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Gene Expression, Neurogenesis, and Healing: Psychosocial Genomics of Therapeutic Hypnosis

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The historical lineage of therapeutic hypnosis in James Braid's "psychophysiology", Pierre Janet's "physiological modification", and Milton Erickson's "neuro-psycho-physiology" is extended to include current neuroscience research on activity-dependent gene expression, neurogenesis, and stem cells in memory, learning, behavior change, and healing. Three conditions that optimize gene expression and neurogenesis—novelty, environmental enrichment, and exercise—could integrate fundamentals of the theory, research, and practice of therapeutic hypnosis. Continuing research on immediate-early, activity-dependent, behavior state-related, and clock gene expression could enhance our understanding of how relaxation, sleep, dreaming, consciousness, arousal, stress and trauma are modulated by therapeutic hypnosis. It is speculated that therapeutic and post-hypnotic suggestion could be focused more precisely with the time parameters of gene expression and neurogenesis that range from minutes and hours for synthesizing new synapses to weeks and months for the generation and maturation of new, functioning neurons in the adult brain.

Keywords: Activity-dependent, behavior state-related, clock gene expression, gene expression, neurogenesis, hypnosis, healing, psychosocial genomics, stress

The Historical Continuum of Therapeutic Hypnosis and Neuroscience

Research in current neuroscience indicates, contrary to 100 years of dogma, that the human brain is capable of generating new brain cells throughout the life cycle (Gross, 2000). *Novelty, environmental enrichment, and exercise* can activate gene expression leading to the differentiation of new neurons from neural stem cells in the adult mammalian brain during salient life experiences that are associated with the generation and reconstruction of memory, learning, and behavior (Eriksson et al., 1998; Gage, 2000a, 2000b; Van Praag et al., 2002). Kempermann and Gage (1999) have summarized the implications of such neuroscience research:

> Contrary to dogma, the human brain does produce new brain cells in adulthood... With continued diligence, scientists may eventually be

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> able to trace the molecular cascades that lead from a specific stimulus, be it an environmental cue, or some internal event, to particular alterations in genetic activity and, in turn, to rises or falls in neurogenesis.
>
> Then they will have much more of the information needed to induce neuronal regeneration at will. Such a therapeutic approach could involve administration of key regulatory molecules or other pharmacological agents, delivery of gene therapy to supply helpful molecules, transplantation of stem cells, *modulations of environmental or cognitive stimuli,* alterations in physical activity, or some combination of these factors (p. 53, italics added).

With the words "modulations of environmental or cognitive stimuli" Kempermann and Gage are intuiting a new neuroscience update of what many would regard as the historical goal of therapeutic hypnosis. James Braid (1855/1970), for example, described the "Physiology of Fascination", an early concept of therapeutic hypnosis, in this way:

> With the view of simplifying the study of reciprocal actions and reactions of mind and matter upon each other... the [hypnotic] condition arose from influences existing within the patient's own body, viz., the influence of concentrated attention, or dominant ideas, in modifying physical action, and these dynamic changes re-acting on the mind of the subject. I adopted the term "hypnotism" or nervous sleep for this process... And finally as a generic term, comprising the whole of these phenomena which result from the reciprocal actions of mind and matter upon each other, I think no term more appropriate than "psychophysiology" (pp. 369-372).

Because of the limitations of psychophysiological techniques of Braid's time, however, his concept of therapeutic hypnosis remained a theoretical hope rather than a verifiable method to guide clinical practice. If we are willing to intuit an association between what Braid called "The Physiology of Fascination" and what now is called *Novelty* by current neuroscientists, however, we can recognize a deep psychobiological lineage between the historical foundations of hypnosis (Tinterow, 1970) and current neuroscience research on gene expression and neurogenesis in memory, learning, and healing.

This psychobiological lineage was reviewed and expanded by Pierre Janet's (1919/1925) historical and clinical study of psychological healing:

> The most important phenomena that have been adduced to substantiate the alleged power of hypnotic suggestion are the *physiological modifications which suggestion is said to have caused*. Normally the power we can exercise over our visceral organs and our physiological functions is greatly restricted, and is usually indirect. Hypnotic suggestion, we are told, can influence these organs markedly and directly. A precise verification of these phenomena, and the

> discovery of the exact mechanisms of their causation, would do a great deal to demonstrate the power of suggestion (Pp. 308-309, italics added).

Janet also noted:

> This historical summary, though cursory and incomplete, is an attempt to display the remarkable evolution of the methods of treatment by gymnastics and education. At the onset, the endeavor was to treat by these means various elementary and circumscribed disorders affecting well-known motor-functions. Then the claims of the gymnastics were enlarged, and they were applied as remedial measures to functions of a more lofty and complicated character. The aim was to practice the gymnastics of emotion and attention just as at an earlier stage there had been practiced the gymnastics of walking and speech... The treatments we have just been discussing were considered under the caption "Education and Re-education" (Pp. 732).

If we are willing to sense and feel an essential similarity between Janet's physiologically oriented concept of "education and reeducation" and "gymnastics" with what neuroscience currently calls "environmental enrichment" and "exercise" in modulating gene expression and stimulating neurogenesis, we may be approaching Janet's scientific ideal about how "the discovery of the exact mechanisms of their causation, would do a great deal to demonstrate the power of suggestion" (Janet 1919/1925. p. 309).

