First publ. in: From the Heart to the Brain / Dieter Vaitl ... (eds.).
Frankfurt am Main : Lang, 1995, pp. 133-149

7. What goes up (from heart to brain) must calm down (from brain to heart)! Studies on the interaction between baroreceptor activity and cortical excitability[1]

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> "But when it comes to finding out how you and I, our children and grandchildren, may become more perceptive, more intensely aware of inward and outward reality, more open to the Spirit, less apt, by psychological malpractices, to make ourselves physically ill, and more capable of controlling our own autonomic nervous system Å when it comes to any form of non-verbal education more fundamental (and more likely to be of some practical use) than Swedish Drill, no really respectable person in any really respectable university or church will do anything about it."
> Aldous Huxley, The Doors of Perception

A. FROM HEART TO BRAIN: THE IMPACT OF THE BARORECEPTORS ON BRAIN AND BEHAVIOR.

1. Introduction

The relevance of baroreceptors for the afferent limb of the blood pressure buffer reflexes is well known. These stretch receptors are located in the carotid sinus, in the aortic branch, and in the heart. Stimulation by distension of the arterial walls in these regions produces a reduction in heart rate via the motor neurons in the nucleus ambiguous and vagus nerve, and a reduced cardiac output complemented by general vasodilation through inhibition of the sympathetic outflow. The goal of this 'baroreflex' is to adjust blood pressure. A less well known aspect of baroreceptor function is their corticopetal influence. Indeed, one major influence of cardiovascular activity on the brain is realized through the baroreceptors, which act on lower brainstem vasomotor centers and Å via the tractus solitarius

[1]Research was supported by the Deutsche Forschungsgemeinschaft (El 101/3)

Å on further systems ascending from the brainstem and the hypothalamus to higher cortical regions (see Dembowsky & Seller, this volume). Apart from their representation in the insular cortex, the baroreceptors influence cortical functioning also via the ascending reticular formation. Information transfer from the baroreceptors to the hypothalamus with sufficiently short latency to permit its participation in reflex cardiovascular regulation was demonstrated by Adair and Manning [1]. Parallel to the baroreflex, inhibitory afferents influence higher brain stem centers mediating cortical deactivation in response to blood pressure increases. Since the early studies of Koch [22, 23] and Bonvallet et al. [4, 5], and Nakao et al. [32], evidence has accumulated suggesting that afferents from the carotid baroreceptors have the potential of producing considerable decreases in electro-cortical concomitants of activation and in cortical excitability, and that this effect is independent of any variations in blood pressure or blood flow. In this paper we will examine recent evidence for this notion (for more extensive reviews of the earlier work see Elbert et al.[12], Gruppe [19] and Rau et al., this volume).

2. Baroreceptor input decreases cortical excitability

One way to evaluate the influence of baroreceptors on higher central nervous, particularly cortical structures in humans is provided by EEG measures. We have used CNV-like brain potentials as markers of cortical excitability. The CNV (contingent negative variation) is a member of a family of slow surface negative shifts which develops in anticipation of an imperative event, i.e. an event which requires a subject½s response (motor, attentional or cognitive). Such slow negative potentials are thought to originate in the depolarization of apical dendrites synchronized via thalamic afferents to layer I. Slow surface negativity, therefore can be considered as an indicator of cortical excitability [9, 10, 11]; for recent reviews on slow brain potentials see [3, 31, 39]. Typically, the CNV can be elicited utilizing the two stimulus (S_1 - S_2) paradigm, in which a warning stimulus (S_1), for instance a tone, tells the subject that an imperative stimulus will be presented a few seconds later. Subjects are asked to press a button as fast as possible to this second stimulus (S_2), which may be a tone also. Trials are presented some twenty times to allow signal averaging.

This was exactly the arrangement in a first study, when we tested the same subjects while they had received either the blood pressure enhancing Norfenefrin-HCl[2] or a saline placebo [25, 26]. CNV-amplitude was significantly

reduced when the a-sympathomimetic agent was administered as compared to placebo (Fig.1a).

