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A New Bioinformatics Paradigm for the Theory, Research, and Practice of Therapeutic Hypnosis

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Abstract

In a 2008 pilot study we used DNA microarrays to explore the historical ideo-plastic faculty of therapeutic hypnosis. We documented how to measure changes in activity or experience-dependent gene expression over relatively brief time periods (1 hour and 24 hours) following a single intervention of therapeutic hypnosis (about 1 hour). In the present paper we utilize bioinformatic software to explore the possible meaning and significance of this ideo-plastic faculty of therapeutic hypnosis. Indications suggest that the ideo-plastic process of therapeutic hypnosis may be associated with (1) the heightening of a molecular-genomic signature for the up-regulation (heightened activity) of genes characteristic of stem cell growth, (2) a reduction in cellular oxidative stress, and (3) a reduction in chronic inflammation. We identify these three empirical associations as an initial beta version of the molecular-genomic signature of the ideo-plastic process of therapeutic hypnosis, which can serve as a theoretical and practical guide for clinical excellence by beginners as well as senior professionals. We propose this molecular-genomic level of discourse as a supplement to the traditional cognitive-behavioral description of therapeutic suggestion, hypnosis, and psychotherapy that is consistent with "translational research" currently funded by the National Institute of Mental Health (NIMH).

Keywords: Bioinformatics, DNA microarrays, epigenetics, hypnosis, ideo-plastic faculty.

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Introduction: Our 2008 Pilot Study of the Epigenetics of Therapeutic Hypnosis

Epigenetics is becoming recognized as a new scientific approach for exploring the interaction of nature and nurture: how genes interact with the environment to modulate behavior and cognition in sickness and health (Hsieh & Eisch, 2010). Recent research has demonstrated that complex 'epigenetic' mechanisms regulate gene activity without altering the DNA code (Tsankova, Renthal, Kumar, & Nestler, 2007). Epigenetics focuses on a special class of genes, often described as activity or experience-dependent genes, which can be turned on (activated) by signals from the physical and psychosocial environment to modulate the complex functions of physiology and psychology (Rossi, 2002, 2004, 2007; Lloyd & Rossi, 1992, 2008). Experience-dependent gene expression is contrasted with constitutive genes, which are inherited by the Mendelian laws of physical inheritance to generate the relatively simple functions of physiology that cannot be modified by the psychosocial signals of culture, learning, and motivation.

In this paper we will first present the basic hypothesis and motivation for our first pilot study utilizing the positive expectations and focused attention of therapeutic hypnosis to modulate activity or experience-dependent gene expression (Rossi, Iannotti, Cozzolino, Castiglione, Cicatelli, & Rossi, 2008). We will review the methods, procedures, participants, data analysis, and results of this initial study. We will then discuss the limitations of this pilot study and our current approach for dealing with these limitations by introducing a bioinformatics paradigm into the scientific literature of therapeutic hypnosis. While this new bioinformatics paradigm is new to literature of professional hypnosis, it has recently become a standard operating procedure for the analysis, meaningful organization, and understanding of the epigenetics of experience-dependent gene expression and brain plasticity in the biological and medical sciences (Akil et al., 2010; Insel, 2009, 2010).

Hypothesis and Motivation of Our Original 2008 Pilot Study

Our original 2008 pilot study addressed the hypothesis that a creatively oriented, positive experience of therapeutic hypnosis, which we call, *"The Creative Psychosocial Genomic Healing Experience"(CPGHE),* could modulate the expression of activity or experience-dependent genes as measured by DNA microarrays (Rossi, Iannotti, Cozzolino, Castiglione, Cicatelli, & Rossi, 2008). DNA microarrays are new technology that enables researchers to identify and assess the biological and psychological states and changes in activity or experience-dependent gene expression in cells and tissues of the brain and body during health and disease with a single experiment (Rossi, 2005/2006). While most of this research has been done with animals for biological and medical research, this paper reviews new epigenetic models of how this DNA technology can be applied to a new era of foundational research on the clinical applications of therapeutic hypnosis and psychotherapy (Rossi, 2002, 2004, 2007).

The *CPGHE* is a new, easy to learn, professional protocol for the induction of focused attention, expectancy, and positive motivation that is characteristic of clinical or therapeutic hypnosis. A manual for the administration, rationale, scoring, and research on the *CPGHE*, which we used in our original 2008 pilot study is freely available (http://www.ernestrossi.com/ernestrossi/Neurosciencresearchgroup.html). The original hypothesis of our 2008 pilot study was motivated by recent research, which documents how many activity or experience-dependent genes assessed by DNA microarrays are expressed in the normal processes of learning, memory, and brain plasticity. The psychobiological states of being awake, asleep, and REM dreaming for example, each have their own characteristic pattern of gene expression (Ribeiro, Goyal, Mello, & Pavlides, 1999; Ribeiro, Mello, Velho, Gardner, Jarvis & Pavlides, 2002; Ribeiro, et al., 2004, Ribeiro, et al., 2007, Ribeiro, Simoes, & Micolelis, 2008). Many psychiatric conditions such as addictions, depression, obsessive-compulsive disorder, and posttraumatic stress syndrome can now be identified by their characteristic patterns of activity or experience-dependent gene expression (sometimes described as their "molecular-genomic signature") assessed with DNA microarrays (Insel, 2009, 2010). Further, many mind-body approaches to ameliorating

psychological and psychiatric dysfunctions via meditation (Dusek et al., 2008), Qigong (Li, Q., Li, P., Garcia, Johnson, Feng., 2005), and music (Bittman et al., 2005), have used DNA microarrays to assess their characteristic patterns of experience-dependent gene expression. Such research suggests that the focused attention, absorption, and positive expectancy associated with therapeutic hypnosis also could modulate experience-dependent gene expression as measured with DNA microarrays. We propose that the analysis of activity or experience-dependent gene expression to identify the molecular-genomic basis of psychopathology and the therapeutic approaches for resolving such psychopathology may become a new way of assessing evidence based mind-body medicine (Eisen, Spellman, Brown, & Botstein, 1998; Rossi, 2002, 2004a, 2007).

