Bio-Psychology and Gene Expression: A Literature Review.

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ABSTRACT

This literature review begins with an introduction to bio-psychology, background and brief explanations of: psychotherapy and neuronal (brain) changes, genetic processes, and neuronal (brain) changes; and potential research problems/challenges to consider while reviewing gene expressions studies. Research is reviewed which supports the theory that any novel, experiential psychotherapeutic intervention can impact gene expression in humans resulting in brain changes, also known as neurogenesis or brain plasticity, and that these processes can be verified by measuring gene expression. Technologies have emerged in the fields of imaging (fMRI - Functional magnetic resonance imaging), psycho-physio-chemical measurement (i.e., hormone expression), and molecular biology that begin to present evidence for the effects that psychotherapy has on neurogenesis. The purpose of this literature review is to explore the existing body of evidence and research within the fields of psychology, biology, and genetics that supports this theory. Before reviewing the existing Bio-Psychology literature, a foundational background of psychotherapy, genetic processes, and neuronal (brain) changes and research challenges are provided. Future directions are explored in the discussion that follows this literature review.

Psychology and Neuronal (Brain) Changes, Background

Brain plasticity is the lifelong ability of the brain to reorganize neural pathways based on new experiences and even injury. Genetic processes have been shown to result in neuronal (brain) growth by changing the internal structure of the neurons, specifically, in the area of synapses along with an increase in the number of synapses between neurons (Neville and Bavelier, 2000; Kandel, 1998, 2001). Brain plasticity is also referred to as neurogenesis (Rossi, 2002). These are the processes responsible for neuronal brain growth by way of genetic processes, also known as brain plasticity, of interest and within the scope of this literature review. Therefore, it is proposed, and of great interest to the scientific and psychological communities, that specific life experience (i.e., trauma, loss, injury, or psychotherapeutic interventions) changes our DNA. Experiences trigger very specific protein synthesis (mRNA) resulting in a chain reaction
with physiological, neuronal and structural consequences (Strachan and Read, 1999).

Genetic Processes and Neuronal (Brain) Changes, Background

Genetics is the study of genes, and the field tries to explain what genes are and how they work. Genes are how living organisms inherit features from their ancestors. The genotype is the genetic makeup of a cell, an organism, or an individual. The genetic code stored in DNA is “interpreted” by gene expression, and the properties of the expression give rise to the organism’s phenotype observable characteristic, including behavior.

Gene expression is the process that can be influenced by environment and experience resulting in phenotypic changes such as neurogenesis. Messenger RNA (mRNA) is an information carrier coding for the synthesis of one or more proteins. Proteins can be synthesized using the information in mRNA as a template. Genes can be turned on or off by messenger proteins.

Many factors determine whether a gene is on or off, such as the time of day, whether or not the cell is actively dividing, its local environment, and chemical signals from other cells. It is the turning on or off of the genes that is believed to affect the very wiring of the brain and body toward the development of disease or improvement of health, thinking, memory, and mood. Research explored in this literature review will provide preliminary evidence of this process (Montag-Sallaz et al., 1999; Ramanan et al., 2005; Pfenning, Schwartz, and Barth, 2007; Yehuda et al., 2009; and Brocke et al., 2010).

A framework for understanding the transfer between DNA, RNA (both nucleic acids), and protein is as follows. There are direct transfers of information (processes) that can occur between DNA, RNA, and proteins. DNA can be copied to DNA (DNA replication). DNA information can be copied into mRNA, (transcription). mRNA then carries a copy of DNA to other DNA, binding to it, then, changing it (gene expression). In general, gene expression is regulated through changes in the number and type of interactions between molecules (proteins) that collectively influence the transcription of DNA and the translation of RNA (Strachan and Read, 1999).

Potential Research Problems/Challenges to Consider while Reviewing Gene Expressions Studies

Methodological problems include possible contamination of samples, false positives for gene markers, expired supplies, problems with study reproducibility due to different laboratories having different procedures and controls, and researcher bias that can influence the search for significance, causing them to rerun the procedures when outcomes are not what are expected (Newbert, Zhang, and Vessell, 2008).

When DNA microarray technology was developed in the early 1990s, it allowed for rapid genome-wide expression profiling. The challenge and part of the above limitations came from a lack of universal methods for data analyses and interpretation. Subramanian et al. (2005) developed and tested a tool, Gene Set Enrichment Analysis (GSEA), to provide standard methods throughout the field of genetics.

