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Prospects for Exploring the Molecular-Genomic Foundations of Therapeutic Hypnosis with DNA Microarrays

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A new perspective on how therapeutic hypnosis and neuroscience may be integrated on the molecular-genomic level is offered as a guide for basic research and clinical applications. An update of Watson and Crick's original formulation of molecular biology is proposed to illustrate how psychosocial experiences modulate gene expression, protein synthesis, and brain plasticity during memory trace reactivation for the reorganization of neural networks that encode fear, stress, and traumatic symptoms. Examples of the scientific literature on DNA microarrays are used to explore how this new technology could integrate therapeutic hypnosis, neuroscience, and psychosocial genomics as a new foundation for mind-body medicine. Researchers and clinicians in therapeutic hypnosis need to partner with colleagues in neuroscience and molecular biology that utilize DNA microarray technology. It is recommended that hypnotic susceptibility scales of the future incorporate gene expression data to include the concept of "embodied imagination" and the "ideo-plastic faculty" on a molecular-genomic level as well as the psychological and behavioral level of ideomotor and ideosensory responses that are currently assessed.

Keywords: Activity dependent gene expression, brain plasticity, DNA microarrays, memory trace reactivation theory, mind-body medicine, molecular-genomic, neuroscience, psychophysiology, psychosocial genomics, stress, therapeutic hypnosis, trauma.

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Introduction: Molecular-Genomic Perspectives on the Interaction between Mind and Body in Therapeutic Hypnosis

Theodore Sarbin's (2005) recent reflections on unresolved issues in hypnosis recommends that we "enlarge the scope" of experimental investigations to explore how humans utilize *"as if" embodied imaginings* to modulate their psychophysiological and psychosomatic responses. This paper proposes that a full understanding of Sarbin's concept of embodied imaginings requires a new molecular-genomic perspective of mind-body interaction in therapeutic hypnosis and neuroscience (Raz & Shapiro, 2002; Rossi, 1986/ 1993, 2002, 2004a, 2005a). We will approach this new perspective by updating Watson and Crick's (1953a, b) original formulation of molecular biology with current research on the new technology of DNA microarrays that enables researchers to assess the states and changes in gene expression in cells and tissues of the brain and body in health and disease. While much of this research has been done with animal models, this paper reviews research models of how this new technology could be applied to foundational research on the clinical applications of therapeutic hypnosis.

A Neuroscience Update of Watson and Crick's Original Formulation of Molecular Biology

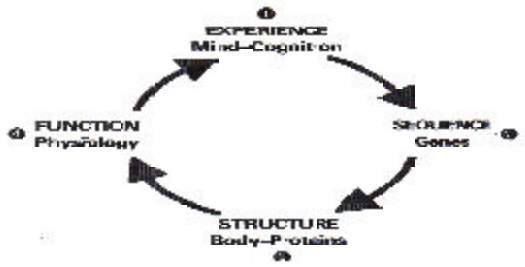
Watson and Crick's (1953a, b) original formulation of molecular biology for which they received the Nobel Prize is illustrated in figure one. Figure 1a outlines how (1) the linear *sequence* of nucleotides of genes functions as a code of biological information that (2) generates the three-dimensional *structure* of the proteins, which (3) then *function* in the physiological processes of the brain and body.

There was no place for psychosocial experiences in Watson and Crick's original formulation of molecular biology. Since that time, however, neuroscience has documented how psychosocial experiences of novelty (Eriksson et al., 1998), psychosocial enrichment (Kempermann, Kuhn, Gage, 1997), mental and physical exercise (Van Praag et al., 2002) can evoke gene expression (genomics), protein synthesis (proteomics), and brain plasticity to modulate the psychophysiological functions of the brain and body. These are all examples of psychosocial genomics: the modulation of gene expression by salient psychosocial experiences and behavioral activities that may be assessed with DNA microarrays.

Such research is the empirical basis for adding the psychosocial genomics of mind and cognition (the subjective experiences of consciousness such as sensations, perceptions, emotions, stress, etc.) to Watson and Crick's original *linear* formulation of molecular biology in Figure 1a. Figure 1b updates the linear formulation of molecular biology with the *circular* mind-body feedback loop of psychosocial genomics (Rossi, 2002, 2003a, 2004a, 2005a). The top-down approaches of current neuroscience document how behavioral and psychosocial states of heightened arousal and rest in the here-and-now moments of trauma, stress, REM sleep, memory, learning, creative work, etc. could modulate gene expression, brain plasticity, and mind-body healing in therapeutic hypnosis as we shall now explore in greater detail.

Figure 1a: The Watson & Crick linear dogma of molecular biology of 1953 with no explicit role for consciousness and psychological experience.

