THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 10, Number 2, 2004, pp. 285–299

Electroencephalographic Cordance Patterns Distinguish Exceptional Clinical Responders with Fibromyalgia to Individualized Homeopathic Medicines

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ABSTRACT

Objectives: To characterize initial central nervous system responses to olfactory administration of homeopathic remedies as biomarkers for subsequently exceptional, simillimum-like clinical outcomes at a systemic level (i.e., both locally and globally).

Design: Double-blinded, randomized, placebo-controlled clinical trial.

Setting: A private homeopathic clinic in Phoenix, AZ, and a university laboratory in Tucson, AZ.

Patients: Sixty-two (62) persons with physician-confirmed fibromyalgia (FM) (mean age, 49 years; 94% women) enrolled; 53 completed the 3-month assessment visit. Exceptional responders ($n = 6$, 23% of active treatment group; none on placebo) were those with improvements in the top one-third for both tender point pain and global health ratings after 3 months.

Intervention: Patients took daily oral doses of treatment solution in LM (1/50,000 dilution) potency (active group received individualized remedy; placebo group received plain solvent).

Dependent measures: Baseline and 3-month difference scores for initial prefrontal electroencephalographic alpha frequency cordance (EEG-C, a correlate of functional brain activity) during 16 pairs of randomized, double-blinded bottle sniffs (treatment minus control solutions).

Results: Exceptional responders versus other patients exhibited significantly more negative initial EEG-C difference scores at prefrontal sites. Right prefrontal cordance findings correlated with subsequently reduced pain ($r = 0.85$, $p = 0.03$), better global health ($r = -0.73$, $p = 0.10$), and trait absorption (genetically determined ability to focus attention selectively and fully) ($r = 0.91$, $p = 0.012$).

Conclusions: These observations suggest prefrontal EEG-C as an early biomarker of individualized homeopathic medicine effects in patients with FM who later exhibit exceptional outcomes. Prefrontal cortex controls executive function, including ability to redirect attention. Interactions between executive function, absorption, and the simillimum remedy could facilitate exceptional responses.

This study was supported by National Institutes of Health (NIH) grants R21 AT00315 (I.R.B.), K24 AT00057 (I.R.B.), P20 AT00774 (GES), and P50 AT00008 from the National Center for Complementary and Alternative Medicine (NCCAM) and NIH HL53938-07S1 (C.M.B.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCCAM or the NIH.

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INTRODUCTION

Classical homeopathy, a 200-year-old form of complementary and alternative medicine (CAM) developed by the German physician Samuel Hahnemann, M.D., is a model system for research on individualization of treatment and outcomes (Jonas and Jacobs, 1996; Lansky, 2003; Merrell and Shalts, 2002; Rowe, 1998; Vithoulkas, 1980). On the treatment side, a single homeopathic medicine or remedy of animal, mineral, or plant origin is chosen to match the whole pattern of the person's bio-psycho-social-spiritual condition. Homeopaths select one medicine at a time from hundreds of different remedies to treat different individuals who carry the same allopathic diagnosis. On the outcome side, when the remedy is correctly chosen, homeopathic theory (Hering's Law of Cure) predicts that the process of healing follows a hierarchical system-wide course of improvements from within outward (from more important to less important organs, e.g., from lungs to skin), from above downward (from head toward toes), and in reverse order of time of original appearance (more recent conditions resolve sooner than more chronic ones).

Nature of healing in homeopathy

Homeopaths claim that the optimally correct remedy, the simillimum, mobilizes system-wide, local and global health improvements (Bell, 2003; Bell et al., 2002a, 2003a, 2003b). Contemporary investigators have proposed that the nature of healing in homeopathy has many parallels to concepts in the modern science of nonlinear complex dynamical systems theory (e.g., self-similarity at every level of scale [fractality]) in the quality of the symptom picture for the correct remedy (e.g., angry behavioral outbursts, sudden violent abdominal pains, angry-looking red skin eruptions) and the self-organization during healing (Bell et al., 2002a; Bellavite and Signorini, 2002; Bellavite, 2003; Hyland, 2003; Hyland and Lewith, 2002; Milgrom, 2002a; Torres, 2002). Homeopathic systems theorists predict that individually salient information from the simillimum will engage higher order control networks (e.g., including the central nervous system) to initiate healing.

The higher order networks then modulate lower order networks to shift function in organs and cells back toward healthier patterns, thereby generating both local and global improvements. Such a model differs from the lock-and-key concept of local cellular receptors and conventional pharmaceutical drugs. A network model for homeopathy suggests that change in central nervous system (CNS) function, which inherently reflects activity of higher order neural networks controlling the organism's behavior and physiological functions (Fuster, 2000; Knight et al., 1999; Ongur and Price, 2000; Peyron et al., 2000; Price, 1999; Quintana and Fuster, 1999), is a practical starting place for research (Ruiz and Torres, 1997; Ruiz-Vega et al., 2002, 2003; Sukul et al., 1986, 2001).

