Sleep-wakefulness: inverse deviation from randomness of neuronal firing patterns in the feline thalamus. A new form of homeostasis?

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Summary. During stereotypic goal-directed behavior, neurons in the feline nucleus reticularis thalami emitted specific temporal patterns, while other patterns occurred much less often than predicted by the random model. During subsequent slow wave sleep, the mean firing rate increased, but the patterns that were emitted during behavior were eliminated or suppressed far below chance level, while those that were previously suppressed became dominant.

The intuitive view is that slow wave sleep (SWS) reflects a homeostatic process aimed at removing the 'wear and tear' or irrelevant plastic changes generated in neuronal systems during goal-directed behavior, cognitive processes, and other functions[1-4]. There is, however, no quantifiable neuronal activity supporting this view because most neurons of the mammalian brain, particularly in the association, i.e. polymodal systems, tend to fire vigorously both during wakefulness and SWS[1,2,4,5]. This is particularly true for neurons in the thalamic reticular nucleus (RN) in which most cells increase their firing and emit long bursts of spikes during the onset of SWS and fully develop sleep[2,4,5].

Unlike the conventional analysis based on the firing rate or its periodicities (e.g. autocorrelation), the aim of the present study is to analyze the intraburst temporal patterns of action potentials emitted by the RN neurons during the animal's purposive behavior (lever pressing for 1 ml of milk reward) and subsequent SWS. The rationale of our experimental design and the working hypothesis stem from the following background. 1. The input-output relations of the RN[7,8], and the timing of the RN activity in relation to that of the thalamic relay nuclei[5,6,9] indicates that RN is critically involved in attention processes and gating of motor output by exerting inhibitory control over transmis-

