The Bioinformatics of Integrative Medical Insights: Proposals for an International PsychoSocial and Cultural Bioinformatics Project

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Abstract: We propose the formation of an International PsychoSocial and Cultural Bioinformatics Project (IPCBP) to explore the research foundations of Integrative Medical Insights (IMI) on all levels from the molecular-genomic to the psychological, cultural, social, and spiritual. Just as The Human Genome Project identified the molecular foundations of modern medicine with the new technology of sequencing DNA during the past decade, the IPCBP would extend and integrate this neuroscience knowledge base with the technology of gene expression via DNA/proteomic microarray research and brain imaging in development, stress, healing, rehabilitation, and the psychotherapeutic facilitation of existentional wellness. We anticipate that the IPCBP will require a unique international collaboration of, academic institutions, researchers, and clinical practioners for the creation of a new neuroscience of mind-body communication, brain plasticity, memory, learning, and creative processing during optimal experiential states of art, beauty, and truth. We illustrate this emerging integration of bioinformatics with medicine with a videotape of the classical 4-stage creative process in a neuroscience approach to psychotherapy.

Keywords: Psychosocial, genomics, bioinformatics, neuroscience, brain plasticity.

Introduction

The bioinformatic foundation of integrative medical insights

Integrative medical insights (IMI) covers the entire range of healing from the modern molecular-genomic foundation of the life sciences to the many varieties of alternative, complementary, and holistic approaches to ameliorating the human condition. Just as The Human Genome Project secured the molecular-genomic foundations of modern medicine with the new technology of sequencing DNA during the past decade, IMI could extend this emerging bioinformatics knowledge base with the technology of gene expression and proteomic microarray research in neonatal development, memory, learning, stress, healing, rehabilitation, and existentional wellness. Figures 1a and 1b illustrate how integrative medical insights could bridge the so-called "Cartesian gap" between mind and body via the concept of biological information.

The current concept of biological information was originally called "the dogma of molecular biology" by Watson and Crick (1953a & b), for which they received the Nobel Prize. The dogma of molecular biology illustrated in figure 1a proposed how (1) the linear *sequence* of nucleotides in our genes is a "code" of biological information that (2) generates the 3-dimensional *structure* of the proteins, which *function* in the (3) *physiological* processes of the brain and body. There was no place for the causal role of human experiences of mind and cognition in their original dogma of molecular biology illustrated in Figure 1a.

Since that time, however, neuroscience research has documented how psychological experiences of *novelty* (Eriksson et al. 1998), *psychosocial enrichment* (Kempermann et al. 1997), mental and physical

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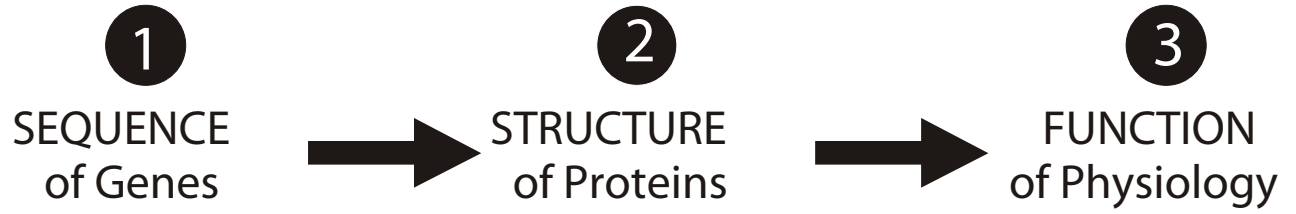

Figure 1a. The Original Dogma of Molecular Biology by Watson and Crick (1953a & b) wherein **(1)** the *Sequence* of nucleotide bases in DNA is a code of information that is transcribed into **(2)** the three dimensional *Structure* of proteins that generate **(3)** the *Functions* of physiology. Note that there is no explicit role for Experience (Mind or Cognition) in this original dogma of molecular biology.

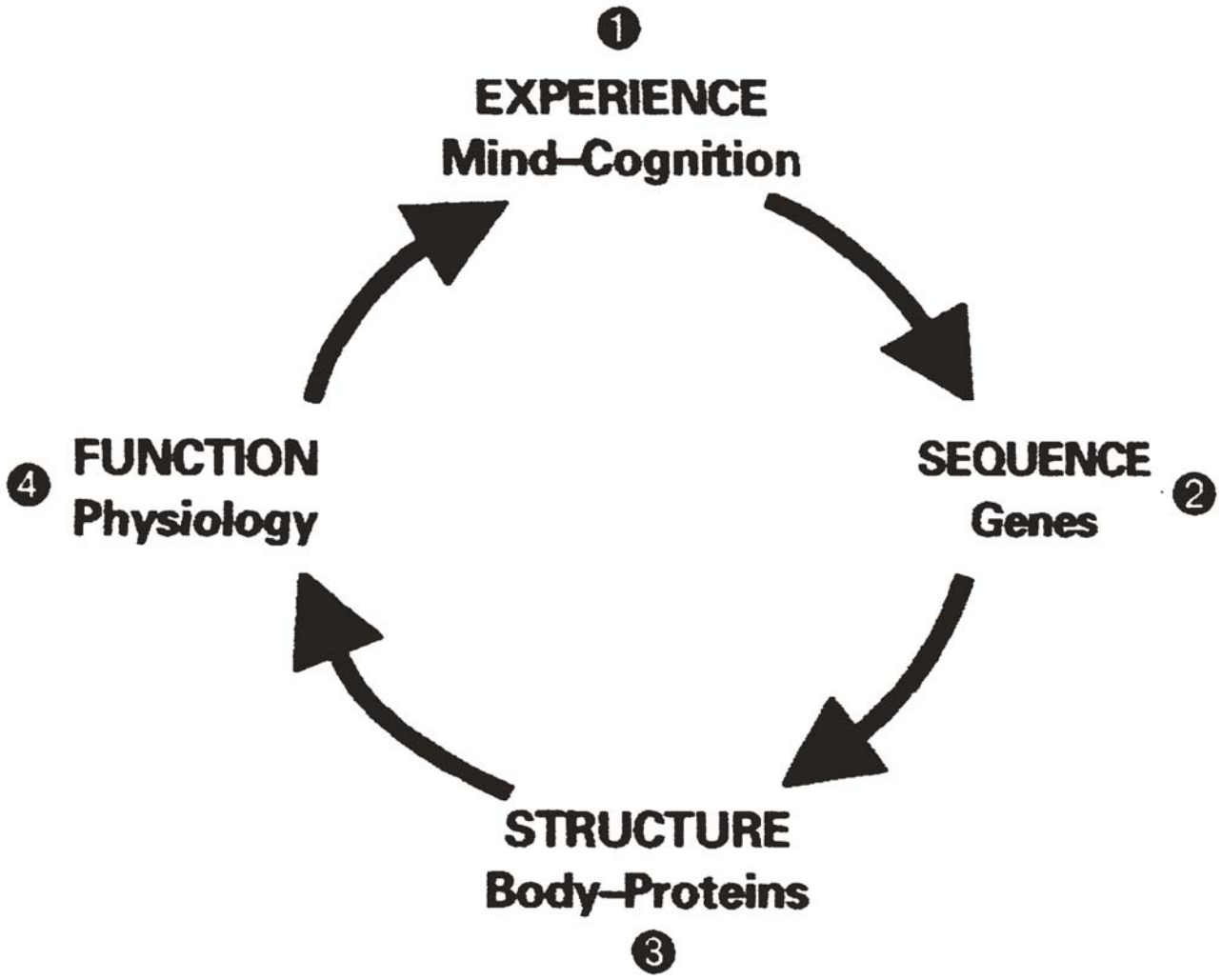

Figure 1b. The Basic Bioinformatics Cycle of Integrative Medical Insights. (1) *Psychological Experience* (mind, consciousness, & cognition) can modulate **(2)** *Gene Sequence*, **(3)** *Protein Structure*, and **(4)** *Physiological Function*.

exercise (Van Praag et al. 1999) can evoke gene expression (genomics) and protein synthesis (proteomics), which generates the *physiological functions* of the brain and body (Rossi, 2002a, 2004a). Such research is the empirical basis for adding the dimension of *Experience (mind-cognition)* to Watson and Crick's linear dogma of molecular biology to construct the causal mind-body loop of integrative medical insights in figure 1b.

