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Epigenetic Effects of PTSD Remediation in Veterans Using Clinical Emotional Freedom Techniques: A Randomized Controlled Pilot Study

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Abstract

Purpose: To assess the feasibility of measuring changes in gene expression associated with post-traumatic stress disorder (PTSD) treatment using emotional freedom techniques (EFT).

Design: Participants were randomized into an EFT group receiving EFT and treatment as usual (TAU) throughout a 10-week intervention period and a group receiving only TAU during the intervention period and then receiving EFT.

Setting: A community clinic and a research institute in California.

Participants: Sixteen veterans with clinical levels of PTSD symptoms.

Intervention: Ten-hour long sessions of EFT.

Measures: Messenger RNA levels for a focused panel of 93 genes related to PTSD. The Symptom Assessment 45 questionnaire, Hospital Anxiety and Depression Scale, Insomnia Severity Scale, SF-12v2 for physical impairments, and Rivermead Postconcussion Symptoms Questionnaire.

Analysis: Pre-, posttreatment, and follow-up mean scores on questionnaires were assessed using repeated measures 1-way analysis of variance. A Student *t* test and post hoc analyses were performed on gene expression data.

Results: Post-traumatic stress disorder symptoms declined significantly in the EFT group (−53%, $P < .0001$). Participants maintained their gains on follow-up. Significant differential expression of 6 genes was found ($P < .05$) when comparing the expression levels before and after the intervention period in participants receiving EFT.

Conclusion: Study results identify candidate gene expression correlates of successful PTSD treatment, providing guidelines for the design of further studies aimed at exploring the epigenetic effects of EFT.

Keywords
gene expression, epigenetics, EFT, emotional freedom techniques, PTSD, veterans

Introduction

The prevalence of post-traumatic stress disorder (PTSD) and its common perception as "a treatment-resistant and refractory condition"[1] has led to extensive investigation of treatments that might ameliorate PTSD symptoms. One such therapy is emotional freedom techniques (EFT). Emotional freedom technique combines elements of established methods such as exposure and cognitive therapies with somatic stimulation in the form of acupressure (fingertip pressure on acupuncture points). It is described in a treatment manual that has been available since the inception of the method.[2,3]

Outcome studies of EFT have assessed its efficacy for a variety of psychological and physical conditions. A number of these examine PTSD symptoms after EFT treatment and find significant treatment effects.[4-10] A meta-analysis of 7 randomized controlled trials of EFT for PTSD found robust treatment effects.[11] Emotional freedom techniques have been

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studied in active duty service members as well as veterans; a service evaluation of 764 participants in Fort Hood's Warrior Combat Stress Reset Program found significant reductions in PTSD, anxiety, and depression—all $P < .01$.[12] Yet despite its simplicity and clinical utility, EFT has faced a considerable degree of difficulty in crossing the "translational gap" between health-care research innovation and mainstream clinical implementation.[13]

Several studies have sought to elucidate the physiological mechanisms of action of EFT. One used electroencephalogram (EEG) to examine the brain waves of motor vehicle accident survivors before and after EFT.[14] Another used EEG to evaluate claustrophobics.[15] Both teams found regulation of the frequencies characteristic of fear. Of particular relevance to PTSD, in which emotional hyperarousal plays a crucial role, functional magnetic resonance imaging studies have shown acupuncture to produce downregulation of the amygdala and other areas of the limbic system activated by the fear response.[16-19]

Another physiological mechanism that has been investigated is endocrinal signaling. A triple-blind randomized controlled trial compared psychological symptoms and levels of the stress hormone cortisol in 83 participants before and after a single-therapy session.[20] One treatment group received a supportive interview (SI), a second, EFT, and a third, no treatment (NT). Overall psychological symptoms diminished more than twice as much in the EFT group. A reduction in cortisol levels of -24.39%, -14.25%, and -14.44% was seen for the EFT group, SI group, and NT group, respectively, which significantly linked to psychological improvement.

Concurrently, recent advances in the field of PTSD research are pointing to the relevance of epigenetic processes to the development and maintenance of symptoms. Although genetic mechanisms describe the stable influence of inherited genotypes throughout an organism's lifetime, epigenetic mechanisms refer to labile molecular processes by which environmental stimuli coming to cells lead to changes in the degree of expression of specific genes within cells.

Epigenetic modifications vary between cell and tissue types, illustrating the potential complexity of environmental effects on gene regulation within any single organism.[21] The most well-studied epigenetic mechanism observed in mammals is DNA methylation,[22] in which DNA methyltransferase enzymes bind a methyl group to DNA nucleotides at particular sites. This methylation blocks access of RNA polymerase to the promoter site of the gene such that the gene cannot be transcribed into messenger RNA (mRNA) and is therefore not expressed via production of the relevant protein by translation.[23] To date, the literature regarding epigenetics and PTSD has predominantly focused on this process of methylation and its role in PTSD risk and fear conditioning. Of the less-studied forms of epigenetic modification, the only one so far to be implicated in fear conditioning is the acetylation of histones,[24] a process by which the histone proteins that form the essential structure of DNA chromatin are modified via acetylation of one of their characteristic histone "tails," resulting in a change to local gene expression.[25]

A number of association studies have been conducted that have linked DNA methylation levels at particular genetic loci in humans with the onset of PTSD following trauma.[26-30] Further studies have identified significant gene $\times$ environmental stressor interactions in the development of PTSD, in the absence of main effects for genotype alone, which indicates that epigenetic mechanisms could be involved in the process (for a review, see Yehuda et al[31]). There appears to be some consensus within the research literature that there is an interaction between inherited genes, "traumatic load" (the number of traumatic events an individual has been exposed to), and epigenetic variation in predicting the onset of PTSD.[32]

It has been suggested that such epigenetic differences within the individual may affect stress regulation by mediating the reactivity of the hypothalamic–pituitary–adrenal axis via the action of glucocorticoids. Zovkic et al[33] found a chromatin interaction in the FK506 binding protein (FKBP5) gene in humans (an important regulator of the stress hormone system) to increase the risk of stress-related psychiatric disorders in adulthood, mediated by childhood trauma-dependent DNA demethylation. In this study, demethylation was linked to increased stress-dependent gene transcription and subsequent long-term dysregulation of the stress hormone system.

