THE CORNER TREASURY OF ARCANE AND NEGLECTED PHILOSOPHICAL GEMS (OF MY OWN MAKING)

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Gem #1: NEURAL *SPONTANEITY* AS THE KEY TO THE ORIGIN OF PRENATAL BEHAVIOR AND SLEEP IN THE ANIMAL KINGDOM

(In the beginning was the burst)

Introduction and summary

A sketch is presented of the necessary physiological properties for developing neuronal networks to be able to display, as a default state, typical quasi-sleep behavior consisting of poly-rhythmical bursts of non-purposive motor discharges. A plea is made for concerted research into this primordial state of being, ending a long period of relative neglect, both for its central theoretical importance and for clues to the etiology of arousal defects in later life. The empirical foundation for attaching so much importance to the earliest stages of brain development has been detailed in several reviews which can be accessed on PubMed or obtained directly from the author: Corner 2008 (*Brain Research Reviews);* Corner 2013a *(Brain Sciences);* Corner 2013b *(Neuroscience Bulletin*); Corner and van der Togt 2012 (*Neuroscience Bulletin)*; Corner and Schenck (*Neuroscience Bulletin 2015*); Corner et al. 2002 (*Neuroscience and Biobehavioral Reviews*).

Basic principles of early behavioral development

Half a century ago a largely unnoticed revolution took place in our understanding of how vertebrate behavior originates. The question of whether localized reflexes become distilled from initially generalized motor responses to sensory stimuli, or whether the former gradually coalesce into increasingly generlized body movements (in fact, both types are present from the very beginning) unexpectedly became rendered irrelevant by the realization that early behavior is of predominantly central nervous origin and has a complex rhythmical basis. This principle was later able to be extended to virtually all multi-cellular animals including invertebrates: the *phylogenetic* generalization (Corner 2013b; Corner and Schenck).

A surprising but important extension of this insight involved the recognition that there is such a smooth transition in endotherms from the primordial motility of the fetus to what in later life is generally known as *rapid-eye-movement (REM)* sleep that the notion that these are two distinct phenomena that just happen to mimic one another can be relegated to the realm of fables. The time spent in REM while asleep declines rapidly in all species so far studied – the *ontogenetic* generalization - but disappears from developing poikilotherms long before they reach maturity, leading to a widespread but erroneous notion that REM must be a late evolutionary development (Siegel).

Spontaneous neuromotor activity is originally generated within the spinal cord (and also in the enteric nervous system!) but gradually loses this capacity as the generator sources move more and more anteriorly. Subliminal spontaneous activity appears to persist throughout the nervous system, however, judging from the presence of an excitatory wave traversing the entire spinal cord regardless of how localized associated muscle

twitches might be (2015). Fluctuations of excitability must therefore be continually taking place within the motoneuron pool, determining which of them will actually discharge action potentials in the course of a wave. [Lifelong persistence of this mechanism presumably underlies the often spectacular display of chaotic spontaneous twitching seen in adult mammals during REM sleep.] Eventually all brain regions studied, including the cerebral cortex, come at least temporarily to display an essentially similar pattern of irregular nested rhythmical discharges (the *physiological* generalization).
Independently in birds and mammals, a powerful linkage has evolved between the brainstem and cerebral cortical whereby the latter's intrinsic bursting activity is inhibited while the former intermittently projects its own synchronized 'PGO' bursts upon the otherwise now largely 'desynchronized' cortex. The periodicity of this circahoralian (i.e., approximately hourly) 'Basic Rest-Activity Cycle' is positively correlated with the body size of the animal, and is typically broken up into shorter episodes of 'phasic' versus 'tonic' activity.The fact that this entire polyrhythmic behavior pattern appears to be programmed into the nervous system already at the early neurula stage (2013a), and that many subsequent growth processes are activity-dependent, implies a high degree of vulnerability of the brain to physiological disturbances, especially if they occur during a 'critical phase' of development (2015).