Reverse Transcription Polymerase Chain Reaction (RT-PCR) is a laboratory technique commonly used in molecular biology where an RNA strand is reverse transcribed back to its DNA source. RT-PCR allows for exponential amplification so a very small number of copies of mRNA can be measured. RT-PCR is often used to validate DNA microarray results, but can also be used as a very precise measurement alone (Singer-Sam, et al., 1990; Bartlett and Stirling, 2003; Zubakov, et al., 2010).

Tight research design and the standardization of procedures can greatly minimize and even eliminate all of the above potential problems with trusting gene expression studies. Awareness of the potential problems, in a field considered one of exact science, assists in correction for the human factor still necessary for its implementation (Mattocks, et al., 2010). Another limitation in conducting gene expression research has been that bio fluid sample collection was mostly limited to blood or tissue samples. It wasn’t until recently that other biological fluids were considered for gene expression measurement. With each new proposed biological sample considered for experiments, the full genome has to be mapped first in order to know what to expect as far as gene expression (mRNA) measurement (Chiappelli, et al., 2006; Hu, et al., 2008). Not without controversy, (Kumar, Hurteau, and Spivack, 2006), saliva as a...
biological sample has potential as an easily collected body fluid for human gene expression and experience research (Park, et al., 2006).

THE BIOLOGY OF PSYCHOTHERAPY

Bio-Psychology is an emerging field with many developments in the last 12 years. Review of the research, investigating psychotherapy’s effect on neuronal growth (brain plasticity), includes studies using various designs, interventions, methods, and a broad variety of subjects. This review will consider research using single or multiple psychological, chemical, physiological, molecular, and brain imaging measures. The research also includes animal models, as it is easier to control conditions such as stress/no stress in mice with cancer. Animal models allow for dissection of brain regions and direct biological sample collection (hormones, gene distribution in brains, etc.) which is data not able to be collected in live human subjects.

Recently, well designed studies including psychological, physiological, and imaging (fMRI) measures in humans are emerging throughout and across the research communities. Due to recent advances, psychotherapeutic techniques such as cognitive behavioral therapy, as well as experiential interventions such as Mindfulness-Based Training, can now be compared to control treatments in human subjects (not just in the physically ill, but in traumatized, anxious, and depressed populations as well). With the above referenced advances in technology, we are on the cusp realizing a great broadening of understanding the biology of psychotherapy.

Questions to be considered while reviewing the current and existing literature are as follows:

- Does the environment and experience reshape the structure and “wiring” of the brain?
- How is psychotherapy believed to impact on gene expression?
- Are experiences such as psychotherapeutic effects measurable through measuring gene expression?

Questions have arisen as to the structural effects of brain plasticity or neuronal brain changes that occur due to environment or experience through learning or brain damage. Eriksson, et al. (1998) were the first to demonstrate structural neurogenesis in the adult human brain using postmortem subjects previously treated for cancer, with a diagnostic drug used for imaging purposes that labeled DNA immunofluorescently. The glowing DNA displayed its proliferation, demonstrating its copying and transcription, gene expression, by even appearing in untreated brain regions. This team was able to demonstrate new neuronal growth in the hippocampus occurred in the brain of adult humans.

To further the evidence of brain plasticity by showing training induced brain changes, Boyke, Driemeyer, Gaser, Buchel, and May (2008) chose healthy elderly subjects and found gray-matter increases in the several brain regions known to correlate with learning and skill acquisition. Gray-matter was measured using MRI scans before juggling training, 3 months after training and again at 6 months post training. With no practice after training, subjects showed an increase in gray-matter at the second scan, 3 months from training, retuning to baseline by the third scan, taken six months after training. The authors reported that the methods were previously used with a 20 year old cohort and the results were the same as to regional gray-matter increases, post training, however, the younger group retained the acquired skill to a much greater degree.

An experiential psychotherapeutic intervention gaining popularity in the psychological field is a practice known as Mindfulness-Based Stress Reduction (MBSR). Hozel, et al. (2011) studied the effects of MBSR on regional brain gray matter density using anatomical magnetic resonance (MR) images. Sixteen healthy, meditation-naïve participants underwent MR imaging before and after an 8 week program of MBSR compared to 17 control subjects, placed on a waiting list. Specific brain regional analysis confirmed increases in gray matter within the hippocampus. Whole brain imaging showed increases in gray matter in the posterior cingulate cortex, the temporo-parietal junction, and the cerebellum in the MBSR group compared to controls. These brain regions are involved in learning, memory, emotion regulation, self awareness processing and objectivity. This research furthers evidence that environment and experience results in neuronal and structural changes in the brain.