Material, Method, and Participants of Our Original 2008 Pilot Study

We used DNA microarrays to explore the molecular-genomic basis of the historical ideo-plastic faculty of therapeutic hypnosis (Wetterstrand, 1902; Tinterow, 1970). The DNA microarray is a standard tool for assessing the expression of the entire human genome in a single experiment. Our initial cohort of three highly susceptible hypnotic subjects (two females and one male) all had advanced academic degrees and were recruited from a university environment by the second co-author (Iannotti) on the basis of a General Psychiatric Evaluation, The Minnesota Multiphasic Personality Inventory (MMPI-2), The Tellegen Absorption Scale (highly correlated with Standard Scales of Hypnotic Susceptibility), and the Spiritual Intelligence Self Report Inventory (high scorers on the SISRI-24 acknowledge heightened experiences related to critical existential thinking, personal meaning production, transcendental awareness, and conscious state expansion). These subjects scored within the normal range of personality characteristics with no evident psychopathology on the MMPI-2. They were all volunteers who responded well to the *CPGHE* with a positive sense of focused attention, expectancy, absorption, and therapeutic well being. A full description of the clinical intervention, rationale sample collection, and microarray analysis has been made publically available (Rossi, Iannotti, et al., 2008). For the purpose of this paper, the clinical intervention of our original 2008 pilot paper can be described briefly as an application of the 4-stage creative process to therapeutic hypnosis as follows.

Stage 1: The induction of hypnosis via permissive ideodynamic suggestions.

Stage 2: Deepening hypnosis via incubation and past problem review to activate positive motivation, expectancy, and inner resources.

Stage 3: Supporting the positive aha or eureka experience of insight.

Stage 4: Awakening with post-hypnotic suggestions for re-integration and reality testing.

Briefly, the overall research procedure can be summarized as follows. Peripheral blood was obtained from these three adult subjects immediately prior to, 1 hour after, and 24 hours after a single session of therapeutic hypnosis according to the protocol of the *CPGHE* initially formulated by Rossi (2004a). Total RNA was extracted from leukocytes, quantified, and purified. Approximately 2.5 ìg of purified total RNA was delivered to the MicroCRIBI Service (University of Padova, Italy) for microarray analysis. MicroCRIBI Service performed the microarray analysis on 21,329 - 70mer oligonucleotides (Operon version 2.0) designed on Human Unigene clusters. For each sample, 1.0 ìg of total RNA was reverse transcribed and labeled with Cy3 and Cy5 fluorophores for two-channel scanning. Fluorophore labeling of "control" (Immediately before hypnosis) versus "treated" (1 hour or 24 hours after hypnosis) samples was counterbalanced, to control for dye bias. The microarrays were scanned with a two channel confocal microarray scanner (ScanArray# Lite, Perkin Elmer,USA) using its dedicated software (ScanArray Express 3.0.0., Perkin Elmer).

Data Analysis, Results, and Limitations of Our Original 2008 Pilot Study

The DNA microarray analysis of the white blood cells of three human participants (with a total of more than 191,961 data points for statistical analysis) was performed immediately before, within one hour after, and 24 hours after being administered the *CPGHE.* DNA microarray results on the three subjects in response in our original 2008 pilot study to the therapeutic protocol within one hour after the treatment indicated that expression of 15 early response genes were up-regulated between 1.2 and 1.8 folds and no gene was down-regulated. The list of the up-regulated genes in our original 2008 pilot study is presented in table one.

Table 1: The Modulation of Gene Expression in Human Leukocytes By a New Protocol for Optimizing Therapeutic Hypnosis and Psychotherapy, *"The Creative Psychosocial Genomic Healing Experience."* The Gene Bank Accession, Gene Symbol, Gene Description and results in fold changes in up-regulated gene expression within one hour in response to therapeutic hypnosis.

GB Accession	Gene Symbol	Gene Description	Fold Change
AK057104		Homo sapiens cDNA FLJ32542 fis, clone SMINT2000537 Sodium-coupled neutral amino acid transporter 2	1.778
NM_000329	RPE65	Retinal pigment epithelium-specific protein (65kD)	1.665
AK055997		Homo sapiens cDNA FLJ31435 fis, clone NT2NE2000612 Ring Finger protein 165	1.618
AK056729		Homo sapiens cDNA FLJ32167 fis, clone PLACE6000450 Serpin B Proteinase Inibitor	1.597
NM_001074	UGT2B7	UDP glycosyltransferase 2 family, polypeptide B7	1.579
BC018130	F2RL1	Coagulation factor II (thrombin) receptor-like 1	1.506
NM_030824	FLJ14356	Hypothetical protein FLJ14356 zinc finger protein 442	1.470
NM_021122	FACL2	Fatty-acid-Coenzyme A ligase, long-chain 2	1.381
NM_004126	GNG11	Guanine nucleotide binding protein 11	1.372
NM_020980	AQP9	Aquaporin 9	1.367
NM_001186	BACH1	BTB and CNC homology 1, basic leucine zipper transcription factor 1	1.331
NM_002921	RGR	Retinal G protein coupled receptor	1.312
NM_024911	FLJ23091	Hypothetical protein FLJ23091 G protein-coupled receptor 177 Isoform 1 and Isoform 2	1.275
NM_000860	HPGD	Hydroxyprostaglandin dehydrogenase 15 (NAD)	1.225
NM_002110	HCK	Hemopoietic cell kinase	1.191

While table one is a standard listing of the raw data of experience-dependent gene expression assessed via DNA microarrays as typically reported in the biological and medical literature, it would be a daunting challenge to understand its meaning and significance for the practioner of therapeutic hypnosis. While our uniform cohort of three highly susceptible hypnotic subjects were controlled for time of day (9:15 - 11:30am), therapist, and hypnotic technique (CPGHE), many other possible sources of genomic variation were a major limitation of this pilot study. A way of coping with some of these limitations is the application of bioinformatic software such as *Gene Set Enrichment Analysis (GSEA)*, which presents us with the rational for using it as a computational tool in conceptualizing a new paradigm for the research and clinical practice of therapeutic hypnosis at the molecular-genomic level.

