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A modern neurobiological concept of vigilance

by Werner P. Koella

(formerly Miescher Institute, P. O. Box 273, CH-4002 Basel), Buchenstrasse 1, CH-4104 Oberwil (Switzerland)

In 1924/25, W.R. Hess in one of his easily most cogent and far-reaching papers – a programmatic treatise on the interrelation between psychic and vegetative functions – hypothesized that the reactivity of the cerebral cortical networks, and, for that matter, of all central nervous networks involved in the organization of (animalic) sensory-motor as well as psychic activities, is under the double – antagonistic – controlling influence of vegetative information channels arising in the brain stem. With this hypothesis Hess anticipated practically everything which later experimentors, through 'dry' and 'wet' – biophysical, biochemical and pharmacological – methodology would prove to constitute the various ascending regulatory systems, including the now modern neurotransmitter channels, that impinge on what is usually referred to as 'higher centers'. And still more importantly, with his notion of an ascending vegetative control, Hess provided the very basic neurophysiological foundation necessary for the eventual development functionally well-defined *concept of vigilance.*

1. Introduction – the problem

The term vigilance was introduced into psychophysiology by Head[22]. For Head, 'vigilance' constituted a neurodynamic variable, a scale, indicating the level of ability of the organism to adapt to changes in environmental conditions. For many later investigators Head's original definition was apparently either too strict or too loose and they chose to deviate, often considerably, from the original concept. Some

decided that vigilance as a variable may replace such quantitative measures as arousal or degree of wakefulness, or attention. Mackworth[58] defined vigilance as 'the state of readiness to detect, and respond to, certain specified small changes occurring at random intervals in the environment'. Jerison and Pickett[28] who, like Mackworth are 'human factors specialists', defined and measured vigilance by the probability of detecting signals in specific tasks.

Dimond and Lazarus[12], dealing with the problem of vigilance in animal life, were somewhat more general in their view when they noted that 'vigilance is an important facet of animal life'. They defined vigilance as being a measure of the probability that an animal would detect a given stimulus at a given instant of time.

Others, evidently not satisfied with Head's behavioral notion of vigilance, introduced neurological or neurophysiological indicators of (what they assumed to be) vigilance; the electroencephalogram (EEG), evoked potentials, DC-potentials (viz., the contingent negative variation), but also autonomic indicators such as skin resistance, heart rate, and pupillary width were used to 'measure' the level of vigilance or arousal. Here one can mention Bente's notion[4,5]. He followed earlier leads set by Lairy-Bounes and Dell[53] and assumed that the pattern of organization of the mature EEG is the bioelectrical correlate of vigilance, which ensures a continuous state of readiness to respond with integrative-adaptive performance.

For some, 'vigilance' lost its meaning as a scale and became a mere 'endpoint'; i.e. a condition characterized by being awake, or aroused, or highly attentive. For those, 'vigilance' indicates a state during which one performs well, for instance in a card sorting test, in the shooting gallery, in a football game, in an examination, when writing an article, when solving a mathematical problem, or - for animals - when persuing prey.

With this diversity of opinions and definitions it has become increasingly difficult to compare the observations and data of the many authors who have used 'vigilance' to describe, or even quantify, certain phenomena in their investigations. This diversity of opinions also suggests that none of the definitions of vigilance proposed in the past has been, or is, entirely satisfactory. In our opinion all of them are too restrictive.

What one needs is a generally acceptable concept that in some way comprises many, if not all, of the above-mentioned definitions. 'Vigilance' should characterize and measure the ability not only of adaptive, but also of reactive and spontaneous behaviors. In fact, the term should be applicable across the whole universum of behaviors, and not be restricted to the behavior inherent in a particular test situation. The term should be applicable to all - or at least all higher - animal species and not only to man, or to mice, or to cockroaches. Furthermore, vigilance must be looked at as a behavioral phenomenon; it must be measured by means of behavioral scalars. Also, as every behavior* is the manifestation of a particular pattern of neuronal activity - in interaction with 'alien forces' - the variable 'vigilance' for a particular behavior must be explained by (but cannot be substituted for) a related condition of the neuronal networks (including glial elements) subserving the making of that particular behavior. Finally, an adequate concept of vigilance must allow insight into regulatory aspects; the introduction of the neuronal interface, mentioned earlier, opens ways and means for a better understanding of such matters of control and - as a fringe benefit - the locus and mechanism of action of pharmacological and other agents bound to modify vigilance. In fact, it seems to us that a good and generally accepted concept of vigilance could be of immense value for the understanding of many a problem in psychophysiology, behavioral sciences, neuropsychiatry, and, as mentioned, psychopharmacology.

Moved by such considerations we have set out to develop a new concept of vigilance, not only bearing in mind the aforementioned stipulations, but also applying Hess' invaluable axiomatic statements made in his 1924/25 paper[25]. Surprisingly enough, these have found little consideration in all earlier works on vigilance. Preliminary reports on our own concept of vigilance have already been published (Koella[43,45]). We present it here in a more complete and developed form.

2. The multidimensional nature of vigilance, its neurobiological basis, and its control

2.1. *A statement about the concept*

The pertinent points of our new concept of vigilance are as follows:

I. Vigilance is the level of *readiness* of the organism ('Bereitschaft' in Hess' vocabulary) to respond with a functionally successful *behavioral act* to a particular set of external and/or internal stimuli. Thus, under physiological conditions, the quality of the behavioral act (in other words, is appropriateness and adequacy with respect to its functional goal) is determined by the level of vigilance. In turn, the level of vigilance

* The term behavior is used here in its broadest sense. There are those actions of the organisms - manifestations of muscular and glandular activities - that can be observed from the outside and that are liable to affect the environment: assumption of specific postures, various movements, speech, blushing, salivation, mydriasis, sighing can be cited as examples of such *extroversive behaviors. Internal behavior,* in contrast, refers to those activities that cannot be (directly) observed from the outside and that can, but must not necessarily, be experienced by the individual. Internal behaviors include a variety of autonomic activities *and* psychic or mental activities, such as cognitive actions, feelings, mood, memory processes, dreaming etc.

can be estimated, under physiological conditions, by assessing the qualtiy of the behavioral response.

