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**Review**

# Lateralized rhythms of the central and autonomic nervous systems *

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This paper reviews lateralized ultradian rhythms in the nervous system and their unique place in evolutionary development. The rhythmic lateralization of neural activity in paired internal structures and the two sides of the central and autonomic nervous system is discussed as a new view for the temporal and spatial organization of higher vertebrates. These lateralized neural rhythms are integral to the hypothesis of the basic rest-activity cycle. Rhythms of alternating cerebral hemispheric dominance are postulated to be coupled to oscillations of the ergotrophic and trophotrophic states. The nasal cycle is coupled to this cerebral rhythm. This lateralized central and autonomic rhythm is discussed in relationship to ultradian rhythms of neuroendocrine activity, REM and NREM sleep, lateralized rhythms of plasma catecholamines, and other lateralized neural events. The relationship of this phenomenon to stress and adaptation is postulated. The effects of unilateral forced nostril breathing is reviewed as a method to alter cerebral activity, cognition, and other autonomic dependent phenomena.

## I. INTRODUCTION

### *I-A. Towards an integration of the temporal and structural organization of higher vertebrates: lateralized ultradian rhythms in the nervous system*

Lateralization of function is a marker of increasing complexity in the evolutionary development of biological systems. Bilateral symmetry is a distinguishing characteristic of invertebrates; only two groups of invertebrates, the gastropod molluscs and the decapod crustaceans, have bilateral asymmetry as a common feature (Chapple, 1977). The obvious benefit of bilateral limbs is improved movement capabilities and bilateral sensory organs provide enhanced awareness of the environment. Any internal duplication of organs enhances survivability in the event of injury and distributes workloads. Prior to the appearance of bilateral symmetry in evolutionary development, the primary structural organization in invertebrates was translational symmetry in which there is a segmental organization along the longitudinal axis; each successive segment is a primitive replica or serial homologue of the one before it (Chapple, 1977).

Bilateral asymmetry appeared after the evolutionary stage at which there was simultaneous activation of the contralateral limbs. Uncoupling of this rigid pattern of activation makes possible more complex functions (Chapple, 1977). The

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mechanisms and structures that allow independent activation of the two sides of the body permit specialization of function, thus adding to biological complexity.

The next major step in the evolution of bilateral asymmetries may be the development of the rhythmic lateralization of neural activity in paired internal structures; the two sides of the central and autonomic nervous systems (CNS and ANS) may become partially independent of each other and complement each other's functions. This partial autonomy can contribute to specialization of each side, adding to the adaptative possibilities of the organism. Paired internal organ systems may also exhibit partial autonomy. One consequence of this autonomy could be the specialized support of different energy producing or conserving activities associated with metabolic states known as the ergotrophic and trophotropic states, or active and resting states, respectively.

While circadian rhythms subserve adaptation to the light–dark cycle, the ultradian rhythms of lateralized neural activities help to organize the functions of biological systems to meet primary bodily needs. These functions are associated with activities such as work (hunting), rest (healing), eating and the many other behaviors that are identified by Kleitman as defining the basic rest-activity cycle (BRAC) (Kleitman, 1982, 1967, 1961). Kleitman does not include lateralized neural rhythms in his definition of the BRAC, and it is the purpose of this paper to demonstrate their relevance. Although it is not clear whether the ultradian or circadian rhythms emerged earlier in evolution, it may be that the ultradian phenomenon of the BRAC is more vital to the integrity of the organism. In the sleep-wake cycle of the newborn human, for example, the ultradian rhythm is apparently more primitive than the circadian rhythm (Hellbrugge, 1974). In fact, there are ultradian rhythms in human fetal motor activity that are the earliest signs of the BRAC (Granat, et al., 1979; Sterman, 1967). This may be another example of how ontogeny recapitulates phylogeny.

The relationship of the BRAC to the lateralized rhythms of the CNS and ANS is the primary focus of this paper. The relationship proposed here for these phenomena provides both a new perspective and a new organizing principle for structural features and temporal activities in higher vertebrates. While metabolic activities in the body can be viewed as a sea of rhythmic changes, ultradian rhythms of lateralized neural activity may be viewed as a fundamental stage in the evolution of organizational development. Studies concerning the self-regulation of this ultradian rhythm of lateralized neural activity are also discussed.

### *I-B. Lateralized rhythms of the autonomic nervous system*

The most obvious rhythmic shift of a lateralized autonomic function is the nasal cycle (Stoksted, 1953; Hasegawa and Kern, 1978; Kayser, 1895, 1889). Although the phenomenon of the nasal cycle is not widely known it has been extensively studied and is defined as an alternating congestion and decongestion of opposite nostrils where there is a vasoconstriction in one nasal turbinate paralleled by vasodilation in the other. The mucosa of the nose are densely innervated with autonomic fibers and the dominance of sympathetic activity on one side produces vasoconstriction in the turbinates, while the contralateral nostril exhibits a simultaneous dominance of parasympathetic activity that causes swelling. Kayser first documented the nasal cycle in 1889 and described it as reflecting the "alternation of vasomotor tone throughout the periphery on the two sides of the body" (Kayser, 1895, 1889). This observation is only now gaining in significance. Studies of the nasal cycle with reviews have been made in 1968 by Keuning and in 1986 by Haight and Cole. In 1951, Beickert looked at other structures in relationship to the nasal cycle and published a study on "Half-sided rhythms of Vegetative Innervation". He observed how lateralized differences in secretions of the nose and the eye varied in phase with the nasal cycle. He also observed how autonomic-related pupillary changes on the two sides could vary with the lateralized changes in the nose under stellate ganglion block.

Keuning (1968) reviewed numerous studies of the nasal cycle and concluded that the average cycle length is about 3 to 4 h and ranges anywhere from 2 to 8 h. Hasagawa and Kern (1978) studied 50 human subjects and found a mean duration of 2.9 h, ranging from 1 to 6 h. These studies were all done under laboratory conditions during the day. Cole and Haight (1986) report results from two subjects which showed the nasal cycle was continuous throughout the 24 h period. Laboratory conditions, which impose resting states, may skew the cycle towards longer than normal periods. The frequency of sampling and what defines a cycle has confounded the discussion of cycles. There are wide variations in the reported length. One subject exhibited a transition in dominance every 20 min for four consecutive cycles during a 90 min recording period (Werntz, et al., 1983). This was observed when a continuous recording was made of nasal dominance. The same subject showed a much longer cycle on a subsequent day. The nasal cycle has also been demonstrated in rats and rabbits (Bojsen-Moller and Fahrenkrug, 1971), in anesthetized pigs (Ashley and Lea, 1978), and cats (Bamford and Eccles, 1982), and may occur in all mammals.

Another example of a normal half-sided reaction in autonomic function exists between the nose and the lung. There is a unilateral nasal-pulmonary reflex mechanism which is clearly elicited when there is a forced inhalation through one nostril producing a significant increase in inflation of the homolateral lung compared to the contralateral lung (Samzelius-Lejdstrom, 1939; Stoksted, 1960; Drettner, 1970; Sercer, 1930). Samzelius-Lejdstrom studied 182 individuals and showed that the movements of one thoracal half were much more inflated compared to the contralateral lung in 94% of the subjects. She also observed that "variations in width of one half of the nasal cavity caused variations in the amplitude of the movements of the homolateral thoracal half". Whether she was aware of the nasal cycle or not, she observed how differences in nasal congestion could affect the lung. She also reports that in cases of tuberculosis where there is primarily a lateralized deficit, there is a simultaneous pathological phenomenon of the homolateral nasal and thoracal halves (Samzelius-Lejdstrom, 1939). Wotzilka and Schramek (1930) studied rabbits under experimental conditions and showed that if coal dust was inhaled through one nasal opening, it was deposited in much larger quantities in the homolateral lung. These studies all indicate that lateralized rhythms of lung inflation are likely to parallel the nasal cycle since a neural reflex exists between the nose and lung. This does not discount the central mediation of a rhythm of lateralized predominance in lung inflation. A dominant nostril on one side has greater sympathetic tone, as would the homolateral lung. However, while sympathetic activity produces vasoconstriction in the nose, it produces vasodilation in the vessels of the lung, thereby producing a unilateral relationship of predominance in activities between the nose and lung.

Neligan and Strang (1952) report another remarkable example of lateralized autonomic tone that they call the "harlequin color change in the newborn". While this study looked primarily at premature infants, or infants born with infections, a few similar observations in normal babies were also reported. The harlequin color change occurs only on one half of the body and lasts anywhere from 30 s to 20 min. The baby can be in almost any position as long as it is mostly turned on one side. The upper half of the body becomes pale and there is always a clearcut line of demarcation running exactly along the midline of the body. The attack could be abruptly curtailed by removing the baby from its side, but in some cases the pale and flushed sides could be reversed by turning the baby onto its opposite side. Neligan and Strang surmised "the precise distribution of the color changes suggests a temporary imbalance in the central nervous system (possibly in the hypothalamus)" and that this phenomenon might be produced by gravity in infants that had labile nervous systems. Although Neligan and Strang were apparently unaware of the nasal cycle as a normal example of lateralized autonomic function, in 1927 Heetderks also observed that lateral recumbancy could induce a switch in autonomic tone as exhibited by a change in nasal dominance. He assumed that this was a gravitational effect and concluded "that the distribution of the nasal vascular contents must be largely controlled by gravitation". In 1934, Kuno described lateralized patterns of perspiration in humans and termed this phenomenon the "hemihidrotic reflex". He stated that "lying on one side caused a remarkable increase in sweating universally over the upper half of the body", suggesting that gravity also played a role. Others have investigated posture and lateralized patterns of perspiration (Takagi and Sakurai, 1950; Kawase, 1952; Takagi and Kobayasi, 1955; Ferres, 1958) and have demonstrated that the lateral recumbent effect can be mimicked while the subject is in a vertical position by applying pressure to an axillary point near the fifth intercostal space. Haight and Cole (1986) studied and reviewed reports on the effects of posture and pressure on the nasal cycle which showed that pressure on the axillary point, and several other areas of lesser affect, can induce the increased sympathetic tonus on the contralateral side of the body and alter the phase of the nasal cycle.