Electroencephalographic cordance

Electroencephalographic cordance (EEG-C) offers a new noninvasive method for examining CNS function in real time. Cordance is a quantitative derivative of absolute and relative scalp EEG power that correlates with patterns of brain blood flow and metabolic functional neuroimaging studies (single-photon emission computed tomography [SPECT], positron emission tomography [PET] scans). By assessing the size of, and relationship between, normalized absolute and relative power at each electrode site, EEG-C provides better information on spatial localization than either relative or absolute EEG power alone. However, studies have not yet reported how well EEG-C captures activity in deeper brain regions. Individuals with organic brain lesions show a positive correlation between greater brain perfusion and increased alpha cordance (Leuchter et al., 1994). In contrast, for persons without organic brain lesions, greater brain perfusion correlates with increased cordance in theta and beta, but decreased cordance in alpha frequency bands (Leuchter et al., 1999). The working interpretation of the inverse relationship in intact persons between cordance and perfusion in the alpha band is that greater EEG alpha represents inhibition of brain activity, thereby reflecting a reduction in brain perfusion.

Differentiating medication responders from placebo responders and all nonresponders with depression using cordance

Using EEG-C, UCLA researchers have found that patients with major depression who turned out to be good clinical responders to an antidepressant medication exhibited greater prefrontal theta cordance at baseline than did poor medication responders (Cook et al., 1999), whereas placebo responders and nonresponders did not differ on cordance at baseline (Cook et al., 1999). They further showed that depressed patients on a variety of different antidepressants of different classes, who later responded to treatment, developed early decreases in quantitative EEG (qEEG) theta cordance in the prefrontal region within 48 hours of beginning treatment, changes that were absent in the medication nonresponders (Cook and Leuchter, 2001). In a recent placebo-controlled study of depressives on either of two different antidepressant medications, Leuchter et al. (Leuchter et al., 2002) extended the work and observed that medication responders again had an early decrease in theta cordance, whereas, on follow-up over 9 weeks, placebo responders had an increase in cordance that grew over time. Clinically, the active and placebo responders achieved indistinguishable, comparable improvements. However, neurophysiologically, their cordance responses went in opposite directions.

Thus, previous cordance studies suggest that the biology of active conventional medication responsivity in the brain is different from that of placebo, the finding is not drug-specific, and prefrontal cordance may be a tool for early iden-

tification of excellent active treatment responders, across different conventional drugs, at least for depression. Cordance offers a possible means to distinguish active antidepressant medication effects from other factors in clinical improvements, such as placebo effects, expectation, natural history of the disease, and regression to the mean (Kirsch et al., 2002).

Need for cordance studies in CAM research

No studies of cordance during CAM treatment of any disorder have as yet been reported. Many homeopaths claim that symptoms reflective of generalities for the whole person (e.g., appetitive behaviors such as food cravings, thirst, libido, sleep and activity patterns, and body temperature), as well as symptoms of the mind, provide major clues to the overall correct remedy selection (Rowe, 1998). Vithoulkas (Vithoulkas, 1980) identifies the brain at the top of the physical hierarchy of self-organization in homeopathic theory. The prefrontal cortex regulates widely distributed networks of neurons that control visceo-sensory function in eating, endocrine and autonomic function, reward, pain responses, mood, sensitizability (susceptibility to amplify host responses over time), and executive function (Knight et al., 1999; Ongur and Price, 2000; Price, 1999; Sorg et al., 2001), perhaps even the sense of self (Vogeley et al., 1999). Thus, it is reasonable to hypothesize that prefrontal cordance may offer an objective early biomarker in individuals who are more likely to show optimal local and global outcomes during homeopathic treatment.

Rationale and objectives for the current study

In a recent randomized clinical trial of individualized homeopathic treatment in persons with fibromyalgia, we demonstrated that those on active/verum had significantly better outcomes than did those on placebo, on average (Bell et al., 2004a). We chose fibromyalgia (FM) as a model disease for (1) its clinical features (i.e., a chronic diffuse musculoskeletal pain disorder, frequently associated with comorbid fatigue and depression, in which CAM use is almost universal [Pioro-Boisset et al., 1996]) and (2) prior evidence of CNS involvement in FM (e.g., elevated cerebrospinal fluid levels of substance P [Vaeroy, 1988]), increased waking EEG alpha activity (Bell et al., 2001), and reductions of right thalamic blood flow on SPECT (Kwiatek et al., 2000). However, we also noted post hoc that a subset of patients on active treatment had exceptional outcomes (i.e., marked improvements in both local tender point pain on examination and global health ratings). The present study tested the hypothesis that these exceptional responders to individualized homeopathic treatment exhibited initial responses in prefrontal EEG alpha cordance during olfactory administration of remedy versus control solutions that differed from those of other study patients.