A New Bioinformatic Paradigm of Therapeutic Hypnosis at the Molecular-Genomic Level

In this and the following sections we explore the bioinformatic theory, research, and practice of linking experience-dependent gene expression with the cognitive-behavioral phenotypes (observables), which are traditionally associated with therapeutic hypnosis. To create an appropriate context for understanding the significance of current bioinformatics we begin with a review of the historical conception of the ideo-plastic faculty in the theory and practice of therapeutic suggestion and hypnosis. We view this ideo-plastic faculty as complementary to the dissociative component of experimental hypnosis measured by the Stanford and Harvard Hypnotic Susceptibility Scales (Hilgard, 1965, 1977; Hilgard & Hilgard, 1975).

Theory: The Historical Ideo-Plastic Faculty of Therapeutic Hypnosis

Our proposed bioinformatic paradigm of therapeutic hypnosis finds its historical source in the pioneering works of Bernheim (1886/1957) and others who described the dynamics of therapeutic suggestion and hypnosis as follows.

> "The one thing certain is that a *peculiar aptitude for transforming the idea received into an act* exists in hypnotized subjects who are susceptible to suggestion. In the normal condition, every formulated idea is questioned by the mind. . . In the hypnotized subject, on the contrary, the transformation of thought into action, sensation, movement, or vision is so quickly and so actively accomplished, that the intellectual inhibition has no time to act. When the mind interposes, it is already an accomplished fact, which is often registered with surprise, and which is confirmed by the fact that it proves to be real, and no intervention can hamper it further. . .There is, then, *exaltation of the ideo-motor reflex excitability, which effects the unconscious transformation of the thought into movement, unknown to the will* . . . There is also, then, *exaltation of the ideo-sensorial reflex excitability, which effects the unconscious transformation of the thought into sensation, or into a sensory image.* . .The mechanism of suggestion in general, may then be summed up in the following formula: *increase of the reflex ideo-motor, ideo-sensitive, and ideo-sensorial excitability* . . . In the same way in hypnotism, the ideo-reflex excitability is increased in the brain, so that any idea received is immediately transformed into an act, without the controlling portion of the brain, the higher centers, being able to prevent the transformation" (p. 137-139, italics in the original).

The idea that hypnosis involved activity via an increase in "sensitivity" and "ideo-reflex excitability" was later described as the "ideo-plastic faculty" by Wetterstrand (1902) who presented the dynamics of therapeutic suggestion and hypnosis with these words.

> "The *ideo-plastic* idea, the suggestive theory, must be explained and how it is possible to dominate and cure pathological conditions by ideas and volition. They [patients]

must be told that no restraint is put upon them, that they are merely shown the way and that their present conditions [pathology] will change, not by any preponderance of another's will. But as the result of a proper effort to aid by using their own will. They are helped to develop the *ideo-plastic* faculty, whereby is meant the power that ideas possess to influence physical conditions, as, for instance, the production of cholera symptoms by fright, or by bleeding marks on hands and feet from profound and continued contemplation of or meditation upon the "Saviors" wounds. They are guided by word and thought without restraint, authority, and command. . . Suggestion, or, rather suggestibility, is composed of two elements: ability to receive an impulse from without, and the *ideo-plastic* faculty. As these are absolutely independent of each other, we must distinguish between them. There are patients, who are very impressionable, and who accept a suggested idea with absolute confidence; the influence, however, of the idea upon their physiological functions is feeble. They do not realize the suggestions, and their morbid symptoms yield with great difficulty, as their *ideo-plastic* conception is small. Others, on the contrary, accept suggestions slowly; they are incredulous and even resist them. Nevertheless, clinical therapy has repeatedly shown that physiological and pathological processes are often easily modified by the psychic influence, sometimes by auto-suggestions. Here, then, the suggestibility is undeveloped and small, being surpassed by the *ideo-plastic faculty*. . .

Above all, the methods in each particular case should be varied with proper guidance and moderation, not because the suggestibility is thereby increased, but because the *ideo-plastic* faculty is thus developed and placed under the influence of a will that knows and directs its tendencies. What we look for is, therefore, a slight receptivity for outside impulses and as great a centralization of psychic functions and the *ideo-plastic* capacity as possible. It is rare to find this combination, but it can be attained by training and education." (Quoted from Tinterow, 1970, pp. 534-537, Italics added here.)

These historical conceptions regarding the "peculiar aptitude for transforming the idea received into an act," "ideo-reflex excitability," and the "ideo-plastic faculty" as the basis of therapeutic suggestion and hypnosis were published approximately a century before our current understanding of "activity or experience-dependent gene expression and brain plasticity" in current neuroscience. From a *neuroscience* perspective "activity or experience-dependent gene expression" is a bridge over the so-called, "Cartesian gap" between body and mind, nature, and nurture. Experience-dependent gene expression and associated brain plasticity is the putative molecular-genomic mechanism underpinning a neuroscience model of the transformations of consciousness, cognition, and behavior observable in everyday life as well as the arts, sciences, and psychotherapy. Activity or experience-dependent gene expression and brain plasticity mediate psychobiological adaptation and creativity in coping with mind-body issues in health, psychosomatic medicine, and rehabilitation (Rossi, 1986/1993, 2002, 2004a, b, 2007).

Pioneering neuroscience research has documented how psychological experiences of novelty (Eriksson et al., 1998; Ribeiro et al., 2008), enrichment (Kempermann et al., 1997; Pinaud, 2004), and exercise (Gordon, Kollack-Walker, Akil, & Panksepp, 2002), *both mental and physical,* can facilitate immediate early and experience-dependent gene expression and brain plasticity (Guzowski, Setlow, Wagner, & McGaugh, 2001; Van Praag, Kemperman, & Gage, 1999, 2000; Van Praag, Schinder, Christie, Toni, Palmer, & Gage, 2002). Our activity-dependent protocol for therapeutic suggestion and hypnosis, the *CPGHE,* was constructed to facilitate these psychological experiences of novelty, enrichment, and exercise (mental

and physical) to optimize experience-dependent gene expression and brain plasticity generating new neurons. Current neuroscience research documents how these new neurons are not necessary for easy navigational tasks, but they are important for complex tasks that required new memory for finer distinctions in the cognitive-behavioral spatial organization of the environment and consciousness itself (Clelland et al., 2009). Experience-dependent profiles of gene expression associated with higher levels of neuronal activity and brain plasticity with broad implications for understanding the creative transformations of human consciousness, cognitive, and adaptive behavior has been noted by Cáceres et al. (2003).