A small number of human studies have sought to compare expression levels of genes in blood samples because expression levels of many genes demonstrate congruence between peripheral blood and brain tissues. Hollifield et al[34] evaluated gene expression in whole blood samples from participants with combat-induced PTSD ($n = 6$) and a control group ($n = 11$). This pilot study identified 4 genes that were consistently correlated with clinical phenotypes, all of which were involved in regulating the inflammatory system. Another group probed a subset of peripheral blood cells (CD14+ monocytes) collected from men (24 PTSD and 25 age-matched trauma-exposed controls) and found 3 genes differentially expressed.[35]

Logue et al[36] examined the association between PTSD and gene expression using whole blood samples from a cohort of trauma-exposed male veterans (115 cases and 28 controls) and identified 41 genes that were differentially expressed, primarily those implicated in glucocorticoid signaling. A larger study measuring whole blood samples from US Marines ($N = 188$) obtained both pre- and postdeployment to conflict zones identified discrete groups of coregulated genes that may represent putative causal signatures for PTSD development.[37] This group replicated the finding in a second nonoverlapping independent data set of US Marines ($N = 96$) and determined that the coregulated genes displayed an overexpression of genes enriched for functions of innate-immune response and interferon signaling. Numerous published reports have noted associations between gene expression and mental health diagnoses ranging from anxiety to phobias to depression.[38]

This body of previous research literature provides an adequate rationale for investigating gene expression in veterans whose PTSD symptoms are remediated after clinical EFT treatment. If EFT is associated with genetic regulation, another plausible physiological mechanism of action may be added to

the neurological and endocrinal evidence already accumulated; measuring such associations was one objective of the study. A second objective was to elucidate the role of epigenetic processes in the etiology of PTSD. The current study assessed the feasibility of measuring gene expression correlates of successful relief from PTSD symptoms following EFT treatment.

Methods and Materials

The study was approved by the institutional review board of the American Association for Acupuncture and Bioenergetic Medicine and posted on ClinicalTrials.gov (NCT01250431). The study was designed to meet the quality criteria of the Task Force on Empirically Validated Treatments of Division 12 (Clinical Psychology) of the American Psychological Association[39-41] as well as CONSORT standards for clinical trials. Recruitment of veterans meeting the inclusion and exclusion criteria occurred through social media and professional referrals. Participants provided informed consent and did not receive compensation for participation.

The Symptom Assessment 45 (SA-45)[42] was used to assess psychological symptoms. This instrument has 2 general scales, one measuring the severity of symptoms (Global Severity Index [GSI]) and the other the breadth (Positive Symptom Total [PST]). It also has subscales that measure 9 conditions. Normalized data for nonclinical populations provide baseline T scores.

Anxiety and depression were also measured using the Hospital Anxiety and Depression Scale,[43] on which scores of 8 or more indicate clinical symptoms. The Insomnia Severity Scale was used to measure insomnia.[44] Scores of 22 or higher indicate severe clinical insomnia, of 15 to 21 moderate, 8 to 14 mild, and 7 or under subclinical insomnia. Physical impairment was assessed using the SF-12v2.[45] The Brief Pain Inventory[46] has 11 items, with a subscale for the intensity of pain and a second for the functional interference produced by pain. Concussive symptoms were measured with the Rivermead Postconcussion Symptoms Questionnaire (RPQ).[47] All of these instruments are supported by validity and reliability data.

Participants were randomized into either an EFT group or a treatment as usual (TAU) group using permuted block randomization (randomizer.org). After completion of a 10-week wait period, the TAU participants received the EFT intervention. To make the results as generalizable as possible, the sole inclusion criterion was a score of >50 on the Posttraumatic Checklist–Military (PCL-M).[48] A score of 35 or greater represents heightened PTSD risk in a military population,[49] and a score of 50 or more indicates the likelihood of a clinical PTSD diagnosis.[48]

Exclusion criteria were a current or past physical or psychiatric disorder that would preclude a participant being able to respond to the psychosocial measures adequately or to give blood safely; immunomodulatory disorders or cancer history, chronic periodontitis, pregnancy, or antibiotic use within 3 months of the recruitment; and a high score on 2 SA-45 questions indicative of the potential for violence.