Milton Erickson (1948/1980) formulated a more recent expression of this historical lineage when he described the "neuro-psycho-physiological" dynamics of "hypnotic psychotherapy," in this way:

> Direct suggestion is based primarily, if unwittingly, upon the assumption that whatever develops in hypnosis derives from the suggestions given. It implies that the therapist has the miraculous power of effecting therapeutic changes in the patient, and disregards the fact that *therapy results from an inner re-synthesis of the patient's behavior achieved by the patient himself.* It is true that direct suggestion can effect an alteration in the patient's behavior and result in a symptomatic cure, at least temporarily. However, such a "cure" is simply a response to the suggestion and does not entail that re-association and reorganization of ideas, understandings, and memories so essential for an actual cure. *It is this experience of re-associating and reorganizing his own experiential life that eventuates in a cure, not the manifestation of responsive behavior, which can, at best, satisfy only the observer...*
>
> *By such indirect suggestion the patient is enabled to go through those difficult inner processes of disorganization, reorganization, reassociating, and projecting of inner real experience to meet the requirements of the suggestion and thus the induced anesthesia becomes a part of his experiential life instead of a simple, superficial response...* [M.H.E. illustrates this with a clinical case.]

> Accordingly, the suggestion was offered that she might develop a generalized anesthesia in terms of her own experiences when her body was without sensory meaning to her. *This suggestion was intentionally vague since the patient, knowing the purpose of the hypnosis, was enabled by the vagueness of the suggestion to make her own selection of those items of personal experience that would best enable her to act upon the suggestion.* She responded by reviewing mentally the absence of any memories of physical stimuli during *physiological sleep,* and by reviewing her dreams of walking effortlessly and without sensation through closed doors and walls and floating pleasantly through the air as a disembodied spirit looking happily down upon her sleeping, unfeeling body. By means of this review she was able to initiate a process of reorganization of her experiential life. As a result she was able to develop a remarkably effective anesthesia, which fully met the needs of the subsequent delivery. *Not until sometime later did the therapist learn by what train of thought she had initiated the neuro-psycho-physiological process by which she achieved anesthesia* (pp. 38–39, italics added).

This quote is an example of the essential dynamics of what Erickson called the *naturalistic and utilization approach* to the *neuro-psycho-physiological* dynamics of therapeutic hypnosis where the ultimate locus of control remains within the patient rather than the therapist (Erickson, 1958/1980, 1959/1980). Erickson encouraged his early colleagues (Gorton, 1949, 1957, 1958) to pursue this neuro-psycho-physiological approach that is currently developing a variety of successful experimental paradigms that are documenting the clinical efficacy of hypnosis (Barabasz, 2002; Gruzelier, Smith, Nagy, & Henderson, 2001; Rainville, Duncan, Price, Carrier, & Bushnell, 1997, 1999). Current neuroscience, however, is extending the domain of psychophysiology far beyond its traditional boundaries, to include what is now called "gene expression" and "neurogenesis" in the construction and re-construction of memory throughout a lifetime.

Fundamentals of Gene Expression and Neurogenesis in Neuroscience

That human experiencing on a psychological level is so intimately associated with gene expression on a deep biological level is one of the most surprising findings of current research in genomic neuroscience (Chin & Moldin, 2001; Pfaff, Berrettini, Joh, & Maxson, 2000). Until now, most research in the Human Genome Project (Collins, 2000) has been conducted on the purely biological and biochemical levels to uncover genes and their molecular structure. As this initial structural phase of the Human Genome Project (Collins, 2000) approaches a conclusion with the identification of a currently estimated 35,000 human genes, however, attention is now shifting to the second or *annotation phase* that explores the functions of genes. *Functional genomics* explores how networks of genes are turned on and off in response to signals from all parts of the body as well as the outer environment. *The popular but over-simplistic idea of genetic determinism is incomplete: It needs to be amended to include the complementary concept that human experience and behavior can modulate gene expression* (Moore, 2001; Ridley, 1999, 2001). While there is as yet no direct experimental documentation of how psychotherapy can modulate gene expression, Stahl (2000) summarizes the

implications of current research:

> But can behavior modify genes? Learning as well as experiences from the environment can give rise to changes in neural connections. In this way, human experiences, education, and *even psychotherapy may change the expression of genes* that alter the distribution and strength of specific synaptic connections. *Thus genes modify behavior and behavior modifies genes.* Psychotherapy may even induce neurotropic factors to preserve critical cells and innervate new therapeutic targets of alter emotions and behaviors (p. 37, italics added).

In a series of pioneering papers, Eric Kandel (1983, 1989, 1998, 2000), the Nobel Laureate for Physiology in 2000, documented how the experience of *activity-dependent gene expression* could account for many of the classical forms of memory and learning as well as clinical phenomena of psychopathology such as chronic anxiety depression, neurosis, and schizophrenia. Kandel's (1998) theoretical and experimental work is one of the clearest and most optimistic expressions of the possibilities of using the associations between gene expression, neurogenesis, and human experiencing as a new psychobiological foundation of psychosomatic medicine and psychotherapy. Kandel (1998) makes an important distinction between (1) classical Mendelian genetics that is concerned with the transmission of hereditary traits from parents to children from one generation to another, and (2) the developmental and adaptive "regulation of gene expression by social factors" (p. 460). The latter is fundamental for understanding the possible role of gene expression, neurogenesis, and psychosocial genomic healing in therapeutic hypnosis (Rossi, 2002a, 2002b).