An early effort in bio-psychology, Ackerman, et al. (1998), sought to test the effects of psychological stress in human patients with
Multiple Sclerosis (MS) compared to normal controls. Multiple physiological and psychological measures were used, as well as the gene expression of Cytokine’s (pro-inflammatory proteins) in subjects exposed to stress inducing situations. The results showed that the stress response did not differ from controls, and psychological stress conditions increased a cellular immune response in both groups. Due to the autoimmune nature of MS, it was suggested that their health could be more negatively impacted by psychological stress causing an exacerbation of symptoms.

In a randomized clinical trial of 227 women being treated for stage II and III breast cancer, Anderson, et al. (2004) compared assessment and group psychotherapy to assessment only. The group psychotherapeutic interventions were conducted in small groups by two clinical psychologists. The treatments were designed to reduce stress, lower emotional distress, and improve quality of life. Measures for both groups included interviews, questionnaires medical and psychological and blood sample collection conducted at the beginning for baseline and after four months, when the treatment group had completed 18 hours of group therapy. It was demonstrated that the treatment group showed across the board improvements compared to control, in all areas reassessed including important T-cell proliferation necessary for fighting and surviving breast cancer. This study demonstrates the quantitative positive effects of psychotherapeutic interventions on physical and emotional health status of women with cancer and was further validated by a similar study that was published in 2009 by Antoni, et al.

This study specifically compared cognitive behavioral stress management (CBSM) treatment and its effects on psychosocial and physiological adjustment to control in women going through treatment for stage I, II, and III breast cancer, 4-8 weeks post surgical. All subjects completed a first assessment and were then randomly assigned to weekly small group CBSM treatment for 10 weeks while control group was invited to a 1-day seminar midpoint of the 10 week period. Reassessment occurred 3 months after intervention ended, 6 months after initial assessment then 6 months later. Psychological, physiological and gene expression measures indicated a significant difference between groups with regards to all measures, showing 10 weeks of CBSM treatment led to an overall improved level of function and adaptation psychologically and physically which held up over 12 months.

Using fMRI brain imaging, Erk, et al. (2010) studied the acute and sustained effects of cognitive emotional regulation in Major Depression. Investigated was the temporal dynamics of emotional regulation. Moderately depressed antidepressant treated patients were compared to a never depressed control group undergoing active cognitive emotional regulation tasks while viewing emotionally arousing pictures. After a 15 minute delay, subjects were presented with the same stimuli only passively viewing. Whole brain fMRI revealed healthy controls engaged the prefrontal cortex while medicated depressed patients did not. Both groups were able to regulate themselves as indicated by fMRI imaging of the amygdala, but depressed patients were unable to maintain regulation. It was concluded that though the capacity for emotional regulation remains in medicated depressed patients, the effect is not sustained due to lack of prefrontal cortex activation during regulation. This would seem to indicate a differential disconnect only partially attenuated by antidepressant therapy.

Expression of immediate-early genes (IEGs) has been studied in mice after exposure to novel stimuli (Montag-Sallaz, et al., 1998). Ramanan, et al. (2005) sought to document the mechanisms of synaptic activity-induced IEG expression and brain plasticity in order to demonstrate the idea that novel experiences translates into neuronal changes by way of serum response factor (SRF). The team proposed that SRF, was needed to “transcribe” activity- and use-dependent neuronal modification in the brain. Using mice, and an SRF-deletion method, they found that other brain areas picked up, or seemed to compensate, where another was blocked by SRF deletion. This research demonstrated a sort of neuronal rerouting mechanism, showing that neuronal changes occur due to the environment and experience.

A different firing pattern of neurons in the hippocampus-amygdala complex has also been demonstrated after exposure to novel stimuli versus familiar, showing the mechanisms of short and long term learning. The mechanism involved in novel versus familiar stimuli assessment was studied and demonstrated in human, epilepsy surgery patients, using a task paradigm, with
measurement down to the firing of individual neurons, with data collected from intracranially implanted microwires (Rutishauser, Mamelak, and Schuman, 2006). Novelty and familiarity “detector” neurons were identified in the hippocampus and amygdala that indicated if stimuli were novel or familiar. This group also found during retrieval testing, 24 hours later, that the “familiarity neurons” remembered better than the subject! That is, after novel exposure the day before, subjects would verbally guess wrong during 24 hour delayed testing as to novel versus familiar stimuli, but the distinct neuronal firing pattern would indicate novelty or familiarity, showing discrimination.