II. Every behavioral act, with the exception of the extremely simple and monotonous ones, consists of a set of *behavioral components* and as such involves a multitude of (but never all) behavioral systems. The necessary condition for adequately performing a behavioral act is a high level of *local vigilance* in those systems that are involved in a particular behavior at any given time. In turn, the levels of the various local vigilances, which when taken together can be spoken of as the *vigilance profile,* can be gauged, under physiological conditions, by assessing the quality of the various behavioral components making up the whole behavioral act.

III. We assume that any behavior, whether it be extroversive or internal, results from, that is to say is organized by, a particular space-intensity-time (SIT) pattern of neuronal (and, possibly, glial) activity. *Local vigilance,* then, must be the expression of the *readiness of the local neuronal* (and glial) *networks* subserving a particular behavioral system to react with an adequate SIT pattern to a particular set of incoming information. *Local vigilance,* at the network level, becomes *local reactivity,* that is to say the ability of the networks to properly handle information; the quality of the local neuronal activity in the networks under consideration. In turn, local reactivity is gauged by phenomena signalling the quality of the local neuronal activity, or then, indirectly, by the quality of the ensuing behavior.

IV. The *control of vigilance* is accomplished through the impact of neurohumoral signals impinging on the networks. Vigilance, as a behavioral quantity - just as behavior per se - cannot be directly affected by controlling influences. The concept of local vigilance also implies that the control of vigilance is *selective* in the sense that the reactivity in the various local networks subserving the organization of the various behavioral components can be influenced individually and independently.

This conceptual construct is depicted schematically in figure 1. In the sections to follow, we shall cite and discuss selected pieces of evidence that attest - at least in a general fashion - to the validity of this new concept.

2.2. *Indicators of local vigilance and its neural foundation*

Man and animals can direct their attention towards specified stimuli; they also can be distracted. This focussing ability has been well documented, at the neural level, by some classical electrophysiological experiments. Hernández-Péon and co-workers[24] recorded click-evoked potentials in the cat's cochlear nucleus. These responses were found to be prominent during quiet waking. But when the cat was confronted with a mouse, the responses became drastically attenuated. They returned to control level with the disappearance of the disturbing sight. Similarly, the potentials were found to diminish in amplitude when the

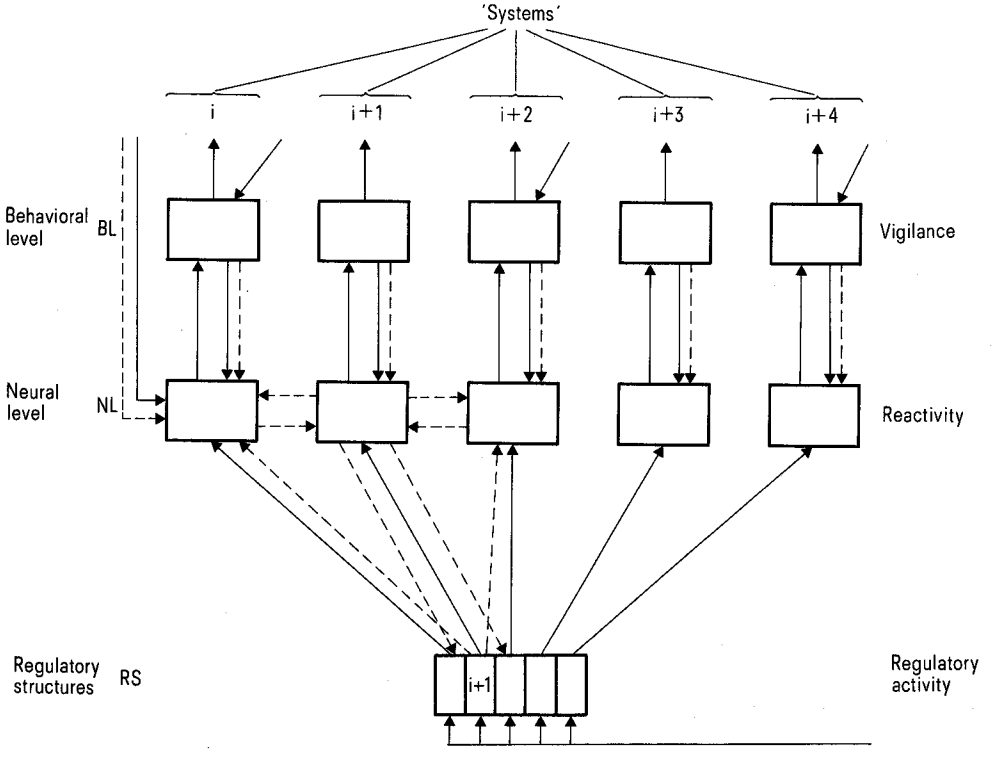

Figure 1. Schematic representation of *Vigilance-Concept* as stated in 2.1. Note 'systems-columns' and behavioral and neural 'strata' with spaces for local vigilance and local reactivity controlled by regulatory structure(s). Included are positive (—) and negative (---) feedback channels between behavioral and neural levels, and ascending as well as descending inhibitory channels from $RS_{(i+1)}$ to $NL_{(i)}$ and $NL_{(i+2)}$ and from $NL_{(i+1)}$ to $RS_{(i)}$ and $RS_{(i+2)}$ as possible instruments for focussing of reactivity and vigilance in $NL_{(i+1)}$ and $BL_{(i+1)}$ as outlined later in this paper.

cats were exposed to fish odor. Garcia-Austt[16], in a similar experiment in rats, investigated evoked responses in the visual cortex produced by electrical stimulation of the lateral geniculate body, or of the chiasma, or, physiologically, by light flashes. He noted that a shift of attention toward other sensory patterns or modalities invariably provoked a decrease in amplitude or the complete disappearance of the (visually evoked) potentials. Morrell[67] observed that an acoustic stimulus - which by itself evoked no response in the cortex - produced a negative going DC-shift when it was reinforced by electrical stimulation in the unspecific thalamus.