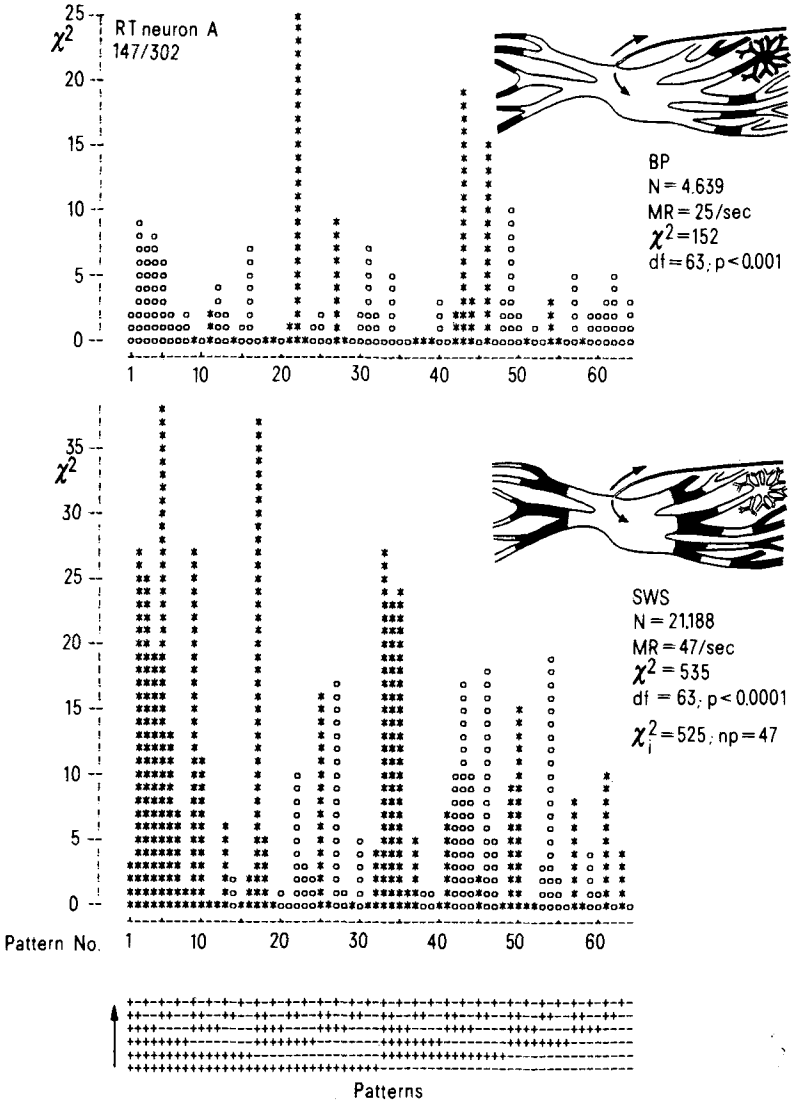

Figure 1. An example of tests for goodness of fit with the random model of pattern distribution in spike trains from 1 neuron during the animal's bar pressing performance (BP) and subsequent SWS. Individual χ^2 values (ordinate) are plotted for each of 64 possible sign permutations of the hexagram patterns (abscissa) shown at the bottom plot; the patterns are printed vertically and are numbered from left to right. A total of 14 patterns that were emitted during BP (starred columns) were subsequently suppressed below chance level during SWS (open circle columns), and, vice versa, 33 patterns that were suppressed during BP were subsequently emitted during SWS. The sum total of these 47 'inverse' pairs of χ^2 values (χ^2_i) indicates how strong was this trend. The BP and SWS episodes if considered separately, each showed highly significant deviation from the random model as indicated by the sum total of the χ^2 values and degrees of freedom (df = 63). Note that the mean firing rate (MR) markedly increased during SWS. The analyzed BP episode is the last one of 3 consecutive records separated by less than 2-min pauses; the firing patterns were virtually identical in all 3 episodes.
The value of N refers to the number of hexagram patterns contained in each sample. In this and other neurons, the inversion of pattern distribution was already evident prior to SWS, after the animal ceased bar pressing (not shown). The 2 inserts represent the soma and proximal dendrites of an idealized reticularis neuron drawn after the Golgi impregnation studies by the Scheibels[27]. To account for the observed inversions in the distribution of firing patterns, it is proposed that the dendritic distribution of synaptic drive associated with bar pressing (black dendritic regions) is substantially different from, and probably inversely related to, the distribution associated with SWS firing patterns. The 2 arrows in the vicinity of the axon hillock indicate the double role of the action potential, one being the propagation of impulses along the axon, and the other representing the repercussive depolarizing influences on the soma-dendrites believed to be crucial in determining the neuron's firing patterns[15].

sion to cortex of sensory input and impulses from the cerebellum[10,11]. These multiple functions and the polymodal input impinging on unusually long dendrites of the RN neurons[8] suggest a great capacity for emitting a wide spectrum of firing patterns. 2. In verified instances, in which neurons receive axonal contacts from more than one pathway, usually mediated by different transmitters, such synapses are not randomly distributed on the soma-dendrites, but are precisely segregated to well defined regions[12-14]. Moreover, if selectively activated, each projection produces specific firing patterns at the axon hillock[14]. The specificity of patterns is determined by many factors, among which the most important are the spatial distribution of synaptic drive and the repercussive, i.e. retrograde depolarizing influences from the axon hillock that invade the soma-dendrites following each action potential and interact with dendritic postsynaptic potentials[15]. 3. Desensitization of receptors for specific transmitters is known to develop readily upon repetitive activation of specific brain pathways[16,17]. Moreover, large (up to 77%) changes in receptors for most putative transmitters occur in behaving animals in relation to sleep-wake cycles[18]. Hence, if desensitization during the animals's long bar pressing performance does not develop randomly, but at specific soma-dendritic sites owing to segregation of synapses, then, upon termination of performance, the patterns controlled by these receptors should not only return to pseudorandom level, but should drop below that level. The momentary pseudorandom neuronal interactions should provide synaptic drive sufficient for the emergence of different patterns determined by more effective receptor patches, presumably adjacent to those that had been desensitized. To our surprise, such inversions of pattern distributions were indeed evident during the onset and fully developed SWS. The working hypothesis is summarized in 2 inserts of figure 1 in which the idealized RN neuron is driven during bar pressing (BP) and SWS by different receptor patches (black dendritic regions) whose spatial distributions are inversely related to one another.

