

EEG ALPHA SENSITIZATION IN INDIVIDUALIZED HOMEOPATHIC TREATMENT OF FIBROMYALGIA

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Received 7 November 2003.

This study was supported by NIH grants R21 AT00315 (IRB), K24 AT000S7 (IRB), P20 AT00774 (GES), P50 AT00008 from the National Center for Complementary and Alternative Medicine (NCCAM) and NIH HL53938-07S1 (CMB). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCCAM or NIH. This article is dedicated to the memory of Kathryn L. Grant, PharmD, who participated in the design of the laboratory component of the study and developed the procedures for preparation of the sniff bottles.

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Fibromyalgia (FM) patients show evidence of sensitizability in pain pathways and electroencephalographic (EEG) alterations. One proposed mechanism for the claimed effects of homeopathy, a form of complementary medicine used for FM, is time-dependent sensitization (TDS, progressive amplification) of host responses. This study examined possible sensitization-related changes in EEG relative alpha magnitude during a clinical trial of homeopathy in FM. A 4-month randomized, placebo-controlled double-blind trial of daily orally administered individualized homeopathy in physician-confirmed FM, with an additional 2-month optional crossover phase, included three laboratory sessions, at baseline, 3 and 6 months (N = 48, age 49.2 ± 9.8 years, 94% women). Nineteen leads of EEG relative alpha magnitude at rest and during olfactory administration of treatment and control solutions were evaluated in each session. After 3 months, the active treatment group significantly increased, while the placebo group decreased, in global alpha-1 and alpha-2 during bottle sniffs over sessions. At 6 months, the subset of active patients who stayed on active continued to increase, while the active-switch subgroup reversed direction in alpha magnitude. Groups did not differ in resting alpha. Consistent with the TDS hypothesis, sniff alpha-1 and alpha-2 increases at 6 months versus baseline correlated with total amount of time on active remedy over all subjects ($r = 0.45$, $p = .003$), not with dose changes or clinical outcomes in the active group. The findings suggest initiation of TDS in relative EEG alpha magnitude by daily oral administration of active homeopathic medicines versus placebo, with laboratory elicitation by temporo limbic olfactory stimulation or sniffing.

Keywords EEG alpha, fibromyalgia, homeopathy, olfactory administration, oscillation, time-dependent sensitization

Fibromyalgia (FM) is a chronic syndrome associated with diffuse musculoskeletal pain, fatigue, and, often, depression (Friedberg & Jason, 2001). Convergent evidence implicates central nervous

system involvement in the experience of lowered pain thresholds (Staud et al., 2001) and increased waking electroencephalographic (EEG) alpha activity (Bell et al., 2001). One study (Granot et al., 2001) of evoked potentials during painful stimuli at tender versus control points demonstrated findings consistent with sensitization of both peripheral tender points and CNS pain pathways. Different investigators have proposed that FM patients may be particularly sensitizable individuals (Bell et al., 2001; Bell et al., 2001; Bell et al., 1998; Ursin & Eriksen, 2001).

Conventional medical treatments offer limited symptomatic relief, and most FM patients seek complementary and alternative medical therapies (CAM) (Pioro-Boisset et al., 1996). One such CAM treatment with prior evidence for efficacy in FM is homeopathy (Fisher et al., 1989). Homeopathy is a 200-year old CAM system of care with an integrative approach to diagnosis and treatment of the patient as a whole, extending beyond disease-specific issues. A single homeopathic medicine is chosen for the total pattern of biopsychosocial symptoms in the person (Merrell & Shalts, 2002; Rowe, 1998; Vithoulkas, 1980). Homeopathic medicines are prepared from animal, mineral, and plant sources by serial dilution in fixed ratios and vigorous shaking (succussion), a process that several basic science studies have found capable of altering the biophysical properties of the agent to differ from those of solvent or dilution without succussion (Bell et al., 2003; Elia & Niccoli, 1999; Rey, 2003). Symptom patterns of each remedy are documented in human testing on healthy individuals ("provings"). Provings are based on the homeopathic model that the direction of response is state-dependent, that is, a remedy that can cause a set of symptoms in a healthy person can reverse a similar set in a sick person (Vithoulkas, 1980).

The mechanisms by which homeopathic medicines may exert their effects are not established, but some evidence suggests bi-directional shifts in host function as a nonlinear system (Hyland & Lewith, 2002). The bi-directional effects of homeopathic medicines in low material doses also may overlap a well-documented process from the field of toxicology termed hormesis. In hormesis, low doses of a toxicant, typically below the no-observed-adverse-effect-level (NOAEL), induce adaptive compensations in the host that oppose the damaging effects of the same toxicant at higher doses (Calabrese & Baldwin, 2001).

One example of nonlinear response patterning is time-dependent sensitization (TDS), in which repeated intermittent dosing of the same exogenous stimulus (chemical, drug, or stressor) induces a progressive amplification of host responses over time (Bell *et al.*, 1999). At the physiological limits of the system, the direction of TDS can reverse and lead to an oscillatory pattern, that is, bidirectionality (Antelman *et al.*, 1997). Davidson (1994) previously hypothesized that homeopathic medicines might act in part via mobilization of TDS. Progressive increases in EEG alpha activity offer a replicable biomarker of TDS in both animal (Stahl *et al.*, 1997) and human studies (Bell *et al.*, 1998). The alpha sensitization reportedly derives from activation of D2 dopamine receptors in the mesolimbic pathway (Ferber & Kuschinsky, 1996; Stahl *et al.*, 1997).

Three factors that can enhance sensitizability (Bell *et al.*, 2001), *i.e.*, female gender (Friedberg & Jason, 2001), history of early abuse (Fernandez *et al.*, 1999), and sensitivity to low levels of environmental chemicals (Slotkoff *et al.*, 1997) all have a higher prevalence in FM patients. Temporolimbic activation via olfactory stimulation (sniffing) is also a strategy with which to elicit transient changes in EEG alpha activity in sensitizable individuals (Fernandez *et al.*, 1999; Schwartz *et al.*, 1994). Homeopaths claim that their medicines can be administered by either an oral or nasal inhalation route (Hahnemann, 1996 [1843]). A testable hypothesis is that repeated administration of individualized homeopathic remedies to FM patients, even with progressively more dilute treatment materials, will produce measurable increases in EEG alpha responses over time, possibly due to a time-dependent sensitization process within the host rather than to the dose size *per se*.

MATERIALS AND METHODS

Participants

Participants were individuals with physician-diagnosed FM recruited from the community who also met American College of Rheumatology criteria for FM (Wolfe *et al.*, 1990) on physical examination of tender points. At baseline, patients completed a 5-item chemical

sensitivity index rating scale (possible range 5–25) (Szarek et al., 1997) and a modified self-rating scale on childhood abuse/neglect (Bernstein et al., 1994). The present sample included patients who completed both the clinical trial and EEG laboratory sessions of the study. At baseline, 3 months, and 6 months, all patients underwent an 18-tender point pain physical examination (with patient pain ratings during standardized pressure on each point ranging from 0–10, total score range 0–180) by a rheumatologist or physician's assistant (same assessor at each session for a given patient) blinded to treatment condition. Before each laboratory session, participants also completed a three-item global health rating (Bell et al., 1998) (current health, health compared with 6 months ago, health compared with peers, possible total score range 3–15) and a Profile of Mood States (POMS) (McNair et al., 1981) scale.

The global health self-rating scale was used to capture the “whole person” effects claimed in homeopathic practice (Vithoulkas, 1980). In conventional medical research, global health self-ratings surpass laboratory tests and physician assessments as strong predictors of health service utilization and mortality (Bath, 1999; Idler & Benyamini, 1997; Idler & Kasl, 1991; Menee et al., 1999). The POMS assessed any within-subject mood variations that might influence EEG.