Figure 1b: Rossi's psychosocial genomics circular loop of mind-body communication (1) The psychological experiences of mind, cognition, stress etc. can modulate (2) the alternative splicing of the *sequence* of gene expression (genomics), (3) protein synthesis and *structure* (proteomics), and (4) the physiological *functions* of the brain and body. The "top-down" experience of psychosocial genomics as illustrated on the right side of this mind-body circle of information transduction is balanced by the more usual "bottoms up" approach of molecular biology, behavioral genetics, evolutionary psychology, and sociobiology illustrated on the left side.



Emerging Molecular-Genomic Foundations for a Neuroscience of Therapeutic Hypnosis with DNA Microarrays

Eisen, Spellman, Brown, & Botstein, (1998) are pioneers in developing the new science and technology of DNA microarrays that allows molecular biologists to assess gene expression at any moment of time under different physiological conditions and states of the organism. They describe how these molecular-genomic patterns can define the states of the organism as follows:

> A system of cluster analysis for genome-wide expression data from DNA microarray hybridization is described that uses standard statistical algorithms to arrange genes according to similarity in patterns of gene expression. The output is displayed graphically, conveying the clustering and the underlying expression data simultaneously in a form that is intuitive for biologists...clustering gene expression data groups together efficiently genes of known similar function, and we find a similar tendency in human data. Thus, patterns seen in genome-wide expression experiments can be interpreted as indications of the status of cellular processes. Also, co-expression of genes of known function with poorly characterized or novel genes may provide a simple means of gaining leads to the functions of many genes for which information is not

> currently available (p. 14863)...*the functional concordance of co-expressed genes imparts biological significance to the broad patterns seen in images* [of DNA microarray data]. . . *it is a comprehensive representation of the cell throughout. . . information on the state of many cellular processes can be inferred quickly by combining and comparing new experiments with the data presented here* (p. 14868, italics added).

Eisen et al. (1998) describe the *"functional concordance of co-expressed genes"* as a new way of defining and identifying the states and transformations of cells and tissues on the molecular-genomic level during biological development, performance, and activity in sickness and health. The "functional concordance of co-expressed genes" means that there are recognizable patterns of gene expression that coordinate physiological functions such as heart rate, digestion, hormones, immune system, brain plasticity, behavioral activity, etc. Fundamental research is now needed to determine whether we could extend the DNA microarray revolution to documenting how salient psychosocial states can modulate gene expression, protein synthesis, and brain plasticity as a new scientific foundation for therapeutic hypnosis (Erickson, 2006). The significance of DNA microarray research for therapeutic hypnosis is that it may enable us to assess any special psychological state as "the functional concordance of co-expressed genes" interacting with the challenges of our physical and psychosocial environment (Erickson & Rossi, 2006a).

Researchers have already utilized DNA microarrays to characterize a variety of psychological states and conditions such as depression (Evans et al., 2004), posttraumatic stress (Segman et al., 2005), depression, aggression and playful social situations (Panksepp, Moskal, Panksepp, & Kroes, 2002). This implies that the functional concordance of co-expressed genes identified with DNA microarrays may become a new way of assessing varying states of consciousness, behavior, emotion, mood, and their transformations in therapeutic hypnosis and perhaps psychotherapy in general. When researchers begin to include DNA microarray data in their factor analytic studies of hypnotic susceptibility scales we may be able relate profiles of gene expression to profiles of hypnotic susceptibility. Likewise, when researchers begin to include DNA microarray data in their standardization of paper and pencil personality scales and clinical interviews, we may be able to relate profiles of gene expression to personality profiles for a new psychosocial genomic science of subjective states and psychotherapy in the future.

The feasibility of such research was implied by Whitney et al. (2003), for example, who documented how individuality and variation in gene expression patterns in human blood can be assessed reliably with DNA microarray technology. The extent, nature, and sources of variation in gene expression among healthy individuals are a fundamental, yet largely unexplored, aspect of human biology and psychology. They state:

> *"Future investigations of human gene expression programs associated with disease, and their potential application to the detection and diagnosis, will depend upon an understanding of normal variation within and between individuals, over time, and with age, gender, and other aspects of the human condition"* (p. 1896, italics added).

This means that DNA microarrays could become a more sensitive, comprehensive, and reliable way of defining and measuring psychobiological states of consciousness, emotions, behavior, and brain plasticity as well as the purported special states of therapeutic

hypnosis. Recent research by Lichtenberg, Bachner-Melman, Gritsenko, and Ebstein, (2000) and Lichtenberg, Bachner-Melman, Ebstein, and Crawford (2004), for example, have documented how certain variations in the COMT (Catechol-O-Methyltransferese) gene are associated with hypnotizability. To determine whether the COMT gene could be assessed via microarray studies of gene expression in human blood, I recently reexamined the Whitney et al. (2003) data with GeneSpring (professional software for evaluating gene expression in DNA microarray data) and here report for the first time that the COMT gene was, in fact, expressed in their samples. This illustrates how DNA microarray data could become a significant source of hypotheses for assessing the molecular-genomic foundations of psychophysiological states in general as well as therapeutic hypnosis in particular.