> "Our results indicate that the human brain displays a distinctive pattern of gene expression relative to non-human primates, with higher expression levels for many genes belonging to a wide variety of functional classes. The increased expression of these genes could provide the basis for extensive modifications of cerebral physiology and function in humans and suggests that the human brain is characterized by elevated levels of neuronal activity" (p. 13030). . . Higher levels of neuronal activity are likely to have important consequences in cognitive and behavioral capacities, and of the genes up-regulated in humans" (p. 13034).

Likewise Nestler (2008) and Preuss, Càceres, Oldham, & Geschwind (2004) have discussed the implications of such research on the molecular-genomic level for understanding the evolution of the special qualities of human consciousness as follows.

> "Microarray analyses of gene-expression differences in humans and chimpanzees have allowed researchers to begin uncovering some of the changes that characterize human brain evolution at the molecular level, including the up-regulation (heightened activity) of many genes. Connecting these data to the critical phenotypes of interest, such as the emergence of language in humans, theory of mind and our particular susceptibility to certain neurological diseases, will require careful gene-by-gene research into the structural and functional context of the neural systems that underlie our remarkable human qualities" (p. 859).

This paper now reviews research with innovative bioinformatic software to assess how therapeutic hypnosis modulated experience-dependent gene expression during our original 2008 DNA microarray pilot study. What is the relevance of such bioinformatic research for the typical professional using psychotherapy and clinical hypnosis today? We propose that bioinformatic research will extend the cognitive-behavioral perspective and efficacy of evidence-based therapeutic hypnosis to include the molecular-genomic level, which is now the standard of clinical excellence recommended by Thomas Insel, the current director of NIMH (Insel, 2009, 2010).

Research: Bioinformatics Software, Gene Set Enrichment Analysis (GSEA)

Researchers at the Broad Institute of MIT have made freely available on the internet a highly innovative bioinformatic tool, *Gene Set Enrichment Analysis (GSEA)*, which generates meaningful information from DNA microarray data such as our initial pilot study. In contrast to methods based on single gene analysis (e.g. Lichtenberg, Bachner-Melman, Gritsenko, & Ebstein, 2000; Lichtenberg, Bachner-Melman, Ebstein, & Crawford, 2004), GSEA software detects changes in sets of genes that have been previously defined based on data from numerous microarray studies across a breadth of topics in biological research, exploring genome-wide gene expression in various functional, developmental, and disease states. GSEA is a computational method that determines whether a set of genes, typically defined by a DNA microarray

exploration of a biological or behavioral activity (such as our 2008 pilot study) shows statistically significant associations between two psychobiological states (e.g. phenotypes or observable states). These gene sets are used to track the biological pathways from the molecular-genomic levels to their phenotype levels of observable expression on the cognitive-behavioral level. This paper pioneers a new application of the GSEA bioinformatics software to therapeutic hypnosis. Details of the theory, research, and practice of bioinformatics via GSEA software for molecular biology may be found on its web site http://www.broadinstitute.org/gsea/ (Bild & Febbo, 2005). We extended the use of DNA microarrays and GSEA to explore the psychobiological underpinning of the ideoplastic processes of therapeutic suggestion and hypnosis.

Genes rarely, if ever, act alone to generate the complex functions of consciousness, cognition, and behavior that are the outcome of dynamic interactions between genomic and environmental factors in health and dysfunction. Current research, for example, is identifying thousands of relatively small single nucleotide polymorphisms (SNPs) and other variations in the DNA of patients with schizophrenia, that collectively add up to a third of the genetic risk (Sanders, 2009) with important associations to the major histocompatibility complex (MHC) of the immune system (see the special issue of Nature, 460 (7256, pp. 744-757). In bioinformatics the coordinated activity of many genes is described as "the functional concordance of co-expressed genes" (Eisen et al., 1998). Figure one illustrates GSEA's integration of the two basic operations required to identify the functional concordance of co-expressed genes with an observable cognitive-behavioral state such as therapeutic hypnosis. As portrayed in figure one, for example, GSEA identified the best match between (1) the checkered pattern of gene expression we actually found in our 2008 pilot study with (2) several thousand gene sets in the GSEA "Gene Set Database" that are associated with a variety of psychobiological processes. GSEA then automatically generates a diagram profiling an "Enriched Set" of genes. This enriched gene set identifies a complex psychobiological state, such as therapeutic hypnosis, that we can observe on the cognitive-behavioral level (Mootha et al., 2003; Subramanian et al., 2005). These GSEA enriched gene sets have been used to trace the epigenetic pathways between the environment and experience-dependent gene expression found in illness, rehabilitation, and health. Recent research, for example, has used epigenetic associations between hippocampal neurogenesis and neuropsychiatric disorders to unravel the role of the genome to understand the mind (Hsieh & Eisch, 2010, Petronis, 2010).

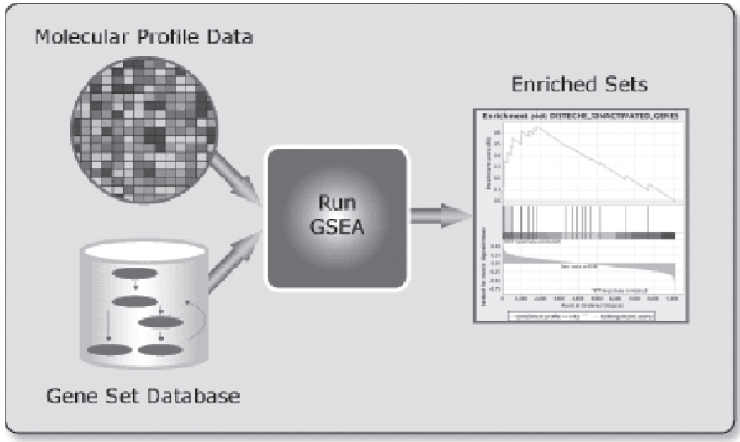


Figure 1: Gene Set Enrichment Analysis (GSEA)isa computational method that can be used to determine whether two sets of genes determined by experiment shows statistically significant differences between two different psychobiological states (e.g. phenotypes such as before and after therapeutic hypnosis in our original 2008 pilot study).

