

Modulating Gene Expression through Psychotherapy:
The Contribution of Non-Invasive Somatic Interventions

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Abstract

Mapping the relationship between gene expression and psychopathology is proving to be among the most promising new frontiers for advancing the understanding, treatment, and prevention of mental disorders. Each cell in the human body contains some 23,688 genes, yet only a tiny fraction of a cell's genes are active or "expressed" at any given moment. The interactions of biochemical, psychological, and environmental factors influencing gene expression are complex, yet relatively accessible technologies for assessing gene expression have allowed the identification of specific genes implicated in a range of psychiatric disorders, including depression, anxiety, and schizophrenia. Moreover, successful psychotherapeutic interventions have been shown to shift patterns of gene expression. Five areas of biological change in successful psychotherapy that are dependent upon precise shifts in gene expression are identified in this paper. Psychotherapy ameliorates (a) exaggerated limbic system responses to innocuous stimuli, (b) distortions in learning and memory, (c) imbalances between sympathetic and parasympathetic nervous system activity, (d) elevated levels of cortisol and other stress hormones, and (e) impaired immune functioning. The thesis of this paper is that psychotherapies which utilize non-invasive somatic interventions may yield greater precision and power in bringing about therapeutically beneficial shifts in gene expression that control these biological markers. The paper examines the manual stimulation of acupuncture points during psychological

exposure as an example of such a somatic intervention. For each of the five areas, a testable proposition is presented to encourage research that compares acupoint protocols with conventional therapies in catalyzing advantageous shifts in gene expression.

Keywords: Acupuncture, DNA, Epigenetics, Exposure, Gene Expression

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Linkages between gene expression and psychopathology are surfacing which “point to new possibilities for conceptualizing, preventing, and treating disorders” (Masterpasqua, 2009, p. 194). The thesis of this paper is that emerging non-drug psychotherapies which utilize somatic interventions are particularly effective in modulating the expression of regulatory genes for psychotherapeutic gain. Eric Kandel, a recipient of the Nobel Prize in 2000 for his research on the physiological basis of memory storage in neurons, delineated the relationships among psychotherapy, gene expression, and brain plasticity, noting in a seminal paper that:

Insofar as psychotherapy or counseling is effective and produces long-term changes in behavior, it presumably does so through learning, by producing changes in gene expression that alters the strength of synaptic connections and structural changes that alter the anatomical pattern of interconnections between nerve cells of the brain (Kandel, 1998, p.140).

Although the implications of this statement are just beginning to be appreciated within psychology (e.g., Gontier, 2008; Masterpasqua, 2009), a paper in *The Journal of the American Medical Association* placed the therapeutic promise of influencing gene expression at “the center of modern medicine” (Feinberg, 2008, p. 1345). The current paper presents evidence regarding the importance of gene expression in psychological health and the impact of successful psychotherapy on gene expression. Five areas of biological change in successful psychotherapy that are dependent upon precise shifts in gene expression are identified. Psychotherapeutic

interventions that are effective in modulating the expression of genes or gene cascades that impact these areas of biological change may produce long-term benefits with surprising speed. A procedure that combines psychological exposure with the manual stimulation of acupuncture points is examined as an example of a somatic intervention that may be particularly effective in facilitating the expression of such genes in ways that enhance mental health.

Gene Expression in Psychiatric Disorders

The presence of a gene does not ensure that the gene is active. Many variables determine whether or not (a) a gene will express and (b) the psychological impact of its expression. For example, vulnerability to posttraumatic stress disorder (PTSD) is related to whether certain stress genes are active or inactive at the time of a traumatic experience (Binder et al, 2008). A person whose genotype includes specific known variations of the stress-related gene “FK506 binding protein 5,” or FKBP5, is more likely to develop posttraumatic stress disorder (PTSD) following a highly traumatic incident than a person who does not carry these variations of FKBP5. However, Binder’s research team discovered that if such a genetically vulnerable individual experienced a supportive, non-traumatic childhood, FKBP5 is less likely to be active than it would be if the person suffered childhood abuse. This is a biological correlate of the clinical observation that people who were abused as children are more likely to develop PTSD after a traumatic experience in adulthood than those who had more favorable childhoods (Widom, 1999). Inherited genetic profiles may make a person more vulnerable to PTSD, but early traumatic experiences increase the likelihood that the salient genes will be expressed and that PTSD will ensue.

When treating PTSD or augmenting resilience against PTSD in vulnerable individuals, a predisposing FKBP5 variation still cannot be altered or removed, but interventions that inhibit its

expression are possible. These interventions might, for instance, mitigate the effects of childhood abuse by introducing corrective therapeutic experiences that turn off FKBP5 or that turn on genes that suppress the effects of FKBP5. The therapist, of course, is focused on the client, not the client's genes, but knowledge of underlying biochemical events can greatly enhance clinical understanding. For instance, in mediating the effects of childhood abuse, procedures such as exposure treatment might result in the expression of genes that, in Kandel's (1998) words, alter "the strength of synaptic connections" (p. 140). Such synaptic changes might lead to the extinction of powerful conditioned fear responses (after Schafe & LeDoux, 2008) that are often the legacy of childhood abuse. Psychotherapy may impact (a) the expression of genes that cause a disorder, (b) genes that suppress a disorder or influence its severity, or (c) genes involved with maladaptive learning and conditioning. Maps of such biological processes are becoming available and augment the clinician's cognitive, behavioral, psychodynamic, and interpersonal models.

Psychopathology and Abnormalities in Gene Expression.

In addition to trauma-based disorders, links between psychiatric conditions and gene expression have been examined in studies of depression (Karssen et al., 2007), anxiety (Kawai et al., 2007), schizophrenia (Bray, 2008), and social isolation (Cole, 2007). Focusing on gene expression allows human development, behavior, and psychopathology to be viewed from the standpoint of the body's most fundamental building block, the cell. Each human cell contains a set of some 23,688 genes (Jensen & Murray, 2005). Genes initiate the synthesis of proteins that regulate almost every function in the body (Touriol, Bornes, Bonnal, Audigier, Prats, Prats, et al., 2003). Beyond the instructions carried in a gene's DNA sequence, signals from the body and the environment affect gene expression, a process called epigenetics. Epigenetic signals impact

cellular activity that is as basic as whether a stem cell differentiates into a kidney cell or a brain cell and as fleeting as whether a white blood cell attacks an invader. The proteins synthesized as a result of gene expression are as diverse as hormones, enzymes, and neurotransmitters. In brief, shifts in gene expression are involved in most physiological events as well as in their psychological counterparts.

At any given moment, some of a cell's 23,688 genes will be switched on while the majority will be switched off. Two chemical processes inhibit gene expression. One involves cytosine, a constituent of DNA. When methyl groups adhere to the cytosine molecule, gene expression is inhibited (Jirtle & Skinner, 2007). The other involves histones, simple proteins around which DNA coils to form chromatin (the chemical basis of the chromosome). Histones have "tails" whose chemical modification influences whether a gene is expressed or silent (van Vliet et al., 2007). Some genes stay switched on or off for a lifetime (Goverdhana et. al., 2005). Other genes may rapidly shift between active expression and inactivity. For instance, "clock" genes turn on and off in regular intervals, governing circadian (daily) and ultradian (intra-day) biological rhythms (Sato et al., 2004). Other such on/off patterns affect bodily processes from metabolism to memory formation to arousing the sympathetic nervous system. Abnormalities in these long-term and short-term patterns of gene expression that are caused by the environment or learning constitute a genetic basis beyond inherited potentials (genotype) for the actual appearance (phenotype) of psychiatric disorders.

