EDITORIAL

Sleep, Dream, Hypnosis and Healing: Behavioral State-Related Gene Expression and Psychotherapy

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Profound advances in research on the molecular-genetic basis of sleep and dreams have important implications for understanding the deep psychobiological dynamics of hypnosis, psychotherapy and healing. The essence of this new view is that Immediate-Early Genes (also called "Primary Response Genes" or third messengers) play a central role in the dynamics of waking, sleeping, dreaming, and mind-body healing at the cellular level. This paper reviews evidence that immediate-early genes (IEGs) function as mediators of information transduction between psychological experience, behavioral states, and gene expression. A wide range of behavioral state-related gene expression (from relaxation, hypnosis and sleep to high arousal, performance, stress and trauma) culminate in the production of new proteins for homeostasis, physical and psychosocial adaptation. Some theoretical and clinical implications of this new view of the deep psychobiology of consciousness, sleep, dreams, hypnosis and psychotherapy are explored. (Sleep and Hypnosis 1999;1:141-157)

Key words: *consciousness, sleep, REM, hypnosis, immediate-early genes, psychobiology, psychotherapy, psychosomatic, behavioral state-related gene expression*

INTRODUCTION

While common experience suggests that behavioral states such as sleep, dreams, and hypnosis are somehow associated with restoration and healing, there is no general agreement about how they are related. We do not have a general theory of how such behavioral states are to be defined or even what the most relevant facts are for understanding them. What level of empirical observation and experimental data, for example, is most fundamental in conceptualizing the relations between waking, sleeping, dreaming and hypnosis? About 100 years ago academic psychology was declared to be an empirical science independent of philosophy on the one hand and biology on the other (1). A direct although unrealized assumption of this endeavor to make psychology an independent discipline was to maintain a spurious separation between the sciences of mind and body. Without quite realizing its implications, the newly created field of academic psychology maintained and even affirmed the Cartesian dualism between mind and body.

Profound advances in psychosomatic medicine, endocrinology, psychobiology, neuroscience, and molecular biology in general now call into question the wisdom of this artificial division of the psychological, behavioral and physiological into different levels of investigation (2,3). With the advent of the near completion of the Human Genome Project the most insightful paradigms of experimental research are becoming more cross-disciplinary (4,5). The intrinsic relatedness of mind, behavior and body are being recognized in the development of new concepts such as "behavioral state-related gene expression" (6; p. 245). Classical genetics has explored biological determinism: the way genes determine the outer, phenotypic expression of life forms and their behavior. Research on the molecular components of the

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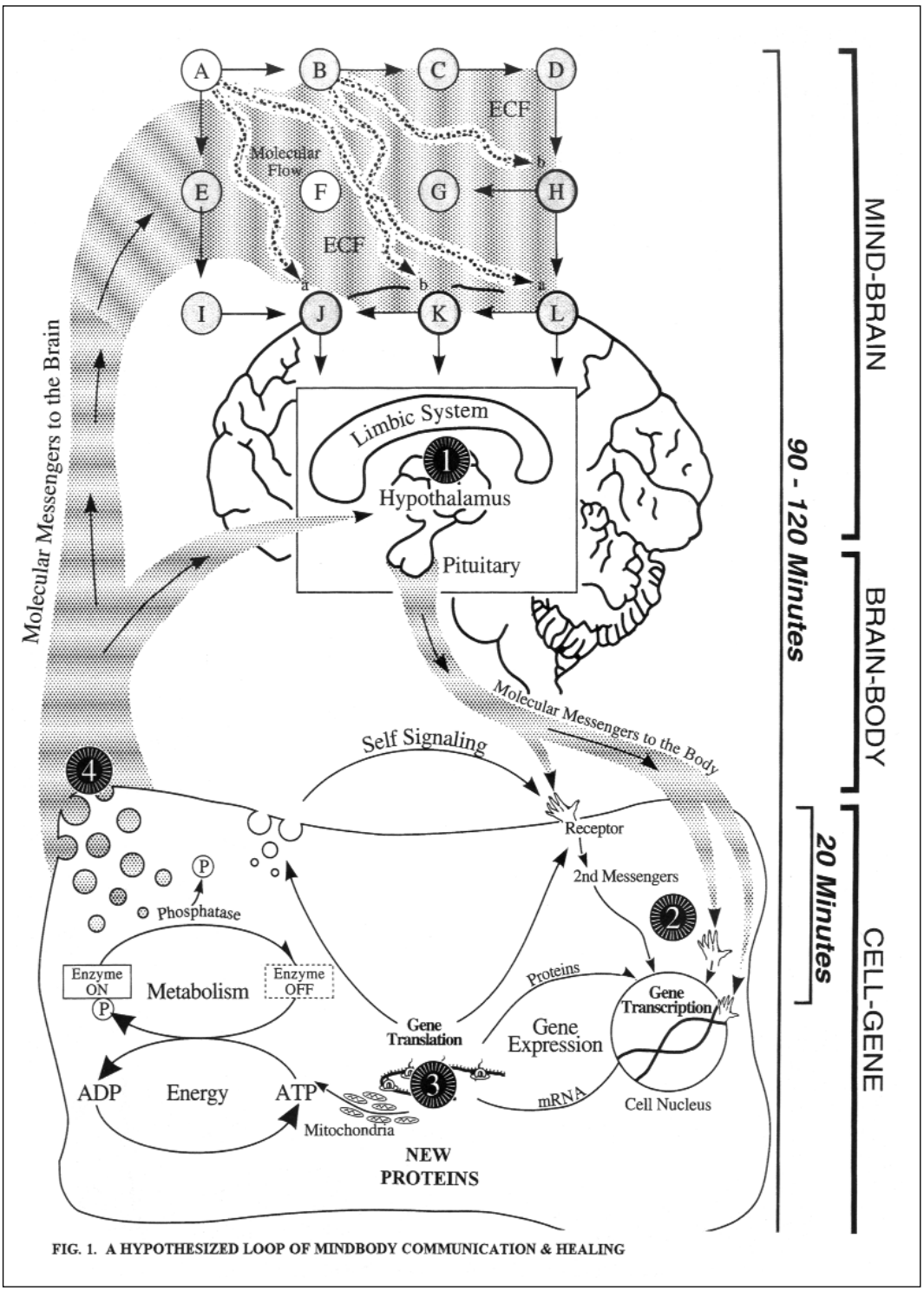


Figure 1. The mind-body communication loop illustrating the "Unification Hypothesis of Chronobiology" wherein the rhythmical flow of messenger molecules such as sexual and stress hormones mediates communication between the mind-brain, brain-body and cell-gene levels in psychological time. The brain's neural networks at the top (symbolized by the rectangle of neural units A through L that receive molecular signalling through the Extra Cellular Fluid (ECF)) are regarded as a field of complex, self-organizing communication processes that are the psychobiological basis of mind, memory, learning, and psychosomatic medicine.

circadian clock in terms of the per and tim genes (7) as well as ultradian rhythms in behavior (8) are examples of such biological determinism. The new interdisciplinary approach of behavioral state-related gene expression, by contrast, is beginning to explore how behavioral states modulate certain patterns of gene expression. This implies that the interaction between the genetic and behavioral levels is a two way street. Genes and behavior are related in cybernetic loops of mind-body communication (9-12). This suggests a deep psychobiological approach for conceptualizing the relatedness of the behavioral states of awake, sleep, dream, and hypnosis and their implications for a new