Table 2 illustrates the significant, positive association we observed between therapeutic hypnosis and the expression of gene sets related to the Zif-268 activity, an immediate-early gene (IEG) that functions as a transcription factor (early growth response; EGR 1,2,3,4), which is associated with adaptive brain plasticity evoked by experiences of novelty, memory, learning, and dreaming, etc. (Baumgartel et al., 2009; Guzowski et al., 2001; Ribeiro et al., 1999, 2002, 2004, 2007, 2008). The up-regulation of this Zif-268 related gene set is significantly associated with therapeutic hypnosis via the *CPGHE* at both 1 hour and 24 hours following the intervention.

Table 3 illustrates genes related to a "molecular-genomic signature" of the up-regulation of genes characteristic of stem cell growth and proliferation in the GSEA molecular database (HSC_MATURE_ADULT, Ivanova et al., 2002) that is positively associated with therapeutic hypnosis via the *CPGHE* at both 1 and 24 hours. In this study, we have looked at gene expression in white blood cells, rather than specifically stem cells, which live in the bone marrow. We are not observing the activation of stem cells directly, but we are seeing, in white blood cells (descendants of stem cells), the up-regulation of genes that are characteristic of stem cell growth and proliferation. This "molecular-genomic signature" of stem cells" is a pro-growth and pro-proliferative expression pattern, characteristic of stem cells and observable in perhaps a variety of stem cell descendants, including peripheral white blood cells.

Table 2: Genes associated with the immediate-early gene Zif-268 (early growth response 1; EGR 1, and related forms (EGR 2, 3, 4) are significantly associated with therapeutic hypnosis.

			1 HOUR			24 HOURS		
GENE SET	DESCRIPTION: Genes with promoter regions near transcription start sites…	# OF GENES	NES	NOM p-val	FDR q-val	NES	NOM p-val	FDR q-val
V$EGR_Q6	containing a motif matching annotation for EGR1, EGR2, EGR3	215	1.67	0.004	0.017	1.64	0.001	0.039
V$NGFIC_01	containing a motif matching annotation for EGR4: early growth response 4	196	1.55	0.010	0.045	1.54	0.014	0.066
V$EGR1_01	containing a motif matching annotation for EGR1: early growth response 1	203	1.51	0.008	0.063	1.49	0.006	0.095

Table 3 also illustrates genes from the GSEA molecular-genomic database involved in the cellular response to ionizing radiation and oxidative stress (UVC_HIGH_All_DN, Gentile et al., 2003) display a reversed pattern of expression in the context of therapeutic hypnosis at 1 and 24 hours. That is, the pattern of gene expression we observed following therapeutic hypnosis is opposite of that observed in cells subjected to ultraviolet C radiation. Additionally, genes from the GSEA database related to chronic inflammation (NING_COPD_UP, Ning et al., 2004) are down-regulated at 1 hour ($p = 0.013$) but not 24 hours ($p = 0.148$) after therapeutic hypnosis. These findings have face validity regarding our expectations of the ideo-plastic faculty of therapeutic hypnosis. These results are consistent with the concept that stress reduction and relaxation associated with therapeutic hypnosis reduces excessive activity and oxidative stress on the molecular level as well as some chronic immune system dysfunctions via the molecular mechanisms of psychoneuroimmunology (Ader, 2007).

Figure 2 illustrates the normalized values for changes in the DNA microarray expression of 15,508 genes within 1 hour and 24 hours of therapeutic hypnosis via our ideo-plastic protocol, the *CPGHE*. This correlation within each subject at 1 and 24 hours (Pearson's r coefficient > 0.80, $p < 0.001$) is a validity and reliability check of our DNA microarray data prior to analysis with the GSEA software.

Table 3: Genes characteristic of stem cell growth and proliferation in the GSEA molecular database are up-regulated, that is, positively associated with therapeutic hypnosis within 1 and 24 hours. Genes from the GSEA molecular database related to ultraviolet radiation, oxidative stress, and inflammation are negatively associated with therapeutic hypnosis within 1 hour.

			1 HOUR			24 HOURS		
GENE SET	DESCRIPTION	# OF GENES	NES	NOM p-val	FDR q-val	NES	NOM p-val	FDR q-val
HSC_MATURE_ ADULT	Up-regulated in mouse mature blood cells from adult bone marrow	290	1.62	0.001	0.151	1.84	0.001	0.001
UVC_HIGH_ ALL_DN	Down-regulated in fibroblasts following high-dose UVC	271	1.60	0.001	0.139	1.44	0.013	0.147
NING_COPD_ UP	Up-regulated in lung tissue of smokers with COPD	139	-1.63	0.013	0.231	-1.25	0.148	0.712

Figure 2: Normalized expression values for the change in the expression of 15,508 genes 1 hour and 24 hours after therapeutic hypnosis via our protocol, The Creative Psychosocial Genomic Healing Experience. Each data point represents the expression of a single gene. Gene expression at 1 hour and 24 hours is strongly correlated (Pearson's r coefficient > 0.80, $p < 0.001$).

