking that, despite the apparently complete absence of such episodes in juvenile cuttlefish, much older ('senescent') ones have been observed to display minute-long episodes of loosely coordinated successive bursts of

Fig. 2. A burst of 'rapid-body-movements' in a sleeping juvenile honeybee. A young post-metamorphic honeybee showing a sleep-like burst of stereotyped motility lasting ~1 s: the head and antenna become elevated and the insect then turns away from the camera and back again (sequential frames taken from unpublished video recordings, courtesy of Prof. Guy Bloch and Dr. Ada Eban-Rothschild of the Hebrew University, Jerusalem, Israel).

PRE-HATCH

Stage XXIX (6)   Stage XXX (9)

[73] *P* = 0.004 [587]

POST-HATCH

Stage XXX (6)   Stage XXIX (6)

[245] *P* = n.s. [152]

*P <0.001 (stage XXX, pre *vs* post-hatch)
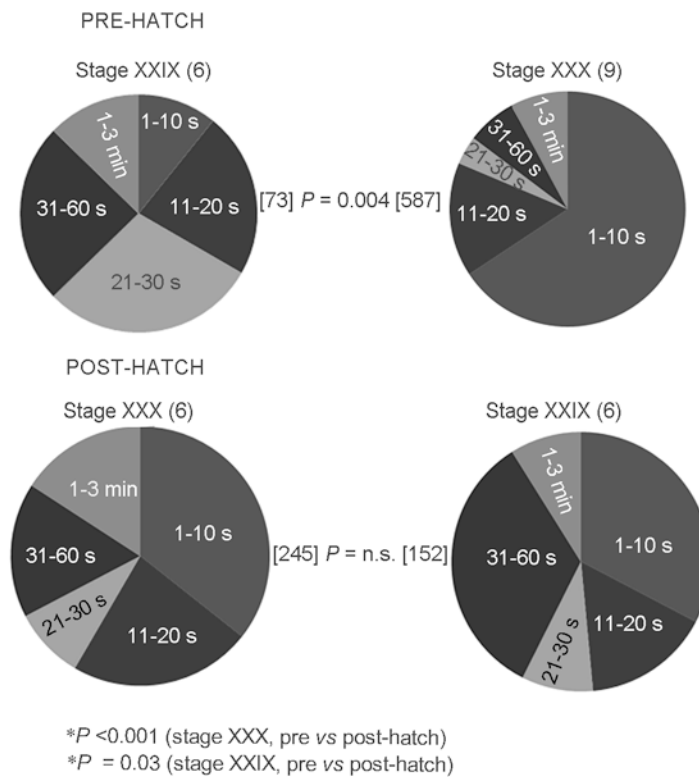*P = 0.03 (stage XXIX, pre *vs* post-hatch)

Fig. 3. Distribution of intervals between the onsets of successive bursts of stereotyped total-body (pumping) movements in late cuttlefish embryos at stages XXIX and XXX, and immediately after removal from the egg capsule at each of these stages. The percentages of values falling within the indicated time bins are represented by sectors in the circle graphs. The number of specimens monitored is given in parentheses, and the total number of intervals measured in each group is shown in brackets. The significance of age changes before as well as after hatching is indicated by *P*, while *P indicates the effect of hatching on spontaneous motility in embryos of both of the ages studied (Mann-Whitney 'U'-test, 2-tailed over all individuals studied, following a *χ2* test comparing the normalized spectra for the groups as a whole).
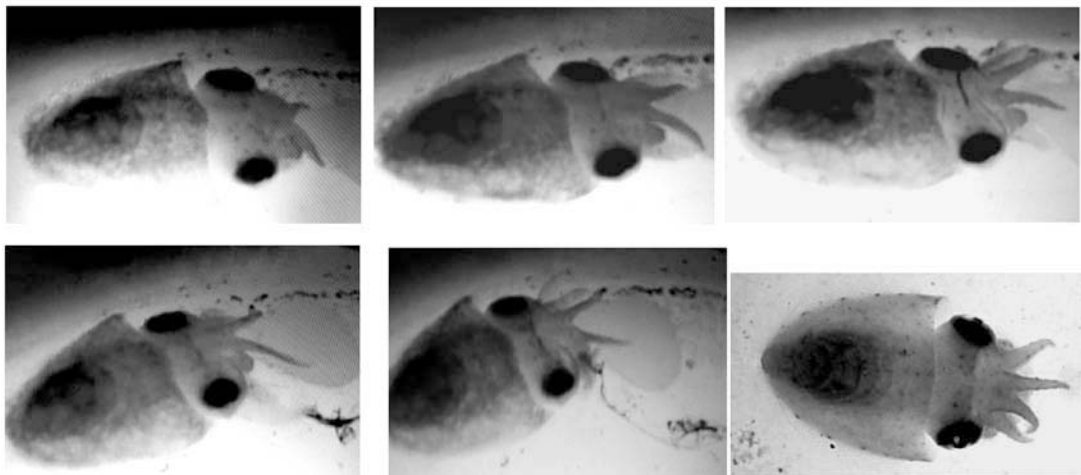