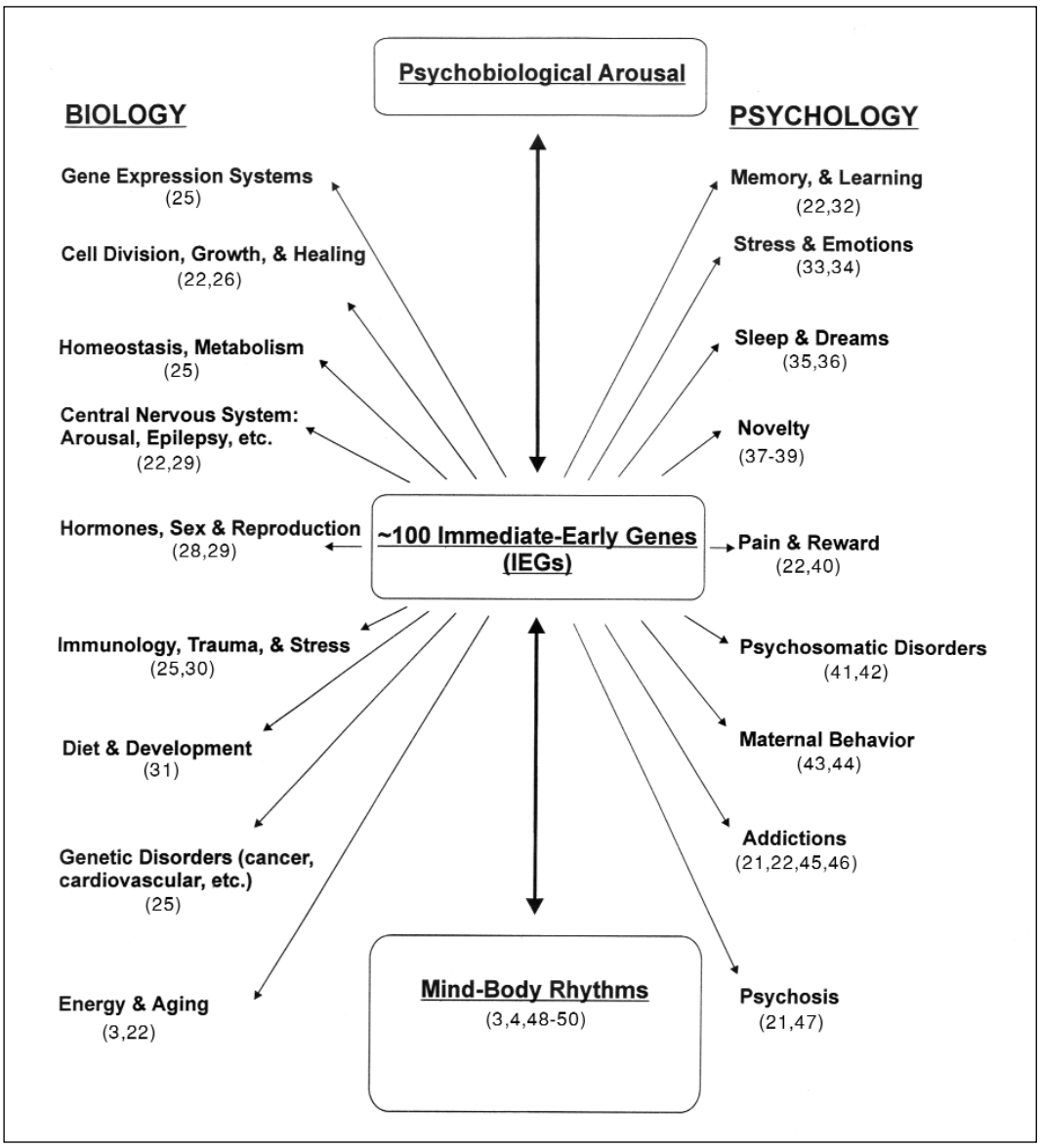


Figure 2. The central role of immediate-early genes (IEGs) in psychobiology. Many arousing stimuli from the physical and psychosocial environment can signal IEGs, which, in turn, initiate a gene-protein cascade in neurons of the brain and other cells of body to simultaneously modulate biological and psychological processes. Note the reciprocal relationships along the central axis between the levels of psychobioloical arousal, IEGs and Mind-Body rhythms. Each of these three levels is a window into the continuum of mind-body communication, adaptation and healing.

model of mind-body communication and healing in psychotherapy as illustrated in Figure 1.

A Four Stage Model of Mind-Body Communication and Healing

A highly simplified four stage model of mind-body communication originally developed to conceptualize healing in hypnosis (10,11) will be extended here to explore the relatedness of the states of awake, sleep, dream and hypnosis at the cellular-genetic level.

Stage One: Mind-Brain Information Transduction. The Limbic-Hypothalamic-Pituitary System is currently recognized as a major information transducer between the brain and the body (13). The Scharrers (14) and Harris (15) documented how the secretary cells within the hypothalamus mediate information transduction between brain and body. We would now recognize their work as an initial step in bridging the historical Cartesian gap between mind and body on the cellular-genetic level as illustrated in Figure 1. Cells within the hypothalamus transform the essentially electrochemical impulses (waves of depolarization) of the neurons of the cerebral cortex (that apparently encode the phenomenological experience of "mind" and

emotions) into the hormonal messenger molecules of the endocrine system. These hormones (now called "primary messengers" or "informational substances") flow through the blood stream in a cybernetic loop of information transduction between brain and body. This complex loop of communication composed of hormones modulates the action of neurons and cells at all levels from the basic pathways of sensation and perception in the brain to the intracellular dynamics of gene transcription and their translation into proteins throughout the body (10,11). It has been proposed that these molecular messengers or informational substances of the endocrine, autonomic and immune systems mediate stress, emotions, memory, learning, personality, behavior and symptoms (11). This communication loop has been described as a "psychosomatic network" (16,17) that is a two way street by which (1) mind can modulate physiology of the brain and body and (2) biology, in the form of informational substances, can modulate mind, emotions, learning and behavior (10-12).

Stage Two: Immediate-early genes mediating behavioral state-related gene expression in awake, sleep and REM sleep. Current theory and research in molecular biology and neuroscience conceptualizes all living cells as information processors and problem solving systems (18,19). Marijuan (20) regards the flow of "bioinformation" through the cell as the basic dynamic mediating "work-cycles" of fundamental life processes such as self-organization, self-modification, and self-reconfiguration. Secondary messengers within the cell (such as cAMP, cGMP, Ca, InsP3, diacylglicerol, ceramide, arachidonic acid, NO) convey the extracellular signals (e.g. the primary messengers of the psychosomatic network described above) to the nucleus of the cell where they initiate gene transcription and translation as illustrated in Stage two Figure 1. Classical genetics regards genes simply as the units of biological heredity that are transmitted from one generation to another through some form of reproduction. Today we know that there are many classes of genes that are activated to carry out the important life functions of homeostasis, adaptation, learning and healing in everyday life. One major class of such genes called "Immediate-Early Genes," (or "Primary Response Genes" or "Third Messengers") are expressed continually in response to hormonal messenger molecules mediating processes of adaptation to extracellular signals and stimuli. Many of these extracellular stimuli ultimately come from the environment outside of the organism such as temperature, food, sexual cues, psychosocial stress, physical trauma and toxins. It is now known that there are persistent alterations in immediate-early gene (IEG) expression in the process of adaptive behavior on all levels from the sexual and emotional to the cognitive (3,21,22).