This result could be validated subsequently in a number of studies in which we used the cervical neck suction technique to stimulate the baroreceptors [13, 34]. The air pressure is varied in an airtight chamber [8] fixed around the subject's neck. Since the baroreceptors are actually stretch receptors which are located in the wall of the carotid sinus and, hence, respond to the pressure difference between the inside and outside of the sinus, a decrease in extra-vascular pressure in the surrounding tissue by e.g. 15-20 mmHg will cause the receptors to fire as if the intra-vascular pressure had been increased by 15-20 mmHg. About 70% of changes in cuff pressure are transduced to the arterial wall. Thus a pressure change of about 20-30 mmHg in a cuff around the neck will mimic a blood pressure shift of 15-20mmHg. The baroreflex is elicited in response to the cervical neck suction, and heart rate drops within a second. This in turn will unload the baroreceptors in the aortic branch to some extent. In our studies, trials with reduced atmospheric pressure in the cuff (baroreceptor stimulation) were intermingled pseudorandomly with control trials, with slight excess pressure (baroreceptor inhibition). The baroreceptor reflex can be reliably elicited by this method, as validated on every individual trial by changes in heart rate (decelerations up to 20 bpm), EKG (T-wave amplitude), digital pulse volume amplitude and R-wave to pulse interval. Again, the CNV which develops under control conditions is markedly reduced under baroreceptor stimulation (Fig.1b).

Changes in blood flow or blood pressure cannot account for the finding of a reduced CNV during stimulation as those were opposite for the pharmacological and for the mechanical baroreceptor stimulation (Fig.1). But still, one could argue that under both conditions the stimulation is the more distracting procedure and distraction has been known to reduce CNV-amplitude for long [46][3]. One problem was to arrange a psychologically equivalent 'placebo' condition. Without an appropriate control procedure, it is difficult to be confident that an observed behavioral effect originates in barorecptor manipulation and not simply from distraction caused by the suction associated sensation. In collaboration with B. Dworkin, we have developed an improved technique of cervical suction that allows for a number of control conditions. The technique simply relies on short changes in cuff pressure tied to different phases within the cardiac cycle (PRES: phase related external suction, see Rau et al., this volume)[4]. As revealed by questionnaires and interviews, subjects did not become aware of the phase relationship between pressure changes with their cardiac cycle and were unable

to distinguish intervals during which the baroreceptors were stimulated from control periods. Nevertheless, CNV-amplitude again turned out to be diminished at times when the baroreflex became elicited (see Rau et al., in this volume, Fig.4).

