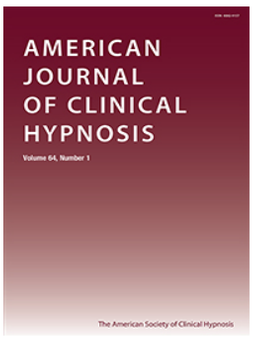

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The psychosocial genomics paradigm of hypnosis and mind–body integrated psychotherapy: experimental evidence

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ABSTRACT

The psychosocial genomics paradigm first proposed by Ernest Rossi established an epistemological shift in our application of hypnosis. We present original experimental research conducted within this paradigm that highlights the mind–gene relationship and, in particular, the positive health effects associated with hypnosis and mind–body integrated psychotherapy. We document that these approaches can stimulate epigenetic modifications and the expression of genes related to anti-inflammatory processes. These strategies strengthen the immune system and reduce oxidative stress both in normal and in oncological participants.

KEYWORDS

Hypnosis; mind–body therapy; mind–body transformations therapy; neuroscience; psychosocial and cultural genomics; psychotherapy

The epistemological contribution that psychosocial genomics (PSG) has made to the psychological, medical and biological community is of inestimable value. PSG was born in 2002 with the extraordinary text *The Psychobiology of Gene Expression* by Ernest Lawrence Rossi in which his theory is spelled out for the first time in a complete way (Rossi, 2002). For the clinicians and researchers at the International Research Laboratory on Psychosocial Genomics, Experimental and Clinical Hypnosis and "Ernest Rossi" Translational Neuroscience at the University of Salerno (Italy) it is a great honor to provide an evidentiary basis for PSG.

A biographical narrative of a paradigm

Psychosocial genomics (PSG) is the science of how sensory, psychological, social, and cultural signals and stressors modulate gene expression and vice versa within the psychobiology of health and illness. We can speculate on PSG from biographical perspective. PSG originated in Rossi's drive to seek a dialogue between opposites and in his deep desire to come to terms with his tormented belonging to two worlds – the Italian one of family and origins and the American one, with all the fractures and contradictions he faced since birth (Rossi, 2021). Already in adolescence, Rossi engaged in comprehensive study in biology, chemistry, philosophy, meditation, and yoga. He had an extraordinary capacity for dialogue and synthesis, which allowed him to integrate such diverse disciplines, and this quality pervaded his entire *oeuvre*. Among Rossi's extraordinary characteristics were his capacity for inner searching for its own sake, always approaching some completion, lasting throughout his life.

At the beginning of the 1960s, Rossi completed a doctorate with Franz Alexander, one of the fathers of psychosomatics. Together with Ferenczi, Alexander developed the concept of

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"corrective emotional experience" (Alexander, 1948) in which the process of therapy involves re-exposing the patient to emotional situations to repair the traumatic influences of the past.

Rossi's encounter with Erickson in the early 1970s had a profound impact on his personal and professional life. Rossi speculated that the utilization of expectancy and surprise in the neuro-psycho-physiological approach of Milton Erickson could generate detectable changes in the dynamics of gene expression and neurotransmission. It was at his last working session with Erickson, right before his death in 1980, that Rossi had the intuition that many years later would give shape to *The Psychobiology of Gene Expression*.

It was in 2002 that a close scientific collaboration between Italy and the United States began. This led to the formation of the International Psychosocial Genomic Team (2006) under the guidance of Ernest and Kathryn Rossi (https://sites.google.com/a/unisa.it/psg-lab/). The interdisciplinary work of psychologists, doctors, geneticists, bioinformaticians, statisticians, and the foundation in 2012 of the International Research Laboratory on Psychosocial Genomics, Experimental and Clinical Hypnosis and Translational Neuroscience Ernest Rossi (PSG Lab) at the University of Salerno in Italy enabled research yielding significant experimental evidence on the reciprocal influence of body and mind that continues to the benefit the international scientific community.

The PSG Lab, directed by Mauro Cozzolino, was the first university research laboratory in the world dedicated to studying the paradigm of PSG in relation to psychotherapy, hypnosis, personal development, and well-being. Subsequently, in 2014, with the Rossis, we founded *The International Journal of Psychosocial Genomics, Health & Consciousness Research* (www.psychosocialgenomics.com), the first international journal dedicated exclusively to this approach. The journal welcomes theoretical and research contributions by scholars from all over the world and currently has contributors from four different continents. Our personal contribution to the PSG paradigm of hypnosis was the experimental verification of the clinical efficacy of the protocols developed by the Rossis.

The psychosocial genomics paradigm

It has been widely documented that genes interact with the environment to modulate behavior and cognition in disease and health conditions through complex mechanisms that regulate their activity (Hsieh & Eisch, 2010). Furthermore, it was demonstrated that these interactions involve a particular class of genes, often defined as activity genes or experience-dependent genes. These genes that are activated – in the process of perceiving (consciously and non-) – by signals from the psychosocial and physical environment modulate complex physiological and psychological functions of the body (Lloyd & Rossi, 2008; Rossi, 2002, 2004). Psychosocial stressors seem to have a dynamic and experience-dependent effect on genomic expression through the involvement of numerous interrelated circuits including the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, and the messengers of the immuno-inflammatory responses (e.g., corticosteroids, cytokines). Ultimately, these pathways convey psychosocial stress via ligands to cell receptors that mount a cumulative pressure to change genomic expression (Morita et al., 2005).