Immediate-early genes (IEGs) have been described as the newly discovered mediators between nature and nurture (12,23). IEGs transduce signals from the external environment to regulate the transcription of other "target genes" that code for the formation of proteins that carry out the homeostatic and adaptive functions of the cell. IEGs can therefore initiate series of molecular-genetic transformations that can transduce relatively brief signals from the environment into enduring changes in the physical structure of the developing nervous system as well as its plasticity in the form of memory and learning throughout life (24). C-fos, for example, is an immediate-early gene that is turned on by arousing or stressful environmental stimuli to activate neurons of the brain where it leads to the production of a protein called "Fos." Fos can then bind on to the DNA molecule where can turn on, that is, lead to the transcription of it other target genes. C-fos in combination with other IEGs such as those in the jun family can regulate and be regulated by other families of genes that are involved in the material, energetic and informational dynamics of the cell in response to psychosocial cues as well as physical stress and trauma.

Most drugs dealing with pain and addictive drugs such as cocaine, amphetamine and the opiates are mediated by immediate-early genes. The implication is that immediate-early genes are central in mediating human moods and behavioral addictions (21). Immediate-early genes are used as markers or indicators of changes in neuronal activity in psychopathological conditions such as schizophrenia. Anti-psychotic drugs are currently being designed to modulate the effects of immediate-early genes on pathways leading to the production and utilization of neurotransmitters such as dopamine, serotonin and noradrenaline that are implicated in the "dopamine hypothesis" of schizophrenia. It is

the simultaneous mediation of both the biological and psychological functions - the psychobiological - that recommends a central role for immediate-early genes in understanding the foundations of psychosomatic and holistic medicine as suggested by the summary illustrated in Figure 2. While more than 100 immediate-early genes have been reported, most of their functions still remain unknown. In this paper we will focus primarily on the newly recognized role of IEGs in the behavioral states of awake, sleep, dreaming and, by implication, hypnosis.

Most arousing environmental stimuli that have been studied can induce immediate-early genes within minutes, their concentrations typically peak within fifteen to twenty minutes and their effects are usually over within an hour or two. These time parameters in IEG expression and their ultimate translation into the formation of new proteins correspond to the parameters for a complete work cycle of mind-body communication and healing as illustrated on the right of Figure 1. The changes in gene transcription and new protein formation initiated in this time frame, however, can lead to lasting changes in the central nervous system by converting short term memory to long lasting learning by the process of long term potentiation (51,52).

The most fundamental experimental evidence that IEG expression is associated with behavioral states of arousal, awake, sleep and dream (REM sleep) in the ultradian time frames (90-120 minutes) of Figure 1 comes from the finding of oscillations in IEG expression during the circadian sleep-wake cycle. Bentivoglio and Grassi-Zucconi (6; p. 241), for example, summarize their findings as follows:

"We observed that Fos immuno-reactivity increased in the brain in parallel with the increase in the proportion of wake in the 1.5 hr preceding sacrifice. In other studies, rats that had been awake in the dark were compared to animals that had been spontaneously awake during the light period for about 30 min before sacrifice, and c-fos expression was found to be higher in the former group than the latter. These studies confirmed an increase of Fos expression after a sustained (1.5-hr) period of spontaneous wakefulness in respect to a short (0.5-hr) period, which, however induced c-fos mRNA expression but was not sufficient for adequate protein synthesis."

The research team of Cirelli, Pompeiano, and Tononi (50; p. 46) confirm this ultradian time frame of the behavioral states of arousal, awake, and sleep associated with IEG expression as follows:

"Over the last few years it has become clear that the activation or deactivation of the expression of specific genes can occur in a matter of hours or even minutes. This time frame is compatible with the duration of sleep-wake states and with the time constants of their regulation. Thus, it becomes relevant to ask whether gene expression in the brain changes across the sleep-wake cycle and after sleep deprivation. A parallel series of studies indicated that after a few hours of sleep deprivation the patterns of IEG expression were remarkably similar to those observed after spontaneous wakefulness, suggesting that such patterns are associated with waking per se, rather than with circadian or stress factors. Recently we showed. that the expression of c-fos during waking is strictly dependent on the level of activity of the noradrenergic system. In our studies, the most consistent increase in Fos expression during waking was found in the preoptic area (POA) of the hypothalamus, a region that has been previously implicated in sleep regulation. Thus, Fos protein expression in the POA during waking may be an integral part of mechanisms that assess the duration and intensity of prior waking and/or the homeostatic or executive mechanisms that bring about sleep."

Fos expression is also used to identify neuronal networks that are associated with REM sleep and dreaming. Merchant-Nancy et al. (53) found c-fos proto-oncogene expression changes in relation to REM sleep duration. The brain distribution of c-fos expression was found to include brain stem regions, the basolateral amygdala and the lateral hypothalamic area which are all part of the neuronal network associated with the dynamics of REM sleep (54). Fos expression was also found in the locus coeruleus, dorsal raphe, medial pontine reticular formation and mesopontine nuclei that contain REM-on and REM-off neurons (55,56). Fos expression was evident in the cat in the pons and medulla, the medial and lateral vestibular nuclei and the motoneurons of the nucleus abducens associated with the generation of pontine-geniculo-occipital (PGO) spikes and REM sleep (57).

Bentivoglio and Grassi-Zucconi (6; p. 249) summarize the current implications of these

and other studies that raise fundamental questions as follows: "The study of IEGs indicates that sleep and wake, as well as synchronized and desynchronized sleep, are characterized by different genomic expressions, the level of IEGs being high during wake and low during sleep. Such fluctuation of gene expression is not ubiquitous but occurs in certain cell populations in the brain. Thus IEG induction may reveal the activation of neural networks in different behavioral states. Although stimulating, these findings leave unanswered a number of questions: Do the areas in which IEGs oscillate during sleep and wake subserve specific roles in the regulation of these physiological states and a general 'resetting' of behavioral state? Is gene induction a clue to the understanding of the alternation of sleep and wake, and of REM and non-REM sleep?

"The inducibility of transcription factors indicates that external cues can modulate cell function through regulation of gene expression. The variation of IEG expression during sleep and wake seems to indicate that this could also be true for internal cues. The high expression of IEGs during wake could be related to the animals activity, to "a momentary excitation of single neurons in the course of transferring physiological 'everyday information'. In view of the role played by transcription factors in neural plasticity, could behavioral state-related IEG induction underlie, at least in part, learning mechanisms? The oscillations of IEGs affects the expression of target genes, and this brings about other questions: May the transcriptional cascade explain the biological need and significance of sleep? Does this explain the molecular and cellular correlates of arousal, alertness, and more in general, of consciousness?"

These fundamental questions raised by researchers on the cellular-genetic level surely indicate that a profound rapprochement will be taking place between biology and psychology in the new millennium. Over twenty-five years ago the author (12) formulated "The Dream-Protein Hypothesis: Recent studies of learning and memory indicate that new experience is encoded by means of protein synthesis in brain tissue. Dreaming is a process of psychophysiological growth that involves the synthesis or modification of protein structures in the brain that serve as the organic basis for new developments in the personality" (58; pp. 1094). Recent research has documented that new proteins are synthesized in some brain structures associated with REM dream sleep such as the nucleus raphe dorsalis and the locus coeruleus (3,36,50,59,60). As a seminal hypothesis for mindbody medicine of the future, I would generalize the dream-protein hypothesis to include all states of creativity associated with the peak periods of arousal and insight generation in psychobiologically oriented psychotherapy (12).