Heightened Gene Expression and Neuronal Activation in the Human Brain: The Ideodynamic Hypothesis of Hypnosis

DNA microarrays have recently offered profound insights into the molecular-genomics of human brain evolution, cognition and behavior summarized by Preuss, Cáceres, Oldham, & Geschwind (2004) as follows:

> Several recent microarray studies have compared gene expression patterns in humans, chimpanzees and other non-human primates to identify evolutionary changes that contribute to *the distinctive cognitive and behavioral characteristics of humans. These studies support the surprising conclusion that the evolution of the human brain involved an up-regulation of gene expression relative to non-human primates, a finding that could be relevant to understanding human cerebral physiology and function.* These results show how genetic and genomic methods can shed light on the basis of human neural and cognitive specializations, and have important implications for neuroscience, anthropology and medicine." (p. 850, italics added)

This molecular-genomic model of human cognition and behavior answers the basic question of how to account for the difference between human and nonhuman primates' consciousness and behavior when they both have about the same number of genes (~24,000) which are more than 99.6 % alike. Cáceres et al. (2003) summarize their research in this area as follows:

> Little is known about how the human brain differs from that of our closest relatives. To investigate the genetic basis of human specializations in brain organization and cognition, we compared gene expression profiles for the cerebral cortex of humans, chimpanzees, and rhesus macaques by using several independent techniques. We identified 169 genes that exhibited expression differences between human and chimpanzee cortex, and 91 were ascribed to the human lineage by using macaques as an out-group. Surprisingly, most differences between the brains of humans and non-human primates involved up-regulation, with ~90% of the genes being more highly expressed in humans. By contrast, in the comparison of human and chimpanzee heart and liver, the numbers of up- and down-regulated genes were nearly identical. *Our results indicate that the human brain*

> *displays a distinctive pattern of gene expression relative to non-human primates, with higher expression levels for many genes belonging to a wide variety of functional classes. The increased expression of these genes could provide the basis for extensive modifications of cerebral physiology and function in humans and suggests that the human brain is characterized by elevated levels of neuronal activity"* (p. 13030, italics added).

This implies that DNA microarrays may be a more sensitive, comprehensive and reliable measure of psychological states of human consciousness, emotions, behavavior, brain plasticity, and mind-body interactions. Cáceres et al. (2003) do not discuss the implications of their research for therapeutic hypnosis but their molecular-genomic outline of heightened neuronal activity in human consciousness suggests such a possibility. Table one lists the genes reported by Cáceres et al. (2003) and others as candidates that I would predict as changing in their degree and patterns of gene expression in DNA microarray studies of the molecular-genomic foundations of therapeutic hypnosis. DNA microarray studies of the applications of therapeutic hypnosis to psychosomatic problems could resolve centuries of controversy about the theory and practice of hypnosis cogently summarized by Weitzenhoffer (2001) as follows:

> My position today (Weitzenhoffer, 2000) is that any theorizing regarding hypnosis has been and continues to be premature. There is still much groundwork to be done before anything fruitful of the sort can be accomplished. Today I have little in the line of a theory—just a few hypotheses which are insufficient to account for all the facts that have been satisfactorily established (p. 157).

Weitzenhoffer (2000) describes the *ideodynamic action hypothesis* as coming closest to a theory of "hypnotic effects" as follows:.

> Few formulations regarding what the suggestion process is, exist that can be called a theory. The most widely accepted and influential so-called theory, still really a hypothesis, is known as the *ideodynamic action theory*, often being improperly referred to as the "ideomotor theory" and as a theory of hypnosis. Strictly speaking, it pertains directly only to suggested behavior. It has nothing to do with hypnosis, but of course, indirectly it does. Of all the hypotheses that have been proposed regarding the production of hypnotic effects (understood as suggested effects), it is the one that comes closest to being a theory and more workers in the field have ascribed to it than any other hypothesis (p. 123).

What is the nature of action in the ideodynamic action hypothesis of suggestion described here by Weitzenhoffer? The DNA microarray research of Preuss et al. (2004), Cáceres et al. (2003), and others (Mikkelsen et al., 2005) is consistent with the history of hypnosis as a way of activating and heightening the efficacy of human cognition, behavior, and mind-body healing. This suggests that DNA microarray assessment of the efficacy of therapeutic hypnosis could be a way of reifying the ideodynamic action hypothesis of hypnosis with research on activity dependent gene expression, brain plasticity, and psychophysiology in the humans. More specifically, DNA microarrays may enable us to identify the range, parameters, and limitations of the efficacy of therapeutic hypnosis in mind-body healing with the modulation of gene expression and brain plasticity in the various branches of psychophysiology such as psychoendocrinology and psychoimmunology.