The paradigm of PSG promotes an integrated perspective of the individual in which therapeutic interventions can be evaluated on the basis of their ability to alter gene-expression that is related to psychosocial and disease-specific stressors (Celia & Cozzolino, 2021; Rossi, 2010).

By "stressors" we mean any factor that immediately recalls neuropsychological, socio-emotional, locomotor, hormonal, and immunological regulatory reactions. Based upon empirical studies, Rossi distilled and refined Erickson's strategic approaches such that the main aspect of the therapy is the utilization of the natural biological rhythm (chronobiology) of the patient to activate body-mind healing processes (Rossi & Rossi, 2008). Rossi thereby opened a new way to conceive of psychotherapy through rigorous scientific study of the intuitions of Erickson. In collaboration with the authors, new technologies allowed for the development of new research areas in the neurosciences and genomics (Celia & Cozzolino, 2021; Cozzolino & Celia, 2016; Cozzolino et al., 2015; Cozzolino, Guarino, Castiglione, Cicatelli, & Celia, 2017; Rossi, 2009).

The specificity of Rossi's approach accesses human functioning on a multisystemic level – molecular-genomic, hormonal, neural, and experiential. This exceeds the traditional and obsolete dualism between mind and body. Both disease and health can be understood from multiple interlacing aspects. Therapy is framed in the light of the principle of biologic utilization of natural rhythms (Cozzolino & Celia, 2016). This principle allows the facilitation of genomic expression, plasticity, and a new level of consciousness, optimizing the problem-solving processes of daily life, promoting resilience and stimulating employment of useful resources for health, healing, and rehabilitation.

Foundations of psychosocial genomics' scientific evolution

Since the first meeting with Ernest and Kathryn Rossi in 2002 until today, our collaboration has pursued a series of developing objectives:

(1) To realize experimental research that could support the epistemological premises of the PSG paradigm and demonstrate the hypothesis that body-mind integrated psychotherapy could provoke positive changes into health-related gene expression.
(2) To translate the PSG paradigm into evidence-based clinical protocols.
(3) To prove the efficacy of Mind–Body Transformations Therapy (MBT-T) in prevention and treatment of Parkinson's disease and breast cancer.

The main studies, led by us to respond to the objectives mentioned above, will be presented below.

An international psycho-social and cultural genomics project for psychotherapy and hypnosis (2006)

In 2006, we proposed (Rossi, Rossi, Yount, Cozzolino, & Iannotti, 2006a) the formation of an International Psycho Social and Cultural Genomics Project (IPCGP) to explore the research foundations of integrative medical insights on all levels from the molecular-genomic to the psychological, cultural, social, and spiritual. Just as The Human Genome Project had identified the molecular foundations of modern medicine with the new technology of sequencing DNA, we hypothesized the IPCGP would extend and integrate this neuroscience knowledge with the technology of gene expression via DNA/proteomic microarray research and brain imaging. Our goal was to show the functioning mechanisms

of stress-modulation by chronicling its role in diseases, healing, rehabilitation, psychotherapy, and hypnosis.

We anticipated that the IPCGP would require a particular international collaboration of academic institutions, researchers, and clinical practitioners for the creation of a new neuroscience of mind–body communication, brain plasticity, memory, learning, and creative processing during optimal psychosocial experiential states. We have created an international research group with the University of Salerno and the Milton Erickson Institute of Central California known as the International Psychosocial Genomics Research Team with the aim of studying the complexity of the interactions between mind–body–gene, nature, and nurture: the phenomenological and the physiological. The central challenge of the group, as stated by Kiberstis and Roberts (2002), is that

> The genes that contribute to complex disease are notoriously difficult to identify because they typically exert small effects on disease risk; furthermore, the magnitude of their effects is likely to be modified by other unrelated genes as well as by the environment factors.. . . With integrated and coordinated approaches efforts of researchers in different disciplines, there is plenty of room for optimism. (p. 685)

The standard approach of modern medicine, the so-called "bottom-up approach," which starts from biomolecular mechanisms, tries to explain every aspect of the functioning of our organism, from genomic, proteomic, physiological, to psychological. Many integrative, complementary, and holistic approaches, on the contrary, typically use a "top-down approach" to enter in the cycle of functioning at the highest level, from the mind, to try to explain the modulation of physiological processes (sympathetic/parasympathetic balance, etc.) and possibly the lower levels, i.e., those of genomic and proteomic expression. We, on the other hand, were convinced that both of these perspectives have highlighted an important part of our functioning but have fallen into the trap of reductionism. We proposed that the top-down approach of integrative medicine and the classic bottom-up approach of modern molecular medicine had to be transactional by exploring the dialogue between psychological experiences and gene expression, protein synthesis and physiological functioning.