In their experiments in man, Haider and collaborators[19] noted that out of a series of 'signal' responses (requiring a key press) only those that were detected were attended by enlarged evoked responses. In Picton and Hillyard's work[73] the subjects had to detect faint acoustic stimuli within a series of stronger, 'non-signal', stimuli. Attention directed towards 'signal' stimuli was found to cause a substantial increase of the N_1- and the P_2-response, without any apparent changes in the earlier components. In Ritter and Vaughan's investigations[78] attention exerted towards weak acoustic stimuli interspersed in a series of stronger ones led to the appearance of a late (450–550 msec latency) positive component. Desmedt and Debecker[9] noted that a late positive wave occurred only under 'attention-condition' and was absent when attention was directed towards other objects.

Two types of transitory DC-phenomena also clearly signal enhanced *local reactivity*. One is the *contingent negative variation* (CNV) as first observed and described in man by Walter[92]. If a subject is given a 'warning' stimulus to be followed, after 1–2 sec, by an 'imperative' stimulus, there occurs in between the two stimuli a pronounced surface-negative DC-shift of from 20–30 μV mainly in the frontal areas. McCallum and Walter[64] found that when the subjects were distracted, i.e. when local vigilance was lowered, the amplitude of the CNV was reduced. Tecce and Scheff[88] found significant relations between: a) distraction and CNV-amplitude, b) distraction and reaction time, and c) CNV-amplitude and reaction time. From this and similar later work, Tecce[87] concluded that 'magnitude of CNV is positively and monotonically related to attention and non-monotonically related (inverted U) to arousal level'. A DC-phenomenon clearly related to 'motor' vigilance is the *readiness potential* (Bereitschaftspotential) as first described by Kornhuber and Decke[49] and then by Gilden and co-workers[18]. This is a complex potential which occurs over the Rolandic area when a spontaneous voluntary movement is intended and then performed. McAdam and Seales[63] have demonstrated that the amplitude of the slow negative component of this potential is enlarged when the motor task demanded is rewarded.

There is another telling example illustrating the principle of local vigilance and reactivity; namely the behavioral and neural changes occurring in man and animals throughout the transition from waking to the various stages of sleep. During quiet waking, most systems - viz. the motor apparatus and the sensory, cognitive, memory, affective, and autonomic mechanisms - reveal an intermediate level of activity, demonstrating an intermediate level of vigilance and reactivity. If man (for animals there is less clear evidence) drifts off into stage-1 (NREM) sleep, responsiveness (i.e. vigilance) in the sensory and motor systems drops; the arousal threshold increases and muscular tonus and reflex excitability are somewhat attenuated. Yet, vigilance in some components of the memory, cognitive, and affective systems seems to 'float' at a fairly high level: we experience the vivid *hypnagogic hallucinations* or microdreams. The EEG-arousal pattern observed during this stage may well be taken as the electrophysiological manifestation of high (local) reactivity, in particular of the cerebral cortex.

With the shift to stages (NREM) 2, 3, and 4, vigilance in the cognitive, memory, and affective systems gradually diminishes; one becomes entirely unconscious and it becomes increasingly difficult to awaken an individual. Yet, one system at least seems to maintain a high level of vigilance: man and animals are capable of differentiating between familiar sensory stimuli on the one hand, and unfamiliar ones - signalling potential danger - on the other. Accordingly, they continue to sleep or they wake up and perform an orienting response. We have referred to this sleep- and individuum-protecting mechanism that clearly stays alert while many other systems exhibit low vigilance, as the *analyzer* (Koella[40]). Lendrem[54] has discovered in birds a behavioral system subserving such protecting function. He noted, and counted as a measure of (typically local) vigilance, eye peeks in sleeping birds, a mechanism of danger detection (birds of prey) active when most of the other systems are in the 'no-go'-condition. The shift from the desynchronized to an increasingly synchronized cortical EEG is quite probably the manifestation of a drop in the local reactivity in networks subserving mainly 'higher' functions.

The vigilance profile, i.e. the level of a variety of local vigilances, changes fundamentally again with the transition from NREM- to REM-sleep. Vigilance in the motor system, where tonus and reflex responsiveness are virtually gone, drops to lowest levels. There are, however, a few exceptions. The system that induces the rapid eye movements - probably subserving a homeostatic function (Koella[40], pp. 157–158) - must retain a high level of vigilance. Furthermore, high vigilance prevails in the cognitive and memory functions. Activity in the former enables us to ex-

perience our dreams; the latter, through read-out, supply engrams to enrich our dreams and, through acquisition, enable us to store the dreams for later recall. We 'learn' our dreams.

Enhancement of local reactivity to ensure high (though probably qualitatively changed) levels of mental activity during dream-sleep is manifested by the appearance of an arousal pattern in the cortical EEG. In experimental animals, viz., the cat, a now qualitatively different type of arousal pattern appears with the onset of paradoxical sleep in the hippocampus; i.e. the characteristic theta-waves that otherwise are seen either during the orienting response (while awake), or following reticular stimulation.

