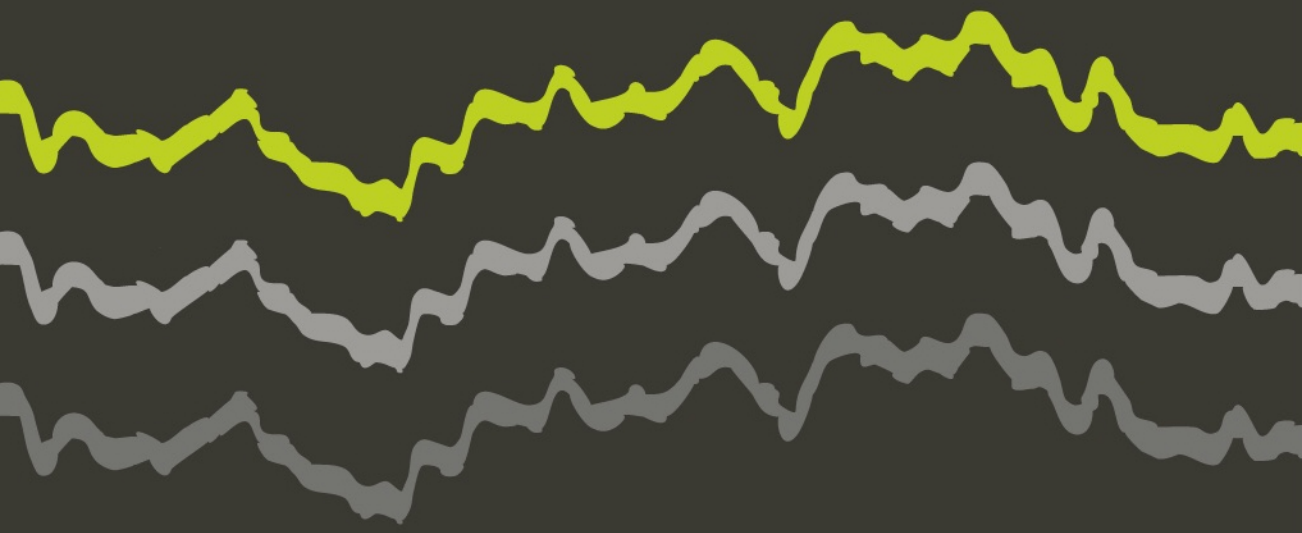
Neurofeedback: How it all started



Martijn Arns
Maurice B. Sterman

Neurofeedback offers exciting potential for understanding the brain and human behavior as well as the treatment of epilepsy and ADHD. Its rich history, from the discovery of the EEG in 1875, via the beginnings of the field of neurofeedback in 1936, to the foundation of the clinical application in the summer of 1969 is finally brought to life.

It's a compelling read, often from an eyewitness account, in which we meet an eccentric Wallstreet millionaire, a telepathy-inspired psychiatrist, a Soviet scientist's encounter with Stalin, a British Baron, a former street gang member and a group of forward thinking West Coast scientists. Discover how they all played a vital role in shaping the future of neuroscience and neurofeedback.

Dr. Martijn Arns, Research Institute Brainclinics, Nijmegen and Department of Experimental Psychology, Utrecht University, The Netherlands. Dr. Arns is specialized in applied neuroscience and personalized medicine and is one of the most published researchers in the field of neurofeedback. He is founding director of Research Institute Brainclinics since 2001, Scientific Adviser to neuroCare Group (a Brainclinics spin-off) and has been affiliated with Utrecht University, Department of Experimental Psychology since 2009.

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NEUROFEEDBACK: HOW IT ALL STARTED

MARTIJN ARNS

MAURICE B. STERMAN

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PREFACE

MAURICE B. STERMAN

Recently I have been encouraged by numerous colleagues to produce a narrative covering my career of some 50 years as a psychologist and neurophysiological researcher interested in mechanisms regulating arousal and sedation in the central nervous system, followed in later years as an investigator seeking to apply what I had learned in the clinical world. In order to share my experiences and contributions across all these years my contribution here will not be a typical scholarly work. It is more like a Power-Point presentation with substantial text and a heavy reliance on visual confirmation of conclusions, consistent with my favorite comment when discussing science, namely: *"show me the data!."*

I will attempt a somewhat detailed review of the history and functional importance of neural inhibition and the work I have done seeking to explore it. But a comprehensive review of the related literature would be difficult, primarily because the work described evolved over an extended period of time with changing research objectives, technology, and conclusions. Thus, it focuses primarily on studies and outcomes from my own laboratory. This work was

initially limited to neurophysiological and behavioral studies in very healthy animals purchased from the University of California at Davis, which raised and maintained a special colony of genetically documented, adult cats specifically for approved research. Speculation was minimal because data were derived both from animals with electrodes placed directly onto or stereotaxically into the brain, and later from behavioral studies with surface electrodes in humans, providing solid empirical findings. These data are peer-reviewed and published. This documentation is fundamental for appreciation of the surprise realization that evolved. In the final analysis, namely that the findings all spoke to the same basic conclusions. Regarding this convergence, I am reminded of the important mantra I learned from reading Pavlov, namely "observe, observe, observe," and the insightful conclusion of my friend Elkhonon Goldberg, who suggests in his most recent book, the "Wisdom Paradox," that we do not necessarily get smarter with age, but we can get wiser!

My first published study with human subjects was with hospitalized neuropsychiatric patients. The findings from this work subsequently led to extensive neurophysiological work with animals (cats, and primates) and eventually to the application of behavioral learning methods of conditioning, from both Pavlov's 'Classical' conditioning and the American school of operant, or sometimes termed instrumental, conditioning, both methods for facilitating or suppressing learned physiological and/or behavioral associations and response outcome consequences, respectively. Thus, the body of work from my laboratory was grounded initially in electrophysiological and behavioral studies with laboratory animals, and subsequently with human subjects. Operant conditioning studies of the EEG eventually became the primary focus of this work and were instrumental in launching a new field called neurofeedback.

As animal studies with cats or non-human primates became more difficult to fund, our efforts were adapted exclusively to human subjects. Because these studies proved to be so successful, I found no reason to abandon neurofeedback in favor of the estimated mathematical EEG derivations and external cortical stimulus imaging methods that have emerged in contemporary behavioral and neurological brain studies.

I asked my very competent, younger friend Dr. Martijn Arns from the Netherlands, to co-author this book with me, and he will add in further historical elements important for understanding the full history of EEG and neurofeedback.

Maurice B. (Barry) Sterman

CHAPTER 1:

HOW DID I GET HERE?

MAURICE B. STERMAN

My interest in this topic was probably unconscious initially, but in retrospect now seems to have arisen from several events encountered in my early years. The first had to do with my oldest of three sisters, who was 11 years older than I. In my childhood and adolescence, she was somewhat of a surrogate parent as, my mother and father have emigrated to Minnesota from a rural life in Eastern Europe. My sister was brilliant and vivacious, having been a popular straight-A student and a talented classical pianist throughout her school years. I was her 'little boy'! She introduced me to music, art, and learning throughout my formative years. When I was about eight years old, she fell in love with a really great guy named Sylvan. I was a tag-along but with no objection from the happy couple. But it was 1943 and he was drafted in to the US Army! After boot camp and before deployment he asked her to marry him, but she wanted to wait until he returned from the war. When he went overseas, she took a job at the high school she had graduated from, operating a 'mimeograph machine' (which was the copying system of the time), copying pages of typing in blue ink onto rolls of paper. She came home each day with blue fingers from the work she was doing.

Unfortunately, Sylvan was killed on the beaches of Normandy! Her life was never the same. She stopped working and playing the piano and went into a profound depression. She still would have talks with me. Often before bedtime we would sit on her bed and chat about many things. To my amazement whenever we spoke about Sylvan her toes would immediately elevate and turn blue! She was totally unaware of this response, and when I pointed it out, I saw that she was crying. We had no explanation for what has caused it. In subsequent months her fingers began turning white and blue whenever she handled a cool or cold object or became upset, and her fingers began to curl in, thus precluding her piano playing. Ultimately, her condition was diagnosed as Raynaud Syndrome, also known as Raynaud's phenomenon. This is a medical condition in which spasms of arteries causes episodes of reduced blood flow. Typically, the fingers, and less commonly the toes, are involved. This outcome resulted in her doctors recommending that our family relocate to a warmer climate, which is how I ended up in Los Angeles California.

Years later as a graduate student at UCLA I built a device for my sister which registered the temperature in her fingers on a vertical light scale and reward her gradually for temperature increases. By this time, I was aware of the training method called operant or instrumental conditioning and hoped that this could help her learn to warm her fingers voluntarily. In fact she eventually was able to raise her finger temperature and showed gradual improvement. She eventually got married and had a child and went to law school. However, keeping her compliant with this treatment was a problem, most likely due to a busy life and slowly emerging psychopathology. Over an extended period of time her condition evolved into a more serious disorder known as Scleroderma, an autoimmune disease of connective tissue. She died at age 61.

What I had learned from her experience was that chronic emotional and behavioral distress can have profound biological consequences, even contributing to peripheral autoimmune disturbances, and is capable of affecting peripheral autonomic and sensory dynamics. In recent years it has also been documented that another autoimmune disorder that alters cortical synaptic transmission dynamics

specifically can result in profound behavioral, neurological and psychiatric symptoms. A new neurological diagnosis called 'anti-NMDR Encephalitis' raises the possibility that chronic emotionally-induced peripheral disturbances, and related genetic influences can, in turn, produce serious autoimmune brain disorders. Today, treatment, with the correct diagnosis can often result in full recovery. A book by a recovered victim Susannah Cahalan, and a resulting movie, both entitled *'Brain on Fire'*, are based on this newly appreciated neurophysiological disorder, and are highly recommended to anyone studying clinical neuroscience or human behavior and mental disorders. Some similar, unappreciated aspect of neural regulation affecting inhibition of peripheral blood flow may well have contributed to my sister's medical history.

Getting back to my personal history living in Los Angeles, I completed high school and was fortunate to qualify for the University of California (UCLA) where I first decided on a major in astrophysics, since I was fascinated by flight and Astronomy. However, I had never resonated with math, and after starting out in astrophysics I realized that math was fundamental to that field, on top of which it was necessary to use a slide rule, the only technical instrument of calculation in use by students at that time. There were no adding machines or calculators. For some reason I had difficulty mastering the slide rule. After getting a B in trigonometry I met with the department chairman and told him that my only concern was the mathematics requirement. He kindly recommended that maybe I should rethink astrophysics.

My next foolish decision was shifting to a pre-dentistry major in order to make my mother happy. In retrospect I realized that being left handed and having a bad back from high school athletics made this a bad choice. However, after one year of classes for that major, as well as in Psychology, in order to be together with a young lady I was attracted to, I had a fascinating experience. While taking a required manual dexterity test for acceptance into dental school on the 8th floor of the Moffitt Hospital in San Francisco, I was sitting next to a window on a very rainy day. I was looking up and stretching my back I looked around the room and saw the room full of hunched-over applicants furiously carving chalk. I turned away somewhat displeased

and looked out the window. The clouds above suddenly opened up and a beam of sunlight came down and landed directly on Alcatraz Island. I looked down and thought, clearly, "He's' trying to tell me something!" I made up my mind right then and there and decided to accept an offer from the Psychology Department at UCLA to study for a PhD in their graduate program. I finished my bachelor's degree in psychology at UCLA in 1960, Cum Laude, and continued in the PhD program, which was completed in 1963.

While a graduate student, I took a course at the affiliated Grace Fernald Psychology School. Fernald had developed the idea that our teaching methods were too heavily based on visual processing, a possible disadvantage for children who were more capable of auditory or kinesthetic processing. The school provided alternative teaching classes and tutoring. I wondered how much data there was for documenting the notion of alternate sensory modality factors in the learning process. Since the University Experimentally Oriented Elementary School was right next door to the Fernald School, I asked the administrators if I could test that hypothesis with some of their students. To my surprise they thought that was a good idea. I put together a set of reading tests involving pages of text from grade appropriate books, similar auditory topic, and wooden block sets with indented letters. These blocks spelling out comparable words to cover visual, auditory, and kinesthetic presentation and compared timing and accuracy of student comprehension performance. The results confirmed visual dominance but also suggested some benefit for the alternate modalities. This study was submitted by my advisers to the California Psychology Society *'First Paper Award'*, contest that year, and took first prize! After this award I was asked to teach and tutor at the Fernald School during my second year.

While tutoring that summer, I encountered an 11th grade student named Tom, who was doing 8th grade work in school. My experience with Tom would strongly influence my further interest in anatomy and physiology, the topics I later specialized in and that formed the core of the rest of my career. Tom only spoke in single syllables, had a pale face, and a stiff posture and gait. Upon initial observation I referred him to the chief-psychologists at the institute who diagnosed

him as schizoid and warned that I would *"not touch him with a 10-foot pole."* At that time, I was taking a course in endocrinology as part of a granted petition to add anatomy and physiology to my curriculum, and it was midterm test time. The test was to be focused on thyroid function, and while sitting there with Tom one day doing some work, I looked at him and realized he checked all the symptoms off the list for hypothyroidism. So, I called his parents and told them that their son might be hypothyroid. I asked if he had ever had a BMR (basic metabolic rate test), which he had not. So, I advised them to have it done. Two weeks later he walked in the door and excitedly said: *"Hey Barry, what are we going to do today?."* What I saw then and there was an unbelievable change. He was less rigid, had color in his face and talked more like a regular kid. It was like a caterpillar that had turned into a butterfly.

The experience with Tom had a big impact on my thinking. I thought that if I'm going to be working with people like this, I've got to know about the brain. I've got to know about why that happened? I've got to understand the endocrinology, which in his case was affecting his brain and interfering with his ability to acquire new information. So, I just changed my whole major.

FROM THE AUTONOMIC NERVOUS SYSTEM TO THE EEG

One professor, I was particularly interested in, named Prof. Marion A. 'Gus' Wenger had written many textbooks about psychology and physiology. In 1944 Wenger had worked at the Santa Ana Army Air Force base, where he was recruited by J.P. Guilford. There Wenger and Guilford together worked on developing a test battery which would improve the selection of Army Air Forces cadets. In this period Wenger had access to 100's and 1000's of cadets and people in the Air Force, and had the notion that, if you could measure all the basic autonomic functions individually and you could link that up, you find correlations with mood. But he wanted to classify mood as patterns of autonomic activity. Hence, Wenger was recording from subjects and presenting them with affective stimuli that made them laugh, or made them sad, and frightened. After the Second World

War ended in 1945, he joined the faculty of the Department of Psychology at UCLA. In 1960 he was one of the founders of the Society for Psychophysiological Research, that started to publish the scientific journal Psychophysiology, four years later, together with other pioneers such as Albert F. Ax, Chester W. Darrow, Robert Edelberg, John I. Lacey and John A. Stern. Eventually, Wenger would be seen as one of the pioneering psychologists that stood at the scientific basis of the field of psychophysiology.

At this time, I was attending graduate school at UCLA and started working at the VA hospital at Sepulveda with Prof. Wenger, recording psychophysiological data in schizophrenic patients under cold pressor stimulation (immersing a foot in ice-water for one minute). The procedure started with placing peripheral autonomic recording electrodes for measuring respiration, heart rate, arterial pressure, skin resistance and pulse volume. My interest in the Central Nervous System (CNS) caused a dispute with other graduate students working in the lab over the polygraphic recording speed. Trends of autonomic measures were recorded slowly and required a relatively slow paper speed on the old paper and ink polygraph recorders of that time. I had hoped to add EEG recordings to the protocol. However, that required faster paper speed to resolve the rhythmic patterns of interest and the other students didn't want to do this, because they were interested in the autonomic system. It didn't ruin the autonomics, it only made it harder to analyze. Thus, I convinced Wenger to include EEG recording electrodes to evaluate brain correlates of the autonomic patterns they observed. EEG electrodes were then attached to the skull in a bilateral array along the anterior-posterior axis. The design provided for a 15-minute pre-stimulation recording from patients lying on a gurney adjacent to a tub of freezing water. A one-minute confirmed submergence of a bare foot adding pressure to a pedal at the bottom of the tub which turned on a red light on the side of the gurney, and a 15-minute recovery recording. Subjects were required to keep the red light on for one minute before removing their foot from the water.

The study, published in 1966 [1], assumed that cold-pressor stimulation would mainly result in a desynchronized EEG where the syn-

chronous alpha activity would desynchronize into low-voltage high frequency EEG pattern during stimulation. This occurred in the majority (75%) of patients. However, we also observed two deviating subgroups, one labeled as 'rapid alpha recovery', where alpha reappeared after 10 sec. of onset of cold pressor stimulation (while cold pressor stimulation went on for 1 min.) and the other labeled as 'prolonged alpha block' exhibiting a longer suppression of alpha beyond the one minute. These two groups also had differing autonomic responses to the cold pressor stimulation, where the rapid alpha recovery group sped up their respiration during cold pressor, followed by a normalized respiration and quicker normalization of arterial pressure. On the contrary, the prolonged alpha block group had a respiratory decrease (e.g. 'holding their breath') during stimulation which increased and remained high for at least five minutes after the cold pressor (*also see Figure 1 for illustration on page 22*).

Thus, by exposing a large group of adult males to a one-minute period of pain and discomfort we learned that they revealed three different patterns of cortical and visceral response. The majority showed stimulus specific physiological arousal, while the two other smaller groups presented two different and opposite patterns of response. One suggested a more chronic level of arousal that was significantly exacerbated by the stimulus, and the other showed only a brief arousal that returned rapidly to baseline. Presumably both genetic and developmental factors contributed to these differences.

I was particularly interested in the rapid recovery group. These findings were reminiscent of the well-known behavioral work of the Russian physiologist Ivan Pavlov. Besides his discovery of 'Classical Conditioning' he also gave us the concept of 'internal inhibition.' Pavlov's study of 'conditional reflexes', led him to elaborate about the problems of higher-order nervous system inhibition. Commenting on the inevitability of this elaboration Pavlov stated, *"...When we come to investigate the highly complex functions of the cerebral hemisphere we naturally expect to come across inhibitory phenomena, for these are very constantly and very intimately mixed up with the positive phenomena of nervous excitation...."* This notion was further supported by examples of dogs 'learning not to respond.'

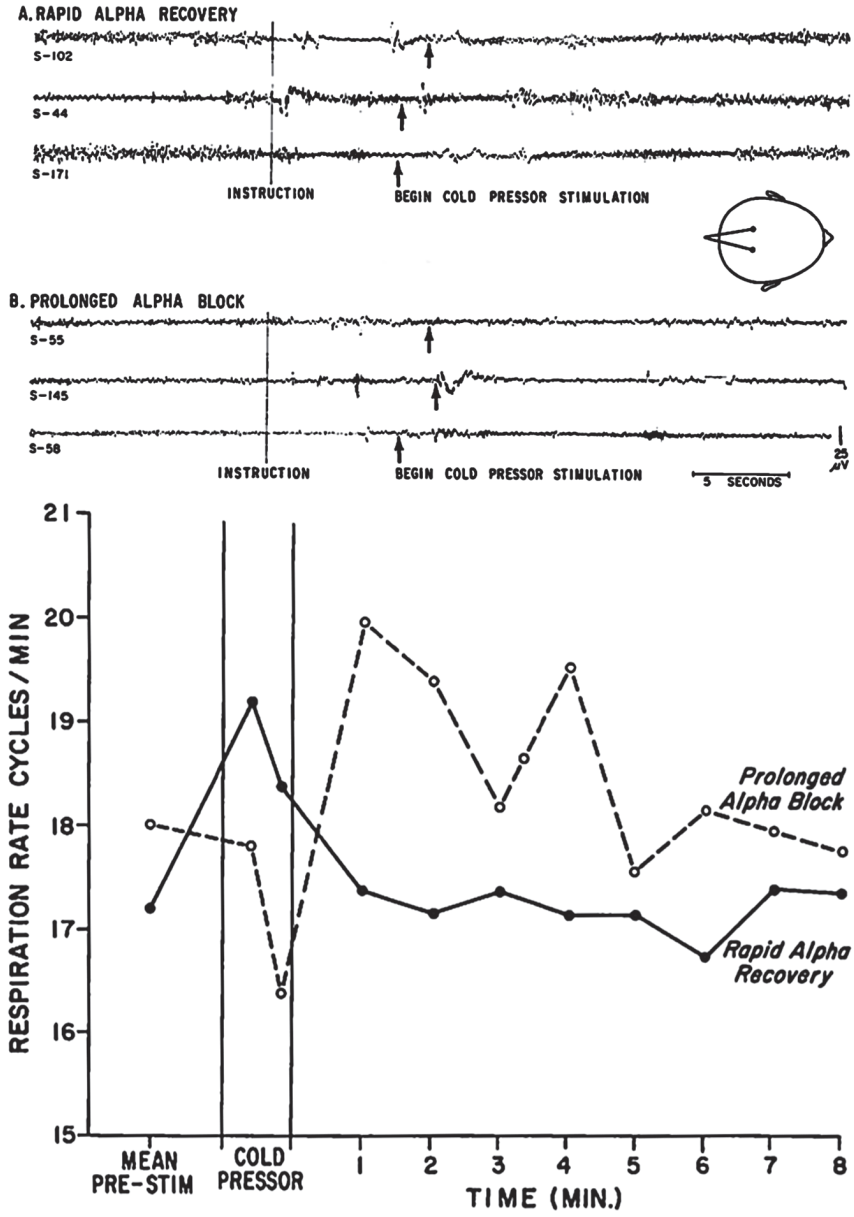


Figure 1: *Top: Examples of rapid vs. prolonged alpha recovery responses in response to cold pressor stimulation, with comparable baseline EEGs. Bottom: Here the respiration rates for the two subgroups Sterman identified are visualized, with the 'Prolonged Alpha Block group' (dotted line) showing a respiratory cessation during the cold pressor followed by increased respiration rates after the cold pressor and the opposite pattern of response for the 'Rapid Alpha Recovery' group (black line).*[1]

Through appropriate experimental manipulations these animals gradually developed a negative conditioned reflex, which he termed 'internal inhibition.' This was distinguished from so-called 'external inhibition' which is the disruption of a conditional reflex due to direct interference from unrelated stimuli. In the case of internal inhibition, *"...the positive conditioned stimulus itself becomes, under definite conditions, negative or inhibitory...."* Pavlov noticed that a prolonged presentation of this type of inhibitory stimulus led invariably to drowsiness and sleep, and he at that time concluded that, *"Sleep and what we call internal inhibition are one and the same process."* So, internal inhibition was seen as an 'internal shutdown' resulting in the state called sleep.

Pavlov's concept of 'internal inhibition', I reasoned, might have been shared by the rapid response cold-pressor patients, something like *"a pox on your experiment, I'm out of here."* Perhaps, Pavlov agreed, for he recognized psychic influences which attracted his interest and led him to devote the rest of his career to an objective study of the nervous activity underlying such states and influences. The study of these conditional reflexes, as Pavlov termed them, brought him into direct contact with the problem of higher order inhibition. The concept of internal inhibition resonated with me and provided an exciting new perspective on mechanisms that I had already learned about from the study of neurophysiology, such as the inter-neuronal feedback circuits protecting against excessive muscle contraction and cortical pyramidal cell excitation. As a result of these and other considerations, the product of my subsequent work has been focused primarily on the EEG, which deals directly with the brain and which was not available to Pavlov at that time.

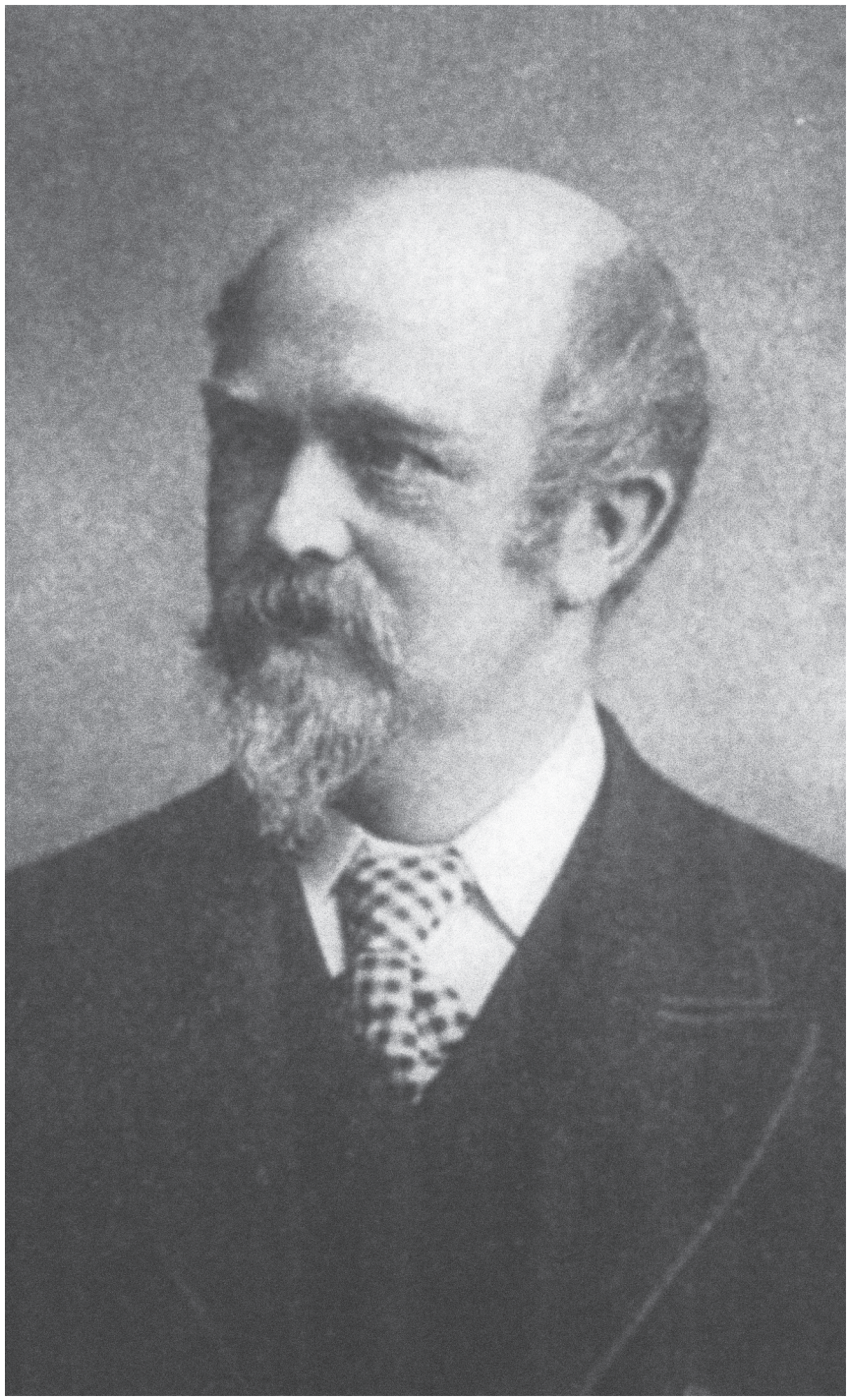
The fact that I obtained, simultaneous rapid EEG and autonomic recovery from an uncomfortable and painful cold-pressor stimulation in humans, and a similar compound 'internal inhibition' response was found by Pavlov when his dogs avoided pain and uncertainty seemed significant. I was also reminded of some earlier studies from two European laboratories showing that electrical stimulation of an area at the base of the forebrain in cats, anatomically including the preoptic and anterior hypothalamic regions, which today we call the

'basal forebrain area', could produce the same autonomic changes that I had seen in these studies. These laboratories had also reported rather unusual changes in motor behavior. The authors had labeled this as 'adynamia' or a 'lack of volition.' These observations raised the possibility that stimulation of this area could also alter EEG patterns, since this question had not been previously examined.

In these early years we thus see some fundamental experiences that shaped me and would all be instrumental in the subsequent stages of my work. These experiences combined with my determination would eventually result in the discovery of the Sensori-Motor Rhythm (SMR) and the subsequent discovery of neurofeedback as a clinically effective technique. The early experience with my sister Esther, where I was able to help her with a first self-constructed temperature biofeedback device, my experience with Tom and his hypothyroidism that triggered my specific interest in neurophysiology, endocrinology and anatomy and my early work with Wenger that bridged the autonomic and central nervous system as well as the emergence of the concept of internal inhibition. As we will see in further chapters this notion of internal inhibition resulted in the basal forebrain studies, the application of conditioning techniques to the basal forebrain and EEG, subsequently resulting in the finding of SMR in the cat, which laid the basis of SMR neurofeedback.

CHAPTER 2:

HISTORY OF THE EEG



A small 20-line summary of an ongoing project published in 1875 in the British Medical Journal by Richard Caton (*left*), is what is generally regarded as the discovery and first description of electrical activity recorded from the brain. In this case an exposed rabbit brain and as Caton described: *"...In every brain hitherto examined, the galvanometer has indicated the existence of electric currents. The external surface of the grey matter is usually positive in relation to the surface of a section through it. Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface, or one electrode on the grey matter, and one on the surface of the skull. The electric currents of the grey matter appear to have a relation to its function. When any part of the grey matter is in a state of functional activity, its electrical current usually exhibits negative variations..."* .[2] These early observations indicated he observed fluctuating brain potentials, that were also functionally related, by for example being responsive to visual stimulation. Furthermore, the negative variations Caton described have also been seen as the first description of evoked potentials. In his 1877 paper he further described the effects of sleep and death, further validating the functional

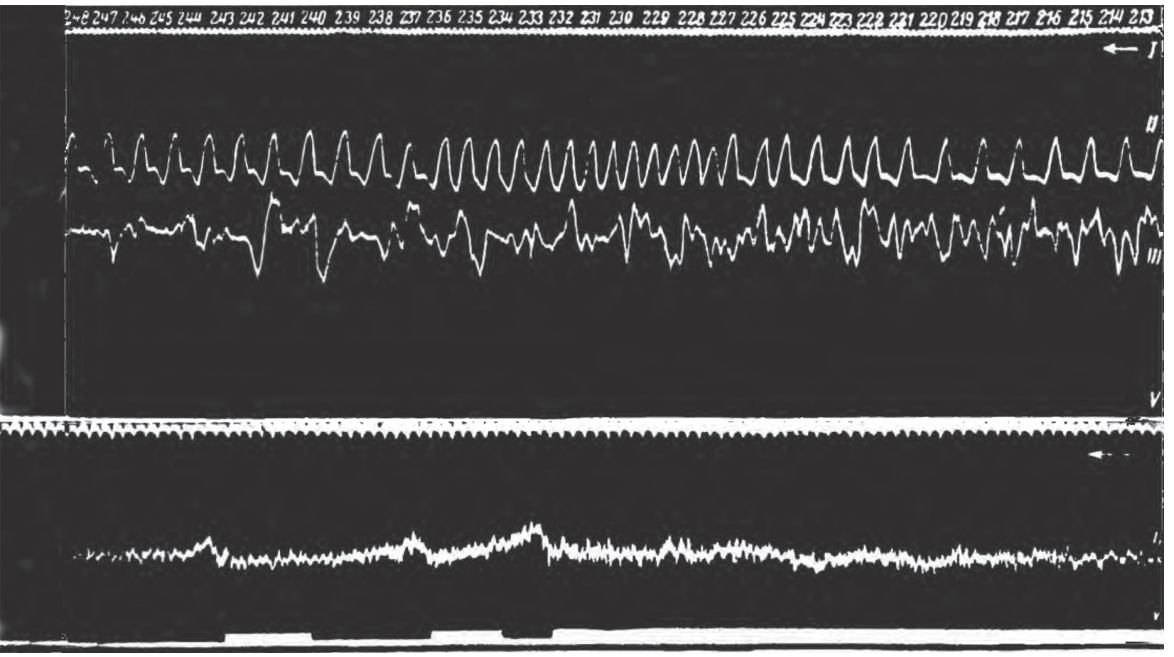


Figure 2: *Top: The first photograph of electrical brain activity or the 'electrocerebrogram', as published by Pravdich-Neminsky (facing page) in 1913 recorded from a curarized dog. The upper traces reflect resting state EEG and bottom traces reflect stimulation of the sciatic nerve (stimulation reflected by lowest white bar). In the upper record the first line (I) is a time marker in fifth of seconds, the second line (II) shows pulsations from an artery in the brain and the third line (III) the galvanometer string, and line V stimulation signal. Figure reads from right to left From: Pravdich-Neminsky, V. V. (1913)* [3]

implications of the brain activity observed. Caton did not pursue this initial work further and in 1891 resigned his professorship of physiology and became Lord Mayor of Liverpool in 1907. At that time, this electrical brain activity was not recorded on paper yet, but the galvanometer used by Caton was a mirror galvanometer, that visualized the electrical currents by a beam of light that was projected onto the wall. Hence, no images exist from the signals recorded by Caton. The first photographic recording of electrical brain activity was reported by Vladimir Vladimirovich Pravdich-Neminsky in 1913 (*see Figure 2* [3]). To this end, Pravdich-Neminsky used an Einthoven string galvanometer in conjunction with moving photographic paper, which was a technique introduced in 1903 by Willem Einthoven for electrocardio-

graphy uses. He recorded electrical activity from the brain, the dura or the intact skull of a curarized dog, and he described a 12-14 Hz rhythm under normal conditions and termed it the 'electrocerebrogram', in a sense this can thus also be seen as the first ever observation of Sensori-Motor Rhythm (SMR).

The fifty years preceding World War I, Eastern European scientists were very talented in electrophysiological neurophysiology, Pravdich-Neminsky just being one example. Learning and conditioning was also investigated intensively in that same period, with a similar leading role for Russian researchers. One of the most influential Russian neurologists at that time was Vladimir Bekhterev, most well-known for noting the role of the hippocampus in memory, his studies on reflexes (objective psychology) and Bekhterev's disease.
At that time, Bekhterev occupied the chair of psychiatry in St. Petersburg, which included clinical neurology. He independently developed a theory of conditioned reflexes which described automatic responses to the environment. What Bekhterev referred to as an association reflex, was called the conditioned reflex by Pavlov. Being a contemporary of Ivan Pavlov, there was some rivalry between Pavlov and Bekhterev.