Methods. Ten adult cats were trained to press a lever for 1 ml of milk reward which was presented on a 1:7 fixed ratio schedule. The implantation of epidural EEG electrodes under anesthesia, the stereotaxic implantation of microelectrodes in the RN for extracellular recording of action potentials, and the verification of recording sites, have been previously described[3,19,20]. The results are based exclusively on neurons located within the narrow band of the RN, according to the stereotaxic atlas[21], in plane +10(L6 to L7; H+6 to H+6.5), plane +11(L6.5 to 7.5; H+3 to H+4), and plane +12(L6; H+4). The 11 neurons, each studied for at least 5 h, yielded a total of 44 long and paired episodes of BP and subsequent SWS. Temporal patterns in neuronal spike trains were analyzed using the non-parametric method which is based on relative relations between sequential spike intervals[3,19,20]. Briefly, the spike intervals were measured with a resolution of 0.1 msec; intervals greater than 800 msec were treated as 'punctuation' gaps, parsing the spike trains into 'phrases' (for rationale of this procedure and 0.1 msec resolution, Marczynski et al.[20]). The intervals were compared in sequential pairs: if the 2nd interval in a pair was greater or smaller than the 1st one, a sign (+) or (−) was entered respectively into sequential memory bins of a PDP-11-45 computer. Each 'phrase' of signs was then parsed into 'words' composed of 6 signs which can occur in 64-sign permutations, if the sequence of signs is taken into account. Each pattern has a specific theoretical probability of occurrence, if the assumption is made that the intervals are random and/or independent from one another[3,19,20]; for instance, in 2 extremes, the probability of pattern (+ − + − + −) equals 0.053968, while that of pattern (+ + + + + +) equals 0.000198. For specific behavioral states, the computer compared the empirical and the theoretical occurrences of each pattern; the differences and the direction of deviation from the random model were quantified using chi square statistics[3,19,22]. Although the mathematical underpinning of the random model has been discussed before[3,19,20], the 2 most salient points deserve mentioning: a) the distribution of patterns is independent from the shape of the spike interval histogram; and b) the random model is sensitive to the history of the spike train, because the sequence of the inequality signs is taken into account, an attribute uniquely suitable for studying neuronal firing presumably endowed with plasticity and 'memory'.

Results. Figure 1 shows a typical example of the analysis of patterns in spike trains from one of the RN neurons. The computer printed the χ^2 values (ordinate) for each of the 64 possible inequality patterns (abscissa) shown at the bottom. The sign patterns are printed vertically and are numbered from left to right. Many of them occurrred much more often, and others occurred less often than predicted by the random model (starred and open circle columns respectively). Specific patterns that were emitted during bar pressing (BP) were subsequently suppressed below chance level during SWS, despite the increase in the mean firing rate (MR). Conversely, patterns that occurred less often during BP than expected on the basis of the random model were subsequently strongly emitted during SWS. Most important, the emission magnitudes of individual patterns during BP and the magnitudes of their subsequent suppressions during SWS were not random, but graded and