Evidence possibly suggestive of hypnotizability as a hereditary trait that is transmitted from parents to children by classical Mendelian genetics was noted by Hilgard and Hilgard (1983):

> A careful study showed that this possibility cannot be ruled out, because there is a low but positive correlation between parent and child, and because identical twins were indeed more alike in their hypnotic responsiveness than either fraternal pairs or non-twin siblings. A study of this kind cannot be fully decisive because identical twins, who look alike are always of the same sex, share a more common environment than fraternal twins. However, the results leave open the possibility of a hereditary component (p. 10).

In addition to this still open question of a (1) Mendelian hereditary component of hypnosis, I propose an extension of Kandel's concept of (2) the everyday modulation of gene expression by social factors, counseling, and psychotherapy to include therapeutic hypnosis. I speculate that therapeutic hypnosis involves "social influences" that can modulate gene expression during salient life experiences but "they are not incorporated in the sperm and egg and therefore are not transmitted genetically" (Kandel, 1998, p. 460) from parent to as is the case with in classical Mendelian genetics.

While current terminology is still fluid, for the purposes of this paper, I will distinguish between (1) the term *genetics* that refers to the Mendelian transmission of

hereditary traits across generations that is the subject of *behavioral genetics* and (2) the term *genomics* that refers to the developmental and adaptive modulation of gene expression by many environmental stimuli, stressors, and psychosocial factors *within the individual's daily life experience* (Ridley, 1999, 2001). Because this paper is primarily concerned with the possibility of the *psychosocial* modulation of gene expression by therapeutic hypnosis, I will focus primarily on what I call *psychosocial genomics—the emerging science of how sensory, psychological, social, and cultural signals and stressors can modulate gene expression and vice versa in the deep psychobiology of* health and illness (Rossi, 1990, 1994, 1999, 2000b, 2000c, 2001a, 2001b, 2002a 2002b). Five areas of research exploring this new perspective of psychosocial genomics are briefly outlined here together with my current speculations about their possible association with therapeutic hypnosis (Rossi, 2002a, 2002b). This initial effort to define the domain of psychosocial genomics as the deep psychobiological foundation of therapeutic hypnosis as well as complementary and alternative medicine is not complete in any sense, however.

1. Immediate Early Gene Expression, Psychosocial Cues, and Adaptation

A special class of genes—called *immediate early genes*—can respond to psychosocial cues and significant life events in an adaptive manner within minutes (Cirelli, Pompeiano, & Tanoni, 1996, 1998). Bentivoglio and Grassi-Zucconi (1999) have summarized their research on the dynamics of immediate early genes (IEGs) and psychological experience as follows:

The study of [IEGs] indicates that sleep and wake, as well as synchronized and desynchronized sleep [REM state dreaming], 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... 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 in a general "resetting" of behavioral states? Is gene induction a clue to understanding the alternation of sleep and wake, and REM and non-REM sleep?… Could behavioral state-related IEG induction underlie, at least in part, learning mechanisms? The oscillation of IEGs affects the expression of target genes, and thus brings about other questions: May the transcriptional cascade explain the biological need and the significance of sleep? Does this explain the molecular and cellular correlates of arousal, alertness, and, more in general, of consciousness? We do not have final answers to these questions (p. 249).

I now speculate that these profound questions raised by biological researchers regarding the psychosocial genomics of consciousness, dreaming, sleep, and the "resetting of behavioral states" have significant research implications for the state concept of hypnosis (Barabasz, 2002). Immediate early genes have been described as the newly discovered mediators between nature and nurture: they receive signals from the environment to activate the genes that code for the formation of proteins, which then carry out the adaptive functions of the cell in health and illness (Rossi, 1996, 2000c, 2002a, 2002b). From this deep psychobiological perspective it seems reasonable to explore how immediate early genes are likely to be key players in the induction,

deepening, and therapeutic phases of hypnosis.

2. Clock Genes, Mind-Body Rhythms, and Psychoneuroimmunology

Psychosocial genomics finds a major experimental database in the so-called "clock genes" that coordinate the chronobiology of life at the cellular level (Dunlap, 1999). In a recent review Reppert and Weaver (2002) have discussed the relevance of the circadian timing of clock genes for understanding human behavior:

> Defining the molecular basis of circadian timing in mammals has profound implications. In terms of fundamental brain mechanisms, the circadian system is among the most tractable models for providing a complete understanding of the cellular and molecular events connecting genes to behavior. Through dissection of the genetic basis of circadian behavior may help to decipher the connections for more complex behaviors. Understanding the molecular clock could increase our knowledge of how gene mutations of the molecular clock could contribute to psychopathology (for example, major depression and seasonal affective disorder). Similarly, such understanding should lead to new strategies for pharmacological manipulation of the human clocks to improve the treatment of jet lag and aliments affecting shift workers, and the clock-related sleep and psychiatric disorders (pp. 935-936).