Although some genes require hours to reach peak expression after being triggered, others (called "immediate early genes") can reach peak expression within seconds (Davis, Bozon, & Laroche, 2003; Kovacs, 2008). Brief peak expression times were essential for evolutionarily adaptive survival strategies such as the fight-or-flight response. Many immediate early genes act

as regulatory devices that trigger a cascade of physiological changes including the production of stress hormones in response to environmental threats (Ising & Holsboer, 2006). The inappropriate or maladaptive activation of fight-or-flight chemistry is, however, the core mechanism in anxiety-based disorders (Barlow, 2004). Heightened reactivity in the hypothalamic-pituitary-adrenal axis (HPA) has also been implicated in a range of stress-based and mood-related disorders, including major depression and PTSD (Roth, Levenson, Sullivan, & Sweatt, 2006). These psychopathological processes are modulated by immediate early genes.

Reciprocal Influences in Gene Expression.

The influence of genes was initially believed to be a one-way process, in the direction of DNA → RNA → protein. Genes were understood as autonomous actors in this straight line, cause-and-effect model of genetic influence (Crick, 1970). Studies of the genetic changes in twins over the lifespan, however, illustrate the influence of *experience* on DNA and explain why twins with the same genotype may exhibit vastly different phenotypes, including the emergence of a major psychiatric disorder in one but not the other. The DNA of monozygotic (single egg) twins is indistinguishable at birth, but “older monozygous twins exhibited remarkable differences in [the] overall content and genomic distribution” (Fraga et al., 2005, p. 10604). DNA that was virtually identical at 50 days may have after 50 years become markedly dissimilar in the instructions it provides due to the effects of experience and environment on the methylation and histone tails that influence gene expression.

With the rapid emergence of the field of epigenetics, it is now understood that the genes affecting behavior are switched on or off through complex interconnections and feedback with the body and the environment (Gottlieb, 2000). In brief, gene expression shapes behavior and behavior shapes gene expression. Emotions are particularly strong purveyors of signals to genes

(Isles, 2008; Stuffrein-Roberts, 2008), but virtually any experience may have an impact, including perceiving, thinking, moving, nurturing, being nurtured, or facing stress. As Rossi (2004) notes, “touch, sensation, movement, mental and physical activity . . . all initiate neural stimulation, which turns on the gene expression/protein synthesis cycle throughout the brain and body” (p. 38).

Animal studies have demonstrated how early nurturing impacts DNA. When rat pups are well-nurtured, gene expression is stimulated in the hippocampus and other brain regions that govern the fight-or-flight response, resulting in adult rats that are better able to manage stressful stimuli than rats who were not well-nurtured (Szyf et al., 2007). Curious about whether human brains would show similar patterns, Szyf’s research group (Poulter et al., 2008) dissected the brains of 24 individuals who had donated their organs to science. Eleven of them were from a non-clinical population who had died in accidents; the other thirteen were schizophrenics who had died by suicide. Although the schizophrenics had all the genes in the hippocampus and other brain areas that are required to dampen the stress response, these genes were methylated, which suppressed their activation. This methylation and consequent suppression of stress-modulating genes was not found in the individuals who had more auspicious childhoods. Other studies have found that depressed people have increased inflammation and impaired cell repair function (Cole et al., 2007). Assays of gene expression in unhappy people correlate with observations that people with pessimistic explanatory styles (who typically experience more negative emotions) do not cope as well with stress and are more susceptible to illness than people with more optimistic explanatory styles (Peterson, Seligman, & Vaillant, 1988). An understanding of gene expression illuminates the important roles of both nature and nurture in psychopathology.

Gene Expression and Psychotherapy

Kandel (1998) predicted that increasingly sophisticated devices for the detection of gene expression would “permit quantitative evaluation of the outcome of psychotherapy” (p. 140). Such technology is now available. For instance, in an investigation of the epigenetic effects of relaxation, a team at Harvard Medical School showed that individuals taught to elicit the relaxation response (Benson, 2000) changed the expression of 1561 specific genes (Dusek et al., 2008). In that study, the genetic profiles of individuals in an experimental group that was not trained in eliciting the relaxation response was compared to the profiles of individuals in a control group that had had such training. The experimental group then received training over a six week period in eliciting the relaxation response. After establishing and practicing this skill, the gene expression of those in the experimental group changed to resemble that of the experienced relaxers. Among the gene groups positively affected were those involved with cellular regeneration and the production of antioxidants.

In a study of a lifestyle intervention, thirty men with low-risk prostate cancer who had declined immediate surgery, hormonal therapy, or radiation participated in an intensive program involving changes in nutrition and stress-related habits while undergoing careful surveillance for tumor progression (Ornish et al., 2008). Included in the program were stress-reduction techniques such as regular meditation and daily walks. At the end of three months, prostate biopsies were compared with those taken prior to the interventions. Expression in 501 genes had been changed, including positive shifts in those that play critical roles in protein modification, intracellular protein traffic, and tumor genesis. Another study found evidence suggesting that a hearty dose of laughter, in addition to the obvious mood-altering benefits, switched the expression of 27 specific genes (Hayashi et al., 2006).

Such gene assays are accomplished through the use of DNA microarrays or “gene chips,” wafers lined with thousands of microscopic sequences of DNA. These DNA lengths will bond with any matching genes in the tissue sample that is being examined. Such DNA microarrays can assess the expression of any combination of genes in the human body during any body activity, making it possible to “identify the activity patterns of gene expression at any given moment in any condition or state of health or illness” (Rossi, 2004, p. 40). This is of obvious value in medicine, where gene expression patterns in a cancerous cell can be compared with the expression of genes in a non-cancerous cell, or differences in gene expression that impact systemic factors associated with healthy vs. pathological kidney function can be established. In psychotherapy, it becomes possible to compare gene expression profiles for chronic stress, anxiety, depression, bi-polar disorders, or psychosis with those of non-clinical populations. This allows gene expression patterns to be differentiated among specific disorders as well as the identification of the changes that are brought about by successful treatment.

Initial studies in which DNA gene chip technology was used to assess the effectiveness of clinical interventions (e.g., Dusek et al., 2008; Ornish et al., 2008) indeed revealed extensive changes in the expression of specific genes and gene cascades. Although microscopic outcomes such as altered patterns of gene expression are not typically monitored in clinical practice, the facts that gene expression *can* be altered *and* that modifications of gene expression *correlate* with cognitive, affective, and behavioral changes, offer a new framework for assessing the effects of psychotherapy. The beneficial alteration of gene expression patterns may, in fact, be the biological common denominator among all successful psychotherapies.