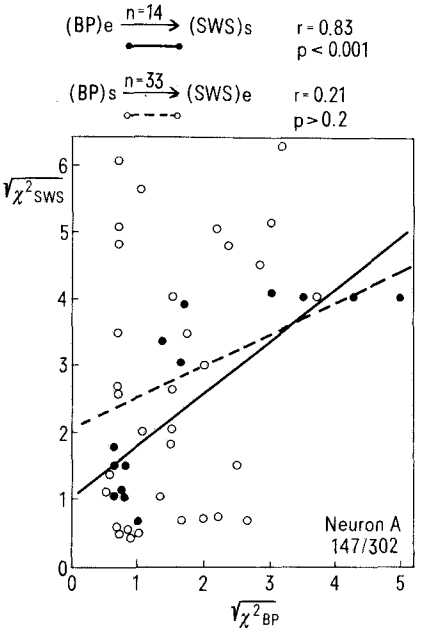

Figure 2. An example from 1 neuron of the correlation between the emission magnitudes of patterns during BP and their subsequent deficits, i.e. suppression below chance level, during SWS (BPe→SWSs). The emissions and suppressions were measured in $\sqrt{\chi^2}$ values (the data are from figure 1). As indicated at the top, a total of 14 patterns showed such reversals. The magnitudes of these inverse deviations from the random model, if plotted against one another ($\sqrt{\chi^2_{BPe}}$ vs $\sqrt{\chi^2_{SWSs}}$), showed a highly significant correlation (filled circles - solid line). In the same neuronal spike trains, a total of 33 reversals going from BP suppression to SWS emission (BPs→SWSe) were also present. However, after plotting these values against one another, no correlation was found (open circles - dashed line).

positively correlated (fig. 2). However, no such correlation was found between the magnitudes of the inversions going from suppression to emission. This behavior of neuron A was not unique, because across all 11 RN neurons studied, and a total of 44 paired BP/SWS episodes which encompassed the distribution of 72,400 and 197,021 hexagram patterns respectively, the correlation between the emission magnitudes and subsequent suppressions below chance level was significant ($r_w = +0.65$; $p \cong 0.02$; weighted correlation coefficient obtained by Fisher's 'z' transformation method of individual r values[23]). However, the magnitudes of reversals going from suppressions to emissions showed no correlation ($r_w = -0.21$; $p > 0.8$).

Discussion. Receptor desensitization is known to be affected by agonist concentration, exposure time, and metabolic alterations, and is therefore a graded process[16,17]. Hence, it offers a plausible explanation for the correlation between the emission magnitudes or patterns and their subsequent deficits. In addition to the RN neurons, comparable inversions of pattern emissions have also been observed in the feline nucleus centrum medianum[24,25]. Such a behavior of single neurons has implications for the function of SWS and its nature, which still remain elusive despite the evidence that SWS is indispensable for normal behavior[1,2] and survival[26]. Hence, the question arises of whether or not there is a good reason to suspect that unabated but inversely distributed patterns of neuronal firing may be linked to a recovery process of SWS. In vitro studies showed that, upon simple removal of a receptor agonist, the resensitization of brain β-adrenergic receptors is a slow process. However, a brief potassium-induced depolarization promptly resensitizes the receptors[17]. Similar results have been reported for cholinergic receptors. This indicates that barrages of depolarizing impulses at soma-dendritic sites, presumably adjacent to those that had been desensitized, may indeed have a recuperative effect during SWS.

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Accumulation of taurine in the nasal mucosa and the olfactory bulb

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Summary. Using whole-body autoradiography of ^{14}C-taurine in mice we have observed a high concentration in the nasal mucosa followed by accumulation in the olfactory bulb at longer survival times. When ^{14}C-taurine was administered in the nasal cavity unilaterally, a high accumulation was observed in the ipsilateral olfactory bulb.

The sulfonic amino acid taurine is known to be involved in the conjugation of bile acids[2,3], and has also been suggested to act as an inhibitory neurotransmitter or a neuromodulator in the eye and in the brain[4–6]. High uptake of taurine has been observed in the retina and in the CNS especially in the olfactory bulb[7].

In our laboratories, the distribution of ^{14}C-taurine in mice was studied using whole-body autoradiography. ^{14}C-taurine, uniformly labeled, with a spec.act. of 113 mCi/mmole was obtained from the Radiochemical Centre, Amersham, England. The radiochemical purity was 99%. Mice of the C57BL strain, of both sexes, were used. Nonpregnant mice weighed about 20 g and the pregnant mice 28–35 g. The day of conception (day 0) was determined by the presence