Whether in the TAU or EFT group, participants were required to remain under the care of a primary care provider. The characteristics of usual care (whether in the group receiving TAU alone or the group receiving EFT supplementary to TAU) were as follows—6 (38%) were under the primary care of the veterans administration and 10 (62%) were also enrolled in private health-care plans. Twelve (75%) reported being under the care of a mental health professional in addition to their primary care physician. Thirteen (81%) had previously received a positive PTSD diagnosis, whereas 3 had not. Pharmaceutical drug use was reported by 8 (50%), with the mean number of drugs being 2, primarily analgesics. Seven (44%) reported using complementary medicine techniques, including the following—acupuncture, Qigong, Tai Chi, Yoga, and herbs. One reported the use of a TENS unit for pain. This profile of standard care is similar to that found in a general veteran population.[50-52]

Emotional freedom techniques were delivered according to *The EFT Manual*[2,3] and treatment fidelity, or consistency of the intervention, was assessed using session evaluation forms structured to assess compliance with the clinical EFT protocol. All practitioners were certified in clinical EFT (EFT Universe, Santa Rosa, California), a manualized, evidence-based form of the EFT method. Treatment sessions followed the protocol described in *The EFT Manual*[2,3]: Participants compiled the lists of traumatic memories in a summary form, eg, ''My buddy Tom stepped on an IED, and we couldn't use a body bag because there wasn't enough of him left'' or ''When I was seven years old, my dad and uncle had a horrible fist fight and there was blood everywhere'' or ''During the Battle of Fallujah I shot a little boy who was running toward me with a grenade, and I see his face in my dreams.''

Participants then rated their degree of emotional distress on a Likert scale ranging from 0 (no distress) to 10 (maximum distress). With the guidance of the practitioner, they then focused on each aspect of the memory while stimulating 1 of the 12 acupressure points described in *The EFT Manual* with their fingertips. When their self-reported emotional distress was 0 or a low number, they moved on to the next memory in their list. When emotions became overwhelming, practitioners used the ''gentle techniques'' described in the third edition of *The EFT Manual*.[3] The above procedure is typical of EFT sessions.

A focused panel of 93 target genes was designed based on published evidence that their products are key regulators of glucocorticoid signaling, innate immune signaling, and systemic inflammation, or that they encode receptors or transporters for these key regulators. Blood samples were processed using the PAXgene RNA stabilization system (PreAnalytix, Doncaster, Victoria, Australia). One blood sample was drawn for each participant before and after the treatment period for the EFT group. For the TAU group, blood samples were collected before and after the waiting period and also after they received their postwait EFT treatment. Messenger RNA was harvested and probed by direct multiplexed polymerase chain reaction using an nCounter Analysis System (Nanostring, Seattle, Washington) for expression levels of the candidate genes.

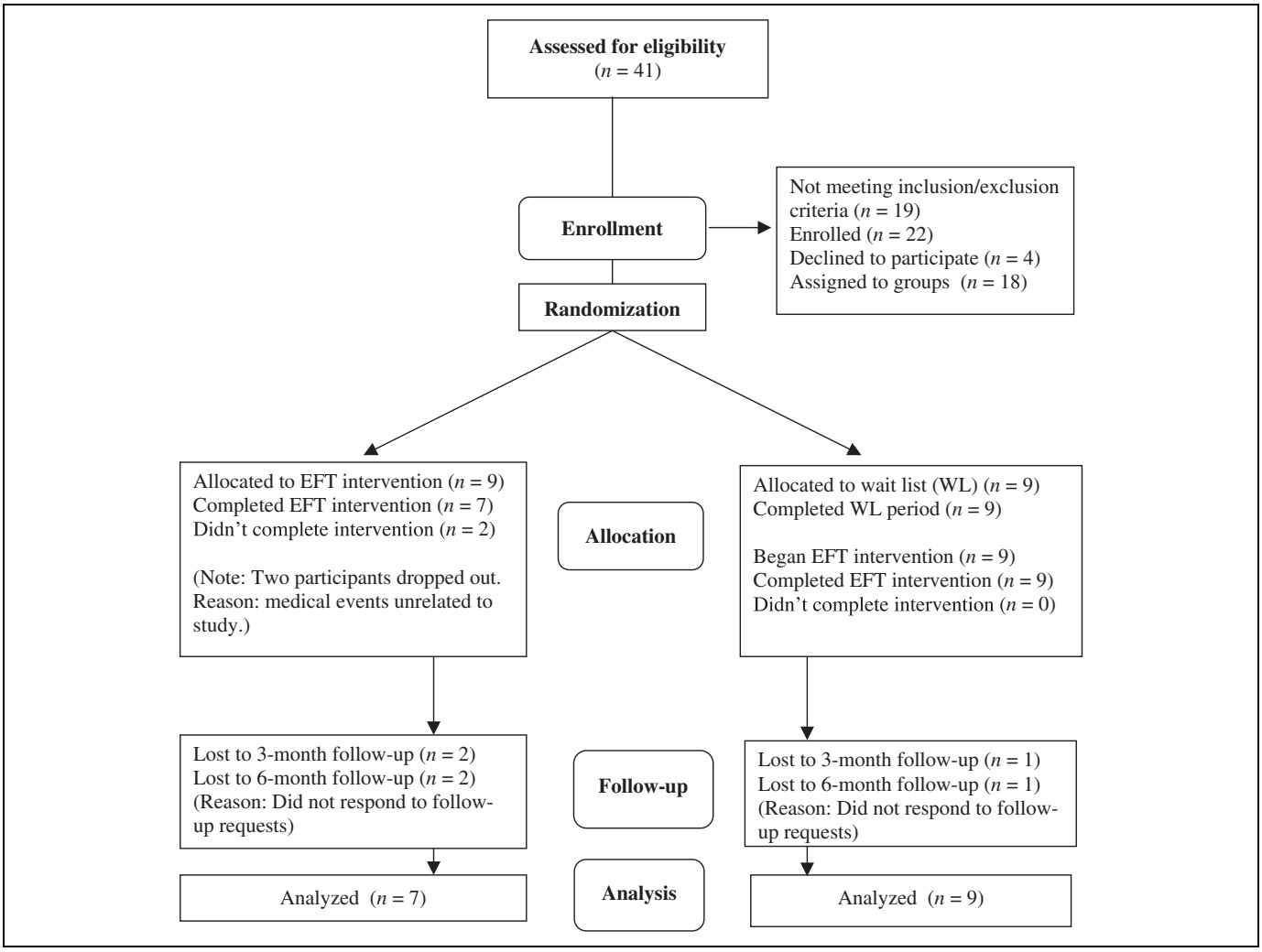

Figure 1. CONSORT flow chart.