Biological Markers of Successful Psychotherapy

A study conducted by the Centers for Disease Control and Prevention (CDC) identified 1058 genes likely to be involved in communication pathways among the nervous, endocrine, and immune systems and whose expression can be readily assessed using clinical tests (Nicholson, Unger, Mangalathu, Ojaniemi, & Vernon, 2004). Although mapping the relationships among genotypes, gene expression, and psychopathology is still in its infancy, numerous biological markers of psychopathology that depend upon gene expression have been identified. Among the most widely recognized of these are: (a) exaggerated limbic system responses to innocuous stimuli, (b) distortions in learning and memory, (c) imbalances between sympathetic and parasympathetic nervous system activity, (d) elevated levels cortisol and other stress hormones, and (e) impaired immune functioning. Whether or not such biological markers are focused upon by a clinical intervention, successful psychotherapy modifies gene expression in ways that tend to exert positive influences in these areas of biological function. Each area is discussed here, and we will return to them in formulating testable propositions regarding the actions of psychotherapy and, in particular, of psychotherapies that utilize somatic interventions.

A. Exaggerated limbic system responses to innocuous stimuli. The acute stress response strategies (i.e., fight-or-flight) that were so adaptive for earlier generations are often liabilities for modern individuals. In Goleman's (2005) popular term, the threat survival response becomes "highjacked" for non-survival and even trivial issues, bypassing reason, squandering biological resources, sabotaging coping abilities, disrupting social relationships, and producing a range of stress-related maladies. Fight-or-flight is a global response that may recruit any of the body's organs or other systems to respond to a potential threat. It activates a cascade of chemical and electrochemical events involving genes that reach peak expression in seconds. It also

initiates electromagnetic cellular signaling, endocrine secretions, rapid production of norepinephrine and other neurotransmitters, and activation of physical structures such as the hypothalamus-pituitary-adrenal (HPA) axis to coordinate complex actions across multiple body systems (Ellis, Jackson, & Boyce, 2006). Meanwhile, biological resources are rapidly redeployed away from systems not essential for immediate survival, virtually shutting down the digestive, reproductive, and immune systems and sending blood from the brain's frontal lobes to the chest and limbs for confrontation or escape (Root, Tuescher, Cunningham-Bussel, Pan, Epstein, Altemus et al., 2009).

When this response is triggered by an unresolved traumatic memory, by a cue that is associated with a traumatic memory such as a loud sound or a tall male, or by compulsive rumination on adverse events that may or may not occur, it is biologically depleting and psychologically destabilizing. An association has been established between traumatic events and illnesses, including diabetes, cancer, and cardiovascular disease. Traumatic events increase chronic inflammation and deregulate both the HPA axis and the sympathetic nervous system (Kendall-Tackett, 2009). Resolving exaggerated responses to stimuli that unnecessarily (a) keep the limbic system in a highly alert state, (b) in a frozen state, or (c) that engulf the person in frequent episodes of acute distress requires new learning and new neural connections. Psychotherapy can alter “the expression of genes that alter the distribution and strength of specific synaptic connections” (Stahl, 2000, p. 37) in a manner that attenuates exaggerated limbic system responses to innocuous stimuli.

B. Distortions in learning and memory. The fight-or-flight response can occur whether the threat is objective and immediate, such as an external predator, or internally-generated, such as a memory, thought, or fantasy (Thayer, 2000). The amygdala plays a central role in

identifying threat, processing emotion, initiating fear-based behaviors, and in storing memories that can be accessed for evaluating future threats (Phelps & LeDoux, 2005). It may be triggered by stimuli that are (a) *hardwired*, such as the rapid entry of an object into one's visual field, (b) *conditioned* based on previous aversive consequences having become associated with the stimulus, or (c) *assessed as dangerous* based on memories stored in the amygdala, hippocampus, and prefrontal cortex (Ruden, in press). In addition to fear-based responses, the whole range of problematic emotions—from anger and jealousy to depression and grief—may be subject to the influence of conditioning, although most existing research has focused on conditioned fear.

In conditioning that forms an association between a sensory cue and a maladaptive response, genes are activated, “inducing them to make proteins” so the stimulus “acquires the ability to elicit strong excitation in the amygdala [and] travel with ease to [the amygdala's] central nucleus, where the floodgates of emotional reactivity are opened” (LeDoux, 2002, p. 215). In more complex responses than simple conditioning, brain regions having to do with the context of the immediate stimulus become involved (e.g., a snake in a forest evokes a different response than a snake in a glass cage at a zoo). The hippocampus governs contextual associations. The hippocampus and the prefrontal cortex are both involved with higher order comparisons and analysis. When experiences involving emotional arousal are stored, the amygdala is able to make such memories more vivid and imbue them with stronger emotional content, potentially leading to what LeDoux (2002) has called the “hostile takeover of consciousness by emotion” (p. 226). Psychotherapy treats distortions in learning and memory by creating corrective experiences which can then be consolidated into long-term memory via the process of gene expression modulating the neuroplastic synaptic connections in the brain.

C. Imbalances between sympathetic and parasympathetic nervous system activity.

The sympathetic and parasympathetic components of the autonomic nervous system maintain a complex homeostatic balance in non-clinical populations (Berntson, Norman, Hawkley, & Cacioppo, 2008). The sympathetic system enhances vigilance and prepares the body for vigorous physical activity by speeding the heart, dilating the pupils, reducing digestive secretions, and contracting the blood vessels. Its actions are opposed by the parasympathetic system, which slows the heart, constricts the pupils, stimulates digestive secretions, and dilates the blood vessels in order to produce relaxation and promote cell regeneration. Prolonged stress suppresses parasympathetic activity, shifting the balance toward sympathetic activity. High sympathetic/low parasympathetic ratios have been linked to both psychological and physiological disorders and may, in fact, “be the final common pathway linking negative affective states and conditions to ill health” (Thayer & Brosschot, 2005, p. 1050). Genes involved with sympathetic activity such as C-fos and Egr-1 switch on during stress, and transient increases in their activity may progress into “prolonged (potentially adaptive or maladaptive) changes in gene expression” (Sabban & Kvetnansky, 2001).

People who are chronically high in sympathetic activation are characterized by impatience and irritability and tend to suffer from stress-related symptoms such as heart problems, high blood pressure, and insomnia (Rechlin, 2002). People who are high on the parasympathetic side may be more calm and enjoy greater physiological equilibrium than others, qualities that are associated with meditators (Wu & Lo, 2008). More frequently, however, this parasympathetic dominance represents a collapse following extended periods of aggravated sympathetic stimulation and is associated with depression, hopelessness, diminished motivation, fatigue, and a weakened immune system. The relative balance between sympathetic and

parasympathetic activity is reflected in variability in the elapsed time between heartbeats, known as heart rate variability (Andrasik & Lords, 2004). Heart rate variability has been used as an assessment of therapeutic progress as well as a real-time clinical biofeedback tool in part because it reliably registers stress, correlating closely with other stress measures (McCraty, Atkinson, Lipsenthal, & Arguelles, 2009). Shifts in sympathetic and parasympathetic balance during the course of psychotherapy may be readily tracked through measures of heart rate variability.