Fig. 4. Spontaneous burst of movements in a recently hatched cuttlefish. A newly hatched cuttlefish showing a ~2 s burst of stereotyped motility (mantle pumping, head retraction and tentacle twitching) ending atypically with a jet of ink and elevation of the dorsal tentacles as an 'oneiric' warning display (five sequential frames taken from a film recording – see Suppl. movie 2). The frame at the lower right shows an isolated 'flamboyant' display involving spread tentacles[36] in a slightly older specimen.
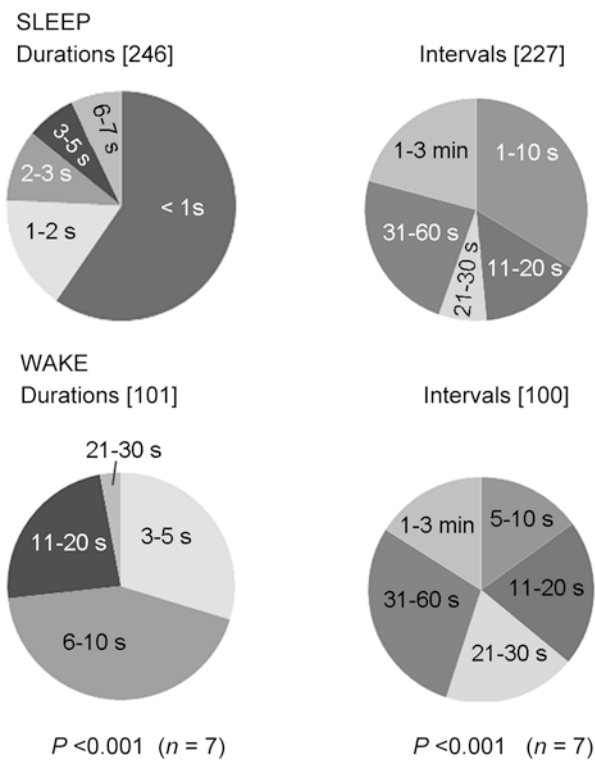
SLEEP
Durations [246]

Intervals [227]

WAKE
Durations [101]

Intervals [100]

$P < 0.001$ ($n = 7$)

$P < 0.001$ ($n = 7$)

Fig. 5. Durations and interburst intervals of postnatal sleep-like *versus* wake-like spontaneous movement patterns in perinatal cuttlefish. Comparison of sleep-like with waking behaviors in one-day-old cuttlefish. The percentages of values falling within the indicated time classes are represented by sectors of the circle graphs. The number of specimens monitored is given in parentheses, and the total number of intervals measured in each group is shown in square brackets. The significance of the differences between sleep-like and waking behavior is indicated by *P* (Mann-Whitney 'U'-test, 2-tailed over all individuals studied, following a *χ2* test comparing the normalized spectra for the groups as a whole).

chromatophore, eye and/or tentacle activity once or twice during the night[35].