Participant Characteristics

Investigators made initial contact with 124 veterans, of whom 41 consented to be assessed for eligibility. Of these, 19 were excluded based on the inclusion/exclusion criteria and 22 enrolled. Four of those enrolling subsequently decided not to participate, and 18 were randomly assigned to 1 of the 2 groups (Research Randomizer; randomizer.org). Participants were assessed on intake, before and after treatment, and at 3 and 6 months. After completing a 10-week wait period, TAU participants received the same sequence of 10 EFT treatment sessions provided to the EFT group after intake. Biological samples were obtained before and after treatment, and for the TAU wait-list participants, at the commencement of the wait period.

After beginning EFT treatment, 2 participants dropped out for medical reasons unrelated to the study, resulting in an *N* of 16 completing the treatment. Three participants did not respond to requests for follow-up data at 3 and 6 months, resulting in a follow-up *n* of 13. Analysis was performed on data from the 16 participants (11 male and 5 female) who completed treatment. Data from the EFT group were combined with that of the postwait TAU group for maximum statistical strength and analyzed blind. No adverse events were reported. The flow of participants through the study is illustrated in the CONSORT diagram in Figure 1.

Table 1. Baseline Participant Characteristics.[a]

Variable	Mean	SD	Minimum	Maximum
Age, year	59.50	8.319	40	69
PCL-M, mean	62.69	9.506	50	85
GSI	68.87	9.486	43	81
PST	68.27	8.762	43	81

Abbreviations: GSI, Global Severity Index; PCL-M, Posttraumatic Checklist–Military; PST, Positive Symptom Total.
[a]n = 16

Demographics and baseline outcome scores are summarized in Table 1. The mean age of participants was 59.5 years (standard deviation [SD] = 8.32). Baseline scores for primary

Table 2. Means and Standard Errors of Participant Symptoms 10 Weeks Prior, Before First Session, After 10 EFT Sessions, and at 3- and 6-Month Follow-Up.

	Pretest (n = 16)		Before (n = 16)		After 10 Sessions (n = 16)		3 Months (n = 13)		6 Months (n = 10)	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PCL-M total	62.69	9.506	59.63	8.318	37.06	13.675	41.77	17.249	42	17.898
SA-45 global scales										
GSI	67.87	9.486	67.73	9.438	60.44	9.743	63.46	12.218	61.54	11.414
PST	68.27	8.762	68.4	8.806	61.69	10.448	64.38	12.901	62.46	11.942
SA-symptom domains										
Anxiety	68.67	9.061	68.73	8.614	61.56	9.259	65.92	11.658	64.77	10.068
Depression	66.4	6.895	65.87	6.833	59.56	8.334	62.38	8.332	59.15	9.634
OC	67.13	10.836	67.27	10.899	62.06	8.948	66.23	11.248	64.77	9.302
Somatization	63.8	9.337	64.2	10.255	61.75	9.227	63.08	11.191	62.85	10.808
Phobic Anxiety	73	6.459	73.07	6.541	68.31	7.863	69.85	7.862	69.69	9.358
Hostility	64.73	11.566	64.67	12.128	57.06	6.748	56.69	5.964	55.46	5.797
IS	64.87	6.599	64.73	5.873	60.06	6.298	62.15	8.174	60.31	7.123
Paranoia	62.73	8.379	62.27	8.013	55.44	8.05	60.46	9.606	58.08	7.836
Psychoticism	63.53	6.728	63.33	6.466	60.88	5.62	62.38	6.539	60.85	6.336
ISI	15.93	5.82	15.40	6.40	11.31	6.69	12.15	7.23	12.77	7.36
SF-12-PCS	42.95	13.02	42.53	13.23	44.63	12.63	44.68	11.85	42.95	11.56
SF-12-MCS	35.29	11.86	33.64	11.37	44.53	16.58	44.22	11.31	45.35	9.60
HADS-A	10.47	4.53	10.13	4.73	7.38	5.03	9.08	6.19	8.69	5.87
HADS-D	8.73	4.51	8.67	4.55	5.69	4.39	6.67	4.52	6.77	5.25
RPQ-3	2.15	2.38	2.00	1.92	2.29	2.59	2.09	2.39	1.50	2.24
RPQ-13	21.00	15.80	22.62	15.20	17.21	15.26	17.45	15.81	12.50	13.53
BPI-PS	4.13	2.06	4.25	2.35	3.13	2.10	3.36	2.42	2.85	1.99
BPI-PI	4.13	3.05	4.06	3.13	2.53	2.56	2.91	3.24	2.92	2.99