Clock genes set the time cycles of many common everyday psychobiological states such as waking, sleeping and dreaming. The time parameters of the gene expression–protein synthesis cycle set the pace and rhythm of many patterns of mind-body communication, health, and healing. The fundamental life processes of metabolism, homeostasis, growth, energy, information flow, behavior, memory, and healing in health and illness are invariably associated with the rhythms of gene expression and the synthesis of their "cognate" proteins over circadian (24 hours) and ultradian time frames (less than 20 hours [Kleitman & Rossi, 1992; Lloyd & Rossi, 1992, 1993; Rossi, 2002a])—typically Kleitman's 90–120 minute basic rest-activity cycle. The fact that Erickson's hypnotherapeutic sessions typically lasted an hour and a half or two is anecdotal evidence for a possible association between the typical time frames for the gene expression—protein synthesis cycle and the effectiveness of his therapeutic approaches (Rossi, 1986, 2001a, 2002a, 2002b).

There is a wide range of time frames for the activation and expression of many clock genes associated with the central nervous system, the endocrine system and the immune system. *Early activated genes,* for example, reach a peak of expression in about an hour, while *intermediate activated genes* peak in about two hours. Early activated genes are of special interest because they mediate some of relationships between mind and body in *psychoneuroimmunology*. Psychosocial stress, for example, can turn off the early-activated interleukin-2 gene so that the immune system cannot communicate well and we are left more vulnerable to all sorts of opportunistic infections (Glaser et al., 1990; Glaser, Lafuse, Bonneau, Atlinson, & Kiecolt-Glaser, 1993; Kiecolt-Glaser, Marucha, Atkinson, & Glaser, 2001). Positive psychosocial experiences, on the other hand, can turn on the interleukin-2 gene within an hour or two to facilitate molecular communication, healing, and health (Castes et al., 1999). *Late activated genes*, by contrast, require as

much as four hours to reach their peak levels of expression. The turning on and off of cascades of gene expression begins within a few minutes of receiving important psychobiological signals and may continue for hours, days, weeks—or even a lifetime (Incyte, 1999; Kaufer Friedman, Seidman, & Soreq, 1998; Rossi, 1999, 2002a, 2002b). Research is now needed to explore the significance of these ultradian time parameters of gene expression for the efficacy of therapeutic hypnosis in psychoneuroimmunology (Gruzelier et al., 2001; Kiecolt-Glaser et al., 2001, Rossi, 2002a).

3. Behavioral State-Related Gene Expression in the Sleep-Awake Continuum

Bentivoglio and Grassi-Zucconi (1999) introduced the concept of "behavior state-related gene expression" to describe their research on immediate early genes in the molecular dynamics of waking, sleeping, and dreaming.

> *In relation to behavioral state-related gene expression, it is interesting to note that Fos [the protein coded for by the immediate early gene c-fos] is induced during wake in thalamic "non-specific" structures, in which it increases after a sustained wake, thus paralleling changes in the physiological activity of these neurons*... In the brainstem, Fos-immunostained neurons were found after a period of wake in the dorsal raphe, locus coeruleus and mesopontine nuclei, central gray, and superior and inferior colliculi. Such activation of the tectal neurons could be related to their role in *sensory processing and in the integration of multi-sensory and sensorimotor functioning. On the other hand, the central gray is involved in emotional behavior-related sensory processing. The role of state-dependent behavior of the monoaminergic brainstem structures, which contain neurons in which Fos is induced during wake is extensively discussed*... (pp. 245-246, italics added).

Different states of behavior and consciousness—waking, sleeping, dreaming, emotions, motivation, and stress—are all associated with different patterns of behavioral state-related gene expression. From this perspective behavioral state-related gene expression is a fundamental link between psychology and biology. This leads me to speculate that behavioral state-related gene expression may be of essence in exploring the deep psychobiology of consciousness in therapeutic hypnosis. The general hypothesis is that behavioral state-related gene expression can be modulated with psychosocial cues and cultural rituals such as therapeutic hypnosis to facilitate health, performance, and healing (Rossi, 2000c, 2002a). Research paradigms utilizing the new DNA microarray technology have been proposed to assess the degree to which behavioral state-related gene expression is actually engaged in the wide range of states from relaxation to arousal and stress that are modulated by therapeutic hypnosis (Rossi, 1999, 2000b, 2002a, 2002b).

4. Stress Related Gene Expression, Psychosomatics, and Healing

Genes whose expression is associated with stress are a category of psychosocial genomics that may become of special interest to therapeutic hypnosis.

The relationship between Posttraumatic Stress Disorder and cholinergic gene expression, for example, has been documented experimentally by Kaufer et al. (1998) and Meshorer et al. (2002) as reviewed by Rossi (2002b). I have hypothesized that stress induced gene expression is the basic but generally unrecognized psychogenomic source of psychosomatic problems that are addressed by therapeutic hypnosis, alternative, and complementary medicine (Rossi, 2000c, 2002a). Figure 1a, for example, illustrates how the stress of maternal separation and a lack of touch results in a sharp decline in expression of the ODC gene (that codes for the synthesis of the Ornithine Decarboxylase enzyme) within 2 hours. This leads to a suppression of growth hormone and DNA synthesis in most organ tissues of the body. Figure 1b, by contrast, illustrates how simple touch can restore ODC gene expression in the brain and heart within the same ultradian time frame.