In 1927, Bekhterev took part in a congress of psychiatrists and neuropathologists in Moscow. He had received a telegram and went to the Kremlin to examine Joseph Stalin and diagnosed him as paranoid. Later that day back at the conference, colleagues overheard him talking about his encounter with Stalin. The next day Bekhterev died of 'food poisoning', and Stalin had Bekhterev's name removed from all Soviet textbooks, rumors being that Stalin had poisoned him out of revenge. The fate was thus decided in favor of Pavlov, hence the magic of conditioned reflexes overshadowed all Soviet neurophysiology by the highest degree .[4] The Pavlovian concept was also closer to the ideology of the regime at that time. The Soviet leadership in EEG and related fields decimated, and at the same time Pavlovian conditioning became the de facto standard. Interestingly, we'll see the successful blending of these two domains of conditioning and electrical brain activity later becoming the ignition of the field of neurofeedback as we know it today.

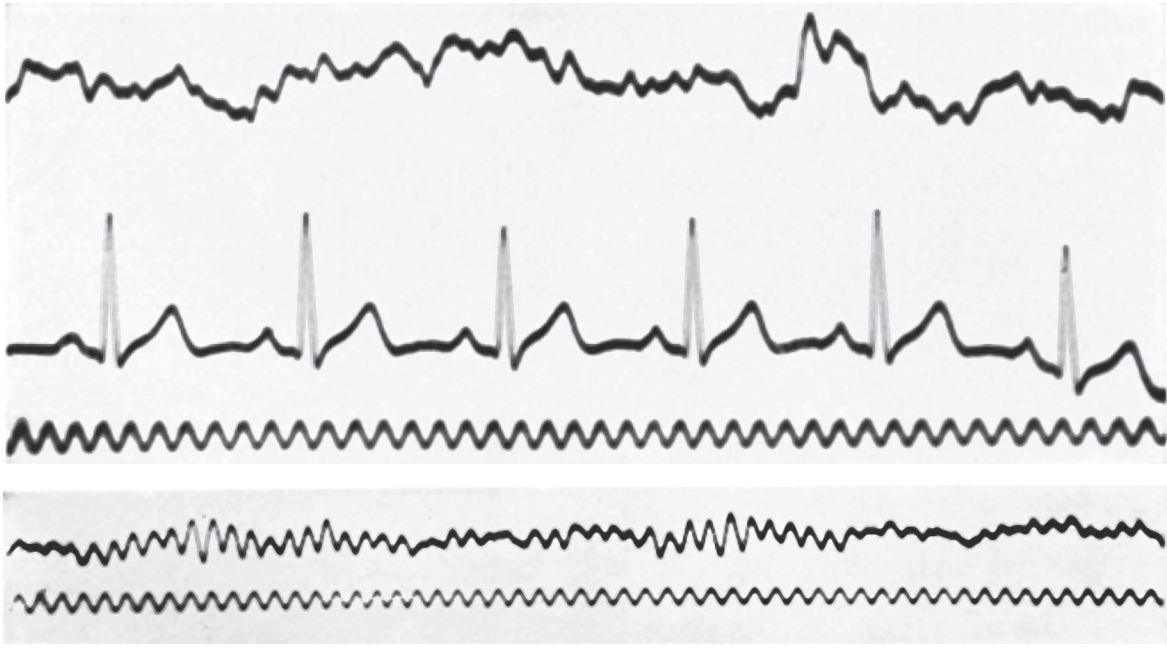


Figure 3a: *The first tracings of the human EEG from the first publication from Hans Berger (1929). Both represent samples of EEG recorded from his son Klaus (16 years old). The bottom figure represents a sample of what he would later call the 'alpha rhythm' (a sinusoidal rhythm of approximately 10 Hz) and the figure above what he would later call the 'beta rhythm' (or a desynchronized EEG with no obvious rhythmicity). The lowest tracing in both graphs is a generated 10 Hz sine wave, and the middle tracing from the top figure is the ECG.* [6]

The galvanometer Caton used had a limited frequency response with a 0-6 Hz range, which limited to some degree what he could pick up[4], hence it took several years before the famous 10 Hz alpha rhythm was first described in human recordings by Hans Berger.

Hans Berger, initially wanted to become an astronomer, but soon after starting his study he enlisted for the Army. While in the Army, an incident took place with a horse that suddenly reared, causing a near fatal accident. His sister, hundreds of kilometers away, had a feeling Berger was in danger and insisted their father send him a telegram. This incident resulted in Berger becoming a firm believer in psychic phenomena or telepathy, serving as an initial motivation to study the

human brain and become neuropsychiatrist.[5] From 1902 to 1910 he started with recordings from the cortical surface of the dog, partly replicating the work of Caton and Pravdich-Neminsky, followed by recording from humans in the 1920's. During World War I he was a Germany Army staff physician, and after the war returned to Jena to become full professor and director of the University Neurology and Psychiatry Clinic in 1919.

In 1929, Berger finally reported in an extensive publication his observations spanning five years' work on what he termed *'das Elektrenkephalogramm'* [6], which would become the seminal paper highlighting the beginning of research on the human electroencephalogram also abbreviated as EEG. In his first experiments he recorded –among others– the EEG from his son Klaus and described extensively the methods he used and what he observed. Figure 3 on page 33 demonstrates two graphs from that first publication recorded from his son. The bottom figure represents the rhythm he would eventually call the 'alpha EEG rhythm' or by others referred to as the 'Berger rhythm' and the top figure represents what he would eventually call the 'beta EEG rhythm' or a desynchronized EEG. In 1934 Adrian and Matthews from Cambridge replicated his work [7], which made EEG a technique that was there to stay. Throughout the 1930's Berger continued his EEG research and he can be credited for many early observations meticulously described in his papers, such as the effects of hypoxia on the brain to first descriptions of epileptic discharges or paroxysmal EEG. According to Niedermeyer and Lopes da Silva, *"...His relationship to the Nazi regime was not good and Berger was most unceremoniously made a professor emeritus at earliest convenience, in 1938..."*

Figure 3b: *Hans Berger (facing page)*

Others however, have drawn a different picture based on historical research, such as Zeitman, Stone and Kondziella [8], claiming he became a supporting member of the SS, and that it is still unknown if: *"...contributions may have been due to ideological support, or to avoid Nazi harassment, especially given the significant Nazification of his university...."*[8] On the other hand, this view was put more into perspective by Schmidt Dieter [9], citing amongst other early EEG pioneers Herbert Jasper and Pierre Gloor who met with Hans Berger around war time and clearly concluding *"...His resistance to the Nazis cost him his life..."* (Jasper) and *"...Berger disliked the Nazis and they retaliated by disparaging his work..."* (Gloor).[9] Eventually, Berger developed a clinical depression and committed suicide June 1st 1941 at the age of 68, in the clinic where he was treated, more suggestive of his frustration under the Nazi regime than anything else. But his discovery of *'das Elektrenkephalogramm'* or EEG remained and became one of the most employed techniques to study brain function since those days.

CHAPTER 3:

HISTORY OF THE EEG IN THE UNITED STATES

Since the initial discovery of the EEG in 1875 by Caton and the first description of the human EEG in 1929 by Berger, much research has been conducted using this technique. In those days, most research efforts were from Europe. In late 1933, Hallowell Davis an American physiologist at Harvard, learned of the early work from Berger and at that time thought that Berger's alpha rhythm was *'undoubtedly artifact'*, since they considered it unlikely that enough axons in the brain could be synchronized to yield such a slow regular 10 Hz rhythm that could also be recorded without exposing the cortex. They therefore decided to replicate Berger's results, and it almost turned out not to replicate hadn't it be for the persistence of Davis as nicely illustrated in the following: *"...In January 1934... Bill Derbyshire and Howard Simpson failed in their attempt to record the Berger rhythm using needle electrodes in the scalp..."* As Davis later related: *"About three weeks later Bill and Howard (who had been working on this in their evenings) came to my office again, looking a bit sheepish. 'You are right, chief', said Bill. 'We have stuck needles in each other's scalps (vertex and occipital). The baseline is unsteady, but we can't see anything like the 10/sec rhythm on the scope. But come and see if we are doing it right before*

we say anything about it.' I went with them to the lab and Bill stuck needles into Howard's scalp. Howard sat in the shielded room and closed his eyes. The spot wobbled unsteadily across the scope. That's what I thought, I said, but three heads are better than two. Put the electrodes on my head. They did, and I sat in the room and closed my eyes. Immediately there were shouts outside: There it is! There it is! It was indeed the Berger rhythm. It seems that I have very strong alpha waves. Bill's and Howard's are weaker, and they were excited, anxious, and perhaps more uncomfortable than I was. Other members of our staff volunteered and they were divided about evenly into 'Bergers' (Davis, Cannon, Lindsley), and 'non-Bergers' (Derbyshire, Simpson, Forbes, Pauline Davis). We were convinced Berger was right. It was some time later that we learned that Adrian had already confirmed him; but at least my alpha rhythm was the first to be recognized as such in the Western Hemisphere. I also soon realized that we were probably watching a new slow potential of neural origin." (cited in Davis, 1975, from: [5]).

This thus turned out to be the first demonstration of alpha activity in the US, albeit not published as a manuscript in the literature. The first real published replication of Berger's work - and the first publication on EEG from the US - was published in Science in 1935 by Jasper and Carmichael.[10] In that study they already confirmed the stability of the alpha frequency over repeated assessments, as well as the existence of a slower rhythm *"...In one or two pathological cases which we have studied a frequency of alpha waves as low as 2 or 3 per second has been observed"* which would later be labeled as delta or theta. Their conclusion *"...It is even possible that this technique may provide information in regard to brain function which will be comparable in significance to the information in regard to heart function which is provided by the electrocardiograph..."* indeed heralded the wider adoption and progress in research on EEG in the US. Soon followed the descriptions of clear three per second spike and wave complexes in patients with epilepsy, first in Davis' lab, that started the field of clinical EEG as a discipline in neurology.

ALFRED LEE LOOMIS

Alfred Lee Loomis was an eccentric Wall Street tycoon, with a passion for science. He initially started as an independent physicist, who built his own private laboratory, the Loomis Laboratory, in Tuxedo Park, near New York, also locally known as the 'Tower House.' In his lab, mainly active during the 1930's, he would come to work on various topics with some of the greatest scientists at that time including Albert Einstein, Werner Heisenberg and Niels Bohr, and possessed the best laboratory equipment available those days. In the early years from 1926 to the 1930's he mainly focused on physics experiments and combined it with his Wall Street activities at Bonbright. In 1928, just before the big Wall Street Crash in 1929, he had converted most of his holdings and investments in gold and several years later he also sold the law firm Bonbright, providing him with substantial wealth, that allowed him to further indulge his scientific hobby and private lab. At that time, he had available the best amplifiers and conducted studies in a 'screen cage', or sort of Faraday cage, that eliminated interfering electrical noise. At this time, he could dedicate himself full time to the further exploration of brain waves as described by Berger.

As described by Herbert Jasper, on one of his visits to Tuxedo Park, Newton Harvey from Princeton was also present, and brought Albert Einstein with him, so they could study Loomis' brain waves: *"...They put him to sleep, and at first he showed the typical slow waves of sleep. Then the EEG changed to the rapid waves of arousal. He awoke suddenly, asking for a telephone. He called his laboratories in Princeton to tell his colleagues there that he had been reviewing his calculations of the day before and discovered an error which should be corrected. This done, he was able to go back to sleep again. We thus had a dramatic demonstration of the sensitivity of the EEG to mental activity..."* (from Jasper [11]). In August 1935, this thus resulted in the first published study by Loomis, together with Harvey and Hobart, on the human sleep EEG and stages of sleep. This was among the first series of US publications on the human EEG, after Jasper's first report in January 1935. Already in this early 1935 report Loomis was the first to describe sleep spindles, also referred to as sigma waves, where they described: *"...but frequently very regular bursts lasting 1 to 1.5 seconds of 15 per second frequency appear. The amplitude builds regularly to a maximum and then falls*

regularly so that we have designated these 'spindles', because of their appearance..." (*Also see Figure 4 from that publication, reproduced below*), with the first published example of sleep-spindles. Sleep spindles are generally considered the hallmark of light sleep and often considered the 'guards of sleep.' In addition, in those publications already the A (alpha EEG states) and B stages (non-alpha stages) were proposed and their relationship to levels of consciousness or vigilance, that are still current and used in for example the EEG vigilance model.

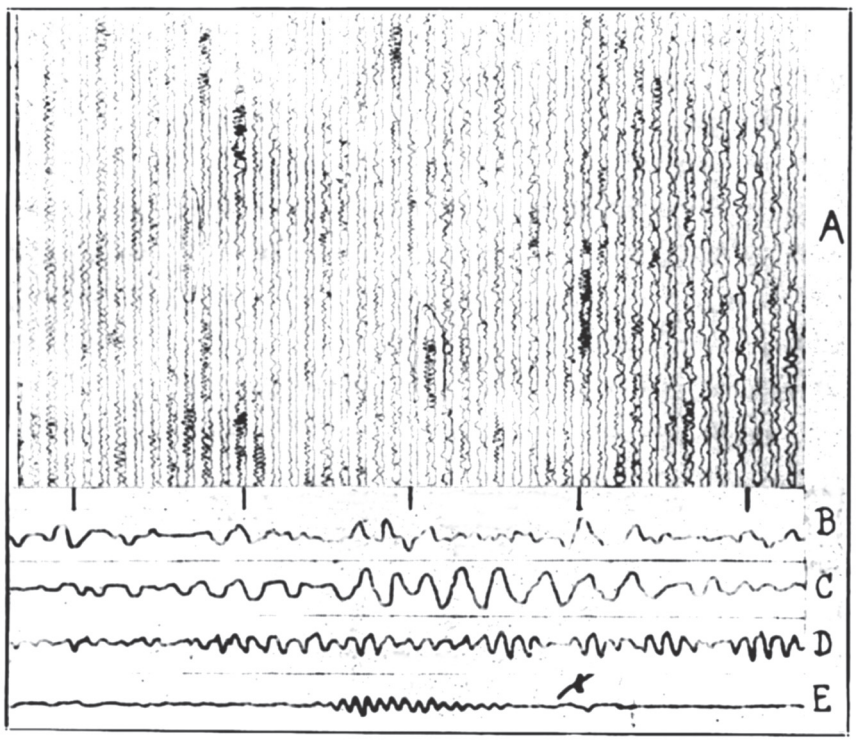


Figure 4: *Alfred Lee Loomis (facing page) and the first ever published sleep EEGs (pictured above, marked A) that would form the basis of polysomnography as it is currently known. The inserts B, C, D and E are enlargements of what Loomis described with the vertical markings above B indicating seconds. Loomis described these examples as (B) 'random', (C) 'sawtooth', or essentially the typical slow wave activity characteristic for deep sleep, (D) 'trains' and (E) 'spindles' which are now known as sleep spindles, here of a nice 14 Hz rhythm.* [12]

This period also marked the earliest period where conditioning was applied to EEG activity, thereby being the first basic demonstration of neurofeedback. As Loomis and colleagues stated on page 270 under 'Conditioning': *"...Another interesting experiment may be described as 'conditioning.' If the subject lies in complete darkness with eyes open, a low tone stimulus lasting 5 seconds will not stop the alpha waves. If the low tone and also light stimulus are both presented simultaneously several times in succession at half minute intervals, the waves will of course stop, due to the attempt to see induced by the light, but if now the tone alone is sounded the waves also stop as the attempt to see is now induced by the sound. However, the effect of the tone alone will not last more than two or three times as the conditioning is not permanent and the sound no longer induces the attempt to see. We have observed this effort on several persons and regard it as quite analogues to a conditioned reflex..."* [13] In addition, the effects of hypnosis were investigated on EEG, and already quickly it was concluded that hypnosis could not be seen as a 'sleep' state due to the clear presence of alpha waves during hypnosis. A further experiment Loomis conducted using hypnosis is reminiscent of what Joe Kamiya would later demonstrate, but then based upon voluntary control and here with hypnosis. In this experiment, Loomis used adhesive tape to keep the eyes of his subject closed and use hypnotic suggestion to induce 'temporary blindness' i.e. suggest the subject saw nothing, resulting in synchronous alpha. When subsequently, with eyes closed, they suggested he saw a spot on the ceiling, the alpha rhythm desynchronized and disappeared, only appearing again when they told the subject he saw nothing. This could be reliably repeated 16 times. [13] Hence, alpha was already brought under control of the 'mind' in this case using hypnotic suggestion.

In 1939, with the unrest and war looming in Europe, Loomis decided to donate his EEG equipment to Davis' group at Harvard Medical School. At that time, he turned his scientific interest to experimental waveform physics and shifted the emphasis from pure science to war-related technology. His efforts would become pivotal in the development of radar technology, long-range radio navigation and the atomic bomb. President Franklin Roosevelt is said to have credited Loomis as second to Winston Churchill in turning the tide of World War II in the Allies favor (from: Stone et al.[5]). Hence, this intriguing

pioneer of EEG in the US, Alfred Loomis – without him knowing or realizing – can be credited with two crucial discoveries and descriptions that would play a major role in the history of neurofeedback, namely applying conditioning principles to the EEG, and the description of sleep spindles, that we later will understand to be a fundamental aspect in understanding the working mechanism of SMR neurofeedback. In addition, his hypnosis experiments actually were already reminiscent of the notion that alpha and alpha-desynchronization can be controlled by the mind, which would be investigated further in the 1950's by Joe Kamiya.

Soon after, in 1936, experimental psychologist Lee Travis at Iowa was one of the first American's to obtain EEG equipment for human recordings, to study brain activity in relation to speech and stutterers, demonstrating the utility of EEG as an experimental tool in psychology. Travis has trained some of the – soon to be – prominent EEG pioneers from the US including Herbert Jasper, John Knott, Charles Henry and Donald Lindsley (from: Stone et al.[5]). Lindsley was also exposed to EEG as a student at Davis' lab at Harvard, where he belonged to the group of 'Bergers' (see beginning of the chapter) and was able to produce good alpha activity, which resulted in him being the subject of the first demonstration at Davis' lab. Lindsley continued to study maturation of the EEG in children and published his first description of maturational differences between children and adults in 1936 [14], where he described that rhythmic alpha was already present at age 3-6 months at a frequency of 4 Hz, that matured to an adult 8-12 Hz alpha at the age of 8-10 years of age. During the mid 1940's, Lindsley worked at the department of psychology at Northwestern University, but had no facilities for his experimental program. In 1947 he was invited by Horace Magoun to set-up his EEG equipment at the medical school in Chicago where their collaboration started.

UCLA AND THE BRAIN RESEARCH INSTITUTE: A HOTBED OF NEUROSCIENCE

HORACE WINCHELL "TID" MAGOUN

Horace Magoun initially started at Northwestern University, Chicago as a professor of microanatomy. In 1947 Donald B. Lindsley started working with Magoun, where Lindsley brought the expertise in EEG. In 1948 Giuseppe Moruzzi joined Magoun's team from the University of Pisa, Italy under a Rockefeller Foundation fellowship, resulting in the famous 1949 'Moruzzi and Magoun' paper describing the brain stem reticular formation as an arousal system: *"...in lightly anesthetized animals stimulation of the brain stem seemed to abolish the cortical EEG waves, however [w]hen amplification of the cortical record [was] by chance turned up . . . [t]hen we saw the large slow waves give way, during reticular stimulation, to a record of low-voltage fast activity, called 'EEG arousal,' a pattern which was characteristic of alert attention in the human EEG"* ('Autobiographical Material', unpublished manuscript, n.d., p. 12 from: Louise H. Marshall [15]). Hence this became known as one of the major breakthroughs in understanding the neural circuitry of the ascending reticular arousal systems, also abbreviated as ARAS, and its functional implications on the EEG.

Later work together with Lindsley and others built further upon these findings and showed that this ascending reticular activating system was shown to be associated with alert wakefulness as a background for sensory perception, higher intellectual activity, for voluntary movements and behaviors, and to provide insights about brain and mind. Magoun was nominated twice for a Nobel Prize for his work. In 1950, Magoun moved to Los Angeles to become founding chair of the department of anatomy at the 'southern branch' of the University of California. His drive and interest in collaborative and interdisciplinary research eventually culminated in the establishment of the Brain Research Institute (http://www.bri.ucla.edu), at UCLA in 1959 and opened its doors in October 1961. At that time, a 10-story building with research laboratories and offices.

Figure 5: *Photo from Giuseppe Moruzzi (left) and Horace Magoun (right) taken in 1958 in Warsaw, Poland, on a return trip from Moscow where they had attended a colloquium.* [16]

While officially established by Drs. John French, Horace Magoun, Donald Lindsley and Charles Sawyer, Magoun is generally considered the driving force behind the foundation of the Brain Research Institute. Magoun, was able to attract prominent researchers among them Arnold Scheibel and Carmine Clemente. In 1961 the BRI had 67 members, thirty years later 162 and today the BRI has around 300 faculty members, also evidence of BRI's leading position in neuroscience.

QUANTITATIVE EEG (QEEG)

Thus far, most of the EEG analysis were conducted by visual inspection, especially in the clinical EEG area. An important development that originated out of UCLA in this early era, was the first demonstration of quantitative EEG or QEEG, where EEG was submitted to computerized analysis, often spectral power decomposition, as well as comparison to a normative group. Ross Adey pioneered the QEEG at UCLA.

Adey arrived at UCLA in 1957, where he became a professor of anatomy and physiology. His group pioneered the use of QEEG at the UCLA Brain Research Institute in the period 1961-1974. They were the first to use digital computers in the analysis of EEG with the production of brain maps and developed the first normative library of brain maps. See Figure 6 for some photos with the first equipment developed to measure EEG in outer space and during driving. As part of the Space Biology Laboratory they studied the effects of outer space and space travel on the brain, to determine whether prolonged space flight would be possible for the human body. As part of this NASA program Graham and Dietlein were the first to coin the term Normative EEG.[17] In addition, Adey was well known for the 'Adey window', which describes the confined parameters under which a very weak electromagnetic signal could exert physiological effects. It could for example explain phenomena such as high-power electric lines' effect on cell growth, or his work showing that brain tissue is sensitive to electromagnetic field radiation at levels that are orders of magnitude lower than classical synaptic excitation. Although this has been received with skepticism, this topic is currently investigated with great detail again in the area of neuromodulation, with Low-Field Magnetic Stimulation or Pulsed Electromagnetic Fields (PEMF).

One other remarkable person from this period was Arnold Scheibel. His initial interest was cardiology, however given the pervasiveness of emotional factors in the disease patterns he saw, he eventually switched to psychiatry. In 1955 he joined the UCLA faculty at the department of anatomy where he eventually became a professor of neurobiology and psychiatry at UCLA and the BRI. Arnold Scheibel did not publish a lot, he was actually a psychiatrist, but he was also a really good neuroscientist and fabulous teacher. He is especially known for having dissected Albert Einstein's brain among others on the basis of which Scheibel and his colleague – and at that time his wife – Marian Diamond proposed the *'efficiency-intelligence'* theory, based on the finding that Einstein had 73% more glial cells per neuron in the left hemisphere relative to others. They reasoned that the more glial cells per neuron the brain has, the 'cleaner' and more efficient the brain can operate, and thus the better the intelligence.

Figure 6: *A photo from 1963 showing the equipment developed by Ross Adey and colleagues to measure EEG in space. Ross Adey – who pioneered QEEG – is the person on the right in the top left picture. The top-right image also shows the UCLA BRI building in the background (Courtesy of the Computer History Museum).*

A great documentary starring many of these early persons can be found at *Closer to Truth* (www.closertotruth.com) with Carmine Clemente and Arnold Scheibel among others.

Figure 7: *Barry Sterman in 1966 at the UCLA BRI operating a Beckman EEG amplifier (right) and on the left a Grass polygraph, while recording cat EEG in one of his studies (Photo courtesy of Maurice B. Sterman).*

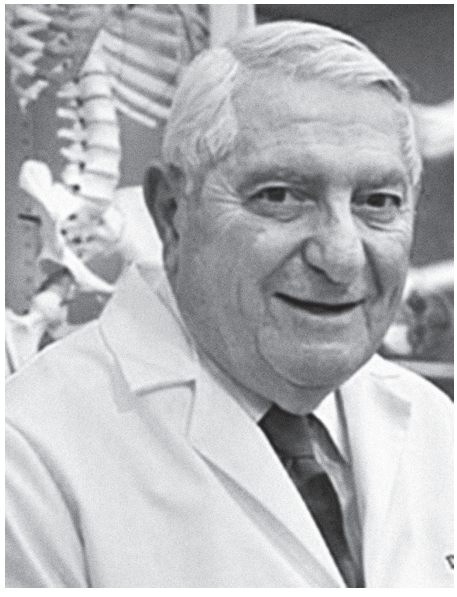
Sterman (*figure 7*) completed his PhD from early 1959 to 1963, and within this same time period the UCLA BRI was established. As became clear above, this hotbed of pioneers including psychophysiologists, brain anatomists and EEG pioneers formed a very fruitful basis for Sterman to develop further. Many of these pioneers had a profound influence on him, but a particularly important influence came from one person in this institute, Carmine Clemente, who became his mentor and father figure for years to come.

As part of his PhD Sterman was required to take two foreign languages. He had already chosen Italian, because, as he stated, it was *'... la lingua dell'amore....'* Regarding the second language he petitioned for an alternative, and instead of taking a second language he could take 20 units in any other course he wanted. So, he chose neurophysiology, where his supervisor was Don Lindsley, including courses like mammalian physiology, anatomy, endocrinology, cell biology etc. As

part of this he did some experiments with dogs in the lab and was looking at some of the same things and he was seeing some responses that were surprising. Don Lindsley thus became Sterman's PhD supervisor. Lindsley as we saw before, was among the first EEG pioneers in the US, had been exposed to EEG in Hallowell Davis' lab at Harvard where he belonged to the group of 'Bergers' and was part of the pioneering team with Magoun on the reticular formation. Lindsley with all this experience had a great influence on Sterman. At this moment Sterman was enjoying this specialized approach greatly which definitively shifted his focus from psychology to neuroscience.

CARMINE CLEMENTE

One of the anatomy professors at that time was Prof. Carmine Clemente. Clemente joined the newly formed UCLA School of Medicine in 1952 as an instructor in anatomy. In 1963 he became professor and chairman of the anatomy department at UCLA and in 1976 he served as director for the Brain Research Institute at UCLA. He was also one of the editors of the famous Gray's Anatomy, textbook of human anatomy. He extensively edited and revised the 30th edition, also the last edition of Gray's anatomy. His early research interests comprised CNS regeneration and later included topics such as sexual and feeding behaviors, and particularly brain systems related to wakefulness and the onset of sleep. Clemente was an anatomist and also taught anatomy and physiology.



While working in Sepulveda in the lab under Wenger on the autonomic system and psychophysiology, Sterman took Clemente's lectures, that inspired him to a great extent. Based on those lectures and the early ex-

periences from the cold pressor study with Wenger, he had many ideas that eventually led to his first experiments on basal forebrain stimulation and classical conditioning of the basal forebrain. In order to understand his rationale behind this, we have to understand the zeitgeist from that moment on how scientists at that time theorized about sleep, and how Sterman's idea of sleep as an active process was quite revolutionary at that time as will be reviewed in the next chapter.

CHAPTER 4:

SLEEP AS AN ACTIVE PROCESS AND DISCOVERY OF THE BASAL FOREBRAIN

For full details and a full review, in the supplement we have also reprinted Sterman's original PhD dissertation introduction from 1963, that has never been published before. Below a summarized version is presented.

CONTEMPORARY INTRODUCTION ON SLEEP AS AN ACTIVE PROCESS.

The scientific investigation of sleep has historically been guided by various concepts. For many years, researchers had attempted to understand the neural mechanism responsible for sleep. Some theories conceptualized *'sleep as a lack of wakefulness'*; that is, sleep emerges passively following the withdrawal of those

influences which maintain a waking brain. Since sleep is generally characterized by a decrease in motor activity and a raising of sensory thresholds, other theories suggested that *'sleep is an active process'* achieved by the nervous system. This implies the operation of some process which is, by definition, antagonistic to excitation, and there has thus been the tendency to apply inhibition as a mechanism in this context. Furthermore, this implies that either specific *'wakefulness centers'* exist (in the passive view) or specific *'sleep centers'* exist (in the active view).

As an example of the passive view, Nathaniel Kleitman concluded: *"There is not a single fact about sleep that cannot be equally well interpreted as a letdown of the waking activity."* [18] Kleitman was one of the first to recognize clearly the importance of past experience in sleep regulation. Emphasizing wakefulness rather than sleep, he spoke of a primitive *'wakefulness of necessity'* induced by proprioceptive and interoceptive impulses. The culmination of the focus on wakefulness came with the conceptualization of a diffuse arousal system, the ARAS, in the brainstem by Moruzzi and Magoun in 1949. [19] They observed that high-frequency electrical stimulation of the reticular formation in the brainstem, and its more rostral extensions into the diencephalon, produced an EEG and behavioral response similar to that normally seen in awakening.

With so much attention diverted to wakefulness, one might think that sleep had been forgotten. On the contrary, during this same period in time an important sequence of discoveries was occurring which was to suggest a quite different interpretation of the phenomenon of sleep. This interpretation centered around the older concept of sleep as an active process induced in the nervous system, but now based on concrete experimental evidence. In his classical studies of salivary and gastric secretion in dogs, Pavlov [20] encountered psychic influences which attracted his interest and led him to devote the rest of his career to an objective study of the nervous system activity underlying their formation and modification. The study of these conditional reflexes, as Pavlov termed them, brought him into direct contact with the problems of higher-order nervous inhibition. Commenting on the inevitability of this contact he says, *"...When we*

come to investigate the highly complex functions of the cerebral hemisphere we naturally expect to come across inhibitory phenomena, for these are very constantly and very intimately mixed up with the positive phenomena of nervous excitation." In strong support of this position were the many instances of dogs *'learning not to respond.'* That is, through the application of appropriate experimental manipulations these animals gradually developed a negative conditioned reflex, which he called 'internal inhibition.' This is distinguished from so-called 'external inhibition' which is the disruption of a conditional reflex due to direct interference from non-related stimuli. In the case of internal inhibition, *"the positive conditioned stimulus itself becomes, under definite conditions, negative or inhibitory."* Pavlov noticed that a prolonged presentation of this type of inhibitory stimulus led invariably to drowsiness and sleep, and therefore concluded that, *"Sleep and what we call internal inhibition are one and the same process."* In summary, then, Pavlov thought that sleep results from a gross irradiation of an internal inhibitory process which is initiated by constant or repetitive stimulation, and which functions to prevent exhaustion of the cortical elements. Thus, with respect to the neural mechanism of sleep, Pavlov also proposed a functional fatigue – but this fatigue provides for the onset of an active process of inhibition.

It is interesting to note that Pavlov also mentioned having observed the sudden onset of sleep in animals, *"exactly at the beginning of the action of the (delayed) conditioned stimulus."* Although he interpreted this as being due to a widespread process of internal inhibition, he did not relate this to the conditional reflex. From his other statements we may conclude that internal inhibition is a learned reflex, and since sleep and internal inhibition are one and the same process, it follows that sleep may also occur as a conditioned reflex. However, Pavlov never actually expressed this rather interesting deduction. Could it be that the originator of the conditional reflex did not recognize this important instance of its occurrence?

Several years earlier, another source of experimental information regarding sleep had arisen from an entirely different context. A strange encephalitic epidemic had spread through the city of Vienna, leaving a disruption of the sleep-waking rhythm in its victims as its primary

symptom, by many also known form the movie and book by Oliver Sacks, Awakenings. Taking advantage of this unfortunate situation, Von Economo distinguished himself by his classic study of the central nervous system pathology involved. [21] By careful comparison of many clinical cases of this encephalitis lethargica, Von Economo described two symptomatic patterns of the disease associated with two localizations of the inflammatory lesions in the nervous system. From these observations Von Economo concluded that the affected areas must constitute a *'Schlafsteuerungszentrum'* or sleep regulating center consisting of at least two parts: a rostral part (at the anterior end of the third ventricle), which when appropriately excited, actively inhibits the thalamus and cerebral cortex and thus causes *'brain sleep'*, and a more caudal part (in the posterior hypothalamus and rostral brainstem) which acts to decrease somatic, autonomic, and endocrine activity and thereby causes *'body sleep.'* To Von Economo, then, sleep was an active inhibitory phenomenon involving both central and peripheral alterations. Further experimental evidence for the concept of an active sleep-inducing mechanism in the central nervous system was given by Hess [22] and Nauta [23], by employing electrical stimulation of specific structures.

To summarize, when we realize the important contributions which a concept of neural inhibition has made toward our understanding of regulation at lower levels of neural function, we are better able to appreciate its potential importance in the more complex functions of the nervous system. Secondly, although some controversy still exists, Sterman wished to demonstrate the fact that most investigators would agree that inhibitory action is in some way involved in the neurophysiology of sleep and show that an increasing interest in the brain mechanisms responsible for this inhibition is today apparent. As a result of these considerations, Sterman's interest became directed toward the basal forebrain region as a site of potential importance in this regard. However, if the influence of this region is generally inhibitory and related to the neural mechanisms of sleep, one might predict an influence directed from this region toward the cerebral cortex. If a reciprocal process between sedation and arousal is expected, most likely via the thalamus, then both general and specific aspects of arousal can be achieved. Since an influence of this kind has

never been described, Sterman's initial experiments involved a neurophysiological exploration of the functional relationships between the basal forebrain region and the cerebral cortex in the cat.