The most profound implication of the causal mind-body loop of Figure 1b is that acute as well as chronic experiences of mind and cognition can evoke and modulate alternative patterns of gene expression and protein dynamics in the complex computations

(iterations and recursions) of psychophysiology, psychosomatic medicine, and integrative medicine via a neuroscience approach to psychotherapy. The causal loop of bioinformatic transduction between mental experience and biological information in Figure 1b is but one general outline of the emerging system dynamics of integrative medical insights reviewed in the following principles.

How the Mind Can Heal the Body

The bioinformatics cycle of integrative medical insights implies a top-down as well as the classical bottoms-up perspective of modern molecular medicine

The standard approach of modern molecular medicine is to enter the bioinformatics cycle of Figure 1b at the levels of *sequence, structure, and physiological function* with drugs, surgery, etc. This is the so-called the *"bottom-up approach,"* by which molecular processes at the bottom are the foundation for the genomic, proteomic, physiological, and finally the psychological experiences at the top level of mind and cognition. Many of the controversial approaches of alternative, complementary, integrative, and holistic medicine, by contrast, typically utilize a *"top-down approach"* to enter the bioinformatics cycle on the top level of mind to reduce stress, for example, and thereby modulate physiological processes (sympathetic/parasympathetic balance, etc.) and eventually the lower levels of gene expression, proteomics, and physiological functioning. How do we integrate these two apparently divergent approaches?

We propose that the top-down bioinformatics approach to integrative medical insights actually complements the classical bottom-up approach of modern molecular medicine by exploring how psychological experiences can modulate gene expression, protein synthesis, and physiological functioning. Classical Mendelian genetics and its application to evolutionary psychology, for example, documents the bottom-up approach of how genes modulate physiological functioning and psychological experience. The new issue brought to light by the top-down bioinformatics cycle of Figure 1b focuses on the reverse: *How does the experience of mind and cognition modulate gene expression, protein structure, and physiology?* Stahl (2000) answers this surprising question in his text on "Essential Psychopharmacology."

> "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 to alter emotions and behaviors*." (p. 37, Italics added)

Recent research extends Selye's (1974) concept of stress and the General Adaptation Syndrome on the *physiological* level to the *proteomic* and *genomic* levels. Kaufer et al. (1998) document how acute trauma and the psychosocial experiences of stress facilitate changes in cholinergic gene expression on the genomic level. In related research Meshorer et al. (2002) describe how psychosocial stress modulates gene expression in humans experiencing posttraumatic stress disorder (PTSD) via stimulus-induced changes in alternative splicing of genes as follows.

> "Traumatic stress is often followed by long-term pathological changes. In humans, extreme cases of such changes are clinically recognized a posttraumatic stress disorder (PTSD). . . . *Stimulus-induced changes in alternative splicing [of genes] have recently emerged as a major mechanism of neuronal adaptation to stress, contributing to the versatility and complexity of the expression patterns of the human genome*." (p. 508, italics added)

This alternative splicing of genes induced by psychosocial stress is a clear example of how the top-down dynamics of how (1) *psychological experience* can modulate information encoded in the (2) *sequence of gene expression,* which in turn modulates (3) the *structure of proteins,* and the (4) *physiological functioning* of the general adaptation syndrome in health and dysfunction in the bioinformatics cycle of Figure 1b.

What Makes Us Human?

Heightened gene expression and neuronal activation distinguishes the human cortex in the bioinformatic cycle of integrative medical insights

We propose the integration of (1) microarray technologies for measuring gene expression (genomics)

and proteins (proteomics) with (2) brain imaging technology (fMRI and PET) to evaluate the anatomical location and levels of neuronal activity of the brain to (3) assess the efficacy of psychosocial and cultural approaches of mind and cognition in Figure 1b. This integrative approach answers another fundamental question: how do we account for the difference between human consciousness and non-human primates when they both have about the same number of genes (~24,000), which are more than 98% alike? Cáceres et al. (2003) summarize their empirical research in this area as follows.

> "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 outgroup. 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. . . . *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.*" (pp. 13030, italics added)

Such research implies that DNA microarrays are a more sensitive, comprehensive, and reliable markers and measures of psychological experiences and states of consciousness, emotions, behavior, and brain plasticity in stress, injury, disease, and medicine in general in Table one.

Cáceres et al. (2003) describe how elevated gene expression levels that differentiate human from non-human primate brain functioning actually generate heightened neuronal activity as the substrate of consciousness and cognition.

> "The identification of the genes that exhibit regulatory changes in adult human cortex provides clues to the biochemical pathways and cell-biological processes that were modified during evolution. *The apparent up-regulation of so many different genes suggests, among other things, that the general level of neuronal activity and the metabolic processes that support it may be unusually high in human cortex*. . . . Recent studies with imaging techniques to measure cerebral glucose metabolism in the conscious state suggest that metabolic rates are as high or even higher in humans than in macaques. *Higher levels of neuronal activity are likely to have important consequences in cognitive and behavioral capacities,* and of the genes up-regulated in humans, *CAMK2A* is involved in learning and memory, and mutations of *GTF2I* (Williams syndrome), *CA2* (marble brain disease), and *SC5DL* (lathosterolosis) have been linked to mental retardation." (pp. 13034, italics added here)

Other recent research supporting this direct association between the genomic and psychological levels suggests how genomic sequences in DNA may also modulate gene expression and associated psychological experiences (Cao et al. 2006; Check, 2006; Popesco et al. 2006). A number of researchers speculate how random RNA L1 sequences could account for probabilistic gene expression that could bind the hyper-associative strings of fragmented memories and diverse sensory-perceptual sources of the holistic experience of consciousness and self-awareness (Holtz, 2006; McKhann, 2006; Vince, 2006). Random RNA L1 sequences in the molecular dynamics of gene expression during REM state dreaming may be a source of the new and creative associations that have been ascribed to dreams (Brooks & Vogelsong, 2000) as well as the flow of consciousness (Rossi, 1972/2000, 2007), foresight (Suddendorf, 2006), and choice in therapeutic hypnosis (Erickson, 1992/2006; Rossi, 2002a, 2004a, 2005, 2007).

Pollard et al. (2006, p. 1) described how an RNA gene expressed during cortical development evolved rapidly in humans.