There is as yet no research exploring the effects of hypnosis, psychotherapy or any other of the approaches of alternative and complementary medicine on the expression of immediate-early genes and their role as transcription factors in regulating a wide variety of target genes and their translation into proteins that regulate mind-body communication and healing. I propose, however, that a truly deep psychobiological model of how psychotherapy operates at the cellular level to facilitate real mindbody healing on a physical as well as on the emotional and mental levels must involve these molecular-genetic levels. An example of how psychosocial stress can activate IEGs that regulate expression of the interleukin-2 receptor gene that is of significance in the informational dynamics of the immune system is described next in Stage 3 of Figure 1.

Stage Three: New Protein Synthesis: Psychoimmunology and Brain Growth. The third stage in the mind-gene communication loop is illustrated as the process of gene translation via the production of messenger RNA (mRNA) and new proteins in Figure 1. We will cite here research in two areas of special interest for their implications for a new appreciation of the deep psychobiology of hypnosis and psychotherapy.

1. Psychoimmunology: The research team of Ronald Glaser (61,62) reported a clear demonstration of how psychosocial stress can modulate gene expression. Their research traced the effects of psychological stress (experienced by medical students during academic examinations) on the transcription of the Interleukin-2 receptor gene and interleukin-2 production. These researchers documented the path of information transduction illustrated in Figure 1 from the (1) the limbic-hypothalamic-pituitary system's hormones (primary messengers) that trigger

(2) cell receptors to initiate (3) a cascade of secondary messengers (cAMP) that mediate gene transcription which leads to messenger ribonucleic acid (the mRNA "blueprint" of the gene) production and the synthesis of new proteins that leads to the formation of (4) other messenger molecules of the immune system that can flow back to the brain via the blood stream to modulate mind, memory, emotions and behavior in a state dependent manner.

Glaser's research has profound significance for a general theory of mindbody communication and healing when we realize that other medical researchers (63) have found that interleukin-2 is a messenger molecule of the immune system that signals white blood cells (cytotoxic T-cells) to attack pathogens and cancer cells. Thus, a purely medical model of research represented by Rosenberg and a holistic model represented by Glaser have found the same foundation in mindbody communication at the level of gene expression in the field of psychoimmunology. It has been proposed (10-12) that such research on the deep psychobiological gene-protein level will become the new criterion for evaluating all forms of mindbody healing in the future - biofeedback, body therapies, message, meditation, imagery, active imagination, hypnosis, prayer, ritual or whatever.

2. Brain Growth: Current research documents how new protein synthesis leads to the actual growth and development of new cells and their interconnections in the hippocampus of the mature human brain that are associated with new memory and learning (27). In mature mice and primates, for example, the experience of enriched environments and novelty initiates IEG cascades leading to the formation of new proteins and 15% more granule cell neurons along with increased synapses and dendrites in the dentate gyrus of the hippocampus that encode memory and learning (38). Other researchers (39) have found that voluntary exercise such as running can double the number of newborn cells in the dentate gyrus of the hippocampus of the adult mouse in amounts similar to enrichment conditions. On the other hand, researchers have documented how excessive trauma and psychosocial stress can lead to a suppression of growth processes in the brain of primates (65) and rats (66).

Such experimental findings present us with a deep psychobiological perspective for a new paradigm of research on hypnotherapeutic approaches in the future. In so far as hypnosis or any other psychotherapeutic approach can contribute to psychobiological arousal, enrichment and relaxation, it may be possible to help people find optimal levels of mental stimulation to facilitate actual growth in the hippocampus of their brain to encode new memory, learning and behavior. This prospect for the future of hypnotherapy in optimizing psychobiological growth and healing echoes the views of James Braid (67) who originally conceptualized hypnosis as the "physiology of fascination." The author (68) has recently emphasized this theme by hypothesizing, "Enriching life experiences that evoke psychobiological arousal with positive fascination and focused attention during creative moments of art, music, dance, drama, humor, spirituality, numinosity, awe, joy, hope, expectation, and social rituals can evoke immediate early gene protein cascades to optimize brain growth, mindbody communication, and healing in the therapeutic applications of hypnosis." Interdisciplinary research on molecular biology of hypnosis will be required to assess this hypothesis and others in the new realm of behavior state-related gene expression.

Stage Four: Messenger Molecules, Brain Growth and State Dependent Memory, Learning and Behavior. Stage Four of Figure 1

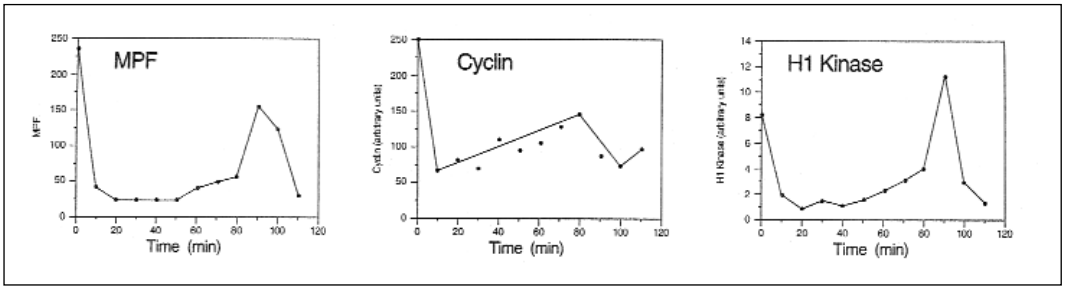


Figure 3. The Cellular-Genetic Level. In this series of graphs it can be seen that a typical 90-120 minute ultradian rhythm is fundamental in cell growth and replication. The approximately 20 minute peak in Maturation Promoting Factor 9 MPF, the protein Cyclin and the enzyme H1 kinase act in concert to signal the final stage of genetic replication and cell division (mitosis) (81). Some researchers believe this may be the basic ultradian pacemaker that sets all other levels such as the metabolic, neuroendocrinological, cognitive-behavioral and the socio-cultural as illustrated below.