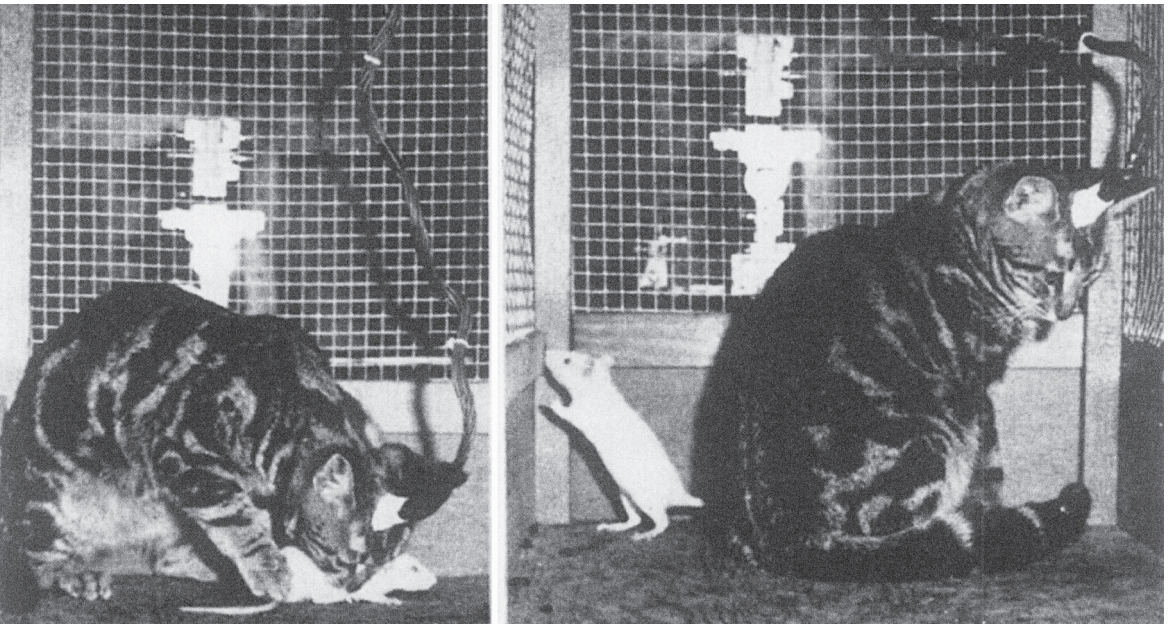
BASAL FOREBRAIN STIMULATION STUDIES

Sterman, still lingering on the results from the cold-pressor study he did with Wenger, with the resonating concept of internal inhibition, and the inspiring neuroanatomy lectures of Clemente, was in need of help to test his ideas. While in the lunchroom of the Sepulveda VA Hospital one day sitting eating his lunch with the food on his tray, Sterman asked Clemente if he could sit at his table and discuss a research idea he had. Sterman and Clemente started talking and Sterman shared with him all his ideas, and Clemente said "…let's test it…." So, after lunch, they went down to the lab that Clemente ran, he prepared a cat (an acute preparation, alert but paralyzed) in a stereotaxic instrument, almost causing Sterman to faint as a 'rookie' due to the smell of ether. The first argument they had, was regarding whether to use an anesthetic or not. Clemente wanted to anesthetize the cat, which is what they did at that time. Sterman said: *"…no, you have to use a topical painkiller, the animal has to be consciousness otherwise there is no sense in doing the study."* As Sterman further elaborated on this in his PhD thesis: *"…Although these experiments were performed upon decerebrate animal preparations, many experiments of this type have been carried out on anesthetized animal preparations, and in this regard some controversy has recently arisen. For instance, it has been reported that stimulation of 'suppressor' cortex 4-S in the unanesthetized monkey causes a reaction quite the opposite of suppression (p. 79). These and other similar findings indicate that anesthesia is a variable which must be considered in the interpretation of these data…"* This turned out to be a critical choice in these experiments, and as Sterman later demonstrated, with barbiturate anesthesia the basal forebrain effects would not have been discovered.

Clemente agreed with Sterman, and he did not anesthetize the cat. He put it into the stereotaxic… put the electrodes in the right area… stimulated, and he said, *"I'll be a son of a gun."* The cortical EEG sud-

denly synchronized, reflective of a 'sleep like' EEG. *"He wrote that on a record, I still have that piece of paper. And from that moment on, we were inseparable."* Sterman said.

This initial work resulted in Sterman's first publications, also part of his PhD dissertation (Chapter II and Chapter III respectively, see Appendix I) and were published in 1962 [24,25] in Experimental Neurology. In these studies, he demonstrated the clear role of the basal forebrain in sleep, using electrical brain stimulation of this area and observing subsequent EEG changes and behavioral changes. Low-frequency stimulation of the basal forebrain resulted in immediate and sustained cortical synchronization. Furthermore, when high-frequency stimulation was applied to Moruzzi and Magoun's brainstem ascending reticular activating areas (ARAS), resulting in desynchronization (cortical arousal), and when at the same time low-frequency basal forebrain stimulation was applied, cortical synchronization was induced (see Figure 9). This demonstrated the functional and opposite roles of these two independent regions as a wake-center and a sleep-center respectively. Furthermore, in freely behaving cats, stimulation of the basal forebrain can result in cessation of ongoing behavior, motor quiescence (also see Figure 8 for an example of this

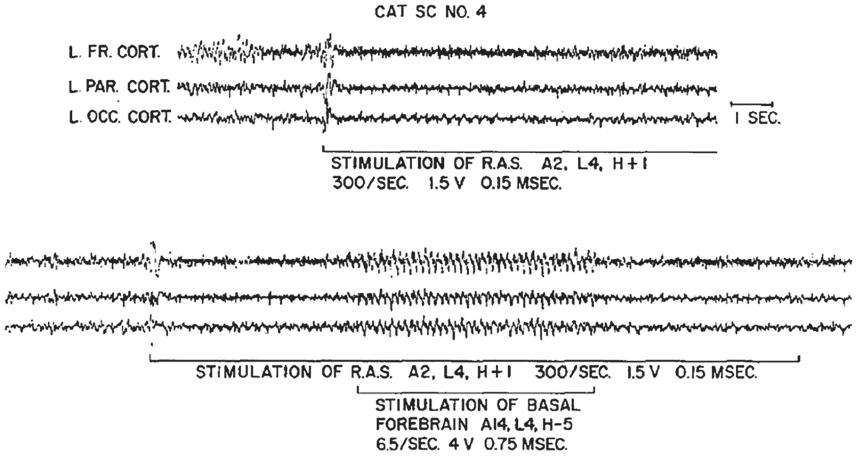


stimulation induced behavior), and potentially sleep, both electrophysiologically as well as behaviorally.

Hence Sterman defined this area the 'basal forebrain synchronizing area' and had discovered the sleep-counterpart of Moruzzi and Magoun's waking reticular activating system, so the UCLA BRI ended up having its Yin and Yang of sleep-wake regulation in the persons of Sterman and Magoun. Another consequence of these results was abundant funding from the National Institutes of Health (NIH) for over 10 years.

Figure 8: *(opposite page) When a cat was engaged in active behavior, such as the 'death grip attack' on a small rat (left), the effect of basal forebrain stimulation was to immediately terminate that behavior and to totally disregard the traumatized rat. The cat appears in a state of motor quiescence or "adynamic" or, to borrow a term from Hess, "without volition."*

Figure 9: *(Below) This figure nicely demonstrates the opposing effects of electrical stimulation of the ascending reticular activating system (ARAS, R.A.S in figure below) – described by Moruzzi & Magoun - resulting in desynchronization or cortical arousal (see top figure) – and the synchronizing effects of basal forebrain stimulation while the ARAS remains being stimulated.* [24]



In summary, Sterman and Clemente's team were able to determine that the basal forebrain area contains diverse inhibitory systems, acting through the release of the inhibitory neurotransmitter GABA to inhibit a variety of incoming neurochemical excitatory pathways. This caused hyperpolarization of associated thalamic relay cells, which sets in motion a rhythmic interaction between these cells and an adjacent second system of GABAergic cells in a nucleus called the nucleus reticularis. Inhibitory input from these cells enhanced and prolonged resulting rhythmic bursts in the thalamic relays. Ongoing attention, motor activity, autonomic excitability, and cognitive arousal, are either collectively or individually altered. It is now clearly known that relevant EEG rhythmic patterns reflect the unique properties of thalamocortical circuits, that they are topographically localized in relation to anatomical organization, and that the interaction between specific and nonspecific sensory and cortical influences determines their frequency and cortical expression. It is important to remember that rhythmic EEG patterns mark the inhibition of their associated functional inputs, and thereby reflect the attenuation of these functions. Was this the network underlying internal inhibition, a system reciprocal to excitation in order to provide for essential regulation? Metaphorically, was this the brake pedal counteracting the gas pedal? Sterman and Fairchild carried out a definitive and rather elaborate study to examine that question in detail, and the forthcoming answer clearly said yes!

To test this hypothesis Sterman used a special test runway, with a chamber on either side of a connecting bridge over water, which they initially developed for studies designed to evaluate motor performance after the administration of various drugs. Animals were trained to run back and forth between the chambers to obtain a mixture of milk and chicken broth delivered into cups built into each chamber as a reward for performance. This performance was measured by the *speed of transit* crossing back and forth between the chambers using photo-electric beams placed along the runway and attached to automatic timers. A stimulating cable, attached to a harness and slip-ring assembly, and carried along an overhead rail-car, prevented tangling of the cable. Motoric arousal level was defined as the average speed of crossing the narrow runway bridge between the

two feeding chambers. Stimulation of the reticular formation resulted in a sustained *increase* in the performance velocity while crossing the bridge. Conversely stimulation of the basal forebrain caused a *clear and sustained slowing* of performance. When both sites were stimulated simultaneously this interaction resulted in a cancellation of effects, and baseline velocities. These results thus clearly confirmed the above notion of independent and reciprocal systems in the mammalian brain for regulating motor arousal and 'volition.' [26]
By the way, no cat ever fell into the water, as expected.

In a next step, Sterman decided to apply classical conditioning to this electrical basal forebrain stimulation. This was described in Chapter IV of his PhD, and also published in the prestigious journal Science in 1962 [27] followed by a more detailed publication in Experimental Neurology in 1963. [28] Here, Sterman described classical conditioning of basal forebrain stimulation being paired to an auditory tone. Already after 6-10 pairings of the auditory tone with the electrical basal forebrain stimulation, the tone itself evoked a burst of synchronized slow wave activity, indistinguishable to the pattern seen as a result of electrical stimulation. In essence, this was his first description where conditioning principles were directly applied to brain stimulation, albeit still based on classical conditioning principles.

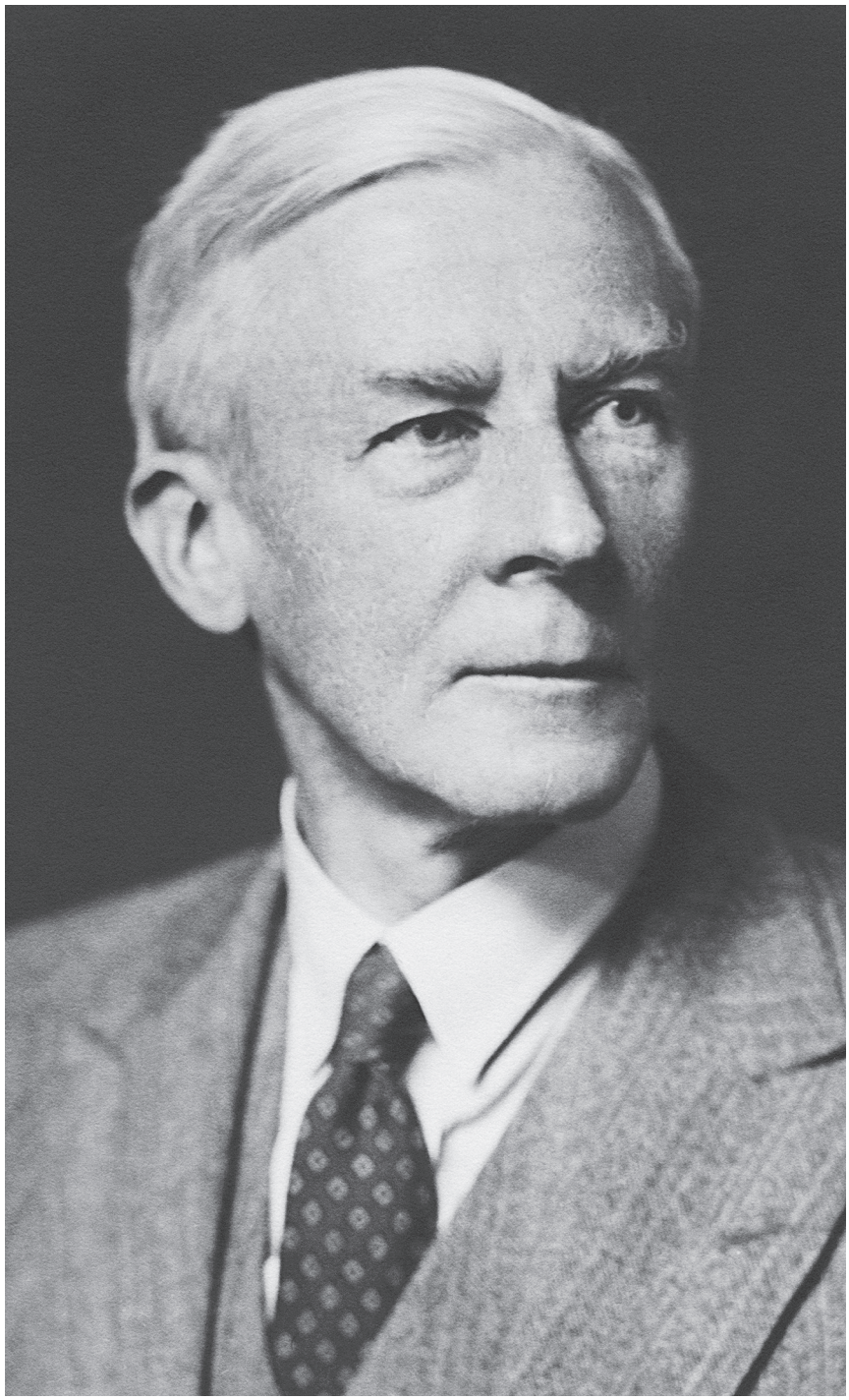
To summarize Sterman and Clemente's basal forebrain studies, there is an active inhibitory process arising from the basal forebrain, and capable of diminishing motor excitability and promoting the onset of sleep.

Eventually, Clemente got Sterman an appointment in the Anatomy Department, and Sterman got his own lab at the BRI, working together with Clemente. For the 10 years to come, they were a very close team, in the sleep field generally known as 'Sterman and Clemente.' During those days, the sleep field was just taking off in the US with people like Will Dement (William C. Dement) and his group. The first meeting Sterman went to was in Northern California, in San Jose, with about 50 attendees, which currently stands at approximately 5,000 people.

As Sterman reminisces: *"...I was taught all this wonderful stuff by Clemente. Clemente was an angel, really. My parents were European, they learned how to speak English, but they weren't well educated, they were good people, but we never talked about ethics or that sort of thing. And he did, he was a mentor to me, and not just science, but in life, which was great. All of those influences that I had at UCLA changed my life..."*

CHAPTER 5:

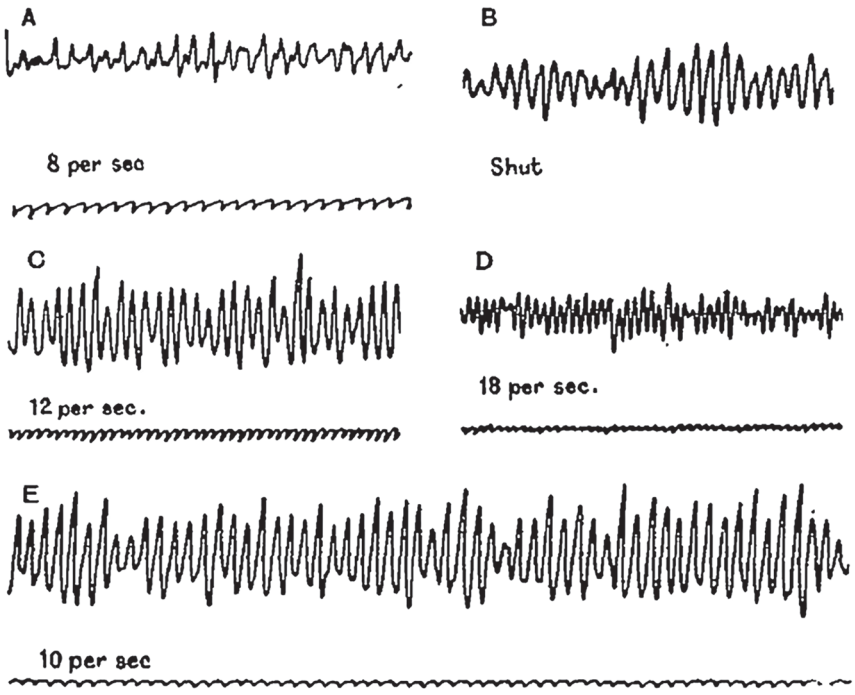
EARLY REPORTS ON CONDITIONING OF THE EEG



In its most basic form neurofeedback can be conceptualized as a learning process applied to the EEG, such as classical or operant conditioning. Or to phrase it in a different way, can brain activity be conditioned? From that angle, the first fundamental observations demonstrating this was true, originate from the beginning days of the discovery of EEG by the same people that pioneered the technique of EEG as we saw in chapters two and three.

The first group that tried to replicate Hans Berger's discovery of the alpha rhythm, was Edgar Adrian (*pictured left*) and Brian Matthews in 1934.[7] They extensively and minutely tested all kinds of alternative explanations that could explain the '*Berger rhythm'* as they called the alpha rhythm and to rule out it was a signal of non-neural origin. In their studies they often used themselves as a subject, which most often would be Adrian, since Matthews probably had a low-voltage alpha EEG as described by themselves: *"...One of us (B.D.A.) gives the rhythm as soon as the eyes are closed, and maintains it with rare and brief intermissions as long as they remain closed. The other (B.H.C.M.) is better in the role of observer than of subject, for in him the rhythm*

may not appear at all at the beginning of an examination, and seldom persists for long without intermission..." [7] page 382). During those experiments Adrian also *'listened'* to his alpha, or as they stated *"...some of the evidence on the effect of opening the eyes in the dark was made by one of us listening to the rhythm from his head in a loud speaker...,"* which in a sense already provided him real-time feedback about his alpha activity. However, in that early report there were no indications of learning, shaping or conditioning, so we cannot attribute this as the first demonstration of neurofeedback. They did however describe the frequency-following response of the EEG, which formed the basis of the many available audio-visual entrainment (AVE) applications. They employed a visual flicker at various frequencies, that would induce alpha activity of that same frequency. See below fascinating examples from their 1934 publication. Note that introspectively they could not draw any associated feelings or states to the different frequencies.



For the first real demonstrations that brain activity adhered to conditioning principles we have to fast forward one year further to 1935. In that year the first observations of classical conditioning of the EEG were published. The first mentioning in the literature was from France by Gustave Durup and Alfred Fessard: [29]: *"...L'idée qu'un conditionnement avait pu se former, par association du stimulus lumineux efficace au stimulus auditif primitivement sans action, se présentait à l'esprit. Des expériences furent reprises, avec des résultats irréguliers, souvent négatifs. Récemment, Loomis, N. Harvey et Hobart ont refait avec succès l'expérience et admettent le conditionnement..."* (*...The idea that conditioning had been formed, by combining the effective light stimulus with the initially inactive auditory stimulus, came to mind. Experiments were repeated, with irregular and often negative results. Recently, Loomis, N. Harvey and Hobart have successfully repeated the experiment and demonstrated conditioning...).* However, Alfred Loomis was credited with the first description of classical conditioning applied to the EEG, albeit only published in 1936. [13] As mentioned earlier under the history of EEG, Loomis and colleagues applied conditioning to the alpha waves they picked up from the EEG, or as they stated: *"...If the subject lies in complete darkness with eyes open, a low tone stimulus lasting 5 seconds will not stop the alpha waves. If the low tone and also light stimulus are both presented simultaneously several times in succession at half minute intervals, the waves will of course stop, due to the attempt to see induced by the light, but if now the tone alone is sounded the waves also stop as the attempt to see is now induced by the sound. ..."* [13]

Figure 10: *(Opposite page) In the second paper ever published on EEG by Adrian and Matthews, the frequency following response was already described, where a flickering light source at various frequencies would induce the same frequency in the occipital EEG, which principle is currently still used in Audio-Visual-Entrainment (AVE) applications. The various letters demonstrate various examples such as (A) a Flicker of 8 Hz, (B) Eyes closed naturally occurring 10 Hz alpha rhythm, (C) Flicker at 12 Hz, (D) Flicker at 18 Hz and (E) Flicker at 10 Hz. From Adrian and Matthews [7] by permission of Oxford University Press.*

In addition, Loomis conducted a further experiment using hypnosis which was reminiscent of what Joe Kamiya would later demonstrate based upon voluntary control, but in this case using hypnosis. In this experiment, Loomis used adhesive tape to keep the eyes of his subject closed and used hypnotic suggestion to induce 'temporary blindness' i.e. suggest the subject saw nothing, resulting in the appearance of alpha. While the subject had his eye closed they suggested via hypnotic suggestion he saw a spot on the ceiling and the alpha rhythm disappeared, only appearing again when they told the subject he saw nothing. This could be reliably repeated 16 times. [13] Hence, alpha was already brought under control of the 'mind' in this case using hypnotic suggestion.

Several years later, in the early 1940's the conditioning of EEG was investigated more systemically. [30-32] These studies investigated in great detail the occipital alpha-blocking response and whether alpha blocking with visual stimulation could be conditioned to an auditory stimulus. In addition, a range of classical conditioning principles were successfully applied, and all of the Pavlovian types of conditioned responses could be demonstrated. [31] In a follow-up study, Jasper and Shagass investigated further whether subjects could also exert voluntary control over this alpha blocking response. In this study they had subjects press a button, which would turn the lights on and off and use sub-vocal verbal commands when pressing the button e.g. 'Block' when pressing the button and 'Stop' when releasing the button. [30] Also see the Figure 11, demonstrating these effects. In the bottom part of the figure, one can see that after five sessions the subject was able to voluntary suppress the alpha rhythm while lights were off (whereas alpha would normally be present with eyes closed). This can therefore be seen as the first study where *'conscious voluntary control'* over EEG activity was demonstrated. In 1943, Shagass and Johnson replicated this finding demonstrating that subjects also could achieve voluntary control over the alpha blocking response by clenching their fist. Even though these studies demonstrated *'voluntary control'* they still relied on classical conditioning principles and it would take another 20 years before operant conditioning of the EEG would be demonstrated. As was seen in the previous chapter, Sterman's early work in 1962 and 1963 also relied on classical conditioning principles but then

applied to electrical brain stimulation of the basal forebrain. However, operant conditioning of brain activity was not shown before this time.

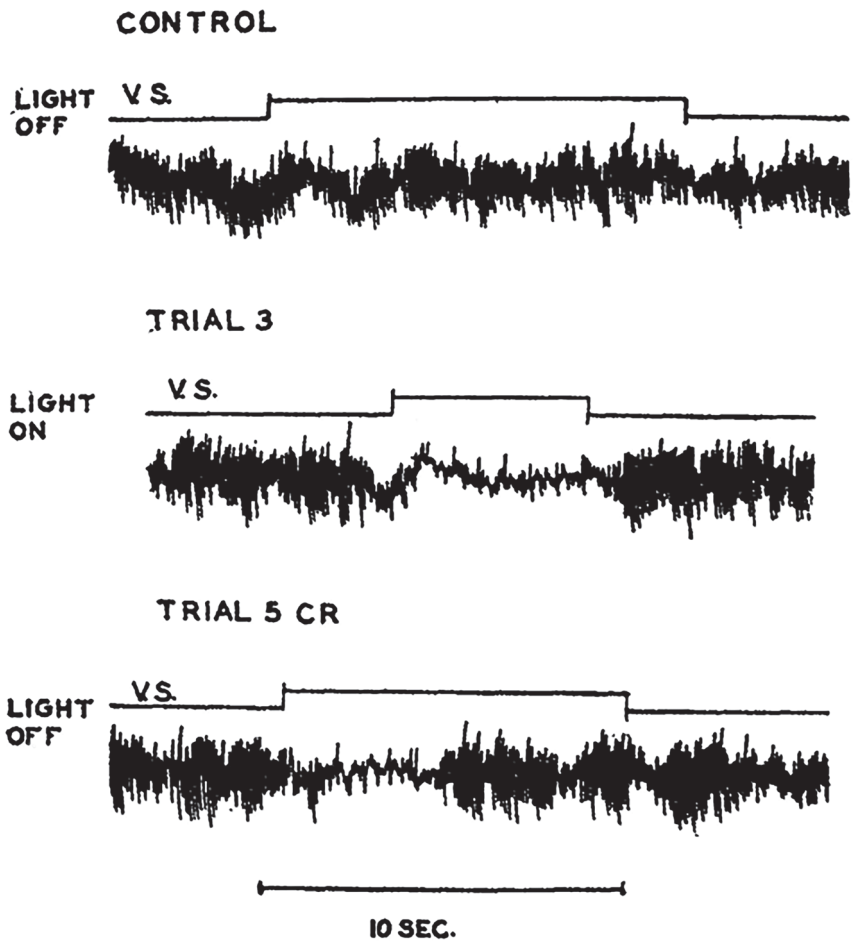


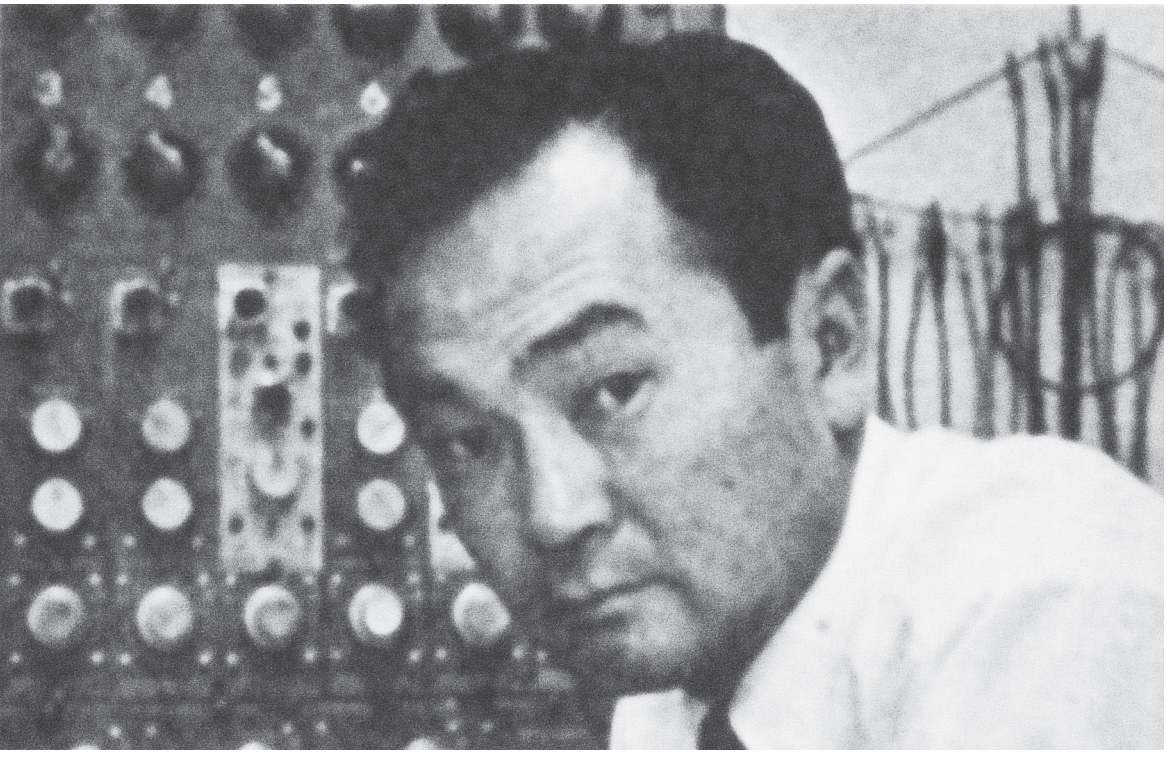
Figure 11: *The first demonstration of conscious control over the EEG alpha blocking response, based on classical conditioning principles as demonstrated by Jasper and Shagass in 1941. The top trace 'CONTROL' indicates the ongoing EEG during 'Light Off' where there is no effect of the subvocal command. Trial 3 shows the conditioning, where the light is switched on at the same time as the subvocal command, and finally Trial 5 where a clear desynchronization as a result of only the sub-vocal command is visible showing the sub-vocal command has been classically condition to result in the same conditioned response as the lights on would have (From: Jasper & Shagass* [30]*, APA, reprinted with permission).*

Other attempts of classical conditioning applied to other EEG rhythms have also been conducted such as classical conditioning of spike-wave discharges in patients with epilepsy which was unsuccessful. [33] Later studies demonstrated operant conditioning of epileptic multi-unit activity, albeit without sustained effects of decreased seizure rates [34,35], recently confirmed by Osterhagen, Breteler and van Luijtelaar [36], who were unable to demonstrate an *increase* in seizure rates in rats when the occurrence of spike-wave discharges was reinforced. These results suggest that spike-wave discharges cannot be 'conditioned' or trained directly. Conditioning principles applied directly to pathological EEG states such as epileptic and paroxysmal EEG activity are therefore an unlikely route to remediate seizures. The difficulty of this direct conditioning of epileptic states is most likely the result of the decreased level of consciousness during such states precluding efficient learning from taking place during the occurrence of a seizure.

So far, we have seen that learning principles, more specifically classical conditioning or Pavlovian conditioning, can be applied to EEG activity. However, only towards the end of the 1950's it was demonstrated that operant conditioning principles could be applied to EEG activity as well, first demonstrated by Joe Kamiya.

CHAPTER 6:

JOE KAMIYA



Joe Kamiya, (*pictured left*) while being a graduate student in the Department of Psychology at the University of California at Berkeley in the 1950's, was interested in the general area of self-perception, such as the perception by subjects of their own features, behavior and bodily processes, including their feelings, emotions, thoughts and memories. Prior to his work in California, Kamiya started his academic career in 1953 at the University of Chicago, studying dreams and sleep in the laboratory of Nathaniel Kleitman, who worked there together with his student William Dement. The University of Chicago at that time was a hotbed of behaviorism and discrimination training with operant conditioning, which resulted in Kamiya's alpha guessing experiment in 1958.

After Kamiya joined the faculty of the Department of Psychology at University of Chicago in 1953, two research activities then ongoing were important in shaping his subsequent thinking. First, across the street from his office was the Department of Physiology, where Nathaniel Kleitman and his student William Dement were following up some of the early work initiated on sleep and dreams in Kleitman's lab-

oratory. They were using the EEG for detecting the electrical activity of the brain and the electro-oculogram (EOG) for detecting eye movements of the sleeping subject. This laboratory was the place where the discovery was made that people would more often report they had been dreaming if awakened during periods of rapid eye movements (REM) sleep, relative to being awakened during periods of deep sleep and slow-wave sleep. Interestingly, the notion that dreaming was confined to REM sleep, was challenged by extensive parametric sleep studies Kamiya had conducted, where he demonstrated substantial non-REM dream recall, actually challenging the notion that dreams only occurred during REM sleep.

Kamiya was excited by the potential contributions this research could make to a wide variety of disciplines, but particularly to the physiology of private experience. He was permitted by Kleitman to use his laboratory to pursue a few research questions raised by their work. Dement, in his last year of medical school at the time, taught Kamiya the technology of EEG and EOG recording of sleeping subjects. While learning the technology of EEG recording his curiosity was piqued by a feature of the EEG alpha rhythm recorded from the occipital regions of the scalp of fully awake young adults, resting with their eyes closed. In the graphic record the trains of these roughly 10 Hz rhythmic waves would appear and disappear in an intermittent and irregular sequence. They would appear roughly from five to 30 times per minute, with the duration of the trains and their absences ranging from only a few tenths of a second to perhaps as long as 15 seconds or more. There were wide individual differences in both number and duration of the alpha wave trains per minute. Kamiya wondered whether these transient fluctuations in an individual were associated with any changes in subjective experience of any sort. Since the earliest days of EEG research in the 1930's it was known that whether the eyes were open or closed clearly affected the dominance of alpha activity. Also, through personal communication from another early researcher in the field, Geoffrey Blundell, Kamiya learned that Grey Walter and colleagues, experimenting informally in the 1930's through the 1940's had observed what had happened in the paper recordings when they entered into specific states of mind. Among the things they found was that whether they had kept their eyes open or closed, if they had engaged in certain mental activ-

ities such as imagining close up visual scenes, and then reviewed how that affected the paper recordings of the EEG, they found reductions in the amplitude of the occipital EEG alpha compared to moments when they were not engaged in such imagery.

So, the mapping of relationships between subjective experience, internal behavior, mental activity and EEG activity had already been conducted in the early years when the EEG was discovered, as described in great detail by researchers like Berger, Adrian and Matthews, Loomis and others. However, Kamiya's concern was whether the more transient durations of the trains of alpha of about two to six seconds might be associated with changes in subjective quality. With no idea of how to explore the possibility, he set the idea aside. A few months later a method of training subjects to detect the fluctuations occurred to Kamiya, and if it was successful, inquiry into their subjective quality might be useful. Kamiya attributes the idea of the method to his second fortuitous contact with the research activity at the University of Chicago, this time in the Psychology Department. Operant conditioning studies with animals were being conducted by Howard Hunt, from whom Kamiya learned much about operant methods. A common method of operant conditioning used a specific discriminative stimulus to control behavior during reward training. This discrimination training is widely used in operant conditioning of the externally observable behavior of humans, including verbal behavior. It typically involves the learning of stimuli that are located in the immediate environment of the trainee, outside his or her body. He became intrigued by the possibility that the same contingencies of training could be used to train participants to discriminate some stimuli inside their bodies, like the ongoing normal fluctuations of some measure of their own physiological activity.

To address the question about alpha and subjective experience experimentally, in 1958 Kamiya thus chose to use discrimination training in which the discriminative stimulus was the presence of an alpha train as opposed to its absence. Note that Kamiya's approach was thus rather different from how many implement 'alpha training' these days, it was not about reinforcing the amplitudes of alpha, but discrimination training, where subjects task was to discriminate two to six seconds of alpha or non-alpha states.

In the early 1960's, Kamiya was visited by the famous B.F. Skinner of Harvard University, who had heard of Kamiya's work, and came to meet at the University of California at San Francisco for the day. He observed Kamiya administering discrimination training to a subject in a sound deadened and darkened room while Kamiya watched a moving strip chart displaying the subject's EEG. It was clear to Kamiya that Skinner was intrigued by the possibilities of this kind of training. Later, from reading one of Skinner's books, Kamiya realized that the internal discrimination he was training clearly fit Skinner's general conception of what he labeled as *'tacting'* – from contacting, as in objects in the environment by naming them – therefore tacting in this case means 'of events internal to the participants'. In his book he had used the word self-tacting to refer to self-perception. It must have been rewarding for Skinner to see the actualization of a method of discrimination training that he had developed for external stimuli now being used for internal stimuli, and the concept of self-tacting, which he wrote about, being displayed before his eyes in live action. But he was a perfectionist. After watching Kamiya for a few minutes he saw that Kamiya sometimes hesitated briefly as he tried to decide if the subject's response was correct for the EEG pattern he was inspecting. He commented in a friendly manner that it might be useful to have a more automatic system for classification of the EEG. He was right, and Kamiya was glad to be able to inform Skinner that such a device was being built as they spoke.