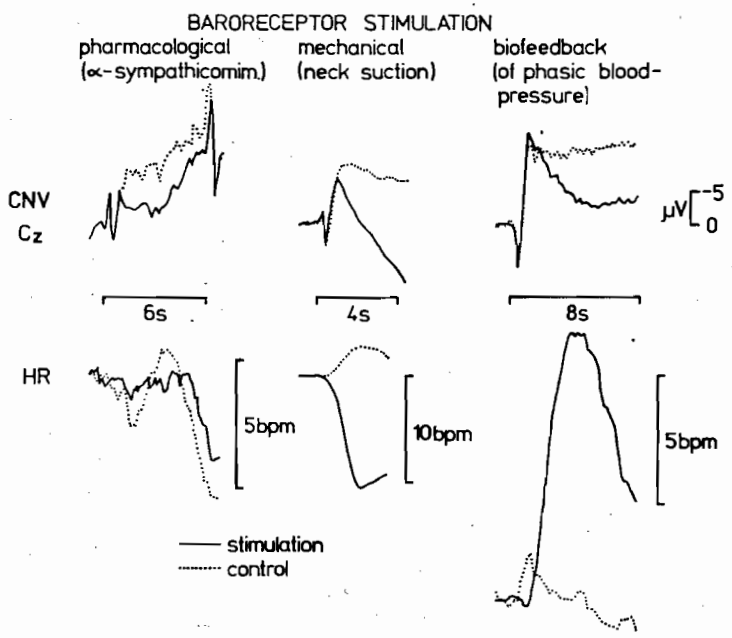

Fig.1: Results form three different experimental techniques to stimulate barorecptors. (a) Either a a-sympathomimeticum (stimulation) or a saline solution (control) is injected intravenuously; (b) either a negative pressure (stimulation) or a positive pressure (control) is applied in a cuff around the neck, (c) by means of biofeedback, the subject has learnt to increase (stimulation) or maintain (control) its phasic blood pressure. Upper panel: heart rate responses. Lower panel: slow cortical negativity (CNV) measured from the vertex in reference to linked ears. Measures for the slow cortical potentials were (1) the averaged change in negative amplitude during second two, in μV (initial or iCNV), and (2) the mean of the sixth second (terminal or tCNV). In all three experiments, the tCNV, but not the iCNV was significantly lowered while heart rate either was the same (a), decelerated (b), or accelerated (c). (Data from Larbig et al.[25], Elbert et al. [11,12,13]).

As a third technique we have employed biofeedback in order to manipulate blood pressure and consequently baroreceptor firing [14]. There were two types of trials, one kind required increase of phasic blood pressure (*'up'*), the other a decrease (*'down'*). Feedback was provided by the outline of a little rocket-ship

which appeared on a TV-screen in front of the subject during eight second intervals. The integral of the mean arterial blood pressure referred to a pre-stimulus baseline (4 seconds), determined linearly the horizontal position of the feedback stimulus. Mean blood pressure was defined as 2/3 diastolic plus 1/3 systolic pressure[5]. A letter 'A' or the letter 'B' appeared in the upper left corner, signalling the subject which of the responses (*up* or *down*) would be rewarded. The sequence of trials alternated randomly, 50% were A trials. Subjects participated in a number of training sessions until they had reached at least 15 net win points (win minus lost points). Net win points increased significantly across sessions. Heart rate increases during the first few seconds of up-trials but then, while blood pressure raises subsequently with some delay, heart rate starts to decelerate in turn (Fig.1c). The average heart rate during the seconds 3-8 amounts to 7.5±1.7 bpm. During *down* trials, heart rate tends to decelerate (-0.7±0.6 bpm, $p<.001$ for the difference between *up* and *down*). Absolute heart rates (not referred to pre-trial baseline) were 83.2 bpm during *up*- and 75.0 bpm during *down* -trials ($F(1/13)=24.5$, $p<.001$).

Consistent with the predictions from the previous experiments, the precentrally dominant terminal CNV turned out to be considerably reduced in amplitude during *up*-trials (Fig.1c). Even more pronounced effects were found over parietal, as well as over frontal but not prefrontal cortex.

Thus, investigations so far are consistent with the interpretation that intensive baroreceptor stimulation provokes a strikingly noticeable reduction in scalp negativity which we interpret as a marked reduction in cortical excitability. This finding was obtained, irrespectively whether or not heart rate had increased simultaneously (like in the biofeedback study), showed no phasic change (under norfenefrin) or decreased as a consequence of the baroreflex elicited by cervical suction or PRES[6].

In addition this impact of baroreceptors on the cortex is lateralized. While stimulation of the baroreceptors of both sides activates the baroreflex arc, peripheral effects were found to differ according to the specific cardiac innervation. Stimulation of the receptors on the right produces a more pronounced change in heart rate than stimulation on the left, whereas the left carotid sinus was found to alter cardiac contractility to a higher degree than the one on the right side [45]. We replicated these effects and demonstrated furthermore that stimulation of the left side reduces negativity to a greater extend over the left than over the right hemisphere [15]. Given the ipsilateral projection of the nucleus of the tractus solitarius, this finding is further support for the view

that baroreceptor input dampens cortical excitability as measured through slow cortical potentials.