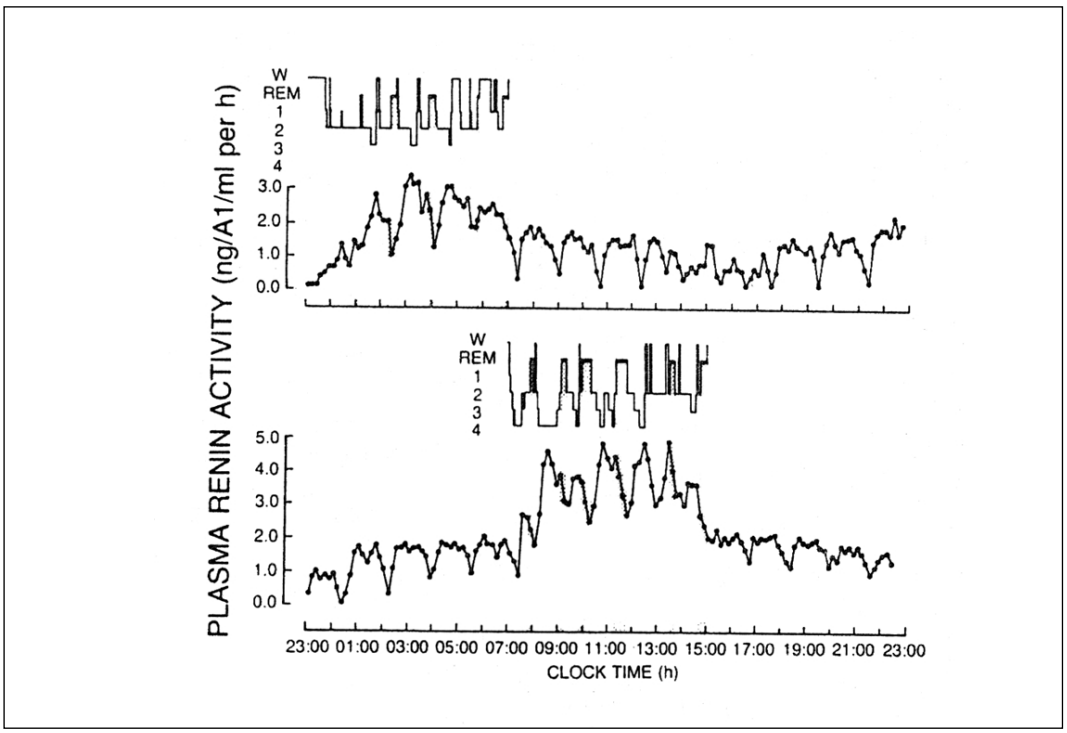


Figure 4. The Endocrine-Behavioral Level. An example of the interaction between the cognitive-behavioral and hormone levels. The typical 90-120 minute ultradian rhythms in the pulsate expression of the endocrine renin-angiotensin-aldosterone system have their higher amplitude peaks shifted to the right by an 8-hour delay of the sleep-wake cycle in the lower graph. The small inset on the upper part of each graph illustrates the relationship between plasma renin and the stages of waking counciousness, Rapid Eye Movement Sleep (REM Dreaming State) and the four major levels of sleep depth (82).

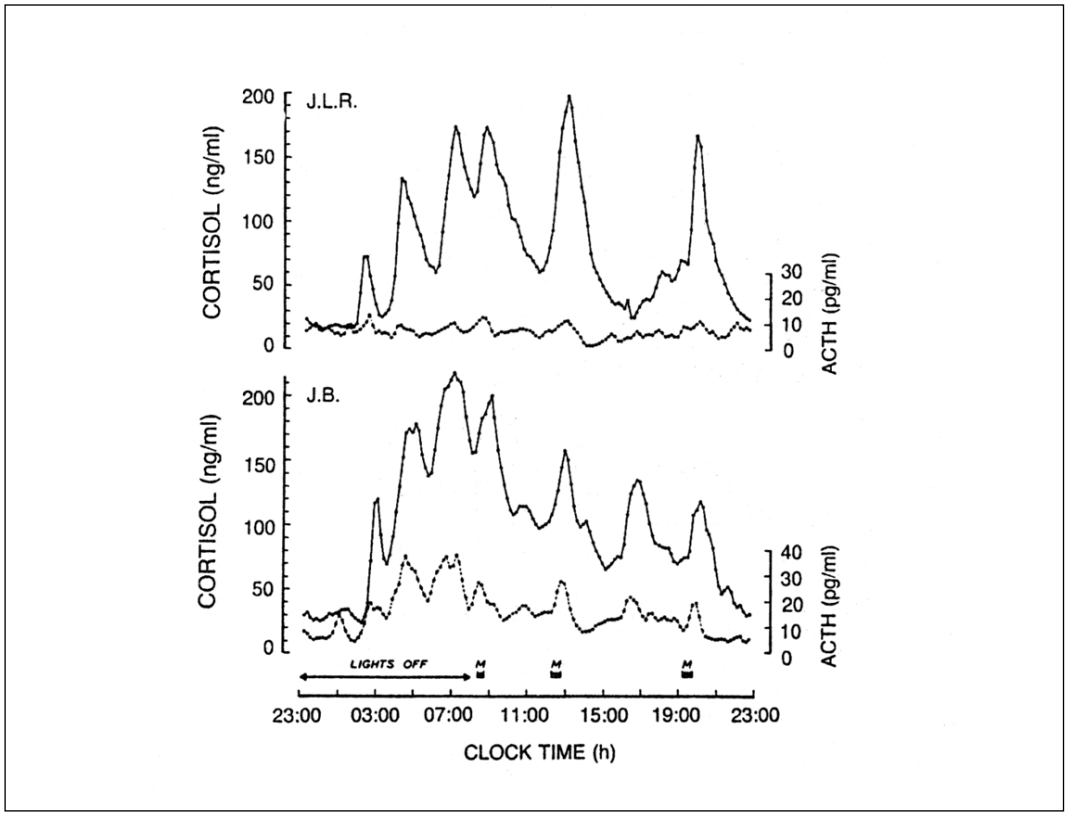


Figure 5. The Neuroendocrine Level. Two profiles of the individual ultradian rhythms in ACTH and cortisol in two subjects when blood samples were taken at ten minutes intervals over a 24 hour period (82). While there are obvious differences they both illustrate 90-120 minute pulsate rhythms with varying amplitudes. The lower profile, which is perhaps the more typical, illustrates how these two hormonal massenger molecules that mediate states of arousal tend to their highest peaks in the early morning hours and gradually dwindle in the afternoon and evening when our energy levels are lower.

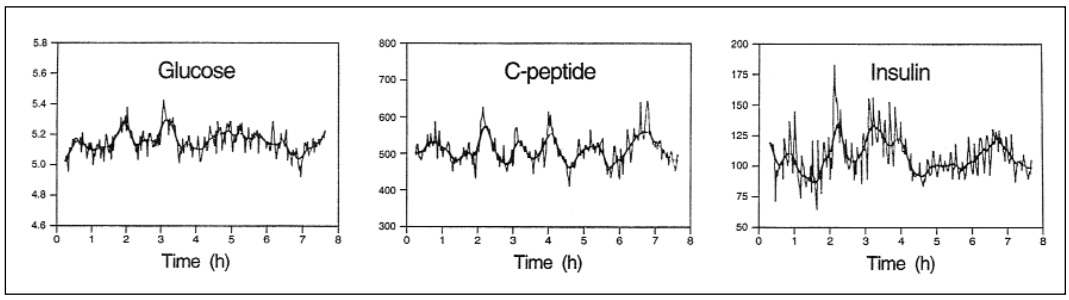


Figure 6. The Endocrine-Energy-Metabolic Level. These three graphs illustrate how the blood glucose (left) and C-peptide (middle) and insulin (right) obtained at two minute intervals during an 8-hour fasting period have rapid 10-15 minute oscillations that are shown superimposed on the approximately 90-120 ultradian rhythms which were obtained by a best-fit curve with a regression algorithm (83).

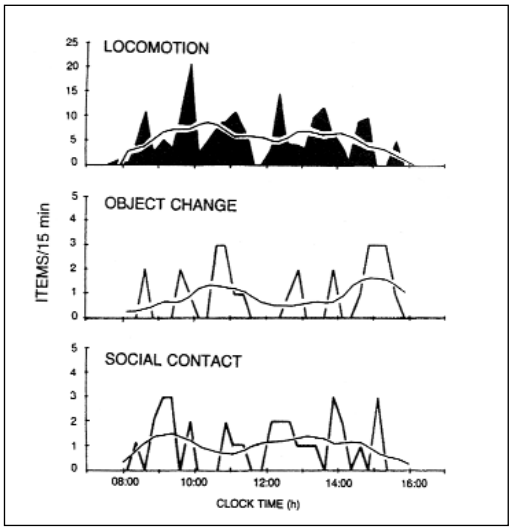


Figure 7. The Behavioral-Social-Cultural Level. Time series illustrating the ultradian rhythms of the locomotion (about 80 minutes), object change (about 65 minutes) and social contacts (about 103 minutes) for the Indian child "Ram" in a naturalistic setting in a small village in India. Similar ultradian rhythms are found in a child !Ko Bushmen and social synchronization in a village community of Colombian Indians as well as free play in highly urbanized children in Germany (84).