Patients were on stable doses of concurrent conventional medications for at least 2 months prior to enrollment. Exclusion criteria were alcohol or drug abuse history, current narcotic analgesic, benzodiazepine or antihypertensive medication use, nasal trauma history, and any history of life-threatening medical illness, psychosis, or acute active suicidality. The study was reviewed and approved by the Institutional Review Board of the University of Arizona.

EEG Acquisition

During each session, subjects underwent hook-up using conductive gel with a latex cap embedded with 19 EEG electrodes positioned via the International 10–20 System (Electrocap International, Eaton, OH). Cap electrode impedances were kept below 5K ohms. EEG referenced to linked ears was recorded while subjects sat quietly with eyes closed. Recordings lasted 5 minutes for the resting, pre-sniff values, and 2-seconds each for the 32 sniff test bottle recordings

per session. The qEEG raw signal was sampled at 512 hertz (Hz) on a Lexicor NeuroSearch 24 apparatus (Boulder, CO) with a 2 Hz high pass filter and a 60 Hz notch filter enabled.

Procedures

Each patient was evaluated and followed in a private Phoenix homeopathic clinic by the same pair of experienced classical homeopaths (from a pool of three homeopaths) throughout their participation, who had to agree on the medicine selection with a high level of confidence (at least 7 out of 10). Individually chosen single homeopathic medicines (19 different single agents for 23 patients in the active treatment group) were prepared in indistinguishable liquid forms of LM potencies, starting for all participants with a daily LM 1 dose by mouth, and progressing up in potency (additionally diluted, additionally succussed against a soft-covered book at home by the patient) on an individualized basis, compatible with usual clinical practice. LM potencies were chosen because of their touted ability in homeopathic practice to minimize the risk of antidoting by conventional drugs and to optimize tolerability versus other dose series (e.g., centesimal or c potencies) in sensitizable individuals (De Schepper, 1999).

LM 1 doses are pharmacy-prepared from a 3c (diluted in a $(1/100)^3$ ratio) starting source, followed by serial liquid dilutions in the ratio of 1 part prepared remedy material to 50,000 parts of water-alcohol solvent. One-hundred succussions follow each dilution step. An LM 3 dose, for example, represents a liquid dilution factor of $(1/50,000)^3$ and a total of 300 succussions. Homeopathic remedies are prepared from natural sources obtained and processed under a standardized protocol, in accord with the Homeopathic Pharmacopoeia of the United States (see www.HPUS.com).

In this study, an FDA-regulated homeopathic pharmacy (Hahnemann Laboratories, San Rafael, CA, USA, <http://www.hahnemannlabs.com/preparation.html>) prepared the treatment bottles. In accord with a randomization protocol, the homeopathic pharmacy dispensed active or placebo treatment solutions blinded by number codes, with a bottle sent directly to the patient and a split sample to the local research pharmacist before each laboratory session. After 4 months, patients were given the option to switch groups, still under double-

blind conditions, from active to placebo or placebo to active for an additional 2 months (optional crossover; Ernst & Resch, 1995).

Immediately prior to each of the three sessions, the local research pharmacist prepared fresh laboratory test sniff bottles by diluting 10 drops of the patient's current treatment solution (active homeopathic medicine for the Active group or placebo solvent for the Placebo group) or plain control solvent (20% ethanol in distilled water) in 150 cc of distilled water and dividing the resultant solutions over 16 randomly-ordered pairs of treatment and control solution opaque bottles/session (adapted from a low-level odor sensitization protocol from prior olfactory research in our laboratory; Fernandez et al., 1999). Laboratory EEG sessions involving olfactory administration of treatment and control solutions occurred three times during the study, that is, on initiation of treatment, 3 months, and 6 months.

In the Tucson-based university psychophysiology laboratory, patients took 2-s sniffs of each test bottle and guessed which of each pair might contain their treatment solution. On all other days during participation, patients took their treatment solutions by mouth at home as clinically prescribed (De Schepper, 1999). The patients and all clinicians and research staff who interacted with patients were kept blinded to bottle contents throughout the study.

Data Reduction and Analysis

After artifact removal (e.g., eyeblink and muscle movement, amplitudes > 50 mv) by a technician blinded to the group assignments and sniff bottle contents, the EEG was subjected to Fast Fourier Transformation. Relative EEG alpha 1 frequency range was set at 8–10 Hz, and relative alpha 2 at 10–12 Hz. Because of high inter-correlations between electrode sites and findings in the same direction, all 19 leads were averaged to yield a single global value for each alpha band, at sitting rest and during sniff tests (16 treatment solutions versus 16 control solutions).

Statistical Analyses

Statistical analyses were conducted with SPSS 11.0 and Statistica 6.0 for Windows using one way analyses of variance (with post hoc

Tukey tests as indicated), chi-square tests, and general linear models, with covariates as indicated for baseline differences between groups (Tabachnick & Fidell, 2001). Multivariate Hotelling's trace statistics were used for EEG repeated measure analyses. Pearson correlations were computed between change scores in EEG and other variables. Levels of significance were set at $p < .05$. Data are shown as covariate-adjusted means \pm standard error of the mean (SEM) unless otherwise indicated.

RESULTS

Patient Characteristics

The present sample with EEG data for baseline and 3-month laboratory sessions ($N = 48$, active, $n = 23$; placebo, $n = 25$; age 49.2 SD 9.8 years, 94% women; mean tender point count 16.6 SD 2.4; mean tender point pain 88.6 SD 30.7; mean FM duration 13.4 SD 13.7 years; mean global health 7.4 SD 2.7; 88% right-handed; mean chemical sensitivity index score 6.9 SD 2.8) was derived from an originally enrolled clinical trial sample of 62 patients (randomized, in complete blocks of six, to active, $n = 30$, and placebo, $n = 32$), of whom $N = 53$ (active, $n = 26$; placebo, $n = 27$) completed the clinical treatment protocol at 4 months and $N = 50$ at 6 months (full clinical trial findings reported elsewhere; Bell et al., 2004a).

Active and placebo groups did not differ significantly in proportion of dropouts or in proportions of each group electing to switch groups, double-blind, at the optional crossover point (4 months). For the post-optional crossover sample, EEG data for all three sessions was available for $N = 41$ patients (active-stay, $n = 13$; active-switch, $n = 6$; placebo-stay, $n = 13$; placebo-switch, $n = 9$). No dropouts reported adverse reactions to remedies or placebo as a reason for leaving the study; the most common reason given was time/travel burden between Tucson and Phoenix (the cities are 120 miles apart in the rural state of Arizona).

Differences in sample sizes for completers between the clinical trial and the EEG components of the study resulted from patients with missing data because of refusal to participate in the laboratory

sessions (pre-crossover, $n = 5$; post-crossover, $n = 6$) due to travel time concerns (half of the patients were from Phoenix and half from Tucson) or reported discomfort from the electrode cap hook-up procedures, or pharmacy errors or patient reversal of decision in implementation of crossover decision (post-crossover, $n = 3$). The findings reported thus reflect all of the complete EEG datasets for the 3-month (48/53 or 91% of the completed clinical sample pre-crossover) and 6-month (41/50 or 82% of the completed clinical sample post-crossover) laboratory sessions.