> "The recent ability to compare our genome to that of our closest relative, the chimpanzee, provides new avenues to link genetic and phenotypic changes in the evolution of the human brain. We devised a ranking of regions in the human genome that show significant evolutionary acceleration. Here we report that the most dramatic of these *'human accelerated regions,'* HAR1, is part of a novel RNA gene *(HAR1F)* that is expressed specifically in Cajal–Retzius neurons in the developing human neocortex from 7 to 19 gestational weeks, a crucial period for cortical neuron specification and migration. *HAR1F* is co-expressed with reelin, a product of Cajal–Retzius neurons that is of fundamental importance in specifying the six-layer structure of the human cortex. HAR1 and the other human accelerated regions provide new candidates in the search for uniquely human biology."

HAR1F is a novel gene that does not encode instructions for making a protein to carry out its

Table 1. A brief sampling of gene candidates for the DNA microarray technology assessment of the bioinformatics of gene expression, brain plasticity, the NNNE, and healing in integrative medicine (Updated from Rossi, 2002, 2004).

Heightened Gene Expression & Neuronal Activation in the Human Cortex	
SYN47	Cáceres et al. 2003;
CAMK2A, IMPA1, CDS2, KIF3A	Preuss et al. 2004
DCTN1, MAP1B, RAB3GAP	
ATP2B1, USP14	
HAR1F	Pollard et al. 2006
DUF1220 Domains	Popesco et al. 2006
Brain Plasticity & NNNE in Consciousness, Memory, Learning	
Arc, Egr 1-4	Li et al. 2005
c-fos, c-jun, krox, NGFI-A & B	Bentivoglio & Grassi-Zucconi, 1999
CREB	Kandel et al. 1998
BNDF	Russo-Neustadt, 2001; Sheng, 2006
CYP-17	Ridley, 1999
~ 100 Immediate Early Genes	Rossi, 2002a, 2004a
Random RNA L1 sequences	Cao et al. 2006; Muotri &Gage, 2006
PirB	Syken et al. 2006
PKMζ	Bliss, 2006; Whitlock, 2006; Pastalkova, 2006
Dreaming and Replay in the Reconstruction of Fear, Stress and Trauma	
Zif-268	Ribeiro et al. 2002, 2004;
	Nader et al. 2000
Chronic Psychosocial Stress and Alternative Gene Expression	
Acetylcholinesterase (AChE-S & AChE-R)	Sternfield et al. 2000
	Perry et al. 2004
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, 2001
NF-κB	Bartek & Lukas, 2006
Psycho-neuro-immunology	
Interleukin 1, 2, 1ß, Cox-2	Castes et al. 1999;
	Glaser et al. 1993
Clock Genes & Behavior State-Related Genes	
About 100 sleep related genes	Cirelli et al. 2004
Clock, Per 1, BMAL	Rossi, 2004; Antoch & Kondratov, 2006
Period 2	Rosbash & Takahashi, 2002
Maternal Behavior, Therapeutic Touch, Addiction, Reward, Hypnosis	
ODC gene	Schanberg, 1995
Opioid Receptor Gene	Moles et al. 2004
COMT	Lichtenberg et al. 2000, 2004
THRA, Per1	Rossi, 2002a, 2004a,e
DRD2 gene	Thanos et al. 2004

function. The HAR1 RNAs of both humans and the chimpanzee form stable structures but there are significant base pair differences between them that generate special properties related to integrative medical insights that are specific to humans. Pollard et al. (2006) hypothesize that these differences preserve the developmental functions of the RNA molecule, but may have something to do with the functional differences between the human and chimpanzee's brain on the experiential level of mind and cognition.

Information, Energy and Entropy

The bioinformatics of circadian & ultradian profiles of psychological experience, gene expression, brain plasticity, and healing

Surprising Integrative medical insights emerged when Rosbash & Takahashi (2002) noted that cancer could be a direct consequence of the stress related disruption of circadian regulation via the Period 2 (*Per 2*) gene. Figure two illustrates the matching of bi-modal circadian profiles of the bioinformatics cycle ranging from measures of the *psychological experiences* in therapeutic hypnosis (Aldrich & Bernstein, 1987), to the *physiological functioning* (body temperature), and the *expression of behavioral* state-related genes related to the being awake such as the *Period gene (Per 1 & Per 2)*, which is in the same family of genes implicated in cancer (Gery et al. 2006; Rosbash & Takahashi, 2002) and sleep *(Bmal 1 gene)*. This matching of the bi-modal bioinformatic circadian profiles of figure two is consistent with–but does not yet prove that bioinformatic approaches and psychotherapy in general, and therapeutic hypnosis, in particular, can be used to modulate body temperature, gene expression and brain plasticity.

The apparently well-matched bi-modal profiles of the bioinformatic cycle on the cognitive-behavioral level (hypnotic susceptibility), the physiological level (core body temperature), and genomic level *(thra & Per 1* genes) in Figure 2 are actually an *ad hoc* assembly from many serendipitous observations of the research literature as cited above (Rossi, 2004e). Systematic research is now required to validate the association of the bioinformatic profiles, circadian and ultradian cycles (less than 24 hours) for optimizing all the cognitive-behavioral and related top-down therapies (Lloyd & Rossi, 1992, 2008). Such research would require the simultaneous utilization of DNA/proteomic microarrays with brain imaging to assess how the changing psychological states of waking, sleeping, and dreaming, as well as therapeutic hypnosis (Rossi, 2002, 2004), meditation (Schwartz & Begley, 2002), psychotherapy (Cozzolino, 2003), creativity (Rossi, 2002, 2004, 2005, 2007), intention (Radin et al. 2004), and reward (McClung et al. 2005) could be efficacious in the top-down modulating of gene expression, brain plasticity, and healing via the bioinformatic cycle as reviewed in the next section.

A number of researchers have discussed the profound but little understood associations between circadian/ultradian rhythms and the more general concepts of *information, energy, and entropy* in life processes on the classical (Stonier, 1990) and quantum levels (Lloyd, 2006; Seife, 2006; Walach & Schneider, 2003), and their implications for a deep psychobiology of psychotherapy (Francomano & Jonas, 2002); Rossi, 2001). Lloyd (2006, p. 40) aptly sums it up. "Ultimately, information and energy play complementary roles in the universe: Energy makes physical systems do things. Information tells them what to do." Current researchers (Kaushik et al. 2005; Vernon et al. 2006) on chronic fatigue syndrome, for example, are using DNA mitochondrial microarrays to assess dysfunctional genes in energy production and utilization that are generating important integrative medical insights as we now review.

These deep associations between information, energy, entropy and the chronobiology of circadian and ultradian rhythms are of something more than mere academic interest. Their ultimate application would be in the creation of a mind-gene transducer described as follows (Rossi, 2004a).

Is a Mind-Gene Biofeedback Device Possible?

> "Will it be possible to develop a *mind-gene biofeedback device* in the future that would allow us to modulate gene expression and brain plasticity just as we now use inexpensive biofeedback devices to modulate muscle relaxation? This would be the ultimate kind of mind-body biofeedback that theoretically could facilitate to any type of psychophysiological healing at the molecular-genomic level.

