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The Bioinformatics of Integrative Medical Insights: The 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 genomic knowledge base with the technology of gene expression via DNA/proteomic microarray research and brain imaging in development, gender, stress, healing, rehabilitation, and 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 as well as dysfunctional states of waking, sleeping, and dreaming. This emerging integration of bioinformatics with medicine is illustrated with a videotape of the classical 4-stage creative process in short term, activity-dependent psychotherapy.

Key Words: Psychosocial, genomics, bioinformatics, neuroscience, brain plasticity.

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"Beauty is truth, truth beauty,

that is all ye know on earth,

and all ye need to know."

John Keats
Ode on a Grecian Urn

Introduction: The Bioinformatic Foundation of Integrative Medical Insights

Integrative medical insights (IMI) covers the entire range of healing from the modern molecular-genomic foundations 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 (Lloyd, 2006; von Baeyer, 2004).

Our current concept of biological information was originally described as "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.

[Place Figure 1a about here.]

Since that time, however, neuroscience research has documented how psychological experiences of *novelty* (Eriksson et al., 1998), *psychosocial enrichment* (Kempermann et al., 1997), and mental and physical *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, 2002, 2004). 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.

[Place Figure 1b about here.]

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 in health and disease. 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 (Hannon & Ruth, 1997; van Hemmen & Terrence, 2006; Sterman, 2000).

1. 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 and experiencing 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), for example, 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.

2. The simultaneous assessment of all four levels of the bioinformatics cycle is essential for validating integrative medical insights.

We propose that a truly comprehensive scientific approach to integrative medical insights utilizes both the top-down and bottoms up perspectives by the simultaneous assessment of what is happening on all four levels of the bioinformatics cycle of figure 1b in real time. 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. Patterns of gene expression/protein profiles with simultaneous brain imaging can be used as a Rosetta stone for assessing and evaluating all the seemingly different therapeutic approaches of modern molecular and integrative medical insights. This bioinformatics approach answers another mind-body 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 99.6 % alike? Cáceres et al. (2003) summarize their empirical 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 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. 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."* (pp. 13030, italics added)

These researchers and others (Preuss et al., 2004) propose that it is the elevated levels of gene expression generate elevated levels of neuronal activity, which distinguish between the performance of human and non-human primate brains in cerebral physiology and associated cognition and consciousness. Whitney et al. (2003) documented how individuality and variation in gene expression patterns in human blood can be assessed with DNA microarray technology to investigate these questions about varying states of health and illness.

> "The extent, nature, and sources of variation in gene expression among healthy individuals are a fundamental, yet largely unexplored, aspect of human biology. *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).

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. Table 1 is a brief sampling of gene candidates for the DNA microarray technology assessment of the bioinformatics of integrative medicine at the levels of gene expression, brain plasticity, immunology, genotoxic stress, etc.

Table 1: A brief sampling of gene candidates for the DNA microarray technology assessment of the bioinformatics of gene expression, brain plasticity 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	
Brain Plasticity in Consciousness, Memory, Learning and Behavior Change	
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, 2002, 2004
Random RNA L1 sequences	Cao et al., 2006; Muotri &Gage, 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 and Therapeutic Touch

ODC gene	Schanberg, 1995
Opioid Receptor Gene	Moles et al., 2004

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. This empirical concept is of profound significance for integrative medical insights.

> "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.* Consistent with this is the up-regulation of genes involved in synaptic transmission, including the control of glutamatergic excitability (*SYN47*, also known as Homer 1b), plasticity at glutamatergic synapses (*CAMK2A*), phosphatidylinositol signaling (*IMPA1, CDS2*), synaptic vesicle release (*RAB3GAP, ATP2B1*),

> axonal transport along microtubules (*KIF3A, DCTN1*), microtubule assembly (*MAP1B*), and targeting of proteins to postsynaptic densities (*USP14*). *We have also found expression changes related to energy metabolism*. For example, *CA2*, which is expressed in glia, has been related to the generation and transport of lactate by astrocytes for use by neurons as an energy source. To our knowledge, the possibility that the human brain has an unusually high metabolism has not been previously considered. Typically, larger brains have lower metabolic rates (per unit of tissue) than smaller brains. Nevertheless, 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 random genomic sequences in DNA may also modulate gene expression and associated psychological experiences (Cao et al. 2006). A number of researchers, for example, speculate how such 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). This has profound implications for the theory, research, and practice of integrative medical insights, as we illustrate in the videotaped demonstration of a bioinformatic approach to activity-dependent psychotherapy in a later section of this paper.

We now propose that such "hyper-associative strings" may be a significant co-adaptive process in the evolution of mind and cognition on the molecular-genomic level that is consistent with Ribeiro's integration of the dynamics of slow wave (SW sleep) and dreaming (REM sleep) in simulating the natural integrative mind-body processes of insight and foresight during dreaming (Ribeiro, 2004; Ribeiro et al., 1999, 2002, 2004). 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, 2002, 2004, 2005, 2007). Because there are as yet no systematic programs utilizing this multi-level approach to integrative medical insights, however, we will now proceed to review a number of partial models assessing the bioinformatics cycle of 1b to guide future theory, research, and practice in the following sections.

3. Integrative medical insights emerge from coordinated profiles of psychological experience and gene expression/protein synthesis in the bioinformatics cycle.

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, 1999) document how acute trauma and psychosocial stress facilitates changes in cholinergic gene expression on the genomic level. In related research Meshorer et al. (2002) describe how psychological stress modulates gene expression humans experiencing posttraumatic stress disorder (PTSD) via stimulus-induced changes in alternative splicing of genes as follows.