Kennedy, et al. (1986) have also studied how sympathetic tonus can differ greatly on the two sides of the body. They looked for differences in sympathetic tone in resting subjects by assaying norepineprhine (NE), epinephrine (E) and dopamine (D) in the antecubital venous circulation in both arms by simultaneously sampling

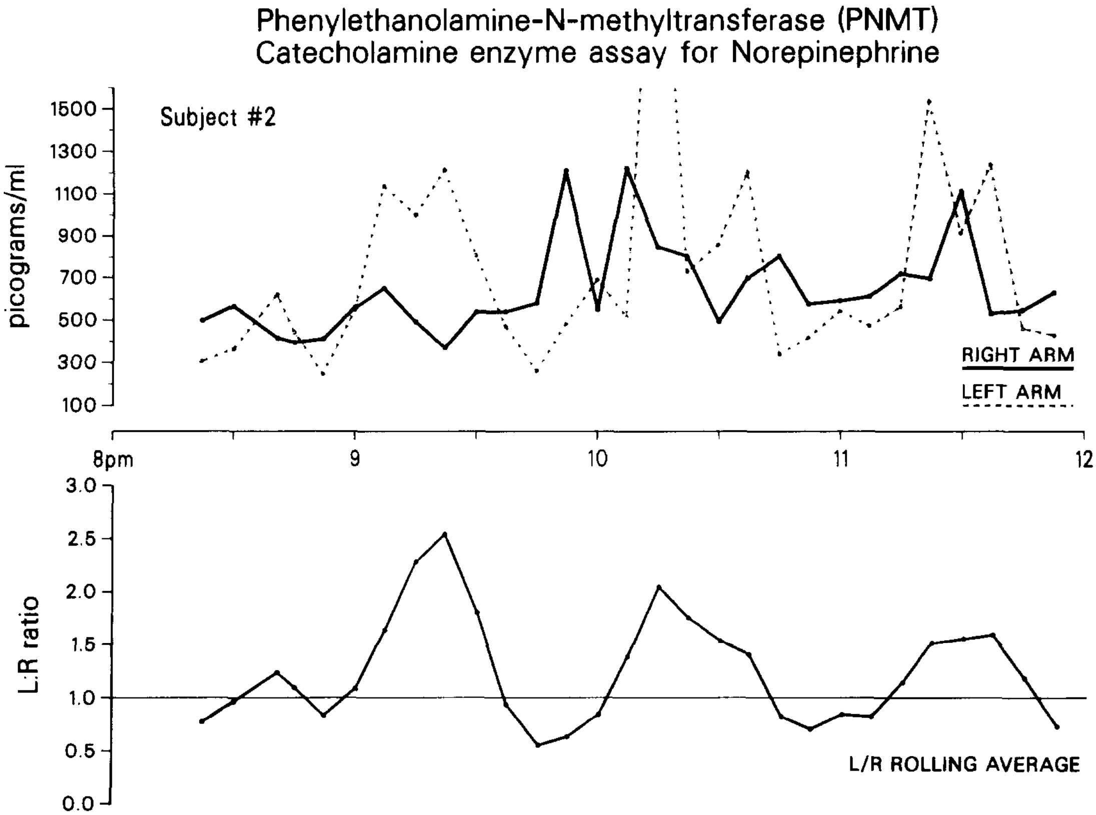


Fig. 1. Top: Variations in plasma NE levels (pg/ml) were measured at 7.5 min. intervals in both right (unbroken line) and left (hatched line) arm. Raw data are represented for subject 2 from 8:22 pm to 12 midnight. NE was measured by radioenzymatic assay with phenylethanolamine-*N*-methyltransferase and ([$^{3}$H]SAM). The 10:08 pm NE value for the left arm is 2874. Bottom: The left: right ratio of the values of the two arms from above are represented as a rolling average. Values in the curve above 1.00 represent greater levels of NE in the left arm and values below 1.00 are greater levels in the right arm. Time scale is as above. (Reprinted with permission from Kennedy, Ziegler, and Shannahoff-Khalsa (1986) Life Sciences.)

every 7.5 min. Fig. 1 with NE and Fig. 2 with D show how levels in plasma catecholamines can alternately rise and fall in the two arms. Fig. 3 shows how NE, E, and D all co-vary with a similar but not identical pattern of variation on the two sides. Fig. 4 shows how the nasal cycle is paralleled by lateralized variations in NE levels even when there is not a complete transition in the nasal cycle. This study demonstrates that lateralized shifts in sympathetic tonus are associated with lateralized shifts in the concentrations of catecholamines in peripheral circulation.

Kalen, et al. (1989) studied extracellular hippocampal NE and serotonin in freely moving rats using a microdialysis technique. Using 30 min sampling over a 24 h period they found "spontaneous" or "substantial fluctuations" which correlate with the activity state of the animal. These fluctuations were not studied in both hippocampi, or as rhythms per se, but eight peaks are shown within the 24 h period.

When Benton and Yates (1990) compared the left and right adrenal blood flows in conscious dogs at rest by simultaneously sampling from the lumboadrenal veins, they found that "there were no cases in which the mean flows were not significantly different". They found that the right adrenal gland averaged 1.8 g in weight and the

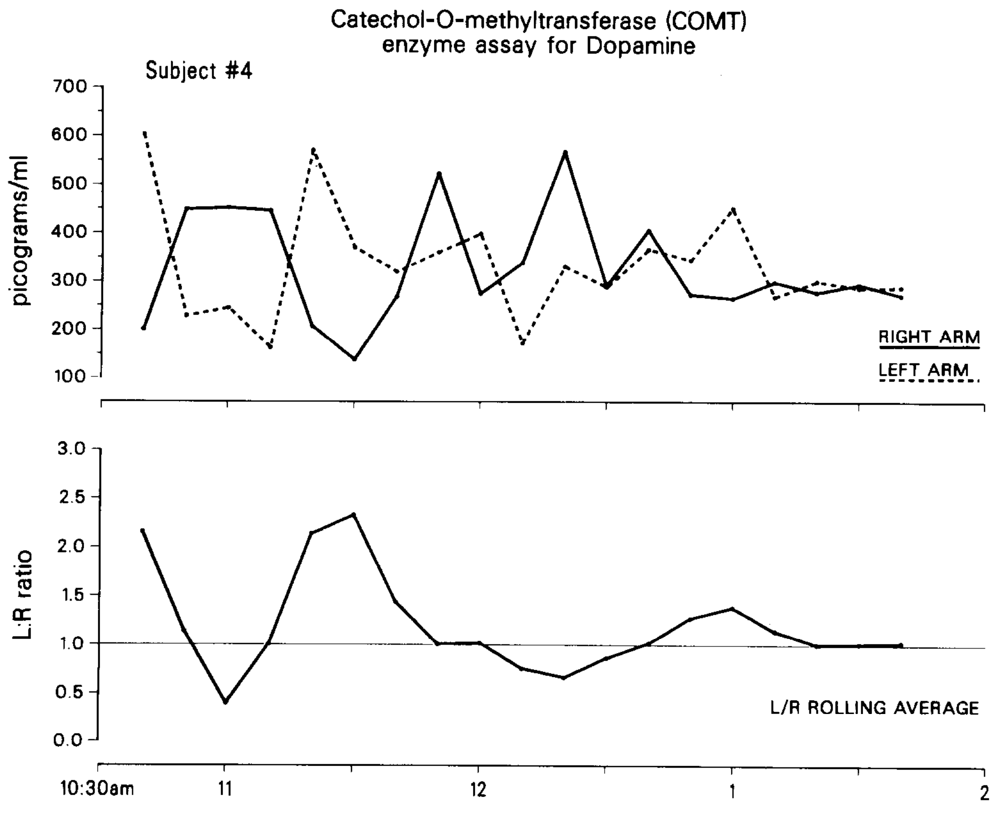


Fig. 2. Top: Variations in plasma DA levels (pg/ml) were measured at 7.5 min. intervals in both the right (unbroken line) and left (hatched line) arms. Raw data for subject 4 are represented from 10:37 am to 1:45 pm. DA was measured by radioenzymatic assay with catechol-*O*-methyltransferase and ([$^3$H]SAM). Bottom: The left: right ratio of the values of the two arms from above are presented as a rolling average. Values in the curve above 1.00 represent greater levels of DA in the left arm and values below 1.00 are greater levels in the right arm. (Reprinted with permission from Kennedy, Ziegler, and Shannahoff-Khalsa (1986) Life Sciences.)

left gland averaged 1.3 g. However, they state that "paradoxically, the flows seemed unrelated to the mass of the glands" and at some points in the recording period there were transitions in which gland had higher rates of blood flow. They also observed an approx. 90 min periodicity in adrenal blood flows and cortisol secrètion rates. These left/right variations in adrenal blood flow are further evidence of a lateralized rhythm in the ANS. Similar findings of lateralized differences in blood flow have also been reported for the two kidneys (Springorum and Centenera, 1938).

### *I-C. Lateralized rhythms of the central nervous system*

Generally, it is believed that the ANS controls only vegetative-visceral and homeostatic systems. However, recently it has been shown that the lateralized rhythms of the ANS are also coupled to and have a major regulatory influence on the CNS. Werntz et al. (1980, 1983) showed that the nasal cycle is coupled to an alternating lateralization of cerebral hemispheric activity in humans. Electroencephalographic (EEG) activity was continuously recorded from homologous sites on the