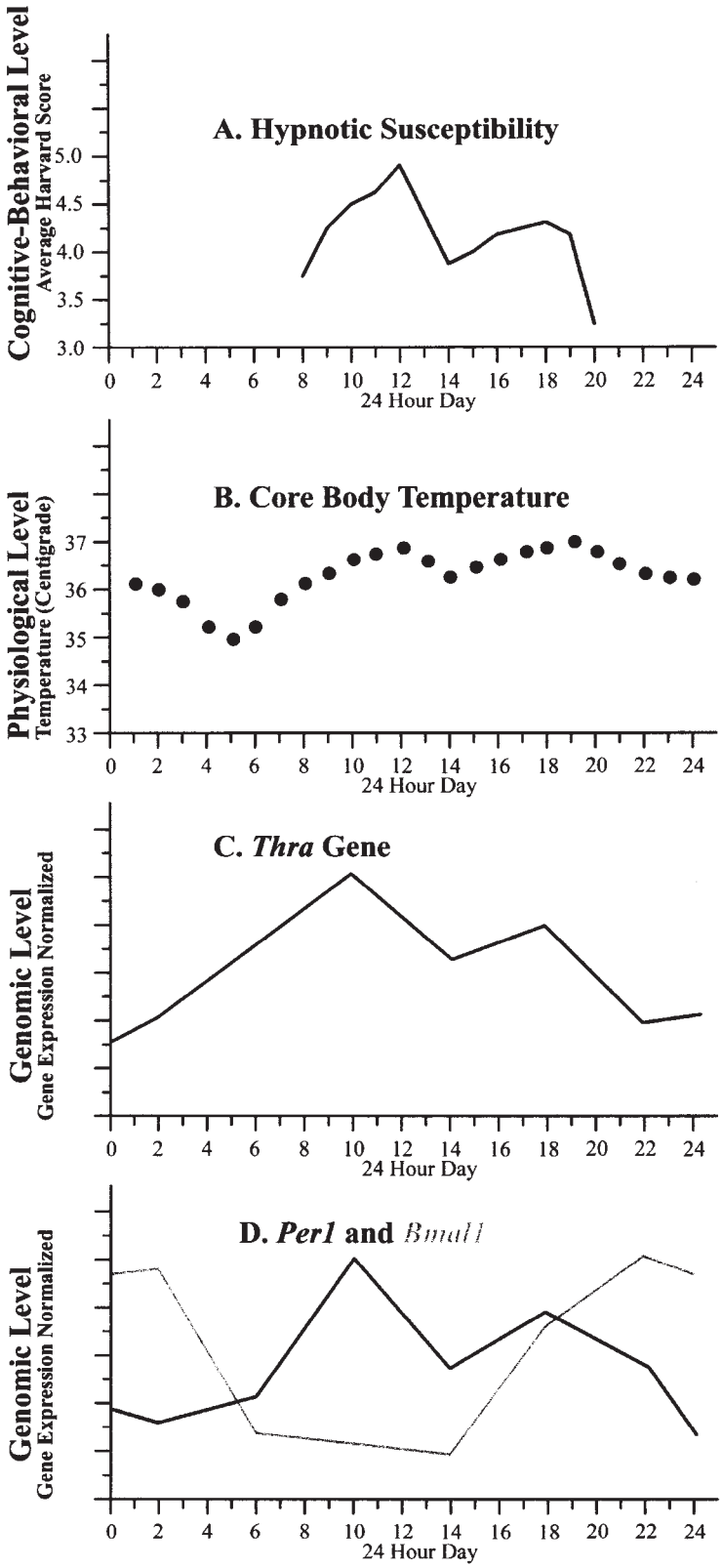

Figure 2. The Matching of Apparently Similar Bimodal Circadian Profiles of Hypnotic Susceptibility, Body Temperature, and Gene Expression. An illustration of the bi-modal relationship between **(A)** the cognitive-behavioral level, **(B)** the physiological level of core body temperature, and **(C)** the *Thra* gene associated with metabolism. The lowest diagram illustrates how **(D)** the circadian profile of the *Per1* gene, while awake, is similar to the *Thra* gene in (C) having a peak of expression about 90-120 minutes before the peak of hypnotic susceptibility and core body temperature around noon. By contrast the circadian profile of the *Bmal1* gene in (D), which is a marker for being asleep, is in *anti-phase* (the opposite of) the awake profiles of *Per1* and *Thra* gene expression associated with peaks of core body temperature and hypnotic susceptibility.

> To make a mind-gene biofeedback device we need a *mind-gene transducer.* That is, we need to invent a transducer or "transformer" that converts a subjective psychological experience (thought or neural energy) into some kind of molecular signal that would turn on gene expression and brain plasticity. Recent research in nano-technology suggests how this may be possible. . .
>
> The heart of these nano-mechanical mind-gene transducers could be a nano-wire sensor that produces an electric signal when it binds to a gene and/or protein as well as a wide range of other biological molecules (Hahm & Lieber, 2004). This electric signal can then be amplified to produce an image on a computer screen that would enable *human subjects to use their consciousness to detect when they are in contact with gene expression and its contribution to brain plasticity–this is what would make direct mind-gene communication possible in real time for a practical mind-gene biofeedback device.* It already has been proposed that such direct detection of gene expression could enable researchers use a single drop of blood to screen patients for all the known human genetic disorders (Goho, 2004)." (Rossi, 2004a, pp.304–305)

Since the original publication of this conception of a mind-gene biofeedback transducer, researchers have demonstrated how the modulation of the quantum properties of matter can influence the course of biochemical reactions (Prokhorenko et al. 2006). Chergui (2006) summarized the implications of this research as follows.

> "Can biological functions, such as vision or photosynthesis, that are driven by incoherent phenomena have anything to do with quantum mechanics, where the wave properties of matter play a key role? The answer is yes. . . Prokhorenko et al. show that biological processes can be manipulated by means of coherent control. . . *Coherent control* refers to experiments that make explicit use of the wavelike nature of matter to direct the behavior of atomic and molecular systems, often to alter the likelihood of a particular chemical reaction.
>
> A feedback loop is used to control isomerization of bacteriorhodopsin. An initial laser control field is created with a pulse shaper (on the right) and is then applied to the protein sample. The action of the control pulse, measured as the difference spectrum of the sample, is used by a learning algorithm to produce an improved field. *Repeated excursions around the loop result in an optimum control.* . . Further work with these coherent tools may allow the exploration of systems considered intractable on an *ab initio* quantum mechanical level. As such, *coherent control experiments represent a new type of "active" spectroscopy for the investigation of dynamics in complex systems.* Although any single experimental spectroscopic observation may unambiguously identify a local region in the dynamics, it would be useful to develop methods where the genetic algorithm uses a ''movie'' of atomic motion obtained from ultra fast imaging techniques, such as those achieved by x-ray methods." (pp. 1246–7, italics added here).

Note how Chergui's phrase *"Repeated excursions around the loop result in an optimum control"* in this quantum device is analogous what apparently happens on the classical level via the circadian and ultradian modulation of our natural psychobiological rhythms on all levels from mind to gene illustrated in Figures 1b, 3 & 4 (Lloyd & Rossi, 1992, 2008; Rossi, 2002a, 2004a). This overlap in the way currently emerging technology is bridging the classical-quantum interface of our natual psychobiological systems strongly implies that a mind-gene transducer is possible and could eventually be the heart of practical mind-gene biofeedback device for integrative medical insights and mind-body healing. We hypothesize that an analogous creative replaying of mind-gene loops is the essential dynamic of the reconstruction of mind, brain, and behavior that occurs in the four stage creative process of activity-dependent therapeutic hypnosis, psychotherapy, and rehabilitation illustrated below in Figures 5a through 5d below.

Art, Beauty, and Truth

The bioinformatics of stem cells are sources of brain plasticity, healing, and rehabilitation on the genomic/proteomic levels, which can be facilitated via the Novelty-Numinosum-Neurogenesis Effect (NNNE) and the placebo response

Current research on stem cells documents how stress, gene expression, proteomics, brain plasticity, and healing are related (Ivanova et al. 2006). Stress on all levels from the psychosocial to the physical trauma generates oxidation, injury, mutation, and malfunction on the genomic and proteomic levels (Gould et al. 1998).