Smolka, et al. (2007) examined genetic associations on central brain processing by genotyping for two particular genes, COMT and 5-HTT, both associated with the “emotional” limbic brain structure, the amygdala. Subjects included in the study were healthy males and were divided into groups based on genotype analysis from peripheral blood samples, then fMRI captured differential brain region activation during subject’s exposure to aversive, neutral or pleasant stimuli. Over activation of the amygdala brain region indicated a state of hyper arousal and emotional distress. Subjects with a particular genotype profile were found to be more reactive and potentially, less resilient to aversive stimuli and therefore, likely, more prone to anxiety and dysphoric mood states. This method may be of future use as a diagnostic for a particular genetic predisposition so that strengthening interventions could be provided before an emotional deregulation emerged.

Pfenning, Schwartz, and Barth (2007) developed a computational, comparative genomic method to identify the processes behind brain plasticity, neuronal changes due to the environment and experience. They demonstrated similar activity-dependent expression pathways with regards to a particular gene set previously theorized to be associated with brain plasticity across mammal species, mouse, rat and humans, using the genomic databases for each, respectively.

The investigators also considered the known commons and differentials genomically, of each species to further compare them using a unique, unbiased computational algorithm, a complex mathematical formula applied to previously collected gene expression data sets. The hopes of this study were to provide a tool useful in future investigation of neuronal brain growth patterns. The authors consider their effort only a beginning in characterizing the brain plasticity transcriptome.

Xiang, et al. (2008) questioned the microbiological underpinnings of major depression using sample tissue from the amygdala, a brain region known to process and regulate emotions. They compared post mortem subjects who were known to have been diagnosed with Major Depressive Disorder (MDD) before death including subjects who died of suicide, and a control group who were not known to have depression in their history, and who died of natural causes. Explored was the dopaminergic system and distribution of gene expression (mRNA) of dopamine (DA) receptors in the amygdala.

A DA subtype, D4 was found to differ with greater expression in a particular amygdala region in MDD subjects compared to control. Some short comings to this study come from the inability to question the subjects’, potential confound of DA alterations that may have been associated with suicide behavior versus MDD and incomplete or unreliable histories that could not have provided important information such possible lack of medication or treatment compliance.

In a recent study using live human subjects, Xiang, et al. (2012) studied the effect of acute psychological stress induced immune response on gene expression measured by analyzing human peripheral blood cells. Specific signal pathways were found to communicate with the central nervous and immune system. Subjects were normal volunteers who completed a series stress tasks with blood drawn before and after each task then 1, 2, 6, and 24 hours later. The study also included psychological measures of stress perception. It was found that acute psychological stress increased the production of pro-inflammatory gene expression patterns and stress hormone release. The bio-psychological implications are that psychological stress effects have neurological implications at micro biological level.

Yehuda, et al. (2009) sought to clarify gene expression patterns associated with PTSD using a uniformly exposed group of subjects after the World Trade Center attacks. Of forty exposed subjects included in this study, 20 met the criteria for PTSD, and were compared to 20 who did not.
Interested in correlating gene expression patterns to cortisol (hormone) levels, they found that specific gene expressions patterns could be predicted by dysfunctions in the physiological stress response system (Hypothalamus-Pituitary-Adrenal axis or HPA axis). After analyzing gene expression profiles of the subjects from blood samples, this team compared the profiles to the Human Genome Database on a large scale in order to show differences between the subjects and the general population. They identified several genes involved in HPA signaling that showed a significantly different expression pattern among those subjects with current PTSD versus those without.

Interested in providing more evidence for the biological mechanisms behind emotional behavior, Brocke, et al. (2010) studied, for the first time in humans, a gene that regulates neural plasticity within the amygdala. The Stathmin (STMN1) gene was previously identified and studied in mice (Shumyatsky, et al., 2005). This study compared men and women, genotyping them for either SNP1 (single nucleotide polymorphisms) or SNP2 of the Stathmin (STMN1) gene. Using an acoustic startle paradigm and multiple measures: physiological, psychological and molecular biological, it was demonstrated that two behavioral mechanisms, the startle response and fight or flight reaction, underlies the neural mechanisms of anxiety and depression on a molecular biological level.