Active and placebo groups did not differ at baseline in age, gender distribution, handedness, degree of chemical sensitivity, childhood abuse/neglect, number of tender points, tender point pain on physical examination, duration of FM, or global health ratings. The active and placebo groups differed significantly for baseline exposure to antihistamine ($n = 4$ active remedy patients: one each on loratadine, fexofenadine, cimetidine, Tylenol Allergy) or expectorant ($n = 3$ active remedy patients: guaifenesin) medications (Table 1). The optional crossover subgroups differed significantly for the baseline POMS depression, POMS anger-hostility, and exposure to antihistamine and/or expectorant medications (Table 1), but not for demographic variables. Post-hoc analyses showed that the active-switch subgroup scored significantly higher than all three other subgroups for depression and anger-hostility. Two patients in the ac-

TABLE 1. Optional crossover group means (SD) for medication use differences and POMS subscales at baseline

	<i>Placebo-stay</i> ($n = 13$)	<i>Placebo-switch</i> ($n = 9$)	<i>Active-switch</i> ($n = 6$)	<i>Active-stay</i> ($n = 13$)
Antihistamines or expectorant ^a	0	0	2 (33%)	3 (23%)
POMS depression ^b	3.5 (4.5)	6.1 (6.9)	18.7 (16.2)	5.0 (7.9)
POMS anger-hostility ^c	2.9 (4.5)	1.6 (2.7)	12.2 (9.3)	2.2 (3.5)
POMS vigor	12.3 (5.4)	9.0 (4.6)	14.0 (6.7)	11.8 (5.9)
POMS anxiety	7.3 (6.2)	7.9 (6.2)	12.8 (8.7)	7.8 (6.0)
Childhood sexual abuse	1.5 (3.6)	2.6 (3.6)	2.4 (3.3)	1.5 (3.2)
Childhood physical abuse	3.4 (4.2)	5.1 (6.4)	4.0 (3.2)	2.9 (4.5)
Childhood physical neglect	1.1 (1.6)	2.3 (2.7)	1.0 (1.0)	1.2 (1.3)

^a $p < .05$, A>P; A-switch, A-stay>P-switch, P-stay.

^bOverall, $F(3,37) = 4.7$, $p = .007$; posthoc $p < .05$: A-switch>A-stay, P-stay, P-switch.

^cOverall, $F(3,37) = 7.2$, $p = .001$; posthoc $p < .05$: A-switch>A-stay, P-stay, P-switch.

tive-switch and three patients in the active-stay subgroups versus none of the placebo-stay or placebo-switch subgroups had the antihistamine/expectorant medication exposure history.

This part of the overall study was not focused on the clinical trial outcomes (Bell et al., 2004a). However, to put the EEG findings in perspective, Table 2 shows outcome data for the subset of patients with EEG data used in the current analyses. Individuals who had been randomized to active remedy, like those in the larger clinical study, showed significantly greater improvements in tender point pain and global health at 3 months compared with patients on placebo. At 6 months, patients with EEG data who chose to stay in the active group throughout the study had a non-significant trend toward less tender point pain and significantly greater gains in global health than did the placebo-switch optional crossover subgroup.

As is standard clinical practice in classical homeopathy, patients received highly individualized remedy choices intended to treat the whole-person pattern of unique bio-psycho-social-spiritual symptomatology, rather than the fibromyalgia diagnosis per se (Bell et al., 2003). Chi-square analysis revealed no significant difference between active and placebo groups or optional crossover subgroups in the patterns of homeopathic prescriptions (overall sources: animal 2%, e.g., *Lac Deffloratum* [skimmed cow's milk]; mineral 56%, e.g., *Calcarea Carbonica* [calcium carbonate]; and plant 42%, e.g., *Rhus Toxicodendron* [poison ivy]).

Relative EEG Alpha Magnitude Data

Consistent with the primary TDS hypothesis, Figure 1 illustrates significant patterns of progressive increases over sessions during the bottle sniffs, in both alpha-1 and alpha-2 magnitude in the active group, whereas the placebo group declined between the initial and 3-month sessions. The findings were elicited by sniffing or olfactory activation (averaged over treatment solution and control solution sniffs), not by the specific contents of the sniff bottles, as there were no significant within-subject interactions between sniff bottle contents and group. Correct guesses as to the contents of the pairs of treatment and control solution sniff bottles were at chance levels and did not differ between active and placebo groups. Active

TABLE 2. Clinical outcomes: Changes from baseline scores on tender point pain and global health ratings by group and optional crossover subgroups for subjects who completed the follow-up laboratory sessions

	Placebo (n = 25)	Active (n = 23)	Placebo-stay (n = 13)	Placebo-switch (n = 9)	Active-switch (n = 6)	Active-stay (n = 13)
3 months (pre-optional crossover)						
Tender point pain change ^a	+3.8 (6.1)	-24.9 (6.4)	+2.7 (7.8)	+6.2 (8.8)	-6.4 (12.0)	-35.4 (7.3)
Global health rating change ^b	-0.57 (0.49)	+1.9 (0.52)	-0.14 (0.56)	-0.55 (0.66)	-0.97 (0.88)	+2.9 (0.5)
6 months (post-optional crossover)						
Tender point pain change ^c	—	—	-6.5 (9.5)	-6.2 (11.3)	+0.08 (17.0)	-33.2 (9.1)
Global health rating change ^d	—	—	+0.70 (0.71)	-1.3 (0.81)	+0.31 (1.3)	+3.7 (0.66)

Note. Means (SEM) adjusted for covariates of medications or medications and baseline POMS scores, as described in the text. The double-blind optional crossover decision occurred at the 4-month point.

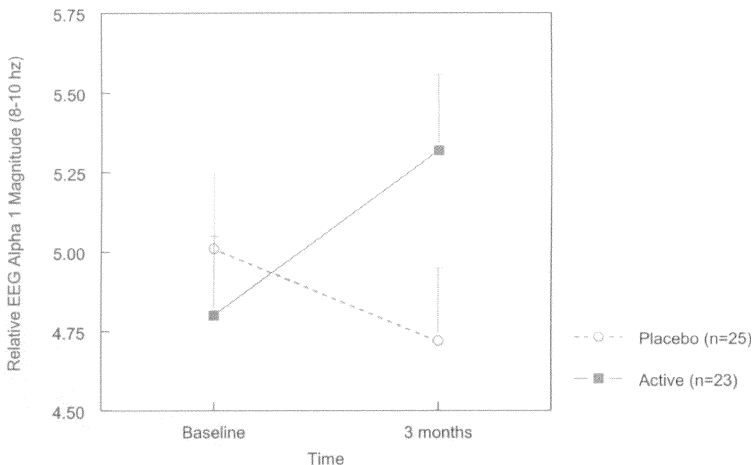
^aActive vs Placebo, $p = .003$; Active group decreased, while Placebo group increased, in tender point pain. After 3 months for the subsequent optional crossover subgroups: Active-stay had improved significantly more than all three other subgroups (posthoc $p < .05$).

^bActive vs Placebo, $p = .002$; Active group improved, while Placebo group worsened, in global health. After 3 months for the subsequent optional crossover subgroups: Active-stay had improved significantly more than all three other subgroups (posthoc $p < .05$).

^c $p = .11$ (trend, n.s.)

^d $p = .01$ over all optional crossover subgroups after 6 months; posthoc, $p < .05$: A-stay>P-switch.

**Changes in Eyes Closed EEG Alpha 1 during Bottle Sniffs
Controlled for Baseline Mood & Medications**



**Changes in Eyes Closed EEG Alpha 2 during Bottle Sniffs
Controlled for Baseline Mood & Medications**

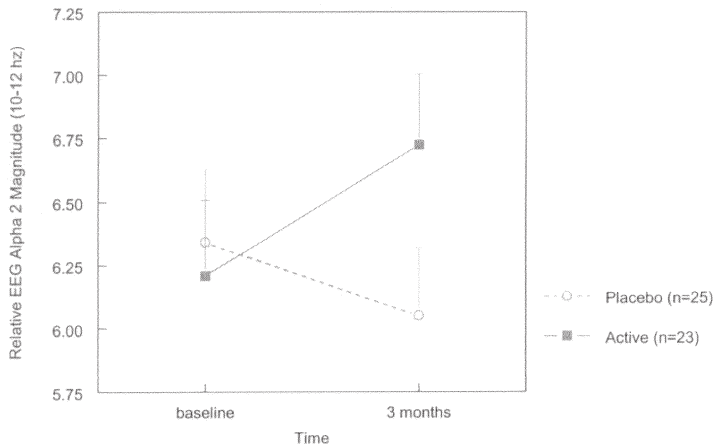


FIGURE 1. Active versus placebo group adjusted means (\pm SEM) for relative alpha-1 (Hotelling's trace $F(1,45) = 5.46, p = .024$) and alpha-2 ($F(1,45) = 5.48, p = .024$) from GLM analyses using covariate of use of antihistamine/expectorant medications. Findings remained significant even if all patients taking antihistamine/expectorant medications were removed from the analysis for alpha-1 (Hotelling's trace $F(1,39) = 5.33, p = .026$) and alpha-2 ($F(1,39) = 5.54, p = .024$).

and placebo groups did not differ significantly for resting alpha magnitudes within or between laboratory sessions.