New research on the cancer stem cell theory

Because normal stem cells in all tissues of the mature organism can replicate endlessly they have time to accumulate cancer-promoting mutations. While this theory of the origin of cancer via stem cells has been speculated about for 50 years, it was the more recent observation that testicular cancer cells had surface proteins like those of stem cells that lead to the current genomic theory of stem cells as potential "bad seeds" for cancers of the prostate, breast, brain, blood, etc. (Al-Hajj et al. 2004; Travis, 2004). As noted above, however, research utilizing DNA/proteomic microarrays is now required to assess whether integrative medical insights could be efficacious in modulating cellular signaling on the genomic and proteomic levels in cancer in stem cells (Karin, 2006).

Stem cells as mother nature's menders in rehabilitation

The presence of undifferentiated stem cells within injured tissues has been proposed as a general mechanism of recovery and rehabilitation from stress, trauma and injury. Adult stem cells are self-replicating, multi-potent cells that continue to exist in adult tissues that may be used as a source of "spare parts" that can replace injured cells and tissues (McLaren, 2000). Stem cells have been described as "mother nature's menders" functioning as reserves within the brain and body (Pluchino et al. 2003; Vogel, 2000). It is hypothesized that the molecular messengers generated by psychosocial stress, injury and disease can activate immediate early genes within stem cells so that they then signal the target genes required to synthesize the proteins that will transform (differentiate) the stem cells into mature well functioning tissues (Rossi, 2004a). Healing via gene expression has been documented in self-renewing stems cells in the brain (including the cerebral cortex, hippocampus, and hypothalamus), muscle, skin, intestinal epithelium, bone marrow, blood, liver, heart, and the immune system (Fuchs and Segre, 2000). This implies that integrative approaches of medicine that purport to facilitate healing by reducing psychosocial stress, promoting relaxation, and wellness must now document their efficaciousness at the genomic and proteomics levels of stem cell healing (Christofori, 2006).

Stem cells in neurogenesis and brain plasticity

Some of the most compelling evidence of a relationship between psychological experience and stems cells comes from the still controversial studies of neurogenesis and brain plasticity (Gage, 2000; Gould et al. 1999a & b; Kuwabara et al. 2004; Sanai et al. 2004). Kandel (1998), a Nobel laureate in medicine or physiology in 2000, discussed the implications of research on *activity-dependent gene expression* in the molecular-genomics of memory, learning, and behavior.

> "Insofar as psychotherapy or counseling is effective and produces long-term changes in behavior, it presumably does so through learning, by producing changes in gene expression that alters the strength of synaptic connections and structural changes that alter the anatomical pattern of interconnections between nerve cells of the brain. As the resolution of brain imaging increases, it should eventually permit quantitative evaluation of the outcome of psychotherapy. ... Stated simply, the regulation of gene expression by social factors makes all bodily functions, including all functions of the brain, susceptible to social influences. These social influences will be biologically incorporated in the altered expressions of specific genes in specific nerve cells of specific regions of the brain. (p.140, italics added).

There are at least three classes of psychosocial experience that generate activity-dependent gene expression and brain plasticity via stem cell differentiation that have important implications for integrative medical insights.

1) *Novelty* (Eriksson et al. 1998; Gage, 2000; Kempermann & Gage, 1999),
2) *Environmental Enrichment* (Kempermann et al. 1997; Van Praag et al. 2000),
3) *Exercise* (Van Praag et al. 1999, 2002).

It has been noted (Rossi 2002a, 2004a, b) that these three psychosocial experiences that evoke gene expression and brain plasticity are similar to the three qualities of original spiritual experience described by Rudolph Otto (1923/1950) as the *numinosum* (*fascination, mysteriousness, tremendousness*). This concordance of psychological and spiritual experience associated with gene expression and brain plasticity is denoted as the *Novelty-Numinosum-Neurogenesis Effect (NNNE)* in creative experience and the placebo response on all levels from mind to molecule (Rossi, 2002a, 2004a, 2005, 2007). The NNNE was proposed as the creative common denominator between art and

science in a new bioinformatic theory of esthetics. Experiences of art, beauty, and truth as well as Einstein's eternal mystery epistemology (Rossi, 2004c, 2005c,d) are the phenomenological correlates of the activation of mirror neurons, the gene expression/protein synthesis cycle, and brain plasticity via the novelty-numinosum-neurogenesis effect as illustrated in the creative bioinformatic cycle of figure three.

Heightened expectancy, pleasure, and surprise turn on the NNNE (Rossi, 2002a,b, 2004a, 2005c). Pleasurable and rewarding surprise is a kind of startle that violates expectancy and thereby activates and focuses our attention in *mysterious yet fascinating and tremendously important* psychosocial experiences (Rudebeck et al. 2006). The final common path of the NNNE in therapeutic hypnosis, the placebo response, creative work, and salient "spiritual" experiences is that they all turn on the gene expression/protein synthesis cycle, brain and behavioral plasticity to facilitate health and healing as illustrated in figure three. It is precisely this integration of (1) *Observing Consciousness* (2) *activating Mirror Neurons to* (3) *turn on their Gene Expression/Protein Synthesis Cycle, and* (4) *Brain Plasticity, which generates the possibility of new consciousness, integrative medical insights, mind-body healing, and rehabilitation that is the most novel hypothesis of this paper Rossi* (2002, 2004, 2007). *A change at any of these four levels generates a mathematical transformation to the next level in iterating the recursive cycles of human experience and healing from mind to gene.*