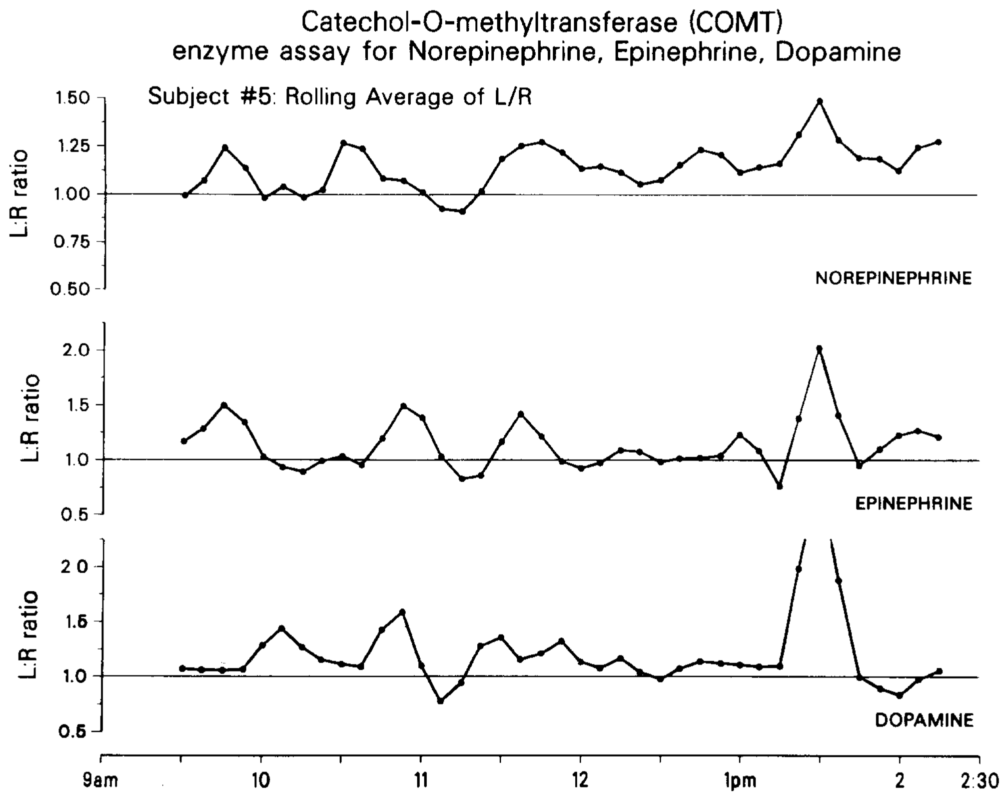


Fig. 3. Top: The plasma variations of the left:right ratio of the two arms of subject 3 are generated by dividing the average value from the triplicate assay for NE at each time point in each arm. NE was determined by radioenzymatic assay using catechol-*O*-methyltransferase and ([$^3$H]SAM). Time scale is 9:30 am to 2:15 pm, with plasma samples every 7.5 min. The rolling average of the left:right ratio is represented. Middle: Plasma concentrations and the rolling average of the ratios for both arms were determined as above using the same blood sample during the same assay for E. Bottom: Plasma concentrations and the rolling average of the ratios for both arms was determined as in the top section using the same blood sample during the same assay for D. Missing value at 1:30 pm is 2.81. (Reprinted with permission from Kennedy, Ziegler, and Shannahoff-Khalsa (1986) Life Sciences.)

two sides of the head, then the signals were rectified, integrated, and subtracted. The right-left EEG difference in each of the four major frequency bands correlates well with the nasal cycle (Fig. 5) in 19 of 19 subjects. Relatively greater EEG amplitudes were contralateral to the dominant nostril. Unless there was a major shift in the nasal cycle, no significant shift was observed in the EEG. Fibers of the ANS travel uncrossed between the CNS and periphery (Sapen, et al., 1976). Therefore, it seems likely that the hemisphere contralateral to the dominant nostril would have relatively greater blood flow due to the dominance in the expected cerebral parasympathetic activity. Several studies have been conducted that confirm this conclusion.

Klein and Armitage (1979) first observed the ultradian rhythms of alternating cognitive performance efficiency by studying verbal and spatial skills. They tested eight subjects with a verbal and spatial task every 15 min for 8 h. They noted ultradian variations with a major peak of activity every 90–100 min. Best performance on the verbal task was 180 degrees out of phase with best

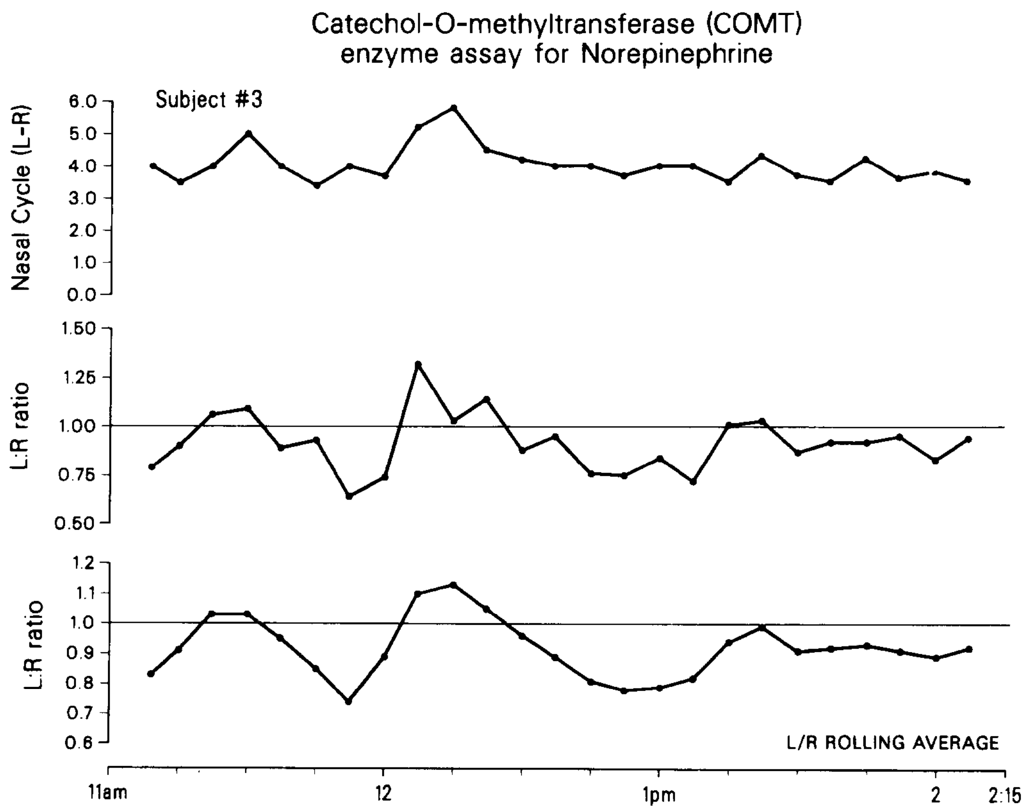


Fig. 4. Top: The nasal cycle determination of subject 3 is plotted as the raw data of the left minus right (L–R) value versus time. The (L–R) value was measured at each time point for blood sampling, every 7.5 min. The subject fluctuates in left nostril dominance during the recording period. The nasal cycle was shifted 7 min. to the left. Middle: The raw data of the plasma variations of the left : right ratio of the two arms of subject 3 are generated by dividing the average value from the triplicate assay for NE at each time point in each arm. NE was determined by radioenzymatic using catechol-*O*-methyltransferase and ([$^3$H]SAM. Time scale is 11:07 am to 2:07 pm NE values greater than 1.00 represent greater plasma levels in the left arm. Bottom: The same data as the middle section is represented here as the rolling average of the ratios, using the formula (1 : 2 : 1). (Reprinted with permission from Kennedy, Ziegler, and Shannahoff-Khalsa (1986) Life Sciences.)

performance on the spatial task. Klein et al. (1986) used the same cognitive tests to assess performance efficiency during different phases of the nasal cycle. They observed significant relationship between the pattern of nasal airflow during normal breathing and spatial vs. verbal performance. Right nostril dominance correlated with enhanced verbal performance, or left brain activity, and left nostril dominance correlated with enhanced spatial performance. Shannahoff-Khalsa et al. (1991) using different cognitive tasks from those of Klein et al. (1986), have also shown that left nostril activity is associated with enhanced spatial skills, while right nostril activity and peak verbal skills are correlated. Leon-Carrion (1989) and Leon-Carrion and Vela-Bueno (1991) have also studied the chronobiological nature of cognitive performance using a test that requires perceptive motor velocity and another that requires peceptive motor velocity and conceptual changes. Both of these tests are thought to differentiate cognitive styles. Their results are similar to that of Klein and Armitage (1979) and also indicate that the two hemispheres alternate in dominance. They find the greatest spectral power in the range between 85 and 100 min, with

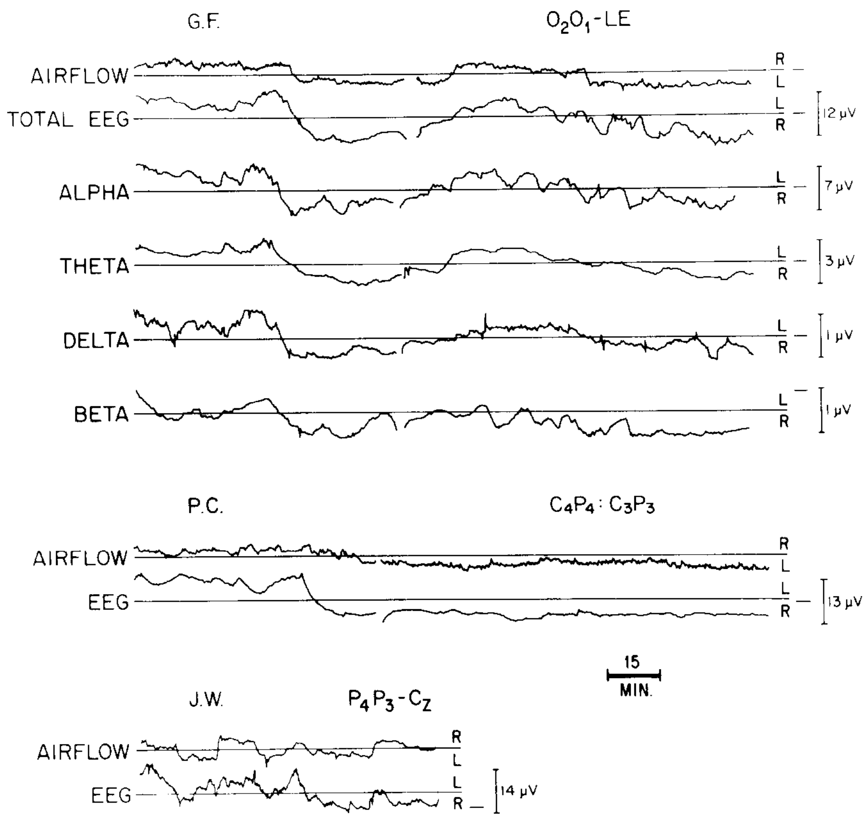


Fig. 5. Airflow tracings: Points above the baseline indicate greater right nostril airflow and points below indicate greater left nostril airflow. Total EEG is 1–35 Hz. Alpha (8–13 Hz.), Theta (4–8 Hz.), Delta (1–4 Hz.), and Beta (13–35 Hz.) tracings were filtered through an analog filter before integration. This baseline is drawn to visually enhance the similarity of the basic correlation of the two phenomena. The dash to the right of the EEG tracings indicates the true zero line where the right and left EEG amplitudes are equal. The bar and its numerical equivalent next to the integrated EEG tracings represent the acutal calibrated amplitudes in microvolts. Three different subjects are exhibited here with their different profiles. (Reprinted with permission from Werntz, Bickford, Bloom, and Shannahoff-Khalsa (1983) Human Neurobiology.)