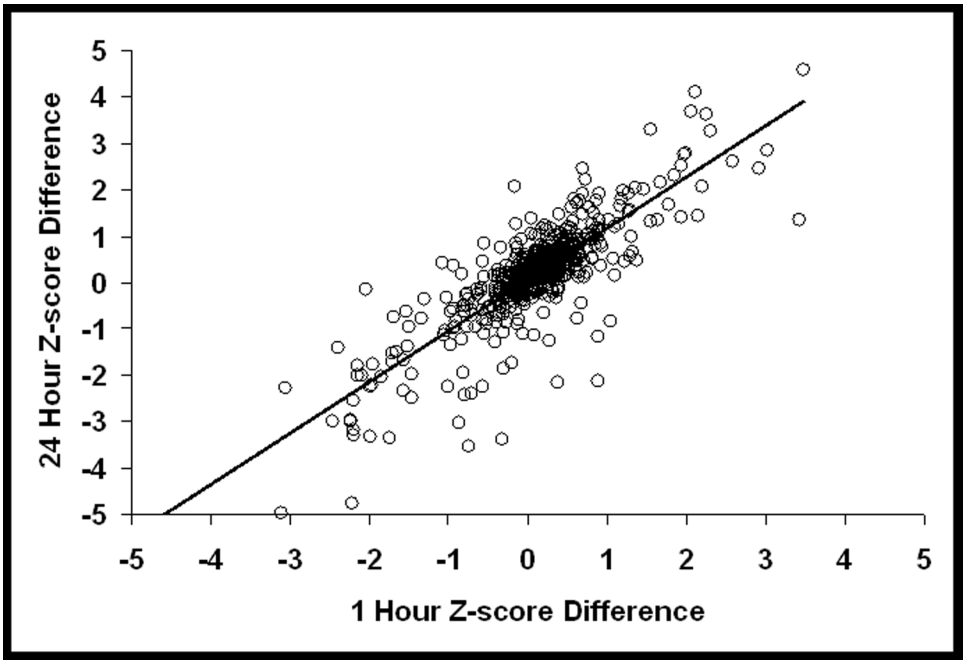


Figure 3 is a new type of scientific diagram characteristic of the GSEA bioinformatic computational software illustrating the intensity and dynamics of gene expression, which is explained in detail at http://www.broadinstitute.org/gsea/. Figure 3 illustrates how within 24 hours of administering the *CPGHE*, a GSEA gene set representing a molecular-genomic signature of the up-regulation of genes characteristic of stem cell growth and proliferation is positively correlated with therapeutic hypnosis. This finding appears to be a desired outcome of the ideo-plastic faculty of therapeutic hypnosis at the molecular-genomic level. This molecular-genomic signature for the up-regulation of genes characteristic of stem cell growth and proliferation, for example, could be associated with the molecular-genomic pathway for facilitating the rehabilitation of strokes and heart attacks (Ohtaki et al., 2008) as well as psychoneuroimmune system dysfunctions (Ader, 2007). The horizontal strip that looks like a financial bar code on the lower part of figure three actually marks the location of individual genes and their relative degree of expression in the in our original 2008 pilot study. Genes on the left side are over expressed and genes on the right are under expressed. Genes toward the center of this bar code are neither over or under expressed, implying that they are not modulated by the experimental variable of therapeutic hypnosis.

Figure 4 illustrates how genes associated with *cellular stress and damage by UVC radiation* in the GSEA molecular database are negatively associated with therapeutic hypnosis within 1 hour ($p < 0.001$) and 24 hours ($p < 0.013$) of therapeutic hypnosis with our protocol for the *CPGHE*. This certainly is a desirable outcome of the ideo-plastic processes of therapeutic hypnosis.

Figure 3: . Genes associated with a molecular signature of stem cell activation in the GSEA molecular database are positively associated with therapeutic hypnosis within 1 hour ($p < 0.001$, FDR < 0.151) and 24 hours ($p < 0.001$, FDR < 0.001). False discovery rate (FDR) is a new statistical method characteristic of research at the molecular-genomic level, which is used in multiple hypothesis testing to correct for multiple comparisons. The experience-dependent gene facilitation by therapeutic hypnosis was greater at 24 hours than at 1 hour (paired t-test $p < 0.0007$).

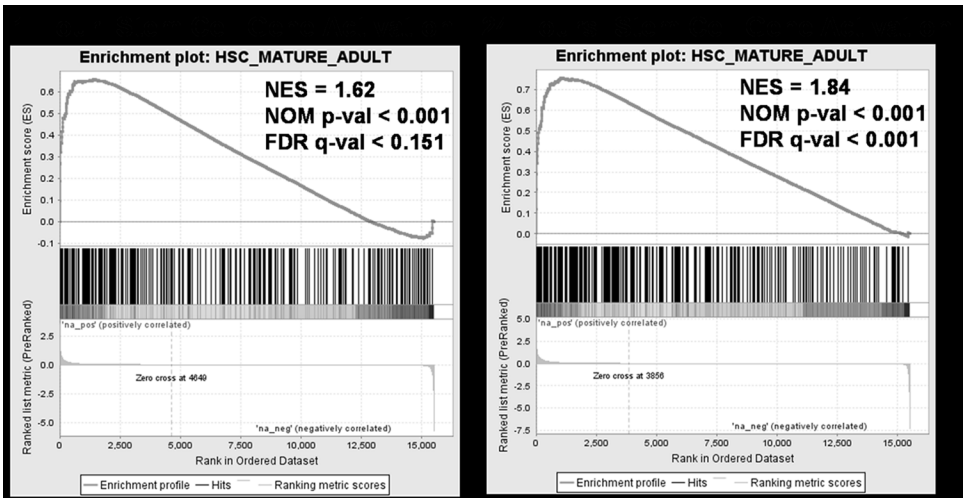


Figure 4: Genes associated with cellular stress and damage by UVC *radiation* in the GSEA molecular database are negatively associated with therapeutic hypnosis within 1 hour ($p < 0.001$, FDR < 0.139) and 24 hours ($p < 0.013$, FDR < 0.147) of treatment.

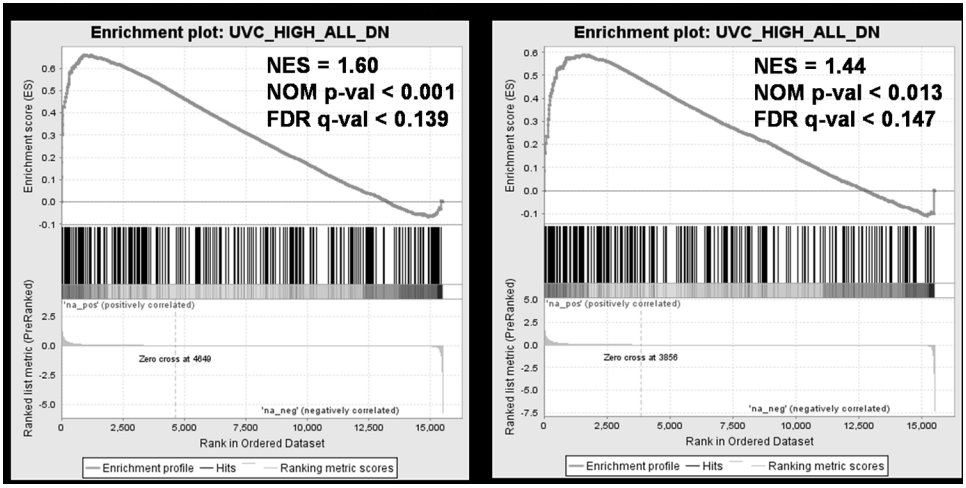


Figure 5 illustrates how genes related to *chronic inflammation* in the GSEA molecular database are negatively associated with therapeutic hypnosis via our protocol for the *CPGHE* within 1 hour ($p < 0.013$) but not within 24 hours ($p = 0.148$). The difference between the 1 hour and 24 hour is statistically significant (paired t-test $p < 0.013$). This desirable outcome of reducing chronic inflammation for at least 1 hour via the ideo-plastic faculty of therapeutic hypnosis apparently does not extend for 24 hours. Further research will be needed to replicate the range and limitations of this important finding with various clinical populations.