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This alternative splicing of genes induced by psychosocial stress is a clear example of how the top-down dynamics of (1) *psychological experience* can modulate information encoded in the (2) *sequence of gene expression*, which in turn modulates the (3) *structure of proteins*, and the (4) *physiological functioning* of the general adaptation syndrome in health and dysfunction in the bioinformatics cycle of figure one. Surprising Integrative medical insights emerge, for example, when Rosbash & Takahashi (2002) noted that cancer can be a direct consequence of the stress related disruption of circadian regulation via the Period 2 (*Per 2)* gene. Figure 2 is an illustration of what a more complete

bioinformatics analysis stretched out over circadian time might look like. Figure 2 illustrates the matching of bi-modal circadian profiles of the bioinformatics cycle ranging from measures of the *psychological experiences* (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 2 is consistent with - but does not yet prove that bioinformatic approaches psychotherapy in general, and hypnosis, in particular, can be used to modulate body temperature and gene expression for therapeutic purposes (Rossi, 2002, 2004).

[Place Figure 2 about here.]

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 an *ad hoc* assembly from many serendipitious observations of the research literature as cited above (Rossi, 2004e). Systematic research is now required to validate the association of the bioinformatic profiles artificially juxtaposed in figure two. Such research would require the simultaneous utilization of DNA/proteomic microarrays with brain imaging to assess how the changing psychological states of waking, sleeping, dreaming, hypnosis, meditation, psychotherapy (Cozzolino, 2003), creativity (Rossi, 2002, 2004, 2005, 2007), and intention (Radin et al.,

2004) etc. could be efficacious in the top-down modulating of the gene expression/protein synthesis profiles of the bioinformatic cycle as reviewed in the next section.

A number of researchers have discussed the profound and still little understood associations between information, energy, and entropy in life processes on the classical (Stonier, 1990) and quantum levels (Lloyd, 2006), and their implications for a deep psychobiology of psychotherapy (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 review in the following sections.

4. The bioinformatics of stem cells are sources of brain plasticity, healing, and rehabilitation on the genomic and proteomic levels accessible to the molecular dynamics of integrative medicine.

Current research documents on stem cells, stress, gene expression, proteomics, brain plasticity, and healing as well as cancer are emerging in integrative medicine (Ivanova et al., 2006). Stress on all levels from the psychosocial to the physical and traumatic leads to the oxidation, injury, mutation, and malfunctioning on the genomic and proteomic levels (Gould et al. 1998).

Here we can only briefly summarize some of the emerging research on the bioinformatics of stem cells for integrative medical insights.

New Research on the Cancer Stem Cell Theory. Because normal stem cells in all tissues of the mature organism can replicate endlessly they have enough 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 much current research on the 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 microarray 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 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, 2004). 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 & Segre, 2000). Most of the integrative approaches of medicine purport to facilitate healing by reducing psychosocial stress, promoting relaxation, and wellness that are efficacious at the genomic and proteomics levels of stem cell healing remains to be demonstrated in detail (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 area 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. *These socially influenced alterations are transmitted culturally. They are not incorporated in the sperm and egg and therefore are not transmitted genetically.* " (p.140, italics added).

Neuroscience research indicates that there are at least 3 classes of psychological 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) E*nvironmental Enrichment* (Kempermann et al., 1997; Van Praag et al., 2000),

3) Exercise (Van Praag et al., 1999, 2002).

It has been noted Rossi (2002, 2004a & b) that these three psychological 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 apparent concordance of psychological and spiritual experience associated with gene expression and brain plasticity is denoted as the *novelty-numinosum-neurogenesis effect* in creative experience on all levels from mind to molecule. The novelty-numinosum-neurogenesis effect is proposed as the creative common denominator between art and science in a new bioinformatic theory of esthetics (Rossi, 2002,

2004a, b, c). Experiences of art, beauty, and truth as well as Einstein's eternal mystery epistemology (Rossi, 2005c, d) are the phenomenological correlates of the activation of mirror neurons, the gene expression/protein synthesis cycle, brain plasticity in the novelty-numinosum-neurogenesis effect as illustrated in the 4 stage creative bioinformatic cycle of figure three.

[Place Figure three about here]

Most significantly for the therapeutic and clinical application of integrative medical insights is how *brain plasticity* can occur via the activation of three neocortical association areas (prefrontal, inferior temporal, and posterior parietal cortex) associated with mirror neurons (Rossi & Rossi, 2005/2006). Brain imaging research (Siegel, 2006 in press) has documented that activity of the mirror neuron system in the medial prefrontal association area is associated with experiences of human relationships and psychotherapy such as morality, intuition, fear extinction, insight, empathy, response flexibility, emotional balance, attuned communication and body regulation. We propose that the activation and facilitation of the creative bioinformatics cycle on all levels from mind to molecule is the essence of all efficacious approaches to facilitating mind-body regulation healing and rehabilitation as illustrated in the videotaped demonstration of our activity-dependent approach to psychotherapy illustrated below.

Stem Cells in Rehabilitation. It has been hypothesized that this 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, 2002, 2004). Hood (2001), for example, has documented activity-dependent gene expression in mitochondrial in skeletal, cardiac and smooth muscle 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 the novelty, environmental enrichment, and exercise, which are required to evoke activity-dependent gene expression in stem cells of the body and brain to facilitate the bioinformatics cycle of healing.