Figure 1a: Maternal separation and deprivation of physical touch results in decreased ODC gene expression in the 10-day-old rat brain within 10 to 15 minutes. Within 2 hours ODC gene expression is less than 40% of normal. Reprinted with permission from Schanberg, S. (1995). Genetic bases for touch effects. In T. Field (Ed.), *Touch in early development.* New York: Lawrence Erlbaum & Associates.

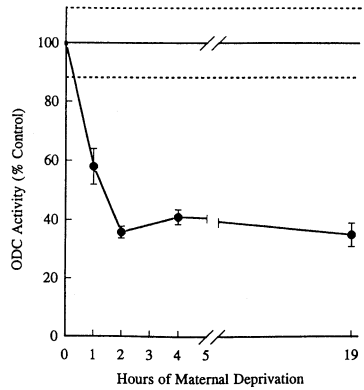
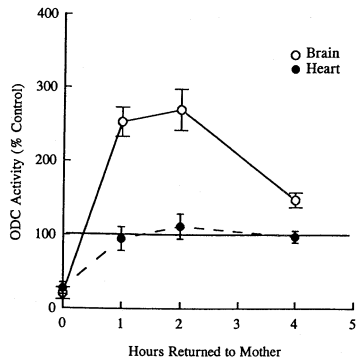


Figure 1b: The recovery of ODC gene expression in the brain and heart after a 2-hour deprivation and the return to the mother. Notice the statistically significant overcompensation that approaches 300% in 2 hours and remains elevated after 4 hours. This "therapeutic effect" of maternal touch is an example of psychosocial genomics—how sensory, psychological, social, and cultural signals and stressors can modulate expression in the deep psychobiology of health and illness. Reprinted with permission from Schanberg, S. (1995). Genetic bases for touch effects. In T. Field (Ed.), *Touch in early development.* New York: Lawrence Erlbaum & Associates.



I speculate that this association between touch, ODC gene expression, growth hormone, and DNA synthesis is an example of the unrecognized psychosocial genomic mechanisms evoked by a wide variety of approaches to healing evident in the "passes" of historical hypnosis (Edmonston, 1986), "therapeutic touch" (Fields, 1995), and the many "holistic" body therapies found in diverse cultures (Rossi, 2000c, 2002a).

5. Activity-Dependent Gene Expression, Neurogenesis, and Healing

Kandel et al. (1983, 1989, 1998, 2000) found in memory and learning experiments that repeated salient stimulation can turn on gene expression to produce messenger RNA (mRNA) that codes for the production of new proteins in neurons. Since gene expression and protein synthesis is dependent on activities of the organism, this is called "activity-dependent gene expression." As reviewed previously (Rossi, 2002a, 2002b), short term memory (1 to 20 minutes) involves rapid neurotransmission from one neuron to another. Long term memory, by contrast, requires the engagement of activity-dependent gene expression over a period of 90-120 minutes. Long term memory and learning engages a molecular communication system in a circular loop of information transduction from the environment to the nucleus of the neuron where the genes are located (Kandel et al. 2000; Stahl, 2000). This activation of gene transcription that is the basis of neurogenesis is called the *"genomic action potential"* (Clayton, 2000). As is typical of the activity-dependent gene expression and protein synthesis cycle through out the brain and body, it requires an ultradian periodicity of about 90–120 minutes (Rossi, 2002a).

Activity-dependent gene expression generates the proteins and growth factors that signal *stem cells,* normally residing in the brain, to differentiate into newly functioning neurons with new connections between them (Gage, 2000a, 2000b; Galli et al., 2000). The direct isolation of human central nervous system stem cells (Uchida et al., 2000), together with their capacity for self-renewal and migration to the loci of pathology in adult brain (Aboody et al., 2000), suggests that they are a natural source of healing that would be of central interest in a psychobiologically oriented theory of therapeutic hypnosis. The search for research paradigms in this area in the future may derive from current neuroscience experiments relating psychological experiences to activity-dependent gene expression and neurogenesis.

Three Psychosocial Factors that Optimize Gene Expression, Neurogenesis, Memory, and Healing

Activity or behavior is the linchpin that connects psychological experience to the three factors that optimize gene expression, neurogenesis, and healing:

1) *novelty* (Eriksson et al., 1998)
2) *environmental enrichment* (Kempermann, Kuhn, & Gage, 1997; Van Praag, Kempermann, & Gage, 2000), and
3) *physical exercise* (Van Praag et al., 1999, 2002).

Activity-dependent gene expression facilitates the generation of functional neurons in the hippocampus of the brain, which encodes new memory, learning, and behavior (Gould et al., 1999a, 1999b; Van Praag et al., 2002). Most significantly, Gould, Tanapat, Reeves and Shors (1999B) document how neurogenesis takes place in three

neocortical association areas (prefrontal, inferior temporal, and posterior parietal cortex) that are involved in behavioral plasticity (that is, behavioral change) and associated transformations of psychological experience. Gould et al. (1999a) conclude, "these new neurons, which are continually added in adulthood, may play a role in the functions of association neocortex" (p. 548).