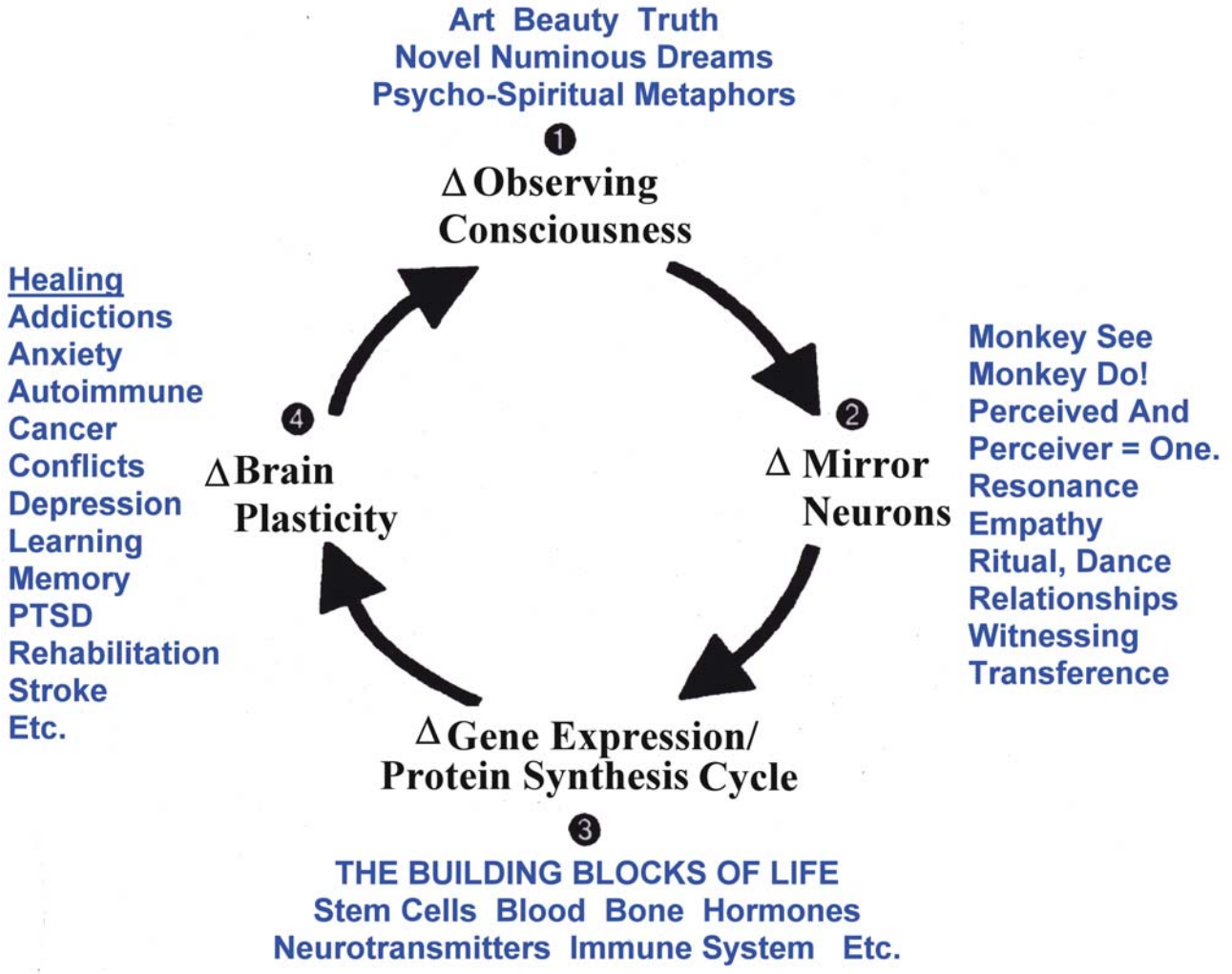

Figure 3. The Bioinformatics Cycle with a Focus on Mirror Neurons and a Myriad of Conditions Associated with Gene Expression and Brain Plasticity. The NNNE is manifest when novel and numinous experiences of **(1)** Observing Consciousness **(2)** activate Mirror Neurons to **(3)** turn on their Gene Expression/Protein Synthesis Cycle, and **(4)** Brain Plasticity, which generates the possibility of new consciousness, integrative mind-body healing, and rehabilitation. A change at any of these four levels generates a mathematical transformation to the next level in iterating the recursive cycles of human experience and healing from mind to gene.

Most significantly for the therapeutic and clinical application of integrative medical insights is how heightened neuronal activation and gene expression occurs in three neocortical association areas (prefrontal, inferior temporal, and posterior parietal cortex) associated with mirror neurons (Rossi & Rossi, 2005/2006). Brain imaging research has documented that activity of the mirror neuron system in the medial prefrontal association area is related to human attitudes, morality, intuition, fear extinction, insight, empathy, response flexibility, emotional balance, attuned communication and body regulation (Siegel, 2006 in press). Virtual Reality (VR) and computer games technologies, for example, are a new research approach to facilitating and assessing appropriate attitude change (Yee & Bailenson, 2006).

We propose that the activation and facilitation of the creative bioinformatics cycle via the pleasurable and rewarding aspects of the NNNE are mediated by heightened levels of dopamine in the nucleus accumbens and its connections with the cerebellum, the limbic system, and frontal lobes as described in current neuropsychological theories of positive experience in general (Pessiglione et al. 2006), addiction (Pineda & Oberman, 2006; Thanos et al. 2004), and music (Levitin, 2006). This is illustrated in the videotaped demonstration of a bioinformatic approach to therapeutic hypnosis and psychotherapy illustrated below (Rossi, 2002a).

Stem cells in rehabilitation

The process of *activity-dependent gene expression* and its consequent *activity-dependent brain plasticity (synaptogenesis and neurogenesis) and stem cell healing* is the molecular-genomic foundation of rehabilitative medicine, physical and occupational therapy as well as the many seemingly different approaches of integrative medicine (Rossi, 2002a, 2004a, 2007). Hood (2001), for example, has documented mitochondrial activity-dependent gene expression in skeletal, cardiac, and smooth muscle cells in response to physical exercise. We now need a systematic research program to investigate the degree to which the many different approaches of integrative medicine, including touch (Schanberg, 1995), can facilitate novelty, environmental enrichment, and exercise, which evoke activity-dependent gene expression in stem cells of the body and brain.

Of greatest interest for the practical applications of integrative medicine in is the ultradian ~1.5 to 2 hour time frame within which new synapses develop in the brain (Cohn-Cory, 2002). *This relatively brief time frame means that we can expect that the molecular dynamics of stem cell healing and brain plasticity could be initiated at the synaptic level within a single therapeutic session.* Once initiated, synaptogenesis in the brain and stem cell healing throughout the body (e.g. the psycho-neuro-immune system) could continue for days, weeks, and months when the patient has been given an adequate way of facilitating their own healing.

Cultural Traditions and Spiritual Healing

The construction and reconstruction of problematic memory, learning, behavior, stress, and symptoms takes place during creative "offline" replays of the bioinformatic cycle of healing and rehabilitation

Cultural traditions of a spiritual (Chez & Jonas, 2003), creative, artistic, dramatic, humanistic, imaginative, or so-called "magical" nature can have value in the therapeutic reconstruction of negative experiences (Greenfield, 1994, 2006; Keeney, 1999–2000; Jung, 1916/1960, 1918/1966; Otto, 1923/1950). Such creative replay in the reconstruction of human consciousness, memory, and problems is recognized in the popular psychotherapeutic concept, *"Every replay is a reframe,"* (De Martino et al. 2006; Rossi, 2002a). Shimizu et al. (2000) demonstrated how *repetition, recall, replay, and reconstruction* are manifest in the transformations of consciousness, memory, and behavior via interactions between the hippocampus and the cerebral cortex. They state, "*memory consolidation may require multiple rounds of site-specific synaptic modifications, possibly to reinforce plastic changes initiated during learning*, thereby making memory traces stronger and more stable. (pp. 1172–1173, italics added)

This concept of positive, creative, therapeutic replay and reconstruction during "offline" psychological states (rest, sleep, dreaming, daydreaming, meditation, prayer, etc.) finds further support in the research of Lisman & Morris (2001).

> "Newly acquired sensory information is funneled through the cortex to the hippocampus. Surprisingly, only the hippocampus actually learns at this time—it is said to be online. *Later, when the hippocampus is offline (probably during sleep), it replays stored information, transmitting it to the cortex. The cortex is considered to be a slow learner, capable of lasting memory storage only as a result of this repeated replaying of information by the hippocampus. .. There is now direct evidence that some form of hippocampal replay occurs . . . these results support the idea that the hippocampus is the fast online learner that "teaches" the slower cortex offline."* (p. 248–249, italics added)

The dynamics of the fast hippocampus teaching the slower cerebral cortex during offline communication, replay, and reconstruction is particularly important for a more precise brain localization of the novelty-numinosum-neurogenesis effect. While authorities now agree that neurogenesis takes place in the human hippocampus throughout life, neurogenesis in the human cortex has always been controversial with current evidence suggesting that neurogenesis does not take place in the mature human cerebral cortex (Bhardwaj et al. 2006; Rakir, 2006).