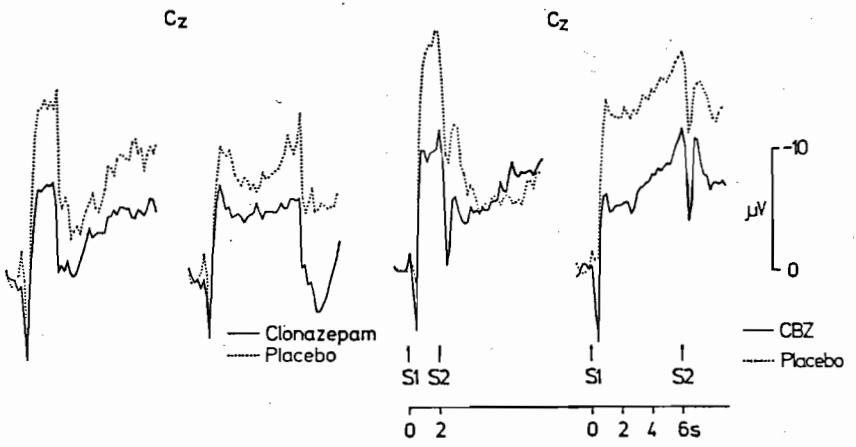

Fig.2: Grand averages of the CNV (slow cortical negativity), recorded in subjects under placebos, the anticonvulsant carbamazepine, or the benzodiazepine Clonazepam (5-(2 Chlorphenyl)-2,3-dihydro-7-nitro-1H-1,4-benzodiazepin-2 one (IUPAC). Within a two-stimulus reaction time paradigm subjects heard one of two acoustic stimuli (S1). The two sounds (white noise of 65 dB each) differed in pitch, which signaled whether the particular S1 would last for 2s or 6s. Each S1 was immediately followed by an imperative stimulus (S2) requesting a fast button press. The S2 was always a tone of 600 Hz, 65 dB. Subjects were asked to interrupt the S2 as fast as possible by pressing a button. Twenty trials with the 2s S1-S2-interval and 20 trials with the 6s S1-S2-interval were presented in pseudo-random order. Inter-trial-intervals varied randomly between 4 s and 19 s.
Compared to Placebo groups (dotted lines), the CNV is reduced under the benzodiazepine Clonazepam (left side) as well as under the anticonvulsant carbamazepine (right side) (Data from Rockstroh et al.[38, 40])
Comparison with Fig. 1 reveals that the reduction in CNV-amplitude for these powerful inhibitory agents is in the same order of magnitude as the one observed during baroreceptor stimulation.

At first glance, the capacity of baroreceptors to influence cortical excitability seems to be astonishingly powerful. This becomes obvious, if the modulation in CNV-amplitude through baroreceptor firing is compared with the one of potent anticonvulsants. Fig. 2 illustrates the effect of the anticonvulsant carbamazepine and the benzodiazepine clonazepam on the CNV. As these results were obtained in our laboratory, using the same experimental design, technology, and with subjects drawn from the same population, it is sensible to compare the CNV

changes, presented in Figures.1 and 2. Obviously, the a-sympathicomimetic agents act as powerful on the CNV, i.e. on phasic shifts in cortical arousal, as prominent inhibitory substances do. In this light, the suggestion by Nakao et al.'s data [32] that baroreceptor input might interrupt seizure activity seems not as strange. Indeed, preliminary evidence (from our lab, as well as from Zabara [53]) suggests that in certain epileptic patients, seizures can be prevented by the patient triggering cervical vagal afferent input during an aura.