We developed several lines of research – both basic and applied – to respond to one of the most important challenges to which we are called as researchers and clinicians: translating new findings into effective strategies of prevention, diagnosis, and therapy. Perhaps the most compelling and mysterious for each of us was *How is healing evoked from top-down and bottom-up perspective*? and more, *How can this be achieved through psychotherapy and hypnosis*?

Preliminary experiments psycho social genomics on "how the mind can heal the mind through psychotherapy and hypnosis" (2008)

By 2008, DNA microarray technology had made it possible to measure the expression levels of many thousands of genes simultaneously. This new experimental approach was revolutionizing molecular biology research and becoming a new standard in personalized medicine (Eisen, Spellman, Brown, & Botstein, 1998). Therefore, we thought that such an innovative and complex method of analysis could also be used in the field of psychotherapy and hypnosis (Rossi et al., 2008, 2006a). To answer some questions about the possible dialogue between mind and genes and its use in psychotherapy and hypnosis, we carried out a first pilot study (Rossi et al., 2008).

This study evaluated the hypothesis that a positive experience could modulate gene expression at the molecular level. In this pilot study, we evaluated DNA microarrays of participants who underwent hypnosis using a new therapeutic protocol "The Creative Psychosocial Genomic Healing Experience (CPGHE)" that was born from the interaction between Ericksonian hypnosis, Jungian psychotherapy, translational neuroscience and genomics (Cozzolino, Cicatelli, et al., 2015). In the CPGHE, a subject is guided through a standardized four-stage creative process via an activity-dependent mirroring hands technique to measure ideo-plastic healing and assess its molecular-genomic impact (Rossi, Cozzolino, Mortimer, Atkinson, & Rossi, 2011).

Pioneering neuroscience research has documented how psychological experiences of novelty (Eriksson et al., 1998), enrichment (Kempermann, Kuhn, & Gage, 1997), and exercise (Gordon, Kollack-Walker, Akil, & Panksepp, 2002), both mental and physical, can facilitate immediate early and experience-dependent gene expression and brain plasticity. 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 to generate new neurons. We expected that it could enhance a wide range of therapeutic approaches such as therapeutic hypnosis, psychotherapy, and rehabilitation (Rossi & Rossi, 2008). To carry out this first pilot study, we recruited three participants (two men and one woman) whose blood was taken before treatment, 1 hour after treatment, and 24 hours after treatment. DNA microarray data analysis was conducted on the white blood cells of each sample.

At the end of the data analysis, although there were methodological limitations of the study (the limited number of participants and the lack of a no-treatment control group), the results indicated that the CPGHE was able to produce a very deep mind–body activation of the participants involved so as to generate the up-regulation of 15 early response genes immediately after the treatment. After 24 hours, the expression of early response genes started previously after the first treatment appeared to initiate a larger gene expression cascade that presented with a difference in gene expression compared to pretreatment in at least 77 genes.

This provided early evidence, pending confirmation, of the mind/gene relationship in the context of therapeutic and hypnotic practice. As a result of this study, we hypothesized that the genes expressed in response to this new protocol could be related to a variety of functions associated with stress, cognition, dreams (Ribeiro et al., 2007) as well as psychiatric conditions (Tsankova, Renthal, Kumar, & Nestler, 2007).

Despite the limitations, this pilot study was unique because most of the previous genomic research was done with animals for biological and medical research. We had opened a frontier by analyzing new models of bioinformatics, epigenetic analysis of therapeutic hypnosis and psychotherapy through the use of DNA technology with human participants (Rossi et al., 2006a).

A new bioinformatics and psychosocial genomics paradigm of therapeutic hypnosis: first experimental evidence of mind–genes dialogue through hypnosis (2010)

In 2010 (Atkinson, Iannotti, Cozzolino, Castiglione, Cicatelli, Vyas, Mortimer, Hill, Chovanec, Chiamberlando, Cuadros, Virot, Kerouac, Kallfass, Krippner, Frederick, Gregory, Shaffran, Bullock, Soleimany, Rossi, Rossi & Rossi), we stated that epigenetics was 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). Furthermore, research had demonstrated that complex epigenetic mechanisms

regulate gene activity without altering the DNA code (Tsankova et al., 2007). This epigenetic modification occurred especially with those activity- or experience-dependent genes that we previously described as sensitive to signals from the physical and psychosocial environment that modulate the complex functions of physiology and psychology (Lloyd & Rossi, 2008).

In 2010, we used bioinformatics software to explore the possible mind–body significance of the genomic effects from the 2008 pilot study. We used an innovative tool that researchers at the Broad Institute of MIT had made available on the Internet known as Gene Set Enrichment Analysis (GSEA), which was able to generate meaningful information from the DNA microarray data. Unlike methods based on the analysis of a single gene (Lichtenberg, Bachner-Melman, Ebstein, & Crawford, 2004), GSEA software detects changes in previously defined gene sets based on data from numerous microarray studies on a wide range of topics in biological research, exploring gene expression of the whole genome in various functional, evolutionary, and pathological states. Aware that genes rarely act alone to generate the complex functions of consciousness, cognition, and behaviors that are the result of dynamic interactions between genomics and the environment, we extended the use of DNA microarrays and GSEA to better explore the psycho-genomic basis of therapeutic hypnosis. The GSEA found the best match between the gene expression patterns that we found in our 2008 pilot study with several thousand gene sets in the GSEA "Gene Set Database" associated with a variety of psychobiological processes. This offered a pioneering insight into the use of bioinformatics software such as GSEA in therapeutic hypnosis.