Table 1: A brief sampling of gene candidates for assessing the possible role of therapeutic hypnosis and related psychotherapeutic processes in modulating gene expression, brain plasicity and mind-body healing via DNA microarray technology.

Hypnosis, Absorption, Personality and Gene Expression		
COMT		Lichtenberg et al., 2000, 2004
THRA		Rossi, 2004a,c
Per 1		
Brain Plasticity in Consciousness, Memory, Learning and Behavior Change		
c-fos, c-Jun, krox, NGFI-A & B		Bentivoglio & Grassi-Zucconi, 1999
CREB		Kandel, 2001
BNDF		Russo-Neustadt, 2001
CYP-17		Ridley, 1999
~ 100 Immediate Early Genes		Rossi, 2002
Heightened Gene Expression in the Human Cortex		
SYN47	DCTN1	Cáceres et al. 2003
MAP1B	CAMK2A	Preuss et al., 2004
IMPA1	RAB3GAP	
CDS2	ATP2B1	
KIF3A	USP14	
ASPM	Mekel-Bobrov, 2005	
MCPH1	Evans, 2005	
Replay in the Reconstruction of Fear, Stress and Traumatic Memories		
Zif-268		Ribeiro et al., 2002, 2004
		Nader et al., 2000a,b
Acute and Chronic Psychosocial Stress		
Nerve Growth Factor (NGF)		Alfonso et al., 2004
Membrane Glycoprotein 6a (M6a)		
CDC-like Kinase 1 (CLK-1)		
G-protein alpha q (GNAQ)		
CRE- dependent reporter gene		Alejel et al., 2002
Acetylcholinesterase (AChE-S & AChE-R)		Soreq & Seidman, 2001
Psychoneuroimmunology		
Interleukin 1, 2, 1ß, Cox-2		Kiecolt-Glaser et al. 2001
p53		Chipuk et. al. 2005; Vousden, 2005
p16, pRB		Campisi, 2005
Clock Genes & Behavior State-Related Genes		
~100 sleep related genes		Cirelli et al., 2004
Clock, Period 1, BMAL		Rossi, 2004
Period 2		Rosbash & Takakshi, 2003
Relationships, Maternal Behavior, & Therapeutic Touch		
ODC gene		Schanberg, 1995
CYP-17		Ridley, 1999
Empathy, Trust, & Sexual Bonding		
Oxytocin gene		Witt, 1995; Kosfeld et al., 2005
V1aR gene		Pennisi, 2005; Hammock & Young, 2005

Trauma, Stress and Environmental Challenges Induce Alternative Gene Splicing: Stress Reduction with Therapeutic Hypnosis

The common applications of therapeutic hypnosis for the treatment of trauma, stress, posttraumatic stress (PTSD), environmental, and psychosocial challenges (e.g. occupational and relationship issues, phobias, examination stress, sports performance, etc) implies there are deep psychobiological associations between stress and its reduction by therapeutic hypnosis on the molecular-genomic level. One of the most common approaches to the experimental study of stress across many model organisms ranging from yeast to primates is described as the *stress induced alternative splicing of genes*.

Phillip Sharp, who won the 1993 Nobel Prize in Physiology of Medicine (Watson, 2005) for his part in discovering gene splicing, recently reported that 10% of genes are subject to alternative splicing of the code *sequence* that gives rise to alternative patterns of protein *structure* and alternative pathways of physiological *function* (illustrated in Figures 1a and 1b). Other estimates suggest that this figure may be as high as 40% (Rossi, 2005a). We now know that a gene does not exist as a single *sequence* of DNA on a chromosome, which codes for one protein. Rather, each gene exists in a discontinuous pattern within a chromosome as a mixture of "exons" that code for parts of a protein and "introns" that do not code for a protein. The introns, originally called "junk DNA" (before research indicated they have adaptive functions), first must be cut out and separated from the protein coding exons. These exons are then "spliced" together to transcribe the gene into its messenger ribonucleic acid (mRNA) *sequence* that will be translated into proteins that will regulate physiological functions.