To clarify the localization of *brain plasticity in humans*, however, we must carefully distinguish between its two components: *neurogenesis* (new neurons generated from stem cells) and *synaptogenesis* (synthesizing new synapses or connections between neurons). In brief: *brain plasticity* via the synthesis, reorganization, and reconstruction of neural networks by *synaptogenesis* takes place in the human cerebral cortex throughout the life cycle when it is prompted by the replaying of new information encoded by the hippocampus (Bliss et al. 2006; Pastalkova et al. 2006; Whitlock et al. 2006). *Current research is consistent with locating the central core of the novelty-numinosum-neurogenesis effect in a neural circuit integrating the cerebral cortex (new cognition via synaptogenesis) with the hippocampus (new learning via synaptogenesis and neurogenesis), the nucleus accumbens (positive numinosum), amygdala (negative numinosum), and the ventral tegmental area (pleasure, motivation, addiction)* (Grund et al. 2006; Hossain, 2000; McClung et al. 2005). The recent longitudinal NIMH study on teenage brain development suggests that the NNNE burns most brightly in adolescence when heightened states of reward and risk-taking behavior are mediated by dopamine via the nucleus accumbens (Galvan et al. 2006; Powell, 2006). Many spiritual and mystical traditions, by contrast, record the early 30s as the age when the founders of the worlds great religions experienced their most salient enlightenment (Bucke, 1901/1967), which we hypothesize is associated with an efflorescence of the NNNE in the more mature brain when cognition and existential meaning hold greater sway in coping with emotional crises and novel life transitions and (Jaynes, 1976).

Until recently the molecular-genomic and anatomical mechanisms of the NNNE and brain plasticity during "offline" psychological states were not understood (Stickgold, 2005; Walker, 2006). One of the most interesting lines of research, however, has found that when mice experience novelty, environmental enrichment, and physical exercise, the *zif-268 gene* is expressed during their REM sleep (Ribeiro, 2004; Ribeiro et al. 1999, 2002, 2004). *Zif-268* is an *immediate-early gene* and *behavioral-state related gene* that is associated with the NNNE that facilitates brain plasticity. Ribeiro et al. (2004) have summarized their research as follows.

> "The discovery of experience-dependent brain reactivation during both slow-wave (SW) and rapid eye-movement (REM) 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 2 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 sleep, may be sufficient to explain the beneficial role of sleep* on the consolidation of new memories." (p. 126–135, italics added)

Such research documenting how *novelty, enriched environments and exercise (mental and physical)* can initiate gene expression and brain plasticity is the basis of our hypothesis about *positive, creative, therapeutic replay and reconstruction during offline periods as the essence of integrative medical healing* illustrated in Figure 4

Figure 4 is a general reference graph profiling patterns of activation, performance, and integrative healing on the genomic/proteomic, behavioral, and experiential levels ranging from high to low states of circadian (~ 24 hours) and ultradian

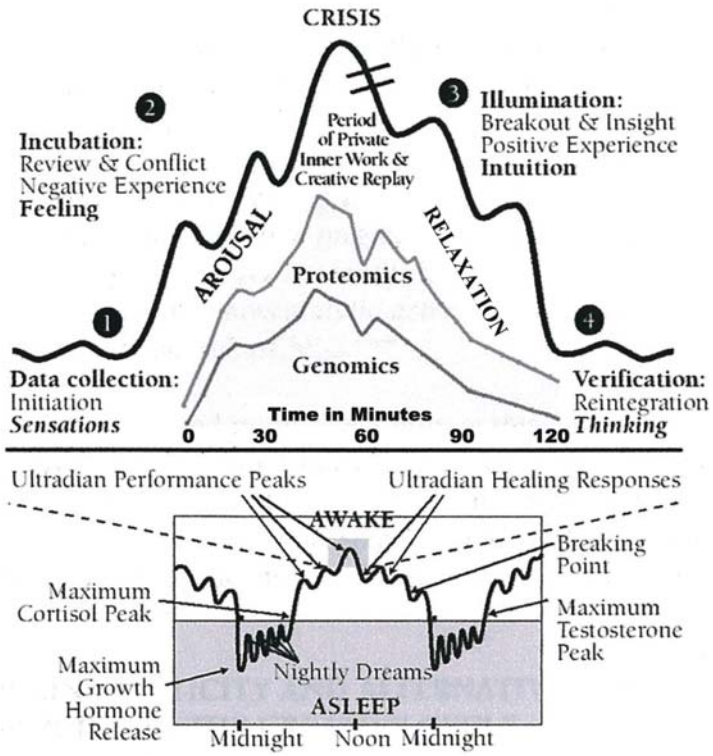

Figure 4. A Profile View of the Bioinformatics Cycle Illustrating Its Circadian (~24 hours) and Ultradian (~1.5 to 2 hours) Rhythms of Genomic, Proteomic, Behavioral, and Experiential Activity. The Upper diagram outlines the typical phenomenological experiences of the classical 4-stage creative process in art, science, and everyday life as well as integrative medical insights. The typical activities of everyday life in experiences of work (e.g. business meetings) and play (movies, sports etc.) typically utilize one ultradian 90–120 minute Basic Rest-Activity Cycle (BRAC) that emerges from the genomics (redrawn from Levsky et al. 2002) and proteomics levels (redrawn from Dill & Bromberg, 2003).

The Lower diagram summarizes the normal circadian (~ 24 hours) profile of alternating 90–120 minute ultradian (less than 20 hours) rhythms of waking and sleeping characteristic of Kleitman's 90-120 minute Basic Rest-Activity Cycle (BRAC) in a simplified manner. The ascending peaks of rapid eye movement (REM) sleep typical of nightly dreams every 90–120 minutes are illustrated with the more variable ultradian rhythms of activity, adaptation, and rest in the daytime. This lower diagram also illustrates how many hormonal messenger molecules of the endocrine system such, as *growth hormone*, the activating and stress hormone *cortisol* and the sexual hormone *testosterone,* as well as the energy (glucose/insulin) and urinary cycles (not shown) typically have 90-120 minute ultradian rhythms within the 24 hour circadian cycle. (From Lloyd & Rossi, 1992; Rossi, 2002a).

(~ 1.5–2 hours) arousal. We hypothesize that many varieties of alternative, complementary, and integrative research on belief systems and spiritual healing (d'Aquili & Newberg, 1999; Glik,1993) achieve their healing efficacy by appropriate modulations of these natural circadian and ultradian profiles of gene expression and brain plasticity (Rossi, 2002a, 2004a, 2007; Rossi & Nimmons, 1991). Our novel and numinous experiences (Otto, 1923/1950) with the mysteries of the world and ourselves excite the mirror neurons of our brain to turn on the activity-dependent gene expression/protein synthesis cycle, brain plasticity and behavioral plasticity. These activity-dependent processes on the molecular-genomic levels generate the continual construction and re-construction of our consciousness and health on implicit (unconscious) levels in our daily life and REM state dreaming as well as psychotherapy illustrated in the following videotape, which is only a brief summary of a complete verbatim transcript presented previously (Rossi, 2002, Chapters seven and eight).

A videotape demonstration of the 4-Stage creative process in bioinformatic activity-dependent approaches to single session psychotherapy

A bioinformatic approach to therapeutic hypnosis and psychotherapy in the accompanying sketches (Figures 5a, 5b, 5c, & 5d) are from a videotape of a young woman presenting severe rheumatoid

arthritis in her hands ("A sensitive fail-safe approach to therapeutic hypnosis," IC-92-D-V9, available from the Ericksonian Foundation, www.erickson-foundation.org) (Rossi, 2002a).