METHODS

The study involved a double-blinded, placebo-controlled randomized clinical trial of individualized homeopathy with EEG recordings during double-blinded, placebo-controlled sniff tests. All homeopathic treatment visits (at baseline, 2 months, and 4 months) took place at the Desert Institute of Classical Homeopathy in Phoenix, AZ, with pairs of experienced classical homeopaths (at least 5 years in practice) who jointly interviewed each patient and recommended treatment. Homeopaths had to agree on a remedy choice with a confidence level of 7 or higher of 10 or patients were not enrolled.

Laboratory EEG recordings were all performed at the University of Arizona in Tucson, AZ, at baseline and 3 months. Half of the patients lived in Phoenix and half in Tucson (the cities in this rural state are 120 miles apart). Homeopaths, conventional medical assessors, and research staff were all blinded to group assignment throughout the study. The institutional review board of the University of Arizona approved the protocol, and all patients gave informed written consent for their participation.

Patients

Male and nonpregnant female patients with FM previously diagnosed by a physician were recruited from the greater Tucson and Phoenix communities by media announcements, newspaper advertisements, flyers in local health food stores, and word-of-mouth in patient support organizations. Inclusion criteria required a history of stable conventional medication doses and any other CAM treatments for at least 2 months prior to enrollment, and willingness to follow typical homeopathic treatment requirements (avoid drinking regular or decaffeinated coffee or using substances with strong odors [e.g., camphor, tea tree oil during participation]). FM diagnosis was confirmed on a screening checklist and rheumatologic physical examination using the 1990 American College of Rheumatology criteria (Wolfe et al., 1990) (two patients with physician diagnoses of FM, with random assignments to placebo, had less than 11/18 positive tender points on initial examination, but both met the diagnostic cutoff on the second rheumatologic examination).

Exclusion criteria

All prospective participants underwent a semi-structured clinical interview for psychiatric and substance abuse disorders prior to enrollment. To minimize confounds in the psychophysiological component of the study, exclusion criteria were a history of alcohol or drug abuse, current narcotic analgesic, benzodiazepine or antihypertensive medication use (orthostatic heart rate variability was another FM outcome measure (Bell et al., unpublished data), or nasal trauma. In keeping with usual homeopathic practice, patients on steroid drug treatment, which is believed to block the ac-

tion of homeopathic remedies, were excluded. Other exclusion criteria for patient safety were anaphylaxis history; diabetes; serious neurologic, heart, lung, liver, or kidney disease; psychosis, and active suicidality.

Baseline questionnaires. At baseline, patients completed the 34-item Tellegen Absorption Scale (Tellegen and Atkinson, 1974) to evaluate a personality trait previously found associated with higher levels of CAM utilization (Owens et al., 1999) and with individual differences in outcomes during various types of CAM treatment (Neff et al., 1983). Absorption is a genetically determined trait that involves openness to experiences and ability to direct one's attention selectively and wholly within an experience or within oneself (Tellegen et al., 1988).

Homeopathic treatment

After the initial interview, the homeopaths sent a fax to the homeopathic pharmacy, Hahnemann Laboratories (San Rafael, CA), with their remedy and dose (potency) choice. The pharmacist then dispensed indistinguishable bottles containing either active or placebo in accord with a randomization protocol developed by the study methodologist (using www.randomizer.org). All patients started the study at LM 1 potencies (1/50,000 dilution factor) and gradually increased the potency over time. Daily doses (1 teaspoon to 1 tablespoon) were taken orally after succussing (vigorously pounding or shaking) the stock bottle 10 times against a book and diluting 1 teaspoon to 1 tablespoon of stock liquid in 4 ounces of water. LM dosing form (De Schepper, 1999) was used to minimize concerns about antidoting by concomitant conventional medication use and about causing homeopathic aggravations in a clinical population believed highly sensitive to exogenous agents of all types (Slotkoff et al., 1997).

The LM potencies from Hahnemann Laboratories involved initial preparation of a 3c ($[1/100]^3$ dilution factor) potency, which was then diluted in the 1/50,000 ratio in liquid solvent for the LM 1 step and beyond. If the source material was soluble, the 3c step was made directly in an alcohol-distilled water solvent dilution. With plants, the source material was mother tinctures for the 3c step, made from maceration (chopping) of the plant parts, soaking in alcohol/water, and filtering. If the source material was insoluble, the 3c step was made by trituration in lactose to a 3c potency and then preparation with the 1/50,000 ratio in liquid solvent for the LM 1 step and beyond. Pharmacy preparation always included multiple succussions after each dilution step.

Homeopaths interviewed all patients at baseline, 2 months, and 4 months; they were allowed to change dosing or remedy selection at any time if clinically indicated. The local study pharmacist received a split sample bottle (without contents identified) of the patient's current treatment solution from Hahnemann Laboratories for preparation of sniff bottles (see below).