3. Changes in spontaneous EEG-activity

EEG synchronization is considered a sign of activation and cortical arousal. If baroreceptors have a relaxing or deactivating effect, EEG synchronization should be enhanced during the stimulation. Indeed, Nakao et al. [32] reported EEG synchronization (2-7Hz) in response to a pharmacological enhancement of the blood pressure in cats. Theoretically, the drug itself may have caused this effect. In our early studies we looked primarily in the EEG-alpha band, where we failed to detect any systematic changes in humans. But then Vaitl and Gruppe [19, 48, 49], see also Vaitl & Gruppe, this volume) observed systematic variations in EEG-theta and also the delta frequency band when they altered body positions of their subjects by means of a tilt table device (head down and head up tilt). Thereafter, we have obtained two results which confirm the hypotheses that afferent baroreceptor input enhances power in the slow frequency range. In one study, together with H. Rüddel and W. Lutzenberger (unpublished data), the EEG was recorded from hypertensive subjects with an implanted carotid sinus nerve stimulator. During bilateral electrical stimulation of the carotid sinus nerve, power of the lower frequencies (up to 6 Hz) were somewhat larger than during stimulation-free periods in all four patients under investigation. The second evidence comes from the study of Rau et al. [34] in which the neck suction technique was used to stimulate baroreceptors. When we reanalyzed the data, subsequently to Vaitl's report, we detected that the theta power was significantly larger during intervals with negative than during those with a positive cuff pressure.

Thus the available EEG data are consistent with the conjecture that afferent baroreceptor dampens cortical arousal, although the nature of the observed changes in theta activity remains to be specified. (Theta-activity during the waking state might indicate lowered arousal, deactivated cortical regions Å 'microsleep', akin a state of pain suppression, cf. Larbig et al.[24])

4. Effects of baroreceptor stimulation on behavior

Already Koch has noted behavioral changes in response to baroreceptor activation, the stimulated dogs became drowsy and sleepy. Dworkin et al. [6] examined the motoric dampening more carefully. They compared the behavior of rats with intact baroreceptors with the one of rats which had undergone a complete surgical denervation of the carotid sinus and aortic arch. When the a-sympathomimetic agent phenylepherine was injected, blood pressure was raised in both groups of animals, but the behavioral responses were very different. Only the intact rats became quiet and appeared to sleep. Randich and Maixner [33] concluded from a series of experiments in rats that baroreceptor activation reduced pain sensitivity and, by using atropine in conjunction with phenylepherine, they further showed that reflex bradycardia was not essential to the anti-nociceptive effect. Such invasive controls are not possible in human studies. However, Zamir and Shuber [53] observed a correlation between blood pressure and pain threshold of greater than r=.70, and showed that hypertensives have pain thresholds nearly twice those of normotensives, which suggested that similar processes might be occurring in man as in the rat. Our studies also provided support for the modulation of nociception through baroreceptors in humans.

In a cross-over design either phenylephrine or saline was administered intravenously in 10 male normotensive volunteers. Then pain sensation thresholds to dental tooth pulp stimulation were measured. Phenylephrine enhanced pain perception, but this effect was less prominent the higher the tonic blood pressure of the subject (r=.80, [37]). Employing the neck suction yielded corresponding results. In the study by Elbert et al. [12] we asked subjects to interrupt increasingly intense electrical stimuli as soon as they were perceived as being painful. Pain threshold was lowered during the negative cuff pressure compared to the control condition in normotensives, but subjects with elevated blood pressure levels (systolic pressure readings during rest above 130 mmHg) exhibited the reversed effect [12]. It is conceivable that appraisal processes and to a lesser extent motoric output is affected [47]. One way to tackle this question further might rely on the investigation of the startle reflex [18] which is thought to be modulated by the current emotional state [20, 50]. If baroreceptor stimulation suppresses affectively negative states, then the magnitude of the startle response should be lower during baroreceptor stimulation than during adequate control conditions. We tested this hypothesis employing conventional neck suction [35]. The result, illustrated in Fig.3, indeed confirmed that the

startle reflex is attenuated during baroreceptor stimulation. Of course, this modulation is not necessarily a consequence of the cortical modulation of the startle response, but may result from the ascending influence of baroreceptors on mesencephalic reticular formation, as this structure is known to be involved in the inhibition of acoustic startle [28, 29]. But the reticular formation, of course, has a high impact on cortical arousal, and the reported cortical effects may well be mediated through reticular afferents in turn [11].