2.3. *Control of local vigilance and reactivity*

We stated earlier (2.1.) that the control of vigilance *must* be accomplished through control of reactivity in the networks subserving the organization of the behaviors (or behavioral systems) whose vigilance is under consideration. There is a large amount of physiological, pharmacological, and biochemical evidence supporting the notion that ascending pathways originating in the brainstem are capable of controlling the activity (the reactivity) of a variety of networks of the forebrain, and thus, indirectly, vigilance. Furthermore, there is some evidence that these ascending pathways can exert their influence in a selective manner, i.e. that they can affect reactivity and vigilance seperately and thus accomplish what one may refer to as a focussing effect.

Moruzzi and Magoun[68] in their classical experiment demonstrated that high frequency electrical stimulation of the mesencephalic reticular formation of cats led not only to the characteristic desynchronized arousal pattern in the cortical EEG, but also - when the experiment was done in the freely moving animal - to a whole package of behavioral signs of high vigilance, such as increased motor activity, orienting response, and typically ergotropic vegetative patterns, e.g. mydriasis and accelerated heart rate. Arduini and co-workers[2] showed that iterative reticular stimulation was followed by a negative-going shift of the cortical DC-potential. The hippocampus was found to react to reticular stimulation with an increased theta-output, the characteristic pattern of local high reactivity of this structure (Kemp and Kaada[37]). It is important to note again here that the same pattern is evident also during paradoxical sleep. In these early days of 'dry' experimentation it was also shown that reticular stimulation improved visual discrimination (Fuster[14]), that it enhanced excitability of the motor cortex (Lilly[57]), and that it facilitated visual, auditory, and somatosensory evoked potentials elicited by electrical stimulation of the specific nuclei of the thalamus (Bremer and Stoupel[6]).

Such experiments also produced preliminary evidence of at least some spatially selective - in our terminology: local - influences of these ascending pathways or mechanisms. According to Cordeau and Mancia[8] 'high' hemi-transection of the midbrain of cats leads to slowing of the EEG (i.e. drop of reactivity) only in the cortex ipsilateral to the lesion, whereas lower transections affect both sides. In our laboratories we could repeatedly observe that the effect of reticular stimulation in cats was confined to the ipsilateral cortex when the stimulating electrode was situated high in the mesencephalon or in the diencephalon, yet involved both sides when the electrodes were placed in the caudal part of the reticular core (see also viz., Koella and Gellhorn[48]). An additional piece of evidence for such selectively controlled behaviors can be seen in the observation that electrical stimulation of pontine sites of cats induces paradoxical sleep (see viz., Jouvet[32]); i.e. a state of evidently high vigilance in behavioral systems subserved by the cerebral cortex and the hippocampus (theta waves!) yet of extremely low vigilance viz. in the motor systems.

The advent of the 'wet' neurophysiology - the 'new science' of the so multifaceted central nervous *transmitter mechanisms* - facilitated a deepening of insight into the very qualitative details of the control of vigilance. The vast amount of work on these humoral transsynaptic information carriers and on their neuronal substrates revealed with ever increasing clarity that the brain (in fact the whole CNS) contains vastly diverging neuronal systems of a variety of transmitter vehicles which appear to be almost tailor-made for acting as reactivity- (and vigilance-)controlling instruments. We recently reviewed this evidence in detail (Koella[44]); in the present paper we can confine the discussion to a few pertinent points.

An overwhelming amount of evidence indicates that enhancement of central *catecholaminergic transmission activity* is followed by a clear increase of activity in a variety of behavioral systems. Amphetamine, known to exert its activity mainly by facilitating the release of noradrenaline (NA) and dopamine (DA), has been shown to enhance orienting activity of rats in the open field and to improve avoidance behavior and intracranial self-stimulation (see viz. Weissman et al.[93]; Hearst and Whalen[23]; Stein[83]). An increased supply of NA and DA at synaptic sites, as induced by pretreatment with L-DOPA, is followed by enhanced 'general' activity and in a shift in the cortical EEG of cats towards low voltage, fast activity patterns (Jones[29]). Increasing more specifically only NA-release from central nerve terminals by such preferential alpha-2-receptor blocking agents as yohimbin, or piperoxan prolongs waking time and - again as a sign of a more 'localized' impact - increases percentage of paradoxical sleep of cats and rats (Leppävuori and Putkonen[55]; Kafi and Gaillard[34]).

Electrical stimulation of the locus coeruleus of cats - the point of origin of an important ascending (and descending) noradrenergic pathway - is followed by an EEG-, behavioral, and autonomic - ergotropic - arousal pattern (fig. 2) not unlike the one produced by the 'classical' reticular stimulation (Koella[42]). Such stimulation also leads to an enhanced release of NA from the cortex (Tanaka et al.[86]).

Injection of *dopamine* into the ventricular system or the hypothalamus of rats enhances motor activity (Benkert and Köhler[3], Geyer et al.[17]). Similar results are obtained with systematic administration of apomorphine, the classical dopamine-receptor agonist (Thornburg and Moore[89]).

In turn, *suppression of central catecholaminergic activity* is followed by signs of lowered vigilance or reduced waking. Inhibition of the synthesis and thus depletion of dopamine and/or of noradrenaline by, viz., alpha-methyl-para-tyrosine in rats and cats is followed by reduced orienting and motor activity (Weissman et al.[93]) and by signs of electrocortical EEG-deactivation (King and Jewett[38]). In such depleted animals the vigilance enhancing effect of amphetamine is no longer produced (Svenson[85]). Poisoning of noradrenergic pathways with intracerebrally administered 6-OH-dopamine in rats leads to *selective slowing of the cortical EEG without affecting to a marked degree motor activity* (Lidbrink[56]; Matsuyama et al.[62]). Reduction of the noradrenaline release by the (preferably) presynaptically acting alpha-2-receptor agonist clonidine also leads to reduced orienting activity and reduced percentage of paradoxical sleep in rats and cats (Kleinlogel et al.[39]; Leppävuori and Putkonen[55]). Physical procedures used to destroy ascending noradrenergic pathways have yielded conflicting results; either the percentage of waking time was reduced, or else, there was no effect (Jones et al.[30,31]). However, those otherwise very well executed studies did not include measurements of the performance of 'higher' functions. So it is of interest to learn from Anlezark and co-workers[1] that lesioning of the locus coeruleus of rats leads to reduction of learning speed. According to Mason and Iversen[60] lesions of the coeruleo-cortical noradrenergic system elevates resistance to extinction of a previously learned runway response for food reward. Mason and Iversen[61] suggest that noradrenaline is involved in *attentional behavior.*