Essential mechanisms of early behavioral development

The emerging picture of sleep originating as a 'default' state of interacting, spontaneously active, neuronal domains which in principle are capable of independent existence implies a number of evolutionary steps before it could have attained its present form. Since none of these steps is a necessary aspect of neural networks per se, each of them must have conferred some unknown survival value during the initial steps of multi-cellular behavioral evolution.
The first, and most important, requisite is that at least some of the neurons are 'pacemakers' that discharge spontaneously, or else leak sufficient excitatory transmitter to generate miniature post-synaptic potentials within the network. When the target cells become responsive enough, action potentials will occasionally be triggered stochastically (2013a) and, because interconnected nerve cells can also excite one another, the incidence of such bioelectric 'events' will vary from mostly isolated spikes and short bursts to, with a steeply decreasing incidence, variable localized clusters lasting up to 15-20 milliseconds (2012).
Another crucial, but often overlooked, phenomenon is the tendency for understimulated excitatory neurons to increase their excitability using a variety of mechanisms, seeking as it were ways of elevating their firing levels to an acceptable level (2002). Developing

networks typically reach a point where stochastic foci of intensified activity begin to appear which are able to trigger stereotyped bursts of synchronized firing which propagate out from the source. Each burst commences with a maximal intensity but ceases firing after several hundred milliseconds at most, owing to two types of synaptic depression: the availability of transmitter limits burst duration while refractoriness of the synaptic membrane causes a transient elevation of the threshold for triggering a subsequent burst (2012). If additional bursts are evoked within a 'relaxation' time lasting not more than minute or so, the buildup of refractoriness may cause clusters of 'phasic' activity to alternate - in variable cycles that typically last several minutes - with 'tonic' episodes of little or no bursting (2015).

By facilitating calcium entry, synchronous bursting opposes the morpho-physiological tendencies of the network towards ever increasing excitability, thus causing spontaneous firing to slowly decline until it falls to a critical level below which cellular excitation again begins to rise. Stereotyped bursting does not necessarily disappear at his point, however, only becoming much weaker. Evidently, while lacking the power to prevent the less active units from again starting to become more and more excitable, some networks are nevertheless still able to discharge in an all-or-none manner. This capability is well illustrated by the surprising sparseness of dendrites and synapses in the embryonic chick cerebrum at the stage when slow-wave sleeplike field potentials are first seen in the EEG (2008). The limiting factor here turns out to be a sudden maturation of glutamatergic excitatory mechanisms. As the growing network then becomes increasingly densely interconnected, the peak amplitude of these stereotyped waveforms increases accordingly until a full-scale slow-wave sleep pattern is attained shortly before hatching. These circahoralian fluctuations – which occur even in isolated tissue cultured *in vitro* (2013a) – are presumably the basis for the 'Basic Rest-Activity Cycle' seen in the brains of intact animals. How the set-points for such an elegant homeostatic mechanism become established so as to stabilize excitability in 'forward reference' for optimal later functioning is presently unknown. Neither is it known if such stabilization is irreversible and/or must occur during a critical period of development, nor why the fluctuations in activity levels need to be so extreme. In any event, already in primordial times, this homeostatic mechanism would have favored group survival by eliminating specimens or brain regions, the intrinsic activity level of which would have been either too low or too high to be viable.

Since synchronous bursting is widespread in embryos and larvae of all known species, one may surmise that for a network to use its own spontaneous activity to monitor and adjust its excitability was a key innovation early in evolution. To Judge from the absence of overt bursting during sleep in adult poikilotherms (2013b), however, these seem to have less and less need for such adjustments as they mature. Sleep deprivation experiments (as well as hibernation!) have demonstrated that, at least in the cerebral

cortex, homeotherms preserve this need throughout life. The plausible suggestion has been made repeatedly that the persistence of such homeostatic regulation long after the establishment of definitive functional parameters has as its primary function the elimination of excessive excitatory connections induced by 'Hebbian' sensory information processing while the animal is awake.