Abbreviations: BPI-PI, Brief Pain Inventory–Pain Interference; BPI-PS, Brief Pain Inventory–Pain Scale; GSI, Global Severity Index; HADS-A, Hospital Anxiety and Depression–Anxiety; HADS-D, H Hospital Anxiety and Depression–Depression; IS, interpersonal sensitivity; ISI, Insomnia Severity Index; OC, obsessive–compulsive behavior; PA, phobic anxiety; PCL-M, Posttraumatic Checklist–Military; PST, Positive Symptom Total; RPQ-3, Rivermead Postconcussion Symptoms Questionnaire for first 3 concussion symptoms (also known as RPQh or RPQ head); RPQ-13, Rivermead Postconcussion Symptoms Questionnaire for remaining 13 general concussion symptoms; SA-45, Symptom Assessment 45; SF-12-PCS, SF-12-MCS, physical and mental health composite scores (respectively).

outcome measures (GSI, PST, and PCL-M) are also recorded. All participants scored at or above the clinical range (<50) on the PCL-M at baseline. The mean score was 62.69 (range: 50-85). There was no significant difference in PCL-M scores between the 2 groups on intake and no significant change in scores in the TAU group between the start and end of the wait period.

Symptom severity (GSI) scores on the SA-45 ranged between 43 and 81, with a mean of 68.87 and an SD of 9.486. Symptom breadth (PST) also ranged between 43 and 81, with a mean of 68.27 and SD of 8.762. For all SA-45 subscales and general scales, 60 indicates clinical symptom levels, and the lowest possible score is either 41 or 42 depending on the gender and condition. Results of the assessments appear in Table 2.

Results

Test of Significance Comparing Psychological Symptom Scores Pretest and After 10 EFT Sessions

Pre- and posttreatment mean scores were assessed using repeated measures 1-way analysis of variance (ANOVA). Table 3 stratifies the means and SDs of each measured parameter and provides a measure of the difference in each score after 10 sessions. The values in the difference column are negative because treatment was associated with a decrease in the average score for each parameter. One-way ANOVA tests for the within-participants variations in each parameter were calculated and produced an F test statistic that was translated into a P value.

Posttraumatic Checklist–Military scores decreased by 25.63 points on average. This decrease was highly statistically significant ($P < .00001$). Treatment was associated with a statistically significant difference at $\alpha = .05$ in all parameters except for SF-12-PCS ($P = .411$) and RPQ-3 ($P = .489$). RPQ13 and somatization both approached significance at $P = .056$. Insomnia declined from the moderate clinical to the mild clinical range.

Comparison of Symptom Means and Standard Errors for Psychological Symptoms After 10 Sessions and 6 Months Posttreatment

To determine whether participants maintained their gains, 3- and 6-month follow-up assessments were analyzed using repeated measures 1-way ANOVA. No significant change was found between posttreatment results and follow-up on any parameter, indicating that treatment results held over time. Paranoia,

Table 3. Test of Significance Comparing Participant Scores Pretest and After 10 EFT Sessions.[a]

	Pretest		After 10 Sessions			
Variable	Mean	SD	Mean	SD	Difference	*P*
PCL-M total	62.69	9.51	37.06	13.68	−25.63	<.00001
SA-45 global scales						
GSI	67.87	9.49	60.44	9.74	−7.43	<.001
PST	68.27	8.76	61.69	10.45	−6.58	<.001
SA-symptom domains						
Anxiety	68.67	9.06	61.56	9.26	−7.11	.001
Depression	66.40	6.90	59.56	8.33	−6.84	<.001
OC	67.13	10.84	62.06	8.95	−5.07	.003
Somatization	63.80	9.34	61.75	9.23	−2.05	.056
Phobic Anxiety	73.00	6.46	68.31	7.86	−4.69	.002
Hostility	64.73	11.57	57.06	6.75	−7.67	.006
IS	64.87	6.60	60.06	6.30	−4.81	.005
Paranoia	62.73	8.38	55.44	8.05	−7.29	<.001
Psychoticism	63.53	6.73	60.88	5.62	−2.65	.01
ISI	15.93	5.82	11.31	6.69	−4.62	.005
SF-12-PCS	42.95	13.02	44.63	12.63	1.68	.411
SF-12-MCS	35.29	11.86	44.53	16.58	9.24	.01
HADS-A	10.47	4.53	7.38	5.03	−3.09	<.001
HADS-D	8.73	4.51	5.69	4.39	−3.04	<.001
RPQ-3	2.15	2.38	2.29	2.59	0.14	.489
RPQ-13	21.00	15.80	17.21	15.26	−3.79	.056
BPI-PS	4.13	2.06	3.13	2.10	−1.00	.025
BPI-PI	4.13	3.05	2.53	2.56	−1.60	.009

Abbreviations: BPI-PI, Brief Pain Inventory–Pain Interference; BPI-PS, Brief Pain Inventory–Pain Scale; GSI, Global Severity Index; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; IS, interpersonal sensitivity; ISI, Insomnia Severity Index; OC, obsessive-compulsive behavior; PA, phobic anxiety; PCL-M, Posttraumatic Checklist–Military; PST, Positive Symptom Total; RPQ-3, Rivermead Postconcussion Symptoms Questionnaire for first 3 concussion symptoms (also known as RPQh or RPQ head); RPQ-13, Rivermead Postconcussion Symptoms Questionnaire for remaining 13 general concussion symptoms; SA-45, Symptom Assessment 45; SF-12-PCS, SF-12-MCS, physical and mental health composite scores (respectively).
[a]n = 16.

Table 4. Means and Standard Errors of Participant Symptoms Posttest and at 6-Month Follow-Up.