a maximum peak at 90 min. Armitage (1986) observed similar ultradian rhythms in EEG activity that were measured during extended task performance. EEG experiments have provided evidence that rhythms of alternating cerebral cortical activity also occur during sleep in humans (Armitage, 1986; Goldstein, et al., 1972; Banquet, 1983). LaBerge and Shannahoff-Khalsa (unpublished results) have studied the nasal cycle in relationship to rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. Preliminary results show that right nostril dominance is correlated with REM sleep and left nostril dominance with NREM sleep stages. Alexiev and Roth (1978) monitored nasal airflow on both sides with stages of REM and NREM sleep. Minor changes in airflow differences may have been obscured since visual methods rather than computer assisted analysis were used to detect changes. In healthy subjects they found that:

"During the first 3 h of sleep slight differences in amplitude were observed in some cases: that is, respiration through the right nostril was relatively weaker than through the left, which remained at a level recorded at the beginning. This change was not permanent and changes in position of the body and movements of the head, as well as REM sleep events, led to an equalization of the

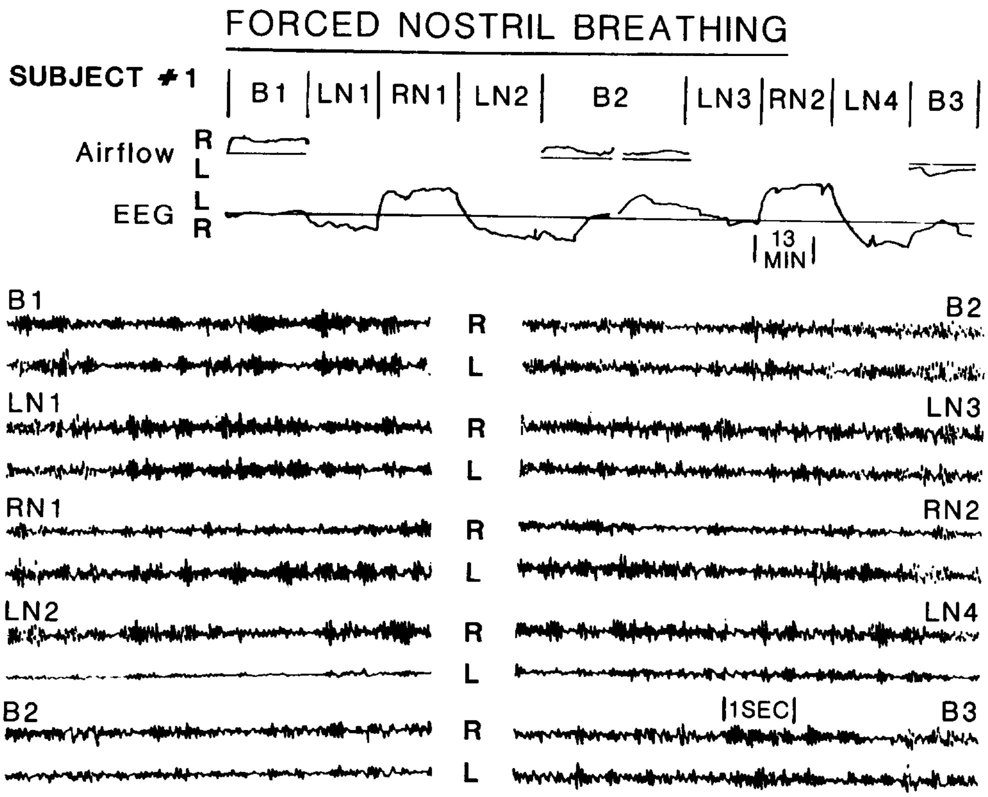


Fig. 6. Effect of forced uninostril breathing on EEG asymmetry. Subject 1 - Trial 2. Top: 'Airflow' tracing - points above the baseline indicate greater right nostril airflow and points below greater left nostril airflow. Periods of forced nostril breathing are indicated. 'EEG' tracing - points above the baseline indicate relatively greater left hemisphere EEG amplitude; points below relatively greater right hemisphere amplitude. B, baseline, LN, left nostril breathing, RN, right nostril breathing. Montage, ($O_2$-$P_4$; $O_1$-$P_3$). Bottom: representative segments of the primary EEG that were integrated and subtracted to produce the tracings in the top section. For each pair the top tracing is from the right hemisphere and the bottom is from the left hemisphere. (Reprinted with permission from Werntz, Bickford, and Shannahoff-Khalsa (1987) Human Neurobiology.)

amplitudes on the two sides. These periods began through NREM stage 2 and continued from several min up to 40 min. In the 4th or 5th h of nocturnal sleep, at the end of the 3rd sleep cycle, several min after the onset of REM sleep, an abrupt change in the pattern of respiration took place: respiration through the left nostril was completely blocked, while that through the right nostril displayed a hyperventilatory type with an amplitude about 3-times greater than that recorded during wakefulness, which continued to the end of REM sleep, respiration through the left nostril was not restored to the original level, and respiration through the two nostrils became more equal after the subjects awakened. With two cases of hypersomnia the right nostril was blocked and hyperventilatory type of respiration took place in the left nostril during REM sleep, and in the remaining part of the night the patients breathed only through the left nostril. In the two cases of narcolepsy-cataplexy the same changes in the pattern of respiration were observed as in hypersomnia, except that during the second night in one of the subjects a sleep onset REM period was recorded during which the passage of air through the right nostril was blocked and this state remained until awakening in the morning."

They were not aware of the phenomenon of the nasal cycle, but concluded "the nasal venous plexi could be a phenomenon similar to the congestion of corpus cavernosum penis leading to penile erection, which is a regular sign of REM sleep."

Goldstein, et al., in 1972 and Barcaro, et al., in 1986 have shown that the EEG amplitudes in the two hemispheres during sleep are related to the phases of REM and NREM sleep. Goldstein, et al., (1972) suggest that "the difference in hemispheric amplitude relationships during NREM and REM sleep may eventually prove to be a neurophysiological concomitant of the change in brain function during these stages". Barcaro et al. (1986) report that, "For 9 out of 11 examined subjects, both a visual comparison with the hypnogram and a statistical analysis showed the existence of cyclic variations during the night in the delta and/or sigma correlation coefficient" of EEG. Other EEG studies in man report similar findings (Rosekind, et al., 1979; Hirshkowitz, et al. 1980; Herman, et al. 1981) although one study failed to find a difference (Antrobus, et al. 1978). Studies by Pivik, et al. (1982) and Moffit et al. (1982) correlated EEG asymmetries with sleep stages and dream recall. Others have reported alternating cerebral dominance in several nonhuman species during sleep using EEG. These include rabbits (Goldstein, et al., 1972; Nelson, et al., 1977), cats (Goldstein, et al., 1972; Webster, 1977), pilot whales (Shurley, et al., 1969; Serafetinides, et al., 1972), dolphins (Mukhametov, et al, 1977), and fur seals (Mukhametov, et al., 1985). There is other evidence in humans which also suggests the existence of a natural rhythm of alternating dominance between the two cerebral hemispheres. Work by Gordon, Frooman, and Lavie in 1982 and by Lavie, Matanya, and Yehuda in 1984 showed that waking from REM and NREM sleep elicits significant differences in the verbal and spatial performance ratios.

Interpretation of results from studies of hemisphere dominance during sleep and EEG studies in general has been difficult since many workers assumed that increasing EEG amplitudes correlate with decreasing mental activity. This assumption arose from work of Adrian and Matthews in 1934 with a simple arousal model in which alpha activity (8 to 12 Hz) was assumed to be inversely related to mental processing. This conclusion was naive, and was shown by Ray and Cole in 1985 to be a misinterpretation of results. They showed that alpha amplitudes depend on where mental attention is focused, i.e., toward internal calculations or events (increased alpha) or toward external events and calculations based on external data (decreased alpha), not whether the eyes are opened or closed. It was presumably this confusion in the EEG literature that led Goldstein, et al. (1972) and others to conclude that greater EEG amplitudes in the left hemisphere during REM sleep indicated that the right hemisphere is the site of REM sleep mentation. Studies of the relationship of the EEG to the nasal cycle in awake subjects, nasal cycle-cognitive studies, and studies of the nasal cycle in relation to REM and NREM sleep all suggest that the left brain is the primary site of REM sleep mentation and that the right brain is the site of NREM mentation.

Two studies provide additional evidence of cerebral rhythms. Folkard (1979) using two separate memory tasks, found that acoustic similarity effect on short-term memory was greater at 10:00 h than at 19:00 h and that semantic similarity effect on long-term memory to be greater at 19:30 h than at 10:30 h. He thought the "time-of-day effects in performance reflect a shift in the degree of cerebral dominance over the day, such that the dominant left hemisphere becomes rather less so in the evening." He concluded after looking at only two time points "It is, however, unclear as to what adaptive function such a circadian rhythm might serve, although it has often been suggested that an ultradian (approx. 90 min) rhythm exists in such dominance." The second set of experiments comes from the work on the spiral aftereffect (SAE); an illusion in visual perception (Lavie, et al. 1975; Lavie and Sutter, 1975). When studied over time, the SAE illusion exhibits as an ultradian rhythm with a periodicity on the same scale as the REM/NREM sleep cycle. In fact, awakening from REM or NREM sleep resulted in different responses to the SAE. "The ranges of the illusion were found to be significantly wider after waking from REM sleep than after waking from NREM sleep" (Lavie and Sutter, 1975). Daytime studies of the SAE show rhythms with a period similar to that of the nasal cycle. Study of regional cerebral blood flow in relation to the SAE shows that this phenomenon is correlated primarily with an increase in right cerebral blood flow (Risberg and Prohovnik, 1983).