DISCUSSION

The science behind merging biology and psychology has proliferated over the last decade with researchers in both fields considering aspects of each. Only recently, has gene expression research begun to emerge that enables scientist to study the psychological effects of experiences including psychotherapeutic intervention effects.

The idea that environment and experience changes the brain “wiring” (neurogenesis) is evolving, even more so, into an accepted reality. Differences in neural pathways may hold the key to finding ways to strengthen the “wiring” through targeted specific gene expression enhancement procedures (i.e., experiential psychotherapy).

With the recent interest and progress in biopsychological research, some of which is presented in the above literature review, investigators are now exploring brain mapping/imaging technology that shows changes in gray and white matter after experiences, gene expression after experiential psychotherapy, and easier ways to collect samples in order to conduct larger scale research projects.

Previously, in gene expression research, blood samples were needed for profiling and analyses. Easily collected fluids such as saliva were dismissed due to several inadequacies. Before the recent advances in technology, saliva was considered to have too much “junk” DNA from viruses and bacteria to discriminate key indicators (Kumar, et al., 2006; Chiappelli, et al., 2006). Before purification and amplification technology advances, saliva also did not seem to have enough mRNA copies to measure. Further, saliva mRNA samples degraded too quickly to facilitate use as a genetic sample (Hu, et al. 2008).

Brocke, et al. (2010) used saliva samples for genotyping, not gene expression. On the horizon are user friendly methods for in-office sample collection, and an opportunity for the fields of psychology and biology to collaborate as they never have before. Technology and agreement among scientists are emerging that will enable saliva collection from subjects before, during and after psychotherapeutic intervention by way of in vial mRNA purification, safe, room temperature storage, amplification, analysis and comparison, within and across subjects.

Implications

What is known through this research is that experience changes the brain “wiring” and structure. This process occurs through the biological mechanisms of immediate early gene expression and activity dependent delayed gene expression described above. The experiential effects can be measured physiologically, chemically, genetically and with imaging (Bradley and Lang, 2000).

What remains to be explored is the full collaboration of the different fields. Psychotherapists have few opportunities to collaborate with molecular biologists or neuroscientists. It is proposed that if these fields were to collaborate, specific experiential psychotherapeutic interventions could be
identified that best change the “wiring” in specific brain regions such as the limbic system and prefrontal cortex. These brain regions are known centers for emotional and cognitive regulation. Measuring gene expression before, during and after psychotherapeutic interventions could help identify specific processes at work in adaptive neurogenesis. Imaging these specific brain regions before and after treatments could provide the concrete evidence needed to validate these endeavors.

Had gene expression research not arrived in psychological research, a major gap in our understanding of how the brain and body work together would remain. Barriers to furthering the above proposed endeavors include a lack of information sharing between universities, research institutes, medical practitioners, and psychological communities. Though global databases of genetics, gene expression profiling, and standardizations of methods exist, a lack of communication and collaboration persists. These are barriers that can be overcome through curiosity, cooperation and determination within these scientific communities.

The overall impact of this research is limited because it is all relatively new, in concept and application. It will be quite some time before what is learned from these endeavors will emerge in common practice. It is hoped that by starting the process of barrier removal through communication and collaboration that society will one day benefit from proven, sharp targeted psychotherapeutic interventions that improves quality of life, physiologically and emotionally, sooner than later.

REFERENCES


**ABOUT THE AUTHOR**

Ms. Beth Robinson graduated from UNC-Wilmington with a B.A. in Psychology, with honors, in 1990, specializing in behavioral pharmacology. After working the field of experimental psychology, she transitioned to the counseling field. Ms. Robinson graduated from UNC-Chapel Hill School of Medicine with an M.S. in Rehabilitation Counseling in 1994. During her training at Chapel Hill, she studied the psychological aspects of all disabilities, then, decided to specialize in mental health counseling. While working in the field for various social work agencies, Ms. Robinson completed the required internship for State of Florida licensure and was licensed in 2004. Immediately after licensure, she began private practice counseling specializing in trauma treatment using EMDR.
(Eye Movement Desensitization and Reprocessing) and has developed an eclectic practice that utilizes many different strategies including cognitive behavioral therapy, meditation and mindfulness based training, classic Ericksonian methods as well as EMDR. Ms. Robinson maintained the neuroscience interest throughout her career and took steps in 2011 to begin a doctoral program with Akamai University in Applied Psychology. With the help of advisors in psychology and mentors in molecular biology, she hopes to publish original psychotherapy and gene expression research conducted in collaboration with the California Pacific Medical Center.

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