Laboratory EEG testing

At initiation of treatment (laboratory session 1) and at 3 months (laboratory session 2), participants were evaluated via physical examination by an otherwise uninvolved conventional medical provider, completion of questionnaires, and EEG recordings. In particular, both a disease-specific primary variable (i.e., tender point pain on physical examination) by a conventional medical provider blinded to and uninvolved in the treatment and a global outcome primary variable (i.e., Global Health Rating Scale scores on a three-item rating scale [five-point Likert ratings of current health, health compared with 6 months ago, health compared with that of peers]; Bell et al., 1998), were assessed. Secondarily, the general and spirituality well-being modules from the Functional Assessment of Chronic Illness Therapy (FACIT) questionnaire were used to characterize the bio-psycho-social-spiritual outcomes (Cella and Nowinski, 2002). Profile of Mood States scales (POMS, Educational and Industrial Testing Service) were completed before each EEG recording for use as a possible confounding variable.

During each session, patients 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), referenced to linked ears. Cap scalp electrode impedances were kept below 5K ohms. The qEEG raw signal was sampled at 512 Hz on a Lexicor NeuroSearch 24 apparatus (Boulder, CO) with a 2-Hz high-pass filter and a 60-Hz notch filter enabled.

Remedy/placebo randomization and EEG testing. Olfactory administration of remedies, which Hahnemann himself used (Hahnemann, 1843/1996), provides the possibility of instantaneous measurement of EEG effects, as opposed to the oral route. With an adaptation of a previous EEG sniff testing protocol for low level chemicals (Fernandez et al., 1999), patients underwent EEG laboratory olfactory recording sessions. All sniff dilution bottles for laboratory sessions were prepared locally in Tucson using materials sent from Hahnemann Laboratories (i.e., the split sample of each patient's treatment solution [verum remedy for those randomized to active and placebo for those randomly assigned to placebo)] and a stock bottle of remedy-free solvent, stored locally. Thus, patients randomly assigned to verum treatment sniffed dilutions of their own active remedy in half of the bottles and remedy-free local stock solvent in other half of the bottles in randomly ordered pairs. Patients randomly assigned to placebo treatment sniffed dilutions of their own placebo in half of the bottles and remedy-free local stock solvent in half of the bottles, in randomly ordered pairs. Thus, the laboratory test materials underwent a sequence of two separate randomization protocols, one implemented in

the homeopathic pharmacy (active versus placebo) and one implemented at the University of Arizona (order of the pairs of sniff bottles).

Treatment solutions were prepared by adding 10 drops of dissolved treatment solution (verum for active; placebo for placebo group) into a 20% alcohol–water solvent, diluting in 150 mL of distilled water, then dividing over 16 opaque bottles, and randomizing in order by pairs with 16 two-second sniffs of similarly prepared control solutions (10 drops of medicine-free placebo, 20% alcohol–water solvent into 150 mL of distilled water, then divided over 16 opaque bottles).

EEG laboratory sessions. The laboratory sessions involved EEG recordings during 5 minutes of resting EEG (sitting with eyes closed) and during presentation of 16 pairs of bottles, each containing their double-blinded treatment solution or control solution. They sniffed each bottle for 2 seconds with eyes closed. The amount of time allowed between presentation of the two bottles within a given pair was 6 seconds. Approximately 60 seconds intervened between consecutive pairs of bottles. After each sniff, patients were asked to guess the contents of the bottle (their own treatment or control solution). The laboratory days were the only times when patients took their daily dose of treatment solution by olfaction rather than by the more clinically typical oral route.

EEG artifact removal and fast Fourier transformation. After artifact removal by a technician blinded to group membership and outcomes (e.g., eyeblink and muscle movement, amplitudes > 50 mV), the EEG was subjected to fast Fourier transformation, setting the frequency range for EEG alpha band at 8–12 Hz. Prefrontal sites (Fp1 and Fp2) were chosen for primary analysis because of the association of prefrontal cortex with widely distributed neural networks controlling multiple behavioral and physiologic functions of the organism (Price, 1999), including pain sensitivity (Peyron et al., 2000), frontal cortex involvement in sniffing and smelling (Schwartz et al., 1994; Sobel et al., 1998), and prior evidence for early prefrontal cordance changes predicting antidepressant responders (Cook et al., 2002).

Cordance computation. Cordance was computed using a previously published algorithm with software available through www.QEEG.org (Cook et al., 2002; Leuchter et al., 1999). First, electrodes were remontaged offline to bipolar channel pairs of nearest-neighbor electrodes that shared a common electrode. For example, Fp1 was referenced to Fp2, F3, and F7; Fp2 was referenced to Fp1, F4, and F8, followed by averaging of the absolute power values for the bipolar pairs. EEG power values were computed for absolute (amount of power in alpha at a given electrode, in μV^2) and relative alpha (percentage of power in alpha relative to the total power in the overall frequency spectrum sampled by the cordance software [i.e., 0.5–20 Hz). Next, absolute and relative alpha power values were normalized across electrode sites using a z-transformation statistic at each site. Finally, cordance was quantified by summing the z scores for normalized absolute and relative power at each site.