*I-D. Laterality and the basic rest-activity cycle*

The emergence of lateralized neural rhythms with evolution reflects the integration of the structural and temporal aspects of an organism's metabolic activities to enhance survival in an ever-changing environment. While lateralized neural rhythms are not incorporated in Kleitman's BRAC hypothesis, the BRAC reflects one of the most elementary needs of any organism–expending energy and resting. Aschoff and Gerkema (1985) see ultradian rhythms as an "economic principle not to spend energy continuously at a relative high level (as demanded at times) but to alternate between expenditure and restoration of energy." Any remaining controversy over the existence of the general phenomenon defined by the BRAC hypothesis, and sometimes for ultradian rhythms per se, is based on two issues. First is the variability in frequency in these rhythms; second is whether there are single or multiple oscillators to drive them. Furthermore, the functional significance of ultradian rhythms has been much debated. Aschoff and Gerkema state, for example, (1985):

> "In considering the functional significance of ultradian rhythms, one should first keep in mind that a rhythmic organization (of whatever frequency) is one of the means to keep temporal order within the organism. Where many processes have to be maintained which to some degree are mutually exclusive, but nevertheless cooperate, a temporal compartmentalization by rhythmic alternation is an obvious solution".

Aschoff and Gerkema conclude "it is impossible to postulate one common mechanism for all ultradian rhythms". However, when the phenomenon of the lateralized neural rhythms of both the CNS and ANS are included, a broader perspective can be conceived for the functional significance of these numerous ultradian rhythms and a structure-function model becomes more apparent. A single oscillator model for hypothalamic regulation and integration of these various rhythms has been proposed (Shannahoff-Khalsa, 1991). This model is an extended BRAC hypothesis that includes lateralized neural rhythms playing an integral role in the organization and function of this more general phenomenon. Shannahoff-Khalsa (1991) has proposed that this phenomenon has evolved as "a neural matrix for coupling mind and metabolism". He argues that these lateralized rhythms manifest as a pendulum of ANS-CNS activity to help maintain homeostasis, "not as a single homeostatic state, but as a continuous alternation between two polar conditions for both mind and metabolism". The alter-

TABLE I-A

*Proposed organization of ultradian rhythms*

Table 1A lists the relationship of various ultradian phenomena and related correlates to two polar and separate states of lateralized autonomic balance, described as: (1) right sympathethic dominance with simultaneous left parasympathetic dominance; and (2), left parasympathetic dominance with simultaneous left sympathetic dominance.

| *Autonomic physiology* | |
|---|---|
| *R Sympath. / L Parasympath. Dominance* | *L Sympath. / R Parasympath. Dominance* |
| Right nostril dominance | Left nostril dominance |
| Right lung dominant | Left lung dominant |
| Right adrenal more active | Left adrenal more active |
| Right side increased perspiration | Left side increased perspiration |
| Right side increased catecholamines | Left side increased catecholamines |
| Ergotrophic state | Trophotropic state |
| Active phase-BRAC-blood glucose up | Resting phase-BRAC-blood glucose lower |
| Generalized sympathetic tonus | Generalized parasympathetic tonus |
| Locomotor activity increased | Locomotor activity reduced |
| Right pupil more dilated than left | Left pupil more dilated than right |
| Heart rate, stroke volume increased | Heart rate, stroke volume reduced |
| Blood pressure increased | Blood pressure reduced |
| Respiration rate increased | Respiration rate reduced |
| Oxygen consumption increased | Oxygen consumption reduced |
| Body temperature increased | Body temperature reduced |
| Involuntary eyeblink rate reduced | Involuntary eyeblink rate increased |
| Intraocular pressure reduced | Intraocular pressure increased |

nating dominance of two polar states of mind would be advantageous compared to a static state of cerebral activity. Alternating cerebral efficiency can accomodate different specific tasks. The alternation can be coupled to metabolic states such as the ergotrophic and trophotropic states

TABLE I-B

*Proposed organization of ultradian rhythms*

Table 1B lists ultradian phenomena that exhibit as cerebral activities and how they correlate with the two polar autonomic states.

| *Cerebral relations* | |
|---|---|
| *R Sympath. / L Parasympath. Dominance* | *L Sympath. / R Parasympath. Dominance* |
| Left hemisphere dominance | Right hemisphere dominance |
| verbal performance increased | spatial performance increased |
| Left hemisphere EEG greater | Right hemisphere EEG greater |
| REM sleep | NREM sleep |
| Cerebral metabolic rate increased | Cerebral metabolic rate reduced |
| Lateralized Immune functions? | Lateralized Immune functions? |
| Daydreaming reduced? | Day dreaming increased? |
| EEG alpha minimum? | EEG alpha maximum? |
| Spiral After effect shorter? | Spiral After effect longer? |
| Depression/Anxiety minimum? | Depression/Anxiety maximum |
| Euphoric-manic state maximum? | Euphoric-manic state minimal? |
| Hysteria reduced? | Hysteria increased? |
| Catatonia reduced? | Catatonia increased? |
| Schizoid - Active Positive syndrome | Schizoid - Withdrawn Negative syndrome |

TABLE I-C

*Proposed organization of ultradian rhythms*

Table 1C lists the ultradian phenomena of neuroendocrine activity with their correlations.

| *Neuroendocrine relations* | |
|---|---|
| *R Sympath. / L Parasympath. Dominance* | *L Sympath. / R Parasympath. Dominance* |
| Cortisol increased | Cortisol reduced |
| Growth Hormone reduced | Growth Hormone increased |
| Luteinizing Hormone increased | Luteinizing Hormone reduced |
| LHRH enhances verbal fluency (males) | |
| LHRH reduces spatial (males) | |
| Prolactin secretion reduced | Prolactin secretion increased |
| Testosterone increased | Testosterone reduced |
| Penile tumescence increased/sleep | Penile tumescence reduced/sleep |
| Parathyroid hormone reduced | Parathyroid hormone increased |
| Calcium (+2) increased | Calcium (+2) reduced |
| Endorphins increased | Endorphins reduced |
| Corticotrophin Releasing Horm. inc.? | Corticotrophin Releasing Hormone red.? |

that may more readily support the respective activities. This alternation may thus be one of nature's ways of maximizing economic efficiency.

What follows is a further history and explanation of various studies of how the BRAC and lateralized rhythms are coupled. Although numerous physiological and psychological phenomena exhibit ultradian rhythms, few have sought relations among these supposedly independent phenomena. This lack of effort has impeded the development of an integrated view of the interactions among various systems, a view that would provide a new understanding of the structural and temporal organization of biological processes.

Tables 1A–D (A-autonomic physiology; B-cerebral relations; C-neuroendocrine relations; and D-behavioral relations) list the proposed relationships among known ultradian rhythms and lateralized autonomic dominance. This domi-

TABLE I-D

*Proposed organization of ultradian rhythms*

Table 1D lists the behavioral relations and their proposed correlations. Phenomena that are listed with question marks have proposed relationships as discussed in text.

| *Behavioral relations* | |
|---|---|
| *R Sympath. / L Parasympath. Dominance* | *L Sympath. / R Parasympath. Dominance* |
| Oral drive increased | Oral drive reduced |
| Hunger sensations increased | Hunger sensations reduced |
| stomach contractions increased | stomach contractions reduced |
| gastric acid secretion increased | gastric acid secretion reduced |
| salavation increased | salavation reduced |
| grip strength increased | grip strength reduced |
| Thorndike Intell. Exam. improved | Thorndike Intell. Exam. reduced |
| Urine flow reduced? | Urine flow increased? |
| Urine osmolarity increased? | Urine osmolarity reduced? |

nance is either right sympathetic and left parasympathetic dominance (right nostril dominance), or the converse. Question marks indicate that correlations are uncertain.

Kleitman (1982; 1967; 1961) may have given us one good example of a theory of interacting systems with his postulation of the BRAC. The BRAC theory had its origins in the discovery that EEG and eye movement patterns change in concert during sleep, giving rise to the concept of REM and NREM sleeps stages. In 1957, Dement and Kleitman reported cyclic variations in the EEG during sleep and their relations to eye movements, body motility, and dreaming. This study also played an important role in Kleitman's later formulation of the BRAC concept which was supposed to explain why some psychological and physiological activities are integrated and account for the obvious patterns of intermixed locomotor activity and quiescent states during sleep. Kleitman (1967) proposed a waking correlate of the sleep pattern, and that "the BRAC is probably a fundamental variation in the functioning of the central nervous system, increasing in duration with phylogenetic progression" where "in each species of mammal studied, the BRAC also lengthens during ontogenetic development". Kleitman proposed the BRAC to be a reflection and variation of integrated events during the 24 h period.

Wada's seminal 1922 studies of hunger and its relation to activity also bear on the issues of endogenous rhythms and homeostasis. Wada proposed that food was the first form of property for primitive man; the value of things supposedly first came to be measured in terms of food, and primitive migration was primarily motivated by food. Wada, therefore, surmised that basic homeostatic mechanisms are coupled to hunger. Investigations of the relation of the hunger rhythm with bodily movements, dreaming, motor activity, salivation, and mental activity led Wada to discover a rhythm of salivary flow that parallels the gastric hunger contraction rhythm. But surprisingly, Wada also found that men dream more at the hunger contraction periods than during quiescence. Motor activity during waking, as judged by a hand-dynamomotor, showed that at hunger contraction periods the power of grip is greater than at the quiescent or after-dinner periods. Hunger contractions also correlated with scores on the Thorndike Intelligence Examination. These studies on the relation of activity to hunger predate Kleitman's concept of the BRAC. Wada recognized that "with the onset of hunger the sleeping baby awakes to feed", and in general, "when the effort to satisfy hunger is thwarted, the whole organism reacts to the situation, or thwarting agent, with such hyper-tension of all organs and muscles and fibers that the excitement may lead to various types of defensive behavior". Therefore, Wada saw the hunger mechanism as one of the most primitive, and as certainly a central regulating aspect of physiology. This primitive rhythm and mechanism is another way of viewing the BRAC: hunt and eat, then rest. An important question is how is this homeostatic rhythm of hunger coupled with those found in more recently discovered phenomena such as the secretion of pituitary hormones.

Richter reported in 1980 that "in rats, lengths of cycles of GH secretion and of cycles of feeding are 3.6–4.0 h" and that they are phase coupled. He also suggested that "these two cyclic phenomena may be manifestations of the same timing mechanism in the brain or they could function entirely independently". GH is known to be secreted predominantly during NREM sleep in humans (Parker and Rossman, 1973; Pawel, et al. 1972). Even though GH secretion does not exhibit an apparent rhythm during much of the 24-h cycle, this link with NREM is an important clue to an association between hypothalamic and cortical rhythms. Pituitary rhythms vary, however, with age, sex, and species, thus complicating any attempt to establish relations among various phenomena.