	After 10 Sessions, n = 16		6 months, n = 10		
Variable	Mean	SD	Mean	SD	*P*
PCL-M total	37.06	13.675	42	17.898	.215
SA-45 global scales					
GSI	60.44	9.743	61.54	11.414	.774
PST	61.69	10.448	62.46	11.942	.845
SA-symptom domains					
Anxiety	61.56	9.259	64.77	10.068	.429
Depression	59.56	8.334	59.15	9.634	.577
OC	62.06	8.948	64.77	9.302	.874
Somatization	61.75	9.227	62.85	10.808	.306
Phobic Anxiety	68.31	7.863	69.69	9.358	.703
Hostility	57.06	6.748	55.46	5.797	.569
IS	60.06	6.298	60.31	7.123	.901
Paranoia	55.44	8.05	58.08	7.836	.096
Psychoticism	60.88	5.62	60.85	6.336	.596
ISI	11.31	6.69	12.77	7.362	.901
SF-12-PCS	44.63	12.6325	42.946	11.5594	.233
SF-12-MCS	44.53	16.583	45.354	9.5984	.749
HADS-A	7.38	5.032	8.69	5.865	.502
HADS-D	5.69	4.393	6.77	5.246	.584
RPQ-3	2.29	2.585	1.5	2.236	.154
RPQ-13	17.21	15.258	12.5	13.534	.101
BPI-PS	3.13	2.1	2.85	1.994	.188
BPI-PI	2.53	2.56	2.92	2.985	1.000

Abbreviations: BPI-PI, Brief Pain Inventory–Pain Interference; BPI-PS = Brief Pain Inventory–Pain Scale; GSI, Global Severity Index; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; IS, interpersonal sensitivity; ISI, Insomnia Severity Index; OC, obsessive–compulsive behavior; PA, phobic anxiety; PCL-M, Posttraumatic Checklist–Military; PST, Positive Symptom Total; RPQ-3, Rivermead Postconcussion Symptoms Questionnaire for the first 3 concussion symptoms (also known as RPQh or RPQ head); RPQ-13, Rivermead Postconcussion Symptoms Questionnaire for remaining 13 general concussion symptoms; SA-45, Symptom Assessment 45; SF-12-PCS, SF-12-MCS, physical and mental health composite scores (respectively).

depression, and hostility dropped below the clinical cutoff after treatment and remained subclinical at 6-month follow-up, with no significant difference between posttreatment and follow-up results. These results are summarized in Table 4.

Test of Significance Comparing Gene Expression Pretest and After 10 EFT Sessions

Gene expression values were normalized according to the average mean counts obtained for 4 control genes that typically display uniform expression under different environmental conditions (glyceraldehyde 3-phosphate dehydrogenase, ACTB, IGSF6, and RPL19) and changes in expression levels were calculated by taking the log transform of the ratio of expression levels with the initial time point as the denominator and the later time point in the numerator. Although fold changes in target genes, or the how much the expression level changes going from an initial to a final value, are reported in Tables 5 and 6,

Table 5. Test of Significance Comparing Changes in Expression Levels.[a]

	TAU (n = 9)	EFT (n = 7)	
Gene	Mean Fold Change	Mean Fold Change	*P*
IL-10RB	1.047	1.170	.019
SELL	1.040	1.203	.025
TNFAIP6	1.058	1.318	.026
CXCR3	1.042	−1.467	.045
IL-18	−1.062	1.177	.046
IFITM1	1.006	1.151	.048

Abbreviations: *CXCR3*, chemokine (C–X–C motif) receptor 3; EFT, emotional freedom technique; *IFITM1*, interferon-induced transmembrane protein 1; *IL-10RB*, interleukin 10 receptor, beta; *IL-18*, interleukin 18; *SELL*, selectin L; TAU, treatment as usual; *TNFAIP6*, tumor necrosis factor, alpha–induced protein 6.
[a]Calculated *P* value from Student's *t* test on log-transformed expression level ratios assuming equal variance between TAU (control) and EFT (treatment) groups. Ratios were calculated by dividing the expression levels measured after a 10-week interval by initial expression levels.

Table 6. Differential Expression Among Treatment Groups.[a,b]

	EFT		TAU (With EFT)		Pooled	
Gene	Mean Fold Change	*P*	Mean Fold Change	*P*	Mean Fold Change	*P*
IL-10RB	1.17	.002	1.093	.01	1.128	<.001
SELL	1.203	.009	1.064	.097	1.127	.002
TNFAIP6	1.318	.001	1.033	.698	1.047	.431
CXCR3	−1.467	.087	−1.279	.095	−1.364	.012
IL-18	1.177	.106	1.09	.241	1.13	.036
IFITM1	1.151	.026	1.051	.103	1.096	.006
CANX	−1.098	.019	−1.008	.765	−1.049	.047
NFIL3	1.206	.048	1.067	.425	1.13	.042
CXCL1	1.312	.097	1.121	.32	1.206	.046
GPR65	1.265	.164	1.118	.243	1.184	.058
EDG1	−1.244	.208	−1.042	.441	−1.132	.133
CASP2	−1.235	.066	−1.039	.49	−1.126	.049
IFNGR1	1.185	.075	1.116	.004	1.148	.003
IFITM3	1.176	.235	−1.007	.928	1.075	.317

Abbreviations: *CANX*, calnexin; *CASP2*, caspase 2; *CXCL1*, chemokine (C–X–C Motif) ligand 1; *CXCR3*, chemokine (C–X–C motif) receptor 3; *EDG1*, endothelial differentiation G protein-coupled receptor 1; EFT, emotional freedom technique (n = 7); *GPR65*, G protein-coupled receptor 65; *IFITM1*, interferon-induced transmembrane protein 1; *IFITM3*, interferon-induced transmembrane protein 3; *IFNGR1*, interferon gamma receptor 1; *IL-10RB*, interleukin 10 receptor, beta; *IL-18*, interleukin 18; *NFIL3*, nuclear factor, interleukin 3 regulated; *SELL*, selectin L; TAU, treatment as usual (n = 9); *TNFAIP6*, tumor necrosis factor, alpha–induced protein 6.