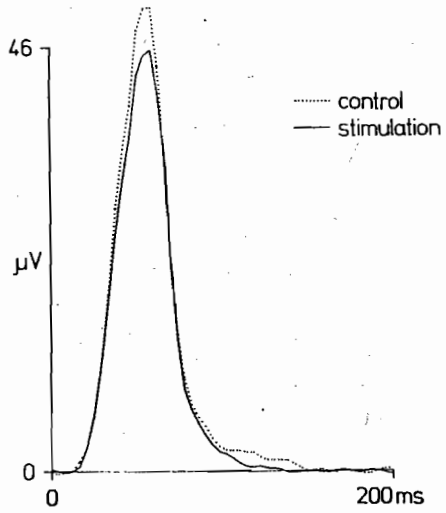

Fig.3: EMG measured from the M.orbicularis occuli in response to a 90dB startle stimulus during trials with baroreceptor stimulation (negative neck pressure, solid) and control stimulation (positive pressure, dotted).

Why should it be possible that cardiovascular afferents exert such a powerful influence on brain and behavior? The reason may be found in the power of the efferent branch. If brain structures can put an extremely high load on the cardiovascular system, then, guarding against overload, a protective, negative feedback is to be required.

B. From Brain To Heart: How Far Can A Cortical Response Drive The Cardiovascular System?

The major output pathways from orbito-frontal cortex control visceral and cardiac responses via pathways to the dorsal hypothalamus and brainstem. Electrical stimulation of the frontal cortex leads to inhibition of the baroreceptor reflex. Stressful conditions may raise cortical arousal above optimal levels of functioning. In parallel, sympathetic outflow may increase considerably, leading to tachycardia, enhanced cardiac contractility and elevated blood pressure. The latter response should in turn lower cortical excitability, as outlined in the previous section. Such a response would not only serve regulatory functioning, it is also protective. But, according to Skinner [43, 44], stressful events can also provoke an elevated dual autonomic tone, i.e. they can enhance the tone of both branches of the ANS at a time. Frontocortical excitability as measured by slow, surface-negative cortical potentials probably boosts the dual autonomic tone. Drugs reduce ANS activity [38] and cardiac arrhythmia [41, 42, 43, 44] in direct proportion to the reduction in CNV-amplitude. Studies in which patients with frontal lobe lesions were trained to regulate their slow potentials upon command indicate that the distortion of cardiac event-related responses parallels the inability to regulate the CNV over frontal areas [27]. In humans, an increased amount of cardiac arrhythmia can be observed under stressful conditions (e.g. in astronauts during maneuvers with high psychological stress; [44]). In patients suffering from cardiac arrhythmia, the CNV amplitude covaried with the degree of cardiac vulnerability, even under non-stressful conditions (choice reaction time task). Skinner speculates, that stressor events (defined as external novel or aversive events which are experienced as stressful by the individual) increase cardiac vulnerability through a learning dependent noradrenergic process in frontocortical neurons.

This would leave the organism in a dilemma when exposed to continuous stress: Either the sympathetic branch dominates, then, there is a hearty dampening effect of the baroreceptors on the brain, cortical excitability will be under control, but the risk of hypertensive development increases. Or the organism responds primarily with an enhancement of the dual autonomic tone. But then cardiac vulnerability, including the incidence of ventricular arrythmias will be high. Only, when there are adequate psychological coping mechanisms for the variety of stressful conditions, cortical, autonomic and cardiovascular excitations will remain within the normal range.

C. Ups And Downs: The Feedback Loop Between The Cardiovascular And The Central-Nervous System

When specifying the influences of cardiovascular manipulations on the brain, it must be kept in mind that we are dealing with a closed loop feedback system with various mutual interactions. Structures on all levels of the peripheral/ autonomic and central nervous systems are involved in cardiovascular regulation, from the spinal cord to the frontal cortex (e.g. Bard, [2]). And all of these structures are affected by the cardiovascular system in turn, and in various ways. Furthermore, we are not dealing with a fixed system. Many of the responses and the relations are plastic and subject to various learning mechanisms.