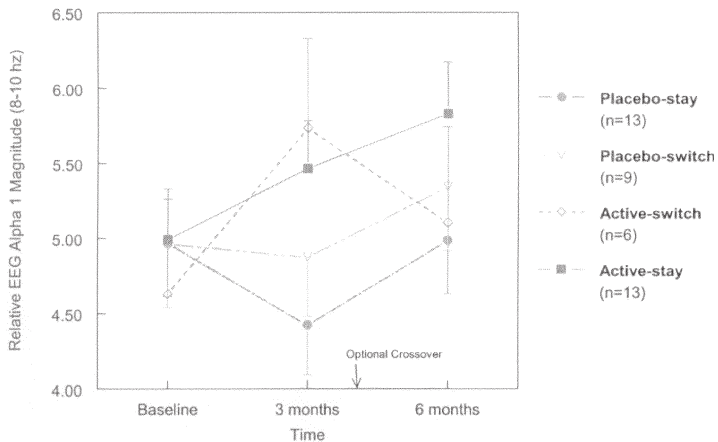
Figure 2 shows the 6-month patterns of sniff-induced changes in the subgroups created by the optional crossover decision at the 4-month point. Notably, the active-stay group continued to exhibit further increases in alpha-1 and alpha-2 magnitude through the 6-month session. The findings were significant for alpha-2, with strong trends for alpha-1. In contrast, although the active-switch subgroup had shown an increase in alpha magnitude prior to crossover, their direction reversed after crossover. The placebo-stay subgroup decreased at 3 months, then returned close to their original baseline at 6 months.

The placebo-switch subgroup showed a slight increase in the alpha-2 band on placebo at 3 months, followed by a somewhat sharper increase, especially in the alpha-1 band, on active treatment at 6 months. Total magnitude of both alpha bands for the placebo-switch group was below the active-stay patients on both follow-up sessions.

During the initial session, all patients received an LM 1 potency of their individualized treatment solution. Active and placebo groups did not differ in progression of homeopathic medicine potency in the LM series at the 3-month visit (mean LM potency 2.4 SD 0.9, or $(1/50,000)^{2.4}$ dilution factor). Switch subgroups began treatment with LM 1 potencies at 4 months, thereby leading to subgroup differences in LM potencies at 6 months ($F(3,33) = 6.2$, $p = .002$ overall, with placebo-switch significantly lower in LM “potencies,” than placebo-stay or active-stay subgroups). At 6 months, the active-stay and placebo-stay subgroups had progressed comparably in LM “potency” (4.8 SD 1.6 versus 4.6 SD 1.3 respectively, or approximately $(1/50,000)^{4.7}$ dilution factor).

After 3 months versus baseline, the changes in alpha-1 and alpha-2 did not correlate significantly with changes in LM remedy potency, depression, anger, vigor, tender point pain, or global health within either the active or placebo group. After 6 months versus baseline, within the placebo-stay subgroup, increases in sniff alpha-1 and alpha-2 correlated with higher vigor (alpha-1: $r = .65$, $p = .015$; alpha-2: $r = .60$, $p = .029$), less anger (alpha-1: $r = -.51$, $p = .07$; alpha-2: $r = .53$, $p = .06$), and lower LM “dose” (alpha-1: $r = -.65$, $p = .04$; alpha-2: $r = -.60$, $p = .065$). In contrast, within the active-stay subgroup, the sniff increases in alpha-1 and alpha-2 at 6

**Changes in Eyes Closed EEG Alpha 1 during Bottle Sniffs
Controlled for Baseline Mood, Emotional Neglect, & Medications**



**Changes in Eyes Closed EEG Alpha 2 during Bottle Sniffs
Controlled for Baseline Mood, Emotional Neglect, & Medications**

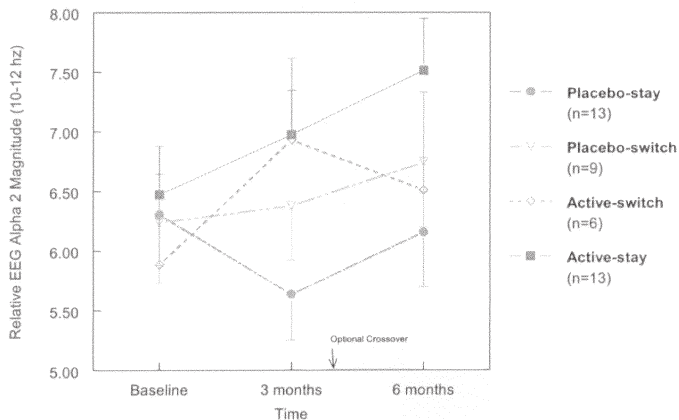


FIGURE 2. Active-stay, active-switch, placebo-switch, placebo-stay subgroup adjusted means (\pm SEM) for relative alpha-1 (Hotelling's trace $F(6,64) = 1.88, p = .097$) and alpha-2 ($F(6,64) = 2.5, p = .031$) from GLM analyses using covariates of baseline POMS depression, POMS anger-hostility, and use of antihistamine/expectorant medications. Findings become stronger when all patients using antihistamine/expectorant medications were removed from the analysis for alpha-1 (Hotelling's trace $F(6,56) = 2.04, p = .076$) and alpha-2 ($F(6,56) = 2.64, p = .025$).

months did not correlate with any clinical change variables, including vigor (alpha-1: $r = .10$, $p = .7$; alpha-2: $r = .05$, $p = .8$), anger (alpha-1: $r = .08$, $p = .8$; alpha-2: $r = -.06$, $p = .8$), LM dose (alpha-1: $r = -.20$, $p = .6$; alpha-2: $r = -.10$, $p = .8$), change in tender point pain (alpha-1: $r = .12$, $p = .7$; alpha-2: $r = -.27$, $p = .4$), or change in global health (alpha-1: $r = -.08$, $p = .8$; alpha-2: $r = -.10$, $p = .7$). However, over the whole sample at the end of the 6-month study, increased alpha-1 and alpha-2 correlated significantly with total amount of time on active remedy treatment (0, 2, 4, or 6 months, as generated by randomized assignment and optional crossover decision) (alpha-1: $r = .45$, $p = .003$; alpha-2: $r = .45$, $p = .003$).

DISCUSSION

The sniff EEG alpha findings may offer an objective biomarker for eliciting evidence of differential effects of active versus placebo homeopathic treatment in FM patients over time. The change in relative alpha magnitude over sessions was time-, but not dose-dependent, and did not correlate with clinical outcomes. Temporolimbic activation via sniffing has previously provided a neurobiological challenge test to demonstrate differences between various patient types and controls (Fernandez et al., 1999; Locatelli et al., 1996; Locatelli et al., 1993). In normals, sniffing odors can produce transient increases in alpha 1 and alpha 2 coherence over several brain regions (Harada et al., 1996). The current findings were present at most of the 19 leads, a global finding consistent with increased coherence, although this parameter was not specifically assessed. The spectral relative EEG alpha sniff findings for the 3-month session differed from those of simple odor responses, however. That is, certain odors acutely induce a brief decrease (Schwartz et al., 1994) or even no change (Masago et al., 2000) in alpha magnitude or power, as opposed to the increases seen in the present study.