The alpha band was chosen because of evidence of (1) increased waking alpha frequency activity at rest (Bell et al., 2001) in patients with FM; (2) lowered right thalamic activity in FM on SPECT scans at rest (Kwiatek et al., 2000); and (3) the association of decreased thalamic activity with increased scalp alpha activity (Lindgren et al., 1999). Notably, in alpha band cordance for persons without organic brain lesions, more negative values are associated with greater metabolic activity on PET brain scans, whereas more positive values are associated with reduced metabolic activity in the brain region of the electrode site (Leuchter et al., 1999).

Statistical analysis

Statistical analyses were performed using SPSS 11.0 (Chicago, IL) and Statistica 6.0 (StatSoft, Inc., Tulsa, OK) for Windows, with general linear models (GLM) for continuous variables and χ^2 tests for categorical variables. Given the small number of subjects, the large numbers of sniffs within each session, and the randomly missing bottle data because of movement artifact, all 16 treatment solution bottle results were averaged to compare to the averaged 16 control solution bottle results, rather than evaluated over time within sessions. The alpha cordance means for control solutions were subtracted from the alpha cordance means for treatment solutions at Fp1 (left prefrontal) and Fp2 (right prefrontal) to generate the primary dependent variables for this study. Post-hoc analyses were performed using Tukey tests. Statistical significance was set at $p < 0.05$ (two-tailed).

Definition of exceptional responder. To provide a satisfactory test of homeopathic clinical claims and related nonlinear systems theory, an exceptional responder within this sample was defined by examining the frequency distributions of the 3-month change scores over baseline on (1) tender point pain and (2) Global Health Rating Scale scores. Individuals falling into the top one third of the sample on both types of outcome variables were classified as exceptional responders ($n = 6/26$ (23%) of active versus none (0%) of the placebo group members). Lesser responders were all others in the active treatment group ($n = 20$) and all patients on placebo ($n = 27$).

The focus of this study was the cordance responses to sniffs of treatment versus control solutions in exceptional responders to active versus all lesser responders. Details of the overall active versus placebo group comparisons per se and of a subsequent optional crossover phase of the study are reported elsewhere (Bell et al., pp. 269–283; Bell et al., 2004a). The results reported represent a modified intent-to-treat analysis (i.e., on all patients with 3-month follow-up data [the first follow-up outcomes assessment after baseline]).

RESULTS

Descriptive features

Figure 1 provides the patient flow chart from enrollment through outcome. Dropout rates were comparable between active and placebo groups ($n = 9$, 14.5%), primarily because of travel and time demands of the study. No dropouts cited the remedies as the reason for leaving the study. Of the 62 patients enrolled, 53 ($n = 26$ on active and $n = 27$ on placebo) completed both the baseline and 3-month follow-up testing. The baseline session sniff cordance difference scores did not differ significantly between patients randomized to active ($n = 26$) versus placebo ($n = 27$) ($p = 0.2$ at Fp1 and $p = 0.5$ at Fp2) or for dropouts ($n = 9$) versus completers ($n = 53$) ($p > 0.4$ at both sites). Neither active versus placebo groups nor responder-type groups differed significantly in rates of correct guesses of the contents of the sniff bottles (sample mean at chance, i.e., 8.5 [SD 2.3] of 16 sniff-bottle pairs correct). Table 1 summarizes the individualized homeopathic remedies selected for each responder-type group ($p = 0.5$, ns). All patients began the study on LM 1 potencies and responder-type groups did not differ in potency "dose" after 3 months (mean LM 2.4 SD 0.9). All six of the exceptional responders stayed on the same initial remedy throughout the study (average number of remedies 1.0 ([SD 0]), whereas all other lesser responders experienced an average of 1.6 (SD 1.7) different remedies over the treatment period ($F(1,51) = 4.6$, $p = 0.037$).

Demographic and clinical variables by responder groups. Table 2 reports the descriptive group findings for demographic and clinical variables by responder-type groups. Responder-type groups (exceptional versus all others) did not differ significantly in age, gender distribution, marital status, ethnicity, handedness, duration of FM, chemical intolerance index scores, baseline Global Health Rating Scale scores, stable conventional medications, or POMS scores. There were trends ($p < 0.10$) for the exceptional responders ($n = 6$) to have less education, fewer comorbid diagnoses of chronic fatigue syndrome (CFS), higher levels of baseline tender point pain on examination, and higher levels of the personality trait absorption compared with all other study patients ($n = 47$; active and placebo lesser responders combined). As a result, the latter four variables were used as covariates in subsequent analyses comparing exceptional responders with all other patients. As exceptional and lesser responders to active remedies did not show trends at $p < 0.10$ toward differing on baseline tender point pain ($p = 0.17$) or trait absorption ($p = 0.11$), only education and comorbid CFS were covariates for those subgroup analyses. Table 3 shows that the exceptional responders overall underwent significantly greater improvements than did all