D. Elevated levels of cortisol and other stress hormones. Where stress-induced sympathetic/parasympathetic imbalance is an *autonomic nervous system* marker of vulnerability to mental and physical illnesses, cortisol and other stress hormones such as dehydroepiandrosterone (DHEA) are prominent *chemical* markers of stress and its sequelae. Cortisol, a hormone produced by the adrenal cortex, influences blood pressure, blood glucose, immune function, and inflammatory responses. During the acute stress response, it is secreted in elevated levels and is responsible for stress-related changes in the body that include quick bursts of energy, heightened memory, increased immunity, and lowered sensitivity to pain (Ebrecht et al., 2004). With prolonged stress, however, chronic high levels of cortisol in the bloodstream produce negative effects such as impaired cognitive performance, increased blood pressure, decreased bone density, compromised muscle tissue, suppressed thyroid function, increased abdominal fat, and lowered immunity. DHEA, also produced by the adrenal cortex, is the most abundant steroid hormone in the bloodstream, playing a central role in the body's unending task of cell regeneration (Morfin, 2002). It is also distinguished by its ability to be converted into other hormones, such as estrogen, testosterone, or melatonin, when their levels become low. Although DHEA concentrations diminish naturally with age, prolonged stress may result in deleterious DHEA deficiencies as its precursors, progesterone and pregnenolone, are recruited to

produce cortisol instead. If stress signals the adrenal medulla to produce a high cortisol output for prolonged periods, both cortisol and DHEA become depleted due to a scarcity of these precursors. This condition is known as “adrenal fatigue.” It has been associated with major depressive disorder and PTSD (Maes et. al., 2007). As psychotherapy reduces stress, it may stimulate the expression of genes such as CREB, AP-1, and Nurr-77 that play a role in adrenal regulation.

E. Impaired immune functioning. Numerous studies have found that successful psychotherapy enhances immune functioning (Atanackovicab, Krögerc, Serked, & Deterb, 2004; van der Pompe, Duivenvoorden, Antoni, Visser, & Heijnen, 1997). Adverse childhood experiences, on the other hand, may compromise immune functioning. A dramatic illustration of the longterm effects of early emotional events on health emerged from a study of 17,421 adults conducted by Kaiser Permanente’s Department of Preventive Medicine, in collaboration with the U.S. Centers for Disease Control and Prevention (Felitti, Anda, Nordenberg, Williamson, Spitz, Edwards, 1998). The researchers collected information about “adverse childhood experiences” (ACE) for each patient and scored them from 0 to 8 in terms of the presence or absence of eight categories of detrimental formative events such as physical, emotional, or sexual abuse, loss of a parent, family violence, or a family member who was chronically depressed, mentally ill, or suicidal or who abused drugs or alcohol. The subjects were followed for 10 years. High ACE scores correlated with high medical utilization and diseases including cancer, heart disease, hypertension, diabetes, and hepatitis as well as behaviorally-induced health disorders such as obesity, fractures, unintended pregnancy, and sexually transmitted diseases. A person with an ACE score of 4 (on the scale of 0 to 8) was, for instance, 390 percent more likely to have chronic obstructive pulmonary disease than a person with an ACE score of 0. Links between childhood

trauma, depression, and a variety of biological markers have also been identified (Heim, Newport, Mletzko, Millera, & Nemeroff, 2008). In a classic study with strong implications for the effects of psychotherapy in counteracting the negative impact of adverse childhood experiences on health, patients who disclosed traumatic events they had not shared with others showed marked improvements in immune function and fewer physician visits (Pennebaker, Kiecolt-Glaser, & Glaser, 1988). The effects of psychotherapeutic interventions on the activation of genes that impact immunity and other systemic health factors is another measure for comparing the effectiveness of psychotherapeutic approaches.

Psychological Outcomes from Exposure/Acupoint Stimulation Protocols

A relatively new genre of psychotherapies—utilizing techniques such as “somatic experiencing” (Heller & Heller, 2004; Levine, 1997), “bilateral stimulation” (Shapiro, 2002), and “integrative energy treatment” (Clinton, 2006)—introduces focused somatic interventions into the clinical process. One such approach combines the manual stimulation (touching, tapping, or massaging) of acupuncture points (acupoints) with psychological exposure techniques (Gallo, 2005). Called “energy psychology,” in keeping with traditional explanations that acupuncture moves “vital” energies in the body (Stux, Berman, & Pomeranz, 2003), the approach utilizes imaginal or in-vivo exposure, the single psychological treatment strategy whose effectiveness has been decisively demonstrated for severe anxiety disorders such as PTSD (Benedek, Friedman, Zatzick, & Ursano, 2009; Committee on Treatment of Posttraumatic Stress Disorder, 2008).

Although some of the procedures in exposure/acupoint treatments resemble those in other exposure therapies, the distinguishing feature is the stimulation of acupoints, sending signals to the amygdala and other brain structures that rapidly reduce hyperarousal (Hui et al., 2005, Fang

et al., 2009). In exposure/acupoint treatments, the exposure increases arousal while the simultaneous acupoint stimulation reduces arousal. These conflicting inputs are resolved, assuming nothing aversive occurs in the environment, with arousal being reduced. The triggering cue then becomes associated with a neutral emotional state. This leads to conditioned fear pathways being overridden (Rothbaum & Foa, 1996/2007) or depotentiated (eliminating long-standing signal transmissions between neurons; Ruden, in press). Acupoint stimulation appears, based on clinical reports and early empirical evidence, to be substantially more powerful than reciprocal inhibition and other exposure strategies that utilize methods such as progressive relaxation or diaphragmatic breathing as the somatic intervention (Feinstein, in press).

In addition to the purported ability of acupoint tapping to enhance the effectiveness of exposure treatments, a review article in *Primary Care and Community Psychiatry* concluded that combining acupoint tapping with talk therapy “vastly enhances the effectiveness of psychotherapy” (Mollon, 2007, p. 127). Another review, after surveying existing studies, concluded that the approach “has reached the minimum threshold for being designated as an evidence-based treatment, with one form having met the APA Division 12 criteria as a ‘probably efficacious treatment’ for specific phobias; another for maintaining weight loss” (Feinstein, 2008a, p. 199). Exposure/acupoint protocols are also leading to reports of unusually rapid and powerful outcomes with disaster survivors, war veterans, and others suffering with PTSD.

The approach typically combines three components. The first is psychological exposure. The client brings to mind and sometimes describes a distressing memory or trigger, such as "My sixth birthday party was spoiled when my mother threw the lamp at my father and it smashed on the wall next to his head" or "Blood and body parts were everywhere when the rocket hit our

camp." The second component is designed to bring about a cognitive shift via wordings that emphasize self-acceptance, realistic possibilities, previous gains, and adaptive beliefs. The third component is the stimulation, usually by tapping with the fingertips, of specified acupoints. The form used in most research protocols, Emotional Freedom Techniques (EFT), employs thirteen acupoints (www.SoulMedicineInstitute.org/EFT.pdf). The client rates the intensity of the memory before and after the procedure and performs the procedure again if the distress level remains high. The protocol takes about a minute and may be performed on several memories during the course of an hour-long therapy session. Related approaches such as Thought Field Therapy (TFT) and Tapas Acupressure Technique (TAT) use different sequences, points, and statements, but all include some form of psychological exposure, cognitive intervention, and acupoint stimulation.