Interruption of dopaminergic pathways by injection of 6-OH-dopamine into the nigro-striatal system is followed by marked reduction of motor activity of rats (Roberts et al.[79]). According to Jones and co-workers[30] stereotactic lesioning of the nigrostriatal pathways of cats is followed by *akinesia and reduction of motor initiative,* without affecting the sleep-waking cycle.

The cerebral content of noradrenaline was found to vary in a circadian fashion and, more or less, in phase with activity (Reis et al.[76]). Chu and Bloom[7] noted a drop in the discharge rate of neurons in the locus coeruleus of rats with the transition from active waking to quiet waking and to sleep. Kovačević and Radulovački[51] demonstrated that the dopamine

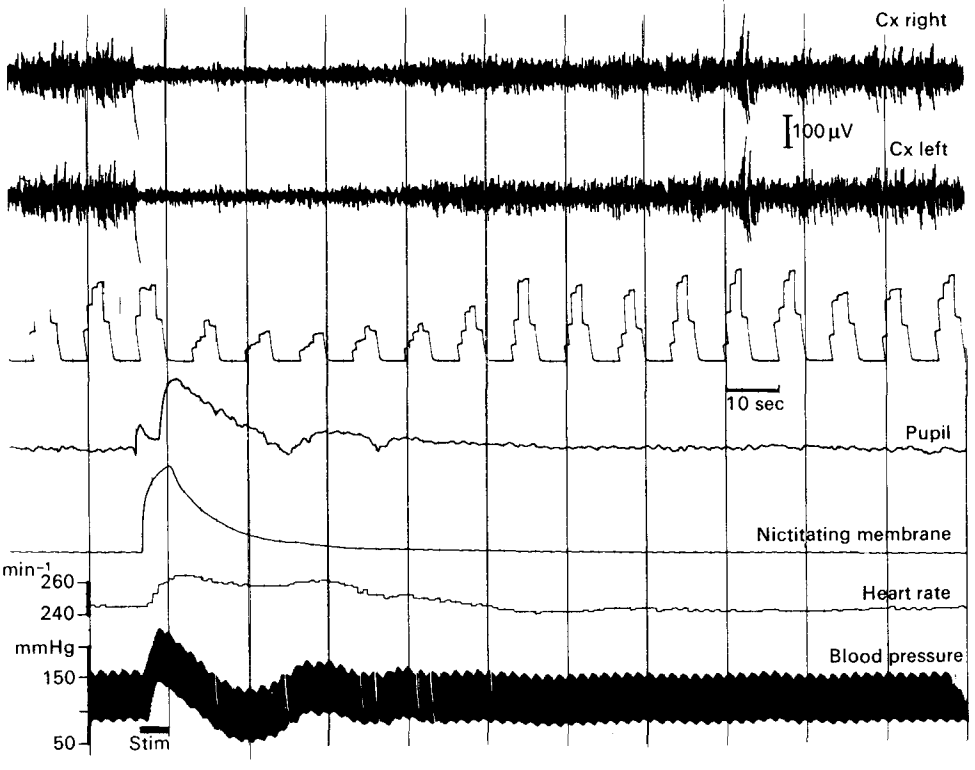

Figure 2. Arousal effect of iterative stimulation of locus coeruleus (5 sec train of 150/sec, 0.5 msec pulses, 2.5 V) in immobilized, nonanesthetized cat. Note typical arousal pattern in both cortices with loss of low and intermediate frequency output, as shown in analyzer-output of left cortex (3rd line from top). Note also mydriasis, as recorded by photo-electric pupillometer, increase of nictitating membrane-tension and of heartrate, and rise in blood pressure (from: Koella[42]).

turnover in the striatum and the thalamus of cats drops with the shift from waking to sleeping, in other words, with the cessation of motor activity. Here one also must mention the new evidence about circadian variations in adreno-receptor sensitivity as evidenced by binding studies in the laboratory of Wirz-Justice and co-workers[95]. This indicates that the supposedly vigilance enhancing effect of noradrenergic activity varies in its magnitude not only in dependence of NE-release but also in dependence of the state of the (adreno-) receptor apparatus.

Cholinergic pathways also appear to be important vigilance-enhancing instruments. Intravenous injection of acetylcholine (Ach), nicotine, physostigmine, and prostigmine leads to a reduction of slow-wave output and an enhancement of beta - activity in the cortical EEG of cats (Yamamoto and Domino[96]; Domino and Yamamoto[13]). Karczmar and co-workers[35] demonstrated that the injection of cholinomimetics causes cats and rats to shift from slow-wave to paradoxical sleep.

Blocking of cholinergic transmission produces clear signs of reduced (local) vigilance or of reduced (local) network reactivity. Already Wikler[94], and after him many others, described the ultra-high and -slow waves in the cortical EEG of cats treated with atropine, the classical muscarinic antagonist. Here though, it is of interest to note that the animals treated with atropine remain active as far as locomotion, grooming and feeding is concerned, but they score poorly in conditioned behavior and in memory tests (Rougeul et al.[80]; Ricci and Zamparo[77]; Deutsch and Rocklin[10]). In cats, hemicholinium, an Ach-synthesis inhibitor, suppresses paradoxical sleep (Hazra[21]). In cats and dogs there is increased Ach-release from the neocortex during waking activity *and* during paradoxical sleep as compared with slow-wave sleep (Jasper and Tessier[27]; Gadea-Ciria et al.[15]; Haranath and Venkatakrishna-Bhatt[20]). Further details on cholinergic influences on arousal, or, as we would prefer to call it, vigilance, are found in the excellent review by Vanderwolf and Robinson[91].