Overall Conclusions Regarding Sleep-Like Behaviors

It is evident, then, that many examples of sleep-like behavior in invertebrates are scattered throughout the literature, but without their potential relevance for the phylogeny of MAS having been appreciated. Since pre- or perinatal spontaneous movements look much the same across the

animal kingdom[10,11], the main distinction between ecto- and endothermic animals could simply be that, whereas in the latter it is the proportion of active (REM) sleep in adulthood that distinguishes one group from another, in the former it is the relative length of time that AS persists after birth and the extent to which it changes in character as it matures. In no species, in any event, has the primitive 'seismic' variant of MAS[3,12] been shown to be restricted to prenatal life or to fail to mature postnatally into a more generally familiar form of MAS[1-12], i.e., characterized by generalized muscle atonia, drastically weakened twitching, cardiac and respiratory irregularity, and/or the appearance of 'paradoxically' wake-like neuronal activity patterns (Fig. 6).

Better quantification of the complex time-structure of spontaneous motor activities is clearly a high priority in order to more accurately evaluate the parallels among distantly related groups. More important in the long run, however, will be to physiologically monitor neuronal and motor activity patterns in the course of maturation. Quasi-rhythmic clusters of phasic neuronal discharges, for instance, might turn out to persist in the absence of any overt behavioral manifestations – as indeed appears to be the case in certain monotreme mammals[37] – while even the existence of intermittent 'aroused' neuronal activity patterns in higher nervous structures during what would otherwise be assumed to be quiet sleep cannot *a priori* be dismissed as being implausible[1,27,37]. In the virtual absence of ontogenetic data, however, all speculations to date about the phylogeny of AS must be regarded as being premature.

Primordial Selection for Spontaneously Active Neural Networks?

Regulation of Excitatory Drive
Even though all sleep-related circuitry could conceivably be descended from one or more spontaneously active primordial 'quasi-coelenterate' burst-generating networks[11,38], it must be emphasized that neurophysiological evolution need not be supposed to have necessarily begun there. There seems to be no compelling mechanistic reason, namely, for excitable membranes to periodically become depolarized or to be set extremely close to the level for triggering action potentials, for synapses to 'leak' transmitter molecules onto downstream receptors, or for excitatory interconnections

ACTIVE SLEEP

Muscles:	Rapid-BODY---Rapid-EYE		
Arousal:	'Seismic sleep'----Paradoxic		
Stage:	Pre,	post-natal,	mature

← O n t o g e n e t i c   g e n e r a l i t y

		Pre	post-natal	mature
P	Placentals[2, 3, 5-9, 11, 12]	+	+	+
h	Marsupials[37]	?	?	+
y	Monotremes[37]	?	+	o
l	Birds[5, 7-9, 11]	+	+	+
o	Reptiles[11]	+	?	o
g	Anurans[10, 11]	+	+	o
e	Teleosts[11]	+	+	o
n	Sharks[11]	+	?	?
e	Cephalopods[29-34]	+	+	?
t	Insects[11, 25-28]	+	+	+
i	Crustaceans[20-22]	+	?	?
c	Tunicates[17, 18]	+	+	?
	Leeches[15, 16]	+	?	?
	Nematodes[13]	+	+	?
	Planarians	?	?	?
	Cnidarians[10, 11]	?	+	o