In order to help the trainer, detect the presence or absence of alpha activity Kamiya had his research technician who was skilled in electronics build a filter with a bandpass of 8 to 12 Hz, to filter out the rest of the EEG. On the following pages see some photos from that time from the original publication in Psychology Today in 1968. This eliminated the confusion for the trainer who without the filter would have had to overcome visually the intrusion of the full range of non-alpha EEG frequencies (roughly from 1 to 45 Hz) output from the EEG amplifier to make a visual judgment of the amplitude of the alpha activity in the graphic record. For some subjects the trainer would not have been able with sufficient reliability to judge the presence or absence of alpha activity without the filter.

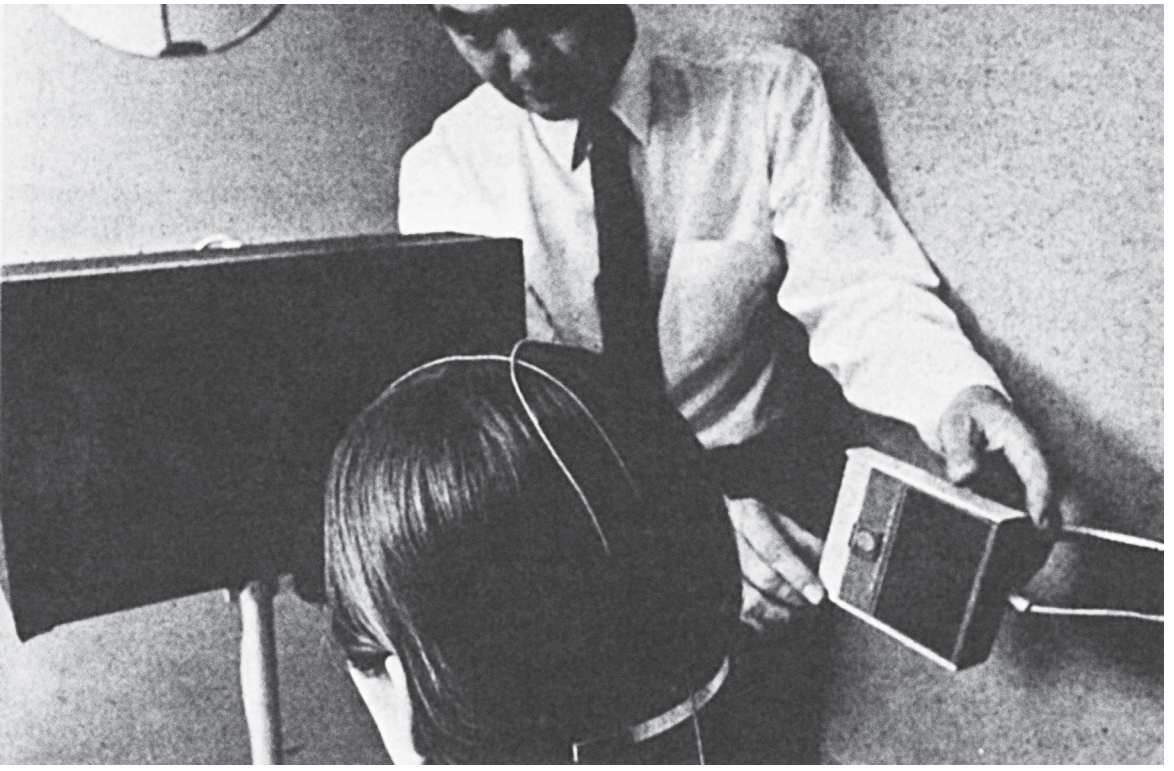


Figure 12: *Some photo's illustrating the early alpha work from Kamiya. Preceding page: Kamiya inspecting EEG traces, looking for alpha activity. Above: a subject engaged in an alpha conditioning session. From: Kamiya (1968; Psychology Today: Copyright Sussex Publishers, LLC).*

Further improvements were later made by adding electronic detection of the amplitude of the filtered alpha activity for later experiments. This completely eliminated the need for the trainer to judge the presence versus absence of the alpha activity.

The abstract in Figure 13 was first presented at the Western Psychological Association in San Francisco in 1962 and summarizes the work on discrimination training done at Chicago. This work continued in the first year or two following Kamiya's acceptance of a position on the faculty of medical psychology in the Department of Psychiatry at the University of California in San Francisco.

CONDITIONED DISCRIMINATION OF THE EEG ALPHA
RHYTHM IN HUMANS

Joe Kamiya, Ph.D.

Abstract of a paper presented at the Western Psychological Association, 1962, San Francisco

Combining methods of behavioral analysis and physiological recording in a study of "introspection", a conditioned discrimination training procedure was used to determine whether there were private stimulus concomitants of the EEG alpha burst. With monopolar recording of the EEG (ear to left occuput, scalp electrodes), and with the subject lying relaxed with eyes closed, E sounded a single ding of a bell aperiodically about 5 times a minute, randomly scheduling the dings to coincide half the time with the occurrence of an EEG alpha burst, and half the time with the absence of alpha. The subject was instructed that with each ding in the training trials he was to try to guess either "yes" or "no", depending on "how he felt" at the time of the bell. The "yes" responses to dings with alpha and the "no" responses to dings without the alpha were reinforced by being called "correct" by the experimenter. Results:

In about 50 to 500 trials, six subjects learned to make nearly 100 per cent correct responses. As a control over the possibility that the bell ding sounded differently on the two types of trials, in a second procedure the subjects were asked to make guesses out loud as to when their "yes" or "no" states occurred, without the aid of the bell. The subjects could do that also. One subject could not offer any verbal description of why he performed so accurately. Five felt that it was related to what they were thinking about or to their efforts to imagine visual scenes. In some of the subjects the discrimination appears possible only if they try deliberately to alternate their states of mind between visual imagination and relaxed inattention in a regular pace so that they can more easily discern their state as required by the experimenter. In a third type of procedure, it is found that the alpha burst can be produced by the subject, upon command from the experimenter, who asks S to produce the states accompanying their verbal responses in the discrimination procedure.

Preliminary analyses of cardiac and respiratory activity, eye movement and muscle tension indicate that these are not stimulus sources accompanying changes in the EEG.

Figure 13: *Reproduction of the first abstract presented by Kamiya at the Western Psychological Association in San Francisco in 1962. This can be considered the first communication about operant conditioning applied to the EEG, more specifically 'conditioned discrimination' and the starting point of Kamiya's work on alpha-neurofeedback.* [37]

It was clear from the beginning that subjects can indeed learn to discriminate the presence versus absence of EEG alpha activity; thereby confirming that the fluctuations have some private stimulus correlates. However due to the frequent shifts from one state to the other, the time allowed for the periods of the two states before

the trainer gave the signal for the subject to choose his response was relatively brief. Each state once selected by the trainer was seldom allowed to exceed more than about six or seven seconds to avoid its ending before the trainer could signal the subject to make a judgment. Perhaps given such brief periods, it may have been easier for the subjects to detect a difference between the two states than to judge what the difference was. This may account for why some subjects had difficulty describing the qualitative differences between the two. Despite this, Kamiya was encouraged to note that the discrimination training method did establish there are private stimulus correlates that permit the discrimination of the two EEG states, even for quite brief transient states of the EEG as seen in the fluctuations of alpha activity.

From the very first participant in the EEG alpha discrimination study, named Bach, it became clear that training participants to discriminate high versus low amplitude EEG alpha rhythms led to their ability to control the rhythms voluntarily upon command by the trainer. Bach reported correctly 65% on the second day of testing, 85% correct on the third day and on the fourth day was able to report correctly 400 times in succession before he made a mistake. The mistake he made then, was a deliberate mistake since he wanted to test if Kamiya was not pulling a trick on him and verify the equipment was working fine. In a second experiment, the subject was able to enter the alpha state or not enter the state on a specific cue. It was thus established that people could control brain waves which had been thought to be involuntary states.

From the very first participant in the EEG alpha discrimination study, it had become clear that training participants to discriminate high versus low amplitude EEG alpha rhythms led to their ability to control the rhythms voluntarily upon command by the trainer. Kamiya undertook work to determine if subjects could be trained to control the rhythm without first conducting the discrimination training. He presented them with an auditory signal that continuously monitored their alpha activity, such that the tone remained on as long as there was alpha activity above an arbitrarily set amplitude threshold. The trainees were asked while they sat alone in a dark room with eyes

closed if they could learn to increase the percent of time the tone was on, and their progress was registered quantitatively every one or two minutes and displayed to the subject during the training period. After about four training sessions the majority of trainees were able to raise their average alpha amplitudes above their starting baselines.

"As far as I know, this experiment, conducted in 1958, was the first to demonstrate that an automated external feedback signal for monitoring a persons' EEG activity was used to train persons in the control of specific features of the EEG..." Kamiya recalls. He felt that an improvement in the design of the experiment was needed; an unknown portion of the increase in percent time of alpha might have occurred over the sessions simply because of the passage of time, perhaps because subjects became more accustomed to being in the laboratory over the several sessions of their participation. Learned EEG alpha control could be more convincingly demonstrated if they could learn to both increase and decrease their alpha activity percentages. So Kamiya decided to train a new sample of subjects. The tone feedback system of the previous experiment was used again, and they were told the percent time of alpha once per minute for five minutes as they tried to increase their alpha activity scores. Then for the next five minutes they were asked, with the aid of the same feedback signal and one-minute performance reports, to decrease their percent time of alpha. The reversing of the task every five minutes was continued to the end of the session. Eight of the 10 subjects were able to achieve some degree of voluntary control of the tone, increasing or decreasing the percent of time that the tone was on, as was requested of them. After forty trials, 20 up and 20 down, the average alpha percent time for increase trials had risen to 53% and for the decrease trials had fallen to 17%. It appears that alternating the blocks of trials as Kamiya did helps the subjects to contrast the two tasks more sharply and improves the rate of learning the control of alpha. The verbal descriptions were more detailed and confident than with the previous method of only increasing the alpha durations. Visual imagery was again reported as effective in decreasing alpha, and sometimes a slight tension in the eye region was mentioned, suggestive to Kamiya of ocular motor involvement, which is known to suppress alpha. Since no hints were given to the subjects on how best to decrease the

tone, it is clear that by trial and error they discovered by themselves what any coached subject could immediately use without any training to produce decreases in alpha. For increasing the percent time of alpha several subjects reported as effective strategies entering into a state of alert calmness, a singleness of attention, and a passive following of the tone. Alpha seems to result from an alert, non-drowsy state, with a minimum of concrete visual imagery. It is important to point out that these qualities are not reported by some subjects, and there were sufficient differences in the reports of the different subjects that Kamiya got the impression that a significant contributor to the differences was differences in the history of language usage and past experience in attending to internal body sensations. *"...I believe that this represents a major challenge for any science of the relationship of subjective experience to physiological processes and that new methods are needed to improve the specification of the subjective properties of the two states..."* according to Kamiya. So far, the concern with the alpha rhythm has been its amplitude, its occurrence and how well it could be brought under control. In those days Kamiya also wondered whether the frequency instead of the amplitude of alpha (the so-called alpha frequency) can be controlled with feedback, and if so, what subjective correlates it may have. Hence this was also the first demonstration of neurofeedback applied to the alpha frequency, that is currently often studied using upper-alpha neurofeedback or other alpha frequency neurofeedback approaches.

Kamiya did not publish much of his work. He gave many presentations at various universities and informal scientific and civic groups and has enjoyed especially sharing in the development of ideas with students. Kamiya was always pleased to hear that others had been influenced by his work.

Kamiya's initial work on alpha control and alpha peak frequency control has resulted in, among others, the application of alpha/theta neurofeedback in the treatment of addictions and optimal performance (reviewed in Gruzelier, 2009 [38]) and inspired several well controlled studies investigating training of upper-alpha power resulting in improved cognitive performance. [39,40]

CHAPTER 7:

THE DISCOVERY OF SMR

As reviewed in chapter 2, under the history of EEG, Pravdich-Neminsky using an Einthoven string galvanometer in conjunction with moving photographic paper photographed the first *'electrocerebrogram'* or EEG ever. He recorded EEG from the brain, the dura or the intact skull of the curarized dog, and he described a 12-14 Hz rhythm under normal conditions. Could that first description and photographically captured rhythm have actually been the first ever observation of Sensori-Motor Rhythm (SMR)? That we don't know, but in the following the actual discovery of the SMR will be outlined in some detail, given the predominant role this rhythm has played in the history of neurofeedback, still as one of the most well investigated and used approaches in the field of neurofeedback.

Sterman's earlier classical conditioning work on the basal forebrain indicated that the EEG could easily be molded by conditioning and was an important stepping-stone in his work. That earlier work had suggested that: 1) EEG patterns evoked by specific brain states provide markers for those states, or more specifically the clearly discern-

ible states of synchronized EEG associated with sleep and drowsiness versus the desynchronized EEG associated with a fully alert state, and 2) that these markers can be conditioned to alter the underlying brain state, or more specifically the tone that after classical conditioning resulted in the same effect as the basal forebrain stimulation, resulting in sleep preparatory behavior and the subsequent EEG synchronization. So here we see a clear dissociation between behavioral states (wake and sleep), with their clear EEG signature (desynchronized versus synchronized), that could now be specifically induced by stimulation of the basal forebrain (sleep promoting) or the ascending reticular activating system (ARAS; promoting alertness), and conversely a neutral tone could be classically conditioned to invoke the same effect as basal forebrain stimulation with the related behavioral state and EEG signature. This led Sterman to modify the expression of these states through directed neurofeedback, and therefore modify their underlying substrates.

To explore this further, it was necessary for Sterman to find a method which might elicit a behavioral inhibitory response resembling internal inhibition in the laboratory. This required a specific initial behavioral response by the subject. The experimental animal of choice among neurophysiological investigators at that time was still the domestic cat. Adult cats were surgically prepared with small stainless-steel electrodes over the coronal gyrus (which is the feline equivalent of the sensory motor cortex) of the frontal cortex, bilaterally, and in an anterior-posterior sequence, 2 mm apart over lateral (also termed marginal) gyrus, on one side. After recovery from surgery the animals were observed individually, and training sessions were carried out for one hour three times a week on alternate days. The animals were food-deprived for approximately 22 hours before being brought to their experimental chamber. They found 0.25 ml of a milk and chicken broth mixture in a feeder cup on one wall of the chamber during initial testing, supplemented by solid food afterwards.

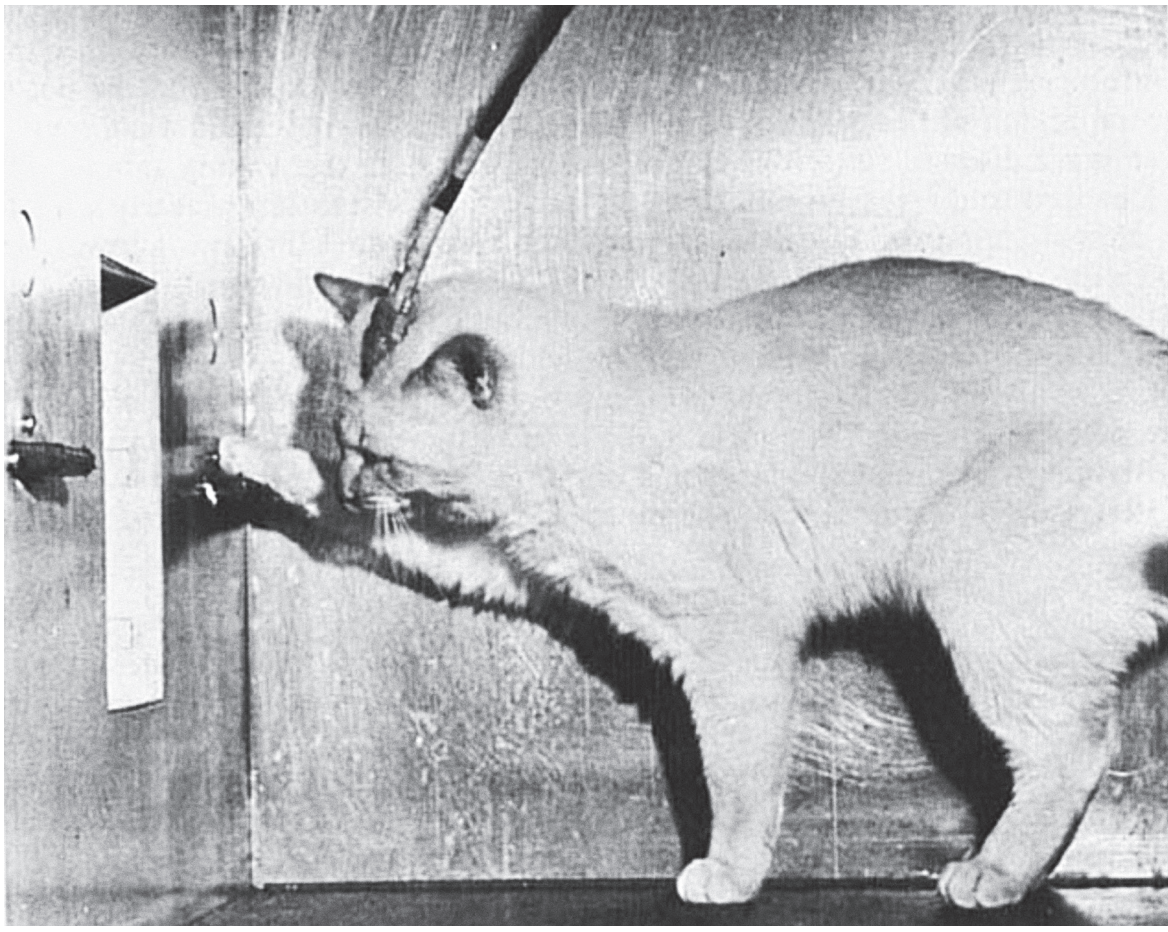


Figure 14: *A visualization of an operant chamber, used for operant conditioning of the bar press response in the initial phase of training prior to the elicited behavioral inhibition response and conditioning of Post-Reinforcement Synchronization (PRS) or SMR activity. A speaker was located above the food cup, lights (L) are right and left above the food cup, and levers are found underneath both lights.* [41]

Cats were subsequently allowed to voluntarily get 0.25 ml of milk and chicken broth reward (which they really like) by spontaneously pressing the lever above the feeder cup (also see Figure 14). They rapidly learned to do this, and the bar-pressing response became conditioned after 10-20 responses. Now, in order to induce a state of behavioral inhibition, resembling internal inhibition, when the bar-pressing response was stable, a 2000 Hz tone was sounded for three seconds. During this tone no reward was delivered when the

lever was pressed, it signaled the cat of an approaching lever-press period. When the tone stopped, and the cat pressed the lever, a three second light came on after which the reward was presented to the animal. So, the behavior to be learned was a *withholding of response* during either tone or light presentation. If the lever was pressed during the tone or the light, it would prolong the signal for three seconds. So, the animal was presented with two delay problems, delay of response during the tone and delay of reinforcement during the light. A 30 second inter-trial interval was used with 50 trials a day and over 75 daily sessions, resulting in highly over-trained animals.

Initially, some cats continued pressing the lever to no avail. Eventually during the period just before the next tone animals stopped approaching the cup and showed stereotyped, motionless behaviors. Simultaneously, a unique sustained 12-20 Hz rhythmic EEG pattern began to arise from the coronal gyrus before, during, and after the tone (see Figure 15). This represented an initially generalized conditioned EEG response to the tone. Eventually this EEG response became essentially simultaneous with the tone and this rhythm became a learned EEG operant response to these states. To confirm this, Sterman used a classical extinction test by terminating the reward after the response became reliable. This resulted almost immediately in the increased occurrence of this EEG response in terms of its expression, amplitude, and duration, thus confirming that it was truly a conditioned response. [42] In an attempt to label this EEG pattern Sterman chose the term *'Sensori-Motor Rhythm'*, or SMR (Sterman strongly preferred anatomy over Greek for labeling). Digital analysis showed its peak frequency to be 13 Hz, with an overall range of 12-20 Hz, and in this context a peak range of 12-15 Hz.

This first observation of SMR as outlined above was published in 1967 in two parallel publications by Roth, Sterman and Clemente [41] and Sterman and Wyrwicka, [43] which was actually unveiled already in December 1965 at the American Electroencephalographic Society (now called the American Clinical Neurophysiology Society (ACNS)) as referenced to in Sterman and Fairchild [26]: *"...in fact, spindle burst activity, which was frequently observed prior to the opening of the chamber door, was still present in many instances after the onset of brain stem*

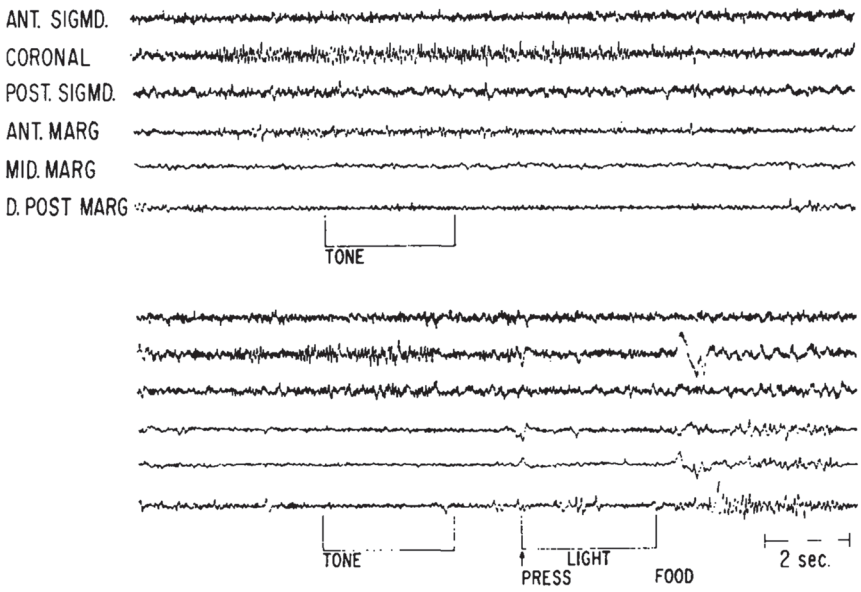


Figure 15: *One of the first reports of SMR in the top illustration, in the coronal gyrus channel during the tone presentation. SMR was elicited by a negative conditioned stimulus, i.e. the animal learned not to press the lever during the tone presentation, which was considered a state of 'internal inhibition.'* [43]

stimulation. This spindle burst activity may be the sensory-motor rhythm associated with the Pavlovian concept of internal inhibition...."

Not only was the concept of internal inhibition instrumental in the discovery of SMR, a parallel line of research on a fascinating rhythm Clemente and Sterman had described as: Post-Reinforcement Synchronization or PRS, was also partly related to this discovery and was actually brought under voluntary control through operant conditioning before SMR was, as will be explained in more detail in the following section.

POST-REINFORCEMENT SYNCHRONIZATION (PRS)

Sterman's first description of Post-Reinforcement Synchronization or PRS, was published in 1964, [44] as part of the studies where Sterman and Clemente taught cats to lever press. Similar EEG synchronizations during alimentary behavior had been described before, but more in terms of satiation and drive reduction. Sterman and Clemente were the first to really observe that this EEG synchronization occurred in response to delivery of a reinforcement and implicate a role of this PRS for learning, motivation and inhibition. PRS was described as *"…A high voltage slow burst of EEG synchronization (100 to 150μV; 4-8 c/sec) was observed to occur after the animal had pressed the cup and during the process of consuming the reward.."* with a posterior topography (parietal cortex). Note that this rhythm thus appeared in response to a reinforcement, so after a conditioned response is demonstrated, whereas, SMR occurred before and during the wait period. Also see Figure 16 for an example. In their early report they described this EEG synchronization or PRS in quite some detail, and to this date, this concept of PRS is a crucial concept in understanding how appropriate conditioning should be performed, especially with implications for neurofeedback that are often ignored. The PRS consequently appeared immediately after the liquid reward was consumed, hence the EEG synchronization was not associated with the conditioning task at hand and also not only reflective of consumptive behavior but was reflective of the 'closure' or consolidation of the operant response.

When they observed the appearance of PRS over training sessions, especially in over-trained animals, they also noticed that EEG synchronization changed from a more diffuse and prolonged pattern, to a discrete envelope of hypersynchronous activity (see Figure 16 for an example). Furthermore, the number of spindles per session also appeared to increase as training proceeded. When the milk-broth reward was substituted by water (which food-deprived cats find less gratifying), cats would still press the bar, however PRS would be abolished (see Figure 16). The cats would taste the reward and try for several times, and then turn away from the feeder, eventually only to return every now and then to press and taste the reward.

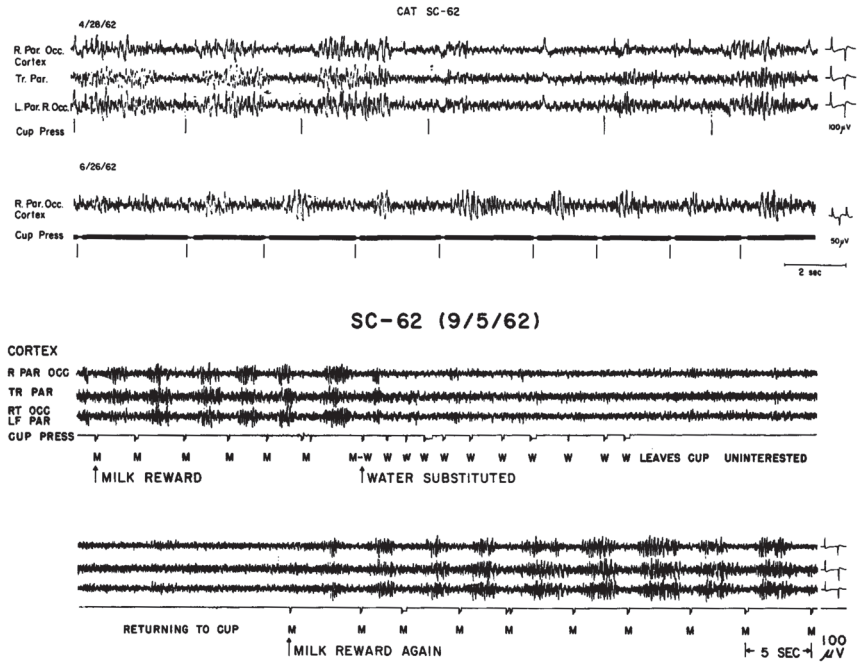


Figure 16: *The top figure shows clear examples of the Post-Reinforcement Synchronization – or PRS, with clear synchronization after every Cup Press (see bottom trace 'Cup Press'). Furthermore, the top trace dated 6/26/62 is after over-training and also visualizes the changes of PRS morphology over time, changing from a more diffuse and longer lasting synchronization (4/28/62) to a more discrete cortical spindle, with larger amplitude and shorter duration (6/26/62). The bottom figure demonstrates the clear association between 'desirability' of the reward and the occurrence of PRS, where water substitution still results in cup-presses, but without the pronounced PRS, and eventual abandonment of the cup pressing. The bottom graph demonstrates a re-instantiation of the learned response when the milk-broth mixture is used again as a reward, and the PRS also occurs again.* [44]

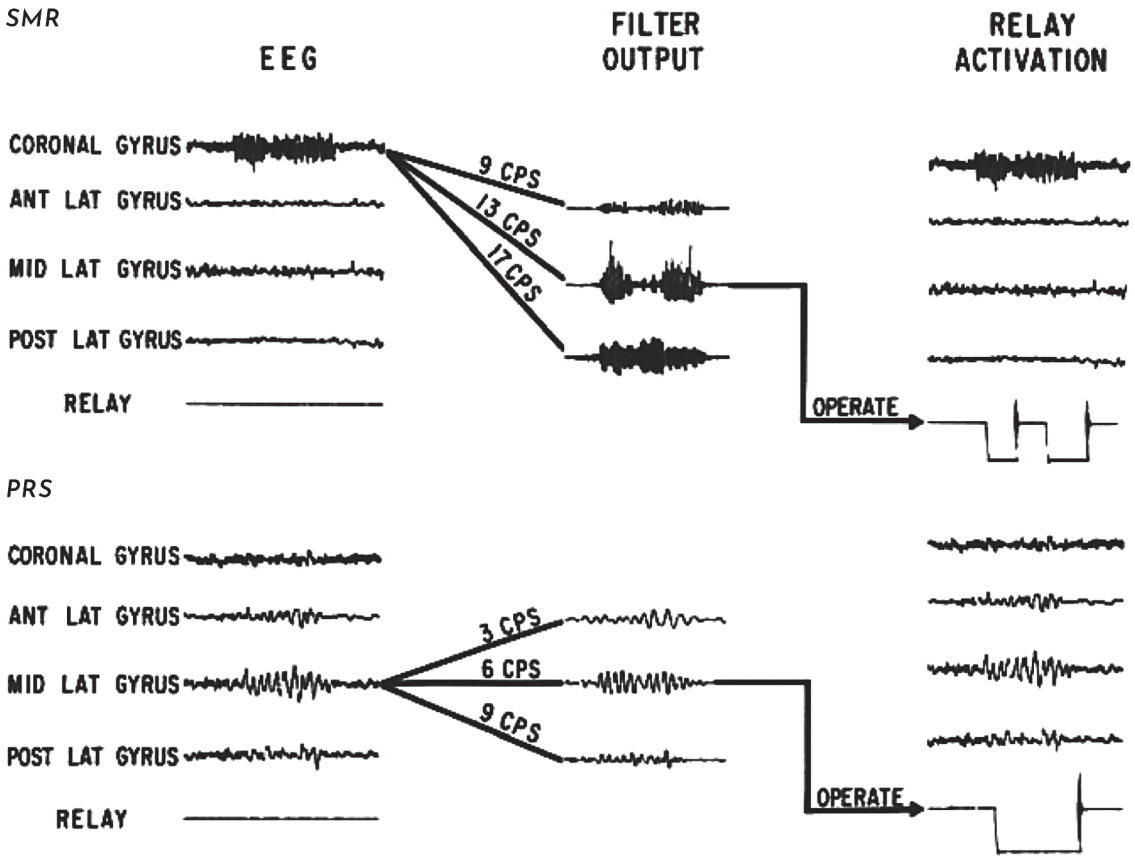
On replacing the water by the original milk-broth mixture, the animal would continue again and exhibit PRS again. Another interesting observation was that an arousing or distracting stimulus right after a bar-press, such as a hand-clap, also completely abolished the subsequent PRS. Interestingly, the implications of this observation are still practiced and experienced by many during some of Sterman's lectures, by Sterman becoming very angry when people present with a ringing phone during one of his lectures (and rightly so), as the

abolishment of PRS due to distracting stimuli basically implies the signature of distraction and thus non-consolidation of the information presented!

In a subsequent study, Sterman and Wyrwicka [43] sought to unravel the behavioral correlate of this PRS further, and to this end decided to instead of rewarding the cat for pressing the bar, they started rewarding the cat for producing PRS, or as they wrote *"...If an untrained hungry animal is placed in the behavior chamber, and the apparatus is arranged to provide food whenever this rhythm appears spontaneously, its behavioral correlate can be actively elicited. This is achieved by passing the PRS rhythm through a series of finely tuned frequency filters to determine the frequency of peak voltage for a given animal. Whenever this frequency occurs at a level significantly above background voltage a relay is closed which, in turn, operates the feeder apparatus..."* The behavior that developed as a result of this PRS-conditioning was interpreted as indicating drowsiness and satiety, Sterman and Wyrwicka proposed PRS was associated functionally with an active process related to the reduction of drive. [43]

These complex technological advances were made possible by Sid Ross, Sterman's engineer, who pioneered the equipment behind these first neurofeedback studies. The equipment had discrete Butterworth 4-pole filters that could isolate specific frequency bands such as SMR, PRS and EMG that could be set one band for one reward and two inhibit channels. When all criteria were met for 0.5 second there was a green light and a ding sound. Inhibits were keyed to red lights. Counters kept track of the number of rewards and inhibits. Microvolt levels for reward and inhibits were set by calibrated helipots.

Figure 17: *(facing page) The implementation of the analog filtering techniques employed by Sterman for the conditioning of SMR (Top figure) and PRS (bottom figure). The filters triggered a relay, which relay would activate the feeding mechanism.* [45]


SMR
EEG
FILTER OUTPUT
RELAY ACTIVATION
CORONAL GYRUS
ANT LAT GYRUS
MID LAT GYRUS
POST LAT GYRUS
RELAY
9 CPS
13 CPS
17 CPS
OPERATE
PRS
CORONAL GYRUS
ANT LAT GYRUS
MID LAT GYRUS
POST LAT GYRUS
RELAY
3 CPS
6 CPS
9 CPS
OPERATE

In that same publication, also the first occurrence of the SMR was observed and the same conditioning procedure was applied to it, but instead by using electrodes placed over the coronal gyrus and employing a frequency of 12-20 Hz. The corresponding behavior that ensued as a result of this SMR conditioning was quite different from the PRS-conditioning, namely the animals were very alert and assumed a stereotyped motionless posture. The characteristic postures varied per animal, but a consistent feature was an almost intense cessation of movement. When the postures were assumed and maintained, SMR always followed, suggesting SMR resulted from the behavior and was not simply a reflection of the sensori-motor strip shutting down. In the same study, correlations between the same electrodes and frequencies where PRS and SMR were recorded were made, but then during sleep, and Sterman described sleep spindles overlapping both in frequency and in location (sensori-motor cortex) with SMR.

Around the same time, Wyrwicka and Sterman also conditioned the 'opposite' electroencephalographic signature of SMR, namely that of a desynchronized EEG activity (low voltage, high-frequency, or simply the *absence* of SMR), after an initial extinction of SMR training. The subsequent behavior related to that state was again rather different, consisting of being constantly active, searching the chamber, circling and performing frequent discrete spontaneous movements. [42] Hence the previously reported behaviors seen with SMR conditioning, namely quiescent and immobile postures were absent from this behavior. When subsequent conditioning of SMR was performed (a so-called A-B-A design) the same behaviors occurred again as previously reported such as motionless stereotyped behavior.

Note however, that a simplistic A-B-A design would implicate; or is often explained as to 'uptrain SMR' in the A leg and 'downtrain SMR' in the B leg, which is not how Sterman operationalized it. Sterman had the notion that *'...what goes up, must come down...'* and was afraid that actively inhibiting SMR or downtraining SMR would be counterproductive and could have detrimental effects. Also, conceptually the operationalization Sterman chose, made more sense, since in EEG the opposing states described are often that off 'synchronous

EEG' e.g. alpha or theta synchronization and 'desynchronized EEG' often termed as a beta EEG. Similar to the classical alpha blocking response described before, when the eyes are closed, there is alpha, and when the eyes are open there is a desynchronized beta EEG. Therefore, the operationalization Sterman used by rewarding the synchronous SMR activity, versus rewarding the desynchronized low-voltage fast EEG is more sensible from a physiological standpoint, rather than only 'downtraining SMR.' Actually, that notion was confirmed several months later, when Joel Lubar who aimed to replicate Sterman's work actually did use SMR downtraining as the 'B-leg' in his study and found a 60% increase in seizures. [46] *"...He had to stop the study, because all his patients started seizing more. So he confirmed our fear..."* Sterman reminisces.