The first discovery of the pulsatile or episodic nature of pituitary hormone secretion in 1966 was the observation by Weitzman, Schaumberg, and Fishbein that discrete pulses of cortisol secretion reflect rhythmic secretion of adrenocorticotropin hormone (ACTH). Pituitary hormones are secreted with an ultradian rhythm (Van Cauter and Honinckx, 1985; Kripke, 1982) and the secretion of several of them are related to REM and NREM sleep. Lutenizing hormone (LH) secretion is coupled to REM sleep at least during puberty (Boyar, et al., 1972). Testosterone (T) secretion was found to be phase linked with cortisol secretion (Van Cauter and Honinckx, 1985) providing evidence for synchronization between the pituitary-adrenal and pituitary-gonadal axis. Testosterone is also known to be secreted in phase with penile tumescent cycles (Schiavi, et al., 1977) during sleep, coinciding with REM sleep cycles (Karacan, et al., 1972). Prolactin secretion was found to increase during NREM periods (Parker, et al., 1974; Weitzman, 1976). However, this finding was refuted by Van Cauter and Honinckx (1985). In adult rats, the 3-h rhythms of GH and corticosterone secretion are 180 degrees out of phase, with GH being secreted during NREM sleep (Kimura, et al. 1985). These phase relations between GH and corticosterone secretion are similar to those in found in adult humans (Takahashi, et al., 1968; Weitzman, et al. 1981). Plasma parathyroid hormone and calcium levels are also related to sleep stages (Kripke, 1978), so that peaks in parathyroid hormone secretion are significantly related to NREM sleep stages 3 and 4, while elevated calcium levels are significantly related to REM sleep. Cross correlation analysis between "humoral endorphin", an endogenous opioid, and sleep stages confirmed a relationship with REM sleep (Sarne, et al. 1981).

One recent study of the secretion of corticotrophin-releasing hormone (CRH), the hypothalamic hormone that initiates and integrates the response to stress, revealed a diurnal rhythm in human males (Watabe, et al., 1987) from four samples per day. Continuous monitoring of CRH in the cerebrospinal fluid of adult male monkeys (Kalin, et al., 1987) by contrast produced profiles characteristic of an ultradian rhythm. CRH, like other hypothalamic-pituitary factors, may thus exhibit variations in levels of secretion that are ultradian. Even though it is considered a "stress" peptide, CRH secretion may co-vary with locomotor activity under normal unstressed conditions. Plasma levels of LH, for example, show a direct relationship to rhythmic motor activity or the ultradian rest-activity cycle in ovariectomized sheep (Rasmussen and Malven, 1981). Rats who have lost their circadian rhythm due to lesions in the suprachiasmatic nuclei show an ultradian phase-locked relationship between locomotor activity and plasma corticosterone (Watanbe and Hiroshige, 1981). Most authors do not ascribe any particular significance to the ultradian nature of pituitary hormone secretion, suggesting that the cause of this rhythmic phenomenon is unknown. However, in light of the available evidence, it is reasonable to propose that such rhythms help modulate and reflect the coupling of the CNS with the ANS. This coupling underlies the BRAC and the accompanying coupling of psychological phenomena with rhythms of the hypothalamic-pituitary-adrenal-gonadal axes. Interestingly, it has been shown in men (but not women) that injections of lutenizing hormone releasing hormone (LHRH) prevent improvement in a spatial orientation task (right hemisphere skill), but enhanced performance on a fluency task (left hemisphere skill) (Gordon, et al., 1986). The resulting increase in LH and correlated enhancement of left hemispheric skills is consistent with elevated LH during REM sleep, also a correlate of an activated left hemisphere.

In addition to Wada's (1922) earlier work on the relation of stomach contractions to dreaming and body movement, there are studies by Friedman and Fisher (1967) showing that "REM periods are related to a cyclic waxing and waning of instinctual drive activity mediated through the limbic system", particularly in eating behavior. They report a statistically significant waking state oral activity cycle of 80–120 min, based on subjects use of drink, food, and tobacco. Another study of human ingestive activity shows a similar activity cycle (Oswald, et al., 1970) of about 90 min. Although both studies show considerable variability in the cycles, the range is not different from that of other ultradian phenomena. Ultradian rhythms of gastric pH in humans during night show a range of 1.07 to 5.5 h, clustering around 2–3 h (Tarouini, et al., 1986). A nocturnal study of gastric secretion in fasting subjects, showed "a wide individual variation and a considerable spontaneous variation of the gastric secretion in the same individual from h to h and also from night to night" (Levin, et al., 1948). In another study, gastric motility and pH were recorded during night sleep and showed a consistent pattern of motility decreasing and acidity increasing in deep sleep relative to wakeful levels (Baust and Rohrwasser, 1969). Motility was markedly enhanced during REM sleep, but there was not a constant relation between the occurence of peristaltic waves and the outbursts of rapid eye movements. Lavie et al. (1978) demonstrated 100 min cycles in gastric motility during sleep and found only minimal relations to REM periods (which may be due to the lack of adaptation nights, and/or a nasogastric tube sometimes with or without a balloon). They conclude, "since hunger and feeding behaviors may be weakly related to stomach contractions, it is still to be determined if appetitive behaviors have any mechanism in common with stage REM".

Periodic interdigestive secretion of the pancreas, liver and stomach were found in canines with a peak interval of 100 min and a range of 80–130 min (Magee and Naruse, 1983).

In 1976 Horne and Whitehead demonstrated an ultradian rhythm in human respiration rates when looking for a correlate of the BRAC. Most subjects showed a periodicity of 90 min ($\pm$15). Bailey, et. al. (1973) observed oscillations in oxygen consumption in resting humans with periods of 1–2 h, with changes in amplitudes of 7–20% of the mean. They conclude "that the oxygen consumption of men and women resting comfortably in the postabsorptive state is not constant, but subject to cyclic variations." Also, "We have no direct experimental or theoretical explanation for cycles of 1–2 h. They may be examples of "hunting reactions" about a set point in the control system for body temperature". Aspects of the BRAC have been studied in rats where an ultradian rhythm in body temperature was found that is coupled to the rhythms of locomotor activity (1985). Honma and Honma state (1985) "Generally, a locomotor burst preceded a rise in abdominal temperature, but occasionally the rise in body temperature preceded the burst of locomotor activity. This reversed pattern seems to preclude the possibility that there is a causal relationship between the two parameters." Therefore, it is likely that these relations are centrally mediated and are two ways of measuring a more extensive phenomenon. In a study of lateralized relations of hand grip strength and body temperature in 48 male subjects (testing only at 4–5 times per day, intervals which are not adequate to elicit ultradian periods), Reinberg, et al. (1988) found a circadian period in oral temperature in humans that was correlated with the grip strength of the dominant hand, but not with the non-dominant hand. They conclude "Thus, circadian rhythms in oral temperature and dominant hand grip strength may be driven by the same oscillator while that of the non-dominant hand may be governed by a different one.... A coherent body of indirect evidence thus emerges supporting the idea that circadian oscillators may well be located in the human brain cortex and not only (or mainly) in the archaic brain as has been shown in animal rodent models." This suggests that the active phase of the BRAC in humans correlates with the left cerebral hemisphere dominance. Other results from Buchsbaum, et al. (1989) give further support for this relationship. They studied cerebral metabolic rates in humans during waking, REM, and NREM periods. They found in comparison to waking controls that there was a 23% reduction in metabolic rate during NREM across the entire brain, while subjects tended to have a higher cortical metabolic rate during REM than in waking subjects. They also found "a greater left than right metabolic rate in REM but a greater right than left metabolic rate in NREM and awake for the cingulum and medial frontal regions; a loss of the normal waking right > left pattern was also seen in temporal cortex and the thalamus in REM."

Taken together, the available evidence suggests that the ultradian rhythms of the BRAC, eating-oral-gastric rhythms, pituitary rhythms, sleep stages, and other cerebral rhythms may have central regulators in common. This conclusion can help reshape how we think about the cerebral-hypothalamic-pituitary-adrenal-gonadal axes. In 1983 Werntz, et al. concluded that the left-brain right-nostril dominant mode is the correlate of the active phase of the BRAC and that the right-brain left-nostril dominant mode is the resting phase of the BRAC. Certainly, many additional experiments must be done to further investigate these relationships.

## II. IMPLICATIONS OF LATERALIZED RHYTHMS FOR STRESS

Selye's (1950) theory of stress is an attempt to relate the whole individual to organ systems even though he emphasized the adrenal cortex as a major organizer of non-specific adaptive responses to environmental demands. Responses to stress include both the active and passive styles of avoidance and while both may tax the adrenal system, perhaps to different degrees, it is clear there are individual differences in these two styles in the behavioral, physiological and endocrine changes that occur in response to stressors in the environment (Bohus, et al. 1987). Despite extensive stress research, Bohus, et al. (1978) state "the problem still remains to link directly the macro- and microworld," and that "Stress, hormonal states and adaptation (in its broadest sense) need to be fitted into one concept." The lateralized rhythms of the central and ANS provide a more integrated view of the "whole individual". This view is that of a balance between two polar states of mind and metabolism in a continuous rhythm to meet the biological needs of the organism. How stress affects the mind-body would now include a consideration of how this pendulum of ANS-CNS activity can be affected by the environment.

It is likely that this pendulum is generated by an endogenous oscillator system within the hypothalamus that reflects patterns of neural excitation and inhibition organized during development. Shannahoff-Khalsa (1991) has proposed a model for the regulation and integration of the various autonomic activities where four major zones of the hypothalamus (right and left anterior regions and right and left posterior regions) are combined to act as an integrated clocklike mechanism in which a metabolic gradient of activity within these zones maintains homeostasis. The shifting relative activities of the different hypothalamic nuclei adjust to meet the shifting needs and patterns of external activity of the organism. The neural circuitry of the hypothalamus thus becomes able to compensate for a range of environmental stressors. It is possible that different regions within the hypothalamus are more frequently activated than others in some daily routines and with specific forms of stress. While this theory does not deny the innate neural relations that have evolved between the hypothalamus and other structures, it emphasizes the frequency of routines where the firing of nerve patterns for certain functions becomes preferred. Stress may therefore be defined as an event that attempts to shift established patterns, while in addition, certain patterns are probably more conducive to a balanced pendulum. Given this view of neural systems supporting the lateralized rhythms of mind and body, it may be easier to understand how laterality plays an important role in states of health and disease (see Shannahoff-Khalsa, 1991, for further discussion).