O n t o p h y l e t i c   g e n e r a l i t y ——→

Fig. 6. Overview of current knowledge about the maturation of motorically active sleep (MAS)-like behavior patterns in different groups of animals. MAS is subdivided pre- and postnatally into 'seismic' and 'paradoxical' sleep (PS) on the basis of the absence or presence of a quasi-waking activity pattern somewhere within the central nervous system. A distinction has also been made between 'rapid-BODY-movement (RBM) and rapid-EYE-movement' (REM) sleep motility in order to call attention to the reduced muscle tonus and strength that typically appear slightly earlier in development than do the 'aroused' neuronal firing patterns during PS. '+' indicates the demonstrated presence of (M)AS (see the corresponding references), 'o' indicates a putative absence of any form of AS, and '?' indicates the absence of published information. Starting from the seminal discovery of PS in adult mammals and birds (enlarged bold-face crosses), the backward arrow above reflects the subsequent generalization of AS (as defined behaviorally) to early postnatal and then to prenatal stages (but note that in highly precocial mammals even the PS stage can occur prenatally). The phylogenetic generalization (downward arrows) conveys the fact that a 'seismic' form of active sleep (SS) has since been discovered to be present prenatally throughout the animal kingdom (for details see text). Finally, the forward arrow at the bottom reflects the recent interest of several investigators in tracking the continuation of (M)AS sleep into the postnatal period in ectothermic animals. SS has not been excluded from the early postnatal period for any group, whether during the RBM or the REM phase. (It should not be forgotten, however, that only a few ectothermic species have been looked at, and then often only superficially.)

to become so predominant over inhibitory ones that 'flash points' for initiating chain-reactions of runaway neuronal activity are created[1,10]. Neither is it immediately obvious why an activity-dependent membrane accommodation or a synaptic depression mechanism for terminating such discharges[23, 39] should be an inherent feature of excitable tissues.

One of the crucial functional properties of even the simplest neural networks, however, is an optimal balance between excitatory and inhibitory interactions among neurons in order to produce an adaptively (re)active organism. Straight-forward selection for specimens with the best 'fitted' epi/genomic[40] repertoire for producing a predetermined balance throughout the life-cycle would, of course, be the classical Darwinian way of achieving this, and would lead to quantitatively differing populations (eventually distinct species) in accordance with reigning ecological conditions. Thus, environments which tend to depress neuronal excitability – one thinks, for example, of certain conditions of temperature, osmotic pressure or chemical milieu – should select for a program of development that favors excitation over inhibition, whereas the opposite would be the case in environments that tend to intensify nervous activity.

Ontogeny of Activity-Dependent Homeostasis

Crucial environmental variables can unpredictably differ from time to time and from region to region; however, it appears to have been a more effective phylogenetic strategy for neuronal development to rely upon activity-dependent epigenetic ('plasticity') rules[1,40] in order to achieve viable levels of spontaneous behavior and sensitivity to sensory stimuli. In the case of overall network excitability, however, an internal source of stimulation would better serve as a monitor than would, for instance, an exhaustive set of sensory receptors covering all of the external influences that could significantly affect neuronal activity levels. Thus, for instance by making inhibitory neuronal maturation and the reduction or depression of excitatory connections depend upon the level of endogenous firing, a hyperactive network would be able to gradually dampen its excitability and a sluggish one to enhance it. Since excitatory connections determine the frequency of activity bursts[1,23,39], while inhibitory connections set limits on the intensity and extent of intra-burst firing[10,41], phasic spontaneous discharges would be an efficient way for a developing neural network to si-

multaneously monitor both of these opposing mechanisms.

Intrinsically-generated neuronal discharges in primitive networks should thus tend towards homeostatically preset levels[1,40], undoubtedly selected for during the earliest stages of behavioral evolution so as to maximize the number of individuals with an optimal responsiveness for survival under the existing environmental conditions. The simplicity of the underlying mechanisms[1,23,39], however, means that many ancestral networks with basically similar properties could have evolved 'convergently' at different times and places. With increasing complexity of nervous systems, differing homeostatic set-points will have had to evolve for different brain components, but our ignorance concerning the very existence of such set-points, to say nothing of the mechanisms underlying their formation and stabilization, must be considered to be one of the most glaring lacunae in theoretical developmental neurobiology.

This paper is dedicated to the memory of Paul A. Weiss, to whose stimulating pioneering ideas, personal instruction and imaginative experimentation[42] much of my own scientific career is an extended footnote.

SUPPLEMENTAL DATA

Supplemental data include three movies and can be found at http://www.neurosci.cn/epData.asp?id=70.

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