Of greatest interest for the practical applications of integrative medicine in urology is the 1.5 to 2 hour time frame within which new synapses develop in the brain. *This relatively brief time frame means that all members of the bioinformatics clinical team 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, presumably, stem cell healing in the body (e.g. the immune system) could, in the ideal case, continue for days, weeks, and months when the patient has been given an adequate way of facilitating their own healing. This leads us to our next insight of how integrative medical approaches can engage brief and efficacious creative psychotherapeutic models wherein patients learn how to solve their own problems privately in their own way.

5. The construction and reconstruction of problematic memory, learning, behavior, stress, and symptoms takes place during creative "offline"

replays of the genomic/proteomic cycle and brain plasticity in the bioinformatics of healing and rehabilitation.

The integrative approaches to bioinformatic facilitation involve the repetition and creative replay of salient, stressful, and traumatic life experiences in "offline" replays of what are typically called "cultural traditions." These cultural traditions may be of a spiritual, political, artistic, dramatic, humanistic, imaginative, or so-called "magical" nature (Greenfield, 1994, 2006; Keeney, 1999-2000; Jung, 1916/1960, 1918/1966; Otto, 1923/1950). The value of creative replay in the reconstruction of human consciousness, memory, and problematic life experience is currently recognized in the popular psychotherapeutic concept, *"Every replay is a reframe,"* (De Martino et al. 2006; Rossi, 2002). This concept finds neuroscience support by Shimizu et al., (2000) who demonstrate how the processes of *repetition, recall, replay, and reconstruction* are manifest in the transformations of consciousness, memory, and behavior via the dynamics of brain plasticity. They conclude "that *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)

Cohn-Cory (2002) provides more detail about the actual time parameters of such "*multiple rounds of site-specific synaptic modifications"* or replay via activity-dependent synaptogenesis and brain plasticity.

> "The anatomical refinement of synaptic circuits occurs at the level of individual axons and dendrites by a dynamic process . . . *As axons*

branch and re-model, synapses form and dismantle with synapse elimination occurring rapidly, in less than two hours. . . hippocampal neurons in which glutamate receptor function was altered demonstrated that synapse disassembly in the CNS occurs rapidly, within 1.5 hours after synapses are no longer functional (p. 771)

It has been hypothesized that just as negative states of emotional arousal can evoke gene expression cascades leading to the synthesis of stress proteins and illness, so can the replay of positive psychological experiences initiate cascades of healing at the gene-protein level (Rossi, 2002, 2004). This implies that the *replaying of positive creative human experiences* of fascination, novelty, mystery, surprise and insight experienced in the dramatic cultural rites of healing in many cultures could facilitate gene expression cascades leading to the synthesis of healing proteins.

This concept of positive, creative, therapeutic replay during "offline" psychological states (rest, sleep, dreaming, daydreaming, meditation, prayer, etc) as potentially important periods for integrative healing 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 . . . hese results support the idea that the hippocampus is the fast online learner that "teaches" the slower cortex offline." (p. 248-249, italics added)

Until recently such molecular-genomic mechanisms of brain plasticity during so-called "offline" psychological states in rehabilitative healing and supportive care were not understood (Strickgold, 2005; Walker, 2006). One of the most interesting lines of research has found that when experimental animals experience novelty, environmental enrichment and physical exercise, the *zif-268 gene* is expressed during their REM sleep (Ribeiro et al., 1999, 2002, 2003). *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. Ribeiro et al (2004) h summarized their results 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. !26 – 135, italics added.)

Research reviewed above describing how *novelty, enriched environments and exercise (mental and physical)* can initiate gene expression leading to the formation of brain plasticity is the basis of our hypothesis about *positive, creative, therapeutic replay during offline periods as the essence of integrative healing* illustrated previously in figure four.

[Place figure four about here.]

Figure four profiles of a continuum of integrative healing ranging from high to low states of circadian (~ 24 hours) and ultradian (~ 1.5 - 2 hours) psychobiological arousal that is consistent with many varieties of research on belief systems and so-called "spiritual healing" that focus on and facilitate different parts of the same psychobiological continuum (d'Aquili & Newberg, 1999; Glik,1993) of the 4-stage creative process profiled in figure four (Rossi, 2002, 2004, 2007; Rossi & Nimmons, 1991).

A Videotaped Demonstration of the 4-Stage Creative Process in Bioinformatic Activity-Dependent Approaches to Single Session Psychotherapy

The four stages of a bioinformatic approach to activity-dependent psychotherapy in the accompanying sketches (figures 5a, 5b, 5c, & 5d) are from a videotaped demonstration with a young woman presenting severe rheumatoid

arthritis in her hands. This hour videotape titled, “A sensitive fail-safe approach to therapeutic hypnosis” (IC-92-D-V9), is available from the Ericksonian Foundation (www.erickson-foundation.org) for study by professionals and students. Rossi (2002) presents a detailed verbatim analysis of the entire videotape from a bioinformatics perspective. Current DNA/proteomic microarray technology is making it possible to assess gene expression profiles in human blood and brain imaging could be used to identify changing psychobiological states. This suggests that we are now able to explore such gene expression profiles to identify the bioinformatics of activity-dependent psychotherapy in real time to empirically validate the therapeutic efficacy of the heightened activity generated by the mirror neurons approach to the bioinformatics of integrative medicine.