Although other reputable researchers have confirmed neurogenesis in the hippocampus and olfactory bulb, however, they have not been able to substantiate Gould et al.'s claim of neurogenesis in the normal adult primate neocortex (Kornack & Rakic, 2001). The current controversy about the validity and extent of neurogenesis in the adult primate association neocortex requires resolution before the most optimistic implications of such neurogenesis could be accepted as a new neuroscience foundation for the theory and practice of psychotherapy, therapeutic hypnosis, and the therapeutic arts in general (Nowakowski & Hayes, 2000; Gould & Gross, 2000).

Van Praag et al. (2002) have presented the most recent evidence in this controversy about the functional significance of neurogenesis in the adult hippocampus.

> There is extensive evidence indicating that new neurons are generated in the dentate gyrus of the adult mammalian hippocampus, a region of the brain that is important for learning and memory... We report that newly generated cells in the adult mouse hippocampus have neuronal morphology and can display passive membrane properties, action potentials and functional synaptic inputs similar to those found in mature dentate granule cells. Our findings demonstrate that newly generated cells mature into functional neurons in the adult mammalian brain... *we have identified one-month-old neurons with functional properties similar to those of mature dentate granule cells in the adult hippocampus. We also show that newly generated neurons are initially smaller and reach a more mature morphology after four months* (p. 1030, italics added).

To understand how such research on the time parameters of neurogenesis could have important implications for the theory, research, and practice of therapeutic hypnosis, psychotherapy, and counseling in general (Gross, 2000; Kandel, 1998), we need to develop new experimental paradigms to explore the relationships between activity, psychobiological arousal, gene expression, neurogenesis, memory, learning, stress, and healing.

Neurogenesis, Long-term Potentiation and Psychobiological Arousal

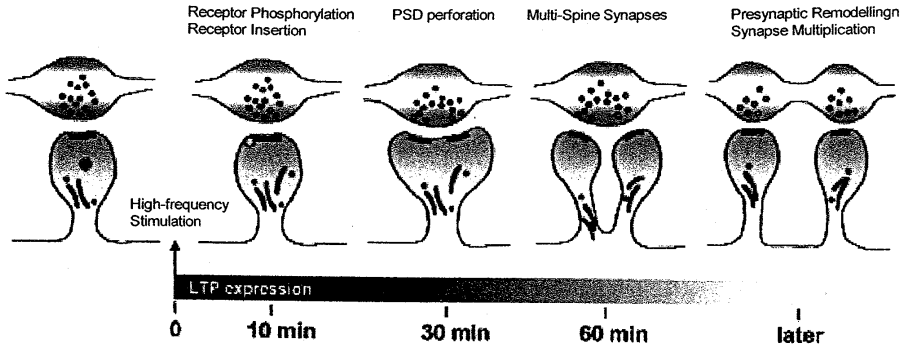
Neurogenesis has been related to studies of memory and learning at the neurobiological level via "long term potentiation" (LTP). Johnston and Maio-Sin Wu (1995) define LTP "as an enduring, activity-dependent increase in synaptic efficiency... *which persists on the order of an hour or more... initiating gene expression*" (p.459, italics added).

A visual model of the dynamic process by which LTP generates the formation and growth of new synapses to encode activity-dependent memory, learning, and behavior has been proposed recently by Lüscher et al., (2000). As illustrated in Figure 2, LTP generates an increase in the number of synapses connecting one neuron with

another within an hour. Within the first 10 minutes of LTP induction, there is an activation of the receptors that are involved in synaptic communication via neurotransmitters. Within the first 30 minutes, the size of the synaptic spine increases leading to an increase in the size of the "post-synaptic density" that will become the receiving site of neurotransmission. Within an hour, some synapses divide in two as illustrated in Figure 2. This leads, in turn, to further growth in pre-synaptic multiplication and remodeling to create new neural networks for encoding memory, learning, and behavior change. I propose this as the neurobiological essence of therapeutic hypnosis, psychotherapy, and many of the alternative and complementary paths to healing (Rossi, 2000c, 2002a).

It is somewhat startling to realize how such experimental research could serve as a neurobiological model for therapeutic hypnosis within the typical time frame of a clinical session of about an hour. Does this imply that a shorter period is not sufficient for the psychogenomic dynamics of therapeutic hypnosis? Not really. Anecdotal reports of Milton Erickson's use of surprise and "psychological shock" to evoke psychobiological arousal in therapeutic hypnosis and post-hypnotic suggestion

Figure 2: Proposed stages in the genesis of new synapses with long term potentiation (LTP). Within 10 minutes of appropriate stimulation there is a series of molecular signals that activate AMPA receptors and an increase in their single channel conductance. Within 30 minutes the size of the post-synaptic density increases and divides in the receiving neuron. Within 60 minutes some synapses divide to generate multi-spine synapses where 2 or more post-synaptic spines connect with the pre-synaptic bouton. Concomitant retrograde communication from the post to the pre-synaptic bouton increases so that the total number of functioning synapses proliferate over time (90-120 minutes to hours). This implies that the activity-dependent generation of new synapses for the construction and re-consturction of the neural networks of memory, learning and behavior may be possible within the typical time frames of many approaches to therapeutic hypnosis and psychotherapy in general. Reprinted with permission from Luscher, Nicoll, Malenka, & Muller (2000), Synaptic plasticity and dynamic modulation of the postsynaptic mebrane. *Nature Neuroscience* 3, pp. 545-567.