The research illustrated the significant and positive association we observed between therapeutic hypnosis and the expression of sets of genes related to Zif-268 activity, an immediate-early gene (IEG) which functions as a transcription factor (early growth response; EGR 1,2,3,4), which is associated with adaptive brain plasticity evoked by experiences such as novelty, memory, learning, and dreaming (Baumgartel et al., 2009; Ribeiro, Simões, & Nicolelis, 2008). The research showed that the genes were related to a molecular genomic signature of upregulated genes characteristic of stem cell growth and proliferation in the GSEA molecular database (Ivanova et al., 2002) which is positively associated with therapeutic hypnosis through CPGHE at both 1 and 24 hours.

In this study, we looked at gene expression in white blood cells, rather than specifically in stem cells, which live in bone marrow. We weren't looking directly at stem cell activation, but we were seeing, in white blood cells (descendants of stem cells), the upregulation of genes that are characteristic of stem cell growth and proliferation. This molecular-genomic signature of stem cells is an advanced and pro-proliferative expression pattern, characteristic of stem cells and observable in possibly a variety of stem cell descendants, including peripheral white blood cells (Atkinson et al., 2010)

In addition, the study also illustrated the genes of the ECG genomic-molecular database involved in cellular response to ionizing radiation and oxidative stress (Gentile, Latonen, & Laiho, 2003) showed an inverted expression pattern in the context of therapeutic hypnosis at 1 and 24 hours. The gene expression pattern we observed after therapeutic hypnosis was opposite to that observed in cells subjected to ultraviolet-C radiation. Also, genes from the GSEA database related to chronic inflammation (Ning et al., 2004) were downregulated 1 hour after therapeutic hypnosis ($p = .013$). These results were consistent with the concept that stress-reduction and relaxation achieved through therapeutic hypnosis reduced excessive activity and oxidative stress at the molecular level as well as some chronic immune system dysfunctions through the molecular mechanisms of psychoneuroimmunology

(Ader, 2007). Normalized values for changes in DNA microarray expression of 15,508 genes within 1 and 24 hours of therapeutic hypnosis through the CPGHE, showed a correlation within each participant at 1 and 24 hours (Pearson's r coefficient > 0.80, $p < .001$).

Experience-dependent genes identified from the GSEA genomic-molecular database suggested that the ideo-plastic process of therapeutic hypnosis may be associated with (1) the enhancement of a genomic-molecular signature for the upregulation of genes characteristic of stem cell growth; (2) a reduction in oxidative stress; and, (3) a reduction in chronic inflammation. In this study (Atkinson et al., 2010), we hypothesized that these three empirical correlations could be considered as an initial beta version of the genomic-molecular signature of the ideo-plastic process of therapeutic hypnosis, thus integrating the excessively linear cognitive-behavioral description of therapeutic suggestion, hypnosis, and psychotherapy.

This finding is consistent with a beneficial outcome of therapeutic hypnosis at the molecular-genomic level. From this we can posit that many classic hypnotic phenomena such as dissociation (agnosia, amnesia, etc.) and the ideo-plastic faculty (ideosensory, ideomotor, ideodynamic, etc.) could be measured more precisely at the level of molecular genomics (Whitney et al., 2003). The number of genes and their patterns of activity correlating with individuals' experiences in psychosocial activities, mental illness, psychological health, and resilience are currently unknown. In the light of this early evidence, it is clear that extensive bioinformatics exploration of mind–body functioning and of mental illness would be required to fully answer the question of how a new epigenetic and psychosocial paradigm can contribute to enhance clinical practice and therapeutic hypnosis.

More experimental data supporting the mind–gene relationship and the use of the psychosocial genomics paradigm in group hypnosis and psychotherapy (2015)

Our next level of investigation aimed to increase the number of participants in order to verify if the mind–gene interaction correlates that were previously obtained when the clinical protocols developed in the PSG paradigm were applied in groups.

For this research (Cozzolino, Cicatelli et al., 2015), we hypothesized changes in gene expression after a single Mind–Body Healing Experience (MHE) as for the previous studies. The MHE was a new version of the previous CPGHE protocol. It is a shorter and easier version to apply.

The MHE study was conducted on a single group of 18 participants. Peripheral blood collected just before and immediately following administration of the MHE. Changes in experience-dependent gene expression over 1 and 24 hours were assessed through microarray analysis. After 1 hour, 46 genes were differentially expressed, and after 24 hours, 154 genes were differentially expressed. Thus overall, a total of 200 genes were differentially expressed (>1.2-fold, $p < .05$). The bioinformatic analysis was performed by Gene Ontology (GO) term enrichment. It is a technique for interpreting sets of genes in which the genes are assigned to a set of predefined bins depending on their functional characteristics. The output of the analysis is typically a ranked list of GO terms, each associated with a p-value. Bioinformatic analysis revealed four significantly enriched GO term pathways (p-value <0.05): acetylation, cytosol, regulation of cell death, and negative regulation of apoptosis (cell death).