Figure 5: Genes corresponding to chronic inflammation in the GSEA molecular database are negatively associated with therapeutic hypnosis within 1 hour (p < 0.013, FDR < 0.231) but not within 24 hours (p = 0.148, FDR < 0.712). The difference between the gene set enrichment at 1 hour and 24 hours is statistically significant (paired t-test p < 0.013).

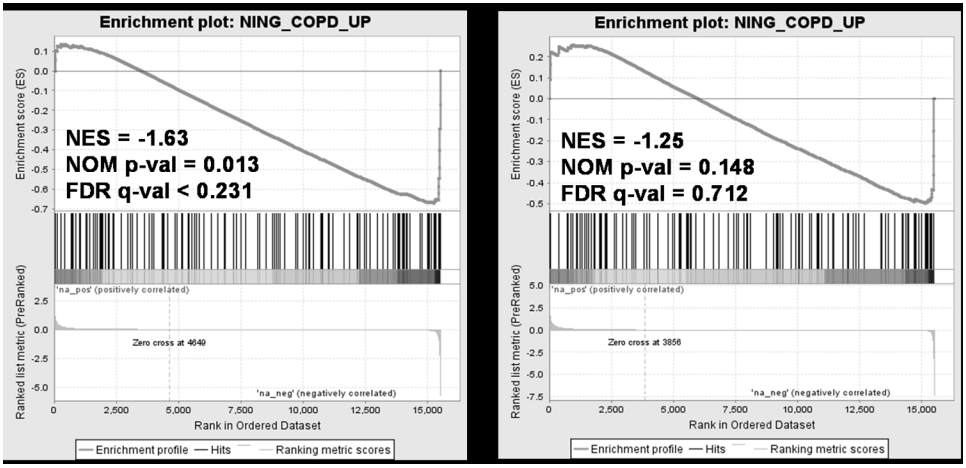
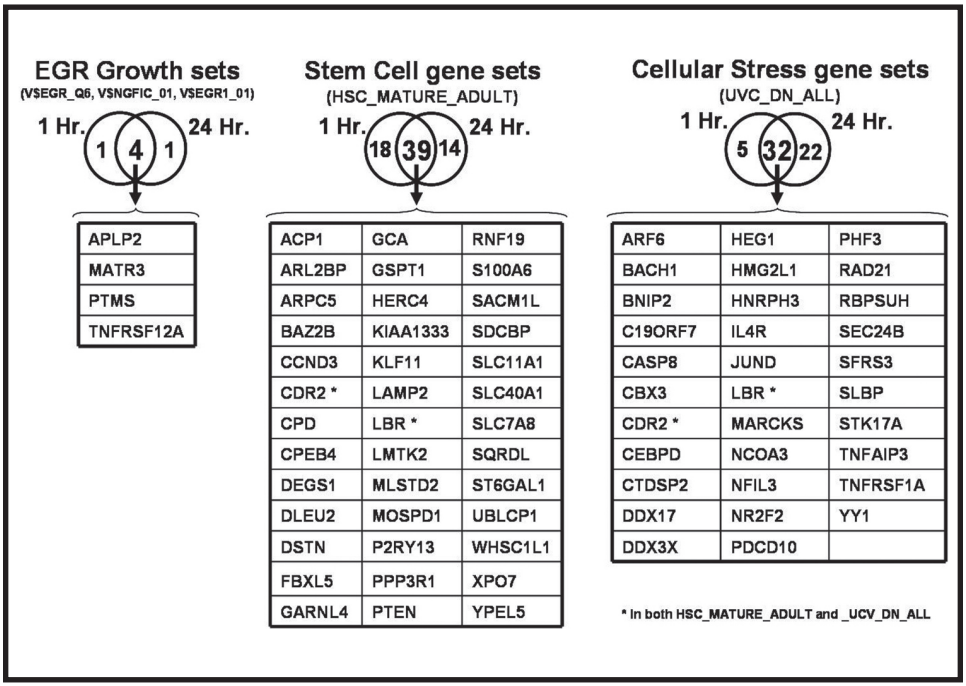


Figure 6 illustrates Venn diagrams of the logic of the beta version of our proposed molecular-genomic signature of therapeutic hypnosis via our new protocol the Creative Psychosocial Genomic Healing Experience (CPGHE), which is freely available at http://www.ernestrossi.com/ernestrossi/Neurosciencesearchgroup.html. Students, researchers, and therapists with basic skills in working with spread sheets on computers can now do original research investigating the molecular-genomic underpinnings of therapeutic hypnosis and related psychological states with little expense using free bioinformatics software such as Gene Set Enrichment Analysis (GSEA) at http://www.broadinstitute.org/gsea and the Database for Annotation, Visualization and Integrated Discovery (DAVID) at http://david.abcc.ncifcrf.gov/." 73 experience-dependent genes were identified from GSEA's molecular-genomic database for their relationship to dynamic cellular processes involved in (1) plasticity associated with memory, learning, novelty, dreaming, etc., (2) molecular-genomic signature of the up-regulation of genes characteristic of stem cell growth associated with mind-body healing and rehabilitation, and (3) stress reduction.

Figure 6: Venn diagrams of a beta version of our proposed molecular-genomic signature of therapeutic hypnosis.



