The Bioinformatics of Integrative Medical Insights:  
The International PsychoSocial and Cultural Bioinformatics Project  
Ernest Rossi, Salvatore Iannotti, Kathryn Rossi, Garret Yount, & Mauro Cozzolino  

Corresponding Editor: Ernest L. Rossi, PhD, 125 Howard Avenue, Los Osos CA 93402, USA Tel: 805-528-0200; Fax:805-528-0700.  
Ernest@ErnestRossi.com  

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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 existential 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.
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 existential 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).

<table>
<thead>
<tr>
<th>Heightened Gene Expression &amp; Neuronal Activation in the Human Cortex</th>
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<tbody>
<tr>
<td>SYN47</td>
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<tr>
<td>CAMK2A, IMPA1, CDS2, KIF3A</td>
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<tr>
<td>DCTN1, MAP1B, RAB3GAP</td>
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<td>ATP2B1, USP14</td>
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<td>Cáceres et al. 2003; Preuss et al. 2004</td>
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<tr>
<th>Brain Plasticity in Consciousness, Memory, Learning and Behavior Change</th>
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<tr>
<td>c-fos, c-jun, krox, NGFI-A &amp; B</td>
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<tr>
<td>CREB</td>
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<td>BNDF</td>
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<tr>
<td>CYP-17</td>
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<tr>
<td>~ 100 Immediate Early Genes</td>
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<tr>
<td>Random RNA L1 sequences</td>
</tr>
<tr>
<td>Bentivoglio &amp; Grassi-Zucconi, 1999</td>
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<td>Kandel et al., 1998</td>
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<td>Russo-Neustadt, 2001; Sheng, 2006</td>
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<td>Ridley, 1999</td>
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<td>Rossi, 2002, 2004</td>
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<td>Cao et al., 2006; Muotri &amp; Gage, 2006</td>
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<th>Dreaming and Replay in the Reconstruction of Fear, Stress and Trauma</th>
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<tr>
<td>Zif-268</td>
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<td>Ribeiro et al., 2002, 2004</td>
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<td>Nader et al., 2000</td>
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<tr>
<th>Chronic Psychosocial Stress and Alternative Gene Expression</th>
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<tbody>
<tr>
<td>Acetylcholinesterase (AChE-S &amp; AChE-R)</td>
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<tr>
<td>Sternfield, et al., 2000</td>
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<tr>
<td>Perry, et al., 2004</td>
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<tr>
<td>Nerve Growth Factor (NGF)</td>
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<td>Alfonso et al., 2004</td>
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<td>Membrane Glycoprotein 6a (M6a)</td>
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<td>CDC-like Kinase 1 (CLK-1)</td>
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<td>G-protein alpha g (GNAQ)</td>
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<tr>
<td>CRE- dependent reporter gene</td>
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<tr>
<td>Alejel, 2001</td>
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<tr>
<td>NF-κB</td>
</tr>
<tr>
<td>Bartek &amp; Lukas, 2006</td>
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Psychoneuroimmunology
Interleukin 1, 2, 1β, Cox-2
Castes et al., 1999; Glaser et al., 1993

Clock Genes & Behavior State-Related Genes
About 100 sleep related genes
Clock, Per 1, BMAL
Period 2
Cirelli et al., 2004
Rossi, 2004; Antoch & Kondratov, 2006
Rosbash & Takahashi, 2002

Maternal Behavior and Therapeutic Touch
ODC gene
Opioid Receptor Gene
Schanberg, 1995
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.

“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 (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 (Bmal1 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 serendipitous 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 stem 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) **Environmental 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,
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 . . . These 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) have 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. 126 – 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
arthriti 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.
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 stumble 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.
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 enriching therapeutic experiences with this unusually enriching, 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 existential 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


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

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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 \textit{Thra} gene associated with metabolism. The lowest diagram illustrates how (D) the circadian profile of the \textit{Per1} gene, while awake, is similar to the \textit{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 \textit{Bmal1} gene in (D), which is a marker for being asleep, is in \textit{anti-phase} (the opposite of) the awake profiles of \textit{Per1} and \textit{Thra} gene expression associated with peaks of core body temperature and hypnotic susceptibility. From Rossi, 2004e.

\textbf{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 \textit{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.