Alternatively, as proposed earlier, progressive increases in EEG alpha magnitude over the 19 averaged electrode sites during sniffs could indicate sensitization of widespread changes in brain activity to the remedies within the novel context of the laboratory (Ostrander et al., 1998; Stahl et al., 1997), for example, EEG recording proce-

dures with olfactory activation (Sorg et al., 2001; Vanderwolf & Zibrowski, 2001). Patients were taking their treatment solutions by mouth once daily at home other than on laboratory session days. As in a typical time-dependent sensitization process (Bell et al., 1999; Ferger & Kuschinsky, 1996; Stahl et al., 1997), the active and placebo groups did not differ in alpha magnitude at rest or in the first session sniff response. They later diverged during bottle sniffs in the 3-month and 6-month laboratory sessions. Consistent with a time- rather than dose-dependent sensitization process (Antelman, 1994), greater alpha activity correlated with more time on active remedy treatment, but not with dose (LM potency) of active remedy per se.

If sensitization occurred, it was related more to the active remedy exposure than to individual difference traits between active and placebo patients. The active and placebo groups did not differ in demographics, degree of CI, or early abuse histories, host factors that have facilitated sensitization in previous studies (Bell et al., 1999). The alpha magnitude findings remained significant after controlling for baseline mood differences and conventional drug exposures, including re-analyses that removed the active group patients taking the antihistamine or expectorant medications (Figures 1 and 2). Ethanol can initiate sensitization (Hosbaw & Lewis, 2001), but both active and placebo patients sniffed bottles containing the same low ethanol concentrations and did not differ in their ability to detect bottle contents.

The finding of a small, pre-crossover increase in alpha-2 in the placebo-switch subgroup and oscillatory (down, then up) changes in the placebo-stay subgroup over the two follow-up sessions, also suggests the possible presence of sensitization-oscillation to non-active treatment procedures as a partial mediator of the response patterns over time. That is, stress alone can initiate or elicit sensitization (Antelman et al., 1980; Sorg et al., 2001b; Sorg & Prasad, 1997), and early environmental impoverishment favors, while enrichment attenuates, sensitization in animals (Bardo et al., 1995).

In TDS, prior history of the individual influences the direction of change from the previous session (Antelman & Caggiula, 1996). In general, women with FM report increased rates of childhood abuse and neglect (Walker et al., 1997). Thus, non-specific stress could

have fostered a mild EEG sensitization or oscillation during olfactory temporolimbic activation in some subjects, as seen previously in sexually abused women sniffing odors (Fernandez et al., 1999) or in women with FM and CI over repeated ingestions of sucrose-water solutions (Bell et al., 2001). At the same time, within the specific subjects who had EEG data, groups and subgroups did not differ significantly from one another in quantified levels of POMS anxiety in the laboratory or self-rated childhood abuse or neglect histories (emotional neglect was significantly higher in the placebo-switch subgroup of the larger sample; Bell et al., 2004b).

Findings may or may not have related to the actual remedy exposure during the laboratory sessions. Two different possibilities could account for the lack of within subject differences between active and control solution bottle sniffs. First, the progressive effects of the oral doses could have initiated the active versus placebo group divergence over time. In that case, the novel act of sniffing, regardless of sniff bottle contents, by itself elicited differences in temporolimbic function (Locatelli et al., 1996). These functional shifts, though not apparent in the resting state, would have resulted from the daily oral remedy treatment but required a novel set of circumstances, that is, the laboratory sniff protocol, to elicit (as in other sensitization studies; Crombag et al., 2001).

Conditioning would not be a sufficient explanation (Newlin & Thomson, 1991), based on the reversal of direction after changing from active to placebo solutions that the active-switch subgroup exhibited under otherwise identical laboratory conditions and cues at 6 months. Progressive lack of molecules of the source materials of the remedies as LM potency increased (with correspondingly greater dilution) is an unlikely explanation for alpha changes within the active-stay subgroup, as their difference scores for LM dose of active remedy between follow-ups and baseline exhibited no correlation with the changes in sniff alpha magnitude over time. Moreover, if simple dilutional effects from a conventional pharmacological perspective had been a key factor, then the complete absence of any possible remedy molecules for the active-switch subgroup, who were sniffing placebo bottles at 6 months, should have led to even larger alpha increases than those seen in the active-stay subgroup at 6 months. Instead, the active-switch subgroup reversed direction at

6 months, whereas the active-stay subgroup continued to exhibit increases in sniff EEG alpha magnitude at their higher potency LM doses of active remedy (more dilute, more succussed).

Second, carry-over effects between active and control bottle sniffs could have obscured acute differences between effects of active and control bottle effects. Homeopathic researchers are generally concerned about the possibility of lingering carry-over effects from active to control conditions in within subjects research designs (Ernst & Hahn, 1998). Clinical (Vitboulkas, 1980) and animal evidence (Sukul et al., 1986) suggests persistent effects after a single dose of active medicine for hours, if not many weeks.

Although carry-over effects on alpha magnitude effects are possible (Antelman et al., 1988), other findings in this study indicate that the treatment and control solution effects did differ significantly during sniffs of active versus control solutions. That is, the subset of active-stay patients with exceptional clinical outcomes (Bell et al., 2004c) diverged from all other study patients for prefrontal EEG cordance (Cook et al., 2002) difference scores between treatment and control solution sniffs during the first laboratory session. Cordance is a spatially-localized derivative of absolute and relative power in a given frequency band, which correlates with brain metabolic activity or blood flow on functional neuroimaging scans (Cook et al., 2002; Leuchter et al., 2002).

One explanation for the discrepancy in bottle content effects between global relative alpha and prefrontal cordance alpha in this study is that prefrontal cordance appears more useful than relative or absolute EEG power at differentiating active responders from non-responders and from placebo responders to antidepressant medications (Cook et al., 2002; Leuchter et al., 2002). The relative alpha data in the present study appeared only to distinguish patients receiving active from placebo treatment, not necessarily those with different degrees of clinical responsiveness. Furthermore, in contrast with the spatially less localized relative EEG reference to linked ears for the present analyses, cordance values were derived from remounting between nearest neighbor electrodes for more precise localization of effects.

Notably, both prefrontal cordance (Cook et al., 2002) and TDS (Antelman et al., 1992; Pontieri et al., 2001; Sorg et al., 1998)

effects in earlier research have occurred across multiple, chemically-dissimilar agents, suggesting a greater mechanistic role for intrinsic host characteristics than for structural properties of any single agent. Perceived threat, foreignness, and/or relevance to the organism, that is, individual salience, is one factor (Antelman, et al., 1992). The latter concept could be especially relevant in accommodating the heterogeneity of individualized homeopathic remedies, where the majority of the patients in a clinical or research setting, including the present study, receive a unique treatment agent chosen for the idiosyncratic presentation of the whole person rather than one homogeneous intervention chosen for a clinical diagnosis (Merrell & Shalts, 2002; Rowe, 1998; Vithoukias, 1980).

Overall, the data suggest that active homeopathic remedies in LM potencies have salient signal properties for initiating and perhaps eliciting sensitization in the brain function (EEG) of the individuals taking them, apart from any clinical effects. If EEG alpha magnitude sensitization occurred, it is possible that dopaminergic D2 receptors in mesolimbic pathways were mobilized (Ferber & Kuschinsky, 1996; Stahl et al., 1997) and/or prefrontal dopamine activity was decreased (Bijjou et al., 2002). That is, the limbic and mesolimbic pathways involved in TDS would have read the daily oral doses of remedy as a recognizable, repeated intermittent signal (Rey, 2003), even with an increasingly “higher,” albeit more dilute and more succussed, dose (Bastide & Lagache, 1997). In this study, if there was no carry-over effect from active to control solution bottle effects, then the temporolimbic activation from sniffing alone, not the bottle contents, elicited the evidence of a persistent, previously established sensitized response during sessions 2 and 3.

The groups were well-matched by random assignment on demographic and most other baseline variables, including non-narcotic analgesic and serotonin reuptake inhibitor drugs. However, the active group did turn out to report greater baseline exposure to antihistamine and expectorant drugs than did the placebo group. Although it would have been preferable to perform this study in drug-free patients, ethical and practical concerns did not make it feasible to deny patients standard of care for any condition for 6 months. Subjects were required to be stable on concomitant medications prior to enrollment.

