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A Bioinformatics Approach to the Psychosocial Genomics of Therapeutic Hypnosis

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ABSTRACT

Therapeutic hypnosis is identified as a neuro-psycho-physiological work function related to the bi-modal circadian profiles of hypnotic susceptibility, body temperature, and gene expression. A bioinformatic approach to computer data mining is used to compare the profile of circadian hypnotic susceptibility to profiles of gene expression while awake and asleep to explore the psychosocial genomic foundations of therapeutic hypnosis. Such research may determine what profiles of gene expression related to health, stress, and illness could be modulated by hypnosis and thereby establish a systematic scientific approach for investigating the possibilities of mind-body healing via therapeutic hypnosis.

ZUSAMMENFASSUNG

Therapeutische Hypnose kann als eine neuro-psycho-physiologische Arbeitsfunktion definiert werden, die mit den bimodalen Profilen der hypnotischen Empfindlichkeit, der Körpertemperatur und dem genetischen Ausdruck in Verbindung steht. Um das Profil der ”circadian” (regelmässig fluktuierenden) hypnotischen Empfindlichkeit mit Profilen des genetischen Ausdrucks im wachen wie im schlafenden Zustand zu vergleichen und die psychosozialen genetischen Grundelemente therapeutischer Hypnose zu erforschen, bedient sich der Autor eines bio-informatischen Ansatzes zur Datenanalyse. Forschung dieser Art kann darüber Aufschluss geben, welche genetischen Profile bezüglich Gesundheit, Stress und Krankheit mit Hilfe von Hypnose verändert werden können und sie kann einen systematischen wissenschaftlichen Ansatz bieten, um die Möglichkeiten des ganzheitlichen Heilens von Geist und Seele über therapeutische Hypnose weiter zu erforschen.

SAMMANFATTNING

Terapeutisk hypnos kan definieras som en neuro-psyko-fysiologisk arbetsfunktion som är relaterad till de bi-modala profilerna i hypnotisk mottaglighet, kroppstemperatur och genetiska uttrycksformer. Författaren jämför profiler för ”circadian” (ung. regelbundet fluktuerande) hypnotisk mottaglighet med profiler för genetiska uttryck i vaket och sovande tillstånd. Författaren närmar sig frågeställningen med hjälp av bioinformatik och datoranalogi. Artikelns syfte är att använda de psykosociala genetiska grundelementen i

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terapeutisk hypnos. Denna forskningsansats kan belysa vilka genetiska profiler avseende hälsa, stress och sjukdom som kan påverkas med hypnos och därigenom etablera en systematisk metod för att undersöka hypnosens möjligheter att läka kropp och själ som en helhet.

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INTRODUCTION:
Therapeutic Hypnosis as a Psychobiological Work Function

Clinicians utilizing therapeutic hypnosis have occasionally commented on the physiological responses of warmth, heat, and sweating that accompanies the intense emotional arousal characteristic of deep catharsis and the re-experiencing of post-traumatic stress symptoms in hypnotherapeutic work. Milton H. Erickson (1948/1980) described these responses as "neuro-psycho-physiological" and his early student, David Cheek, used them to assess the validity of Ideodynamic finger signaling in therapeutic hypnosis as summarized in Box one.

Box 1. Temperature and Psychobiological Work in Therapeutic Hypnosis

"Milton H. Erickson's patients often became emotionally excited and aroused: they might weep or rage or became '*hot and actually sweat during the psychobiological work of their hypnotherapeutic sessions* (Erickson 1958/1980)." (Rossi, 2002, p.143, italics added here). David Cheek, used perspiration as a physiological index in what he called the 3-stage sequence for assessing the validity of the hypnotic recall of emotionally meaningful memories of stress and trauma with ideomotor finger signals as follows. *"True unconscious ideodynamic signals are always repetitive and often barely visible.* Sometimes we must rely on the slight vibratory movements shown by the tendon leading to a designated finger. With recall of stressful experiences, it is sometimes possible to see an accelerated release of droplets of perspiration around the tip of a finger that eventually will lift. This is a physiological response preceding the skeletal muscle lifting that finger. My basic clinical hypothesis is that there is a definite three-stage sequence involved in the valid recall of meaningful material." (Rossi & Cheek, 1988, p. 21-22)

3-Stage Criteria for Assessing Validity of Ideodynamic Signaling

1. *Emotional and physiological memory* can be seen first through changes in respiration, pulse rate, and emotional reactions [such as feeling hot, facial and/or finger flushing, and perspiration]. These occur very rapidly and must occur *before* a designated finger lifts to show an inner orientation to the time of an important experience.