Parkinson's disease as multisystem disorder: new clinical and experimental findings with psychosocial genomics paradigm of psychotherapy and hypnosis

The next study (Cozzolino, 2016) had two goals. The first was more theoretically focused on more integrated forms of clinical intervention for Parkinson's Disease (PD) as a multisystemic disorder. The second was to determine if the CPGHE would result in a downregulation of SNCA gene expression in participants who were not affected by PD. SNCA is considered, among other specific genes, causative of monogenic manifestations of PD codes for the alpha-synuclein protein. Dysfunctions of the SNCA gene are known to be associated with autism, schizophrenia, Parkinson's disease, Alzheimer's disease, alcoholism, aging, and stress-related dysfunctions. Although the function of alpha-synuclein is not well understood, studies suggest that it plays a role in restricting the mobility of synaptic vesicles, consequently attenuating synaptic vesicle recycling and neurotransmitter release.

SNCA may help regulate the release of dopamine, a type of neurotransmitter that is critical for controlling the start and stop of voluntary and involuntary movements. At least 18 mutations in the SNCA gene have been found to be associated with Parkinson's disease. It is unclear how alterations in SNCA gene expression are related to Parkinson's disease, but it is known that misfolded or excess alpha-synuclein proteins may cluster together and impair the regulation of dopamine in specific regions of the brain. The excess alpha-synuclein protein is related to increased expression of SNCA mRNA levels in dopaminergic neurons (Gründemann, Schlaudraff, Haeckel, & Liss, 2008). The loss of dopamine regulation weakens communication between the brain and muscles (Braak et al., 2003).

The research was conducted on participants who were not affected by PD. The most surprising thing was that among the genes that expressed themselves differently, the SNCA gene was downregulated much more than all the others. This study (Cozzolino, Tagliaferri, et al., 2015) experimentally documented how the SNCA gene was highly and stably down-regulated in lymphocytes of the human peripheral immune system within 1 and 24 hours after treatment with the CPGHE. In our study, the more frequently represented biological pathway was related to regulation of apoptosis: negative regulation (13 genes), regulation of

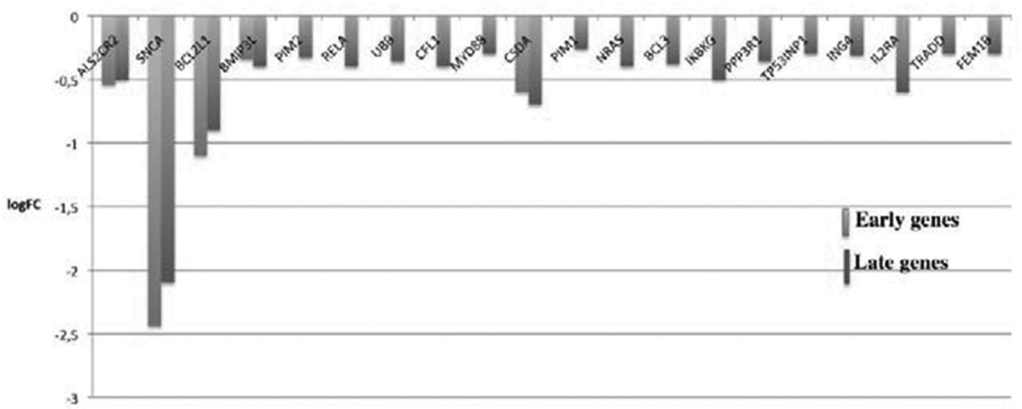

Figure 1. The MHE protocol regulates the SNCA gene expression.

apoptosis (20 genes) and anti-apoptosis (9 genes). They were found as illustrated in Figure 1.

This analysis documented that only the SNCA gene transcript was downregulated with the highest log fold change value (−2.5) documented in Figure 1. The downregulation observed in the other genes of the same biological pathway, had a log fold change value about −0.5/-1, suggesting that the psychobiological effects of the CPGHE treatment may facilitate cellular homeostasis to achieve this effect.

It is interesting to note that the U.S. Patent and Trade Office granted a patent on a molecular-genomic agent for inhibiting SNCA gene expression for the treatment of neurodegenerative disorders. Our major unexpected finding that the SNCA gene was deregulated within human peripheral blood lymphocytes motivates this discussion of its possible implications for human health and the epigenomics of consciousness research. This surprising result must now be replicated by other research groups with larger human clinical populations and more extensive controls to achieve scientific reliability and validity.

First findings on the epigenetic effects of hypnosis and mind–body transformation therapy

The Mind–Body Transformations Therapy (MBT-T) is a shorter and easier to administer version than CPGHE and MHE (Cozzolino, Tagliaferri, et al., 2015). The protocol is also based on the four-stage creative process (Rossi et al., 2011) and the procedure is easy to learn, allowing individuals to obtain stress-reduction without the need for complex and intricate methods.