[a]Calculated *P* value from Student *t* test on log-transformed expression level ratios assuming equal variance to test significance of differential expression (DE). Ratios were calculated by dividing the expression levels measured after a 10-week interval by initial expression levels. Top third—group of genes with significant DE identified from between group comparison (EFT vs TAU); Middle third—genes with significant DE in EFT group. Bottom third—fold changes in EFT group exceeding 15%.

[b]n = 16.

all statistical analyses were performed using log-transformed ratios. Strict quality control measures were applied to the data using MATLAB Statistical Toolbox (Mathworks, Natick, Massachusetts) prior to testing experimental hypotheses. A conservative cutoff for signal strength was applied (30 counts), which eliminated 25 of the target genes from further analyses.

As a prelude for parametric statistical analysis, data for each group were evaluated for normal distribution and homoscedasticity by Lilliefors test and 2-sample *F* test, respectively. An additional 12 targets were eliminated because they had moderate significant fold changes in the control group by Student *t* test ($P < .15$) and another 4 due to mean fold changes in excess of 10%. A comparison was also made in the magnitude of the response in the EFT group as compared to the magnitude of the change in the TAU group to ensure adequate signal to noise, eliminating 17 targets for which apparent responses in the EFT group were not greater than changes in expression levels seen in the TAU group.

A Student *t* test was performed on the data from gene targets with a robust signal to noise ratio (35 genes), comparing expression levels before and after the intervention period between EFT and TAU groups. Significant differences ($P < .05$; see Table 5) were found for 6 genes—chemokine receptor 3 (*CXCR3*), interleukin 18 (*IL-18*), interleukin 10 receptor beta, tumor necrosis factor alpha–induced protein 6, leukocyte-endothelial cell adhesion molecule 1 (selectin L), and interferon-induced transmembrane protein 1. These target genes are generally known to be involved in the regulation of cellular immunity and inflammation and are associated with stress.[53-58]

A post hoc analysis was performed to attempt to detect additional genes of interest by looking solely at the changes in expression pre- and posttreatment. Two previously unidentified genes had significant differential gene expression by Student *t* test on log-transformed ratios ($P < .05$) and 6 additional genes had fold changes in excess of 15%. A comparison of the performance of the identified genes was conducted for the TAU group after they received comparable EFT treatment as well as to the pooled data from both groups. A 2-sample Student *t* test comparing the fold changes between TAU after receiving treatment and fold changes from the EFT group showed no significant differences ($P > .05$). Interestingly, the fold changes are almost all uniformly smaller in the TAU group, though consistent in sign and supportive in strengthening the statistical significance when pooled with the EFT group. The results are summarized in Table 6.

A paired-sample Student *t* test was also performed within the TAU group comparing *t* test statistical significance for the identified genes before and after the wait period. Two of the 6 genes, *CXCR3* and *IL-18*, approached statistical significance ($P < .15$).

To assess whether differential expression was correlated with clinical phenotypes, a correlation analysis was performed on the log-transformed ratios and the 3 comprehensive clinical parameters—PCL-M, GSI, and PST. Pooled data from all participants were considered to attain the highest statistical strength. The differences in clinical parameters pre- and posttreatment determined above were used for this analysis. Pearson product-moment correlation coefficients were calculated using the log-transformed ratios from the pooled treatment group of the genes identified in Table 6. Two genes were found to have fold changes moderately correlated with GSI that were statistically significant: calnexin (*CANX*; CC = 0.516;

$P = .041$) and G protein-coupled receptor 65 (*GPR65*; CC = −0.575; $P = .02$).

Power analysis was performed to predict how an increase in sample size would enhance statistical significance and potentially reveal other genes of interest when comparing responses between separate treatment and control groups. The R package pwr (version 1.2) was used that utilizes Cohen's *d* effect size to determine sample size. Based on the underlying variability of the control and treatment groups and the calculated changes in expression levels, these data predict that a sample size of 50 would yield 20 genes that would have log ratios significantly different from 0 ($P < .05$) with 80% power.

Discussion

Analysis of the symptom data showed that 10 sessions of EFT was associated with highly statistically significant reductions in self-reported PTSD symptoms. Other markers of psychological health—anxiety, depression, obsessive–compulsive behavior, phobic anxiety, hostility, interpersonal sensitivity, paranoia, psychoticism, insomnia, and pain—all also showed statistically significant improvements. There were no significant differences in scores, on any of the symptom data, between those assessed immediately following the 10 EFT sessions and at 6-month follow-up, showing that therapeutic gains from the intervention were maintained. The mean participant score on the PCL-M at 6-month follow-up assessment was below the threshold for likely PTSD diagnosis by a significant margin. Reductions in PTSD symptoms were similar to those noted in previous research.