2. *Ideodynamic finger signals* indicate the accessing of memory at an unconscious level. They usually occur a few seconds after the appearance of physiological memory. At the moment the finger lifts signaling this second, higher level memory, the patient still does not have a verbal level of awareness of the experience; there are only feelings of anticipation, vague unrest, or discomfort.

3. *Verbal reporting* of the experience follows these physiological and ideomotor indications of the inner accessing of meaningful material. To reach this conscious horizon of verbal thought, the entire experience may have to be reviewed repeatedly. The patient is told that one finger will lift to signal the beginning of an experience and another finger to signal its ending. The number of required repetitions to elevate the memory from deep unconscious zones of memory storage depends upon the gravity of the experience.

While the therapeutic applications of hypnosis have focused on relaxation or what is now called "low phase hypnosis", research by Hautkappe & Bongartz (1992) and Unterweger et al. (1992) suggests that hypnosis engages a significant *"work function"* that operates differently in high and low hypnotic susceptibility subjects. Consistent with Cheek's recognition of heart and pulse changes as an index of responsiveness in therapeutic ideomotor signaling, Hautkappe & Bongartz (1992) found that heart rate variability is a useful physiological index for discriminating high and low hypnotic susceptibility. High susceptible hypnotic subjects have less heart rate variability. "High susceptible subjects do not have to work as hard on passing a suggestion as do low susceptibles" (Unterweger et al., 1992, p. 87). Milton Erickson often described good hypnotic subjects as having higher *"response attentiveness"* or focus of attention so their mind-body system does not require an indiscriminate massive arousal to do certain tasks (Erickson and Rossi, 1979). Erickson actually used psychological shocks and creative moments to focus attention in what we would now call "high phase" hypnosis (Rossi, 2002). We may hypothesize that high hypnotic susceptibility is associated with a more efficient psychobiological use of information and energy. More recently Barabasz and Barabasz (1996) have documented how "alert hypnosis" can facilitate neural biofeedback in children with attention deficit hyperactivity disorder (ADHD). From a historical perspective this clinical and experimental research may be interpreted as consistent with Braid's conception of hypnosis as a state of *monoideism*.

While it is generally believed that that the molecular-genomic revolution initiated by Watson & Crick (1953) and others fifty years ago eventually will serve as a foundation for all the medical and psychological disciplines (Hood & Galas, 2003), it has had relatively little impact on the field of clinical and experimental hypnosis at this time (Rossi, 2002, 2003a & b). In this conceptual review I outline evidence indicating how the psychobiological foundations of therapeutic hypnosis may be extended to the genomic level by adopting the research strategies of current neuroscience, functional genomics, and chronobiology (Rossi, 2000 a, b, c).

A Bioinformatic Approach to the Psychosocial Genomics of Therapeutic Hypnosis

Following the author's assembled evidence for an hypothesized association between therapeutic hypnosis, circadian physiology, and behavior (Rossi, 1990, 1992, 1996, 2002), a number of pilot studies reported tentative support (Aldrich & Bernstein, 1987; Sanders & Mann, 1995). The experimental documentation of a circadian profile of hypnotic susceptibility by Aldrich & Bernstein (1987) appears, in retrospect, to be the most seminal in relation to current research on circadian profiles of behavior, physiology, and gene expression (Panda et al., 2002 a & b; Storch et al., 2002; Ueda et al., 2002). Panda et al. (2002 a) conceptualized this new systems approach embracing all levels from the molecular and genomic to the physiological and complex cognitive-behavioral as follows.