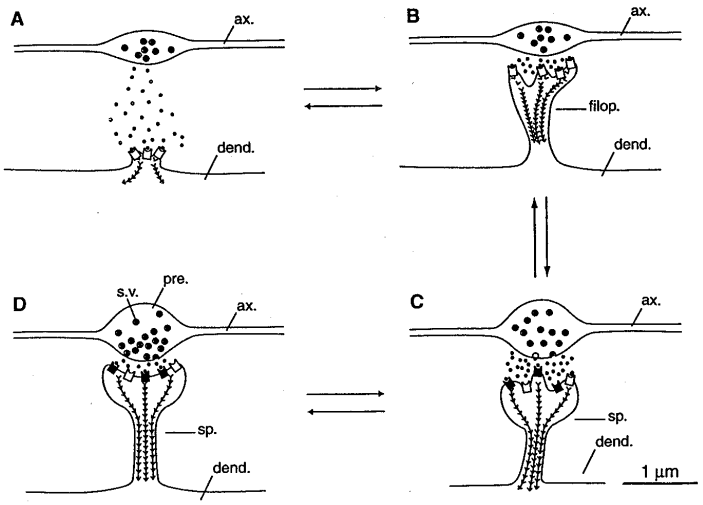


(Erickson, 1964/1980; Rossi, 1973, 2002a, 2002b), for example, indicates that a brief but memorable experience of a few seconds or minutes can change one's perspective and behavior for a lifetime. A variety of clinical research paradigms utilizing the new DNA microarray technology for assessing the efficacy of therapeutic hypnosis in the typical time frames of gene expression and neurogenesis have been outlined (Rossi, 1999, 2000a).

Stages and Reversibility of Activity-Dependent Neurogenesis in Hypnosis?

A closer look at the details of the actual growth process at the synaptic level of neurogenesis by Matus (2000) fills in some of the details of the mechanisms proposed by Lüscher et al (2000). Matus begins by noting that during brain development, neurogenesis proceeds in a number of distinct stages. The first stage, which takes place during embryogenesis, involves the initial creation of neural networks under the

Figure 3: A hypothetical illustration of the dynamics of glutamate receptors in the reversibility of synaptic development in the construction and reconstruction of neural networks. (A) Stimulation of NMDA receptors (white boxes in the receiving dendrite [dend.]) generates branching actin strings at the newly developing synaptic sites leading to (B) the outgrowth of motile filopodia (filop.) making connection with the pre-synaptic axon (ax.). The acquisition of AMPA receptors (black boxes) and the formation of synaptic contacts is accompanied by reduced motility. (D) Activation of AMPA receptors further suppresses motility and stabilizes spine (sp.) morphology. Neurotransmitter molecules of glutamate are illustrated as black spots inside the pre-synaptic vesicles (s.v.). The reversible arrows between stages A, B, C and D mean that these connections form new structures and neural networks that remain reversible and plastic (changeable) in time with changing patterns of activity-dependent stimulation. Reprinted with permission from Matus, A. (2000). Actin-based plasticity in dendritic spines. *Science*, 290, 754-758.



guidance of neurotropic messenger molecules. The second stage takes place after birth, during a relatively short critical period when synaptic connections are refined by activity-dependent sensory and motor experience. The third and fourth stages, which are active throughout the lifespan, engage activity-dependent memory and learning as well as the reversible synthesis and re-synthesis of synapses as illustrated in Figure 3.

Figure 3 illustrates reversible formation of synapses at the level of dendritic growth in the shifting dynamics of neural networks as proposed by Matus. Stages A and B in Figure 3 illustrate the initial steps of dendritic outgrowth, which appears to be stimulated by the activation of NMDA receptors that are known to be involved in memory and learning. Stages C and D of Figure 3 illustrates the experience or activity-dependent gene expression leading to the generation of proteins in the formation and placement of AMPA receptors that stabilizes the growth of synaptic connections between neurons.

Current research suggests that the four transition states (A, B, C, & D in Figure 3) in this sequence of development are reversible depending on the strength and maintenance level of activity-dependent stimulation at the pre-synaptic terminal. *It is of greatest importance to recognize psychological implications of the reversible arrows between the four phases of neurogenesis at the level of dendritic synaptic development and stabilization. This reversibility illustrates a fundamental psychogenomic mechanism for*

(1) the creation and maintenance of memory and learning
(2) the molecular dynamics of forgetting, amnesia and dissociation as well as
(3) the change, transformation and re-synthesis of memory and behavior associated with further activity-dependent gene expression and neurogenesis.

Matus (2000) summarizes the interaction between the psychological level of memory and learning and the molecular level of neurogenesis at the dendritic level in this way:

> Such a scheme may help explain experience-dependent [that is, activity-dependent] shaping of neuronal circuits because it would make sense to require a mechanism that depends on strong stimulation, like that of NMDA receptor activation, for the initiation of new connections but to then support them with a mechanism sensitive to low rates of neuronal activity, like that of AMPA receptor activation. Learning responses could thus be maintained during periods when they are not actually being used. Similarly, should synaptic stimuli fall below a certain threshold indicative of disuse, it would be appropriate for synaptic connections to be broken *and re-formed in new configurations* (p. 757, italics added).