In the first randomized controlled trial using an exposure/acupoint protocol with PTSD, 41 of 49 veterans, all of whom exceeded the PTSD cutoff score on the military version of the Post-Traumatic Stress Checklist before treatment, were no longer within the PTSD range after 6 one-hour sessions (Church et al., 2010). Mean scores decreased from 63 to 36 (the PTSD cutoff is 50) while scores for a waitlist control group remained essentially unchanged. These findings are corroborated by earlier outcome studies with both veterans (Church, 2010; Church, Geronilla, & Dinter, 2009) and with disaster victims (Feinstein, 2008b). Preliminary findings with adolescents have been even more encouraging, with a *single* session of EP reliably reducing scores on standardized tests from above to below PTSD cutoffs in two independent studies. Fifty adolescents who had been orphaned and traumatized twelve years earlier by the ethnic cleansing and warfare in Rwanda still exhibited symptoms of PTSD. On average, they were well above the cutoff for PTSD on two standardized measures, one a self-report inventory and the other an

inventory completed by one of their caretakers at the orphanage. After a single imaginal exposure/acupoint session of 20 to 60 minutes combined with approximately six minutes learning two relaxation techniques, the average scores on both measures were substantially below the PTSD cutoff ($p < .0001$ on each). Interviews with the adolescents and their caretakers indicated dramatic reductions of symptoms such as flashbacks, nightmares, bedwetting, depression, withdrawal, isolation, difficulty concentrating, jumpiness, and aggression. On post-tests one year later, scores on both inventories held, and interviews with the teens corroborated the durability of the improvements (Sakai, Connolly, & Oas, 2010). In an RCT with 16 abused male adolescents who scored above PTSD thresholds, each subject in the treatment group ($n = 8$) scored below PTSD thresholds thirty days after a single treatment session while none in the wait list control group ($n = 8$) showed significant change (Church, Piña, Reategui, & Brooks, 2009).

Meanwhile, in one of the strongest studies demonstrating the efficacy of Cognitive Behavior Therapy (CBT), widely considered the “treatment of choice” for PTSD (Bryant et al., 2008, p. 555), 60 percent of subjects still met the criteria for PTSD after 12 sessions and 50 percent showed no symptom relief at all (Monson et al., 2006), a finding that is consistent with other CBT studies (Barlow, Allen, & Choate, 2004; Bryant, 2008). The contrast between these findings and the findings reported in preliminary studies of exposure/acupoint treatments with PTSD are so large that additional mechanisms of action, as described above, have been postulated. When a trauma-related memory or cue is activated via psychological exposure, causing limbic hyperarousal, extinction can be facilitated by simultaneously stimulating acupoints that send signals to the amygdala which reduce hyperarousal. This explanation is supported by fMRI studies of the impact that stimulating specified acupoints has on downregulating limbic system activity (Hui et al., 2000, 2005; Dhond, Kettner, & Napadow,

2007). To provide a more vivid understanding of the outcomes reported in the studies of PTSD treatments that utilize exposure/acupoint protocols, a 10-minute video is recommended that includes brief excerpts from the exposure/acupoint treatments of four war veterans and of pre- and post-treatment interviews (retrieved November 17, 2009, from <http://www.vetcases.com>). A case study that is also representative of the outcomes found in the studies mentioned above can serve this purpose as well:

A U.S. Coast Guard veteran who had served as the only female in an elite search and rescue unit had been on medical disability since 1993 for both psychiatric causes (PTSD) and physical conditions (spinal injury and tendonitis). She had frequently been in life-threatening situations during non-combat rescue operations and had also suffered severe sexual assaults while in the military. She scored 76 on the military version of the standardized PTSD Checklist (scores above 49 exceed the PTSD cutoff) administered immediately before commencing exposure/acupoint treatments in April of 2008. Severe sleep disorder was a pervasive underlying symptom. Previous treatment included years of individual and group counseling at the Veterans Administration, psychiatric medications, a course of in-patient treatment as a result of high suicidality/homicidality, PTSD Awareness Training, a program at the University of New Mexico that focused on reducing nightmares in PTSD patients, and a variety of auxiliary approaches such as Transcendental Meditation and nutritional counseling. None provided significant or sustained symptom reduction.

Treatment consisted of four 90-minute telephone sessions using an exposure/acupoint approach known as EFT (“The Emotional Freedom Techniques”) administered over a 10-day period. One month after the final session, the PTSD Checklist scores had dropped from 72 to 47, falling below the PTSD cutoff, and the sleep disorder symptoms had resolved. At that time, the patient provided a written narrative, commenting that after all her previous treatments: “I still couldn’t fall asleep. I couldn’t remain asleep without waking up repeatedly during the night. And I was plagued by repeated traumatic nightmares every night. Sleep was my enemy, and I fought it every night, waking up exhausted and tired . . . Within two sessions [of EFT], I felt myself release all the associated trauma, emotions, and obsessions that interfered with my sleep. Sleep became an easy and gentle activity free from worry and fretting. . . . No more nightmares.” One-year post-treatment, she reported having self-applied the tapping protocol almost daily and her PTSD Checklist score was down to 32. (This case was provided by the practitioner, Ingrid Dinter).

Physiological Outcomes from Exposure/Acupoint Stimulation Protocols

Reports such as the above, where exposure/acupoint treatments were effective after extensive CBT and other therapies were not, are appearing with increasing frequency and are backed by the preliminary empirical studies and reviews that were cited. Emerging explanatory models for these outcomes draw upon current understanding of conditioning and extinction in the use of exposure techniques for treating anxiety disorders (e.g., Lane, 2009).

One of the most puzzling outcomes of exposure/acupoint treatments, however, is their apparent effectiveness with conditions for which exposure treatments are not usually considered effective, including improvements in a varied range of other psychological as well as physical conditions. That exposure/acupoint protocols would produce effects with other emotional conditions that are similar to those it produces with anxiety-based disorders is not entirely surprising. Since the amygdala governs a wide range of emotions (Phelps & LeDoux, 2005), any maladaptive emotion that is activated while a deactivating signal is sent to the amygdala (via acupoint stimulation) could plausibly undergo the counter-conditioning seen in the treatment of anxiety disorders. But this same protocol has also been reported as efficacious in overcoming physical symptoms that would not be expected to radically improve based on psychotherapeutic interventions alone.

A website (<http://emofree.com>) that has archived several thousand case reports using EFT, one of the most popular psychological exposure/acupoint protocols, describes more than a hundred cases where EFT is reported to have produced distinct improvements in headaches, back pain, stiff neck, joint pains, cancer, chronic fatigue syndrome, lupus, ulcerative colitis, psoriasis, asthma, allergies, itching eyes, body sores, rashes, insomnia, constipation, irritable bowel syndrome, eyesight, muscle tightness, bee stings, urination problems, morning sickness, PMS, sexual dysfunctions, sweating, poor coordination, carpal tunnel syndrome, arthritis, numbness in the fingers, stomachaches, toothaches, trembling, and multiple sclerosis among many other physical conditions. In addition to these anecdotal accounts, a peer-reviewed case history database on exposure/acupoint treatments, which requires an initial physician diagnosis of medical conditions and a post-treatment physician diagnosis, can be found at

<http://www.casehistorydatabase.org> (log in as “guest,” password not required). Three representative samples from that database follow.