Finally, it should be mentioned that some *polypeptides* may also be involved in the priming of those mechanisms that enhance vigilance in some systems. For instance, Kelley and co-workers[36] have shown that the injection of D-ala-met-enkephalin into the ventral tegmental area - nucleus A_{10}, the point of origin of the mesolimbic dopaminergic system - enhances motor and orienting activity of rats and intensifies the driving effect of amphetamine. Injection of thyrotropin-releasing factor (TRH) or of growth-hormone-releasing factor antagonizes the sedating effect of phenobarbital (Prange et al.[75]; Plotnikoff et al.[74]). ACTH 4-10, a polypeptidic fragment of ACTH, was found by de Wied[11] to facilitate retention of a conditioned avoidance response. In a more recent piece of work, Urban and de Wied[90] showed that ACTH 4-10 facilitated theta activity in the hippocampus of rats as produced by reticular stimulation. Here it is of importance to recall that such rhythmic activity in this part of the limbic system indicates activation along the midbrain-limbic pathways which may, but must not be, accompanied by activation of motor components. Again, this is an example of hightened *local* reactivity or vigilance.

Already the early experimental work quite clearly revealed that there are, in addition to the ascending 'activating' influences, also ascending 'depressing' influences impinging onto 'higher' structures, that the - in our terminology - vigilance - modulating systems follow the 'rules' well known and established for autonomous output, namely that control is either always, or nearly always, *antagonistic in nature.* The effect of an activating or facilitatory controlling component is counteracted by the one of an inhibitory component. As to vigilance, Hess[26], and a host of subsequent investigators have shown that low-frequency stimulation of the mid-line thalamus of cats (and dogs) elicits sleep. Here, a 'tuning' phenomenon is of interest: the hypnogenic effect is produced only with low frequency stimulation whereas higher stimulation rates induce arousal. Other authors - viz., Sterman and Clemente[84], Parmeggiani[71], Magnes et al.[59] - have produced evidence that in cats electrical stimulation of the basal forebrain, the fornix, or the area of the solitary tract nucleus, respectively, induces sleep, or at least, isolated signs of sleep such as 'presomnic' symptoms or increased output of slow waves in the electrocorticogram. The production of paradoxical sleep - in fact, in our view a phenomenon signalling increased local vigilance - by pontine stimulation, was mentioned earlier. Of interest in connection with these 'hypnogenic' stimulation effects is the fact that they involve rather wide-spread areas; i.e. vigilance is lowered in a multitude of behavioral system. At the very least it can be said that while the activating invluence of (rostral) reticular stimulation is restricted to the stimulated hemisphere, the hypnogenic effect involves the whole brain. It is the whole animal, and not just one side that sleeps.

An antagonistic innervation of the forebrain is also quite evident for the 'wet' controlling systems; the vigilogenic transmitter pathways - catecholamines, acetycholine - seem to be opposed by at least one 'wet' vigilosuppressive mechanism. *Serotonin* (5-HT), i.e. serotonergic pathways, while subserving a number of other functions such as temperature regulation, endogenous analgesia, immuno-mechanisms, blood-clotting, most definitely is involved, in the organization, the induction and maintenance of mainly the slow phase of sleep, i.e. in the shift in a variety of systems towards lowered local vigilance. Again we will refrain from citing all this evidence and refer

merely to our recent review (Koella[44]); in the present connection we make reference to only a few of the more important findings. Serotonin, injected in doses of 10–50 ng into the 4th ventricle of freely moving cats invariably induces sleep – mainly its slow-wave variety (Koella[41]). Serotonin precursors, injected systemically, enhance slow-wave sleep (Jouvet[33], Koella et al.[46]). Electrical stimulation of the raphe nuclei, the area of origin of the ascending serotonergic pathways, induces sedation and sleep in rats (Kostowski et al.[50]). Reduction of the central concentrations of serotonin by either synthesis inhibitors or by surgical lesions in the raphe nuclei produces insomnia (Koella et al.[46]; Jouvet[33]). Cerebral serotonin and its metabolite, 5-hydroxy-indoleacetic acid, vary in their concentration in a circadian fashion; 'highs' coincide with periods of greatest densities of sleep – an obvious phase-shift in comparison with noradrenaline (see viz., Scheving et al.[81]).

Some polypeptides also seem to be involved in the organization of sleep, or, at least, of a rather widespread deactivation. Pappenheimer and co-workers[70], Pappenheimer[69], and Krueger and collaborators[52] isolated from cerebro-spinal fluid of sleep-deprived goats and, more recently, from human urine, a polypeptide – substance S – which, if injected into the ventricles of rats and other species, exhibits sleep-promoting activity. Monnier and Schoenenberger[66] have succeeded in isolating and chemically characterizing a nonapeptide (the delta-sleep-inducing-peptide, DSIP) which if injected into rabbits enhances delta-wave output in the cortical EEG and brings about signs of sedation. According to Pavel and co-workers[72], vasotocin, a nonapeptide from the pineal organ, has sleep-promoting abilities if given to cats and man.

3. Interpretation

In the present conceptual construct, vigilance assumes an exclusively behavioral dimension. It is universal in the sense that it does not single out any particular behavior in any particular species.

As a behavioral variable, vigilance must be 'measured' by behavioral techniques. In turn, reactivity of the networks subserving the organization of the behaviors under consideration is a neurophysiological variable; it is, and must be, 'measured' by neurophysiological (biophysical, biochemical, and systems-analytical) techniques.