Research with humans provides some of the clearest evidence of how psychosocial stress modulates alternative gene splicing to generate the dynamics of psychoimmunology (Kiecolt-Glaser, Marucha, Atkinson, & Glaser, 2001) and psychosomatic medicine in general (Kaufer, Friedman, Seidman, & Soreq, 1998; Soreq & Seidman, 2001). Acute and chronic environmental and/or psychosocial stress can induce a series of changes in the splicing of the acetylcholinesterase (AChE) gene, for example, that gives rise to the Posttraumatic Stress Disorders (PTSD) and related mind-body dysfunctions (Rossi, 2002, 2004a). This means that psychosocial stress actually changes the way a gene is spliced together to alter its *sequence* to generate the *structure* of alternative proteins and their *physiological functions* (Stamm et al., 2005) as illustrated in Figure 1b. This is a functional but temporary change in the way the DNA code of the AChE gene is expressed to alter protein structure and physiological functions under the impact of stress. This is not a permanent change in the DNA code (such as a gene mutation) that would be transmitted genetically to the next generation. Sternfeld et al. (2000) describe how many forms of stress induced alternative gene splicing generate changes in the hippocampus of the brain that modulates memory and learning.

> We recently reported massive induction of a unique mRNA species encoding the rare "read-through" variant of acetylcholinesterase (AChE-R) in brains of mice subjected to forced swimming stress. AChE-R differs from the dominant "synaptic" variant, AChE-S, in the composition of its C-terminal sequence...In hippocampal brain slices, induced AChE-R seemed to play a role in delimiting a state of enhanced neuronal excitation observed after acute cholinergic stimulation. This observation suggested that AChE-R acts as a stress modulator in the mammalian brain." (p. 8647).

The major feedback loops between AChE-S (synaptic AChE) and AChE-R (read-through AChE) has been called "the vicious circle of stress and anticholinesterase responses" (Kaufer, Friedman, & Soreq, 1999). This is but one salient example of how psychosocial stress can modulate the circular loop of information transduction between psychological experiences, sequences of gene expression, structures of proteins, and their physiological functions illustrated in Figure 1b.

AChE-S, the principle normal form of acetylcholinesterase, is found in the synapse where it regulates classical excitatory function of acetylcholine neurotransmission between neurons in the brain mediating visual, motor, and emotional experiences in normal and highly aroused states of consciousness as well as REM dream sleep and at the neuromuscular junctions in the body. AChE-R (R is for *read-through* because of the alternative way it is spliced together) accumulates in the brain and the blood in response to acute psychological stress and trauma as well as toxins from the environment. These alternative forms of gene splicing under normal (AChE-S) and stress conditions (AChE-R) present an inviting target for exploring the efficacy of therapeutic hypnosis in stress reduction in PTSD and related dysfunctions on the molecular-genomic level with DNA microarrays.

Dreaming and Neural Replay in the Reorganization of Fear, Stress and Stress and Traumatic Memories: The Memory Trace Reactivation and Reconstruction Theory of Therapeutic Hypnosis

Recent neuroscience research has found that when experimental animals experience significant *novelty, environmental enrichment and exercise* during their waking state, the *zif-268 gene* is expressed during their REM sleep (Ribeiro, et al., 2002; Ribeiro, et. al., 2004). *Zif-268* is an immediate-early gene and behavioral-state related gene that is associated with the generation of proteins and growth factors that facilitate brain plasticity as described by Ribeiro, et al (2004):

> The discovery of experience-dependent brain reactivation during both slow-wave (SW) and rapid eye-movement (REM, dream) sleep led to the notion that the consolidation of recently acquired memory traces requires neural replay during sleep..Based on our current and previous results, we propose that the two major periods of sleep play distinct and complementary roles in memory consolidation: pretranscriptional recall during SW sleep and transcriptional storage during REM sleep...In conclusion, *sustained neuronal reverberation during SW sleep, immediately followed by plasticity-related gene expression during REM [dreaming] sleep, may be sufficient to explain the beneficial role of sleep* on the consolidation of new memories (p. 126-135, italics added).

I recently outlined how this "sustained neuronal reverberation during SW sleep, immediately followed by plasticity-related gene expression during REM sleep" may be an important process in the reorganization of fear, stress, and traumatic memories and symptoms via therapeutic hypnosis (Rossi, 2005b). Neuroscience research documents how the classical process of Pavlovian fear conditioning requires the recall and reactivation of a conditioned memory before it can be extinguished and/or reconstructed at the level of gene expression and protein synthesis. Nader, Schafe, & Le Doux, (2000a, b) summarize their research in

this area with these words: **"***Our data show that consolidated fear memories, when reactivated, return to a liable state that requires de novo [gene expression] and protein synthesis for reconsolidation.* These findings are not predicted by traditional theories of memory consolidation." (p.723, italics added).