The therapist typically begins a session with a series of open-ended questions (or implicit processing heuristics), which tend to evoke and replay the person's personal history and the state-dependent sources of their problems. When emotional problems and highly numinous personal issues are discussed they will naturally evoke *immediate early genes*, *behavioral state-related genes and activity-dependent gene expression* via the NNNE that generate the possibility of Darwinian natural variation and selection in new cascades of protein synthesis, brain plasticity that may generate problem-solving and mind-body healing.

The therapist models a delicately balanced and symmetrical hand-position a few inches above the lap to initiate a bioinformatic approach to therapeutic hypnosis and psychotherapy. The therapist initially wonders what stage of Kleitman's Basic Rest-Activity Cycle (BRAC) the patient may be experiencing. He wonders whether CYP17—the social gene—is becoming engaged as a natural manifestation of the psychotherapeutic transference, and to what extent immediate-early genes such as c-fos and c-jun—associated with a creative state of psychobiological arousal, problem solving, and healing, particularly of the psycho-neuro-immune system—are becoming engaged.

She now experiences psychobiological arousal (associated with behavioral state-related gene expression (BSGE) as evidenced by the very slight, rapid, involuntary shaking and twitching of her hands and fingers. She is surprised, embarrassed and confused about these unusual sensations and involuntary movements that were *not* suggested by the therapist. This surprising, novel and numinous experience is evoking a heightened behavioral state-related gene expression that the therapist would like to use for therapeutic purposes. The therapist wonders, for example, how to facilitate the psychosocial genomics of immunological vari-

Figure 5a. Stage One of a Bioinformatic Approach Psychotherapy: Open-Ended Questions Initiate the NNNE to Facilitate Immediate Early Gene Expression in Preparation for Problem Solving.

Figure 5b. Stage Two of the Creative Cycle: Incubation, Creative Replay, and Psychobiological Arousal Evokes Behavior State-Related Gene Expression.

ables such as the interleukins associated with Cox2, which have been implicated in rheumatoid arthritis, which is her presenting symptom. Currently available DNA microarray/proteomic array technology with simultaneous brain imaging assessments could provide profiles of the patient's therapeutic bioinformatic states in real time.

Therapist and patient now experience a playful frame shift (De Martino et al. 2006), with the mirror neuron activity of shadow boxing as a creative breakout of her typically restrained hand and finger movements, which she attributes to angry feelings about her boss, her boyfriend, and her rheumatoid arthritis. Future research will be needed to determine if activity-dependent gene expression (ADGE)—such as the CREB related genes and proteins associated with new memory and learning illustrated in figure 2—as well as the ODC and BDNF genes associated with physical growth and brain plasticity are actually being engaged during the replay of such creative moments in psychotherapy.

After flexing her hands and fingers to assess her pain relief she received a standing ovation from the audience. The therapist speculates silently to himself that the zif-268 gene will be expressed in her REM dream states tonight to encode her new, novel, and enrichening therapeutic experiences via the NNNE with this enrichening experience of psychosocial support.

There is as yet no comprehensive program of experimental research investigating the bioinformatic cycle of integrative medical insights via genomic/proteomic microarrays, brain imaging, and virtual reality technologies as illustrated in Figures 5a–5d. This may be why the National Institute of Mental Health (NIMH) is no longer supporting funding for psychosocial research on a purely cognitive-behavioral level without regard for the fundamentals of mental illness on molecular-genomic level (Holden, 2004; Kaiser, 2004). We therefore propose the formation of an International Psycho-Social and Cultural Bioinformatics Project to coordinate integrative medical insights on the role of experienced based gene expression and brain plasticity in facilitating existentional wellness. Government and private funding agencies are now calling for such broadly based and fundamental research.

Figure 5c. Stage Three of the Creative Cycle: Illumination, Insight, and Cognitive Behavioral Therapy via Activity-Dependent Gene Expression and Brain Plasticity.

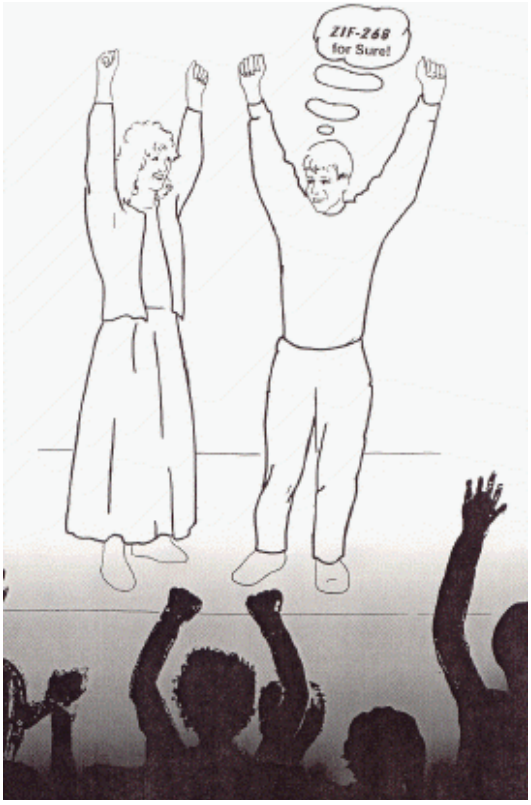

Figure 5d. Stage four: Verification, Social Support, and the Possibility Zif-268 Gene Expression Facilitating Brain Plasticity.

For example, The National Institutes of Health (NIH) has recently issued a Program Announcement titled: "Methodology And Measurement In The Behavioral And Social Sciences" that invites research proposals to develop innovative interdisciplinary, multi-method, and multilevel research designs for use in behavioral and social science research, with special emphasis on both developing new technologies and addressing the analytical complexities associated with the integration of behavioral, social, and biological data.

The James S. McDonnell Foundation (JMSF) is another potential funding source for such an endeavor. This private foundation supports cross-disciplinary research within program areas that are germane, including: "Bridging Brain, Mind, and Behavior" and "Studying Complex Systems." Of particular relevance, the JMSF offers Collaborative Activity Awards designed to initiate interdisciplinary discussions on problems or issues and to help launch interdisciplinary research networks.

We would also propose that the U.S. Congress request the National Academy of Sciences for a "State of the Art" (SOAR) paper in preparation for a congressionally initiated and funded program. It would be appropriate for The National Institute of Mental Health (NIMH) and other NIH Institutes to form a Round Table on this proposal. A multi-university research initiative (MURI) would be desirable to coordinate the project on the national and international levels.

Summary

This paper presents a neuroscience approach to integrative medical insights based on the bioinformatics cycle of creative human experience on all levels from molecular-genomic to brain plasticity and consciousness in sickness and health. Just as The Human Genome Project identified the molecular foundations of modern medicine with the new technology of sequencing DNA during the past decade, we propose that a new International PsychoSocial and Cultural Bioinformatics Project (IPCBP) could identify the profiles of gene expression and brain plasticity associated with stress, healing, and rehabilitation via the wide variety of techniques associated with alternative and complementary medicine such as meditation, prayer, the placebo effect, psychotherapy etc. We anticipate that the IPCBP will require a unique collaboration of governmental agencies, academic institutions, researchers, and clinicians for a greatly enriched bioinformatics of mind-body healing, brain plasticity, memory, learning, and creative processing during optimal experiences of art, beauty, truth and wellness.

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