Figure 5a. Stage one of the Bioinformatic Activity-Dependent Approach Psychotherapy: Open-Ended Questions (Implicit Processing Heuristics) Facilitating Immediate Early Genes in Preparation for Problem Solving.

The typical psychotherapeutic session ideally begins with patient and therapist cooperating in a search for the problems and issues that the patient hopes to resolve. The therapist's role in this initial stage is to facilitate this search with familiar yet mildly provocative open-ended questions such as: What is on your mind today? What is most alive in you, right now!? Well, what is your truth and beauty these days? I now call these evocative openings "implicit processing heuristics" in keeping with the current neuroscience use of the word "implicit" to describe the "unconscious" or "off-line" dynamics of memory, motivation, and bioinformatic transductions on all levels from molecule to mind. They often serve as mini-rites of transition between the everyday world of congenial talk to the more focused creative work of the therapy session (detailed in chapter 9 of Rossi, 2002).

From our current neuroscience perspective, these open-ended implicit processing heuristics tend to evoke and replay the person's personal history and the dissociated (state-dependent) sources and encoding 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* that generate the possibility of Darwinian natural variation and selection in new cascades of protein synthesis, brain plasticity, 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 (IEGs) such as c-fos and c-jun — associated with a creative state of psychobiological arousal, problem solving, and healing, particularly of the psychoneuroimmune system — are becoming engaged .

Figure 5b. Stage two of the Bioinformatic Activity-dependent Approach in Psychotherapy: Incubation, Creative Replay, and Psychobiological Arousal Evokes Behavior State-Related Gene Expression.

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 variables such as the interleukins associated with Cox2, which have been implicated in rheumatoid arthritis, which is her presenting symptom. Currently available DNA microarray/proteomic assessments could provide profiles of the patient's deep bioinformatic states in real time. The therapist supports her with *non-directive implicit processing heuristics* like, "Do you have the courage to allow that to continue for another moment or two until. . .?" Until what? Hopefully, until she stumbles by random Darwinian chance into association patterns about the source of her problems that may set the stage for their creative resolution in stage three.

Figure 5c. Stage three of Bioinformatic Psychotherapy: Illumination via Activity-Dependent Gene Expression and Brain Plasticity.

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 associates with 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 as 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.

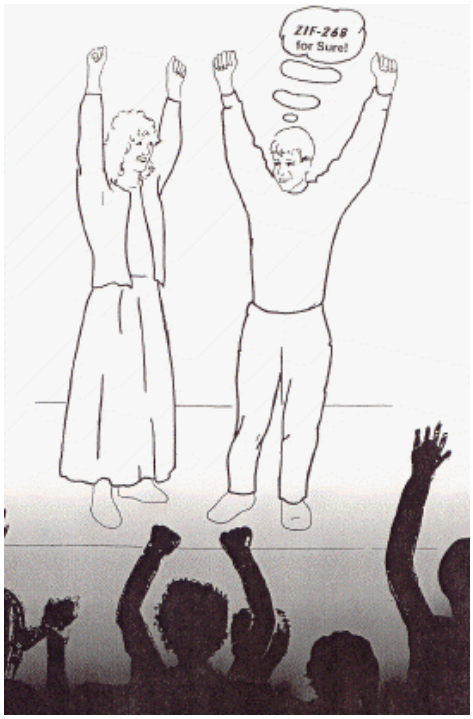

Figure 5d. Stage four of Bioinformatic Psychotherapy: Verification, Social Support, and the Possibility Zif-268 Gene Expression Facilitating Brain Plasticity. After flexing her hands and fingers with a mixture of pain and relief she received a standing ovation from the audience. The therapist speculates 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 with this unusually enrichening, perhaps once-in-a-lifetime show of psychosocial support. Recent research documents that the zif-268 gene codes for a protein important for brain plasticity during changes in memory and learning while awake as well as during creative replays of salient daytime experiences during our REM dreams while asleep at night (Ribeiro et al., 2004).

Summary: An International PsychoSocial and Cultural Bioinformatics Project for research in integrative medical insights

This conceptual review proposes a comprehensive approach to integrative medical insights based on the bioinformatics cycle of human experience on all levels from molecular-genomic and proteomic to brain plasticity and consciousness in sickness and health. The bioinformatics of mirror neurons and brain plasticity is a new model bridging the Cartesian mind-body gap for the creation of optimal states of existentional transition and wellness. Much of this integrative view of medicine remains highly controversial, however, and will require researchers and clinicians to adopt the techniques of modern neuroscience, functional genomics, DNA microarray technology, and brain imaging in the simultaneous assessment of our innovative bioinformatic activity-dependent approaches to psychotherapy.

At the present time, however, is there is as yet no comprehensive program of experimental research investigating the bioinformatic cycle of integrative medical insights as proposed here. This may be why the National Institute of Mental Health (NIMH) is no longer supporting funding for psychological 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 PsychoSocial and Cultural Bioinformatics Project to coordinate integrative medical insights of how the Novelty-Numinosum-Neurogenesis Effect in optimal human experiences of art,

beauty, and truth could facilitate existentional wellness associated with mind-body healing and rehabilitation.

References

Alejel, T. (2001). Effect of antidepressives and psychosocial stress on the Expression of a CRE dependent reporter gene in the brain of transgener mice. Philipps University Theisi, Marburg. http://archiv.ub.uni-marburg.de/diss/z2002/0040.

Alfonso, J., Pollevick, G., van der Hart, M., Flügge, G., Fuchs, E., Frasch, A. (2004). Identification of genes regulated by chronic psychosocial stress and antidepressant treatment in the hippocampus. *European Journal of Neuroscience, 19: 3.* 659-666.