Such research has important implications for understanding the controversial tradition of using hypnosis to facilitate memory recall and emotional re-experiencing. I hypothesized that the common psychotherapeutic practice of intentionally recalling the memory of a traumatic experience and then reframing it is precisely what took place during many historical approaches to reactivating traumatic memory recall and their "Mental Liquidation" (Pierre Janet's original words, 1925/1976, pp. 589) via therapeutic hypnosis. I proposed that this activity-dependent process of reactivating a fear, stress and traumatic memory in order to re-construct it on the level of gene expression, protein synthesis, and brain plasticity is the psychosocial genomic essence of therapeutic hypnosis and psychotherapy (Rossi, 2002, 2004a, 2005a,). I have generalized this molecular-genomic essence of therapeutic suggestion to the creative process in cultural rituals and the humanistic arts (Rossi, 2004d, 2005a,b,c, 2006). They all typically facilitate salient psychobiological arousal and the ideodynamic recall and replay of memory in the therapeutic reconstruction of human learning and behavior. This may be a way of updating our understanding of Erickson's (2006) "neuro-psycho-physiological process" in popular psychotherapeutic metaphors such as "Every Replay is a Reframe."

Figure 2. The Psychosocial genomics model of the ideodynamic action hypothesis of therapeutic hypnosis. This proposed feedback loop of bioinformatic information flow between therapeutic suggestion, the activity dependent gene expression/protein synthesis cycle, brain plasticity (synaptogenesis and neurogenesis) illustrates the memory trace and reconstruction theory of fear, stress, and traumatic memory and symptoms (Rossi, 2005b).

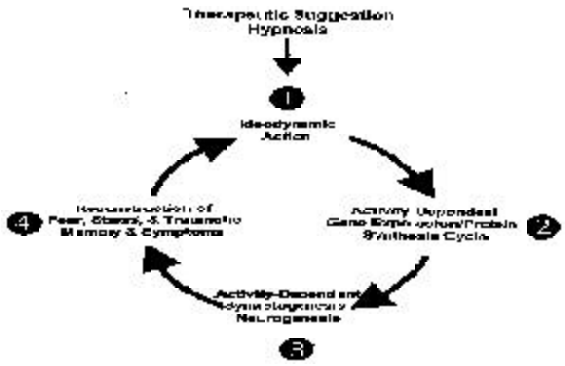


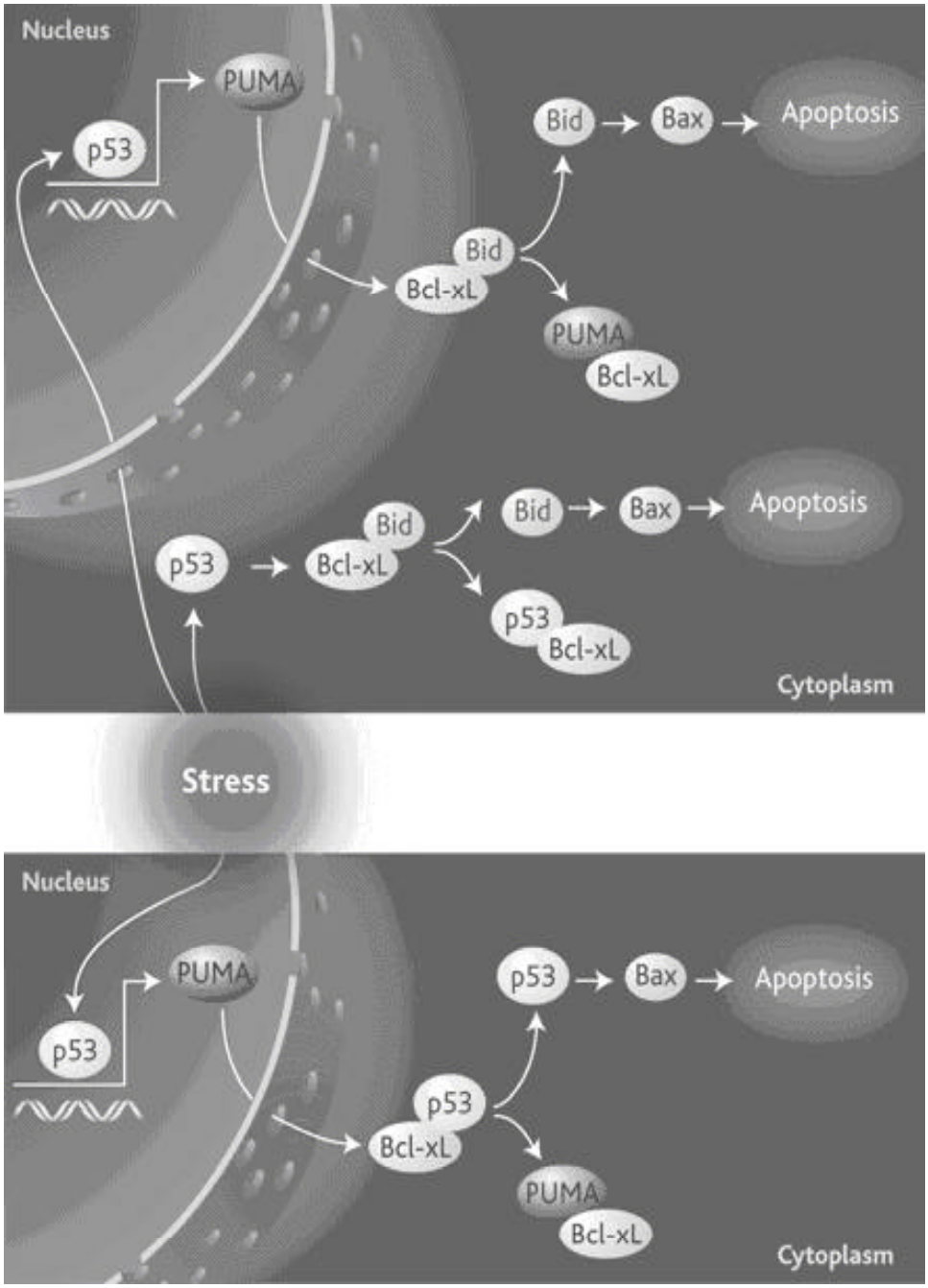
Figure 2 is an overview of how the ideodynamic action hypothesis of suggestion and therapeutic hypnosis may evoke the activity dependent gene expression/protein synthesis cycle and brain plasticity in the reactivation and reconstruction of traumatic memories and symptoms of stress in a manner that is consistent with the Ribeiro, et al. (2002) and Ribeiro, et al (2004) description of the normal daily cycle of sleep and dreaming as well as Nader, et al.'s (2000a, b) research on the reactivation and reconstruction theory of memory and