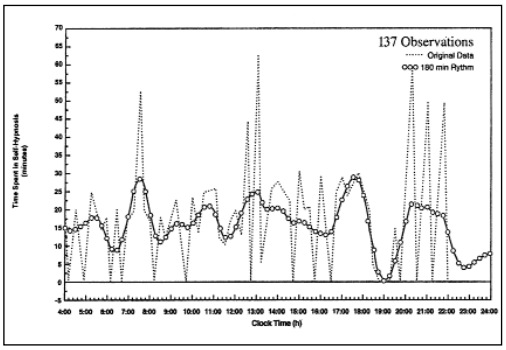


Figure 8. The Cognitive-Behavioral Level. An illustration of the approximately 180 minute ultradian rhythms (averaged data) of self-hypnosis that were recerded by 16 subjects in their diaries (From Rossi, 79). Similar rhythms are found in the time series of subjects who were instructed to simply enjoy and "ultradian healing response" whenever they felt a need to throughout the day.

illustrates how messenger molecules that have their origin in the processing of the larger protein "mother-molecules" in stage three may be stored within the cells of the brain and body as a kind of "molecular memory." These molecular messengers are released into the blood stream where they can complete the complex cybernetic loop of information transduction by passing through the "blood-brain barrier" (69) to modulate the brain's neural networks illustrated by the block of letters A through L at the top of Figure 1. Such localized neuronal networks of the brain are modulated by a complex field of messenger molecules that can reach the limbic-hypothalamic-pituitary system as well as certain areas of the cerebral cortex. This completes the cybernetic loop of information transduction and communication via the messenger molecules of the psychosomatic network between mind and body.

If we are willing to grant that communication within the neuronal networks of the brain is modulated by changes in the strengths of synaptic connections, then we could say that meaning is to be found in the complex dynamic field of messenger molecules that continually bath and contextualize the information of the neuronal networks in ever changing patterns. Most of the sexual and stress hormones that have been adequately tested, for example, have state dependent effects on our mental and emotional states as well as memory and learning. Freeman (70), for example, has pointed out how oxytocin is a hormonal informational substance released during lactation and sexual arousal to encode state dependent memory and learning. Oxytocin in concert with other messenger molecules in the extracellular fluid of the brain would make up the constantly changing dynamical field of meaning that would be expressed in the phenomenological experience of "mind" and behavior.

Research indicates that most forms of learning (Pavlovian, Skinnerian, imprinting, sensitization, etc.) are now known to involve these hormonal messenger molecules from the

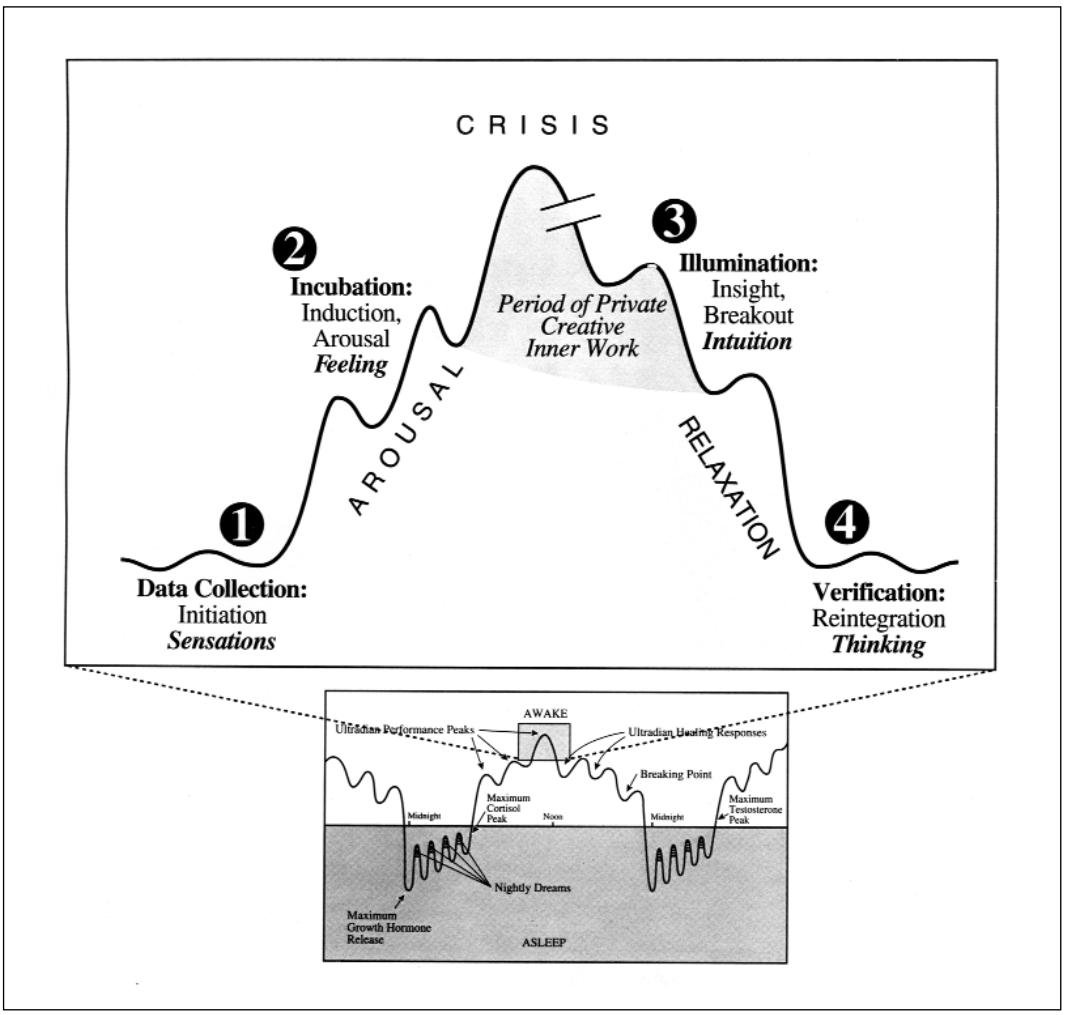


Figure 9. The four stages of the creative process in psychobiologically oriented psychotherapy in the upper part of the diagram is a utilization of one of the natural 90-120 minute ultradian rhythms that take place throughout the 24 hour circadian rhythm of waking and sleeping illustrated in the lower diagram. The lower diagram summarizes the alternating 90-120 minute ultradian rhythms of the awake and sleep states of an entire day in a simplified schematic manner. The ascending peaks of Rapid Eye Movement (REM) sleep characteristic of nightly dreams every 90-120 minutes or so are illustrated along with the more variable ultradian rhythms of activity, adaptation and rest in the daytime. This lower figure also illustrates how many hormonal messenger molecules of the endocrine system such as growth hormone, the activating and stress hormone cortisol and the sexual hormone testosterone have typical circadian peaks at different times of the 24 hour cycle.