To address the differential medication exposure, we performed the EEG repeated measure analyses both with the drug variable as a covariate, as recommended in standard statistics texts (Tabachnick & Fidell, 2001), and with exclusion of all patients on the antihistamine/expectorant medications from the analyses. The results remained the same, suggesting that differential conventional medication exposure did not account for the sensitization findings. Moreover, the medications were split fairly evenly between the active-stay and active-switch subgroups. The direction of EEG patterns of those subgroups after optional crossover diverged as a function of homeopathic treatment condition at 6 months (the independent variable—active or placebo), making the conventional drugs an unlikely explanation for the alpha sensitization. Finally, all of the groups were stable on concomitant medications and did not differ in resting or sniff EEG alpha magnitude in the first session. If the drugs had exerted a physiologically confounding effect of changing nasal patency and/or elevating alpha activity in the group on active remedy, it should have been observed for all three sessions, but was not.

Skeptics might argue that the homeopathic remedies would have been active only at the doses that contained physical molecules of the original source material. All patients received LM doses probably in the material dose range (LM 1) in session 1, and some reached into the range beyond Avogadro's number in follow-up sessions, that is, 6×10^{23} (given the LM starting preparation at 3c $(1/100)^3$ and subsequent dilution steps of $(1/50,000)$, this ultra-dilution dose occurs around LM 4 to 5 and higher, comparable to the centesimal potency series where a 12c $(1/100)^{12}$ potency and higher contains no remaining source molecules). On the conservative assumption that remedies used at 6 months may not have contained any original source molecules, the continued growth of the EEG alpha response over time in the active-stay subgroup suggests remarkably persistent effects of the initial doses of homeopathic remedies in the host, beyond those typically associated with pharmacokinetic or pharmacodynamic properties of conventional drugs, even long-acting exogenous hormones.

Again, apart from the as-yet unresolved debates concerning structural alterations of solvent (Bell *et al.*, 2003; Elia & Nicolli, 1999; Rey, 2003) and biological activity in ultra-high dilutions of homeo-

pathic remedies (Jonas et al., 2003; Langman, 1997; Linde et al., 1997; Vandenbroucke, 1997), a TDS model can accommodate the present observations for the LM potencies. For example, sensitization to repeated, low levels of environmental chemicals can induce a long-lasting change in adrenal steroid hormone response patterns of the host (Sorg et al., 2001a). Hormetic compensation within the host for the effects of the initial, low material doses of remedy could also contribute to the current findings (Calabrese & Baldwin, 2001).

To determine any differential signal properties of different doses (Bellavite & Signorini, 2002), it will fall to future studies to examine EEG alpha sensitization in persons or animals receiving homeopathic remedies only in the material dose (low potency) range versus only in the above-Avogadro's-number range (high potency). It may be possible to study some clinical populations other than FM for 3–6 months under conventional drug-free conditions, which would definitively address concerns mentioned above. The feasibility and plausibility of such research are emerging, given (a) prior animal research showing a longer duration of action of higher potencies of various homeopathic remedies versus lower potencies of the same remedies or conventional haloperidol on restraint-induced catalepsy (Sukul et al., 1986); and (b) the recently demonstrated ability of homeopathic remedies prepared beyond Avogadro's number to exert biophysical effects (thermoluminescence patterns) characteristic of their original source material and different from plain solvent (Rey, 2003).

In summary, the present findings during sniffing suggest that time-dependent changes in EEG alpha magnitude responses may offer an objective way to differentiate active from placebo homeopathic treatment. These observations are supportive of Davidson's hypothesis (Davidson, 1994) that host responses to homeopathic remedies may involve time-dependent sensitization. However, homeopathy is a controversial form of CAM (Bellavite & Signorini, 2002; Ernst & Hahn, 1998; Langman, 1997; Vandenbroucke & de Craen, 2001; Vickers, 1999, 2000), and research in this field has long been hampered by problems in reproducibility (Jonas et al., 2003; Linde et al., 1997; Linde et al., 1994).

This study is the first to examine TDS of spectral EEG as a

possible objective correlate of homeopathic remedy effects during a controlled clinical trial. Taken together with prior animal EEG studies (Ruiz-Vega et al., 2002) and bottle contents-related sniff EEG prefrontal cordance findings in this study (Bell et al., 2004c), the present data support the need for replication and extension of the current protocol, with additional EEG investigation of homeopathic medicine effects in larger samples of FM and other clinical conditions (Bell et al., 2002). Future studies will need to address methodological limitations of the current investigation and test the generalizability of using EEG as a biomarker. Nonetheless, this study provides a start towards a rational, systematic approach for clinical neurophysiological research in homeopathy.

REFERENCES

- Antelman, S. M. (1994). Time-dependent sensitization in animals: A possible model of multiple chemical sensitivity in humans. *Toxicology & Industrial Health*, *10*(4–5), 335–342.
- Antelman, S. M., & Caggiula, A. R. (1996). Oscillation follows drug sensitization: Implications. *Critical Reviews in Neurobiology*, *10*(1), 10 1–117.
- Antelman, S. M., Caggiula, A. R., Gershon, S., Edwards, D. J., Austin, M. C., Kiss, S., & Kocan, D. (1997). Stressor-induced oscillation. A possible model of the bidirectional symptoms in PTSD. *Annals of the New York Academy of Sciences*, *821*, 296–304.
- Antelman, S. M., Eichler, A. J., Black, C. A., & Kocan, D. (1980). Interchangeability of stress and amphetamine in sensitization. *Science*, *207*(4428), 329–331.
- Antelman, S. M., Knopf, S., Kocan, D., Edwards, D. J., Ritchie, J. C., & Nemeroff, C. B. (1988). One stressful event blocks multiple actions of diazepam for up to at least a month. *Brain Research*, *445*(2), 380–385.
- Antelman, S. M., Kocan, D., Knopf, S., Edwards, D. J., & Caggiula, A. R. (1992). One brief exposure to a psychological stressor induces long-lasting, time-dependent sensitization of both the cataleptic and neurochemical responses to haloperidol. *Life Sciences*, *51*(4), 261–266.
- Bardo, M. T., Bowling, S. L., Rowlett, J. K., Manderscheid, P., Buxton, S. T., & Dvoskin, L. P. (1995). Environmental enrichment attenuates locomotor sensitization, but not in vitro dopamine release, induced by amphetamine. *Pharmacology, Biochemistry & Behavior*, *51*(2–3), 397–405.
- Bastide, M., & Lagache, A. (1997). A communication process: A new paradigm applied to high-dilution effects on the living body. *Alternative Therapies in Health & Medicine*, *3*(4), 35–39.
- Bath, P. A. (1999). Self-rated health as a risk factor for prescribed drug use and future health and social service use in older people. *Journal of Gerontology, Series A*, *54*(11), M565–M570.
- Bell, I. R., Baldwin, C. M., Fernandez, M., & Schwartz, G. E. (1999). Neural sensitization model for multiple chemical sensitivity: Overview of theory and empirical evidence. *Toxicology & Industrial Health*, *15*(3–4), 295–304.
- Bell, I. R., Baldwin, C. M., & Schwartz, G. E. (2001). Sensitization studies in chemically intolerant individuals: Implications for individual difference research. *Annals of the New York Academy of Sciences*, *933*, 38–47.