The concept of local vigilance implies – in fact, it stresses – *focussing*; it emphasizes *concentration* of the state of readiness for action and of reactivity upon the systems – and only those systems – necessary for a particular behavioral act. Thus, it provides for checking against 'cross-talk' and against generalization; and it provides for 'economy' of vigilance. Consequently this concept ascribes to the vigilance-controlling mechanisms a functional role as a *selective device.*

With our theory of local vigilance we are in the position to challenge Vanderwolf and Robinson's recent 'critique of the arousal theory'[91]. These authors interpreted the finding of low voltage fast EEG-activity in sleeping animals – in particular during paradoxical sleep – to indicate that there is a non-correlation between this EEG-pattern and vigilance, as, according to these authors, sleeping animals are uniformely in a state of low vigilance. The fact that locally restricted areas can indeed reveal high reactivity, and thus high levels of vigilance, while large parts of the organism impress by their state of low vigilance, is apt to invalidate those authors' claim. In fact, the dynamics of sleep – the drastic changes in vigilance profile during the transition from quiet waking, via the various stages of NREM- to REM-sleep – serves as one of the most telling examples in support of the theory of local vigilance. These pre-programmed variations in local vigilance of the many behavioral systems are so obvious that one may seriously consider using the vigilance profile as the foundation for a badly needed, new *functional principle of sleep staging.*

Introducing network-reactivity as organizational 'interface' allows for the better – i.e. truly neurobiological – understanding of the mechanisms of action in operation with the vigilance-controlling apparatus. There is indeed a wealth of experimental data to clearly indicate that such controlling mechanisms exist and that these mechanisms have a certain capability to exert their influence in a spatially, i.e. behaviorally, selective manner. In addition to the older 'dry' evidence cumulating in the concept of the ascending, diffusely projecting activating system(s) and its counterpart, the 'hypnogenic' system, there is now ample information that some of the ascending (and descending), mainly monoaminergic, neurotransmitter pathways are primarily involved in this control of vigilance. The fact that more than one transmitter is participating in the enhancement of vigilance adds a 'qualitive' dimension to the hitherto mainly 'binary' notion of control, and supports the concept of the selective abilities of the controlling apparatus. It is of interest to note here that the transmitter agents which are involved in this central control mechanism, act also, to a large extent, as vehicles in peripheral autonomic controlling mechanisms; this again confirms Hess' almost prophetic statement when he referred to these central ascending pathways as 'vegetative innervation of the cortex'.

Relatively simplistic experimental procedures with little ability to differentiate between various behavioral target areas indicate a general activating influence of *noradrenergic* mechanisms on behavior. More detailed experimental procedures (and the cognizance

that the typical projection sites of the noradrenergic systems – i.e. the neocortex, hippocampus, amygdala, basal forebrain, yet little toward the basal ganglia – strongly suggest that noradrenergic mechanisms may be mainly and selectively responsible for the hightening of local vigilance in those behavioral systems that are organized by the aformentioned structures – i.e. in what one is ready to refer to as 'higher functions'. The observation that elimination of the noradrenergic pathways by 6-OH-dopamine deactivates the cortex (of rats) but leaves the 'primitive' locomotor activity unaltered (Lidbrink[56]) supports this notion – as do the findings that elimination of the pathways originating in the locus coeruleus impairs memory functions but leaves the subcortically organized sleep-waking cycle untouched, and that mild and controlled reductions of noradrenaline-release by alpha-2-receptor activation is followed by a reduction of paradoxical sleep. The failure to observe a 'dewaking' effect – i.e. no reduction of 'primitive' activities – following surgical elimination of the coeruleo-cortical and coeruleo-limbic systems must not militate against the notion that intact noradrenergic activity *is* important for the maintenance of proper reactivity in those networks (only) that subserve higher behavioral functions; also it well recognized that surgical procedures never can be as selective as the newer methods using neurotoxins or strictly biochemical techniques. As to the mechanism of action by which noradrenaline enhances local reactivity, little is known as yet. Still, Moises and co-workers[65] have demonstrated that this catecholamine, applied to single cells of the cerebellar cortex, while inhibiting these cells, enhances their responsiveness to a variety of aminoacidergic transmitter substances. The ensuing increase in the 'signal-to-noise-ratio' may well be one component of 'increased local reactivity'.

Cholinergic influences again seem to exert their 'vigilogenic' influence mainly toward limbic and neocortical structures – i.e. networks that typically participate in the organization of higher functions. Thus it is understandable that atropine in proper dosage does not affect locomotion, grooming, and feeding – in fact it may facilitate these activities; yet it deactivates the EEG of the neocortex and impairs functions that depend on these higher structures, namely conditioned behavior and memory performance. For both the adrenergic and cholinergic pathways then there is some good, if not irrefutable, evidence pointing towards their role as vigilance enhancing instruments, especially in the realm of higher functions. Yet for many writers, the present one included, this degree of selectivity is probably not high enough to attest to the validity of the concept of a locally controlled vigilance. One could imaging though that better selectivity could be achieved through a kind of a point-to-point arrangement when single, or a few, adrenergic or cholinergic fibers would make contact with small and well defined areas of the higher structures; i.e. systems-specific but transmitter-unspecific innervation would be the basis of local control. However, the arrangement of the, viz., noradrenergic fibers with their amazingly high degree of divergence tends to militate against this notion. So, we may have to wait for future research to discover additional channels that are capable, in a transmitter-specific manner, to influence the various local vigilances individually. There is, though, a third possibility of a mechanism involved in the focussing of local reactivity, i.e. vigilance. One could accept the fact that both, noradrenergic and cholinergic mechanisms have little ability to single out relatively localized functional areas and exert their influence, a priori, in an over-all fashion over the whole field of higher functions and do this in a kind of an *anticipatory fashion.* The final and definite adjustment and focussing of vigilance, within one or a few behavioral systems, could be assumed to be the result of other mechanisms, called into action secondarily in a kind of a *'follower' fashion.* In fact, we have discovered a system that may well be suited to narrow the focus of high reactivity through feedback inhibition of neighboring areas (Koella and Ferry[47]). We demonstrated that in cats the manipulation of the reactivity of one cortex – by application of barbiturates or by electrical polarization – led to, viz., a decrease of the amplitude of locally recorded evoked potentials, while the equivalent potential in the contralateral cortex was enhanced under these conditions (fig. 3). We explained this reciprocal pattern as being the result of activity in a cortico-reticular feedback