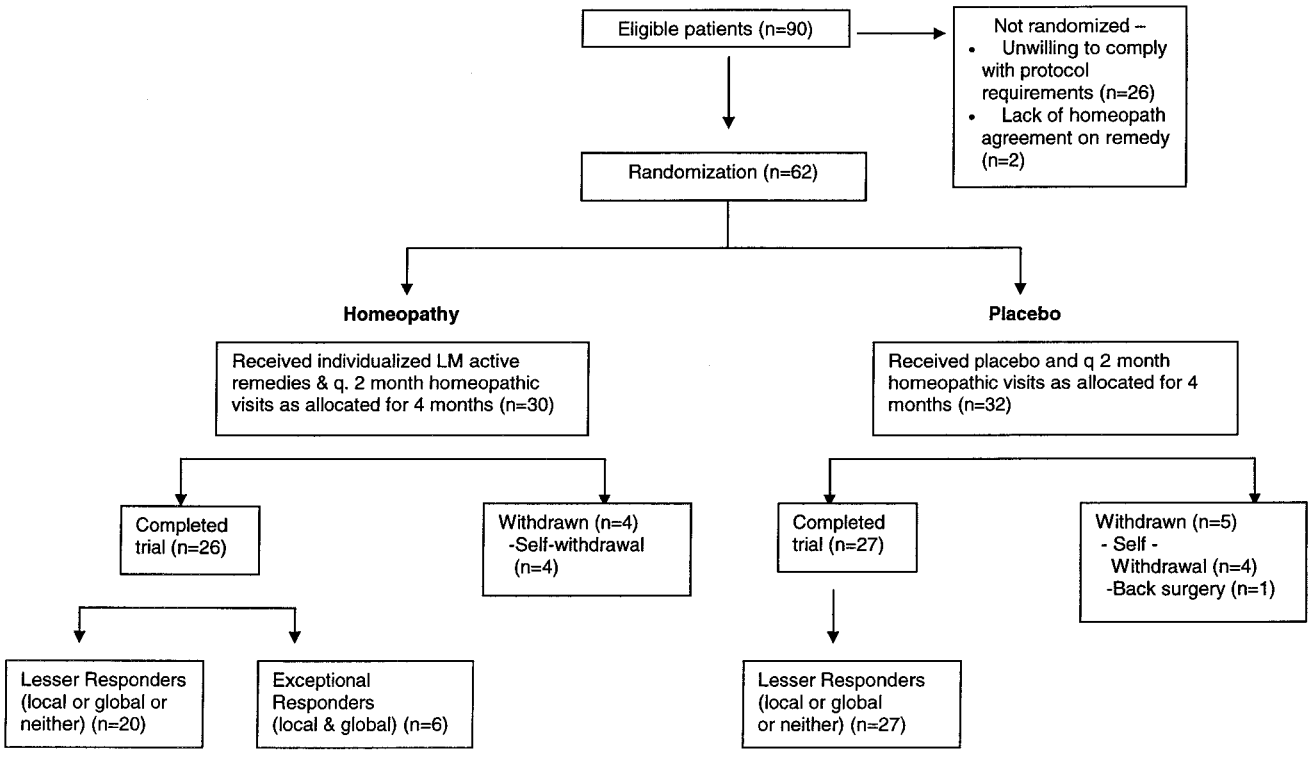

FIG. 1. Patients entered, randomized, and withdrawn from the study, with outcomes.

Table 1. Individually Chosen Remedies at Baseline Listed by Outcome

	Exceptional responders active (n = 6)	*Lesser responders active (n = 20)*	*Lesser responders placebo (n = 27)*	*Dropouts (n = 9)*	*Totals by remedy (n = 62)*
Aethusa			2		2
Arsenicum Album			2		2
Bamboo		1			1
Baryta Muriatica			1		1
Belladonna			1		1
Calcarea Carbonica	2	1	1		4
Calcarea Phosphorica		1			1
Calcarea Sulphurica	1				1
Carcinosin				1	1
Causticum	1	1	1		3
Cimicifuga		1		1	2
Cocculus Indica				1	1
Conium		1			1
Cyclamen		1			1
Helleborus			1		1
Ignatia		1		1	2
Iodum			1		1
Kali Carbonicum		1	1		2
Kali Phosphoricum		1	1		2
Lac Defloratum		1			1
Lycopodium			1		1
Magnesia Muriatica			1		1
Magnesium Sulphuricum		1			1
Medorrhinum				1	1
Mercurius vivus		1			1
Natrum Carbonicum				1	1
Natrum Muriaticum		1			1
Nitric Acidium			1	1	2
Papaver		1	1		2
Phosphorus			2		2
Platina	1		1		2
Pulsatilla			2		2
Rhododendron			1		1
Rhus Toxicondendron		2	2		4
Ruta Graveolens		1			1
Sepia				1	1
Silica			2		2
Staphysagria		2			2
Thuja	1				1
Veratrum Album				1	1
Zincum			1		1

No placebo patients showed an exceptional response at 3 months into the study.

other responders between baseline and 3 months on the FACIT well-being ratings over multiple outcome dimensions (physical, emotional, functional, spiritual).