APLP2
MATR3
PTMS
TNFRSF12A

ACP1	GCA	RNF19
ARL2BP	GSPT1	S100A6
ARPC5	HERC4	SACM1L
BAZ2B	KIAA1333	SDCBP
CCND3	KLF11	SLC11A1
CDR2 *	LAMP2	SLC40A1
CPD	LBR *	SLC7A8
CPEB4	LMTK2	SQRDL
DEGS1	MLSTD2	ST6GAL1
DLEU2	MOSPD1	UBLCP1
DSTN	P2RY13	WHSC1L1
FBXL5	PPP3R1	XPO7
GARNL4	PTEN	YPEL5

ARF6	HEG1	PHF3
BACH1	HMG2L1	RAD21
BNIP2	HNRPH3	RBPSUH
C19ORF7	IL4R	SEC24B
CASP8	JUND	SFRS3
CBX3	LBR *	SLBP
CDR2 *	MARCKS	STK17A
CEBPD	NCOA3	TNFAIP3
CTDSP2	NFIL3	TNFRSF1A
DDX17	NR2F2	YY1
DDX3X	PDCD10	

* In both HSC_MATURE_ADULT and _UCV_DN_ALL

Discussion

Bioinformatics of the ideo-plastic faculty of therapeutic suggestion and hypnosis

Since our original 2008 pilot study of the bioinformatics of the ideo-plastic faculty of therapeutic hypnosis had only 3 subjects cross validation is now required with more subjects with a variety of diagnostic classifications to document the validity, reliability, and limitations of using DNA microarrays and bioinformatics to assess the value of therapeutic suggestion and hypnosis via the *CPGHE*. At this point we prefer to refer to our proposed "molecular-genomic signature of suggestion and therapeutic hypnosis" as a temporary *beta version* until it is replicated by independent research groups. It will require further assessment by students and researchers who are able to compare our results with a similar DNA microarray and bioinformatic methodology (figure 1) to update the traditional measures of hypnosis such as the Stanford Scale of Hypnotic Susceptibility (Hilgard, 1965, 1977), The Harvard Group Scale of Hypnotic Susceptibility (Shor & Orne, 1962), and The Hypnotic Induction Profile (Spiegel & Spiegel, 1978). We hypothesize that these well documented scales, with their stronger emphasis on the *dissociative component* of hypnosis rather than the *ideo-plastic* processes of *The Creative Psychosocial Genomic Healing Experience*, would identify different molecular-genomic signatures.

This bioinformatic process of identifying the molecular-genomic signatures of psychological states of consciousness as well as diagnostic classifications assessed by clinical interview and self-report inventories is more general than the limited scope of this paper's focus on the ideo-plastic process of therapeutic hypnosis. Integrative, translational research now is required to document the efficacy of the molecular-genomic approach (Nestler, 2008) to define and differentiate between the biological underpinnings of stress, trauma, and PTSD (Yehuda et al., 2009) and the ameliorating responses of therapeutic hypnosis in mind-body medicine (Cuadros & Vargas, 2009). We propose that the deep psychobiological correlates of many classical hypnotic phenomena such as *dissociation* (agnosia, amnesia, etc.) and the *ideo-plastic faculty* (ideosensory, ideomotor, ideodynamic, etc.) could be conceptualized and measured more precisely on the molecular-genomic and bioinformatic level of human individuality (Whitney et al., 2003).

There is as yet no comprehensive program of research investigating psychotherapy and therapeutic hypnosis via the methodology of DNA microarrays and bioinformatic analysis illustrated in this paper. This may be part of the reason why the National Institutes of Health (NIH) and the National Institute of Mental Health (NIMH) are limiting funding for psychosocial research on a purely cognitive-behavioral level without regard for the fundamentals of mental illness on molecular-genomic level (Holden, 2004; Kaiser, 2004, 2009).

The lack of a firm molecular-genomic foundation for therapeutic suggestion and hypnosis also could be related to the recent American Medical Association's (AMA) concern about the American Society of Clinical Hypnosis (ASCH) and the Society of Clinical and Experimental Hypnosis (SCEH) making the inaccurate statement that hypnosis is approved by the AMA as a legitimate therapy for medical or psychological purposes.

We therefore proposed the formation of an International Psychosocial and Cultural Bioinformatics Project to coordinate integrative psychobiological insights on the role of activity and experience-dependent gene expression and brain plasticity in facilitating translational research with therapeutic suggestion and hypnosis (Rossi, E., Rossi, K., Yount, Cozzolino & Iannotti, 2006). The number of activity and experience-dependent genes that are linked to psychosocial activities, mental illness, psychological health, and resilience is

unknown at the present time. Extensive exploration of the DNA microarray and bioinformatic model of psychological adaptation, mental illness, and psychotherapy will be required to fully answer the question of whether it can contribute to a new epigenetic and psychosocial genomic paradigm for clinical practice of therapeutic hypnosis.

Summary

This selective review emphasizes that therapeutic hypnosis is an ideo-plastic aptitude for transforming an idea into an act in receptive subjects. The idea that therapeutic hypnosis involves an *increase in "sensitivity" and "ideo-reflex excitability"* has been described as its ideodynamic or *"ideo-plastic faculty."* We explored an emerging bioinformatic theory, research, and practice of linking epigenetic, experience-dependent gene expression and brain plasticity with the positive experiences we traditionally associate with therapeutic hypnosis. We proposed that such bioinformatic theory and research will extend the cognitive-behavioral perspective and efficacy of evidence-based therapeutic hypnosis to include the molecular-genomic level, which is the current standard of clinical excellence being promoted by the NIMH. We documented how we can measure changes in activity or experience-dependent gene expression (1) over relatively brief time periods (1 hour and 24 hours) following (2) a single experience of therapeutic hypnosis (about 1 hour). This ideo-plastic process of therapeutic hypnosis was associated with (1) the heightening of a molecular-genomic signature for the modulation of experience-dependent gene expression characteristic of stem cell growth, (2) a reduction in cellular oxidative stress, and (3) a reduction in chronic inflammation. We propose these three empirical associations as an initial beta version of the molecular-genomic signature of the ideo-plastic process of therapeutic hypnosis via the *CPGHE*, which can serve as a practical guide for the professional practice of psychotherapy and clinical hypnosis.

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