This pendulum is the key to understanding how many apparently independent physiological and psychological phenomena might in fact be coupled together. The pendulum of autonomic activity sets the frequency at which various activities are entrained. In addition, conditions which overstimulate one-half of the CNS-ANS circuitry may actually have an impact on cerebral activities and personality profiles. Stress may be defined by how long or how frequently a particular position of the pendulum is maintained. Too much left-brain activity and right sympathetic dominance may indeed be what we normally think of as stress or over-activity. It is easy to envision both acute swings and prolonged shifts toward one position of this pendulum.

Hess (1954) coined the terms of "ergotrophic" and "trophotropic" to describe ANS functions. Ergotrophic reactions are "coupled with energy expenditure" and an endophylactic-trophotropic system "provides for protection and restitution" (Hess, 1954). Gellhorn (1967) discusses these concepts at length in his discourses on ANS-somatic integration. The key concept is the antagonistic relationship of the sympathetic and parasympathetic systems in maintaining balance between these two polar states.

Left nostril/right brain dominance is unlikely to underly the fight-or-flight response as it appears to represent the resting state of generalized increased parasympathetic tone which is antithetical to the stress response. It is also likely that peaks of immune function, regeneration, and healing occur during the increased parasympathetic state of right brain/left nostril dominance. Neveu (1988) has recently reviewed how lateralized lesion studies in the neocortex of the rat can demonstrate how the two hemispheres play profoundly different roles in regulating activities of the immune system. He states "the asymmetry in the cerebral control of immune responses should represent a phylogenetic advantage which has to be elucidated". He summarizes the effects of lateralized neocortical lesions on spleen weight, thymus weight, number of T cells, percent of helper T cells, percent of cytotoxic/suppressive T cells, antibody production, T and B lymphocyte proliferation, and natural killer cell activity. These lateralized differences in immunomodulation suggest that cerebral rhythms also play an important role in the health and homeostasis of immunity. Our understanding of psychoneuroimmunology may be increased by considering how the ANS acts as a neural matrix for coupling mind and immunity. Different stressors may play key roles in how the pendulum of CNS-ANS activity effects immune functions. Over-stimulation or abnormal activity of one hemisphere may over- or underactivate different immune functions. It is even possible that a selective stimulation of one side of the brain may have beneficial effects on specific immune disorders.

It may be that dramatic increases in CRH release are coupled to right nostril/left brain dominance during the fight-or-flight response, as the apparent ultradian rhythms of CRH are likely to have their peaks during the active phase of the BRAC. Certain observations in two case studies of multiple personality disorder (MPD) are suggestive of this lateralized ANS relationship. In 1955, Ischlondsky reported significant lateralized findings during a neurological examination of two different patients with similar personality traits where each patient had:

"two diametrically-opposed personality types. One was an impulsive, irresponsible, mischievous and vindictive personality, full of rebellion against authority and of hate towards the people around her, the patient in this phase was extremely aggressive, using abusive language and scaring other patients with lurid tales of state hospitals, sex relations, etc.; in the opposed behavioral pattern to which the first personality would suddenly switch, the patient appeared dependent, submissive, shy, self-effacing, affectionate, and obedient. In a very timid way she expressed friendliness, sought affection, acceptance, and approval from the same personnel she had reviled and abused. There was no trace left of any inappropriate word or expression, no manifestation of hostility to her surroundings, and not the slightest reference to sex. In fact, any sex thought or word would induce in her extreme fears of perdition, feelings of guilt and anxiety, depression, and shame."

In each of these two opposed mental states there was amnesia to the other, which is characteristic of MPDs. "A strong stimulus was capable of evoking the antipode of the existing mental condition". During the aggressive or active phase of the patient's behavior (Ischlondsky, 1955):

"examination revealed that the left and right sides of her body responded differently to sensory stimulus: while the right side was hypo-sensitive the left side displayed hyper-sensitivity. Thus, vision and hearing were unclear and far away on the right side but very clear and close on the left side. Her response to touch and pain showed a high threshold on the right, and a low threshold on the left side. Characteristically, with regard to the olfactory sense the patient in this mental state manifested a diametrically opposed attitude: she was hyper-sensitive to smell on the right side and her *right nostril was clear*, while on the *left side* her sense of smell was absent and the *nostril congested and closed* (emphasis added). With regard to the other neurological signs such as the size of pupils, reflexes, salivation, sweating, there was a similar difference in the response of the two sides of the body: the aggressive personality type displayed on the right side, a small pupil, a hypo-secretion of saliva, absence of sweating on sole and palm and lack of abdominal reflexes, while on the left side there was a large pupil, hypersecretion of saliva, very strong sweating on palm and sole and extremely strong abdominal reflexes". (It is difficult to account for the observation of pupil size etc. inconsistent with nasal congestion.) And just as fast as the psyche switched to the shy, passive, and permissive personality all neurological manifestations also switched to reverse dominance, where the "olfactory sense proved now to be very sharp on the left side while completely absent and with nostril congested and closed on the right side". This extraordinary case study showing that lateralized ANS phenomena switch instantaneously with the psyche in two patients suggests that right nostril dominance or sympathetic dominance on the right side of the body correlates with the active phase of the BRAC and the fight-or-flight response pattern.

Sudden cardiac death accounts for approx. 25% of all deaths in the industrialized world. Lane and Schwartz (1987) proposed a neurophysiological mechanism for stress-induced cardiac arrhythmias in cases where no previous heart disease can be demonstrated. They suggest that there is a lateralized CNS effect that can be generated by strong emotions which then change the balance of the sympathetic and parasympathetic activities of the heart. Natelson (1985) reviews the lateralized pathways of autonomic innervation to the heart and their effects on heart activity and concludes "activation or interference with specific sites in either the CNS and peripheral nervous system may selectively affect heart rate and rhythm". Therefore, an acute or prolonged imbalance in lateralized autonomic stimulation of the heart may lead to sudden death. It is possible that this could occur especially from prolonged periods of the "active phase" of the BRAC.

## III. IMPLICATIONS OF LATERALIZED RHYTHMS FOR ADAPTATION AND HOMEOSTASIS

Adaptation is defined here as the adjustment of the organism to environmental conditions. The only certainty in nature is change, and survival of the fittest implies the ability to adapt to change when necessary. This requires both skill and flexibility. The lateralized rhythms of the central and ANS may be one of the clearest examples of how higher vertebrates have developed the flexibility to adapt to change. These rhythms are an economic means of organizing the temporal and structural elements of biological systems for both adaptation and the maintenance of homeostasis. In any living system it is not possible to maximize all "housekeeping" functions simultaneously, just as the ergotrophic and trophotropic states cannot co-exist. The lateralized specialization of the cerebral cortex makes it possible to have two diverse repertoires of mental skills to provide solutions to problems. The cerebral rhythm, in part, creates the opportunity to cope with changes by alternating between two views of reality. In addition, when emergency situations exist, survival is increased by maximizing a mental and metabolic relationship that has evolved to cope best with a threat. The lateralized switching in the MPD is an excellent example of the neurology of this adaptive mechanism. However, the switching between these two states in the MPD are extreme examples in shifts of the pendulum. Although the fight-or-flight mechanism is a well studied example of adaptive mechanisms, the example of adaptation by the passive mode in the subjects with MPD is also important. The apparent right-brain left-sided sympathetic dominant mode is the polarity of the fight-or-flight state. This passive state may have its correlate in other species which "play dead" in certain situations to avoid attack. It may be that humans become more prone to depression (a right cerebral disorder), when they are forced to accomodate a passive state for prolonged periods or are forced to cope with situations where they have no control and the outward fight-or-flight response is not an option. Any environmental condition which demands the over use of one cerebral state may have a negative impact both psychologically and physiologically, as unbalanced metabolic shifts are likely to occur. This time inequality in lateralized activities may be a primary determinant of disease.

The relationship of lateralized neural rhythms to the BRAC would predict that the right side of the body would undergo greater sympathetic activity during the active phase of the BRAC. Selye (1946) also showed that stress is marked by adrenal enlargement. Therefore, it is likely that the right adrenal gland may be somewhat larger than the left due to greater use. Benton and Yates (1990) studied the right and left adrenal activities in resting dogs and observed not only "90 min" ultradian rhythms in adrenal blood flow that differed on the two sides, but also that the right adrenal gland averaged 1.8 g in weight and the left adrenal gland averaged 1.3 g, a statistically significant difference. This is either a developmental difference in size, or the hypothesis that more work (stress) yields a larger gland could account for the difference. In humans the right suprarenal vein drains into the inferior vena cava while the left side empties into the renal vein. This anatomical arrangement indicates that right adrenal activity may have quicker metabolic impact due to its more direct influence on circulation. Besides in this case of a larger right adrenal gland, the right lung is also larger. Developmentally, it may be more important to have the larger lung on the right side as enhanced sympathetic activity in the lung induces vasodialation in contrast to vasoconstriction in most other tissues. This would provide for greater blood gas exchange during the active phase of the BRAC. Classically it is reasoned that the left lung is smaller to accomodate for the position of the heart. These relations reflect nature's economic considerations.

Selye (1946) described stress induced diseases or "diseases of adaptation" (ulcers, hypertension, cardiac infarct, psychiatric disturbances, immune diseases) to in part come from an excess of corticoids and catecholamines. He also saw this as an imbalance in the proportion of the prophlogistic and antiphlogistic hormones secreted from the adrenals. In Selye's thesis the prophlogistic corticoids stimulate the proliferative ability and reactivity of connective tissue, thus enhancing their "inflammatory potential", while the antiphlogistic corticoids apparently depress the "inflammatory potential". Selye also recognized that changes in the activity of the ANS played an important role in diverse stress-induced diseases. He and others called this a "vegetative total reorientation" which is in essence a modification of the relative predominance of sympathetic or parasympathetic nervous impulses. Selye's "diseases of adaptation" may also be accounted for by an imbalance in the lateralized neural rhythms that as postulated here organize the BRAC. Greater right-sided sympathetic tone would correlate with the active phase of the BRAC and in general a greater sympathetic state of arousal, or the ergotrophic state.