SMR CONDITIONING CONTINUED

Sterman's success with this procedure raised the prospect of forgoing the lever press entirely and using the spontaneous emergence of the SMR pattern itself as the response that was rewarded. This addressed the question as to whether or not one could directly alter the physiological generation of spontaneous EEG characteristics with operant conditioning! To accomplish this Sterman used a slightly new approach. During initial exposure to the chamber, milk reinforcement was presented randomly in the cup. Starting by the fourth session visual detection of a spontaneous episode of SMR activity, which is typically associated with behavioral stillness, lasting for at least one-half second and with an amplitude 100% above baseline levels was utilized as a criterion for manual milk reinforcement in the feeder cup. The discrete nature of this rhythm and the contrasting low-voltage pattern of desynchronization in its absence made this criterion quite reliable. After one such *'shaping'* session, reinforcement of the SMR was accomplished automatically. Sensori-motor EEG signals were fed into a series of solid-state amplifier networks. These networks were tuned to select a narrow 12-14 Hz frequency band and reject all others, including harmonics. Interestingly, this method produced a reliable conditioned SMR response within fewer trials than had been required for learning the lever press. He had successfully

brought the SMR response in the EEG under laboratory control, allowing evaluation of accompanying physiology. With this control, subsequent studies confirmed simultaneous reductions in anti-gravity muscle EMG, associated motor unit activity, as well as reductions in heart and respiration rates, [42] also see Figure 18.

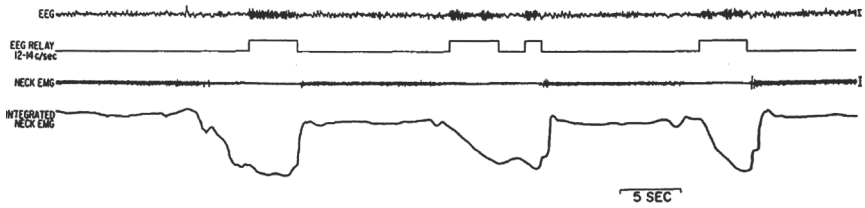


Figure 18: *The interrelationship between SMR production and motor excitability is nicely visualized in this figure, where the bursts in the EEG channel that trigger the EEG Relay are SMR spindles. Note the motor quiescence already occurring prior to the SMR spindle as visualized in the integrated neck EMG channel.* [47]

SMR AND SLEEP SPINDLES

As was highlighted above, in those early studies, Sterman already observed that the specific electrodes that picked up SMR, were also the exact same electrodes where sleep spindles were picked-up during stage two sleep. Furthermore, sleep spindles were also of the exact same frequency as SMR activity, suggesting an interesting overlap between these two rhythms, that are visible in the opposing states of sleeping (sleep spindles) and waking (SMR). In his next experiment, Sterman thus decided to see if increasing the density and magnitude of SMR activity with neurofeedback could have any effect on spindles during sleep. [48] To this end, Sterman trained eight cats each to either suppress SMR activity by reinforcing the absence of SMR, operationalized as a low-voltage fast (LVF) EEG state, or rewarding SMR activity in the other group. After 2-4 weeks they were tested and to control for order effects, the sequence of training conditions in the two groups was reversed, so that each group received each treatment but in opposite order from the first series. Sleep studies were obtained for both groups before and after each period. Sleep studies following training showed that sleep spindle activity in the EEG

was significantly increased exclusively after SMR training, regardless of the order in which they received the conditions. However, when SMR increase training was preceded by SMR suppression training, the increase during SMR training was enhanced, and continued significantly during the post training assessment after one month and beyond, with increases of more than 40%. Further, during the SMR training phase only, in both orders, the incidence of body movements during sleep was significantly reduced. However, when LVF training followed after SMR training the increase in sleep spindles would be counteracted. We can conclude from these findings that the mechanism for sleep spindles and the accompanying functional state is directly related to the mechanism for SMR production and is in both states directly related to motor inhibition. Independent human studies have also demonstrated that SMR neurofeedback during waking results in increased sleep spindle density during sleep, [49] clinically relevant improvements in sleep duration and sleep quality in patients with insomnia [50], and in sleep improvements in patients with Attention-Deficit/Hyperactivity-Disorder, or ADHD. [51]

FROM THE DISCOVERY OF AMPHETAMINES TO SMR AND SEIZURES

Gordon A. Alles was professor of pharmacology at UCLA who conducted much research on the properties and isolation of insulin. He was also the inventor of methylenedioxyamphetamine, also called MDA or the original *'ecstasy'* and the inventor of amphetamine, for which he sold the patent to Smith, Kline & French (SKF, which later would become GlaxoSmithKline). At the time he sold the amphetamine patent to SKF and SKF started marketing the drug as Benzedrine, or colloquially referred to as bennies. Note at that time no specific indication was required yet, as is required these days by the Food and Drug Administration (FDA), hence they sent out the drug to many doctors to also get feedback on what would be a good indication for this new drug. One of the doctors that used Benzedrine in those early days was Charles Bradley at the Emma Pendleton Bradley Home in Rhode Island. He first prescribed the drug in children as an attempt to alleviate headaches, however, in 1937 he noted improved school performance, social interactions and emotional responses, as

an unexpected 'side effect', whereby the foundation of psychostimulants as a treatment of ADHD was laid. [52] Interestingly, the first report on EEG patterns in 'behavior problem children' – considered the first description of EEG in what we now call ADHD – was reported just a year after this initial Benzedrine study, together with Charles Bradley and Herbert Jasper. [53] In this study, they already described two important EEG signatures in ADHD, that are still recognized as important ADHD EEG subtypes to this date. The first signature they described was: *"...There were occasionally two or three waves also in the central or frontal regions at frequencies below what is considered the normal* α *range, that is, at frequencies of 5-6/sec...",* [53] only later in 1944 termed as Theta activity by W. Grey Walter and Dovey. [54] The second group they labeled as *'A sub-Alpha Rhythm'*, that was '5-6/sec' but was responsive in a similar way as alpha, which we now interpret as a slowed alpha peak frequency.

During the 1960's the United States and the Soviet Union were engaged in an intense competition to develop the means for human travel into space. Because of physics and biology the requirements necessary to achieve this goal were shared by the two nations. As a result both were experimenting with high-thrust propellants and seeking protection for technicians and crews exposed to these toxic substances. Consisting mainly of hydrazine compounds (MMH), the fuels, shown through accidents in handling, proved to be convulsant at relatively low exposure doses via any route and fatal at higher doses. During the early Apollo orbital flights during a debriefing a number of the astronauts reported, that natives on Pacific Islands waved to them as they went overhead. Since that was technically impossible, it caused concern about the possibility that fumes were leaking into the cabin and disturbing cognitive functioning. The U.S. Air Force initiated a scientific program to determine the biochemical mechanism of this toxicity and to search for protection and post-exposure treatment in the case of accidental exposures. They also became particularly interested in the possible performance consequences of low-dose exposure in crew members while in flight.

During this time, Gordon Alles was contracted to test toxicity of this MMH rocket fuel – together with David Fairchild. However, in Jan-

uary 1963, Gordon Alles died after having returned from a Tahiti trip to investigate the traditional Kava roots as a source of new tranquilizers. The cause of death was ironically, diabetes, of which he was unaware, and for which he had developed the drug that treated it: insulin. The fortunate aspect of this was that Fairchild asked Sterman to help him finish the work on MMH. Sterman and Fairchild started evaluating MMH in more detail in cats through studies of sub-convulsive exposures. It was their practice at the end of a given experiment, if necessary, to re-use those animals where needed.

Accordingly, Sterman entered the cats from the SMR sleep study into the MMH study. To Sterman's surprise, the three animals that were previously conditioned to produce SMR during the sleep studies were resistant to the seizures, albeit they did demonstrate the prodromal symptoms of MMH such as restlessness, vomiting, vocalization, panting and salivation. Somehow, the SMR training had increased the threshold for the MMH inducing a seizure. [55] The evidence of decreased motor excitability during SMR was consistent with these findings. Furthermore, these serendipitous findings were made more than three months after the sleep study mentioned earlier, also demonstrating the lasting effects of the SMR neurofeedback.

But would this procedure also possess anticonvulsant properties in humans? Sterman recalled how he made the actual step from the cat study to his first human case: *"...We had already seen the positive therapeutic effects on seizures in cats of SMR neurofeedback, so we had during those years a work student program, so students who couldn't afford college were allowed to be paid for working in laboratories, and the one that came into our lab was a young lady. She was very capable, but she happened to be an epileptic. And that was Mary Fairbanks. She was actually doing all the coding. She was a student. Mary, she was in the lab, and we ran her systematically...it actually took five years for her seizures to stop completely..."* Mary Fairbanks was 23 years old while she worked in Sterman's lab. She was epileptic since she was sixteen years of age and experienced on average two seizures per month but had meticulously kept a log of her seizures for eight years prior, which proved to be valuable in what was to come. While she had not benefited from comprehensive evaluations at two prestigious institutions, nor from

anticonvulsant medications, an unequivocal cessation of her Grand Mal Seizures was documented during the first three months of SMR feedback training. Her overall seizures were progressively reduced during the next two years of treatment, resulting finally in her being issued a California driver's license in 1975. SMR training took place on a device again built by Sid Ross on a bipolar recording channel comprised of one of the (needle) electrodes at FC3 and the other at CP3. The journal Electroencephalography and Clinical Neurophysiology, was at that time considered one of the main EEG journals (nowadays this journal is called Clinical Neurophysiology), and they published it after one week of submission. *"...The editor read it, send me a letter and that was that..."* Sterman recalled.

As a result of these findings, comprehensive long-term studies were launched by Sterman's team and others to evaluate the potential protective effects of SMR training for human epilepsy, see Figure 19 for a great mechanistic example. Early replications of the anticonvulsive effects of SMR neurofeedback were done by Finley [56] and Seifert and Lubar. [57] In a 2000 review article, summarizing the literature on SMR neurofeedback, Sterman found that 82% of patients treated demonstrated a significant (>30%) seizure reduction, [58] also supported by a later independent meta-analyses. [59]

As a remarkable twist of history, it thus turns out that the inventor, Gordon Alles, of the most widely used drug treatment for ADHD, amphetamine derivatives such as Ritalin, was also instrumental (by absence) in the discovery of the non-pharmacological treatment SMR neurofeedback, that eventually would also have its main use in the treatment of ADHD.

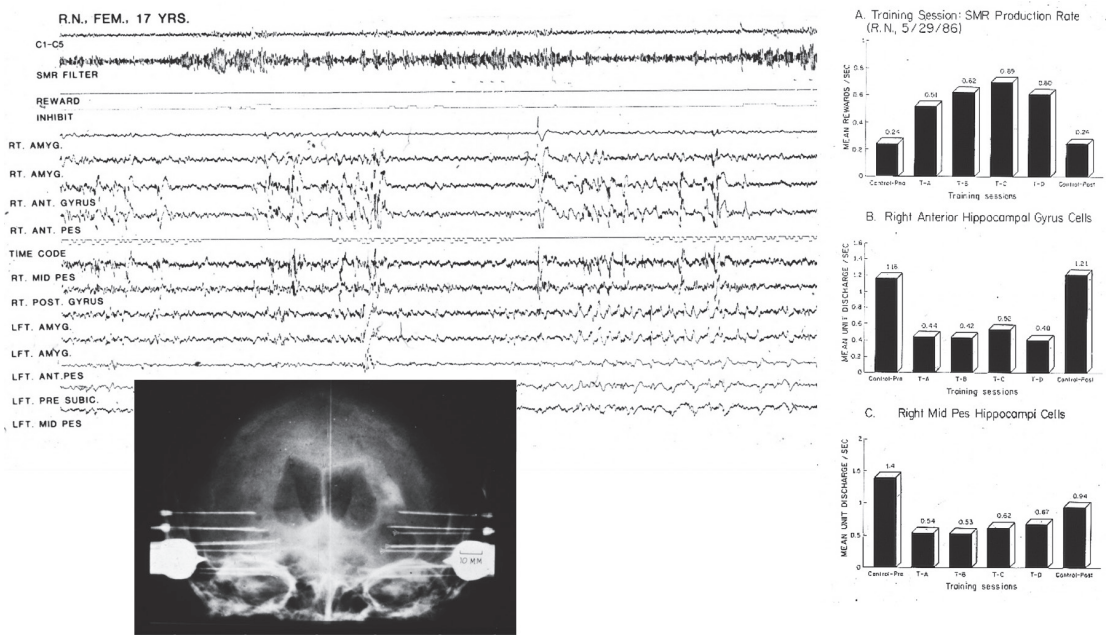
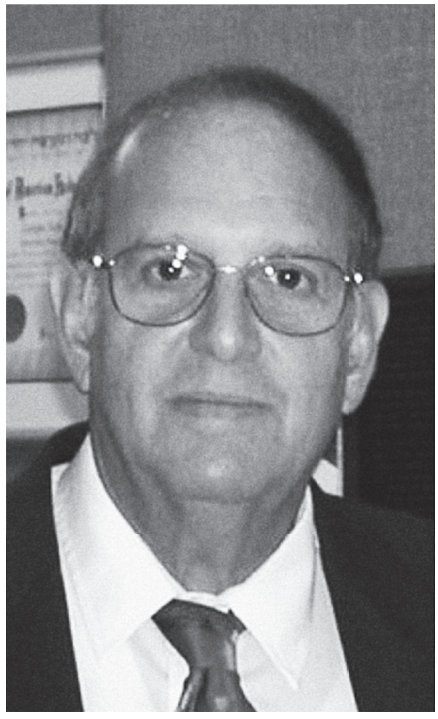


Figure 19: *Compound figure showing placement of monitoring electrodes in limbic brain sites for monitoring spontaneous interictal discharge in a partial complex epileptic patient, together with rewarded SMR and EEG activity. Note cessation of interictal discharge during appearance of SMR bursting in relation to their facilitation shown in training profile at right (Unpublished data, Sterman).*

JOEL LUBAR

In 1975 Joel Lubar from the University of Tennessee (Knoxville) applied SMR neurofeedback in six epileptics of whom five demonstrated a marked seizure reduction, [57] thereby replicating Sterman's earlier work. This led Lubar to apply for a grant and in 1976 Lubar spent nine months at Sterman's lab on a National Science Foundation grant, where he learned directly from and worked with Sterman and where the foundation was laid for the application of SMR neurofeedback in hyperkinetic syndrome, a condition closely resembling what is now termed ADHD.

After having worked with several seizure patients who were high



school or college students, Lubar observed improved concentration and attention in some of these patients. In 1976, Lubar (*left*) together with Margaret Shouse [60] then described the successful application of this technique in a child with hyperkinetic syndrome. In this initial study, Lubar also demonstrated that when the contingencies were reversed, where SMR was inhibited and 4-7 Hz theta was increased, the child demonstrated a gradual behavioral deterioration, which was normalized again when the original contingencies were re-instantiated. Several years later, these findings were replicated in a larger study, [61] whereby the foundation for SMR neurofeedback in the application of ADHD was laid.

Lubar was initially inspired by the work of Satterfield, often referred to as the *'low-arousal hypothesis'* of ADHD. This hypothesis is actually quite similar to the more recent work on EEG-vigilance applied to ADHD, [62] where the impairments in attention are a result of the low-arousal or low vigilance, and the hyperactivity can be seen as a compensatory behavioral response to keep awake, maintain vigilance or increase arousal (also termed vigilance autostabilization behavior). Lubar reasoned that resting state EEG activity comprised alpha and theta, and when the brain is activated by for example a cognitive challenging task, it shifts towards beta activity above 14 Hz. He thus reasoned that children with ADHD would be less able to produce this >14 Hz activity and have relatively more of the 4-8 Hz theta activity [63], and thus conceptually the Theta/Beta ratio was born. [64] As part of Lubar's clinical work in his clinic that he initiated since 1976, he observed that the more inattentive children were exactly characterized

by what he had conceptualized before, characteristic excess 4-8 Hz theta and deficient in the production of beta activity. After several studies where Lubar compared children with and without ADHD, he eventually got together with Vince Monastra and proposed the ratio of Theta over Beta (Theta/Beta Ratio, TBR) as an 'attentional index.' This TBR showed a strong association with age, with the TBR decreasing when children are older; a significantly higher TBR in patients with attention deficit disorders, and when applying a cut-off based on the non-ADHD sample a high sensitivity and specificity for identifying patients with attention deficit disorders. [65] This TBR was most often classified at the vertex (Cz) or frontal (Fz) locations. Subsequent neurofeedback studies also employed this TBR neurofeedback protocol in the treatment of ADHD, where 4-8 Hz is down-trained and at the same time 13-21 Hz is rewarded.

Note that the above implications, suggestive of a specific effect of SMR neurofeedback on hyperactivity and of TBR neurofeedback on inattention, was mostly based on Lubar's clinical observations and clinical work. To date, these differential effects have not been demonstrated in larger controlled studies and overall SMR and TBR neurofeedback have comparable effects on the domains of inattention, impulsivity and hyperactivity. [51,66]

CHAPTER 8:

DISCOVERY OF SLOW CORTICAL POTENTIAL NEUROFEEDBACK AND THE TÜBINGEN GROUP

In parallel to the historical development of SMR and alpha related *'frequency'* neurofeedback or Alternating Current (AC) Neurofeedback at the end of the 1960's, another parallel development took place with its roots in those same years, namely that of the discovery of Slow Cortical Potential (SCP) and the first demonstration that such potentials (more specifically the *'Contingent Negative Variation'* or CNV) could be brought under voluntary control as was demonstrated in 1966 by McAdam and colleagues. [69]

Two years earlier this brain potential was first described by William Grey Walter. In 1964, Walter described that beyond the traditional ERP components, there was also a *"...much more prolonged surface negative component which may last several seconds, particularly in children..."* [70] Walter termed this phenomenon the 'Contingent Negative Variation' or in short CNV, due to its dependence on the statistical relationship between the conditional and imperative stimuli. The CNV would mainly be observed during an interval where an individual is attentive and waiting to respond (often also explained as waiting in front of a traffic light for the red light to turn green), which

was actually better captured in the term Hans Helmut Kornhuber assigned to this phenomenon one year later, who termed it the 'Bereitschaftspotential' or 'Readiness Potential', which he observed in response to action preparation. [71,72] Walter furthermore described several requirements in order to measure these slow oscillations reliably, such as the use of non-polarizable electrodes (in today's terms that implicates Ag/AgCl or sintered electrodes) and directly coupled amplifiers (DC Amplifiers), which basically implicates amplifiers that have no high-pass filtering applied in the hardware.

These CNV's are much slower than most of the traditional frequencies described up to that moment and thus considered part of the family of Slow Cortical Potentials (SCP's). These SCP's are more referred to as slow oscillations or the Direct Current (DC) component of the EEG, and do not adhere to specific frequencies. The CNV for example, is visible during a 'wait interval' and will remain present during that interval, whether the interval is three or six seconds. Therefore, these are better described by their polarity. In the case of SCP Neurofeedback, feedback is thus not provided only based on the amplitude or power of a given frequency band, but more on the polarity of the slow EEG content, e.g. surface-positivity or surface-negativity. As we have seen above, McAdam and colleagues demonstrated in 1966 already that the CNV could be brought under voluntary control. However, years later this was picked-up more systematically by Thomas Elbert, Werner Lutzenberger, Brigitte Rockstroh and Niels Birbaumer [73,74] as well as Herbert Bauer and Wolfgang Lauber [75], who pioneered the first published studies on voluntary control of slow cortical potentials (SCPs) employing a biofeedback procedure. Interestingly, Herbert Bauer had already worked with Niels Birbaumer before at Rohracher's lab, suggesting Rohracher's lab to have been fertile ground for the development of SCP applications.

Birbaumer's group was inspired by the possible implications of these SCP's for epilepsy, based on the observation that pro-convulsive procedures such as hyperventilation resulted in increased surface-negativity and anticonvulsants resulted in decreased surface-negativity. Among other studies, this SCP procedure was investigated in drug refractory epilepsy patients in a double-blind placebo controlled de-

sign. In this study SCP neurofeedback was compared to alpha-power neurofeedback, and only the group who received SCP neurofeedback demonstrated a significant reduction in seizure frequency. [76] In order to understand the historical context about this SCP neurofeedback better, in the following we will talk more about Niels Birbaumer.

NIELS BIRBAUMER

Niels Birbaumer, born in Ottau, Czechoslovakia in 1945 just three days after the end of the second World War, spent most of his youth in Vienna, Austria where his parents ended up after they fled from Czechoslovakia. In his teenage years, Birbaumer was member of a teenage street gang in Vienna and at a specific moment at the age of 15, Birbaumer was arrested after having stabbed a scissors into a competing street gang member's foot who stole his sandwich. After this incident his dad picked him up from the police station, he threatened to force him to start working as an upholsterer, and actually had him work at an upholsterer's workshop. This made the young Birbaumer realize that staying in school was a better alternative. In addition, he made a deal with his father that he changed schools and by this internal realization as well as change of environment, was able to flourish and deviate the course he was on or as he stated in his book 'Your Brain Knows More Than You Think': *"...I was able to break out of the gang and eventually graduate..."* This initial event demonstrates a central point in Birbaumer's thinking, about the capacity of our brains to change, adapt and reorganize, rather than accepting the notion of the brain as a fixed system, and thus individuals as 'unchangeable', such as for example the psychopath that should be locked behind bars forever, or the locked-in Amyotrophic Lateral Sclerosis (ALS) patient whose will should be willfully executed, without accepting the notion a patient might have different experiences and thoughts at this moment. As we will see, this notion of the capacity to change, has been a central theme in many of Birbaumer's research studies he would embark in later, and provide very valuable insights.

In later years, Birbaumer discovered his passion for literature, and while having attempted to study the German language and literature, he decided *"...It was a catastrophe. Boring..."* Of great importance for his career was the compulsory lecture *'Introduction to Psychology'* by Hubert Rohracher. Rohracher was a psychologist, but an anti-Freudian and positivist and read about brain and behavior. That impressed Birbaumer (*pictured right*) and he left German studies and switched to psychology as his main subject. Rohracher – who would eventually become Birbaumer's mentor – was an early EEG pioneer and his first EEG works can be traced back to 1933, just years after Berger. In 1944, Rohracher discovered microvibrations in muscles, which were weak mechanical vibrations in the body surface with the limbs in a totally relaxed state and he observed the vibrations were in the 8-12 Hz range, since then replicated by many researchers. Since these microvibrations only occurred in warm-blooded animals he reasoned these microvibrations must play an important role in maintaining a constant body temperature. Furthermore, it would help keep the body musculature in a constant state of readiness, thereby making possible rapid motor responses. Noting the remarkable similarity between these 8-12 Hz microvibrations and the 8-12 Hz EEG alpha rhythm, implied a possible causal connection according to Rohracher, which however never got substantiated by empirical data. The International Congress of Psychology in Paris in 1937 was one of the few congresses where Hans Berger was actually present, and Rohracher and Adrian were also present at that conference. According to Birbaumer, they had a big discussion there, where in line with the above reasoning of microvibrations, Rohracher reasoned that alpha was related to the metabolic activity of the brain to keep itself warm, which was a mechanism to keep the metabolism in the brain going and keep the brain warm.

While at Rohracher's lab in 1969, Birbaumer had to come in every morning at 7:30, wear a white coat as a doctor, and open the door when the professor came in, open a lift door, and go to his room without saying anything and then the professor would give Birbaumer orders. One day Rohracher gave Birbaumer the assignment, *"... you have to find out thinking in the EEG..."* Birbaumer thought *"what?"* Rohracher said, *"...I give you a sentence... 'THINKING NEEDS*

TIME'... and I want you to do these experiments that you get a read-out of the EEG pattern and decode these words..." Birbaumer wanted to comment, but chuckled his words, because at that time you didn't question what the professor asked. The only machine they had at that time was Grey Walters EEG machine, which produced enormous heat, but also produced frequency spectra. So, since Birbaumer was not allowed to discuss the impossibility of the assignment with Rohracher, he went to the basement where the machine was located, knowing it would never work, he did the experiments. After half a year, Birbaumer went up to Rohracher and said: *"...Herr Professor, I'm very sorry but it didn't work..."* Rohracher responded angry, *"...what, it didn't work? I bought you that amplifier that you wanted, and you cannot even show me these sentences in the EEG?..."* And Birbaumer said, *"...I'm sorry, I cannot do this..."* Then he punished Birbaumer and said, *"...from now on you will only do microvibration research. If you cannot see the thinking in the brain, we'll try to find it in the muscles..."*

Retrospectively this turned out to become the exact question Birbaumer spent most of his life on solving, even to this date, trying to decipher someone's thoughts from their brain activity, or a brain computer interface (BCI) as we know it today.

When the roaring 1960's were in full swing and the student movement arrived in Vienna in 1969, Birbaumer was among those who agitated particularly aggressively; teach-ins, protest notes, political events, that were tolerated by Rohracher. However, when Rohracher retired in 1969, Birbaumer was fired by one of the less tolerant senior assistants. Thereby his chances of getting into any German speaking university were gone, which made him decide to work in the department of psychiatry in Middlesex Hospital in London in 1969-1970, where he learned behavioral therapy and did treatment of obsessive-compulsive disorder patients and neurosis. Then in 1970 he came back to Germany as an assistant professor at University of Munich, and in 1975 he accepted the position as professor of Clinical and Physiological Psychology in Tübingen, where most of his pioneering work on Slow Cortical Potentials, neurofeedback and brain computer interfaces started.

SCP NEUROFEEDBACK

Being not very impressed with the types of control conditions that were used in the early alpha and theta studies, Birbaumer conducted a series of studies on theta neurofeedback in the 1970's. In the first neurofeedback studies he published in 1975 he failed to find an effect of contingent feedback on theta activity [77], followed-up by a 2nd study in 1976 where he added heart rate and EMG biofeedback prior to the theta neurofeedback, that was partially successful. The first initial motivation to investigate biofeedback of Slow Cortical Potentials (SCP) was based on the observation of a build-up of negativity in the EEG prior to a seizure. This was the primary motivation of the Birbaumer group at that time to embark on this form of neurofeedback, albeit it took until the 1980's before that work was published, with the first publication on SCP neurofeedback and epilepsy in their 1982 book "Slow Brain Potentials and Behavior." [78] *"...Each patient took about 40 sessions, they had untreatable seizures, and a treatment took about 1-2 years, hence it took so long to collect enough data to have something that would be publishable..."*, Birbaumer recalls about the time it took.

The first study in the scientific literature on SCP neurofeedback applied to drug refractory epilepsy patients using a double-blind controlled design. In this study, SCP neurofeedback was compared to alpha-power neurofeedback, and only the group who received SCP neurofeedback demonstrated a significant reduction in seizure frequency with six participants having longer seizure-free periods (as summarized in: Rockstroh et al. [76]). In 2001, these results were further confirmed in a larger study by Boris Kotchoubey in the journal Epilepsia [79], where SCP neurofeedback resulted in a similar and significant decrease in seizure rates compared to anticonvulsant medication, whereas no effects were found for a semi-active control condition of respiration biofeedback. SCP resulted here in an on average 30% reduction in seizure rate, and these effects were maintained during 10 years follow-up, as well as the ability to self-regulate SCP's in the desired direction! [80]

With the results noted above one would have expected this technique to be more widely adopted in neurology, which is still not the

case to this day. The main issue is most likely that the neurologists do not come from a *'learning'* background and cannot understand how a procedure like SCP Neurofeedback can help an epilepsy patient, whereas a psychologist is not specialized in epilepsy and has more difficulty using equipment in treatment. Furthermore, neurofeedback has for long been surrounded by criticisms as well, sometimes correctly so, but often not for the right reasons. At one moment, Birbaumer was faced with such a critical doctor, Valentino Braitenberg, who was director of the Tübingen Max Planck Institute, a very intelligent man. He did not believe that SCP Neurofeedback had any effect in the treatment of epilepsy. Birbaumer said, *"...OK, c'mon, let's train. So, we trained negativity instead of positivity and he got a seizure. And he said never anything critical about neurofeedback in his live anymore... He never had epilepsy, never, and afterwards also nothing. So, it was really caused by the SCP neurofeedback..."* This also clearly demonstrates that if a treatment is effective, such a treatment can also have side effects.

The first published studies in the scientific literature on operant conditioning of SCP's in healthy volunteers were published by Thomas Elbert [73] and Werner Lutzenberger. [74] In these early studies, before the more clinical studies, they investigated what the SCP actually reflected in a more causal way, confirming whether the cortical negative shifts were indeed seen to reflect expectancy, attention, conation, motivation, and response preparation and cortical positivity as relaxation processes. [73] They reasoned that if they could teach someone operant control and thus manipulate the SCP's, they could more causally address the functional meaning of these potentials. In Figure 20, the original feedback screen that was used in the 1970's for the visual feedback is shown, and it bears a high similarity with current screens still in use to date for SCP neurofeedback, except the *'rocket'* being changed to a fish.

In the study by Lutzenberger, [74] a yoked control and a real SCP neurofeedback group were used, and they concluded that a shifting of cortical potentials *"...facilitates attentional processes..."* That same group actually further investigated the link with attention in children with attentional dysfunctions and found they could learn SCP

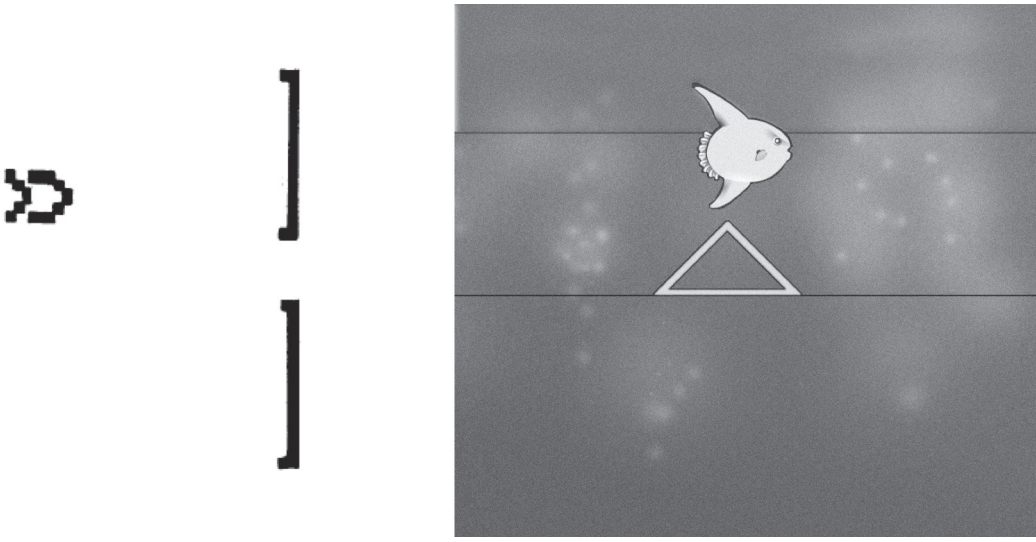


Figure 20: *The original feedback screen used in the first SCP studies (left) and the feedback screen that is still used to date in the NeuroPrax SCP software (right), showing a striking similarity, maybe also related to the high consistency of clinical effects reported for SCP neurofeedback.*

control when feedback was provided, albeit this study did not investigate the clinical effects of the SCP neurofeedback. [81] As these first studies already highlighted, making changes in attention turned out to become one of the major uses of this specific neurofeedback protocol, namely in the treatment of Attention-Deficit/Hyperactivity Disorder or ADHD.

SCP NEUROFEEDBACK IN ADHD

It was not until 2004 that the first report emerged of SCP Neurofeedback applied to ADHD, by Hartmut Heinrich and Holger Gevensleben from the University of Göttingen [82], who were encouraged by Aribert Rothenberger to initiate the neurofeedback studies at that time. Heinrich reasoned that in ADHD a typical deviating neurophysiological signature, namely a diminished Contingent Negative Variation (CNV) was observed. This CNV is basically an SCP in response to an attention demanding continuous performance task

(CPT) and reduced negativity was observed in ADHD. In addition, Heinrich reasoned that ADHD is also characterized by impaired self-regulation skills, hence in his 2004 pioneering study he confirmed these ideas. [82] After 25 sessions of SCP neurofeedback he demonstrated not only behavioral improvements on inattention, hyperactivity and impulsivity but also that the neural signature that initially inspired him, a reduced CNV, also normalized after successful treatment. Eventually this work was followed-up and replicated further by Ute Strehl from the Tübingen group, and both Heinrich's [83] and Strehl's groups [84] have published independent multicenter randomized controlled trials demonstrating the efficacy of SCP neurofeedback in the treatment of ADHD, making this protocol currently the most well investigated neurofeedback approach in ADHD. In addition, Strehl and colleagues also published the longest follow-up results for neurofeedback in the treatment of ADHD after two years, where clinical benefit was not only stable, but had improved further – without additional sessions carried out in the mean time – and children were still able to self-regulate their SCP's in the desired direction, [85] similar to what was found in the epilepsy follow-up. In this study results applied both to SCP neurofeedback as well as to Theta/Beta neurofeedback, as initially described by Joel Lubar.

Accidentally, Birbaumer's path already crossed with Joel Lubar even before either of them got interested in neurofeedback. Lubar was a biological psychologist and an animal researcher at the University of Tennessee. Since Birbaumer at that time was writing a German textbook about biological psychology and was inspired by Lubar's textbook on physiological psychology, he visited Lubar in Tennessee. Birbaumer wrote him a letter and said: *"...I'm writing a book on physiological psychology and I want to hear how you arranged this, that's how I met Joel. And later on, it turned out he became a biofeedback guy..."*

BRAIN COMPUTER INTERFACES (BCI)

Brain Computer Interfaces or BCI's, are conceptually rather similar to neurofeedback. The main difference being that with neurofeedback the main aim is to remediate clinical symptoms of a specific disorder, whereas with a BCI application the primary goal is to use the technology as a Brain Computer or Brain Machine Interface, to re-establish communication with a patient that for example has locked-in syndrome as a result of Amyotrophic Lateral Sclerosis (ALS). These patients progressively lose all control over their musculature while leaving the sensory tracts largely intact, hence the term 'locked-in' (although other disorders can also cause a 'locked-in' state, such as a stroke). These patients thus can perceive everything around them (mostly sensory and auditory, given they have lost control over their musculature and thus eye lids also prevent the eyes from being moistened, and thus mostly the eyes are closed).