At the present time we can only speculate about the implications of such "experience-dependent shaping of neuronal circuits" for facilitating the deep psychobiology of therapeutic hypnosis. When "synaptic connections [are] broken"

we wonder, for example, if this can be the psychobiological basis for ordinary forgetting as well as a number of classical phenomena associated with hypnosis such as amnesia and dissociation (Janet, 1919/1925). When "synaptic connections [are] re-formed in new configurations" we wonder if this could be the psychobiological foundation for the re-association, reorganization, and re-synthesis of psychological experience during therapeutic hypnosis proposed by Milton Erickson (1948/1980). A variety of new research paradigms have been outlined (Rossi, 2000b, 2000c, 2002a; Rossi & Cheek, 1988) to assess the fundamental psychobiological dynamics of experience or activity-dependent gene expression and neurogenesis could account, at least in part, for the efficacy of therapeutic suggestion pioneered by James Braid, Pierre Janet, and Milton Erickson.

Summary: Implications of Gene Expression and Neurogenesis for Therapeutic Hypnosis Today

There is no research that directly validates the hypothesized associations between gene expression, neurogenesis, and healing with the practical techniques of therapeutic hypnosis that are in use today. New experimental paradigms combining recent studies on the psychobiological localization of hypnotic experience in the brain and body (Barabasz, 2002; Gruzelier et al., 2001; Kiecolt-Glaser et al., 2001; Rainville et al., 1997, 1999) with the most successful research designs for identifying the locus of gene expression and neurogenesis (Van Praag et al., 2002) are needed. Until such research is carried out, any attempt to generalize the proposed associations between the gene expression, neurogenesis, healing, and psychotherapy (Gross, 2000; Kandel, 1998) to the psychobiological domain of therapeutic hypnosis remains speculative. Given this caveat, however, researchers, clinicians and students may choose to explore the implications of current neuroscience research for understanding and facilitating the efficacy of therapeutic hypnosis in the following ways.

- Exploring the new theory, experimental techniques, and research base of current neuroscience has a potential to vastly expand the scientific status and domain of therapeutic hypnosis. Such research could integrate interdisciplinary research among psychology, biology, and medicine with the "psychophysiological" foundation of therapeutic hypnosis pioneered by James Braid, Pierre Janet, and Milton Erickson.
- The fundamentals of gene expression, neurogenesis, and healing by the differentiation and maturation of stem cells may be the common denominator that integrates modern molecular medicine with alternative and complementary medicine. The ambiguous borderlines between therapeutic hypnosis and the cognitive-behavioral therapies, as well as the holistic and spiritually oriented therapeutic arts of many cultures throughout human history, could be clarified with a common yardstick that measures precisely what each approach contributes to facilitating healing via gene expression, neurogenesis, and stem cell healing.
- The time parameters of gene expression and neurogenesis in the synthesis and re-synthesis memory, learning and behavior ranging from seconds to minutes, hours, days, weeks and months can sharpen the clinician's awareness of the potential value of the many time-related techniques of therapeutic hypnosis. These

include the momentary value of "psychological shock" and surprise to optimize psychobiological arousal and its evocation of immediate-early, behavioral state-related, activity-dependent, and clock gene expression—as well as the traditional use of relaxation for the mitigation of stress-related gene expression in facilitating healing within minutes to hours.

- Research on the proposed associations between gene expression, neurogenesis, healing, and therapeutic hypnosis could enhance our understanding of how to optimize the duration of suggestions to facilitate healing with the varying states of highly focused attention, relaxation, dreaming, and sleep. Therapeutic hypnosis and post-hypnotic suggestion could be focused more precisely with the natural time parameters of gene expression and neurogenesis, for example, that can range from minutes and hours to facilitate the differentiation of new synapses, to 4 weeks for the generation of young functioning neurons, to 4 months for their maturation. *The implication is that if therapeutic suggestion is to endure over time (more than the typical short term memory of 15 or 20 minutes), it must engage gene expression to facilitate long term potentiation, synaptogenesis, neurogenesis, and healing.* Such research could lead to new criteria for the resolution of the controversies about the duration of the effectiveness of therapeutic hypnosis in facilitating optimum performance, habit change, symptom amelioration, and healing.

- Therapeutic hypnosis has traditionally facilitated the motivation (fascination, arousal, interest) for *"activity"* and the actual means (techniques, behavioral prescriptions, approaches) for *"doing"* to help people help themselves. Indeed, facilitating activity or behavior could be described as the essential purpose of "suggestion." Therapeutic suggestions are offered in the hope of helping people *do something* to facilitate their learning, problem solving, and healing. Current neuroscience research now traces the deep psychobiology of cognitive-behavioral activity to "activity-dependent gene expression," which can facilitate "activity-dependent neurogenesis and healing." This implies that *novelty, environmental enrichment, and exercise*—the three factors that optimize gene expression, neurogenesis, and healing—could become new guidelines for crafting therapeutic suggestions with hypnosis as well criteria for evaluating their effectiveness.

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