An interesting study of how lateralized changes in hypothalamic activity occur under stress adaptation comes from the work of Bakalkin, et al. (1984). Their study shows an asymmetrical luteinizing hormone releasing hormone (LHRH) distribution in the rat under normal conditions. Wistar rats exhibit higher LHRH content in the right hypothalamus and albino rats exhibit higher LHRH content on the left. Bakalkin, et al. (1984) state that LHRH content changes from side to side over a 24-h period and that unilateral castration or cold stress leads to a shift in the LHRH distribution in the hypothalamus. This may be one example of how lateralized changes in metabolism accomodate changes in the environment.

## IV. SELF-REGULATION OF LATERALIZED COGNITIVE ACTIVITIES

After the evolutionary development of the lateralized rhythms in the CNS and ANS, it appears that the next major development regarding laterality, is the human trait of the ability to be consciously aware of this rhythm and to learn how to self-regulate the phase of its activity.

The concept for the study by Werntz, et al. (1980, 1983) on the nasal cycle and the cerebral rhythm came from yogic medicine. For thousands of years yogis have been aware of the nasal cycle and its mental correlates and have experimented with how breathing patterns can affect states of mind and metabolism. This group of early experimentalists viewed the breath as the link between the mind and body. They discovered that altering the nasal cycle by occluding the dominant nostril and force breathing through the congested side could affect mental experience. This effect was documented by Werntz, et al. (1981,1987) by using the EEG. They demonstrated how unilateral forced nostril breathing could stimulate the contralateral hemisphere producing relatively greater amplitudes in the EEG.

Work by Kristof et al. (1981) suggests that the electrographic activity generated by nasal (versus oral) breathing is produced by a neural mechanism in the superior nasal meatus. This activating effect could also be produced by air insufflation into the upper nasal cavity without inflating the lung. Local anesthesia of the mucosal membrane suppressed the cortical effects of airflow stimulation. The lateralized effect on the cortex is analogous to that found in the studies with the homolateral nasal-lung reflex which suggests sympathetic activation (Sercer, 1930; Wotzilka and Schramek, 1930; Samzelius-Ledjstrom, 1939; Stoksted, 1960; Drettner, 1970). Servit et al. (1981) showed how deep breathing through one side of the nose could activate abnormalities in epileptic patients with unilateral focal or lateralized paroxysmal abnormalities in the fronto- or occipitotemporal region. "The abnormalities of this type were significantly more activated from the ipsilateral nasal cavity". However, these paroxysmal abnormalities were also generated with contralateral breathing to the foci in 60% of the patients. These abnormalities are not equivalent to the sustained contralateral increases in EEG produced in the Werntz et al. (1981, 1987) studies, as this paroxysmal activity manifests as intermittent spikes in only a small fraction of the record with epileptic patients. However, it is an example of how lateralized EEG activity can be affected by unilateral nasal airflow.

The relationship of EEG amplitudes reflecting mental activity or inactivity is an important issue here. Yogis believe that forced nostril breathing on one side "exercises" the opposite hemisphere. The study by Klein et al. (1986) showed that right nasal dominance is coupled to increased verbal performance, or left brain activity, and left nasal dominance with spatial or right hemispheric skills. They were not able, however, to demonstrate the effects of forced nostril breathing with their subjects, possibly due to errors in experimental design. Shannahoff-Khalsa, et al. (1991) have shown that unilateral forced nostril breathing can alter cognitive performance in the manner predicted by yogis, when 30 min of unilateral forced nostril breathing was used to affect task performance of the opposite hemisphere. The Study by Klein et al. (1986) used tasks that may not have been as well lateralized, and, in addition, the testing was usually done after the breathing exercise, whereas Shannahoff-Khalsa, et al. (1991) tested while subjects maintained the nasal block. The study by Klein et al. (1986) also used shorter breathing times of 15 min as well as 30 min during their procedures. The tests used, breathing times, and keeping the nostril blocked during testing are all critical. The interpretation of the expected functional relationships based on the lack of crossover by autonomic fibers coincides with the yogic interpretations. It appears that nasal airflow may stimulate sympathetic dominance on the homolateral body half. Therefore, it is possible that direct stimulation of one half of the cortex may occur by sympathetic stimulation and thus result in vasoconstriction. It is also possible that increased parasympathetic activation may occur simultaneously in the contralateral hemisphere.

Block, et al. (1989) studied the influence of unilateral forced nostril breathing on cognitive performance. Their results showed a mixed pattern. In males uninostril breathing appeared to have an ipsilateral increase in performance, but "unilateral breathing influences female performance contralaterally, but only on the spatial task". These results were obtained after only 5 min of breathing exercise. In contrast to the results of past studies they state "These differences within and between sexes may exist because unilateral nostril breathing differently activates the two hemispheres and thereby facilitates performance, or because attempts of the brain to control the nasal cycle unilaterally interfere with performance". The Klein et al. (1986) study found no differences with nostril dominance and hemisphere relations between the two sexes. Also, the study by Shannahoff-Khalsa, et al. (1991) used only males and found a contralateral relationship of activity. It is not likely that the ANS circuitry differs between sexes. Additional studies using a minimum of 30 min stimulation, and established lateralized cognitive measures, with a continuous blocking of the nose during testing will help to confirm the expected contralateral relations. Brain imaging other than EEG may also be helpful to clarify relations.

## V. SELF-REGULATION OF LATERALIZED AUTONOMIC ACTIVITIES

In 1948 Friedell reported an interesting clinical result, he found that "diaphragmatic breathing with attention to both phases of respiration and the intervening pauses" coupled with "alternately closing one nostril while inhaling slowly through the other" had 'profound effects on patients with angina pectoris. The 11 patients in this study all experienced relief from symptoms using this breathing practice and were able to eventually curtail the use of nitroglycerin. It is likely that the effect of the alternate nostril breathing technique can directly affect the lateralized sympathetic and vagal input to the heart, thereby inducing a balance in ANS activity. This may help to reset the electrical patterns affecting the heart muscle.

Yogis were also the first to discover how posture could alter the nasal cycle and corresponding mental state. Novice practioners learned to lean on the "yoga danda" stick for altering the cerebral rhythm. As mentioned in section I.B. (Haight and Cole, 1986) pressure on the fifth intercostal space can induce a shift in the nasal cycle. This non-invasive mechanism was used by the less adept to shift mind-body states.

An advanced yogi can consciously select which hemisphere he wants to use within the span of one breath. He can switch back and forth fully activating one side of his brain within this very short time. The autonomic phenomenon becomes a consciously regulated activity. This level of development reflects a very advanced stage in the discipline of "self-regulation". In normal individuals right-left cerebral balance is only a transition state that is short-lived. However, the advanced yogi can choose to operate from this state for prolonged periods. Perhaps this is the most advanced stage of lateralized development.

The case reports of Ischlondsky (1955) represent an adaptive form of this mechanism in lateralized switching. Gott, et al. (1984) report a study of a 31 year-old woman, unaware of the phenomena of cerebral rhythms and nasal cycles. She was self-trained, without fully understanding her achievement, and was able to voluntarily select and hold either of two qualitatively different states of consciousness. When studied in the laboratory she gave evidence of differential dominance of the left or right hemisphere. "Asymmetries of EEG alpha and task performance scores indicated a state dependent shift in functional lateralization." The woman reported "that her state switch had been involuntary from early childhood. At age 16 she learned to select her state at will, thereby improving her school work and personal behavior".

Recent papers by Backon (1988), Backon and Kullock (1989), and Backon, et al. (1989), all demonstrate the effects of forced unilateral nostril breathing on other autonomic related phenomena. As proposed by Werntz et al. (1983), right nostril dominance correlates with the "activity phase" of the BRAC. Backon (1988) shows how right forced nostril breathing significantly increases blood glucose levels and left nostril breathing lowers it, supporting this thesis. Backon and Kullock (1989) also showed how unilateral breathing patterns can effect involuntary eyeblink rates. They found that right forced nostril breathing reduced blink rates and that left forced nostril breathing increased involuntary blink rates. They suggest that this differential effect reflects a lateralized variation in dopamine activity in the two hemispheres. It is also possible that the forced right nostril breathing increases the general sympathetic tone, thus minimizing blink rates and that the left nostril breathing increases blink rates via a more "parasympathetic state" which coincides with the "resting phase" of the BRAC. Backon et al. (1989) also showed how intraocular pressure can be selectively altered by forced uninostril breathing patterns. In their paper they cite references that suggest that vagal tone is increased in glaucoma simplex, reflecting high intraocular pressure. They find that right forced nostril breathing leads to an average decrease of 23% in intraocular pressure and that left nostril breathing increases it by an average of 4.5%. This is further evidence that right nostril breathing increases the generalized sympathetic tone of the body, thus correlating with the "active phase" of the BRAC as proposed by Werntz et al. (1983).

In 1957, Riga published observations on unilateral chronic nasal obstruction which he thought might predispose people to a variety of disorders. Patients presented with a range of symptoms which he classified as:

"local disorders; nasal respiratory insufficiency, hypertrophic rhinitis of the obstructed nostril and allergic disorders, and neighboring disorders; spontaneous painful sensitivity in the periphery, sinusitis, cattarh of the Eustachian tube, hypacousia and otorrhea, bronchorrhea all on the obstructed side, and distant disorders; intellectual asthenia with frequent amnesia, headaches, hyperthyroidism, cardiopulmonary asthenia with tachycardia and asthmatic disorder with sometimes hypertrophy of the left cavity of the heart and pulmonary emphysema, hepatic and gall bladder, gastritis, enterocolitis, sexual disorders, dysmenorrhea, and decrease of virility".

89% of the cases with right nasal obstruction were found to be afflicted to some degree with this widespread and apparently unrelated array, but only 26% of the cases with left nasal obstruction were afflicted. This suggests that a right-sided obstruction may more seriously affect health.

It is possible that chronic unilateral obstruction may alter both the peripheral ANS activity and possibly the balance of the cerebral rhythm. Deviated septums are common and may impair health in unexpected ways by off-setting the CNS-ANS rhythm. The pressure reflex mechanisms on the sides of the body that affect autonomic and probably cerebral balance present an interesting approach for methods of self-regulation. Yogic techniques which involve lateralized breathing patterns for self-regulation have been reported (Shannahoff-Khalsa, 1991). As laterality has played a fundamental role in the development of higher vertebrates, it is possible that these subtle differences may lead to an increased understanding of methods for treating stress-related disorders, psychopathologies, and the maintenance of general well-being.

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