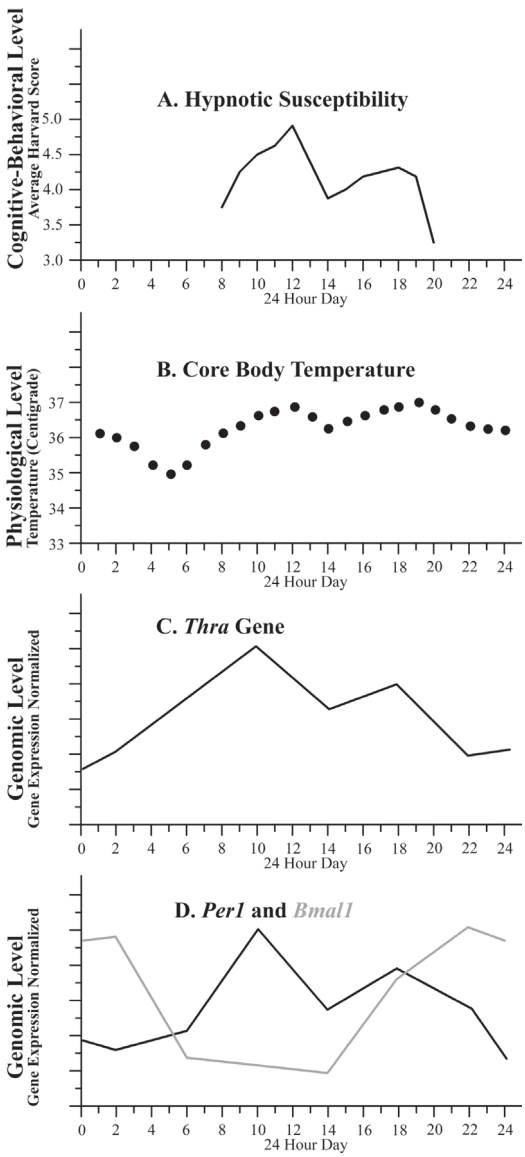
Although the molecular mechanism by which the central oscillator controls timekeeping is becoming increasingly clear, knowledge of how this timing information is transmitted to regulate behavior and physiology is only just emerging. A common theme in connecting the clock to physiological outputs has been the identification of cycling components, followed by molecular genetic and histological tests to establish a connection. (p. 333)… *The exciting possibility that complex behaviors can be described at the molecular level, and are well conserved across species, underscores the importance of the use of model organisms and comparative behavioral genomics*. (p. 334, italics added)

Figure 1 illustrates how this new conceptual approach to psychosocial genomics can be applied by juxtaposing Aldrich & Bernstein's (1987) circadian profile of hypnotic susceptibility (the cognitive-behavioral level), with a typical circadian profile of core body temperature (the physiological level that Aldrich & Bernstein hypothesize as underlying hypnotic susceptibility) in humans with the circadian profile of the *Thra* gene (the genomic level) in tissues of the heart and liver of the murine rodent (Storch et al., 2002). Aldrich & Bernstein (1987) summarize their results as follows.

Figure 1 [redrawn here as Figure 1a] shows the distribution of the mean HGSHS: A scores for each hour at which groups were hypnotized. The *distribution is bimodal, with peaks at 12:00 noon and 4:00 – 6:00 p.m.* and a local minimum at 2:00 p.m.

(p. 143, italics added)… The results provide preliminary evidence that hypnotizability may be related to the circadian rhythm of body temperature. (p. 144).

As may be seen, the circadian profile of core body temperature in Figure 1b is also bimodal and closely approximates the circadian profile of hypnotic susceptibility in Figure 1a. Figure 1c illustrates the circadian expression profile of the *Thra* gene, which is also bimodal and resembles the circadian profiles of hypnotic susceptibility and body temperature.



The *Thra* gene is well known for its relation to thyroid hormones that are fundamental in regulating metabolism and body temperature (Storch et al., 2002). Figure 1d illustrates the circadian expression profile of the clock gene *Period* (*Per 1),* which is associated with many daytime activities in humans, and resembles the circadian profiles of hypnotic susceptibility and body temperature even more closely than the *Thra* gene. Notice how the circadian profiles of the *Per1* and *Thra* gene are similar in having a peak of expression about 90-120 minutes *before* the peaks of core body temperature and hypnotic susceptibility around noon. This is consistent with the fact that about 90-120 minutes is required for many (but certainly not all) genes to be expressed via gene transcription and translation into the proteins that ultimately generate physiological and cognitive-behavioral effects (Rossi, 2002).