Al-Hajj, M., Becker, M., Wicha, M., Weissman, I., & Michael F Clarke, M. (2004). Therapeutic implications of cancer stem cells. Current Opinion in Genetics & Development, 14 , 43-47.

Antoch, M. & Kondratov, R. (2006). Clock of ages. Nature, 422, 488-489.

Bartek, J. & Lukas. J. (2006). The stress of finding NEMO. Science, 311, 1110-1111.

Bentivoglio, M. and Grassi-Zucconi, G. (1999). Immediate early gene expression in sleep and wakefulness. In Lydic, R. and Baghdoyan, H. (1999). *Handbook of Behavioral State Control: Cellular and Molecular Mechanisms.* New York: CRC Press, 235-253.

Birikh, K., Sklan, E., Shoham, S., & Soreq, H. (2003). Interactionof “readthrough” acetylcholinesterase with RACK1 and PKCßII correlates with intensified fear-induced conflict behavior. *Proceedings of the National Academy of Scientists,* 100:1, 283-288.

Brooks, J. & Vogelsong, J. (2000). The Conscious Exploration of Dreaming: How We Create & Control our Dreams. N.Y.: 1st Books Library.

Cáceres, M., Lachuer, J., Zapala, M., Redmond, J., Kudo, L., Geschwind, D., Lockhart, D., Preuss, T., and Barlow, C. (2003). Elevated gene expression levels distinguish human from non-human primate brains. Proceedings of the National Academy of Scientists, 100, 13030-13035.

Cao, X., Yeo, G., Muotri, A., Kuwabara, T., & Gage, F. (2006). Noncoding RNAs in the Mammalian Central Nervous System. Annual Review of Neuroscience. doi:10.1146/annurev.neuro.29.051605.112839).

Castes, M., Hagel, I., Palenque, M., Canelones, P., Corano, A., & Lynch, N. (1999). Immunological changes associated with clinical improvement of asthmatic children subjected to psychosocial intervention. *Brain & Behavioral Immunology, 13(1),* 1-13.

Cheung, M., Chavez, L., and Onuchic, J. (2004). The energy landscape for protein folding and possible connections to function. *Polymer,* 45, 547-555.

Cirelli, C., Gutierrez, C., & Tononi, G. (2004). Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron,* 41, 35-43.

Christofori, G. (2006). New signals from the invasive front. Nature, 441, 444-450.

Cohen-Cory, S. (2002). The Developing Synapse: Construction and Modulation of Synaptic Structures and Circuits. Science 298: 770-776.

Cozzolino, M. (2003). La Comunicazione Invisible: Gli Aspetti Non Verbali Della Comunicazione (Invisible Communication: Aspects of Non Verbal Communication). N.Y.: Firera Publishing Group.

d'Aquili, E. & Newberg, A. (1999). The Mystical Mind: Probing the Biology of Religious Experience. Minneapolis: Fortress Press.

De Martino, B., Kumaran, D. Seymour, B. & Dolan, R. (2006). Frames, biases, and rational decision-making in the human brain. Science, 313, 684-687.

Dill, K. & Bromberg, S. (2003). Molecular Driving Forces: Statistical Thermodynamics in Chemistry and Biology. N.Y.: Garland.

Erickson, M. (1992/2006). (Rossi, E., Erickson-Klein, R. & Rossi, K., Editors) **CD.** The Neuroscience Edition. The Seminars, Workshops, & Lectures of Milton H. Erickson. Volume 4: Creative Choice in Hypnosis. Phoenix: The MHE Foundation Press.

Eriksson, P., Perfilieva, E., Björk-Ericksson, T., Alborn, A-M., Nordborg, C., Peterson, D., & Gage, F. (1998). Neurogenesis in the adult human hippocampus. Nature Medicine, 4, 1313-1317.

Fuchs, E. & Segre, J. (2000). Stem cells: A new lease on life. Cell, 100, 143-155.

Gage, F. (2000). Mammalian neural stem cells. Science, 287, 1433-1438.

Gery, S. et al. (2006). Periodic regulation. Nature, 441, 386.

Glaser, R., Lafuse, W., Bonneau, R., Atkinson, C., & Kiecolt-Glaser, J, (1993). Stress-associated modulation of proto-oncogene expression in human peripheral blood leukocytes. *Behavioral Neuroscience*, 107, 525-529.

Glik, D. (1993). Beliefs, practices, and experiences of spiritual healing adherents in an American industrial city. In W. Andritsky (Ed.), Yearbook of Cross-Cultural Medicine and Psychotherapy. Berlin: Verlag fűr Wissenschaft und Bildung, pp. 199-223.

Gould E., Tanapat, P., McEwen, B., Flügge, G., & Fuchs, E. (1998). Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proceeding of the National Academy of Sciences, 95, 3168-3171.

Gould, E., Alison, J., Reeves, A., Michael, S., Graziano, S., & Gross, C. (1999 a). Neurogenesis in the neocortex of adult primates. Science, 286, 548-552.

Gould, E., Tanapat, P., Reeves, A., & Shors, T. (1999b). Learning enhances adult neurogenesis in the hippocampal formation. Nature Neuroscience, 2(3), 260-265.

Greenfield, S. (1994). A model explaining Brazilian spiritist surgeries and other unusual religious-based healing. Subtle Energies, 5, 109-141.