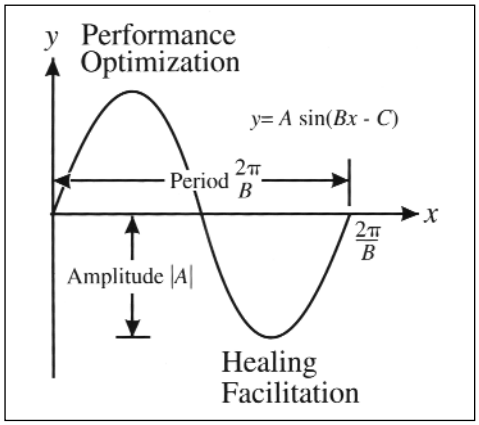
body that can reach the brain to modulate the neural networks that encode mind, memory, learning and behavior. Insofar as these classical forms of learning use messenger molecules, they ipso facto have a "state-dependent component" (10,11,71,72). It is important to understand what state dependent memory, learning and behavior actually means. When subjects are given memory and learning tasks while under the influence of stress hormones such as adrenocorticotropic hormone (ACTH), epinephrine or sex hormones (or even psychoactive drugs that mimic these natural hormonal messenger molecules) there is a varying degree of amnesia when the stress hormone or drug has been metabolized out of the system. That is, when memory is encoded under conditions of high emotional arousal, sex, stress or trauma, it tends to become state-dependent or statebound to that psychobiological condition. Memory and learning is state dependent on the original psychophysiological conditions when it was first encoded. This state dependent memory becomes dissociated or apparently "lost" after the person apparently recovers when the stress or sexual hormones are metabolized and return to normal levels. Reactivating stress or sex in another context, however, has a tendency to reestablishes the original encoding condition and the emotions and varying degrees of memory of the trauma. This is the psychobiological basis of much psychopathology related to early sexual and stressful life events as uncovered by classical psychoanalysis.

It is important to note that this stress induced model of mindbrain communication is a two-way street; it shows how the molecules

of the body can modulate mental experience as well as how mental experience can modulate the molecules of the body. This is the basis for emphasizing the hypothesis that state-dependent memory, learning, and behavior (SDMLB) is the common denominator that bridges the mindbody gap: the so-called Cartesian dichotomy between mind and body.

What is most interesting about these experiments is that they enable us to study the parameters of "reversible amnesia," which have been important criteria in understanding the phenomenology of psychoanalysis and therapeutic hypnosis (10,11). Just as most experiments in state-dependent memory and learning demonstrate that this "reversible amnesia" is only partial. That is, there is usually some memory and learning available even in the dissociated condition after the stress hormones return to normal levels, so most of the hypnotic literature documents that hypnotic amnesia is usually fragile and partial in character. A full amnesia that is completely reversible is relatively rare in state-dependent memory and learning experiments as well as in psychoanalysis and therapeutic hypnosis. In the historical literature of hypnosis and psychoanalysis this same fragile and partial character of reversible amnesia may have been responsible for many of the puzzling and paradoxical features of memory that remain the source of continuing controversy that challenges the validity of the various theories of depth psychology (73). Since the earliest days of psychoanalysis it has been noted that a sudden fright, shock, trauma and stress could evoke "hypnoidal states" that were related to amnesia, dissociated and neurotic behavior (10,11,12,71).

These recently recognized relationships between (1) the primary messenger molecule-cell receptor systems of the psychosomatic network, (2) Immediate-early genes and target gene expression, (3) protein formation and learning and (4) state-dependent memory, stress, and traumatically encoded mind-body problems suggest a new research frontier for the psychobiological investigation of many classical psychoanalytic concepts such as repression, dissociation, and emotional complexes. A new paradigm for such research has been provided recently by Cahill et al. (75) who compared the effects of the beta-adrenergic receptor antagonist propranolol hydrochloride on the long term memory for an emotionally arousing and emotionally neutral short story. Their results supported their hypothesis that the enhanced memory associated with emotional experiences involves activation of the messenger molecules of the beta-adrenergic system. It would require only a



Box 1. Toward a Mathematical Model of Hypno-therapeutic Work

An illustration of the parameters of a mathematical model of how hypnotherapeutic work may entrain and utilize psychobiological rhythms.

Amplitude refers to the absolute value of the height or depth of a cycle or rhythm of responsible behavior: it measures how far rhythm deviates from its mean level. The amplitude may correspond to a “hypnotic constant” that refers to the hypnotizability of a subject or the degree to which hypnotherapeutic work may optimize performance variables or healing parameters.

Period is the time required for one complete cycle of a rhythm; the length of time after which one cycle recurs. The period is frequently a highly variable parameter of psychobiological rhythms that may be contracted or stretched by hypnotherapeutic work. The frequency is the reciprocal of the period.

Phase is that part of the cycle that is associated with behaviors of interest; it is the instantaneous state of a cycle within its period. The crest or peak phase of chronobiological behavior is often associated with activation (sympathetic system) while the low or trough phase is often associated with relaxation (parasympathetic system) behaviors. The number C/B, called the phase shift, is a measure of the degree to which certain portions of chronobiological behavior can be modulated or entrained with hypnotic work.

Entrainment or synchronization refers to the interaction of psychobiological rhythms (x and y below) with a psychsocial cue such as hypnotherapeutic work (H below) that leads to the phase resetting (phase preservation, locking or trapping) of certain parts of a chronobiological cycle. Many hypnotherapeutic responses may be conceptualized as phase locked portions of the Basic Rest-Activity Cycle (BRAC) that are utilized for enhancing performance or facilitating healing. A mathematical model of the hypnotherapeutic entrainment of a Van der Pol oscillation of psychobiological rhythms (adapted from Kronauer, 103) is illustrated below where H is the “influence coefficient;” x and y are the natural frequencies of individual or systems of psychobiological rhythms x and y; k may be a constant associated with the intrinsic entrainability of a particular psychological rhythm by psychosocial cues.

k2x + kx (-1 + x2)x + 2x x + Fyxky = 0 ,
(k = /12)
k2y + ky (-1 + y2)y + 2yy + Fxykx = Fy
H=Fzy cos(kz + z

simple extension of their method of telling subjects short stories to apply their approach to documenting the activation of similar messenger molecule-receptor systems in the arousal phase of a psychobiologically oriented psychotherapy that is mediated by the rhythms of the neuroendocrinal system as proposed in this paper.

Non-Linear Dynamics of the Chronobiology of Sleep, Dream, and Hypnosis

Detailed research on the genetic, neuroendocrinal and psychosocial levels suggests that the 90-120 minute ultradian rhythm (4,9), originally described as the Basic Rest-Activity Cycle (BRAC) by Kleitman (76,77), is a fundamental "work cycle of life" that has been entrained by the circadian cycle (the 24 hour rhythm) of light and darkness. Ultradian in this context means any rhythm faster than the 24 hour circadian cycle. Figures 3 through 8 illustrate some of the major 90-120 ultradian rhythms on the genetic, endocrine and cognitive-behavioral levels during sleeping and waking that are coordinated in psychobiological time. A number of studies (78-80) indicate that hypnosis, or at least the periodicity of self-hypnosis illustrated in Figure 8, may be related to the deep psychobiology of ultradian rhythms and Kleitman's BRAC.