Where in SCP neurofeedback a patient is taught voluntary control over his Slow Cortical Potentials, i.e. at will demonstrating positivation or negativation, in a BCI application this voluntary control can thus be used to communicate. In its simplest form, negativation implies 'yes' and positivation implies 'no.' More complex letter-selection schemes also exist, where patients can select various letters on a screen, where half of the letters are assigned to 'positivation' and the other half to 'negativation' and after a first selection step, the remaining letters are split in half again. A BCI thus not (yet) provides a literal read-out of the brain, but the principle of voluntary control provides a means of control. In earlier stages of the disease when some muscles can still be used, simpler forms of BCI are most often used, such as eye movement.

In order to understand and place some of Birbaumer's work and views into the right perspective, the influence and research of Neal Elgar Miller is crucial.

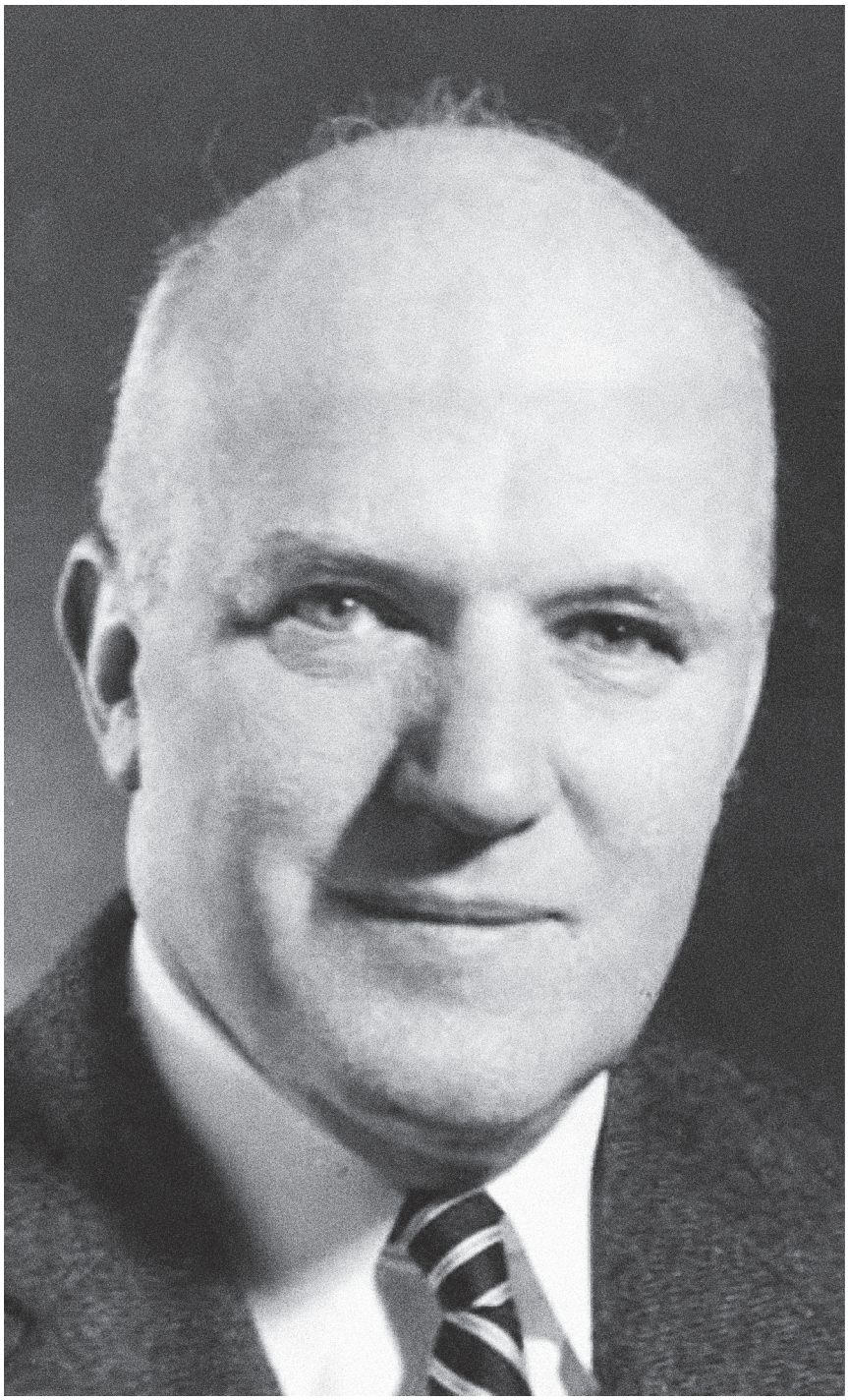
THE EAST-COAST EXPERIENCE AND THE VIENNA CONNECTION:

NEAL E. MILLER

Miller (*facing page*) studied psychology at University of Washington and continued for his master's at Stanford University in 1932 where he worked with Lewis M. Terman, the famous IQ researcher. There he further followed the topic of experimental psychology with Walter R. Miles, who would eventually invite him to pursue his doctoral work at Yale. While at Yale he worked with Clark L. Hull who infused him with the principles of Pavlovian classical conditioning applied to Thorndike's trial-and-error learning, verbal learning and higher mental processes. Similar to Sterman, Neal was intrigued by Pavlov's concept of internal inhibition and noted a similarity with Freud's conception of repression. As a result, Miller obtained a postdoctoral fellowship to actually study in Vienna at Freud's Psychoanalytic Institute where he underwent a didactic analysis with one of Freud's students Heinz Hartmann. In 1935 he supposedly *"...long regretted he had turned down at least one analytic session with Freud himself because an hourly $ 20 fee, for which Freud in a letter apologized as necessarily high to support his own family, seems more than Neal could afford..."* (From: Coons [86]).

Later, back at Yale, Miller continued his research and among other things proposed the 'drive-reduction hypothesis' together with Hull. During the second World War Miller served as a captain and later major. After the war he returned to Yale and in the early 1950's his interest in psychophysiological interventions was awoken, thereby being able to further investigate the drive-reduction hypothesis of reinforcement in greater detail, by investigating differentially the rewarding effects of food offered directly or indirectly via stomach fistula, thereby bypassing the taste and swallowing sensations. In 1966 he moved to Rockefeller University.

Later, in the 1960's Miller posed the notion that autonomic responses



– contrary to the notion of 'autonomic' – could be conditioned, and thus rather than 'autonomic' could be conditioned into 'voluntary' responses. To that date, internal physiological processes controlled by the autonomic nervous system were regarded as operating beyond conscious awareness or control, and thus not be subject to operant conditioning. In those early days it was thought that the autonomic nervous system would only be subject to Pavlovian conditioning, not operant condition, whereas only the skeletal responses could be operantly conditioned. Therefore, this line of thinking was quite a deviation from the traditional beliefs at that time.

In a first experiment Miller demonstrated that thirsty dogs could be trained to increase or decrease their autonomic salivation response, as a result of reinforcement with water. However, they also noted the dogs used specific postures in either condition, causing him to wonder if these motoric observations mediated the conditioned response. In order to rule these out he expanded on his famous experiments on curarized rats. Curarization implicates the exposure to curare, the poison formerly used by South American indigenous people on arrows, that completely paralyzes voluntary muscles by blocking the nicotinic acetylcholine receptor, leaving autonomic visceral muscles intact. During such a state it can be excluded that any influence over the biofeedback applied is mediated by the motor system or the muscles. Miller reported initially successful operant conditioning of different types of autonomic functions (by using as a reward electrical stimulation of the medial forebrain reward centers in the brain), such as heart rate, blood pressure, intestinal activity, but also the EEG. In an extreme example they even demonstrated that a conditioned rat, could increase blood pressure in one ear while at the same time decrease it in the other ear. These initial results fueled the biofeedback community and opened up almost unlimited opportunities for biofeedback, such as treating vascular issues, arrhythmias etc., simply by biofeedback. Since his results implied the motor system was not a requirement for the operant response that was learned, it was primarily the autonomic system that could be conditioned by itself.

In the early 1970's, Niels Birbaumer, impressed by Miller's early work, traveled to Miller's lab at Rockefeller University at 1st avenue in order

to learn more from him on his curare work. They had an immediate click after having exchanged experiences about Vienna, where Miller had studied with Freud's group and where Birbaumer did his first studies with Rohracher. Birbaumer saw many labs and experimental setups but did not see any of the famous setups where the curare experiments were performed. After asking about those labs, he would often get deviating responses and eventually was told by Miller the responsible post-doctoral student was not there, so he could not show him the curare experiments. During that visit Birbaumer also met Barry Dworkin, with whom he developed a close collaboration on the treatment of scoliosis among others. At that visit, Dworkin shared with Birbaumer they had problems with the replication of the curare experiments, and in the decades to come, Dworkin spent much of his time trying to replicate the earlier curare experiments throughout the 1960's to 1980's but failed to replicate the earlier findings. In the early years some replications were published, but all subsequent replications showed a diminished effect, also visualized in the Figure 21, from Dworkin and Miller's publication *'Failure to Replicate Visceral Learning in the Acute Curarized Rat Preparation.'* [87] Here an almost linear decrement of effect over the years of publication is visible, reminiscent of what is currently very well known as the 'winner's curse', where for example in genetic studies early studies find large effects, and subsequent studies find diminished or no effects anymore. A similar effect was published for the Theta/Beta ratio as a differentiator between ADHD and non-ADHD populations, see right Figure 21. So actually, we could consider this unfortunate finding of Neal Miller the first example of this winner's curse.

However, the implications of the non-replication of Miller's work, are still felt today and puzzling researchers including Birbaumer: *"... This is crucially important for the paralyzed people I have here, if this is true and you cannot instrumentally condition any physiological variable, without the muscular system, this was the question of Neal Miller, then if you treat the brain as guts, the guts produce feces, but the brain produces thoughts as 'feces', but if this is true then biofeedback in the sense of an instrumental conditioning without the muscular system cannot work, never. That is the danger here on the horizon. And nobody since then who have tried to replicate it, nobody could. Barry Dworkin gave up, and*

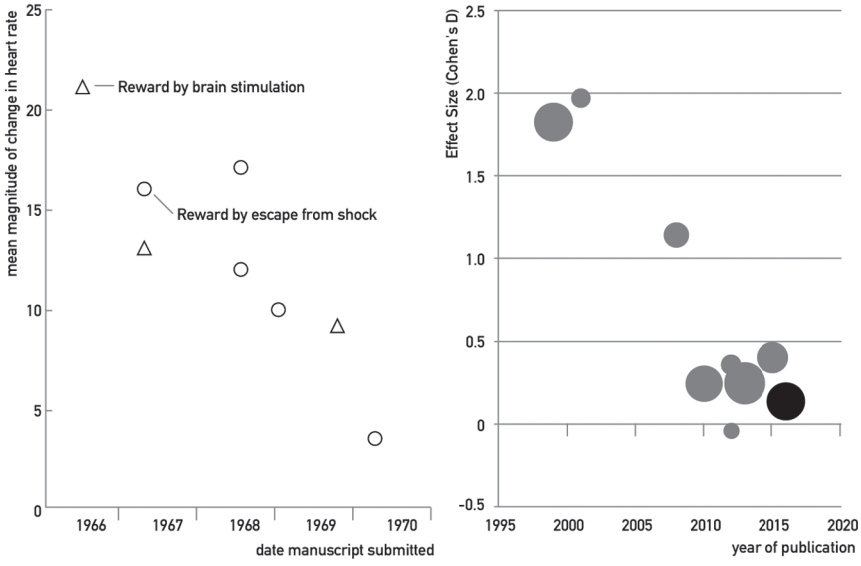


Figure 21: *Left figure from Dworkin and Miller (1986)* [87] *and right figure from Arns and colleagues.* [67] *Left figure from Dworkin and Miller demonstrates how the change in HR as a result of conditioning in the curarized rat diminished over the years, eventually resulting in non-significant effects. On the right we see a similar trend, here for Theta/Beta ratio (TBR) as a differentiator between ADHD and non-ADHD samples, where the effect size diminishes significantly over the years. This effect has also been dubbed the 'winner's curse', where sometimes, large effects diminish over time. Sometimes such effects can be explained (e.g. in the TBR case by children sleeping less in 2010-2015 compared to 2000), at other times, it can be considered a true 'winner's curse', what the exact cause was in the Dworkin and Miller case is, remains unknown to this date.*

after 20 years trying to replicate it, he was fed up with it, ... It means that if we want to do instrumental learning of the internal organs, maybe the brain, we need an intact muscular system. If this is true, then everything we do here, spending millions and millions of dollars on implanting electrodes in completely paralyzed people will never work, never. This is the danger, and I can tell you in two months. That means everything we do in neurofeedback, like in epilepsy, hyperactivity, we train a – I shouldn't say muscular – we train a postural or muscular pattern, which maybe invisible, maybe very small, but we train something somatic and that is transferred to the brain and changes the brain and then you get the effect you get with hyperactivity. That is possibility number one, but possibility number two is that the brain is not a 'feces' producing organ,

which I have my doubt, but if it is not, but only part of it is somatic, like the motor system and the other part is not, then the question is, can the non-somatic part of the brain learn like you and I want, and the answer from Neal's experiment I think is No, it is not, it means the motor system has to be intact, in the brain, but with an intact motor system in the somatosensory system in the brain you can affect the internal organs, and then you can also train heart rate, blood pressure etc. whatever you have, by activating the motor system. That answer, to that question, even if it doesn't work in my patient, I don't have an answer to, because in ALS the motor system is destroyed, but not completely. So what's happening what I see, when I put an electrode in a completely paralyzed person's brain, which we do now, you see a completely normal cellular activity. At the level of the apical dendrites, oscillations, action potentials, but at the axonal level there is nothing coming out. That is why they are paralyzed. So even if it works, or if it does not work, I cannot answer the question which Neal Miller asked, to prove that neurofeedback is possible. Because even Neal, we became friends, at his death bed he said, of course it is possible, neurofeedback he says, or instrumental learning of cellular responses or anything in the brain is possible. It functions the way as Skinner said. But other people like Ed Fetz who did the first cellular conditioning in the monkey with neurofeedback, says, without the motor system, nanana... it doesn't work, but he didn't prove it. So, this is a difficult question..." For neurofeedback itself, clinically speaking this should not have a major impact, but from the mechanistic point of view and especially the application of BCI in completely locked-in patients this is a fundamental and important question.

On the other hand, some fear the data from those initial experiments were simply fabricated by Leo Dicara who at that time conducted those studies. One of the other researchers involved at that time in Miller's lab with the replications, Dr. David VanDercar stated about this: *"...That first year I was with Miller, DiCara – who carried out the original studies – was still there, so I asked him for help in duplicating his experiments. But DiCara refused to give me any assistance. Then I asked for the data on the research and he said it was lost... The only way we could get any help from DiCara was for Miller to pressure him into demonstrating the technique.... How he did it. Even at that, he only spent four hours of one day doing this and it was unsuccessful... Last*

summer DiCara... who in the meantime had gone from post-doctoral to assistant professor to associate professor to full professor on the basis of these studies... went to the shredder and fed into it all of the work he had ever published and then went home and committed suicide..." (The Evening Independent, October 3rd, 1977). Although there has been no official report as to the reason of his suicide, this has fueled speculations about the scientific integrity of DiCara, however, with his suicide, he took the mystery to his grave and to this date it is still a mystery if the initial findings were real or not. Furthermore, at one moment, according to Birbaumer and Sterman, Miller was even shortlisted for a Nobel Prize for his discovery. However, the controversy that had arisen most likely prevented that from happening.

Patients in varying stages of ALS thus have been able to learn to control and use a BCI, however, most patients that were already in the completely locked-in state without any remaining muscle twitch or remaining motor control when starting BCI training, were unable to learn any voluntary brain control. Limited success has been reported for a pH-value based communication device using the acidity value or pH-value of the mucous membrane in the mouth using mental imagery of drinking a glass of milk versus drinking lemon juice as a binary yes-no classifier. However, the question still remains; is this the inability to learn in the locked-in state, as explained above by Birbaumer, or is this simply a limitation of the BCI technology not being specific enough?

Based on these observations Birbaumer has proposed the *'goal directed thought extinction hypothesis'*, which states that all directed, output oriented thoughts and imagery extinguishes in the complete locked-in state because no reliable contingencies exist in the environment of a completely locked-in patient. Any particular thoughts related to a particular outcome such as *'I would like to be turned around'* or *'I would like to see my friend'*, are not followed by the anticipated or desired consequence. Therefore, extinction in the conditioning sense takes place, within the first weeks or months of the complete locked-

in state. Such a negative learning process can only be abolished, and voluntary, operant control can be reinstated if reliable contingencies re-occur. This *'goal directed thought extinction hypothesis'* is further supported by the failures to replicate Neal Miller's earlier work as was explained above. Therefore, Birbaumer generally recommends early initiation of the BCI training before a patient enters the completely locked-in phase.

Thus far, the longest someone has been able to use a NIRS based BCI, is for more than a year: *"...one day of the week the husband of one of my patients asks her questions and they can communicate in a yes-no fashion, she cannot formulate anything. No one has come beyond one year of successful BCI communication..."* One interesting observation Birbaumer has done is that when people learned to control the BCI at a late stage of ALS, but not being fully locked-in, it seemed as if the progression slowed down, as if the BCI procedure itself had a protective effect, however, this is very difficult to proof scientifically. It will not be a curative effect, but more a protective effect on the progression of the disease Birbaumer stated. So, often the patient learns to communicate with yes and no with the EEG or NIRS and suddenly the disease progression stops. That is why he now focuses more on completely locked in patients, in such a late stage of the disease, to see if it does not progress that much, a patient can still do a lot with for example an eye tracker.

ETHICS

One interesting aspect with ALS, is that most people that would imagine themselves being in the complete locked-in state, would state that they would like euthanasia applied or life-support to be turned off. While this would make a lot of sense to many, the interesting aspect is that the quality of life in ALS patients in the locked-in state is actually very high. [88] Birbaumer has investigated this systematically using a BCI, and his results have been independently confirmed. One illustrative case described by Birbaumer is the example of Hans-Peter Salzmann, who suffered from ALS. Salzmann was a judge, and after receiving the diagnosis meticulously drew up his liv-

ing will (that stated he wished not to be artificially ventilated) that he put away in his desk drawer. At some point in time, his ALS progressed rather rapidly, and he was put on artificial respiration by the emergency doctor, who was unaware of his will. After some time, when Salzmann became aware of Birbaumer's BCI program, he enrolled in the program and he was able to establish communication using a BCI, even to such a degree he could dictate entire sentences, which even appeared in the prestigious journal Nature [89], as the first communication about an ALS patient having achieved brain-to-computer communication using the EEG, in this case SCP's. During all these 'conversations' he did not mention a single word about his living will that was still in the desk drawer for eight years! Later, when he told Birbaumer about his living will, and Birbaumer inquired if he was happy no one had found his living will, he replied: *"...Even judges sometimes get it wrong..."*, still demonstrating he had not lost his sense of humor.

This case nicely demonstrates the *'capacity to change'* as highlighted in the first part of this chapter that is so central to Birbaumer's view, that what one considered to be an immutable decision in one part of life, but completely inconceivable in another circumstance, most likely due to neuroplastic changes in the brain. The interested reader is also referred to Birbaumer's excellent book *'Your Brain Knows More Than You Think'* on this fascinating topic. Therefore, at least one important value of a BCI is to verify someone's decision in these late stages where communication is normally no longer possible.

In Tübingen the standard approach for ALS patients – with or without a living will – is that they are accepted in the clinic (the 'Haus CERES' center), however under the condition that no euthanasia is conducted within the first 12 months after artificial ventilation is initiated. If patients persist, and after 12 months indicate they want euthanasia, at least they can in such circumstances apply an ethical and humane form of euthanasia using a benzodiazepine and a dose of morphine, to put them asleep peacefully. Here it is crucial to note the alternative, that is applied in the majority of clinics and cases where ALS patients end up. According to their will they most likely have stated they want life-support to cease, causing the ventilator

machine or artificial feeding to be suspended. On the outside nothing will be noticed as a result of such a process, but if we are reminded about what ALS actually is, that all sensory pathways are intact, consciousness is intact, only the motor-control that is lacking, then we can now understand that to be a very inhumane and excruciating death, where patients actually are *consciously* dying of suffocation or starvation. This is an important aspect to consider when looking at the ethical side of locked-in-syndromes such as ALS and the use of a BCI versus active will, especially that a living will is *"...usually signed without the requisite knowledge. At the moment of signing, a signatory to a living will cannot know how he or she will feel at the time the will comes into force..."* [90]

ALPHA AND THETA REVISITED

Reflecting on the alpha and theta works and the altered states of consciousness research from the early biofeedback years, Birbaumer describes these as interesting years and mutual interest and fascination between the 'meditators' (or *'levitators'* as Sterman used to describe them) and the 'scientists.' In Birbaumer's studies he found that the meditative state was mostly characterized by theta, and thus had a similar EEG signature as is found in slow wave sleep, which unimpressed him and at some stage stopped him going to meetings such as the Association for Applied Psychophysiology and Biofeedback (AAPB) meetings, due to the lacking scientific rigor. However, recently, his interest in these early theta works is reawakened by the ALS work he did. *"...These people are completely paralyzed, one could also say completely relaxed, because their muscles are dead. So, what is the difference between a meditative state and these people with ALS who are completely locked-in? I look at these patients now for more than 30 years, and they look very similar. When you look at the EEG of a long-term locked-in patient, it looks like one of these meditators, theta, all the time theta. They can communicate, but they're not asleep. It is very difficult to define sleep in these patients, we did a huge sleep study in ALS that is now coming out, but during these theta states they are really attentive, they can communicate. But when they sleep, they have a similar sleep EEG..."* The majority of the eight ALS patients Birbaumer studied

with polysomnography demonstrated a non-fragmented sleep EEG, timed similar to normal sleep and the circadian system being intact. So, at this stage Birbaumer has left his old prejudices against the theta and meditation literature and thinks there is really something to it, albeit also noting it should be studied more rigorously.

BIRBAUMER'S VIEW ON THE FUTURE OF BCI AND NEUROFEEDBACK

About the future of BCI/neurofeedback in the light of recent developments where BCI technology has been developed further such as Elon Musk's NeuraLink and Facebook's Building 8 project that are supposedly working on the future of BCI to replace our mouse and keyboard, Birbaumer stated: *"...Socrates already said: ... the only intelligent man or the person who should run the state, has to be the philosopher. What is a philosopher? A philosopher is somebody who only talks to himself and discusses in Socratic dialectics his thoughts, so it has to be a person who is not moving but thinking dialectically, movement is no good. Sports, no good. So, where are we going? We are going in complete paralysis as a voluntary state, that is where we go. What is this NeuraLink doing, and other futuristic BCI's? What I did for it, I constructed it for the paralyzed, so at the end we will all be in bed and have this shitty BCI in our head, you don't have to move. The end of mankind as Socrates predicted is a completely thinking brain, that is all what is left, but nobody moves anymore. If you ask me, what is the use of this? I don't know, I doubt it is very useful. But why do Musk and others want to sell this? Running the computer with your brain? Give me a break, I can do that with my finger, and as long I'm not paralyzed I don't use a BCI. BCI is useful, neurofeedback is useful, and BCI is nothing else then neurofeedback. It's all based on self-regulation...."*

CHAPTER 9:

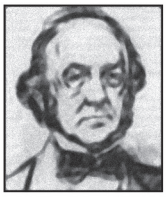
THE SUMMER OF ‘69: FROM THE BIOFEEDBACK RESEARCH SOCIETY, CLAUDE BERNARD CLUB TO AAPB

The year AAPB was founded comprised an exciting period, as eloquently summarized by Donald Moss under: The Birth of Biofeedback: 1969: *"...A new interdisciplinary paradigm emerged throughout the late 1960's, unifying developments from the diverse fields of psychology, neurophysiology, cybernetics, and medicine, culminating in a number of key publications in the final year of the decade: In 1969 Neal Miller published an article in Science on the 'Learning of Visceral and Glandular Responses.' Elmer Green was senior author for two classic articles in the same year 'Self-Regulation of Internal States' (in Proceedings of the International Congress of Cybernetics), and 'Feedback Technique for Deep Relaxation' (in Psychophysiology)... 'Biofeedback' as a model and technique was ready to be born: A scientist applies sensitive electronic instruments to provide meaningful information about physiologic processes to an animal or human subject. In turn, the subject gains greater awareness and control over the physiology and self-regulates more effectively. Bio-feedback, the providing of information back to a subject about life processes, contributes a powerful new tool for self-mastery, research, and clinical intervention..."* [91]

On the initiative of the first biofeedback meeting in 1969 that resulted in the formation of the Biofeedback Research Society (BRS) at the Surfrider Inn, in Santa Monica, Sterman recalls: *"...Joe Kamiya called me and said .'..Barry, we are doing the same work, why don't we get a group of other interested people involved and have a meeting.' And I said, great idea...when the society was formed, we called it the Biofeedback Research Society, that was the first name. I wanted to call it self-regulation, but we had a vote and most people voted for biofeedback. But there was a real well-known neuroscientist by the name of Molly Brazier. Molly was walking down the hallway one day, and she said, 'heard you've called this new society biofeedback? Well bio means life and feedback means 'returning life', you are not doing that, right? Are you?' I never liked that name. But things just happened, that's just amazing..."* Eventually, the BRS was renamed to Biofeedback Society of America in 1976 and eventually to its current name of Association for Applied Psychophysiology and Biofeedback (AAPB) in 1988, for which both Sterman and Birbaumer were great advocates.

The early meetings were characterized by an *'interesting'* combination of scientists as well as meditation guru's in white wardrobes, or *'levitators'* as Sterman likes to refer to them. This also nicely fitted the *'zeitgeist'* of the year 1969, which was the year of the Apollo 11 moon landing and Woodstock. Analogously, it was also 1969 where *'rocket science'* literally led to Sterman's first report on the clinical benefit of SMR neurofeedback for the treatment of epilepsy, and the foundation of the BRS with its strong focus on meditation and altered stated of consciousness. In a way, here the EEG and application of neurofeedback that was initiated in 1969, could be seen as the Yin and the Yang and as an excellent metaphor for the mechanistic researchers (aka the high tech *'rocket science'*) contending with humanistic meditators (aka the *'flower-power'* approach). However, this diversity would accompany the *'field of biofeedback and neurofeedback'* for years to follow and still to this date a dividing line of the hard science of neurofeedback, which has been the main focus of this book, and the more *'alternative and spiritual'* neurofeedback where *'no data is required'* and keywords are altered states of consciousness, meditation, etc.

While at an international anatomy meeting in Vancouver, Sterman and John Basmajian, while strolling through the hotel noticed a meeting room with a plaquette stating that the *'Cajal Club'* was meeting there that afternoon. They found that interesting and wanted to attend that meeting. When they showed up at the specified time and place and wanted to go into the room they were stopped and told that it was a private meeting only for members of the Cajal Club. The club was founded in honor of Santiago Ramón y Cajal, a very famous Spanish histologist, considered the pioneer of modern neuroscience due to his discovery of visualizing neurons using a Golgi staining technique. Thus, Sterman and Basmajian asked what was required to become a member of the Cajal Club. The requirement turned out to be a minimum of two publications – peer reviewed – on topics relevant to Santiago Ramón y Cajal's work. Neither of them had papers on that topic but realized that was a very intelligent way to encourage scholarship on the overall membership, and it dawned on them the same approach could be valuable to the biofeedback society as well, which was increasingly becoming less scholarly. And thus, the Claude Bernard Club was born, in honor of Claude Bernard who was a physician and the founder of the concept of homeostasis.



Claude Bernard Club

Dedicated to Excellence in Science

Claude Bernard

Figure 22: *The logo from the Claude Bernard Club, a club of like-minded researchers founded by Barry Sterman and John Basmajian.*

Interestingly, while searching online for the *'Claude Bernard Club',* almost nothing can be found about this *'mysterious club'*, except that many prominent biofeedback researchers have listed their membership of this club on their CV, including Niels Birbaumer, Gary Schwartz, Herta Flor, Thomas Elbert, Paul Lehrer, Edward Taub and Barry Sterman. After having been impressed by the beauty of the is-

land Saba, Sterman organized the first Society for the Advancement of Brain Analysis (SABA) in 2001. The name of the organization having been made up to match the name of the island. SABA continued for 16 years and was an effort to have a good scientific meeting in a place that people could enjoy, with overall high caliber speakers.

Several years after its inception, in 1972, when AAPB was still called the Biofeedback Research Society, Jay Gunkelman attended the meeting and Gunkelman would subsequently play a major role in the understanding and application of quantitative EEG or QEEG.

JAY GUNKELMAN

Jay Gunkelman at the age of 21, started his first lab in 1972 with the first State Hospital based biofeedback laboratory in North Dakota together with Larry Woodard. At the State Hospital, they would have a lot of freedom in the work they did, and they applied biofeedback and neurofeedback to patients. In this lab, Gunkelman and Woodard also conducted sensory deprivation studies where people would lay in flotation tanks with salt water and underwater speakers, where at the same time they recorded EEG. This was not trivial being able to record EEG in a salt water flotation tank, so the EEG electrodes were fixed with collodion and subsequently covered with greasy petroleum gel. At that time, Transactional Analysis Therapy was just coming along, and many therapists at the hospital were interested in that approach, where scripts would be used. Thus, the idea developed to present personalized scripts in the flotation tank, and also linking that to the EEG, where the script would only be presented when the subject showed theta activity and switching back to pink noise when theta dropped (or when someone paid attention) as to present the scripts during deeper states of consciousness or hypnagogic states. Eventually, they treated several patients in this set-up, where the therapist would provide the script, and the personalized scripts would be played back to the patient in the flotation tank, with the purpose to reprogram patient's thought patterns, which usually required 4-6 sessions. In a sense this was thus based on *'brain-washing techniques.'* Gunkelman and Woodard never publicized anything of this work,

afraid that such work could fall into the wrong hands. Eventually, their budgets were cut, and Gunkelman decided to go to California.

In 1976, Gunkelman, together with Woodard and initially Jim Hardt started Spectral Data Systems, where they produced their own 1 channel pocket sized EEG device that had three controllable feedback bands. *"You could listen to your EEG walking up-and-down the street."* Gunkelman spent about $ 150.000 to make the cases for the device, however they sold none of them! This is where Gunkelman's saying: *"... how do you make a small fortune in neurofeedback? Well, start with a large one..."* originated from. After this experience, Gunkelman started looking for a joblisting in the newspaper, and he found a company called TeleDiagnostic Systems (TDS) in San Francisco, where he was hired. In 1976, Gunkelman became EEG technologist, later Chief EEG Technologist, at TDS. TDS, formerly known as Parallel Data Systems, was developed for regional clinical EEG, receiving-interpretation centers, serving a group of remote community hospitals to assist in diagnostic testing. TDS had the first system capable of transmitting real-time EEG via a standard telephone line, which can now be considered one of the first real examples of Tele-Medicine, well before the term Tele-Medicine was coined. These hospitals would send through their clinical EEGs by a device that transformed the 8-channel EEG into an audio signal that could then be transmitted to TDS, where another device would extract the EEG from that signal again, where it would subsequently be printed on an ink-writer. Actually, the first ever EEG processed in that way by TDS, was from the Gibbs' lab, who were famous pioneers in EEG and well-known for their early handbooks of EEG (see Figure 23). At TDS, he worked – as he referred to - in 'The Pit', (depicted in Figure 23) which in Jay's words: *"...had the whole room surrounded on the perimeter of the room with writer units. Grass Model eight channel, Grass Model 6's, Grass Model 8's, Nihon Kohdens, Beckmans, and phones hanging all over everywhere..."* Here, over 100's of EEGs from remote locations came in via telephone lines from about 400 hospitals. In this period, Gunkelman thus evaluated over half a million EEG's, making him one of the most experienced EEG interpreters worldwide. This rich experience has resulted in his proposition of the 'EEG Phenotype model', which essentially was a retrospective qualitative clustering of EEG patterns

that explained most of the variance in the many EEGs he had seen before. At the time, when Gunkelman conceived of the concept of EEG Phenotypes, genetics was coming-up, albeit not that successful. Several of the proposed phenotypes – mainly low voltage and epileptiform EEG – had a quite well described genetic backgrounds, hence he conceptualized them as 'EEG Phenotypes.' Due to the 'retrospective' nature of how the EEG Phenotypes were comprised, prospective validation was an important step, and recently several of these EEG phenotypes have been validated such as the slow alpha peak frequency, as a predictor for non-response to methylphenidate in adolescent boys with ADHD [91]. In 2002, Gunkelman established Q-Metrx together with the late Jack Johnstone, and several years later he co-founded Q-Pro Worldwide and Brain Science International, specialized in EEG interpretation services.