Greenfield, S. (2006). Religious altered states and cultural-biological transduction in healing. Paper presented for the Congresso Brasilerio de Etnopsiciatria, Fortaleza CE, September 28-30. To Appear in Portuguese in the Revista Brasileria de Etnopsiquiatria.

Holden, C. (2004). NIMH takes a new tack, upsetting behavioral researchers. Science, 306, 602.

Holtz, R. (2006). Brain's Darwin's Machine: Scientists fine evidence of a perpetual evolutionary battle in the mind. The process, they suspect, is the key to individuality. Dana Foundation Brain in the News, 13(4). 2.

Hood, D. (2001). Plasticity in skeletal, cardiac, and smooth muscle. Invited review: Contractile activity-induced mitochondrial biogenesis in skeletal muscle. Journal of Applied Physiology, 90, 1137-1157.

Hannon, B. & Ruth, M. (1997). Modeling Dynamic Biological Systems. N.Y.: Springer.

Ivanova, N., Dobrin, R., Lu, R., Kotenko, I., Levorse, J., DeCoste, C., Schafer, X., Lun, Y., & Lemischka, I. (2006). Dissecting self-renewal in stem cells with RNA interference. Nature, 442, 533-538.

Jung, C. (1916/1960). The Transcendent Function. In The Structure and Dynamics of the Psyche. Bollingen Series XX, Volume 8. The Collected Works of C. G. Jung. (R. F. C. Hull, Trans.). New York: Pantheon Books, pp. 67-91.

Jung, C. (1918/1966). The Synthetic or Constructive method. In Two Essays on Analytical Psychology. Bollingen Series XX, Volume 7. 2ed edition. The Collected Works of C. G. Jung. (R. F. C. Hull, Trans.). New York: Pantheon Books, pp. 80-89.

Kaiser, J. (2004). Report seeks stability for behavioral sciences. Science, 306, 1878-1879.

Kandel, E. (1998). A new intellectual framework for psychiatry. The American Journal of Psychiatry, 155, 457-469.

Karin, M. (2006). Nuclear factor-κB in cancer development and progression. Nature 441, 431-436 (2006).

Kaufer, D., Friedman, A., Seidman, S. & Soreq, H. (1998). Acute stress facilitates long-lasting changes in cholinergic gene expression. Nature, 393, 373-377.

Kaufer, D., Friedman, A., & Soreq, H. (1999). The vicious circle of stress and anticholinesterase responses. The Neuroscientist, 5, 1-9.

Kaushik, N., Fear, D., Richards, S., McDermott, C. et al. (2005). Gene expression in peripheral blood mononuclear cell from patients with chronic fatigue syndrome. J. of Clinical Pathology, 58, 826-832.

Keeney, B. (1999-2000). Profiles in Healing. Volumes 1 to 4. Philadelphia: Ringing Rock Press.

Kempermann, G. & Gage, F. (1999). New nerve cells for the adult brain. *Scientific American,* 280, 48-53.

Kempermann, G., Kuhn, G. & Gage, F. (1997). More hippocampal neurons in adult mice living in an enriched environment. *Nature,* 386, 493-495.

Kuwabara, T., Hsieh, J., Nakashima, K., Taira, K. & Gage, F. (2004). A small modulatory dsRNA specifies the fate of adult neural stem cells. Cell, 116, 779-793.

Levsky, J., Shenoy, S., Pezo, C., & Singer, R. (2002). Single-Cell Gene Expression Profiling. Science*,* 297, 836-840.

Lisman, J. and Morris, G. (2001). Why is the cortex a slow learner? *Nature*, 411, 248-249.

Lüscher, C., Nicoll, R., Malenka, C., & Muller, D. (2000). Synaptic plasticity and dynamic modulation of the postsynaptic membrane. Nature Neuroscience 3, 545-567.

Lloyd, D. & Rossi, E., (Eds.), (1992). Ultradian Rhythms in Life Processes: A Fundamental Inquiry into Chronobiology and Psychobiology. New York: Springer-Verlag.

Lloyd, S. (2006). Programming the Universe: A Quantum Computer Scientist Takes on the Cosmos. N.Y.: Knopf.

McKhann, G. (2006). Findings in genetics alter our thinking about brain processes. Dana Foundation Brain in the News, 13(4). 3.

McLaren, A. (2000). Cloning: Pathways to a pluripotent future. Science, 288, 1775-1780.

Meshorer, E., Erb, C., Gazit, R., Pavlovsky, L., Kaufer, D., Friedman, A., Glick, D., Ben-Arie, N. & Soreq, H. (2002). Alternative splicing and Neuritic mRNA translocation under long-term neuronal hypersensitivity. Science, 295, 508-512.

Moles, A., Kieffer, B. & D'Amato, F. (2004). Deficit attachment behavior in mice lacking the u-opioid receptor gene. *Science, 304,* 1983-1986.

Muotri, A. & Gage, F. (2006). Generation of neuronal variability and complexity. Nature, 441, 1087-1093.

Nader, K.. Schafe, G., & Le Doux, J. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406,* 722-726.

Otto, R. (1923/1950). The Idea of the Holy. NY: Oxford University Press.

Perry, C., Sklan, E., & Soreq, H., (2004). CREB regulates AchE-R - induced proliferation of human glioblastoma cells, Neoplasia*,* 6:2, 1 – 8.

Pluchino, S. et al. (2003). Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. Nature, 422, 688-694.