Our view of early sleep as a global default state consisting of multiple, semi-autonomous, weakly interacting domains of intrinsically generated neuronal discharges would be incomplete without mention of the final crucial element, viz., a network of reciprocally connected inhibitory neurons interspersed among the excitatory ones (2008, 2012). Without such elements, namely, the network would behave paroxysmally, i.e., be prone to continual epileptiform bursting and an excessive recruitment of neurons as each burst propagates through the excitable tissue. Normally, however, the build-up of feed-forward inhibition triggered by the excitatory wave limits the amount of neuronal participation and eventually prevents synchronous firing from spreading beyond a domain – the exact placement of which in the intact brain will depend on exactly where the discharge originates - measuring on the order of several millimeters in diameter. Neighboring domains sometimes burst simultaneously but in general are sufficiently independent that differential field potential (EEG) recordings, in vitro as well as in vivo, give essentially the same picture as do monopolar recordings.

Some unanswered questions concerning primordial sleep ontogeny and its value for the organism

Neuronal firing profiles within an isolated domain are remarkedly stable over many weeks in culture. Although bursts gradually become shorter due to loss of pre- and after-discharges, the main features are well preserved: each participating neuron has a characteristic onset, duration and firing profile within each burst, and these scarcely change with maturation. Detailed examination of successive bursts, however, reveals that subtle differences in the precise sequential activation of different neurons are quite common, even when bursts begin at the same site (2015). There even appear to be recognizably distinct families of interneuronal interval sequences which pop up irregularly from burst to burst. Since even weak electrical stimulation can accelerate the normal shortening of the overall burst as cortical networks mature, activity-dependent interactions among domains might well be a regular feature of normal development. One parameter that does show surprisingly large fluctuations from one day to the next is the mean firing level. These occur mostly independently at any given site but intriguing instances of both reciprocal and parallel changes without any visible effect on the overall firing level of the network, have also been observed. If this much dynamic complexity is

present even in a simple network, it is only to be expected that interactions among domains will add a further level of unpredictability even within a given brain region. At a still higher level of complexity will be the interactions among distinct brain regions, the differentiation of which into functionally specific patterns such as thalamic spindling and hippocampal theta waves remain to be investigated but may be safely presumed to involve some degree of dependence on the stimulation they receive from other regions. If such influences were to deviate from normal during a critical period, the induced abnormalities could become frozen into a stable feature of the mature brain or else manifest themselves under pathological conditions (2015).

So far I have emphasized only those factors which the sleeping brain exerts upon the development of neuronal activity patterns during sleep itself, but perhaps a more important question is the extent to which sleep-like synchronous slow waves also operate in 'forward reference' to the maturation of systems required for the organism to awaken and function optimally. A modest begin has been made in this direction by the observation that developing neocortical networks in culture, after having been deprived of spontaneous burst/slow-wave (i.e., sleep-like!) activity for a number of hours prior to being assayed, display a long-lasting reduction in both short- and long-term responsiveness to cholinergic agonists (2013a). Similar deprivation experiments targeting receptors for monoamines and other neuromodulators crucial for the aroused behavioral states that we call 'wakefulness' would seem to be invaluable, not only from an ontogenetic theoretical, but also from a putative clinical point of view.

The importance of cholinergic mechanisms for regulating behavior even during sleep is seen in the remarkable resurgence of quasi-fetal bursts of 'motor activity in neonatal chickens and rats when prevented from awakening by means of immobilization in fetal position (2015). These bursts are not specifically linked to either slow-wave or 'paradoxical' sleep, and normally disappear gradually as wakefulness becomes the predominant state of being. Their pathological persistence in children diagnosed as suffering from 'REM sleep behavior disorder' (RBD) could therefore have resulted from earlier severe interference with the activity dependence maturation of arousal mechanisms. A milder developmental disturbance of the same sort might well remain unnoticed until it erupts later in life in consequence of a general weakening of regulatory mechanisms with aging or illness. In particular, cholinergic and other arousal mechanisms, the continued low level activity of which during sleep may be responsible for suppressing such primordial behavior patterns, would not be strong enough to fulfill this function.

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