Cancer. A 52-year-old woman was diagnosed in March 2004 with metastasized Stage IV breast cancer and given a four-month terminal prognosis. Her physician advised an aggressive course of surgery, chemotherapy, and radiation. The patient was a professional health care worker who had witnessed the diminished quality of life of patients undergoing similar protocols, and she elected to have no treatment. She had used EFT on a number of personal issues and decided to pursue EFT treatments that focused on the emotional issues that had surfaced after her diagnosis. She received six sessions lasting between 60 to 90 minutes shortly after the cancer diagnosis. According to the practitioner’s report on the database, these sessions “collapsed core negative beliefs around body and health.” During and following the treatments, the patient reports having tapped on herself almost every day and often many times a day focusing on traumatic childhood memories and other emotional issues. A follow-up examination by the diagnosing physician eight months after the initial diagnosis found no trace of cancer in her body; only scar tissue where the tumors had been.

Allergies. A 54-year-old woman had developed allergies to more than 80 substances, ranging from cats and dogs to grass and trees. She sought treatment with an allergy specialist in December 1999 but gained little relief and no cure from medical treatments provided by him or by two subsequent physicians. In 2003, her husband, who had recently been introduced to EFT, applied it to one of her allergies, lawnmower exhaust. Her report in the data base describes how “The

allergy went completely away. That got my attention and, for the next 3 months, we used EFT consistently for my allergies and all allergies are now gone from my system. During this time I dropped all medications.” Medical tests in March 2004 confirmed that she was indeed free of all allergies. Her husband’s comment in the database is that, “This was astonishing to me. My wife was near having to live in a bubble. [Now] she has no allergic symptoms whatsoever.”

Fibromyalgia. A 54-year-old woman was diagnosed with fibromyalgia, chronic fatigue syndrome (CFS), and PTSD in March 1993. Over the next decade she was prescribed numerous medications, but she received little benefit and the side effects worsened her overall health. In February of 2005, she began using EFT. Her practitioner’s description on the database describes severe overall body pain: “It hurt to walk, sit, lie, or move. Even her eyelids hurt and pain persistently pulsed throughout her body. On pain scale of 0-10, her pain was almost perpetually at a 10. She had complained of sleeplessness for a few years but was reluctant to take sleep medication. Her cognitive abilities were thus very poor, mainly from lack of sleep.” Seven in-office EFT sessions were provided along with e-mail and telephone support for back-home application. The patient was able to discontinue all pain and sleep medication within weeks, and a medical diagnosis in June 2006 showed her to be free of the three initial conditions. The patient’s statement on the database: “I no longer have any symptoms of fibromyalgia, CFS, pain, PTSD, or insomnia. Diligent use of EFT was the only healing method that created this result.”

An unpublished case study by one of the authors (Church) used pre- /post-laboratory tests in comparing changes in stress as measured by cortisol levels following two treatment conditions. A 57-year-old male psychiatric nurse suffering from depression was provided with a 50-minute supportive counseling session based on the principles of Cognitive Behavior Therapy (after listening to his concerns, the therapist suggested adopting new cognitions that were formulated to modify habitual errors in thinking associated with depression). A month later, at the same time of day (cortisol levels vary with time of day), he was provided with a 50-minute EFT session. The EFT session focused on a distressful memory and treated it using a standard exposure/acupoint protocol. Cortisol readings were taken immediately prior to each session and thirty minutes after the session (a delay necessary for cortisol reuptake). Cortisol levels following the supportive therapy session increased 40 percent while levels following the EFT session decreased 48 percent, suggesting that the supportive therapy treatment activated the cortisol but did not resolve the distress while the EFT both lowered the cortisol and the distress.

The above instances of exposure/acupoint protocols resulting in improvements in physical conditions are limited to anecdotal reports and single-case studies. A number of systematic investigations have also been conducted. In a randomized controlled trial, 26 women diagnosed with fibromyalgia who had been on sick leave for at least three months were taught EFT using an internet-based training program and were provided personal e-mail support (Brattberg, 2008). At the end of the eight-week treatment program, they showed significant improvement, as compared to a wait list group, in measures including pain, anxiety, depression, vitality, social function, activity level, and performance problems with work due to physical limitations.

A recent study of 216 health care workers found a 68% reduction in self-reported physical pain on an 11-point Likert-type scale after twenty minutes of self-applied EFT ($p < .001$) administered in groups during presentations at five professional conferences (Church & Brooks, in press). This was one of five outcome studies that showed improvement on the somaticization scale of the Symptom Assessment-45 inventory (SA-45) before and after exposure/acupoint protocols. The SA-45 is a short form of the Symptom Checklist 90 (SCL-90) and assesses the same nine symptom domains as the SCL-90, such as somatization, anxiety, depression, hostility, and obsessive-compulsive tendencies. It also has two global scales, the Global Severity Index and the Positive Symptom Total, which assess the severity and breadth of symptoms. Both forms have been well validated (Davison et al., 1997; Maruish, 1999). The five studies included both clinical and non-clinical populations, and their findings on four measures of the inventory are summarized in Figures 1 – 4. The groups included:

1. 216 participants in professional conferences who attended a workshop on EFT (Church & Brooks, in press).
2. 39 participants of a “Healing the Cycle of Addiction” weekend EFT workshop which included practitioners specializing in addiction as well as individuals wishing to address their own addiction issues (Church & Brooks, 2009).
3. 102 participants in an 18-hour EFT weekend training (Rowe, 2005).
4. 11 military veterans or family members with PTSD or PTSD symptoms who received 10 to 15 hours individual EFT sessions over a 5-day intensive treatment period (Church, 2010).
5. 7 military veterans who received six EFT sessions focusing on combat and other traumatic memories (Church, Geronilla, & Dinter, 2009).

In all five studies, pre-/post-test improvements on the SA-45 were found across all nine domains as well as on the two global scales. All five studies administered the SA-45 immediately before and immediately after the EFT workshop or treatments. Two of the studies made additional assessments 30 days pre-treatment and immediately before the start of treatment, indicating no significant change in symptoms due to the passage of time. The zero value on the X axis in Figures 1 - 4 is the lowest possible normal score on the SA-45, while clinical conditions are indicated by a value above 20. Subjects in three of the studies were just below 20 at pretest while subjects in two of the studies, veterans with PTSD or PTSD symptoms, had high clinical scores. In addition to a global severity index for all five groups (Figure 1), values on three of the nine specific scales are presented for comparison purposes: somatization (Figure 2), anxiety (Figure 3), and depression (Figure 4).