EEG alpha cordance difference score analyses

Laboratory session 1 sniff findings. In computation of all difference scores, the values for the remedy-free solvent control were subtracted from the values for the individual's treatment solution (verum remedy for the active group; placebo for the placebo group). Consistent with the hypothesis, Figure 2A and 2B demonstrates that during the first laboratory session, the patients who became exceptional responders 3 months later showed significantly more negative cordance at Fp1, with a similar trend at Fp2, in the mean difference scores between their treatment and control solution sniff tests than did all other patients in the study (all lesser responders on active and placebo combined). When the analysis was restricted to patients randomly assigned to active treatment, the Fp1 finding was again significant, and the Fp2 finding remained a trend (Fig. 3A and 3B).

Table 2. Summary of Demographics and Outcomes by Responder-Type Group of All Patients with Three-Month Follow-up Data ($n = 53$)

	Exceptional responders active treatment (n = 6)	*Lesser responders active treatment (n = 20)*	*Lesser responders placebo treatment (n = 27)*
Age	54.2 SD 7.1	49.5 SD 10.4	48.8 SD 11.4
Female gender	6 (100%)	19 (95%)	25 (93%)
Marital status (married)	3 (50%)	14 (74%)	17 (63%)
Self-identified ethnicity (non-Hispanic white)	5 (83%)	17 (85%)	26 (96%)
Educational Level[a]	1.8 SD 0.8	2.5 SD 0.7	2.3 SD 0.7
Right-handedness	6 (100%)	18 (90%)	23 (85%)
Duration of FM (years)	18.8 SD 18.2	14.4 SD 14.1	11.4 SD 11.4
Met criteria for CFS dx	3 (50%)	18 (90%)	23 (85%)
Chemical intolerance index score (5–25)	6.0 SD 1.9	7.9 SD 2.7	6.8 SD 3.1
Absorption scale (0–34)	24.2 SD 5.8	19.4 SD 6.4	18.3 SD 7.5
Baseline tender point pain score (0–180)	106.8 SD 26.5	87.3 SD 30.1	80.8 SD 33.2
Baseline Global Health Rating Scale score (3–15)	7.2 SD 1.8	7.5 SD 2.5	7.7 SD 3.1
Change in tender point pain score at 3 months	−61.2 SD 30.4	−7.8 SD 23.9	+2.0 SD 22.2
Change in Global Health Rating Scale score at 3 months	+4.3 SD 1.5	+0.06 SD 2.6	−0.12 SD 2.2

[a]Educational level: 1 = high school or less; 2 = some college; 3 = college degree or more.
FM, fibromyalgia; CFS, Chronic Fatigue Syndrome, dx, diagnosis.

Within the exceptional responders ($n = 6$), more negative Fp2 cordance difference scores at baseline correlated highly with reductions in local pain ($r = 0.85, p = 0.03$) and increases in global health ($r = -0.73$, $p = 0.10$) after 3 months, as well as trait absorption ($r = 0.91$, $p = 0.012$), but not with the baseline Fp1 difference scores ($r = -0.14$, $p = 0.8$). The correlations were reversed in pattern for the lesser responders to active treatment ($n = 20$); their Fp2 difference scores at baseline had no correlation with change in local pain ($r = -0.22$, $p = 0.4$) or global health ($r = 0.08$, $p = 0.8$) 3 months later, or with trait absorption ($r = -0.25$, $p = 0.3$), but did with the baseline Fp1 difference scores ($r = 0.82$, $p < 0.001$).

Similar findings over time: laboratory sessions 1 and 2 sniff cordance analyses. Group differences that were observed in session 1 did not change significantly as a function of time in the study (i.e., from session 1 to session 2). That is, there were no significant interactions of responder-type group by session. However, the main effect averaged over

Table 3. Scores at Three-Month Follow-up for FACIT Well-Being Subscales in Exceptional Responders versus All Lesser Responders