The chronobiological relationships between psychobiological arousal, sleep, dream and hypnosis evolved gradually in three stages over the past twenty-five years. The first stage was in the initial explorations of the periodicity in Milton H. Erickson's approach wherein his hypnotherapeutic sessions typically lasted between 90-120 minutes – the typical period of Kleitman's basic rest activity cycle during waking and sleeping (76,77). This led to the second stage consisting of clinical/experimental research assessing a series of hypotheses about the chronobiological aspects of hypnotic susceptibility and self-hypnosis. The initial assessment of the chronobiological suggestion was carried out by Aldrich and Bernstein (85) who found that "time of day" was a statistically significant factor in hypnotic susceptibility. They reported a bi-modal distribution of scores on The Harvard Group Scale of Hypnotic Susceptibility (HGSHS) in college students with a sharp major peak at 12 noon and a secondary, broader plateau around 5 to 6 p.m.. It was then found that the time of day for optimal susceptibility to hypnosis was related to whether the subject was more alert in the morning (Larks) or evening (owls) (80,86), temperature (87), light (88), stress and self-actualization (89). Other studies have evaluated ultradian parameters of the chronobiology of hypnosis (78,79,90-93) as well as related research in the periodicity of imagery experience (94-96).

One of the most significant conclusions of these studies is that the chronobiology of hypnotic susceptibility does not operate with regular periodicity like a clock (97). All psychobiological processes are manifest as rhythms of adaptation to the varying contingencies of everyday life. Special stressors, motivations, demands and expectations in normal living can shift the normal ultradian and circadian pulsations in arousal and stress hormones and their associated psychobiological processes on all levels from the behavioral to the cellular-genetic (4). The highly adaptive dynamics of all psychobiological and chronobiological processes are best described mathematically by the non-linear dynamics of modern chaos and adaptive complexity theory (12,68,97,98).

Current explorations of the non-linear dynamics of the chronobiology of consciousness (74,98), sleep, dreams (12) and hypnosis (11) is leading to an integration of all previous work on the creative dynamics of psychotherapy and holistic healing in theory and practice (99). An overview of this chronobiological approach to integrating the deep psychobiology of sleep, dreams, hypnosis and healing in psychotherapeutic practice is illustrated in Figure 9. When the 90-120 ultradian cycles of mindbody communication (illustrated in Figure 1) are unfolded over time they may be viewed as graphs of the alternating rhythms of activity and rest illustrated on the lower part of Figure 9 (12). The coordination of the diverse systems and levels of traditional psychophysiology via their time parameters (Figures Three through Eight) has been called the "Unification Hypothesis of Chronobiology" (4,10,80). The field of chronobiology from the cellular-genetic to the cognitive-behavioral levels becomes a new database for understanding the dynamics of mindbody communication and healing in hypnosis and

psychotherapy.

The lower part of Figure 9 summarizes the alternating 90-120 minute ultradian rhythms of the awake and sleep states of an entire day in a simplified manner. The ascending peaks of Rapid Eye Movement (REM) sleep characteristic of nightly dreams every 90-120 minutes or so are illustrated along with the more variable ultradian rhythms of activity, adaptation and rest in the daytime. Figure 9 also illustrates how many hormonal messenger molecules of the endocrine system such as growth hormone, the activating and stress hormone cortisol and the sexual hormone testosterone have a typical circadian peak at different times of the 24 hour cycle. Because the non-linear chronobiological release of many of these hormones are recognized as having profound state dependent effects on memory, learning, emotions and behavior throughout the day, it is important to consider their relevance for new models of hypnosis and psychotherapy.

One recent example of the theoretical and practical implications of such chronobiological relationships between hormones and behavior is the so-called "human alarm clock" effect. It has been found that people who are able to awaken in the morning at a specific time experience a greater release of adrenocorticotropin (ACTH) and cortisol in their blood stream just before their alarm clock rings (49). Figure 9, however, illustrates that there is a normal peak in cortisol just before awakening. This implies that the conscious intentionality to awaken at a specific time in the morning is able to utilize a normally involuntary circadian hormonal rhythm to control the desired behavior of awakening at a certain time. We have long known that body processes can modulate conscious experience and behavior; the human alarm clock effect clearly documents the reverse-a conscious intentionality can modulate a normally involuntary circadian hormonal rhythm of the body across the transition between waking and sleeping. It is precisely this reciprocal relationship between mind and body that is the psychobiological basis of mindbody communication and healing as proposed earlier in stage one of Figure 1.

A Mathematical Model of Sleep, Hypnosis and Psychotherapy?

The upper part of Figure 9 illustrates my conjecture (4,11,12) that the natural unit of psychobiologically oriented psychotherapy may be a utilization of one 90-120 ultradian cycle of activity and rest. In support of this idea we may cite much research of the type illustrated by Iranmanesh et al. (100) and Felker and Hubbard (101) who documented how the ultradian peaks of cortisol secretion that lead to psychophysiological states of arousal every 90-120 minutes or so throughout the day (that I label as "Ultradian Performance Peaks" in Figure 9) are typically followed after about 20 minutes by ultradian peaks of beta-endorphin that lead to rest and relaxation that I Label as "Ultradian Healing Responses" in Figure 9 (99). It appears as if nature has built in a natural but flexible and highly adaptive ultradian rhythm of activity, rest and healing, the "work cycle of life" mentioned above, every 90-120 minutes.

What, exactly, is the "work" that is done in each 90-120 minute ultradian cycle? The essence of such psychobiological work is the formation of new proteins for a creative response to changing environmental conditions, stress and healing described in the research of Todorov (102). The chrono-biological dynamics of new protein formation, healing and psychotherapy in Figure 9 leads to a new understanding of the role of suggestion in hypnotherapy. What has been traditionally called "clinical hypnosis" or "therapeutic suggestion" may be, in essence, the accessing, entrainment and utilization of ultradian processes of mindbody communication on all levels from the cellular-genetic to the behavioral that respond to psychosocial cues. Within this framework, the classical phenomena of hypnosis may be conceptualized as extreme manifestations and/or preservations of time-dependent psychobiological processes that are responsive to psychosocial cues (11). What the biologist calls the "entrainment of ultradian and circadian rhythms by physical and psychosocial stimuli" is the psychobiological basis of what psychotherapists call "hypnotherapeutic suggestion to facilitate mindbody healing."

This leads us to the conjecture that we may be able to formulate a mathematical model of hypnotherapy as outlined in Box One. Proposals for research that could validate this and other mathematical models of the psychobiological relationships in sleep, hypnosis, dreaming and psychotherapy have been proposed (11,12). Practical approaches to the utilization of ultradian dynamics and four

stage creative process in hypnosis and psychotherapy have be published in great detail (11,12).

Summary

This paper outlines an evolving view of how self-organizing systems of mind-body communication across all levels from the cellar-genetic to the psychosocial could lead to a unified psychobiological theory of awake, sleep, dreaming, hypnosis and healing. Research in the areas of behavioral state-related gene expression, psychoimmunology, and state dependent memory, learning and behavior is integrated with the chronobiology of ultradian rhythms as a new window into the psychobiology of trauma and stress as well as brain growth and healing. This new psychobiological approach to conceptualizing the fundamental dynamics of sleep, dreaming and hypnosis on the cellular-genetic level may have the potential breath and depth to integrate the classical phenomenological dynamics of psychoanalysis and psychosomatic medicine with the modern neuroscience of memory, learning, and behavior in the new millennium.

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