In 1992, Gunkelman as part of his environmental work was exposed to a strong alkaline that resulted in a burn on his arm. After several months it did not heal as expected and after some blood work, the doctor referred him to the hospital where a pituitary tumor was discovered the size of a golf ball, for which he was subsequently treated. That event would have a major impact on his further life, where he realized and learned to live with the finiteness of life. Before his brain tumor he would have never considered lecturing at conferences for MD's, PhD's and professors, but after the brain tumor he did which became a major part of his life. Or in Gunkelman's words, *"as a tech, you don't do talks."* At that time, he shared an office space with Julian Isaacs, and when Isaacs was not seeing a patient, he would walk in where Gunkelman was sitting with all the EEG equipment, and asked Gunkelman *"...oh what is that? Lambda... How do you know it's Lambda... And what is this?..."*, and after a few years of the *'what's that's'* he understood the same Gunkelman did, and he invited Gunkelman to give a lecture for the first time at Key West EEG meeting (later known as Rob Kall's Futurehealth meeting). As Sterman recalls about that meeting: *"...I was lecturing and he walked in to that lecture with all his backpack on with all his medicine stuff and started a spousing, you know how Jay is, like all this knowledge he has. And I thought, what the*

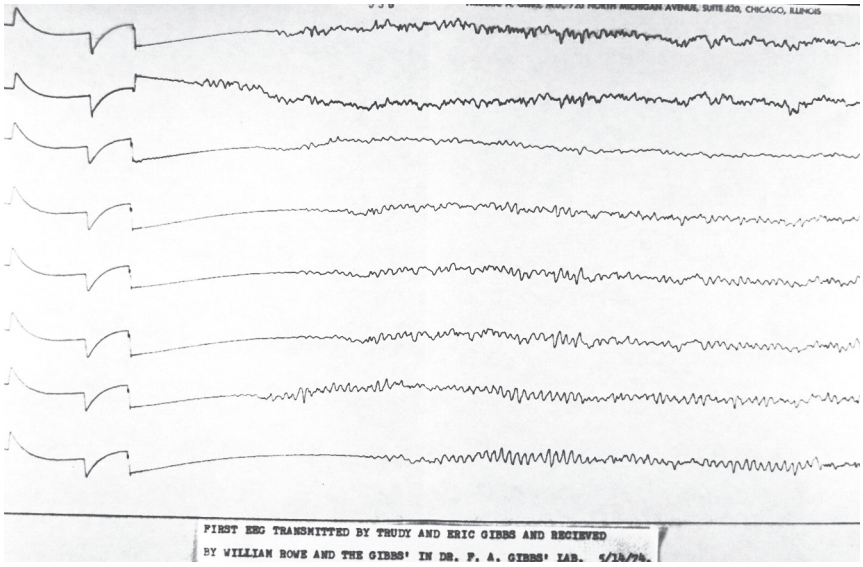


Figure 23: *The first EEG transmitted over a telephone line by the Gibbs' lab (top). Below: Jay Gunkelman working in the 'Pit', where 100's of EEGs came in from various hospitals, surrounded by many EEG writer units such as Grass Model eight channel, Grass Model 6's, Grass Model 8's, Nihon Kohdens, Beckmans.*

hell are you doing, you're messing up my lecture here." Sterman summarized his recollections from Jay as: *"…Jay is a smart man, talks too much. Very good about dealing with his illnesses. Should have finished his degree. But he has really done quite well. He's got out with some novel new stuff. He's been a force in the field, which is good…."* After that meeting Gunkelman was asked to co-chair the SNR (now called ISNR) meeting in Aspen in 1997, and so began a long series of meetings he would co-organize, both neurofeedback meetings and TMS meetings. In 2001, Gunkelman in his role as past-president of SNR encouraged European colleagues at the meeting in Monterey, California to create a European chapter, where Juri Kropotov was elected first president of this European Society for Neuronal Regulation or SNR. Those plans were further presented to a broader audience at the 6th annual Biofeedback Foundation of Europe (BFE) meeting held in Amsterdam, The Netherlands, which resulted in the first successfully combined meeting between the BFE and European SNR in Winterthur, Switzerland in 2004. Gunkelman also successfully applied his expertise on signal processing in his environmental work, where he pioneered a laser-based pollution detection system that is mandatory to be installed at California refineries at this moment.

Reflecting on the history of neurofeedback Gunkelman reminisces: *"…It was still EEG biofeedback then. So, it was simplistic and linear. The models were like an equalizer; will you make more of this and less of that. And it's not like that. The brain, you don't just slide up the alpha switch and make more of it. You know, it's much more complex than anything anybody thought of back in the 1960's and 1970's when the field was just starting…"*

EPILOGUE:

MODERN TIMES

MARTIJN ARNS

The primary focus of this book has been the old EEG history, including some early highlight of EEG conditioning work as a prelude to neurofeedback and the first 25 years of EEG Biofeedback roughly ending the focus of this book around the mid 1990's. Incidentally the 1990's were also a time where neurofeedback laid dormant for quite a while, until reawakening towards the end of the 1990's before the big neurofeedback revival started in the beginning of the 21st century. We have explicitly focused on the first 25 years, since in order to write a history book, time must have had its cleansing effect, and one should be able to look back for a long enough time to see the threads and place developments in context. However, in this epilogue we'll close the circle of how the two authors of the book got to know each other and *'how it all started'* leading to the perspective of this book.

In February 2002, the 6th meeting of the Biofeedback Foundation of Europe (BFE) took place in Amsterdam. During this meeting, several presenters from the US were present, including Barry Sterman and Joel Lubar. While in Amsterdam, there were complaints about

the outside temperatures (albeit for local norms it was reasonably warm though), which was indeed not comparable to the sunny Californian climate. Besides workshops, one day of the conference was fully dedicated to scientific presentations. It was here that a new young researcher held his first ever presentation for a neurofeedback audience. His presentation was titled: *'Targeting the Deficit for Neurofeedback Treatment in ADHD: A Multicentre Study'* and outlined a plan for a multicenter study, setup and data collection using the Brain Resource International Database and investigating the efficacy of neurofeedback in the treatment of ADHD. The audience included the aforementioned pioneers in the field of neurofeedback. Although a little nervous, the young researcher appeared to be very enthusiastic about his project and rather knowledgeable too. After his presentation the audience was given the opportunity to respond and it was here that Sterman stood up, clearly annoyed and accusing the young speaker of presenting an approach that was in his perception no more than a fishing expedition. The reputation of good science was at stake here. Although surprised by these accusations, the young speaker remained calm. The debate lasted for several minutes and caused the audience to be fully awakened. The young speaker turned out to be me, Martijn Arns, and this was our first acquaintance between myself and Barry Sterman. I soon realized the importance of Sterman's credo *'Show me the data'*, which I was not able to show at this first encounter. However, in subsequent years I had come to my senses and produced enough data to have won the confidence of Sterman, of which these pages are the result.

In June 2005, I took part in Sterman's 4th annual Society for Advancement of Brain Analysis (SABA) meeting on a cruise from Vancouver to Anchorage, and in October 2005 Sterman gave a workshop and several lectures in Nijmegen, the Netherlands organized by myself and Rien Breteler, which was a great success and infused the local interest and knowledge about neurofeedback to a great degree. A year later, in 2006 Sterman was a keynote speaker at the 1st inaugural meeting of the Society for Applied Neuroscience (SAN) in Swansea (UK), that came forth from the initial eSNR/BFE initiative, where Sterman presented on *'The Pause that Refreshes: EEG Rhythms and Learning.'* The photo on the next page shows an interesting line-up of characters,

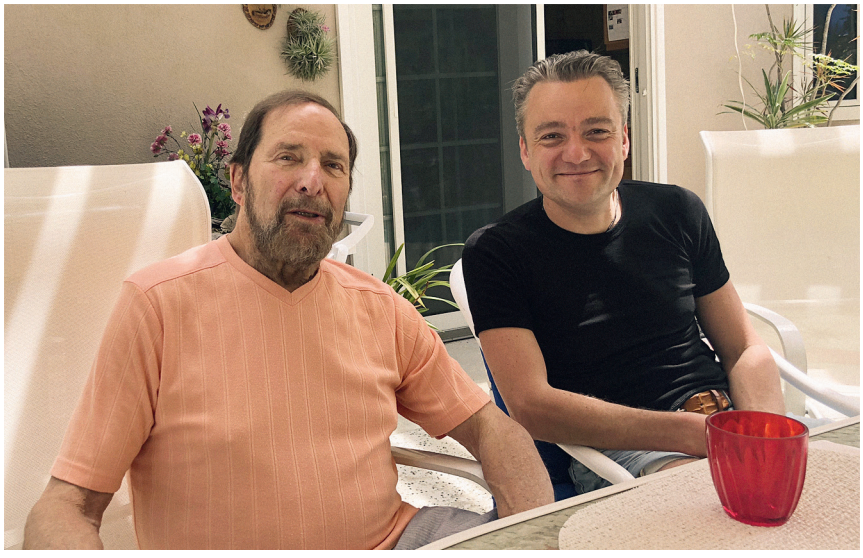
most still involved in neurofeedback research and major contributors to the current developments in the field of neurofeedback, and *likely* major characters in a subsequent book covering the second 25-year period in the history of neurofeedback. Just to highlight a few, Marco Congedo from Grenoble, France, one of the pioneers behind LORETA neurofeedback, independent component analysis (ICA) and other advanced processing techniques; Roger deBeus from Asheville, who conducted one of the earliest double-blind placebo controlled studies, and also one of the PI's on the latest double-blind placebo controlled NIMH sponsored ICAN study (International Collaborative ADHD Neurofeedback study); Tomas Ros, from Geneva, Switzerland who has done a lot of cross-modal neurofeedback work, measuring the impact of alpha desynchronization neurofeedback on fMRI and TMS parameters and Leslie Sherlin, who has been an important driver behind many of the ISNR conferences and working hard to get neurofeedback implemented in sports applications.

Figure 24: *Photo taken at the 1st Society of Applied Neuroscience meeting (SAN) in Swansea (UK) in 2006, from left to right, Cédric Gouy-Pailler, Marco Congedo, Roger deBeus, Barry Sterman, Tomas Ros, Martijn Arns, Leslie Sherlin and Andreas Wehowski.*

In 2018 I visited Barry Sterman on February 28th in Beverly Hills and during that meeting Barry suggested to write a book together about 'how it all started.' During subsequent meetings in LA in May 2018 and in February 2019 the outline of the book was discussed and planned in more detail, with the final result in front of you.

We hope you've enjoyed the book!

Kind regards, Barry and Martijn.



Work in progress, Barry Sterman and Martijn Arns at work in LA, May 2018

ACKNOWLEDGMENTS:

This book would not have been possible without the support and contributions from many, whom we'll wish to acknowledge here:
Niels Birbaumer for his great insightful views on the history of SCP's, BCI and Neal Miller backgrounds. Joe Kamiya for the initial correspondence in 2010 on his early work.
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And finally, Nicole, Rumo and Sia, for bearing with me all those endless nights dad had to spend time on his laptop again.

APPENDIX 1:

INTRODUCTION TO THE ORIGINAL INTRODUCTION OF MAURICE B. STERMAN'S PHD DISSERTATION

On the following pages we have reprinted Maurice B. Sterman's original introduction of his PhD thesis which provides a nice window in the state of research up-to 1963. In this introduction the contours of Sterman's further work are emerging already. Main themes to be aware of when reading this work are the historical context with a strong emphasis on Pavlov's work on conditioning, learning theory and internal inhibition and the notion of sleep as an active process, as also further detailed in chapter 4 and 7. In some instances, the behaviorist in Sterman is clearly captured such as in: *"…If the word had been available, it is not unlikely that Claparéde would have here used 'conditioned' in place of 'instinctive'…"* Also, his main inspirators come to the foreground in this piece such as the early work from Horace Magoun on the arousal system, who was also considered the founder of the Brain Research Institute at UCLA, where Sterman spent most of his career, and still is professor emeritus. Finally, this introduction culminates into the rationale why Sterman in those early days came to investigate the role of the basal forebrain in sleep, these days generally considered an acetylcholinergic structure involved in maintaining wakefulness and arousal.

His first publications part of this PhD thesis were published in 1962 in Experimental Neurology as Chapter II and Chapter III (see below) respectively, where he indeed demonstrated the clear role of the basal forebrain in sleep using electrical brain stimulation of this area and observing subsequent behavior and EEG changes. Interestingly, to date these two papers are still among the 10 most widely cited papers Sterman has published, which is impressive for a first two publications emerging from a PhD thesis. Chapter IV titled *'Conditioning of induced EEG and behavioral sleep patterns'* was published in the prestigious journal Science in 1962 followed by a more detailed publication in Experimental neurology in 1963. In these, Sterman described classical conditioning of this basal forebrain stimulation being paired to an auditory tone, where after an average of 20 pairings a conditioned EEG and behavioral response became apparent. In essence, this was his first description where conditioning principles were directly applied to brain stimulation, albeit based on classical conditioning principles. Chapter V titled *'Other experiments dealing with the forebrain synchronizing area'* is a collection of other experiments.

Sterman's original PhD consisted of the following chapters:

1. **CHAPTER I: INHIBITION AND SLEEP.**

Reprinted on the following pages.

2. **CHAPTER II: CORTICAL SYNCHRONIZATION INDUCED BY BASAL FOREBRAIN STIMULATION**

Sterman, M. B., & Clemente, C. D. (1962). Forebrain inhibitory mechanisms: Cortical synchronization induced by basal forebrain stimulation. *Experimental Neurology, 6*, 91-102.

3. **CHAPTER III: SLEEP PATTERNS INDUCED BY BASAL FOREBRAIN STIMULATION IN THE BEHAVING CAT**

Sterman, M. B., & Clemente, C. D. (1962). Forebrain inhibitory mechanisms: Sleep patterns induced by basal forebrain stimulation in the behaving cat. *Experimental Neurology, 6,* 103-17.

4. **CHAPTER IV: CONDITIONING OF INDUCED EEG AND BEHAVIORAL SLEEP PATTERNS**

Wyrwicka, W., Sterman, M. B., & Clemente, C. D. (1962). Conditioning of induced electroencephalographic sleep patterns in the cat. *Science, 137,* 616-8.
Clemente, C. D., Sterman, M. B., & Wyrwicka, W. (1963). Forebrain inhibitory mechanisms: Conditioning of basal forebrain induced EEG synchronization and sleep. *Experimental Neurology, 7,* 404.

5. **CHAPTER V: OTHER EXPERIMENTS DEALING WITH THE FOREBRAIN SYNCHRONIZING AREA**

ORIGINAL INTRODUCTION
PHD
MAURICE B. STERMAN
(1963)

ABSTRACT OF THE DISSERTATION

Brain Mechanisms in Sleep

by

Maurice Bernard Sterman

University of California, Los Angeles, 1963
Professor Donald B. Lindsley, Chairman

In general, the scientific investigation of the problem of sleep has been guided by concepts which were current at any given time. The earliest investigators did not appreciate the importance of the brain in accounting for conscious activity, and, thus, the central position of the nervous system in these matters was only gradually realized. When, in the 19th century, it was observed that pathological sleep-states were often associated with inflammatory lesions of the central gray matter in the rostral brainstem, some concluded that a functional break at this same level could account for natural sleep. This ushered in a long series of "deactivation" theories, some of which persist to the present day. However, an entirely different approach to the problem was made possible by the gradual elucidation of the process of neural inhibition. This facilitated the understanding of integration at increasingly higher levels of nervous function, and was finally invoked to explain sleep. The finding that direct stimulation of certain areas in the nervous system can induce many of the signs of natural sleep reinforced this approach. In the present study, neurophysiological and behavioral techniques were employed in the description and evaluation of such an area at the base of the rostral

forebrain in the cat. The effect of electrical stimulation of this area upon simultaneously recorded EEG activity was noted in both acute, immobilized and chronic, unrestrained animal preparations. Bipolar stimulation was delivered to these sites through stereotaxically placed concentric and "strut" type electrodes. A slow-wave synchronous EEG pattern was directly induced in both types of preparation by the application of bilateral basal forebrain stimulation, with a rapid transition from alert waking behavior to apparent sleep accompanying stimulation in the unrestrained animal. The forebrain area, which was defined by its capacity to induce these effects, included the basal aspects of the diagonal band (of Broca) and the adjacent rostral and lateral extent of the preoptic area in the hypothalamus. Behavioral studies demonstrated that the EEG and behavioral manifestations of sleep resulting from both high and low frequency stimulation of this area can be conditioned to an external sensory stimulus. Such stimulation can also effectively interact with the excitatory effects of rostral brainstem stimulation. The knowledge of a possible forebrain inhibitory mechanism and the factors which may affect its activity, together with the knowledge of excitatory mechanisms in the brain, provided for the development of a multifactor approach to the problem of the brain mechanisms involved in sleep.

CHAPTER I

INHIBITION AND SLEEP

In the course of their daily cycle of activity, many animals demonstrate a complex pattern of behavior which results in an almost complete cessation of somatic motor and perceptual function. This rather remarkable sojourn which we also experience is generally referred
to as sleep. For many years investigators have attempted to understand the neural mechanism responsible for this state and recently an even greater interest has become evident. This interest may represent the sequel to the success achieved in elucidating the neural mechanisms involved in wakefulness and behavioral arousal. This interest may also be due to an increased awareness of the similarities between sleep and such states as catatonia, narcolepsy, depression, and hypnosis, since similar brain mechanisms which normally provide for sleep may also be responsible for these other interesting phenomena.

Some investigators believe that sleep is simply a lack of wakefulness. That is, sleep results passively following the withdrawal of those influences which maintain a waking brain. Others do not consider the explanation to be quite so simple. Since sleep is generally characterized by a decrease in motor activity, a raising of sensory thresholds, and a relatively stable sequence of antecedent adjustments, it has been suggested that sleep is actively achieved by the nervous system. This implies the operation of some process which is, by definition, antagonistic to excitation, and there has thus been the tendency to apply inhibition as a mechanism in this context. The organization of inhibitory phenomena in the nervous system, like other important neural functions, has certainly become 'encephalized' with phylogenetic evolution, and there would seem to be some justification for applying the concept to such complex neurophysiological operations. In the pages to follow the origin and development of ideas concerning neural inhibition will be reviewed. Since the present investigations were primarily concerned with the role of such neural processes in the initiation of sleep, the extension of these ideas to integrative function, and their more general application to the problem of sleep will also be discussed.

DEVELOPMENT OF THE CONCEPT OF NEURAL INHIBITION

The need for some means of blocking contraction in certain muscles appears to have provided an early vehicle for the concept of a neural inhibition. Descartes, who conceived of the nerves as hollow tubes for conducting the animal spirits, proposed that the nerves serving antagonistic sets of muscles contain valves which block the flow of spirits into one set while the other is active (17). He, thus, anticipated the principle of reciprocal innervation which was to develop in the late 19th century. However, it was earlier in this same century that the real foundations for the concept inhibition were to be laid. Sir Charles Bell (13) felt that too much attention had been given to the nerves as "instruments for stimulating the muscles, without thought of their acting in the opposite capacity." He pointed out the imposed relaxation in an extensor muscle during the contraction of its antagonistic flexor. These early demonstrations of active muscular relax-

ation must have been very convincing, for a short time later some investigators concluded that contraction was an innate property of the muscular fiber, and that the nerves supplying muscle functioned solely to "restrain" contraction rather than to evoke it (137).

It was in the realm of autonomic function, however, that the important implications of a neural inhibition were first realized. Volkmann (134) had observed the inhibitory action of the vagus upon the heart, but considered it to be due to an experimental error. In 1845 the Weber brothers (136) reported that voltaic stimulation of both vagi of the frog produced an indisputable inhibition of the heart, characterized by a slowing or temporary cessation of its beat in systole. Some twenty years later, the Russian physiologist, Sechenov, (122) was to state that "Weber's contemporaries wondered and wondered" about this "abnormal action," but finally the accumulating facts" strengthened the belief of physiologists that there exists in the animal body nervous influences by which involuntary movements are depressed." These accumulating facts were: Claude Bernard's observation of the regulatory (stimulatory and inhibitory) action of the chorda tympani on the submaxillary blood vessels, and thus on salivation (14); Pflüger's demonstration of inhibition of intestinal movements with stimulation of the splanchnic nerves (106); the initial description by Rosenthal (115) of inspiratory inhibition mediated by the superior laryngeal nerve during contraction of the expiratory muscles, which was later verified and associated with the swallowing reflex by Kronecker and Meltzer (77).

A broader interpretation of the concept of inhibition evolved from the developing principles of reciprocal innervation, exemplified by the autonomic nervous system. Von Cyon (63) reported an inhibitory influence upon cardiac rate produced by afferent impulses from the aorta and the heart itself, and shortly afterwards Hering and Breuer (56) expanded the concept of self-regulating mechanisms by describing respiratory reflexes which operate via the pulmonary vagus to inhibit inspiration. Recognition of the existence of antagonistic systems of nerves for the control of visceral activity can be traced to the work of Gaskell (42) in 1886.

During the latter half of the 19th century, however, a fundamental division developed among scientists investigating nervous inhibition. This was not a polemical division, but one necessitated by an advancing technology. There were certain investigators who concerned themselves with the higher functions of the nervous system, such as somatic and visceral integration, and learning processes. In contrast to this, there was an ever expanding group of biologists interested in basic inhibitory mechanisms who sought the answer to the question stated originally by the Webers at a cellular level. How can excitation of a nerve cell result in an inhibition of adjacent nerve cells or effector organs? The first major advance in this regard was achieved by Gaskell (43), who came to the conclusion that there were two separate types of nerves with opposite metabolic influences involved in the innervation of all tissues. He showed that stimulation of an anabolic (inhibitory) nerve, the vagus, resulted in a decided increase of electrical positivity in quiescent muscle tissue of the tortoise heart, an effect now termed hyperpolarization. A continuing assault upon the mechanisms of nerve cell inhibition can be traced from these pioneering efforts.

INTEGRATED INHIBITORY ACTION

In addition to these considerations, and by no means less important, is the question of how the nervous system integrates its widespread capacity for inhibitory action since integration is the primary task of the nervous system. We have already mentioned the early appreciation for regulatory mechanisms within the realm of autonomic function. Here, sensory information from the viscera was observed to affect higher centers, which in turn functioned to adjust the activity of the viscera according to the requirements of the organism at any given moment. Inhibition, directed by these centers, is an important part of this capacity for adjustment.

One of the first men to demonstrate that higher centers in the nervous system can function to regulate its peripheral output was Ivan Sechenov (122), the so-called father of Russian physiology. His experiments on frogs, together with rapidly accumulating evidence from

the study of the autonomic nervous system, prompted the conclusion that "physiologists could now accept the existence of mechanisms which retard reflex movements in the human body (or, more accurately, in the brain, for our will acts only through this organ)." To Sechenov, these mechanisms were nerve centers in the broadest sense of the word. He described such a center in the brainstem of frogs, and showed that its excitation with salt crystals inhibited a flexion withdrawal reflex. It was Sherrington, however, who clearly established the role of inhibitory mechanisms at all levels of the nervous system. His studies on somatic reflex patterns in mammals (125) demonstrated integration of excitatory and inhibitory mechanisms in the spinal cord. In addition, he stressed the point that these reflexes were under the control of higher centers in the nervous system. Thus, he states that "by these higher centers, this or that reflex can be checked, or released, or modified in its reaction (and) it is urgently necessary for physiology to know how it intrudes and makes its influence felt upon the running of the reflex machinery." Sherrington also anticipated the possible application of the principles of reflex action to these higher level functions. He suggested that some extension of the processes operative in simultaneous and successive combination of reflexes should apply here also. In describing the inhibitory process, in motor neurons, he and his collaborators (27) presented some conclusions which would appear, in light of more recent evidence, to find application in any discussion of higher-order mechanisms. The inhibitory process, according to these investigators, has the properties of threshold, gradation, and summation. It is quantitatively antagonistic to excitatory states, and its effectiveness varies inversely with excitation. The generality of these properties will become apparent in the course of our discussions.

With the perfection of techniques permitting direct electrical stimulation of brain structures, the study of inhibitory mechanisms at these levels took on a new complexion. It was possible to observe the effects of brain stimulation upon behavior, and thus make some statements about the actual physiological functions of structures investigated. On the basis of such studies, Magoun and Rhines (87) concluded that the bulbar reticular formation contains a general inhibitory mechanism which conducts its influence to the motor neu-

rons or the spinal cord by way of reticulospinal pathways. Electrical stimulation of the caudal portion of the brainstem reticular formation inhibited evoked spinal reflexes, and in addition reversed the extensor rigidity characteristic of decerebrate animals. It had previously been found that a strip of motor cortex (area 4-S) had a "suppressor" influence on motor tone and motor responses when activated in the anesthetized monkey preparation (34, 62). The bulbar inhibitory area was found to occupy the same reticular region to which cortical area 4-S was known to project. Connections to this brainstem area from the caudate nucleus, putamen, and the anterior lobe of the cerebellum have also been described. These structures were also found capable of exerting an inhibitory influence on extensor reflex activity. It was thus concluded that the bulbar inhibitory area constituted a funnel through which inhibitory influences from the brain regulate motor activity in the cord. Although these experiments were performed upon decerebrate animal preparations, many experiments of this type have been carried out on anesthetized animal preparations, and in this regard some controversy has recently arisen. For instance, it has been reported that stimulation of "suppressor" cortex 4-S in the unanesthetized monkey causes a reaction quite the opposite of suppression (79). These and other similar findings indicate that anesthesia is a variable which must be considered in the interpretation of these data.

With the acknowledgment of integrated inhibitory function at higher levels in the nervous system, it was inevitable that the phenomenon of inhibition would find additional application in many of the theories of sleep which were developing during this period.

INHIBITION IN SLEEP MECHANISMS

The multitude of sleep theories which have accumulated over the years has made it necessary for reviewers to try to fit them into some arbitrary classification. These classifications are usually based upon the complexity and breadth of a given theory, upon the system implicated (metabolism, circulation or nervous action), or upon the actual mechanism proposed to account for the sleep state. In exploring this

literature two rather basic approaches to the mechanism involved can be distinguished. One considers sleep to be a release phenomenon consequent upon a withdrawal (either active or passive) of the sensory input to the cerebral cortex or of cortico-petal impulses in general. The other considers sleep to be induced upon the cortex and higher nervous centers by some active process which interferes with the functional requisites of waking behavior at these levels. Since the approach to this question is fundamental to any interpretation of the sleep phenomenon, it appears to provide a meaningful basis for classification. A second, more subtle question also arises. Are the biological alterations which result in sleep set-off by internal shifts exclusively, or can they be additionally triggered by external conditions? In other words, does learning assume some role in the initiation of sleep? The present survey will discuss these various aspects of the problem of sleep because of their relevance to the experiments to be reported here. More extensive reviews have been written in the past by Pilron (107) and Kleitman (73).

EARLY THEORIES OF SLEEP AS AN INDUCED STATE

The earliest thinkers who concerned themselves with the problem of sleep were almost universally of the opinion that it was a state forced upon the organism. According to Kleitman (73), the first sleep theory on record was proposed by a contemporary of Pythagoras in the 6th century, B.C., who felt that sleep resulted from a retreat of the blood into the veins. This idea can be listed as a forerunner of the "cerebral anemia" theories of sleep which were to evolve many years later. The vascular system was also implicated by Aristotle in the 3rd century, B.C. He felt that "sleep is evidently a privation of waking," attendant upon the process of nutrition, and mediated by the blood (10). Most scholars of this early period did not appreciate the importance of the nervous system in these matters, and could not have given much scientific consideration to the role of learning. However, by the 19th century, some advances were made along these lines. It was in 1843 that Johannes Müller's "Elements of Physiology" (98) presented the first consolidated treatise on human physiology, and this included a chapter on sleep. Müller recognized the brain as the organ of mind,

and of sleep he said, "the organic processes in the brain which attends an active state of mind, gradually render that organ incapable of maintaining the mental action, and thus induces sleep, which is to the brain what bodily fatigue is to other parts of the nervous system."

Müller believed that a changed state of the brain, resulting from its own organic activity, resulted in sleep. He inadvertently alluded to the contribution of other factors with the introspection that "in many persons, for instance in myself, sleep is brought on at will by the assumption of the recumbent position, while the thoughts are kept in an unexcited state,"

The late 19th century really marked the beginning of a serious attack on the functions of the nervous system, an important part of which was an increasing interest in the problem of sleep. In 1890 Brown-Sequard (20) related the onset of sleep to an inhibitory reflex associated with closure of the eyelids. He localized the center for this reflex at a subcortical level due to his observation that decerebrate pigeons continue to sleep. Some years later Ramón y Cajal (112) suggested an intriguing mechanism to account for both inhibition and sleep. He thought that he had observed ameboid-like motion in the dendritic processes of neuroglia cells, and proposed that their movement in or out of the synaptic gap between two adjacent neurons could regulate post-synaptic activity. Sleep could be conceived of as a generalized interruption of synaptic conduction. An entirely different approach was introduced by Claparéde in 1905 (26). His physiological considerations resembled those of Müller, in that he considered sleep to be a protective process which prevents exhaustion or damage from the toxic byproducts of continued wakefulness. He added, however, the conviction that sleep is an active phenomenon, an instinct which involved the active participation and will of the organism, resulting from a loss of interest in the environment and an instinctive inhibition of reactivity. If the word had been available, it is not unlikely that Claparéde would have here used "conditioned" in place of "instinctive."

Another early theory which has current implications is the one proposed by Barbara in 1920 (119). The rapidly accumulating knowledge of autonomic function was combined with some of the older

metabolic notions to provide an explanation for the cyclic aspect of human behavior. Wakefulness was characterized as the 'catabolic phase' due to a predominance of 'excitocatabolic' or 'sympathicotonic' substance in the circulation. Sleep resulted from an insufficiency of these, combined with a predominance of antagonistic parasympathetic substances and vagal influences (the 'anabolic phase').

SLEEP AS A RELEASE FROM AFFERENT STIMULATION

This second school of thought regarding sleep was not actually characterized by the use of the term "release." This interpretation is, however, implied by the common position that a cerebral cortex deprived of sensory input will "go to sleep," and so to speak, take the body with it. One of the first of these "congestive" theories, by Piéron's classification, was that proposed by Pürkinje in Wagner's "Handbook," published in 1846 (111). The thalamic sensory radiations were thought to be interrupted by a compression of the corona radiata resulting from a hyperemia of the basal ganglia. This prevents sensory input to the cortex and brings on sleep. Osborne later proposed a swelling of the choroid plexus as the antecedent of sleep, for the consequent distention of the ventricles could block afferent impulses mechanically (104).

Mauthner (91) was the first investigator to anticipate more recent findings by focusing attention on the midbrain, and more specifically on the area surrounding the nucleus of the third cranial nerve. In 1890 he reported some observations on the pathology of an encephalitic condition called 'nona,' in which somnolence was a primary symptom. Post-mortem examination indicated involvement of the central gray matter in the area of the oculomotor nucleus, and from the proximity of this area to the main sensory projections on their way to the thalamus, Mauthner concluded that sleep resulted from a break in these conduction pathways due to a "temporary cessation of function of the central gray." According to Mauthner, sleep results from an isolation of the cortex from the environment. In 1912 Trömner (133) reported a case of narcolepsy in which the pathology involved an abscess in the thalamus. He accepted Mauthner's con-

cept of neural blockade, but elected the thalamus as the site of action. Sensory projections to the cortex could be effectively blocked here and sleep cycles in a decorticate animal could be explained by the action of a thalamic sleep center upon lower structures. The thalamus was also considered a primitive sleep regulatory center by Spiegel and Inaba (128). on the basis of somnolence resulting from massive thalamic lesions in one dog. The internal capsule, subthalamus and hypothalamus of this animal were also damaged, which would appear to account for their observations in light of more recent findings (114). An interesting corollary proposed by Spiegel (127) suggested that the cerebral cortex could influence the thalamic mechanism via excitation or inhibition. Thus, he acknowledged the influence of cerebral factors on the regulation of the sleep-waking cycle.

By 1935 it was apparent that the diencephalic-brainstem junction had important functions with regard to sleep and wakefulness. After performing a mesencephalic transection of the brainstem caudal to the nuclei of the third cranial nerve, Bremer (18) observed that the functional condition of the diencephalon and of the cortex resembled the electrical and behavioral characteristics of sleep. From the study of such animal preparations, he concluded that a sleep-like functional depression of the telencephalon and diencephalon is "linked with the suppression of the continuous flood of ascending dynamogenic impulses" to the cerebral cortex. Bremer's conceptions regarding the neurophysiological mechanisms involved in sleep were to be greatly influenced by the later discovery of an arousal system in the reticular core of the brainstem (19)]

Reflecting a growing conviction among theorists, Kleitman (73) culminated his extensive review by stating that "there can be little doubt that the subcortical center (in the mesencephalon, hypothalamus, and thalamus) is really a wakefulness center whose continuous activity is necessary to maintain a state of wakefulness." His extensive observations, in collaboration with Camille (74), on decorticate dogs apparently convinced him that the cerebral cortex could not be regarded as the place where sleep is initiated. In fact, he rejected the entire concept of sleep as an actively initiated process, shifting his attention instead to wakefulness.

According to Kleitman, "There is not a single fact about sleep that cannot be equally well interpreted as a letdown of the waking activity" (73). Kleitman was one of the first to recognize clearly the importance of past experience in sleep regulation. Again emphasizing wakefulness rather than sleep, he spoke of a primitive "wakefulness of necessity" induced by proprioceptive and interoceptive impulses. As the cerebral cortex became elaborated through phylogenetic development, and past experiences were able to provide for "critical reactivity" a "wakefulness of choice" became possible, which enabled the organism to react differentially to the various stimuli disturbing its sleep.

The same year that Kleitman's review appeared (1939), another more specific treatment of the subject was prepared by Ransom and Magoun (114), in which an attempt was made to localize anatomically what they also felt was a "waking center" rather than a sleep center. Employing a Horsley-Clarke stereotaxic instrument, small electrolytic lesions were placed in the hypothalamus and brainstem of cats and monkeys, and post-operative sleep behavior was then observed. They found that the integrity of the central gray matter at the level of the transition of the cerebral aqueduct into the third ventricle (corresponding approximately to the area specified by Mauthner) is not essential for the maintenance of the waking state. Large lesions in the thalamus also failed to produce any signs of sleep (a contradiction of the position taken by Trömner and by Spiegel and Inaba). However, bilateral lesions in the lateral hypothalamic areas posterior to the tuberal level were most effective in producing somnolence. Some evidence of an extension of this effective region into the rostral part of the mesencephalon was also presented. Furthermore, electrical stimulation caused a generalized somatic and visceral activation in unanesthetized cats. This observation led to the conclusion that "in the hypothalamus and particularly in the posterior part of the lateral hypothalamus is located a mechanism which when activated excites the entire organism. Here we have the 'waking center.'" These investigators were cautious in interpreting the role of afferent stimulation in relation to the physiology of sleep, stating that ''While neither normal sleep nor the somnolence caused by hypothalamic lesions is due to the blocking of afferent impulses to the cerebral cortex, it is

certainly true that the quiet and relaxation involved in body sleep decreases the number of afferent impulses reaching the brain." Thus, the decrease in afferent stimulation resulting from "body sleep," a term borrowed from Von Economo (35), is relegated from the rank of initiator of sleep to that of a potentially important antecedent of Von Economo's "brain sleep."

This course of events had led to a dominating interest in wakefulness as the active state in the sleep-waking cycle. Sleep was more or less abandoned in favor of these more tangible considerations. The ascendance of the concept of subcortical waking mechanisms was increasingly apparent from the literature, but the culmination of this trend came with the conceptualization of a diffuse arousal system in the brainstem by Moruzzi and Magoun in 1949 (96). These investigators observed that high-frequency electrical stimulation of the reticular formation in the brainstem, and its more rostral extensions into the diencephalon, produced an EEG and behavioral response similar to that normally seen in awakening. The wealth of afferent collaterals to the reticular formation from virtually every sensory pathway, together with descending projections from the cerebral cortex, provided for the realization of a system involved in the waking process, and potentially capable of important integrative functions (85,86). It was also found that the classical sensory pathways could not maintain the brain and behavior in a waking state when the mesencephalic tegmentum was destroyed, whereas the reverse condition (intact reticular formation with severed lemniscal pathways) resulted in an otherwise normal waking animal (81).