Figure 1d illustrates the circadian profile of the *Bmal1* gene associated with the sleep state *(the opposite of the Per1* and *Thra* gene profiles associated with being awake). Storch et al. (2002) research on the circadian modulation of gene expression related to body temperature, psychosocial stress (the glucocorticoids), and the immune system (tumor necrosis factor alpha) are of great interest for a psychobiologically oriented approach to therapeutic hypnosis and psychoneuroimmunology at the genomic level. Note the striking similarity of their description of the bimodal circadian profile of gene expression with the bimodal distribution of hypnotic susceptibility scores reported above by Aldrich & Bernstein.

Many mammalian peripheral tissues have circadian clocks; endogenous oscillators that generate transcriptional rhythms thought to be important for the daily timing of physiological processes. (p. 78) … The *distribution of phases is essentially bimodal, with most genes showing peak expression between circadian time 6 h and 14 h, and a smaller group peaking in phase at about circadian time 20 h* (p. 81).

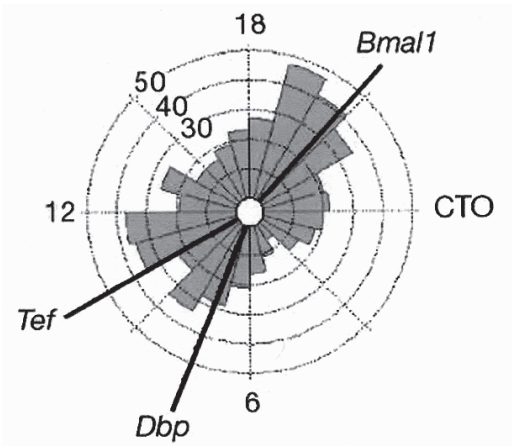
Innovative researchers investigating circadian profiles of gene expression in the brain, heart, liver, and immune system such as Storch et al. (2002) and others (Panda et al. 2002 b; Ueda et al., 2002; Rosbash & Takahashi, 2002), however, do not discuss the implications of their findings for the therapeutic applications of hypnosis. The assemblage of matched bi-modal circadian profiles of Fig. 1 is consistent with *but certainly do not yet prove* that there are

causal and reciprocal relationships in the complex interactions between the cognitive-behavioral level of hypnotic susceptibility, physiology, and gene expression (Rossi, 1996, 2002, 2003a & b). Such proof would require many novel types of integrative psychobiological research by the hypnosis community to which we will now turn our attention.

Is Therapeutic Hypnosis a Psychogenomic State More like Sleep or Awake?

Figure 2 is a phase histogram that illustrates a more global type of circadian bi-modal profile of gene expression in the heart and liver that suggests how the new data and methods of systems biology could be adopted for exploring associations between gene expression, physiology, and complex behavior such as hypnosis. In support of this approach Panda et al. (2002 b) have stated, "The circadian control of transcription in higher organisms is integrated with the spatial control of *gene expression to target rate-limiting steps in major pathways in their relevant organs, resulting in a systems-level temporal orchestration of behavior and physiology for optimal adaptation of the organism to its environment.*" (p. 317, italics added)

Global circadian profiles of gene expression such as figure 2 may enable us to get a precise answer to centuries of controversy regarding the fundamental psychobiological basis of the hypnotic state: Will the circadian profiles of gene expression found during hypnosis be more closely associated with sleep as proposed by Pavlov (1927) or the awake state as maintained by Hull (1933/1968)? This question can be answered on the genomic level by investigating the implications of research by Ueda et al. (2002), which they summarize, "Here we demonstrate the role of the Rev-ErbA/ROR response element in gene expression during circadian night, which is in phase with *Bmal1* [during sleep, which Pavlov would predict as associated with hypnosis], and in antiphase to *Per2* oscillations [while awake, which Hull would predict as associated with hypnosis]." (p. 534).