learning while awake. Figure 3 illustrates models of the ultimate molecular-genomic source of stress and its resolution in the nucleus and cytoplasm of the cells of the brain and body that are described by Vousden (2005) as follows.

> Despite its importance in protecting us from malignancies, the specific activities of the p53 protein that allow it to function as a tumor suppressor have been hard to reconcile. A paper by Chipuk *et al.* [2005] now promises to reduce the complexity of *the p53 response to cellular stresses* by bringing together two seemingly separate activities of p53—one nuclear and one cytoplasmic—into a single, unified model. The ability of p53 to function as a transcription factor is generally considered to be its main physiological property. Expression [DNA] array technology has revealed long lists of potential gene targets of p53, with the accompanying problem of sorting the wheat from the chaff. Analysis of cells defective in some of these p53-target genes have established several of them as important mediators of the p53 response. . . Combined with compelling evidence that the ability to function as a transcription factor is essential for the anti-neoplastic activity of p53, it is tempting to conclude that *the regulation of gene expression is the key to its suppressive effects on tumorigenesis. . . A number of studies have shown that p53 moves to the mitochondria in response to stress*, suggesting that translocation and binding of p53 to mitochondrial Bcl2 and Bcl-xL may also trigger apoptosis. . . While providing elegant support for the activator function of p53, this observation does not preclude a function for p53 as an enabler and overall it seems likely that coordination of *the nuclear, cytoplasmic, and mitochondrial functions of p53 will contribute to the ultimate response to stress* (pp. 1685-1686, italics added).

The "stress" that is illustrated in Figure 3 is the generic "oxidative stress at the molecular-genomic level of the cell" as it is generally described by the molecular biologists (Chipuk et al., 2005) who did the research illustrated in figure 3. It is now known, however, that sources of such "oxidative stress," can be induced by anything from extremes of temperature, food deprivation, physical toxins and trauma, to *psychosocial stress* in the classical research of Selye (1974) as well as more recent investigators such as Kaufer et al. (1998, 1999), Soreq & Seidman (2001), Sternfeld et al., (2000), Stamm et al. (2005) and others. Insofar as therapeutic hypnosis is used to reduce "psychosocial stress," it is reasonable to hypothesize that hypnosis may be utilized to modulate the ultimate molecular-genomic source of stress. This remains merely a hypothesis, however, until further research documents it. Such research with DNA microarrays could then outline the methods, parameters, and limitations in the use of therapeutic hypnosis in accessing and facilitating mind-body healing associated with stress amelioration at the molecular-genomic level. This suggests a deeper need for understanding the concepts and processes shared by therapeutic hypnosis and neuroscience at the molecular-genomic level.

Figure 3. Stress at the molecular-genomic level that may have implications for therapeutic hypnosis. Stress activates p53 as a transcription factor within the nucleus of the cell to activate expression of gene targets such as PUMA, which then moves to the cytoplasm and mitochondria where it interacts with anti-apoptotic members of the Bcl2 family of proteins. Mitochondria are well known as the "energy factories" of the cell that may be compromised by stress leading to the experience and dysfunctions commonly associated with "fatigue"and Post Traumatic Stress Syndrome (PTSD). Image with permission from Vousden, 2005.