Psychological conditions such as depression and anxiety were also reduced after treatment, whereas the general measures of the SA-45 showed both a broad and deep treatment effect. The severity of other conditions commonly noted as sequelae of traumatic stress, such as pain and insomnia, also declined, suggesting a general stress-reduction effect. Participants may have developed better long-term coping skills, as the stress-related conditions of paranoia, depression, and hostility all went from above to below the clinical cutoff after treatment and remained so on at 6-month follow-up.

Analysis of the gene expression data demonstrated that changes in expression levels for specific genes are measurable following EFT. The results also highlighted some of the challenges inherent in the analyses of gene expression in humans. Low-expression levels and a high degree of variability in expression levels under control conditions and between individual participants necessitated the use of rigorous metrics and statistics to obtain a comprehensive indication of data quality. More than half of the target genes were eliminated from the analysis due to the quality controls. Significant changes in expression levels of genes passing quality controls must be also be interpreted in the context of the magnitude of those changes. For example, the pooled fold change in expression levels for *GPR65* that were found to be significantly correlated with GSI was approximately 18%, whereas that for *CANX* was only 5%, which is close to the level of changes observed for genes under control conditions.

The study had a number of limitations. Perhaps the most important of these was the absence of an active control group receiving a treatment of demonstrated efficacy such as cognitive processing therapy. Without such a control, it is impossible to determine how the psychological and gene expression changes after EFT compare to a similar dose of known efficacious treatment.

A portion of the observed changes may have been due to the nonspecific effects observed in any therapy, such as therapist allegiance, expectancy effects, and sympathetic attention. However, there is no evidence in the literature that the nonspecific effects of therapy can remediate PTSD.[59,60] An earlier study comparing a single session of EFT to a supportive interview found more than double the reduction in psychological symptoms in the EFT group,[20] and a study carefully designed to control for variables such as expectancy and therapeutic allegiance demonstrated that the observed effects were due to EFT treatment.[61]

Another factor that might have affected the expression of certain genes assessed in this study is the use of analgesics by participants. Analgesics such as nonsteroidal anti-inflammatory drugs suppress inflammation and may have suppressed signaling in inflammatory genes. Although analgesics use is ubiquitous among veterans, any extension of this study should control for this class of drugs.

Another limitation is the small sample size. Our data predict that a minimum sample size of 50 participants per experimental group would be required to determine the involvement of a set of 20 genes with sufficient power. Two previous small studies have applied a similar approach to identify epigenetic changes associated with cognitive behavioral therapy and found increases in blood FKBP5 mRNA expression following therapy.[62,63] FK506-binding protein was included in the set of target genes for our study, but no significant change in expression level was detected. Future studies might examine whether there are distinct epigenetic pathways shared by both EFT and cognitive behavioral therapy.

A fourth limitation is the self-report nature of the assessments, and the absence of a diagnosis by a qualified mental health professional. Although the PCL-M has shown convergent validity with observer-rated measures,[64] it is not in itself sufficient for a categorical diagnosis of PTSD. Although 83% reported a prior diagnosis of PTSD, an independent diagnosis should be made at the outset using an observer-rated measure such as the Clinician Administered PTSD Scale.[65] We therefore report these results as reductions in self-reported PTSD symptoms rather than the remediation of PTSD itself.

Despite these limitations, the findings of the present study are consistent with previous research measuring PTSD symptoms before and after brief courses of EFT treatment.[4-10] Since EFT research has exceeded the threshold of the Division 12 criteria to meet the standards for an "established treatment" for PTSD, it seems likely that further quantitative evaluation will only replicate the existing data. Research resources would be better allocated to (1) investigating physiological mechanisms, (2) assessing its utility and feasibility in a primary care setting,

and (3) characterizing the qualitative phenomenological experience of clients.

The current study is the first to evaluate the epigenetic potential of EFT treatment and to identify some of the genetic pathways that may mediate the efficacy of the intervention. The candidate genes identified in this study are involved in stress response pathways and are critical to the regulation of cellular immunity and inflammation. This result is consistent with our prior work[20] demonstrating reduced levels of the stress hormone cortisol in participants after a single EFT therapy session. Our findings are also consistent with the studies by Hollifield et al[34] and Logue et al[36] that found evidence for differential baseline expression of genes responsive to glucocorticoid signaling and inflammatory pathways in a cohort of trauma-exposed male veterans with PTSD.

The psychological results are remarkably similar to those obtained in other studies, with significant symptom reductions of over 50%, and indicate that EFT is an effective evidence-based treatment for PTSD. It shows that improvement in mental health is not confined to the psychological dimension of the client but has significant medical utility as well. The study lays the groundwork for future research in the physiological mechanisms of action of EFT and, taken together with similar studies, demonstrates that effective psychotherapy can be considered an intervention with the ability to influence health at the epigenetic level.

SO WHAT?

What Is Already Known on This Topic?

Outcome studies of EFT for patients with PTSD have assessed a variety of psychological and self-reported physical symptoms and shown significant treatment effects.

What Does This Article Add?

The study is the first to evaluate the potential of EFT treatment to influence the regulation of gene expression. The results identify some of the genetic pathways that may mediate the efficacy of the intervention and, taken together with previous outcome studies, demonstrate that effective psychotherapy can be considered an epigenetic intervention.

What Are the Implications for Health Promotion Practice or Research?

The study lays the groundwork for future research into the physiological mechanisms of action of EFT and other effective psychotherapies. The results identifying some of the genetic pathways that may mediate the efficacy of the intervention represent a critical step toward leveling the playing field for psychotherapy modalities in the arena of biomedical research relative to conventional medicines such as pharmaceutical drugs.

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Declaration of Conflicting Interests

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