- Bell, I. R., Baldwin, C. M., & Schwartz, G. E. (2002). Translating a nonlinear systems theory model for homeopathy into empirical tests. *Alternative Therapies in Health & Medicine*, 8(3), 58–66.
- Bell, I. R., Baldwin, C. M., Stoltz, E., Walsh, B. T., & Schwartz, G. E. (2001). EEG beta 1 oscillation and sucrose sensitization in fibromyalgia with chemical intolerance. *International Journal of Neuroscience*, 108(1–2), 31–42.
- Bell, I. R., Baldwin, C. M., & Schwartz, G. E. (1998). Illness from low levels of environmental chemicals: Relevance to chronic fatigue syndrome and fibromyalgia. *American Journal of Medicine*, 105 Supplement(3A), 74S–82S.
- Bell, I. R., Baldwin, C. M., Stoltz, E., Walsh, B. T., & Schwartz, G. E. R. (2001). Concomitant environmental chemical intolerance modifies the neurobehavioral presentation of women with fibromyalgia. *Journal of Chronic Fatigue Syndrome*, 9(1–2), 3–19.
- Bell, I. R., Koithan, M., Gorman, M. M., & Baldwin, C. M. (2003). Homeopathic practitioner views of changes in patients undergoing constitutional treatment for chronic disease. *Journal of Alternative & Complementary Medicine*, 9(1), 39–50.
- Bell, I. R., Lewis, D. A., Brooks, A. J., Lewis, S., & Schwartz, G. E. (2003). Gas discharge visualization evaluation of ultramolecular doses of homeopathic medicines under blinded, controlled conditions. *Journal of Alternative & Complementary Medicine*, 9(1), 25–38.
- Bell, I. R., Lewis, D. A., Brooks, A. J., Schwartz, G. E., Lewis, S. E., Caspi, O., Cunningham, V., & Baldwin, C. M. (2004b). Individual differences in response to randomly-assigned active individualized homeopathic and placebo treatment in fibromyalgia: Implications of a double-blind optional crossover design. *Journal of Alternative & Complementary Medicine*, 10, 269–283.
- Bell, I. R., Lewis, D. A., Schwartz, G. E., Lewis, S. E., Caspi, O., Scott, A., Brooks, A. J., & Baldwin, C. M. (2004c). Electroencephalographic cordance patterns distinguish exceptional clinical responders with fibromyalgia to individualized homeopathic medicines. *Journal of Alternative & Complementary Medicine*, 10, 285–299.
- Bell, I. R., Lewis, D. A., Brooks, A. J., Schwartz, G. E., Lewis, S. E., Walsh, B. T., & Baldwin, C. M. (2004a). Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. *Rheumatology*, 43, 577–582.
- Bell, I. R., Schwartz, G. E., Hardin, E. E., Baldwin, C. M., & Kline, J. P. (1998). Differential resting qEEG alpha patterns in women with environmental chemical intolerance, depressives, and normals. *Biological Psychiatry*, 43(5), 376–388.
- Bell, I. R., Warg-Damiani, L., Baldwin, C. M., Walsh, M. E., & Schwartz, G. E. (1998). Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings. *Military Medicine*, 163(11), 725–732.
- Bellavite, P., & Signorini, A. (2002). *The emerging science of homeopathy complexity, biodynamics, and nanopharmacology* (2nd ed.). Berkeley: North Atlantic Books.
- Bernstein, D., Fink, L., & Handelsman, L. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry*, 151, 1132–1136.
- Bijjou, Y., De Deurwaerdere, P., Spampinato, U., Stinus, L., & Cador, M. (2002). D-amphetamine-induced behavioral sensitization: Effect of lesioning dopaminergic terminals in the medial prefrontal cortex, the amygdala and the entorhinal cortex. *Neuroscience*, 109(3), 499–516.
- Calabrese, E. J., & Baldwin, L. A. (2001). Hormesis: A generalizable and unifying hypothesis. *Critical Reviews in Toxicology*, 31, 353–424.
- Cook, I. A., Leuchter, A. F., Morgan, M., Witte, E., Stubbeman, W. F., Abrams, M., Rosenberg, S., & Uijtdehaage, S. H. (2002). Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology*, 27(1), 120–131.
- Crombag, H. S., Badiani, A., Chan, J., Dell’Orco, J., Dineen, S. P., & Robinson, T. E. (2001). The ability of environmental context to facilitate psychomotor sensitization to amphetamine can be dissociated from its effect on acute drug responsiveness and on conditioned responding. *Neuropsychopharmacology*, 24(6), 680–690.

- Davidson, J. (1994). Psychiatry and homeopathy. Basis for a dialogue. *British Homoeopathic Journal*, 83, 78–83.
- De Schepper, L. (1999). LM potencies: One of the hidden treasures of the sixth edition of the Organon. *British Homoeopathic Journal*, 88(3), 128–134.
- Elia, V., & Niccoli, M. (1999). Thermodynamics of extremely diluted aqueous solutions. *Annals of the New York Academy of Sciences*, 879, 241–248.
- Ernst, E., & Hahn, E. G. (Eds.). (1998). *Homeopathy. A critical appraisal*. Oxford: Butterworth-Heinemann.
- Ernst, E., & Resch, K. L. (1995). The “optional cross-over design” for randomized controlled trials. *Fundamental Clinical Pharmacology*, 9, 508–511.
- Ferger, B., Kuschinsky, K. (1996). Effects of cocaine on the EEG power spectrum of rats are significantly altered after its repeated administration: Do they reflect sensitization phenomena? *Naunyn-Schneideberg's Archives of Pharmacology*, 353, 545–551.
- Fernandez, M., Bell, I. R., & Schwartz, G. E. (1999). EEG sensitization during chemical exposure in women with and without chemical sensitivity of unknown etiology. *Toxicology & Industrial Health*, 15(3–4), 305–312.
- Fisher, P., Greenwood, A., Huskisson, E.C., Turner, P., & Belon, P. (1989). Effect of homeopathic treatment on fibrositis (primary fibromyalgia). *British Medical Journal*, 299, 365–366.
- Friedberg, F., & Jason, L. A. (2001). Chronic fatigue syndrome and fibromyalgia: Clinical assessment and treatment. *Journal of Clinical Psychology*, 57(4), 433–455.
- Granot, M., Buskila, D., Granovsky, Y., Sprecher, E., Neumann, L., & Yarnitsky, D. (2001). Simultaneous recording of late and ultra-late pain evoked potentials in fibromyalgia. *Clinical Neurophysiology*, 112(10), 1881–1887.
- Harada, H., Shiraishi, K., Kato, T., & Soda, T. (1996). Coherence analysis of EEG changes during odour stimulation in humans. *Journal of Laryngology & Otolaryngology*, 110(7), 652–656.
- Hoshaw, B. A., & Lewis, M. J. (2001). Behavioral sensitization to ethanol in rats: Evidence from the Sprague-Dawley strain. *Pharmacology, Biochemistry & Behavior*, 68(4), 685–690.
- Hyland, M. E., & Lewith, G. T. (2002). Oscillatory effects in a homeopathic clinical trial: An explanation using complexity theory, and implications for clinical practice. *Homeopathy*, 91(3), 145–149.
- Idler, E., & Benyamini, Y. (1997). Self-rated health and mortality: A review of twenty-seven community studies. *Journal of Health and Social Behavior*, 38, 21–36.
- Idler, E. L., & Kasi, S. (1991). Health perceptions and survival: Do global evaluations of health status really predict mortality? *Journal of Gerontology*, 46(2), S55–S65.
- Jonas, W. B., Kaptchuk, T. J., & Linde, K. (2003). A critical overview of homeopathy. *Annals of Internal Medicine*, 138(5), 393–399.
- Langman, M. J. S. (1997). Homeopathy trials: Reason for good ones but are they warranted? *Lancet*, 350, 825.
- Leuchter, A. F., Cook, I. A., Witte, E. A., Morgan, M., & Abrams, M. (2002). Changes in brain function of depressed subjects during treatment with placebo. *American Journal of Psychiatry*, 159(1), 122–129.
- Linde, K., Clausius, N., Ramirez, G., Melchart, D., Eitel, F., Hedges, L. V., & Jonas, W. B. (1997). Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet*, 350, 834–843.
- Linde, K., Jonas, W. B., Melchart, D., Worku, F., Wagner, H., & Eitel, F. (1994). Critical review and meta-analysis of serial agitated dilutions in experimental toxicology. *Human Experimental Toxicology*, 13, 481–492.
- Locatelli, M., Bellodi, L., Grassi, B., & Scarone, S. (1996). EEG power modifications in obsessive-compulsive disorder during olfactory stimulation. *Biological Psychiatry*, 39(5), 326–331.
- Locatelli, M., Bellodi, L., Perna, G., & Scarone, S. (1993). EEG power modifications in panic disorder during a temporolimbic activation task: Relationships with temporal lobe