Recently, through the use of DNA microarray technology on leukocytes, we (Cozzolino, Cozzolino et al., 2017) have verified that implementation of a single session of the MBT-T protocol is a suitable stress-reduction intervention in academic settings, with implications for decision-makers regarding the psychological support programs made available for students in such settings. Using this technique, we have noticed a growth in the expression of experience-dependent genes associated with activation of stem cells, cell stress-reduction, and reduction of inflammation. The bioinformatics analysis conducted to better understand its study of the differentially expressed genes showed that most prominent pathways involved emerge above related to cell growth, apoptosis, inflammatory processes, and immune response (Lloyd & Rossi, 2008).

In previous research, we tested the hypothesis that our clinical protocols (CPGHE and MHE) were able to activate the expression of genes by DNA microarray. In this study, unlike the previous ones, we verified whether (MBT-T) could also produce epigenetic changes. In this case, we focused on the methylation of cytosine. The use of particular biomolecular investigations and the use of specific Bayesian-type biostatistical approaches allowed us to verify, in a group of 20 participants, the presence of a treatment-related epigenetic response (Lloyd & Rossi, 2008).

The analysis revealed that participants showed a decrease in epigenetic variability, and a significant increase in the homogeneity of the epigenetic profile from prior to the administration of the MBT-T to 1 hour after the treatment and to an even greater extent 24 hours after later. In short, the mind–body treatment was associated with epigenetic profiles converging toward a homogeneous DNA methylation status.

These results show that the MBT-T therapeutic intervention of the group is able to influence the epigenetic status of the participants subjected to this mind–body therapy. This research documented that just as stress is able to activate specific inflammatory pathways, psychotherapy and mind–body treatments may improve mental and physical health through the modulation of the stress response patterns reducing the expression of pro-inflammatory genes. These mind–body therapeutic approaches seem to be involved in modulating immune function and inflammatory response.

The psychosocial genomics research program in oncology – PSGPO

In our first studies, our team has set the goal of empirically verifying that our therapeutic intervention protocol is able to trigger genomic-molecular mechanisms that enforce stem cells activation, chronic inflammation reduction, and cellular oxidation, thus promoting mind–body healing. On the basis of the obtained data and with the goal of increasing our knowledge of genomic mechanisms, further studies have been conducted analyzing different aspects of MBT-T therapy protocol and its applications in different diseases (Cozzolino et al., 2021)

With this aim, we initiated research in the field of oncology: *the Psychosocial Genomic Research Program in Oncology – PSGPO* (Cozzolino & Celia, 2016). The goal of PSGPO is to promote growth, knowledge, and development of therapeutic interventions as well as innovative and evidence-based research pathways, based on experimental methodology on mind–body integration, simultaneously analyzing mind–gene multilevel connections (Cozzolino & Celia, 2016).

In the present research, we formulated a hypothesis that the MBT-T is able to modulate experience-dependent gene expression by reducing the activation of inflammatory pathways in women undergoing treatment for breast cancer.

Breast cancer (BC) is the most common malignant neoplasm and the second most common cause of cancer-related death in women. Furthermore, we know that where cancerous cells and their microenvironment are co-protagonists, the inflammatory process has to be considered a crucial mechanism for recurrence and metastasis (Mantovani, Romero, Palucka, & Marincola, 2008). When the inflammatory stimulus persists, the inflammation becomes chronic. In the inflamed site, a complex signaling network is created, involving a large number of growth factors, cytokines, different types of leukocytes, lymphocytes, other inflammatory cells, and chemokines. Chronic inflammation is involved in all phases of tumor development: initiation, progression, and metastasis. A key aspect of the tumor microenvironment is the cytokine-mediated communication between tumor and peritumoral cells, where cytokines and chemokines show many activities that allow cell–cell communication (Szlosarek, Charles, & Balkwill, 2006). One of the main differences between normal cells and tumor cells is represented by the continuous proliferation of the latter, which soon results in a deficiency of nutrients and oxygen; the state of hypoxia created during tumor growth induces many cytokines and chemokines (Mancino et al., 2008).

The transition from healthy woman to BC patient is generally associated with significant physical, psychological, and social challenges. Elevated stress levels can in turn heighten inflammation and seem to be maintained during the post-treatment period in breast survivors as well (Shrout et al., 2020).

Recent evidence suggests that positive psychosocial experiences, including psychotherapeutic interventions and therapeutic mind–body protocols, can modify the transcriptional dynamics of leukocytes under pathological conditions related to stress. In people suffering from chronic disease, cancer, and psychiatric disorders, such positive experiences can reduce the expression of genes associated with inflammatory response and stress-related pathways, and improve mind–body health through a proper negotiation of pathways to stress response (Antoni et al., 2012).

For these reasons, the development of multidisciplinary, evidence-based care during the post-treatment phase is a key area of cancer research. Several studies have elucidated the role of neuroendocrine regulation of downstream physiological and biological pathways relevant to cancer development, also demonstrating how subjective stressful experiences may influence tumor growth and progression, via sympathetic nervous system and hypothalamic-pituitary-adrenal axis activation (Antoni et al., 2012). Also, the inflammatory process has been recently associated with neoplasm transformation and tumor growth. Specifically, the NF-KB-mediated signal transduction is implicated in the regulation of viral replication, autoimmune diseases, inflammatory response, tumorigenesis, and apoptosis.