The brain, anticipating baroreceptor stimulation, counteracts the expected effects. For instance, in the Elbert et al.(13] study, the early CNV was found to be already significantly enhanced at a point in time at which pressure change and the baroreflex could not have produced any effect. This turned out to be a consequence of Pavlovian conditioning, as tested more radically and confirmed by the study of Rau et al. [34]. We have interpreted the enhancement of the CNV to the signal for baroreceptor stimulation as a conditioned response, serving to compensate for the expected cortical inhibition through an UCS, namely the afferent baroreceptor input.

This example highlights the problems associated with the external manipulation of elements in conditionable feedback loops. We believe that some of the problems can be circumvented by taking into account the dynamic properties of the system. Such methods have been developed recently (e.g. [21]) and have produced some interesting insights into the regulation of the cardiovascular system [30]. The assumption that physiological, specifically cardiovascular processes may be governed by the rules of deterministic chaos is not entirely new. In fact, ventricular fibrillation has already been characterized as chaotic [16, 17]. Mayer-Kress et al. [30] investigated the variability of the heart period (RR(n+1)-RR(n))/RR, over periods of about 20-30 min. For the average pointwise dimension they obtained 5.8±2.4 and 5.6±1.6, a result, if confirmed, would propose that the attractor of the system determining the heart rate is low in dimensionality and that it is probably chaotic. As a result, much of the variations in heart rate and blood pressure might be intrinsic to the properties of the feedback loop. Furthermore it is an interesting feature of variables governed by chaotic processes that the long-term averages are not necessarily stable. Therefore such a system would, by its inherent dynamics, allow the slow drift of

the blood pressure out of the preset (normal) range. Whether operant mechanisms are a dominant driving force for such a drift, whether they act in conjunction with classical conditioning or whether dynamic properties inherent in the design of cardiovascular-CNS interaction play a dominant role remains the 100,000 $ question at present. It will be a future task to specify these circumstances.

Only then, when we will be able to specify the psychological malpractices which make ourselves physically ill, only then we really will be able to do something about it as requested by Aldous Huxley years ago.

APPENDIX

2 Novadral (1-(3'-Hydroxyphenyl)-2-aminoethanol is a sympathomimetic agent with vasoconstrictive effects. Direct actions on the CNS are unknown.

3 This may be true, however, for the early portion of the CNV only. We have demonstrated that the later component (terminal CNV) which peaks just prior to the response may become larger in amplitude when distracting background stimuli are present [36].

4 Because the carotid stretch receptors are not only sensitive to the pressure level, but in particular to rate of change [7], it is possible to manipulate receptor firing rate through the application of short changes in cuff pressure tied to different phases within the cardiac cycle (PRES: phase related external suction): A brief external suction during systole has potent stimulatory effects on baroreceptors while the application of the very same pressure pulse during diastole disfacilitates the firing burst associated with the pulse wave. In order to allow an ongoing period of stimulation, a sequence of alternating negative/positive pressure pulses is applied. (In the stimulation condition the ECG R-wave triggers a negative pulse which is followed by a positive one during diastole. In the control condition this relationship is reversed. The technique and its evaluation is described in the chapter by Rau et al., this volume).

5 Finger aterial blood pressure was continuously monitored by means of an Ohmeda *Fin.A.Pres.* device (e.g. [51, 52]).

6 The relatively small effects using PRES might result from a non-linear relationship of the posutlated impact, baroreceptors might have on higher CNS-structures. We should assume that changes of baroreceptor activity which do not surmount the range within typical cardiac cycles should have no or a qualitatively different effect than variations of barorecpetor input which are beyond normal fluctuations, and which ought to evoke alarm-like reactions, in higher brain centers as well.

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