These various findings seemed to indicate that sensory involvement in the waking process was managed indirectly at this subcortical level. Thus, while these investigators disclaimed some of the older notions about participation of direct sensory reduction in the etiology of sleep, others used these findings to provide a more comprehensive mechanism for just such a process, and the advocates of this position were quick to incorporate a diffuse arousal system into their conceptions about the neurophysiology of sleep. Bremer (19), for instance, came to explain sleep as a "cumulative deactivation" which he felt was initiated by a "neuronal fatigue (at cortical, diencephal-

ic, or reticular levels)." In explaining this concept he proposes that, "a slackening of activity of any region of the brain must result in a lowering of excitatory state in areas or nuclei - including the reticular formation - with which the region in question has facilitating relationships, and so the whole of the synergic structures are gradually affected. Doubtless, the functional depression of the reticular formation... plays a preponderant, if not always an initial, role in this process of cumulative 'de-facilitation.'" Bremer, still stressing the importance of sensory afflux, continued to reject the hypothesis of the existence of a hypnogenic center or of an active sleep mechanism, preferring instead to invoke a neuronal fatigue process reminiscent of the organic fatigue proposed by Müller back in 1843.

RECENT THEORIES OF SLEEP AS AN INDUCED STATE

With so much attention diverted to wakefulness, one might think that sleep had been forgotten. On the contrary, during this same period in time an important sequence of discoveries was occurring which was to suggest a quite different interpretation of the phenomenon of sleep. This interpretation centered around the older concept of sleep as an active process induced in the nervous system, but was now based on some concrete experimental evidence.

In his classical studies of salivary and gastric secretion in dogs, Pavlov (105) encountered psychic influences which attracted his interest and led him to devote the rest of his career to an objective study of the nervous activity underlying their formation and modification. The study of these conditional reflexes, as Pavlov termed them, brought him into direct contact with the problems of higher-order nervous inhibition. Commenting on the inevitability of this contact he says, "When we come to investigate the highly complex functions of the cerebral hemisphere we naturally expect to come across inhibitory phenomena, for these are very constantly and very intimately mixed up with the positive phenomena of nervous excitation. " In strong support of this position were the many instances of dogs "learning not to respond." That is, through the application of appropriate experimental manipulations these animals gradually developed

a negative conditioned reflex, which he called "internal inhibition." This is distinguished from so-called "external inhibition" which is the disruption of a conditional reflex due to direct interference from non-related stimuli. In the case of internal inhibition, "the positive conditioned stimulus itself becomes, under definite conditions, negative or inhibitory." Pavlov noticed that a prolonged presentation of this type of inhibitory stimulus led invariably to drowsiness and sleep, and therefore concluded that, "Sleep and what we call internal inhibition are one and the same process." He explained this by recourse to another theoretical process which his empirical observations led him to propose, the irradiation of an inhibitory process from a definite point of the cortex into surrounding cortical regions. With frequent or prolonged sensory stimulation the cortical elements were thought invariably to enter sooner or later into an inhibitory state. This is because the cortical elements are extremely sensitive and are thus "functionally exhausted with comparative ease." The process of inhibition "which itself cannot be regarded as a functional exhaustion, but which is a result of exhaustion," assumes the role of a protector against this exhaustion. The irradiation of internal inhibition over the entire cerebral mass "under conditions in which a great number of cortical points are repeatedly entering into a state of excitation," is said to result in sleep. In summary, then, Pavlov thought that sleep results from a gross irradiation of an internal inhibitory process which is initiated by constant or repetitive stimulation, and which functions to prevent exhaustion of the cortical elements. Thus, with respect to the neural mechanism of sleep, Pavlov also invokes a functional fatigue - but this fatigue provides for the onset of an active process of inhibition.

It is interesting to note that Pavlov also mentions having observed the sudden onset of sleep in animals, "exactly at the beginning of the action of the (delayed) conditioned stimulus." Although he interprets this as being due to a widespread process of internal inhibition, he does not relate this to the conditional reflex. From his other statements we may conclude that internal inhibition is a learned reflex, and since sleep and internal inhibition are one and the same process, it follows that sleep may also occur as a conditioned reflex. However, Pavlov never actually expressed this rather interesting deduction.

Could it be that the originator of the conditional reflex did not recognize this important instance of its occurrence?

Several years earlier, another source of experimental information regarding sleep had arisen from an entirely different context. A strange encephalitic epidemic had spread through the city of Vienna, leaving a disruption of the sleep-waking rhythm in its victims as its primary symptom. Taking advantage of this unfortunate situation, von Economo distinguished himself by his classic study of the central nervous system pathology involved (35). By careful comparison of many clinical cases of this encephalitis lethargica, von Economo described two symptomatic patterns of the disease associated with two localizations of the inflammatory lesions in the nervous system. In those cases in which somnolence and ophthalmoplegy were the distinguishing symptoms, the lesions were regularly found in the posterior wall of the third ventricle, continuing caudally to the level of the oculomotor nucleus. In contrast to this, there were other cases in which insomnia and chorea were observed. The inflammation in these patients was associated with the rostral hypothalamus, the tuberal region, and adjacent portions of the striatum. From these observations von Economo concluded that the affected areas must constitute a "Schlafsteuerungszentrum" or sleep regulating center consisting of at least two parts: a rostral part (at the anterior end of the third ventricle), which when appropriately excited, actively inhibits the thalamus and cerebral cortex and thus causes "brain sleep," and a more caudal part (in the posterior hypothalamus and rostral brainstem) which acts to decrease somatic, autonomic, and endocrine activity and thereby causes "body sleep." To von Economo, then, sleep was an active inhibitory phenomenon involving both central and peripheral alterations.

The observations and theoretical formulations of another European group are worthy of discussion because of the breadth and foresight they seem to reflect. In 1929, Marinesco, Sager and Kreindler (89,90) reported the confirmation of an observation made earlier by Demole (31), showing that sleep resulted from the injection of calcium chloride into the hypothalamus of cats, and excitation from a similar injection of potassium chloride. It is their interpretation of these findings,

however, which is of interest here. They maintained that sleep is not brought about by a single center, but by the action of a system. This system corresponded, more or less, to the rostral part of von Economo's sleep center. Furthermore, they implicated parasympathetic tone in the mechanism initiating sleep, and, in addition, felt that sleep was a combination of both unconditioned (humoral-vegetative) and conditioned (quiet, darkness, position) reflexes. To these investigators, sleep resulted from the activity of a neural system which was responsive both to internal necessity and to external command.

The concept of an active sleep inducing mechanism in the central nervous system was given a sound experimental basis for the first time by Hess (57). Hess had perfected a method of stimulating the brains of unanesthetized, unrestrained cats for several hours following surgical placement of electrodes. Using low frequency and low voltage stimulation he reported sleep-like behavior obtained as a direct stimulation effect (58,59). Stimulation of a variety of points situated lateral to the ventral half of the massa intermedia in the thalamus resulted in a response which varied between drowsiness and a behavior which could not be distinguished from the cat's normal sleep. He points out that the stimulation does not cause the cat to "pass out," but instead, to "seek a comfortable position, which may not be found until after a few postural adjustments." Sleep is obtained after several minutes of intermittent stimulation, and may be interrupted by the application of adequate sensory stimuli. Raising the frequency or intensity of stimulation, however, results in a reversal of effect, sleep being replaced by excitation. A second sleep-like response was observed upon low frequency stimulation in the lateral anterior hypothalamus, including the preoptic and supraoptic hypothalamic areas. This response was termed "adynamia," and was characterized by a fall in blood pressure, assumption of abnormal postures, and muscular plasticity. But, Hess insisted that this adynamia was something other than sleep, being likened more to a lack of volition. Nevertheless, he pointed out that an "inhibition" of motor activity was characteristic of both of these patterns of response. As for the thalamic zone, Hess felt that stimulation here initiated an active process of centrally mediated behavioral inhibition leading gradually to sleep.

These conclusions were vigorously attacked by Harrison (53) in Ranson's laboratory, who reported that sleep was only observed under the condition specified by Hess in animals whose post-mortem histology showed electrolytic lesions at the stimulation points, and, thus, was due to an interruption of the waking mechanism. As was later pointed out (99) however, the somnolence exhibited in animals lesioned by Ransom and his collaborators persisted for several days, whereas Hess' cats slept for only a short time, and could be easily awakened. The acceptance of the findings reported by Hess was only gradually gained in subsequent years, and then only by virtue of an increasing weight of supporting evidence.

One strong bit of evidence suggesting that sleep is an actively induced state was forthcoming from the laboratory of Nauta at Utrecht, Holland. Seriously considering the earlier observations of von Economo, Nauta set forth to put them to an experimental test in rats (99). Using a well controlled surgical approach, he made transections across the base of the brain at various frontal planes, and then observed the post-operative behavior of these experimental animals. As might be expected, transections placed in the posterior hypothalamus produced a state of persistent somnolence, and, thus, led to the interpretation that the "waking centre" had been separated from the rest of the forebrain. On the other hand, transections placed in the rostral half of the hypothalamus, particularly at a suprachiasmatic level, produced a complete insomnia uncomplicated by hypothermia or infection, and leading invariably to a state of lethal exhaustion. Sleepless behavior was only observed following bilateral and complete transections, and was found to be a continuation of relatively normal waking patterns rather than the onset of any bizarre motor activity. From these observations, Nauta concluded that "the rostral half of the hypothalamus, roughly conforming to the suprachiasmatic and preoptic areas, is the site of a nervous structure which is of specific importance for the capacity of sleeping." He disagreed with von Economo's interpretation of a thalamic or cerebral inhibition, suggesting instead, a direct inhibition of the waking center in the posterior hypothalamus. Thus, the sleep cycle was thought to result from periodic decreases in the activity of the waking center, brought about by periodic increases in discharge from the sleep-center in the

rostral hypothalamus. Nauta also pointed out that several parasympathetic functions appear to be localized in the preoptic region. Since the transition from the waking to the sleeping state corresponds to a shift from sympathetic to parasympathetic predominance in the autonomic sphere, he suggests that the rostral parasympathetic area may likewise regulate the sympathetic discharge from more caudal hypothalamic levels. Thus, Nauta also considered the possibility of an active inhibition of lower levels in the nervous system by a more rostral forebrain "center," this being reflected by a decrease in somatic and vegetative functions which is so characteristic of the sleep state.

Although this selective review has considered studies up to about 1950, it is clear that the questions underlying the classification schema remain unresolved. It is true that the concept attributing sleep to a decrease in the sensory afflux to higher centers was strengthened by the discovery of a diffuse reticular mechanism serving to monitor all sensory modalities in establishing conditions favoring wakefulness. But, it was also demonstrated that sleep could be induced directly by stimulation of certain brain structures, or prevented by destruction of others. Thus, sleep could still be interpreted either as a release of higher centers from the waking influence of lower ones, or as a state induced upon these higher centers by a direct process. In either case, and particularly in some of the more recent proposals, the concept of inhibition has become implicated. It was used in reference to a given behavioral pattern by Pavlov and Hees, and to sensory, somatic, and autonomic alterations by Hess and Nauta. To these investigators, the process of inhibition was felt to be of primary importance as a neural mechanism involved in sleep.

EXPERIMENTAL MANIPULATIONS OF THE CNS PRODUCING SLEEP-LIKE ALTERATIONS

We have already seen how experiments employing neurosurgical intervention had served to point out some of the structures involved in the regulation of sleep. Today, it is recognized that several sites within the nervous system are related to the mechanism of sleep regulation. It is significant that these effective regions are rather discrete in nature, and are not so numerous as to place their validity in question. The regions involved are the medial thalamus, caudate nucleus, and caudal brainstem. Other structures also appear to be implicated by virtue of a variety of less direct observations. In the section to follow, these studies will be reviewed in order to amplify the considerations which led to the present investigations.

THE MEDIAL THALAMUS

The forerunner of most of these studies was the classical investigation of the cat diencephalon by Hess (58,59). His observations have already been discussed in relation to the affirmation of active sleep mechanisms in the nervous system. Over a period of some twenty years, Hess collected a wealth of meaningful information from his unanesthetized cat preparations. He did not employ electrical recording techniques in these studies, but relied on the observation of behavioral changes produced by direct stimulation of brain structures. It was in the course of these observations that he discovered a zone in the ventral and medial part of the thalamus which, upon low frequency stimulation, appeared to induce sleep in a previously alert animal. Hess reported that this effect was observed shortly after the cessation of several applied repetitive stimulations, and resembled natural sleep in every way. When high frequency stimulation was delivered to these same sites, however, the animal showed quite the opposite response, one of excitation and arousal. However, Hess chose to refer to this region as a "hypnogeneous zone" due to its ability to "inhibit higher centers" and thereby produce sleep when stimulated at low frequencies. His experiments were repeated some years later by Akert, Koella, and Hesa, Jr. (2) who, additionally recorded ongoing EEG activity. When low frequency stimulation was applied to the

internal medullary lamina of the thalamus, sleep was invariably seen after a delay of a few minutes. Within the first minute after cessation of stimulation, the normally flat EEG pattern of the waking cat was replaced by a pattern of slow wave, spindle burst activity similar to the EEG pattern seen during naturel sleep. These EEG and behavioral changes associated with low frequency stimulation of the intra laminar nuclei of the thalamus are today well documented (3,92).

Additional support for a thalamic synchronizing mechanism was gained from the early work of Morison and Dempsey (32,94) who proposed the existence of a non-specific thalamocortical system arising from the midline and intralaminar nuclei. These investigators observed that low frequency stimulation of the intralaminar group of thalamic nuclei induced recurrent spindle-like potentials in widespread areas of the cerebral cortex, and that these potentials were facilitated by administration of barbiturates, Starzl and Magoun (130) later demonstrated that the "recruiting" response could also be elicited from some of the more rostrally located midline nuclei of the thalamus. This diffuse thalamic projection system, as it was subsequently described by Jasper (64), corresponds roughly to hypnogenous zones stimulated by Hess.

There are, however, several objections to the interpretation that the midline thalamus is a functional sleep center. One is the extreme dichotomy of stimulation effects observed, dependent on the frequency of stimulation. Thus, it has been found that high frequency stimulation (above 30 cps) results in behavioral arousal rather than sleep. This response cannot be distinguished from that produced by stimulation of the mesencephalic reticular formation, and is observed at voltage values far below those capable of inducing the recruiting response at low frequencies of stimulation. One exception to this reaction is the reversal reported by Grastyan and his collaborators in relation to the anterior extent of the nucleus centralis lateralis and parts of the dorsomedial nucleus. Stimulation of these structures at all frequencies is found to induce a behavioral inhibition accompanied by slow wave EEG potentials (51). Monnier *et al*. (93) proposed the existence of reciprocal systems in the medial thalamus, explaining that excitatory drugs increase the high frequency effects of the

so-called ascending reticular relays in the medial thalamus, and simultaneously depress the intralaminary component responsible for recruiting responses at low stimulus frequencies. Moderating drugs (tranquilizers) developed the opposite effects. Intercollicular decerebration lowered thresholds for recruitment, whereas the thresholds for high frequency activation were "greatly increased."

This last observation is of particular interest in view of the more recent findings by Schlag and Chaillet (120). They discovered that lesions in the vicinity of the posterior commissure completely abolished the arousal properties of the medial thalamus, and concluded that thalamic arousal must be effected by projections back to the brainstem from the thalamus. The idea of a functional antagonism mediated rather than generated by the medial thalamus would, thus, appear to make more sense. Such a conclusion would also be more consistent with the fact that complete destruction of these thalamic zones does not alter the sleep cycle (114). Finally, the recruitment induced by thalamic stimulation tends to be limited to association cortex (32, 130), with primary sensory areas developing poor recruiting responses. The EEG sleep patterns commonly observed in the cat are on the contrary, most prominent over other cortical areas (80).

THE CAUDATE NUCLEUS

The caudate nucleus is another brain structure which has been implicated with regard to the regulation of sleep and wakefulness. In a single, rather brief report, Heath and Hodes (54) first described the induction of sleep by electrical stimulation of the caudate nucleus in a rhesus monkey and in a schizophrenic patient with subcortically placed electrodes. This interesting report is difficult to interpret because of an incomplete description of the procedures employed and an apparent lack of follow-up reports. Recently, Stevens, *et al*. (131) noted the onset of quietude and drowsiness with low frequency electrical stimulation delivered to the caudate nucleus in the cat. Compatible EEG changes were also mentioned, but again the description of procedure was scanty, since the primary interest of the authors was directed toward the effects of chemical stimulation.

Somewhat clearer are the studies on the so-called "caudate spindle" by Buchwald and his associates (21,23,24,60). They report that a brief, single electrical shock to the head of the caudate in cats produces a train of high voltage, rhythmical oscillations, which are most prominent in frontal EEG recording leads. The occurrence of these spindles appears to be related to the state of the animal, being facilitated by fatigue and pentobarbital administration, and abolished by simultaneous stimulation of the mesencephalic reticular formation. However, high frequency stimulation of the caudate nucleus evoked the behavioral and EEG manifestations of arousal. On the basis of a series of anatomical and behavioral studies, these investigators have proposed that the caudate nucleus and the related non-specific thalamic nuclei constitute an inhibitory system which effectively "balances and counteracts the system of Moruzzi and Magoun and thus, plays an important role in wakefulness, attention, integration, discrimination, and learning." Studies which have reported the onset of locomotor hyperactivity and other behavioral alterations following caudate lesions (28,29) can be cited in support of this proposal. On the other hand, as far as the behavioral consequences of caudate manipulation are concerned, there have recently been some observations which are inconsistent with previous reports. For instance, Knott, Ingram and Correll (75) found that neither stimulation nor lesioning of the caudate nucleus had any significant effect on rate of bar pressing in trained cats.

A basic question might be raised with regard to the effects of high frequency stimulation. The problems which were discussed in relation to the thalamus apply here as well. It is difficult to explain how primary systems can be functionally capable of opposite influences dependent upon the frequency of discharge. The localization of evoked spindles is another factor which also must be considered. Spontaneous spindles which appear in natural sleep and drowsiness are most prominent over the posterior aspects of the cerebrum. Yet, the spindles resulting from caudate and thalamic stimulation are often restricted to frontal leads, and are clearly more prominent there. As a matter of fact, a rather consistent relationship emerges between the caudate nucleus, anterior thalamic nuclei, and the motor cortex. Together with the well-documented association between the caudate

and corpus striatum (22 ,6 7), these relationships bring to mind the older interpretation of caudate function relating it to somatomotor functions. It could be, however, that the so-called "caudate-loop" is a part of a more general inhibitory system, concerned, perhaps, with an expression of its motor influences.

THE BRAINSTEM

The long awaited description of a waking mechanism in the core of the brainstem was so well received by the world of neurophysiology that it was only natural for many to consider this end of the neuraxis as entirely excitatory, with the exception of its pontine and medullary portions, to which were relegated the autonomic reflex and descending somatic functions. Over the years, however, there have been scattered reports of drowsiness, sleep, and even EEG synchronization encountered when low frequency stimulation was applied in these areas (8,25,110). As a result of several decisive studies, some re-evaluation of brainstem function seems to be in order. Lynes (82) in 1960 reported the specific observation of long-latency, diffuse rhythmical oscillations in the EEG of cats during low frequency stimulation of points in the mesencephalic reticular formation. These same points produce a classical arousal reaction when stimulated at high frequencies. The administration of low doses of pentobarbital facilitated the synchronization elicited with low frequency stimulation. Shortly thereafter, Magnes, Moruzzi, and Pompeiano (84) reported that electrical stimulation in the region of the nucleus of the solitary tract in the medulla, elicits a generalized EEG synchronization in "encaphale isole" cat preparations. Synchronization produced by unilateral stimulation in this region was always expressed bilaterally in the EEG, usually generalized to the entire cerebral cortex, although more marked in occipital and temporoparietal leads, and critically dependent on the type of EEG background activity. EEG activation due to pain or any other overt or implicit disturbance rendered the stimulation ineffective. Thus, it was often necessary to administer small doses of barbiturate in an effort to obtain these effects. With regard to stimulation frequencies, it was found that stimulation rates below that of spontaneous spindling (10-12/sec.)

produced synchronization corresponding to the inherent EEG frequency. Stimulation at slightly higher frequencies caused the repetition rate of the response to follow that of the stimulus, and any further increases in frequency produced EEG arousal. Another group of investigators found very similar effects, but from more diffuse stimulation sites. Favale, Loeb, Rossi, and Sacco (37), in Genoa, observed a generalized EEG synchronization induced by stimulation applied at low frequencies to a variety of midbrain, pontine, and medullary loci within the reticular formation. Extra-reticular points in the brainstem were either ineffective or had excitatory effects at low frequencies of stimulation. Here, also, background EEG activity proved to be a critical variable. Accordingly, "Synchronizing effects could consistently be elicited only when the EEG activity was of the type usually observed in the relaxed waking animal. No EEG-synchronizing effect could be obtained on a background of complete desynchronization such as that occurring during alertness, nor could it be recognized on background of continuous synchronization accompanying sleep." Behavioral effects were only observed in these experiments in relaxed (and apparently only in reclining) animals with the appropriate EEG background, and only after repeated stimulations was a tendency to sleep observed. Barbiturates at first appeared to facilitate the EEG response, but when barbiturate EEG patterns are seen, the synchronizing effects were lost. When stimulation frequencies exceeded 20 per second, the typical EEG of behavioral arousal was once again observed.

It is now apparent that under certain conditions, direct stimulation of the brainstem can elicit EEG synchronization and a tendency toward behavioral sleep in animals. This ability is, however, extremely sensitive to ongoing levels of activity in the cerebral cortex, and, like all of the other synchronogenic structures which have been discussed, appears entirely dependent upon the frequency of stimulation applied. Unlike these other structures, the induced cortical synchronization is very similar to the spontaneous rhythms of natural sleep. There is also a difference in the effects of barbiturates on brainstem induced synchronization and the synchronization induced by thalamic or caudate stimulation. In the former, barbiturates facilitate the induction of synchronization, at least initially, whereas

in the latter, potentiation of the actual evoked response is observed.

Although it is well known that lesions placed in the mesencephalic reticular formation produce somnolence and coma, complete transection of the brainstem at various levels is observed to produce some different, but equally interesting effects. Such a transection at a midpontine, pretrigeminal level results in a preparation which is in the waking state both behaviorally and in terms of EEG patterns (12).

In contrast to this, the preparation with a cervical spinal cord transection is observed to show increasing drowsiness and sleep patterns in the EEG. This suggests that certain structures lying between these levels can exert a synchronizing influence on the EEG, perhaps related to that observed under appropriate conditions by the electrical stimulation of these structures.

THE BASAL TELENCEPHALON AND PREOPTIC AREA

In the course of his studies, Hess described a state, which he termed "adynamia," and which was obtained upon stimulation of the supraoptic and preoptic areas in the lateral anterior hypothalamus. It was characterized behaviorally by a lack of spontaneous activity, assumption of abnormal postures, and a decrease in muscle tone. Even when manipulated these cats remained entirely unreactive, thus, prompting his conclusion that "the responsiveness of certain central nervous structures is reduced considerably." Hess went on to differentiate this area (including the septum) from the more posterior portions of the hypothalamus, describing it as a "phylactic" or "trophotropic" zone responsible for protective mechanisms in relation to visceral and somatic function. It is now well documented fact that the rostral region at the base of the forebrain exerts an inhibitory action upon a number of visceral, somatic, and endocrine systems. Included in this region are the preoptic and the supraoptic areas of the rostral hypothalamus and the basal telencephalic structures underlying the olfactory tubercle, diagonal band (of Broca), and the amygdaloid nuclei.

The evidence of such influences can be drawn from several excellent

sources. In addition to the detailed descriptions provided initially by Hess, there have been more recent reviews of this work containing additional and supporting evidence (1,47). Other investigations have been performed on anesthetized animals by Ranson and his collaborators and are presented collectively in an extensive review by Ranson and Magoun (114). Another detailed series of experiments involved stimulation of the cortical surface of the basal and medial forebrain in a variety of animals, and in a number of different experimental conditions (70,71). In addition to these major works, there were many other equally competent researches to which we shall refer in viewing the influences of the rostral basal forebrain on the rest of the nervous system.

STIMULATION EFFECTS

A) *Autonomic.* Low frequency electrical stimulation of the lateral preoptic area and supraoptic region of the hypothalamus results in a lowering of arterial pressure which is usually associated with a drop in heart rate and a cutaneous vasodilation (1,47,50,52,59,113). A decrease in rate and amplitude of respiration, with a tendency toward inspiratory arrest is also seen during stimulation in these areas. Stimulating a specific zone extending from the septum, through the diagonal band to the preoptic area, Kabat, Magoun, and Ranson (72,113) also observed a consistent fall in the arterial pressure of the cat. When high frequency (40-60 cps) stimulation is applied to the posterior orbital cortex, olfactory tubercle, and telencephalic sites adjacent to the posterior olfactory tract and trigone, a marked drop in arterial pressure was observed together with a reduction of inspiratory amplitude, or complete respiratory arrest (70). Stimulation of the medial aspect of the amygdaloid complex also produced these effects. Lateral preoptic stimulation, in addition, resulted in pupilloconstriction and protrusion of the nictitating membrane in cats (1,47,70). It is also noteworthy that penile erection is frequently observed upon stimulation of preoptic and basal telencephalic sites (83).

B) *Somatic.* Several authors, including Hess, have reported motor inhibition upon stimulation of rostral hypothalamic and preoptic

areas. In some instances this is evidenced by a marked decrease in motor activity accompanied by a general atonia of the musculature (1,47,50,59). In others, a cortically induced reflex movement was blocked by simultaneous stimulation of these areas (1,44, 50). Working within another context, Heminway *et al*. (55), noted a suppression of peripherally recorded shivering in anesthetized cats during preoptic stimulation. Kaada (70) described two cortical zones capable of inhibiting spontaneous movements, cortically induced movements and spinal reflexes. One area was the rostral portion of the limbic gyrus surrounding the genu of the corpus callosum and the other consisted of the basal telencephalic region mentioned in relation to autonomic alterations in the previous section. It is interesting to note that both Hess, working in the preoptic area, and Kaada, exploring basal telencephalic zones, reported the observation of eye closure associated with the other somatic responses resulting from stimulation.

C) *Endocrine.* Although neuroendocrinologists have been exploring the brain for some years in an effort to locate structures mediating the release of the pituitary hormones, it is only in recent years that an appreciation of hormone inhibiting influences has been realized. Thus, Slusher and Hyde (126) reported that stimulation of certain limbic sites resulted in significant decreases in corticosteroid levels in the adrenal venous effluent of cats. The sites yielding the greatest decreases were the preoptic region, the diagonal band (of Broca), and the lateral amygdala. Conversely, cooling of the preoptic area resulted in an increased liberation of thyroid hormone, which suggested that this area exerts a tonic inhibition of thyroid activity which is released by cooling (5). Additionally, von Euler and Folkow (36) have reported a fall in catecholamine secretion during stimulation of posterior orbital cortex at voltage levels below the threshold for blood pressure effects, and Goldfien and Ganong (49) have recently observed a similar tendency when suprachiasmatic and prechiasmatic basal regions were stimulated.

D) *Cortical.* As early as 1943 Morison, Finley and Lothrop (95) had lowered exploratory electrodes into basal forebrain areas and recorded EEG patterns simultaneous to the delivery of electrical stimulation. They noted a slight inhibition of the intermittent 6 to 10 per

sec. bursts which characterize the EEG of barbiturate-anesthetized preparations and they concluded that sensory and extrapyramidal fiber systems, passing through these zones went being stimulated on their way to the thalamus. Kaada (70, 71), on the other hand, stimulated the olfactory, tubercle, orbital and rostral piriform cortex, and the anterior limb cortex and observed an augmentation of the intermittent bursting activity in the EEG of anesthetized cats. A striking corollary to this finding was the tendency of unanesthetized animals to show sleep-like behavior during stimulation of these zones. This is particularly interesting in view of an earlier observation made by White (138). In the course of a series of therapeutic surgical interventions into the third ventricle of patients, he noted that "Mechanical stimulation during dissection in the region of the optic chiasm and uncovering the anterior portion of the hypothalamus produced a striking parasympathetic response in all of the patients where (only) local anesthesia was employed." To this he added that "drowsiness, which may merge into unconsciousness within a few minutes, is a common sequel to operative manipulation above the chiasm. This develops suddenly and synchronously with the reflex slowing of the heart." A cortical influence would seem to be implicated by these observations.

LESION EFFECTS

We have already seen how Nauta's suprachiasmatic transections across the base of the forebrain in rats produced a condition of sleeplessness and lethal exhaustion (99). It is a well documented fact that lesions placed in these basal telencephalic and preoptic regions produce rather marked alterations in behavior, which may be generally classified as 'hyperactivity.' Investigators have noted excessive locomotion and insomnia brought about by preoptic, anterior hypothalamic (16, 41,88) posterior orbital cortex or basal olfactory lesions (108, 118). These patterns have been observed in rat, cat, dog and monkey. In addition to this, marked emotional changes which may take the form of apparent viciousness (16,41) or a pattern referred to as "sham-rage" (129) have been described in association with pre-chiasmal lesions at the base of the brain or confined to the olfactory tubercle and septal region. An increase in arterial pressure and pulse

rate has also been observed following anterior hypothalamic lesions (45).

Thus, it may be concluded that transections separating the basal telencephalon from the diencephalon, or ablations destroying the basal telencephalic and anterior hypothalamic region produce an increase in somatic, visceral, and certain endocrine functions, and this may be characterized as a release from some restraining or counteracting influence. On the other hand, stimulation of the basal telencephalon and preoptic area evokes a restraining influence upon these same functions. Taken together, these facts suggest that the anterior hypothalamic and preoptic areas and the basal telencephalic region lie in close functional relation to these organ systems. It would appear to be entirely proper to describe this relationship as inhibitory, since the collective influence upon peripheral function is, in almost every case, similar to the type of response to which the term inhibition has been applied in the past. Additionally, the type of functional change which is induced by stimulation of these areas is also very similar to those changes which are observed to accompany the natural onset of sleep. As we have seen, several investigators have even noted sleep-like behavior during manipulation of these sites (70,138). Here, then, is a region in the nervous system to which inhibitory action can be empirically ascribed and which may also be involved in the phenomenon of sleep.

The purpose of this rather extensive introduction has been twofold. When we realize the important contributions which a concept of neural inhibition has made toward our understanding of regulation at lower levels of neural function, we are better able to appreciate its potential importance in the more complex functions of the nervous system. Secondly, although some controversy still exists, we wished to demonstrate the fact that most investigators would agree that inhibitory action is in some way involved in the neurophysiology of sleep, and show that an increasing interest in the brain mechanisms responsible for this inhibition is today apparent.

As a result of these considerations, and those mentioned previously, our interest became directed toward the basal forebrain region as a site of potential importance in this regard. However, if the influence of this region is generally inhibitory and related to the neural mechanisms of sleep, one might predict an influence directed from this region toward the cerebral cortex. Since an influence of this kind has never been described, our initial experiments involved a neurophysiological exploration of the functional relationships between the basal forebrain region and the cerebral cortex in the cat.

Pages 203-214: *A facsimile of the original bibliography of Barry Sterman's PhD Dissertation*

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ABOUT BRAINCLINICS

Research Institute Brainclinics was founded in 2001 as an independent research institute by Dr. Martijn Arns (biological psychologist).
Brainclinics specializes in advancing our understanding of the brain and the results of our research are a valuable aid in the treatment and prevention of symptoms such as mood-, concentration-, impulse control-, and sleep-problems, often seen in disorders such as depression, ADHD, and insomnia.
In addition, a key topic of our research revolves around 'personalized medicine', going beyond the traditional 'diagnostic-thinking' and focusing on individual differences that can help optimize and individualize treatment and prevent symptoms from occurring.

Brainclinics researchers have published over 100 scientific publications on these and related topics and continue to collaborate with researchers and universities around the world ranging from Australia, Germany, Belgium, the United States to Colombia.
Brainclinics pioneered the application of neurofeedback in the treatment of ADHD and insomnia, was one of the first to recognize the importance of sleep problems underlying many symptoms like loss of concentration and impulse control while also pioneering and refining magnetic brain stimulation (rTMS) in the treatment of depression and obsessive–compulsive disorder (OCD).
Our research has resulted in several spin-offs, such as Brainquiry, neuroCademy and, more recently, an international network of neuroCare clinics, where our knowledge and expertise are applied to benefit people worldwide.

Brainclinics Insights is the publishing division of our institute. Our mission is to make our knowledge, expertise and especially 'Insights' gained through our research, widely available through books and interactive media.
All proceeds of the publishing division are fully invested back into the research that is conducted at Research Institute Brainclinics, which creates an unprecedented synergy between these divisions and generates new future insights.
Please visit brainclinics.com to learn more.

Neurofeedback offers exciting potential for understanding the brain and human behavior as well as the treatment of epilepsy and ADHD. Its rich history, from the discovery of the EEG in 1875, via the beginnings of the field of neurofeedback in 1936, to the foundation of the clinical application in the summer of 1969 is finally brought to life.

It's a compelling read, often from an eyewitness account, in which we meet an eccentric Wallstreet millionaire, a telepathy-inspired psychiatrist, a Soviet scientist's encounter with Stalin, a British Baron, a former street gang member and a group of forward thinking West Coast scientists. Discover how they all played a vital role in shaping the future of neuroscience and neurofeedback.

Dr. Martijn Arns, Research Institute Brainclinics, Nijmegen and Department of Experimental Psychology, Utrecht University, The Netherlands. Dr. Arns is specialized in applied neuroscience and personalized medicine and is one of the most published researchers in the field of neurofeedback. He is founding director of Research Institute Brainclinics since 2001, Scientific Adviser to neuroCare Group (a Brainclinics spin-off) and has been affiliated with Utrecht University, Department of Experimental Psychology since 2009.

Dr. Maurice (Barry) Sterman, Professor Emeritus, Departments of Neurobiology and Biobehavioral Psychiatry, David Geffen School of Medicine, University of California, Los Angeles, CA.
Dr. Sterman had faculty appointments at Yale, UCLA, Tokyo University, University of Alberta (Edmonton) and is generally considered the founder of neurofeedback and specialized in the study of neural mechanisms underlying neurofeedback.

Brainclinics® INSIGHTS

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