Figure 1: Global Severity Index of All Psychological Conditions

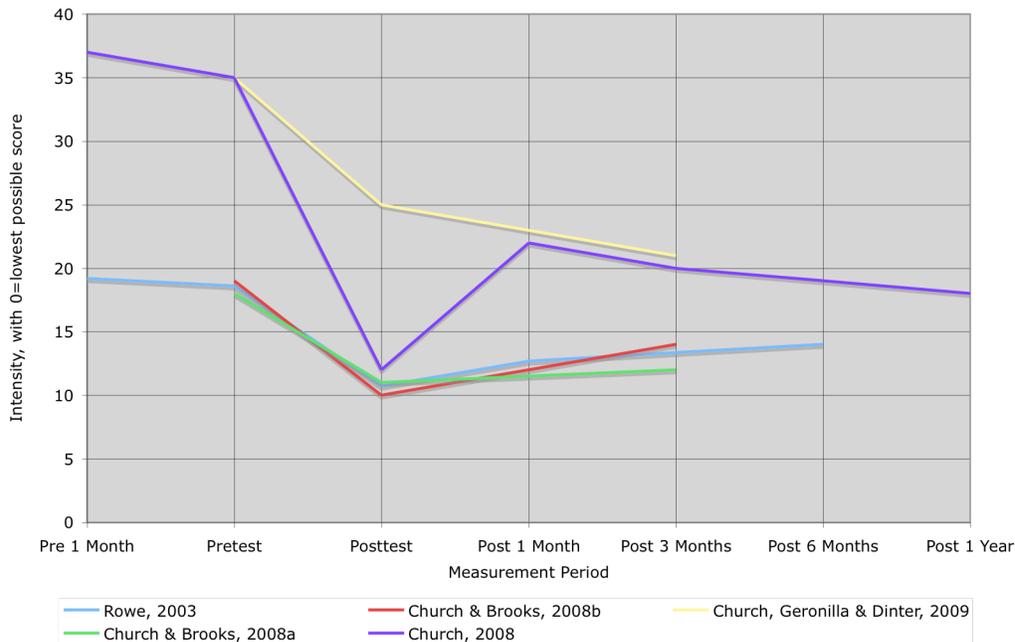


Figure 2: Somatization

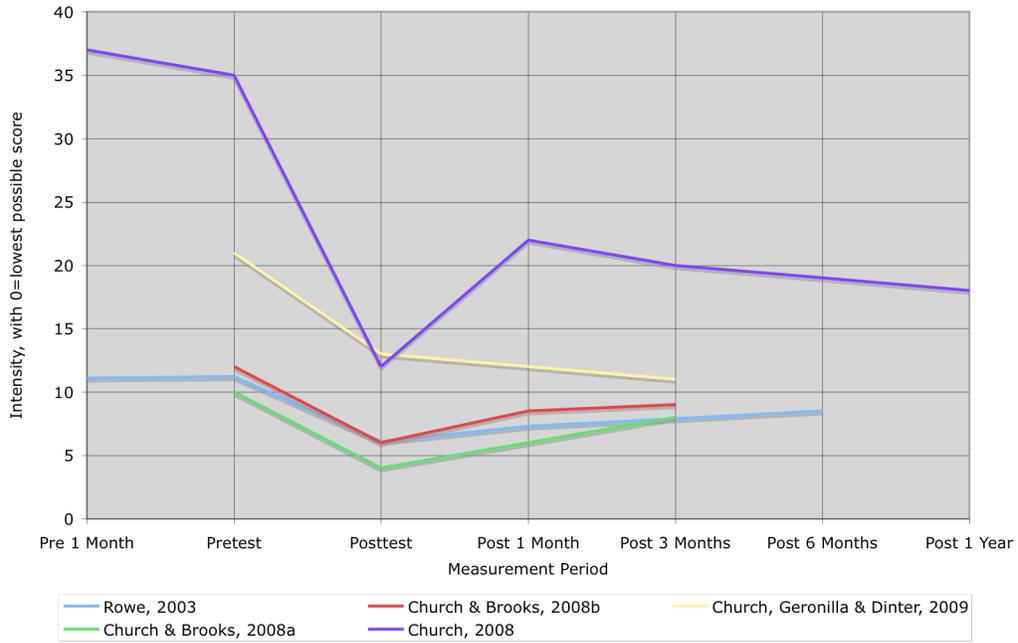


Figure 3: Anxiety

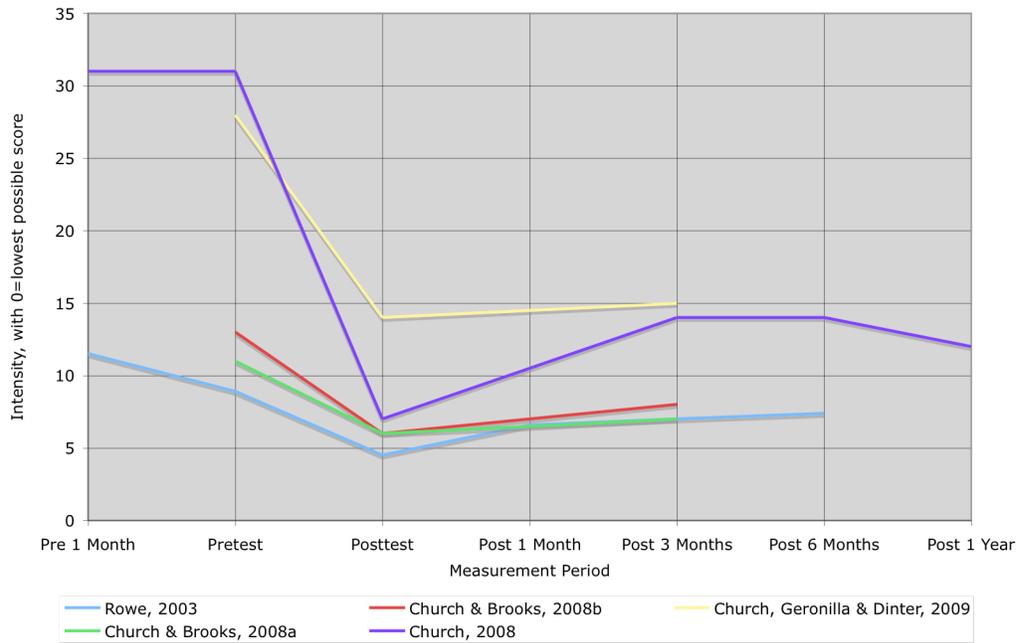
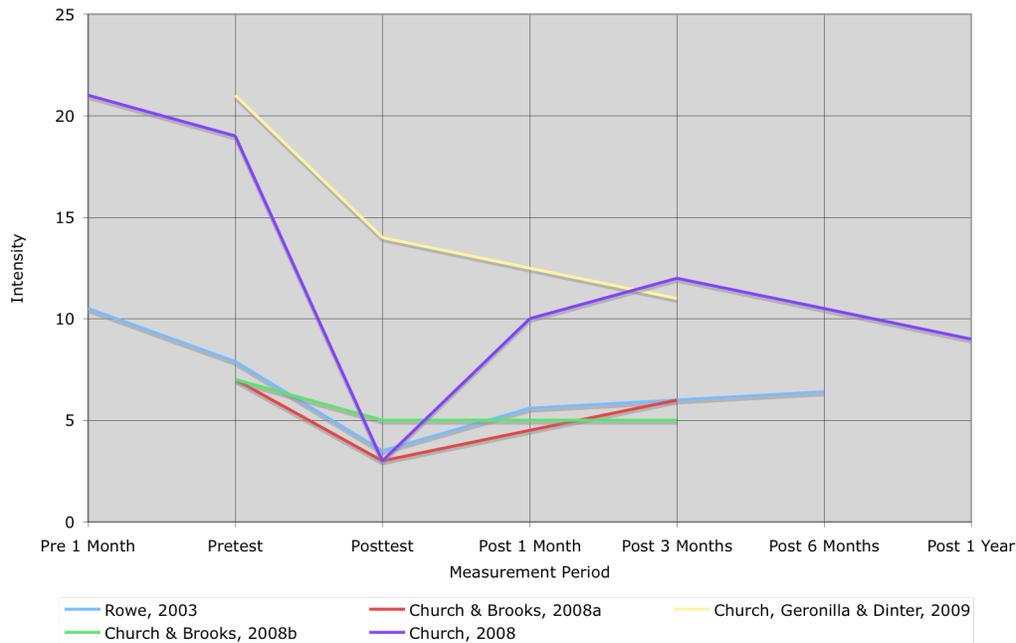