Preuss, T., Caceres, M., Oldham, M., Geschwind, D., (2004). Human brain evolution: Insights from microarrays. Nature Reviews Genetics, 5:850-860.

Radin, D., Taft, R., & Yount, G. (2004). Effects of healing intention on cultured cells and truly random events. The Journal of Alternative and Complementary Medicine, 10, 103-112.

Ribeiro, S. (2004). Towards an evolutionary theory of sleep and dreams. A Mente Humana #3, 1-20.

Ribeiro, S., Goyal, V., Mello, C. & Pavlides, C. (1999). Brain gene expression during REM sleep depends on prior waking experience. Learning & Memory, 6: 500-508.

Ribeiro, S., Mello, C., Velho, T., Gardner, T., Jarvis, E., & Pavlides, C. (2002). Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. Journal of neuroscience, 22(24), 10914-10923.

Ribeiro, S., Gervasoni, D., Soares, E., Zhou, Y., Lin, S., Pantoja, J., Lavine, M., & Nicolelis, M. (2004). Long-lasting novelty-induced neuronal reverberation during slow-wave sleep in multiple forebrain areas. Public Library of Science, Biology. (PLoS), 2 (1), 126-137.

Ridley, M. (1999). *Genome: The Autobiography of a Species in 23 Chapters.* N.Y.: HarperCollins.

Rosbash, M., & Takahashi, J. (2002). Circadian rhythms: the cancer connection. Nature, 420, 373-374.

Rossi, E. (1972/2000). Dreams and the Growth of Personality: Expanding Awareness in Psychotherapy. New York: Pergamon Press. Updated in the 3ed edition as Dreams, Consciousness, and Spirit. Phoenix, Arizona: Zeig, Tucker, Theisen.

Rossi, E. (2001). The deep psychobiology of psychotherapy. In Corsini, R. (ed.) Handbook of Innovative therapy. N. Y.: Wiley, 155-164.

Rossi, E. (2002). The Psychobiology of Gene Expression: Neuroscience and Neurogenesis in Therapeutic Hypnosis and the Healing Arts. NY: W. W. Norton Professional Books.

Rossi, E. (2004a). (Translator & Editor, Salvador Iannotti: Saiannot@tin.it) Discorso Tra Geni [Italian]. *A Discourse with Our Genes: The Psychosocial and Cultural Genomics of Therapeutic Hypnosis and Psychotherapy.* Benevento, Italy: Editris SAS Press. [Available in Italian and English editions] New York: Zeig, Tucker, Theisen.

Rossi, E. (2004b). Sacred spaces and places in healing dreams: Gene expression and brain growth in rehabilitation: Psychological Perspectives, 47, 49-62.

Rossi, E. (2004c). Art, Beauty and Truth: The Psychosocial Genomics of Consciousness, Dreams, and Brain Growth in Psychotherapy and Mind-Body Healing. Annals of the American Psychotherapy Association, 7, 10-17.

Rossi, E. (2004d). Stress-Induced Alternative Gene Splicing in Mind-Body Medicine. Advances in Mind-Body Medicine, 20:2, 12- 19.

Rossi, E. (2004c). A Bioinformatics Approach to the Psychosocial Genomics of Therapeutic Hypnosis. Hypnos, 31:1, 15-21.

Rossi, E. (2005a). The Bioinformatics of Integrative Medicine in Urology. In Currow, D. & Norman, R. (Eds.) Supportive Care for the Urology Patient. Oxford: Oxford University Press, pp 92-107.

Rossi, E. (2005b). The Memory Trace Reactivation and Reconstruction Theory of Therapeutic Hypnosis: The creative replaying of gene expression and brain plasticity in stroke rehabilitation. Hypnos, 32, 5-16.

Rossi, E. (2005c). Einstein's eternal mystery of epistemology explained: The four stage creative process in art, science, myth, and psychotherapy. Annals of the American Psychotherapy Association, 8, 4-11.

Rossi, E. (2005d). (Laurent Carrer, Translator & Editor). Cinq essais de psychogénomique – Exploration d'une nouvelle démarche scientifique axée sur l'interaction entre l'esprit et la molécule [Five essays on psychosocial genomics: Exploration of a new scientific approach to the interaction between mind and molecule]. Encinitas, CA, USA: Trance-lations.

Rossi, E. (2007, In Press). The Breakout Heuristic: The New Neuroscience of Mirror Neurons, Consciousness and Creativity in Human Relationships: Selected Papers of Ernest Lawrence Rossi. New York: Zeig, Tucker, Theisen.

Rossi, E. & Nimmons, D. (1991). *The Twenty-Minute Break: The Ultradian Healing Response.* Los Angeles: Jeremy Tarcher. New York: Zeig, Tucker, Theisen.

Rossi, E. and Rossi, K. (2005/2006). The Neuroscience of Observing Consciousness & Mirror Neurons in Therapeutic Hypnosis. American Journal of Clinical Hypnosis. 48: 283-278.

Russo-Neustadt A, Ha T, Ramirez R, Kesslak J. (2001). Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model *Behavioral Brain Research,*120,87-95

Sanai et al., (2004). Unique astrocytes ribbon in adult human brain contains neural stem cells but lacks chain migration. Science, 427, 740-749.

Schanberg, S. (1995). The genetic basis for touch effects. In T. Field (ED.), Touch in Early Development. (pp. 67-79). N.Y.: Lawrence Erlbaum.

Selye, H. (1974). Stress Without Distress. New York: Signet.

Sheng, M. (2006). A neuroscientist looks at life and death in the brain. Nature, 442, 5.