In this context, we took into account a holistic perspective in order to integrate mind and body within a single comprehensive framework (Cozzolino et al., 2017). This kind of intervention, aimed to reduce symptoms related to stress diseases, can affect relevant processes related to cancer growth and progression by reducing the inflammation status and augmenting the immune response (Antoni, 2013; Atkinson et al., 2010; Rossi et al., 2008). Functional genomics studies have shown that mind–body therapies are able to generate an overall reduction of the expression of factors related to inflammatory response, such as NF-KB, and to regulate numerous pathways involved in apoptosis and cell proliferation (Antoni et al., 2012). In cancer patients, the effects of these interventions are able to counter processes related to cancer growth through the reduction of inflammation and the increase of immune response (Antoni, 2013). mind–body therapies are able to reduce stress, eliciting the relaxation response, which in turn modulates gene expression.

For these reasons, we (Cozzolino, Cocco, et al., 2021) decided to evaluate the cytokines profiling in the sera of breast cancer patients enrolled in control and experimental arms at baseline (T0), 1 hour after the first MBT-T treatment (T1), and the end of the MBT-T treatment (Tf). In particular, the results have shown that the release of SCGF, SDF-1a, MCP3, and IL-18 was significantly reduced in sera of patients collected after just 1 MBT-T (T1) compared to the control group (non-treated patients), while the reduction of MCP3, GROa and LIF was observed at the end of treatment (EOT). All these significant cytokines, found to be decreased in the MBT-T-treated group, are known to be pro-inflammatory. This confirms that their decrease can be considered as an index of an anti-inflammatory effect of the MBT-T treatment. In particular, high levels of stem cell growth factor (SCGF) high levels of stem cell growth factor (SCGF) have been implicated in the malignant progression in cancer (Mego et al., 2016). IL-18 acts on both Th1 and Th2 inflammatory responses and is involved in several cancers, which correlates with development of chemoresistance, higher staged cancer, and mortality (Fung, Nguyen, & Putoczki, 2020). Gro-a (CXCL1) is a chemokine associated with cancer growth and proliferation, angiogenesis, and metastasis in which up-expression was found in patients with different cancers. In BC patients CXCL is correlated with tumor grade, disease recurrence and decreased survival (Zou et al., 2014). The expression of chemokine SDF-1a is associated with increased

invasion, mammo-sphere formation, metastasis, chemoresistance, angiogenesis, and a poor prognosis in breast cancer (Kang et al., 2005) MCP-3 (monocyte chemotactic protein-3) is a chemokine that plays a pivotal role in tumorigenesis, promoting cancer progression by supporting the formation of the tumor microenvironment and facilitating tumor invasion and metastasis. Moreover, high mRNA levels of MCP-3 were related to decreased overall survival and relapse-free survival (Thomas, Mir, Kapur, Bae, & Singh, 2019). LIF (leukemia inhibitory factor) up-expression has been verified in many cancers, including breast cancer, and associated with poor prognosis of recurrence-free survival.

Participants' well-being, anxiety, and depression were also evaluated through psychological scales from breast cancer patients enrolled in control and experimental arm,

at baseline (T0) and at the end of the MBT-T treatment (Tf).

Results of the 2 × 2 mixed design factorial ANOVA showed not statistically significant interaction between time and condition in participants' well-being, anxiety, and depression ($F(1,8) = 1.302$; $p = .287$; $F(1,12) = 1.948$; $p = .188$; $F(1,12) = 1.470$; $p = .249$, respectively,).

This is a major limitation of the psychological measures part of the research. However, even though the results showed non-significant interactions, they appear (Figures 2, 3 and 4) to be in the expected direction. Participants in the experimental condition showed an increase in well-being and a reduction in the level of anxiety through T0 and Tf as compared to participants in the control condition, who showed a reduction in well-being and an increase in anxiety and depression (Cozzolino, Cocco, et al., 2021). As can be seen from the literature, psychology tools generally require higher samples while those used for genomic measurements which, even if with a few subjects, work with hundreds or thousands of genes at the same time as in the case of the DNA Microarray. The non-significant statistic of the results is probably due to the smallness of the sample (<15 per group) and to the fact that psychological tools are created to give meaningful results on larger samples. Only when we have the definitive results with the expected sample of 90 patients will we be able to understand whether our hypothesis will be rejected or not.