A Deeper Understanding of Concepts and Processes Shared by Therapeutic Hypnosis and Neuroscience

While the Ideodynamic action hypothesis of suggestion has played an important role toward the development of a theory of hypnosis for over 100 years, it has not been integrated with current concepts of neuroscience and the functional molecular-genomic foundations of cognition and behavior. Here, for example, is an example, of how the "ideoplastic faculty" facilitated by hypnosis was described by Wetterstrand (1902) more than a century ago well before neuroscience was organized as a distinct discipline in the middle 1970's:

> *"The ideo-plastic idea, the suggestive theory, must be explained and how it is possible to dominate and cure pathological conditions by ideas and volition.* They [patients] must be told that no restraint is to be put upon them, that they are merely shown the way and that their present conditions will change, not by any preponderance of another's will, but as the result of a proper effort to aid by using their own will. *They are helped to develop the ideo-plastic faculty, whereby is meant the power that ideas possess to influence physical conditions,* as, for instance, the production of cholera symptoms by fright, or that of bleeding marks on hands and feet from profound and continued contemplation of or meditation upon the crucified Saviour's wounds" (As quoted in Tinterow, 1970, pp. 534-535, italics added here).

Without acknowledging the historical priority of hypnosis, neuroscientists are rediscovering many phenomena previously subsumed under the *ideo-plastic faculty* and *ideodynamic action hypothesis.* Neuroscientists now give these hypnotic phenomena different names derived from recent experimental research on *activity-dependent gene expression, behavior state-related gene expression, experience-related gene expression,* and *activity-based competition in brain plasticity* (Hua, Smear, Baier, & Smith., 2005). There has been little or no communication between the disciplines of therapeutic hypnosis, neuroscience, and psychosocial genomics (Rossi, 1986/1993, 2002, 2004a, 2005a, b, c, 2006). Table 2 is an intuitive and heuristic clustering of many overlapping concepts and terms of historical hypnosis and neuroscience that may have a molecular-genomic foundation in common.

Summary: Prospects, Implications, and Recommendations

The correspondence between major concepts of therapeutic hypnosis, neuroscience, and psychosocial genomics suggests that there are excellent prospects for exploring the molecular-genomic foundations of therapeutic hypnosis with DNA microarrays. DNA microarrays are a new research technology that may enable us to identify the range, parameters, and limitations of the efficacy of therapeutic hypnosis in mind-body healing with the range, parameters, and limitations of psychosocial experiences in modulating gene expression, brain plasticity, and psychophysiology reported in the neuroscience literature. DNA microarray research may offer a new approach to defining and assessing the special state concept of hypnosis, the psychobiology of hypnotic induction, the nature of hypnotic phenomena, and the molecular-genomic processes that are the common foundation of therapeutic hypnosis and neuroscience.

This suggests that researchers and clinicians in therapeutic hypnosis need to partner with their colleagues in neuroscience and molecular biology that have laboratory facilities for DNA microarray research. Hypnotic susceptibility scales of the future must incorporate DNA data to include the concept of "embodied imagination" and the "ideo-plastic faculty" on a molecular-genomic level as well as the phenotype level of ideomotor and ideosensory responses that are currently assessed. With the development of such tools, therapeutic hypnosis will be able to advance with the current leading edge of neuroscience.

Table 2: A list of concepts and processes shared by therapeutic hypnosis and neuroscience. There are many suggestive conncections but few exact one-to-one correspondences between the Therapeutic Hypnosis and the Neuroscience columns.

Therapeutic Hypnosis	Neuroscience
The State Concept	
Special State	Functional Concordance of Coexpressed Genes
Trance	Experience Dependent Gene Expression
Monoideism	State Dependent Gene Expression
Hypnotic Induction	
Focused Attention, Motivation	Heightened Neuronal Activation
Fascination, Absorption	Novelty
Enchantment, Education	Enrichment, Brain Plasticity
Thinking & Feeling with	Brain Plasticity, Neural Entrainment
Shock, Surprise	Arousal, Exercise
Group Hypnosis	Mirror Neurons
Repetition	Brain Plasticity
Touch, Mesmeric Passes	ODC Gene Expression
Hypnotic Phenomena	
Amnesia, Dissociation	State Dependent Memory & Learning
Automatisms, etc.	Neural Trace Reactivation
Memory Revivification	Neural Trace Reactivation
Post Hypnotic Suggestion	Off Line Neural Replay
Role Playing	Creative Neural Replay
Mind-Body Relationships	
Ideo-Plastic Facility	Brain Plasticity
Ideodynamic Activity	Activity Dependent Gene Expression
Ideomotor Activity, Doing	Behavior State-Related Gene Expression
Embodied Imagining	Brain Plasticity
Neuro-Psycho-Physiology	Psychoimmunology
Psychophysiological	Psychoendocrinology

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