Siegel, D. (2006, in press). An Interpersonal Neurobiology Approach to Psychotherapy: Awareness, Mirror Neurons, and Neural Plasticity in the Development of Well-Being. Psychiatric Annals.

Shimizu, E, Tang, Y., Rampon, C., & Tsien, J. (2000). NMDA receptor-dependent synaptic reinforcement as a crucial process for memory consolidation. Science, 290, 1170-1174.

Sklan, E., Lowenthal, A., Korner, M., Ritov, Y., Landers, D., Rankinen, T., Bouchard, C., Leon, A., Rice, T., Rao, D., Wilmore, J., Skinner, J., & Soreq, H. (2004). Acetylcholinesterase/paraoxonase genotype and expression predict anxiety scores in health, risk factors, exercise training, and genetics study. Proceedings of the National Academy of Scientists, 101:15, 5512-5517.

Stahl, S. (2000). Essential Pharmacology. Cambridge: Cambridge University Press.

Sterman, J. (2000). Business Dynamics: Systems Thinking and Modeling for a Complex World. N.Y.: McGraw-Hill.

Sternfeld, M., Shoham, S., Klein, O., Flores-Flores, C., Evron, T., Idelson, G., Kitsberg, D., Patrick, J., & Soreq, H. (2000). Excess "read-through" acetylcholinesterase attenuates but the "synaptic" variant intensifies neurodeterioration correlates. Proceedings of the National Academy of Sciences, 97, 8647-8652.

Stickgold, R. (2005). Sleep-dependent memory consolidation. Nature 437, 1272-1278.

Stonier, T. (1999). Information and the Internal Structure of the Universe. N. Y.: Springer-Verlag.

Suddendorf, T. (2006). Foresight and Evolution of the Human Mind. *Science,* 312, 1006-1007.

Travis, J. (2004). The bad seed: Rare stem cells appear to drive cancers. Science News, 165, 184-185.

Van Praag, H., Kempermann, G., and Gage, F. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nature Neuroscience, 2, 266-270.

Van Praag, H., Kempermann, G., and Gage, F. (2000). Neural consequences of environmental enrichment. *Nature Reviews: Nature Neuroscience,* 1, 191-198.

Van Praag, H., Schinder, A., Christie, B., Toni, N., Palmer, T. and Gage, F. (2002). Functional neurogenesis in the adult hippocampus. Nature, 415, 1030-1034.

Van Hemmen, J. & Sejnowski, T. (2006). 23 Problems in Systems Neuroscience. Cambridge: Oxford University Press.

Vernon, S, Whistler, T., Cameron, B., Hickie, I., Reeves, W., & Lloyd, A. (2006). Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after infection with Epstein Barr Virus. http://www.biomedcentral.com.

Vince, G. (2006). Watching the brain 'switch off' self-awareness. Dana Foundation Brain in the News, 13(4). 2.

Vogel, G. (2000). Stem cells: New excitement, Persistent Questions. Science, 290, 1672-1674.

Von Baeyer, H. (2004). Information:The New Language of Science. Harvard University Press: Cambridge: Massachusetts.

Walker, M. (2006). Sleep to remember. American Scientist, 94, 326-333.

Watson, J. & Crick, F. (1953a**).** A structure for deoxyribose nucleic acid, Nature, 171, 737-738.

Watson, J. & Crick, F. (1953b). Genetical implications of the structure of deoxyribonucleic acid. Nature, 171, 964-967.

Whitney, A., Diehn, M., Popper, S., Alizadeh, A., Boldrick, J., Relman, D. & Brown, P. (2003) Individuality and variation in gene expression patterns in human blood. Proceedings of the National Academy of Sciences,100, 1896-1901.

Figures

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, or cognition) can modulate (2) *Gene Sequence*, (3) *Protein Structure*, and (4) *Physiological Function*. Modern molecular medicine focuses on the bottom-up direction of information transduction wherein genes, proteins, and physiological functions modulate psychological experience. Current

Figure 2. The Matching of Apparently Similar Bimodal Circadian Profiles of Hypnotic Susceptibility, Body Temperature, and Gene Expression that Now Requires Independent Experimental Confirmation. This *ad hoc juxtaposition*

of many serendipitous observations in the cited research literature illustrates a possible bi-modal bioinformatic 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 notice how 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. From Rossi, 2004e.

Figure 3. The Bioinformatics Cycle with a focus on Mirror Neurons and Brain Plasticity. A Neuroscience Model of How the Observing Consciousness and Psychosocial Experiences Update and Reconstruct the Physical Brain. Novel and numinous experiences of (1) Observing Consciousness can (2) activate Mirror Neurons to (3) turn on their Gene Expression/Protein Synthesis Cycle, and (4) Brain Plasticity, which generate the possibility of new consciousness, integrative mind-body healing, and rehabilitation. The delta sign (triangle) means that 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. The outer labels (blue) suggest some of the *Psycho-Spiritual Metaphors, Rituals, and*

Experiences that may mobilize *The Building Blocks of Life* to facilitate *Mind-Body Healing of many apparently unrelated dysfunctions from addictions to depression and stroke* (From Rossi 2007, in press).

Figure 4. A Profile View of the Bioinformatics Cycle Illustrating Its Circadian (~24 hours) and Ultradian (~1.5 – 2 hours) Rhythms. 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 (eg. 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, 2002).

Figure 5a, 5b, 5c, & 5d with captions are presented above in the text.