- clinical symptomatology. *Journal of Neuropsychiatry & Clinical Neurosciences*, 5(4), 409–414.
- Masago, R., Matsuda, T., Kikuchi, Y., Miyazaki, Y., Iwanaga, K., Harada, H., & Katsuura, T. (2000). Effects of inhalation of essential oils on EEG activity and sensory evaluation. *Journal of Physiological Anthropology & Applied Human Science*, 19(1), 35–42.
- McNair, D. M., Lorr, M., & Droppleman, L. F. (1981). *Manual for the Profile of Mood States Scale (POMS)*. San Diego, CA: Educational and Industrial Testing Service.
- Menec, V. H., Chipperfield, J. G., & Perry, R. P. (1999). Self-perceptions of health: A prospective analysis of mortality, control, and health. *Journals of Gerontology Series B-Psychological Sciences & Social Sciences*, 54(2), 85–93.
- Merrell, W. C., & Shalts, E. (2002). Homeopathy. *Medical Clinics of North America*, 86(1), 47–62.
- Newlin, D. B., & Thomson, J. B. (1991). Chronic tolerance and sensitization to alcohol in sons of alcoholics. *Alcoholism: Clinical & Experimental Research*, 15(3), 399–405.
- Ostrander, M. M., Hartman, J., Badiani, A., Robinson, T. E., & Gnegy, M. E. (1998). The effect of environment on the changes in calmodulin in rat brain produced by repeated amphetamine treatment. *Brain Research*, 797(2), 339–341.
- Pioro-Boisset, M., Esdaile, J. M., & Fitzcharles, M. A. (1996). Alternative medicine use in fibromyalgia syndrome. [comment]. *Arthritis Care & Research*, 9(1), 13–17.
- Pontieri, F. E., Monnazzi, P., Scontrini, A., Buttarelli, F. R., & Patacchioli, F. R. (2001). Behavioral sensitization to heroin by cannabinoid pretreatment in the rat. *European Journal of Pharmacology*, 421(3), R1–R3.
- Rey, L. (2003). Thermoluminescence of ultra-high dilutions of lithium chloride and sodium chloride. *Physics A*, 323, 67–74.
- Rowe, T. (1998). *Homeopathic methodology. Repertory, case taking, and case analysis*. Berkeley: North Atlantic Books.
- Ruiz-Vega, G., Perez-Ordaz, L., Leon-Hueramo, O., Cruz-Vazquez, E., & Sanchez-Diaz, N. (2002). Comparative effect of Coffea cruda potencies on rats. *Homeopathy: the Journal of the Faculty of Homeopathy*, 91(2), 80–84.
- Schwartz, G. E., Bell, I. R., Dikman, Z. V., Fernandez, M., Kline, J. P., Peterson, J. M., & Wright, K. P. (1994). EEG responses to low-level chemicals in normals and cacosmics. *Toxicology & Industrial Health*, 10(4–5), 633–643.
- Slotkoff, A. T., Radulovic, D. A., & Clauw, D. J. (1997). The relationship between fibromyalgia and the multiple chemical sensitivity syndrome. *Scandinavian Journal of Rheumatology*, 26(5), 364–367.
- Sorg, B., Bailie, T., Tschirgi, M., Li, N., & Wu, W. (2001a). Exposure to repeated low-level formaldehyde in rats increases basal corticosterone levels and enhances the corticosterone response to subsequent formaldehyde. *Brain Research*, 898(2), 314–320.
- Sorg, B. A., Bailie, T. M., Tschirgi, M. L., Li, N., & Wu, W. R. (2001b). Exposure to repeated low-level formaldehyde in rats increases basal corticosterone levels and enhances the corticosterone response to subsequent formaldehyde. *Brain Research*, 898(2), 314–320.
- Sorg, B. A., & Prasad, B. M. (1997). Potential role of stress and sensitization in the development and expression of multiple chemical sensitivity. *Environmental Health Perspectives*, 105(Suppl 2), 467–471.
- Sorg, B. A., Tschirgi, M. L., Swindell, S., Chen, L., & Fang, J. (2001). Repeated formaldehyde effects in an animal model for multiple chemical sensitivity. *Annals of the New York Academy of Sciences*, 933, 57–67.
- Sorg, B. A., Willis, J. R., See, R. E., Hopkins, B., & Westberg, H. H. (1998). Repeated low-level formaldehyde exposure produces cross-sensitization to cocaine: Possible relevance to chemical sensitivity in humans. *Neuropsychopharmacology*, 18(5), 385–394.
- Stahl, D., Ferger, B., & Kuschinsky, K. (1997). Sensitization to d-amphetamine after its repeated administration: Evidence in EEG and behaviour. *Naunyn-Schmiedebergs Archives of Pharmacology*, 356(3), 335–340.

- Staud, R., Vierck, C. J., Cannon, R. L., Mauderli, A. P., & Price, D. D. (2001). Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain, 91*(1–2), 165–175.
- Sukul, N. C., Bala, S. K., & Bhattacharyya, B. (1986). Prolonged cataleptogenic effects of potentized homeopathic drugs. *Psychopharmacology, 89*, 338–339.
- Szarek, M. J., Bell, I. R., & Schwartz, G. E. (1997). Validation of a brief screening measure of environmental chemical sensitivity: The chemical odor intolerance index. *Journal of Environmental Psychology, 17*(4), 345–351.
- Tabachnick, B. G., & Fidell, L. S. (2001). *Using multivariate statistics* (4th ed.). Boston: Allyn and Bacon.
- Ursin, H., & Eriksen, H. R. (2001). Sensitization, subjective health complaints, and sustained arousal. *Annals of the New York Academy of Sciences, 933*, 119–129.
- Vandenbroucke, J. P. (1997). Homeopathy trials: Going nowhere. *Lancet, 350*, 824.
- Vandenbroucke, J. P., & de Craen, A. J. (2001). Alternative medicine: A “mirror image” for scientific reasoning in conventional medicine. *Annals of Internal Medicine, 135*(7), 507–513.
- Vanderwolf, C. H., & Zibrowski, E. M. (2001). Pyriform cortex beta-waves: Odor-specific sensitization following repeated olfactory stimulation. *Brain Research, 892*(2), 301–308.
- Vickers, A. J. (1999). Independent replication of pre-clinical research in homeopathy: A systematic review. *Forschende Komplementarmedizin, 6*(6), 311–320.
- Vickers, A. J. (2000). Clinical trials of homeopathy and placebo: Analysis of a scientific debate. *Journal of Alternative & Complementary Medicine, 6*(1), 49–56.
- Vithoulkas, G. (1980). *The science of homeopathy*. NY: Grove Weidenfeld.
- Walker, E. A., Keegan, D., Gardner, G., Sullivan, M., Bernstein, D., & Katon, W. J. (1997). Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: II. Sexual, physical, and emotional abuse and neglect. *Psychosomatic Medicine, 59*(6), 572–577.
- Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., Tugwell, P., Campbell, S. M., Abeles, M., Clark, P., Fam, A. G., Farber, S. J., Flechter, J. J., Franklin, C. M., Garter, R. A., Hanaty, D., Lessard, J., Lichtbroun, A. A., Niasi, A. T., McCain, G. A., Reynolds, W. J., Romano, T. J., Russell, I. J., & Sheon, R. P. (1990). The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the multicenter criteria committee. *Arthritis Rheumatism, 33*, 160–172.