A more direct assessment of the circadian correlates of hypnosis would be to continuously measure core body temperature and gene expression in high hypnotic susceptible subjects during their sleep. When their temperature is at its lowest point during sleep we could induce hypnosis without awakening the subject (*sleep induced hypnosis*) and keep them occupied with personally relevant inner work during hypnosis for an ultradian period of 90-120 minutes. If Pavlov is correct (hypnosis is like sleep) their core body temperature should remain low while their "Rev-ErbA/ROR response element in gene expression" and *Bmal1* gene expression remains at a peak illustrated in figure 1d (indicating that the circadian night profile of gene expression prevails during sleep and hypnosis). If, on the other hand, Hull is correct we would expect the reverse: core body temperature should rise during the hypnosis and hypnotically induced inner work while subjects were sleeping; on the genomic level their Rev-ErbA/ROR response element and *Bmal1* gene expression should go down in antiphase with their *per1* gene expression should go up toward a peak as is characteristic of the awake state. Such research would be an important step in answering on the genomic level an issue first raised by the author 20 years ago regarding the degree to which therapeutic hypnosis may *modulate*, *entrain* or *shift* the *phase response curves* (Johnson, 1999) of circadian and ultradian rhythms during health, stress, and illness (Rossi, 2002).

Extending this type of thought experiment even further, it may be possible to differentiate between waking consciousness and hypnosis on the level of gene expression. If a difference is found, for example, between the profiles of gene expression in *sleep induced hypnosis* versus a control group (where subjects are simply awakened from their sleep and kept awake for a similar 90-120 minute ultradian period), these *circadian difference gene expression profiles* may be useful in distinguishing between gene expression during hypnosis, normal waking

consciousness, and the spectrum of consciousness in creative states and meditation (Wilber, 1993) as well as during stress and illness. This may enable us to determine precisely which profiles of gene expression could be modulated by hypnosis during health, stress, and illness to eventually establish a firm systematic scientific foundation for the psychosocial genomics of therapeutic hypnosis.

SUMMARY AND PROSPECTS FOR THERAPEUTIC HYPNOSIS TODAY

Throughout its colorful history hypnosis has expressed its creatively protean nature by continually updating itself by assimilating the scientific methods and healing metaphors of its prevailing culture (Carrer, 2002). Today the current scientific methods of neuroscience and the healing metaphor of The Human Genome Project is the prevailing culture that hypnosis needs to assimilate. It is now possible to assess the entire human genome from a few drops of blood with DNA microarray technology (Rossi, 2000b). It is no longer visionary to believe we can assess gene expression and brain plasticity within the time frame of a typical session of therapeutic hypnosis (Rossi, 2000c, 2002, 2004). The community of therapeutic hypnosis needs to summon its collective intelligence, will, and resources to meet this challenge for its current and future development.

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Legends for Figures

FIGURE 1: Matching apparently similar circadian profiles of hypnotic susceptibility, body temperature, and gene expression. This may be an unusually clear illustration of the psychosocial genomic relationships between the cognitive-behavioral level of hypnosis in (1a), the physiological level of core body temperature in (1b), and expression of the *Thra* gene in (1c) associated with rate of metabolism and body temperature. Figure (1d) illustrates how the circadian profile of the *Per1* gene, typical for the awake state, is similar to the *Thra* gene in (1c) having a peak of expression about 90-120 minutes before the peak of hypnotic susceptibility and core body temperature around noon. By contrast notice how the circadian profile of the *Bmal1* gene in (1d), which is a marker for the sleep state, is in *antiphase* (the opposite of) the awake profiles of *Per1* and *Thra* gene expression associated with peaks of core body temperature and hypnotic susceptibility.

FIGURE 2: A phase histogram of circadian gene expression in the murine heart and liver. *Bmal1* is a gene with a known robust circadian expression during sleep while the *Dbp* and *Tef* genes serve as phase markers associated with being awake. This circular histogram resembles a circadian 24 hour clock face but with CT0 (Circadian Time Zero) on the right representing awakening (or the standardized initial point of data collection such as when movement and physical activity occurs). The nested numbers from the periphery toward the center (50, 40, 30) are the number of genes expressed in each circadian phase of the histogram during this particular experiment. (With permission from Storch et al. 2002).