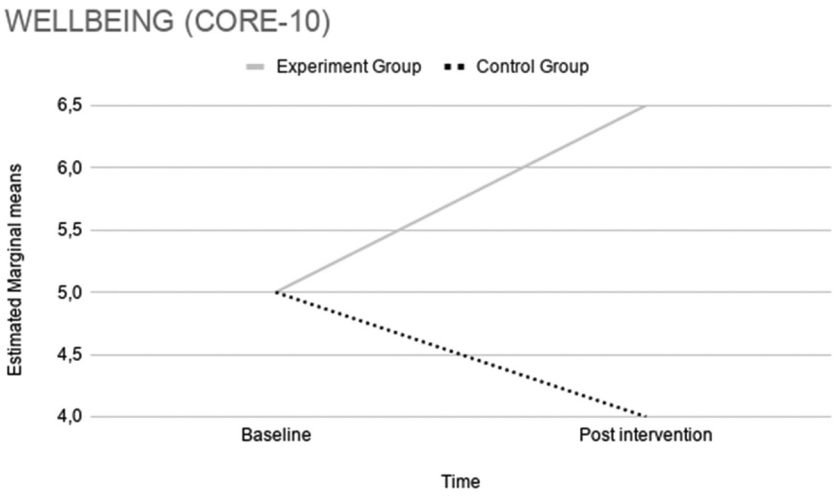

Figure 2. Mean differences in well-being levels.
Statistically not significant interaction effect of well-being ($F = 1.302$; $p = .287$).

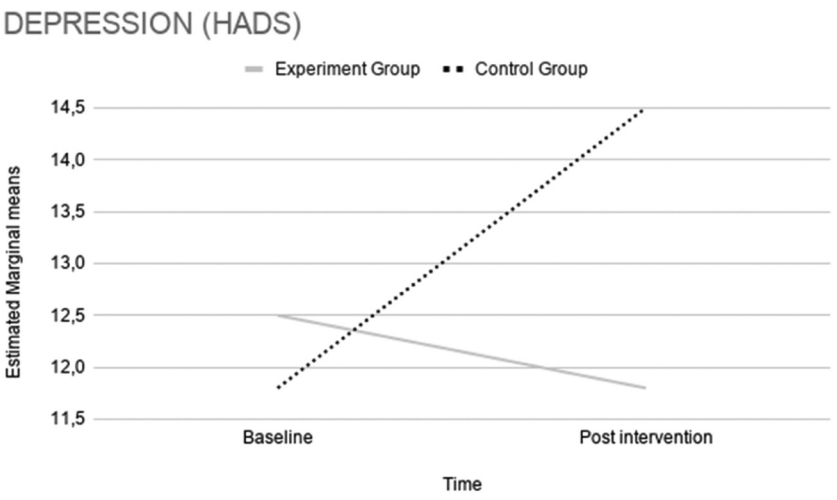

Figure 3. Mean differences in depression levels.
Statistically insignificant interaction effect of depression ($F = 1.948$; $p = .188$).

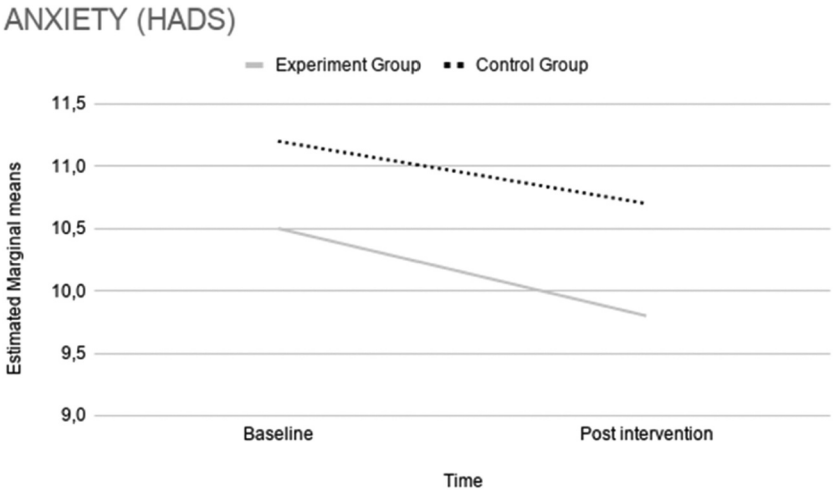

Figure 4. Mean differences in anxiety levels.
Statistically not significant interaction effect of anxiety ($F = 1.470$; $p = .249$).

Conclusion

This comprehensive review of our research related to mind–body therapy and hypnosis in relation to gene expression illustrates the effectiveness of Ernest Rossi's psychosocial genomics paradigm in modulating gene expression. His groundbreaking approach was tested through several lines of research exploring the ability of the mind to heal the body. Our studies evidenced how specific kinds of hypnosis and psychotherapy (CPGHE, MHE, MBT-T) modulate expression of genes associated with stress, inflammations, and other conditions. These findings reveal psychosocial genomics as a new and valid scientific approach to treatment of both physical and mental diseases. Therapeutic hypnosis has shown to invert expression of genes involved in cellular responses to

oxidative stress and chronic inflammation. These findings are consistent with a beneficial outcome of therapeutic hypnosis and mind–body therapy in problem-solving, stress-reduction, and mind–body symptom resolution. The studies regarding particular conditions such as Parkinson's Disease and breast cancer illustrate the role of psychotherapy and mind–body treatments in such contexts. These classes of treatments have been proven effective in improving mental and physical health through stress response pattern modulation and pro-inflammatory gene expression reduction. The promising results form a strong basis for replication of these studies with larger human clinical populations and more extensive controls. At the same time, this research offers genomic and epigenetic evidence that demonstrates the efficacy of therapeutic hypnosis and psychotherapy.

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