Figure 4: Depression



In all five studies, pre- to post-treatment decreases in the nine specific scales as well as the two global scales were significant. As seen in the representative scales in Figures 1 – 4, symptom scores consistently decreased immediately after treatment, increased somewhat in the subsequent period, and then leveled off, remaining significantly lower than pre-treatment scores. Permanent improvement occurred in psychological symptoms, stress levels, and physical complaints (captured in the somatization measures) following the treatment. Although these were uncontrolled outcome studies, they allow comparisons of an exposure/acupoint protocol with varying populations and treatment conditions and, as noted earlier, their findings are corroborated by two recent RCTs (Church et al., 2010; Church, Piña, Reategui, & Brooks, 2009). We propose that the wide range of conditions improved by these therapies is not because the exposure/acupoint protocols target each specific condition but because of the generic effects of shifting gene expression in the five areas discussed earlier.

Changes in Gene Expression as the Best Available Explanatory Mechanism

Preliminary empirical evidence regarding exposure/acupuncture treatments—which has progressed from clinical reports to outcome studies with standardized pre/post-measures to a handful of RCTs—consistently points toward efficacy. Explanatory models that identify the mechanisms involved in the exposure/acupoint treatment of conditions other than anxiety-based disorders are not, however, available. The need to “delineate the mechanism of action that produces [the] observed efficacy” of psychotherapies that utilize the stimulation of acupoints was, in fact, highlighted in a recent review of theoretical and methodological problems in research on exposure/acupoint protocols (Baker, Carrington, & Putilin, 2009). In attempting to address this need, we formulated the following hypothesis, based on the biological and clinical data presented above, to account for the range of clinical outcomes being reported following exposure/acupoint treatments:

Exposure/acupoint treatments modulate, with unusual speed and power, gene expression for specific as well as systemic therapeutic gains.

An example of a “specific” therapeutic gain would involve activating the genes that produce synaptic changes that result in the extinction of a maladaptive conditioned response. A

“systemic” gain might be the restoration of balance between the sympathetic and parasympathetic nervous systems or the reduction of chronically elevated cortisol levels.

Comparisons with other forms of psychotherapy would be a next step toward investigating this hypothesis.

An Experimental Plan

A number of propositions can be tested which would confirm or disconfirm the above hypothesis. These propositions are keyed to the earlier discussion of five areas of biological change in successful psychotherapy that are dependent on shifts in gene expression patterns.

Based on existing clinical reports and early empirical evidence about exposure/acupoint protocols, a post-treatment prediction is formulated for each of the five areas of biological change:

1. *Exaggerated limbic system responses to innocuous stimuli.* Gene expression analysis, as well as MRI, SPECT, and PET brain scans, will show decreased post-treatment limbic system activity in response to the mental activation of cues that had initiated the stress response at the onset of treatment.
2. *Distortions in learning and memory.* Gene expression analysis will show that corrective therapeutic experiences using somatic interventions such as acupoint stimulation will lead to the expression of genes involved in the encoding of long-term memory.
3. *Imbalances between sympathetic and parasympathetic nervous system activity.* Gene expression analysis, as well as heart rate variability measures, will show an increase of post-treatment parasympathetic activity and a decrease in sympathetic activity following treatment.
4. *Elevated levels of cortisol and other stress hormones.* Gene expression analysis, as well as stress biochemistry tests, will show decreased immediate post-treatment cortisol levels in the short term and, over time, a regularization of the diurnal cortisol cycle and (assuming sufficient pregnenolone and progesterone are bioavailable) an increase of overall DHEA levels.
5. *Impaired immune functioning.* Gene expression analysis will show increased expression of the genes that promote immune function and that reduce chronic inflammation following treatment that addresses early childhood trauma.

Moreover, we predict that these outcomes will be stronger for exposure/acupoint treatments than for therapies that do not have a psychoactive somatic component such as acupoint stimulation. Finally, we predict that dismantling studies examining the efficacy of the somatic and the cognitive components of exposure/acupoint protocols will show that both together are more efficacious than either in isolation.

Unresolved Issues

As research evidence supporting the effectiveness of exposure/acupoint protocols has been accumulating, a number of controversies have emerged regarding the way the approach may be best understood and applied (Feinstein, 2009). In addition to unresolved issues involving efficacy and the mechanisms of action, questions still remain regarding the most effective protocols, the conditions most likely to respond to treatment, and the relationship of the method to other forms of clinical practice. For instance, most clinicians use exposure/acupoint stimulation as a supplemental technique rather than an independent, self-contained modality, applying it during peak engagement with stressful content or for shifting maladaptive response patterns that are uncovered in the therapy. Although this reflects the flexibility of the approach, it confounds attempts to isolate its active ingredients or establish the most effective procedures.

Questions also remain regarding similarities and differences in the active ingredients of exposure/acupoint protocols and other somatic interventions, such as Levine's (1997) "somatic experiencing," Shapiro's (2002) "eye movement desensitization and reprocessing" (EMDR), and Clinton's (2006) "integrative energy treatment." Some practitioners, such as Ruden (in press), believe that virtually any innocuous sensory stimulation while an anxiety-producing memory or cue is mentally activated can permanently reduce physiological arousal to the memory or cue. Although

there is some evidence that stimulating specific acupoints sends regulatory signals to the limbic system, it is also possible that the procedure simply sends the amygdala physiological information that is incongruent with the fearful content of the memory or cue that has been mentally activated, resulting in rapid inhibition of the acute stress response. As we point out to our students, “In the language of evolutionary biology, you wouldn’t be tapping if you were being chased by a tiger.”

Conclusion

The decisive role of gene expression in mental health that has been established in recent years underscores the need for and the potential of non-drug therapies that are particularly effective in modulating the expression of regulatory genes for psychotherapeutic gain. Five areas of biological change in successful psychotherapy that are dependent upon precise shifts in gene expression produce specific (e.g., extinguishing maladaptive conditioned responses) as well as systemic (e.g., redressing sympathetic/parasympathetic nervous system imbalances) outcomes. Preliminary evidence suggests that combining somatic interventions—acupoint stimulation in particular—with other clinical procedures may increase the speed and power of the treatment. These provocative findings may be explained in terms of the ability of specific non-invasive somatic interventions to bring about a favorable orchestration of gene expression. This proposition may be tested by using available technologies for analyzing gene expression and other biological markers to compare exposure/acupoint protocols with other therapies. If it is confirmed that an exposure/acupoint approach is more effective for producing the rapid modulation of psychologically advantageous gene expression than therapies that do not include a somatic component, the integration of exposure/acupoint protocols into established therapies would be indicated.

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