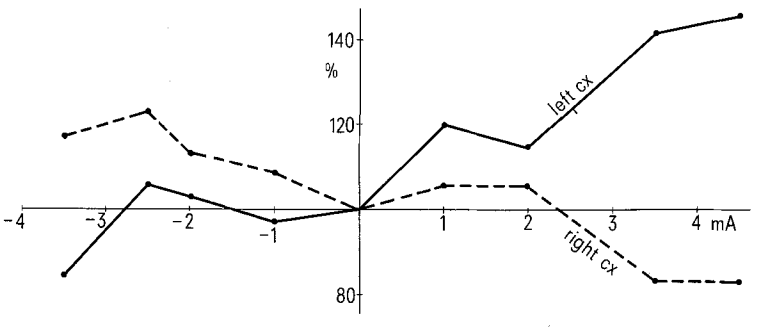

Figure 3. Relative amplitude of negative afterswing of evoked potential in left (—) and right (---) sensory-motor cortex, elicited by electrical stimulation of both superficial ulnar nerves in nonanesthetized, immobilized cat. Left cortex is subjected to electrical DC-polarization between electrodes placed in Ringer's pool over entire (left) cortex, and a set of intracerebral electrodes. Abscissa in mA; (+) and (−) refer to surface positivity and negativity, respectively. Note quasi-linear increase of negative afterswing with polarization current changing stepwise from −3.5 to +4.5 mA. Note reciprocal pattern in contralateral (non-polarized) cortex (Redrawn from Koella and Ferry[47]).

system. There is, we think, good reason to assume that such a feedback arrangement is liable to suppress, through a process akin to lateral inhibition, reactivity in extrafocal areas of the ipsilateral cortex too.

Dopaminergic pathways seem to be involved in the making of what one may refer to as 'motor vigilance'. Bilateral interruption of the dopaminergic pathways leads to akinesis and reduces 'motor initiative', yet leaves the cortical arousal mechanisms intact. This interpretation is supported by clinical observations in Parkinson patients who - due to hypodopaminergia in the nigro-striatal pathways - are slowly moving and akinetic, yet are not impaired, except in terminal cases, in their mental abilities. There is though evidence that schizophrenics suffer from hyperdopaminergic activity (Snyder et al.[82]) and that the neuroleptics act mainly through their blocking abilities on dopamine receptors. To what extent the disturbance of the higher functions in schizophrenic patients relates to a disturbance in dopaminergic activity is not yet clear.

Serotonin, in turn, seems to act as a 'general' antagonist of the catecholamines and of acetylcholine. From all what we know, this indoleamine evidently acts as a more universally effective (because it is less selective) vigilance-reducing agent that provokes, in many different areas and networks of the CNS, those functional changes that we refer to as sleeping patterns.

We have produced evidence that serotonin, in addition to its (putative) direct sleep-promoting effect, acts also as an 'antiwaking' agent (Koella[41,44]); its seems to enhance amplification in a reticulo-solitario-reticular feedback loop and thus to reduce activity in the ascending arousal systems.

As to the various polypeptides, there is no evidence (as yet) that they are involved, as ascending and diffusely projecting systems in the innervation of higher centers in a manner akin to that of the aminergic pathways. The polypeptides may act, however, as locally active modulators of transmitter release mechanisms and/or of the sensitivity of the various receptors. As to the 'sleep-inducing' peptides, there is cause for the assumption that they play a role as carriers of information signalling 'tiredness' in various areas of the CNS; information that needs to be conveyed to the brainstem centers that organize sleep. As regards the activating peptides, the available evidence is still too scanty to even attempt an interpretation concerning detailed mechanisms.

4. Application

We mentioned at the outset of this paper that a proper and universally applicable and acceptable concept of vigilance may be of paramount importance for the better understanding and clarification of many a problem in psychophysiology and psychopathology. The application of this concept for a 'new look' of the organization and regulation of sleep is the topic of a separate paper to be published shortly (Koella, this journal 1983). Here, we would like to elaborate briefly on this statement with just a few examples. There is, as was discussed earlier in this paper, rather convincing evidence that noradrenergic, dopaminergic, serotonergic, and cholinergic mechanisms are locally selective (or at least semi-selective) vigilance-modulating instruments. Is it then to be considered as merely a matter of chance that the drugs used in the treatment of the major mental diseases - the neuroleptics and the antidepressants - seem to exert their therapeutic action, in part at least, via interaction with these transmitter systems, and that the agents best suited to produce model psychosis or delirium - LSD-25, amphetamine, deliriants of the atropine-type reserpine - also seem to act via distorsion of these very same humoral systems? Are we to assume then that mental disease, as well as model psychosis and delirium are the behavioral manifestations of a disturbed (local) vigilance-regulating mechanism and thus of a faulty vigilance profile? Or are, in the light of modern views on cerebral asymmetry, the psychoses the result of an incorrect balancing of the left- and right-side vigilances? Can we look forward to the time when we will be able to reestablish the correct vigilance profile, through highly selective drugs that can be directed exclusively at the faulty vigilance locus, and thus begin to treat the disease in a truly causative manner?

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