FACIT Subscale	*Exceptional responders (n = 6)*	*All lesser responders (n = 43)*[a]	*Unadjusted difference in 3-month values (exceptional—all lesser)*	*Adjusted difference in 3-month values (exceptional—all lesser)*
Physical	23.2 (2.5)	16.3 (5.3)	6.8 (2.4 to 11.3)**	8.2 (5.5 to 10.9)***
Emotional	20.7 (2.4)	16.6 (4.4)	4.1 (0.36 to 7.8)*	3.0 (0.53 to 5.4)*
Functional	21.5 (3.0)	14.8 (5.1)	6.7 (2.4 to 11.0)**	6.3 (3.0 to 9.6)***
Social-family	18.8 (4.6)	15.2 (6.5)	3.6 (−1.9 to 9.1)	2.4 (−0.9 to 5.6)
Spiritual	41.8 (3.2)	31.4 (9.6)	10.4 (2.4 to 18.5)*	8.9 (3.7 to 14.0)***

Means (±SD), mean group differences with 95% confidence intervals (exceptional—all lesser responders), unadjusted and adjusted for covariates of baseline value for each FACIT subscale, baseline tender point pain, education, presence of criteria for chronic fatigue syndrome diagnosis, and trait absorption. Groups did not differ significantly on the FACIT at baseline.

[a]Note: 4 of 47 lesser responder patients did not complete these forms at both time points. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Overall multivariate Hotelling's trace over baseline values of all five FACIT subscales, covaried for baseline tender point pain, education, chronic fatigue criteria, and trait absorption, was not significant ($F(5,42) = 0.2$, $p = 0.98$).

Overall multivariate Hotelling's trace over all five 3-month values of FACIT subscales, covaried for baseline values of each subscale and baseline tender point pain, education, chronic fatigue criteria, and trait absorption, was not significant: $F(5,34) = 7.4$, $p < 0.001$.

FACIT, Functional Assessment of Chronic Illness Therapy; SD, standard deviation.

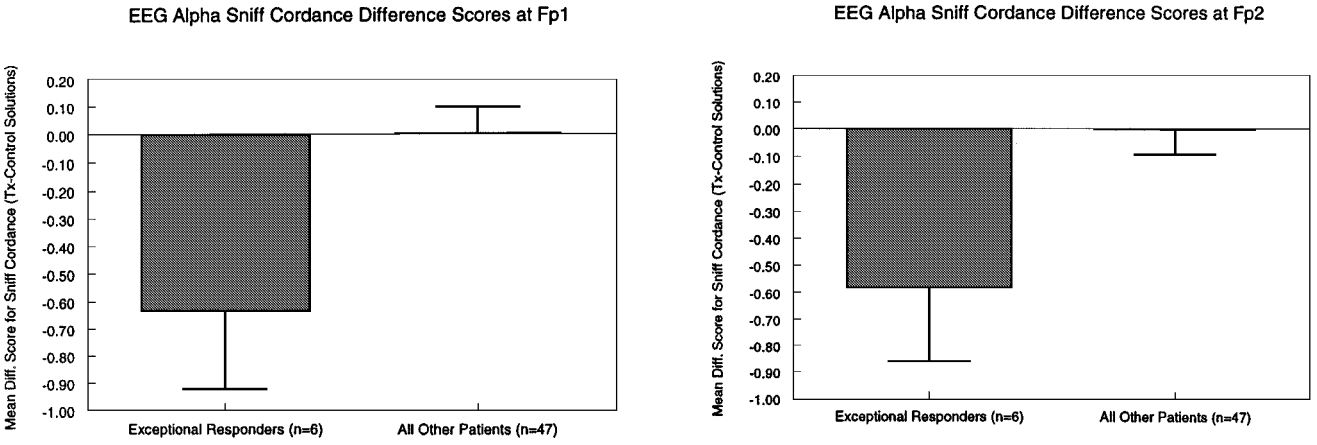

FIG. 2. Electroencephalographic (EEG) cordance difference scores at the first laboratory session between sniffs of treatment and control solutions at prefrontal electrode sites for subsequently exceptional responders to active remedies ($n = 6$) and all lesser responders ($n = 47$, active and placebo combined). Means (standard error) adjusted for covariates of baseline tender point pain levels, education, presence of criteria for chronic fatigue syndrome diagnosis, and trait absorption. Fp1 (left prefrontal): $F(1,47) = 4.2$, $p = 0.047$; Fp2 (right prefrontal): $F(1,47) = 3.7$, $p = 0.06$; Four of the six exceptional responders had negative difference scores for both Fp1 and Fp2; all six exceptional responders had negative difference scores for at least one of the two prefrontal sites.

baseline and 3 months for responder-type group was significant at Fp1 ($F(1,40) = 6.2$, $p = 0.017$) and Fp2 ($F(1,40) = 4.5$, $p = 0.04$) for the exceptional active responders (covariate-adjusted means over both sessions: Fp1: −0.54 SE 0.23; Fp2: −0.32 SE 0.17) versus all-other-patients (covariate-adjusted means over both sessions: Fp1: +0.086 SE 0.08; Fp2: +0.077 SE 0.06). Again, in the restricted analysis focused on only patients who received an active remedy, the exceptional responders still exhibited significantly more negative difference scores Fp1 ($F(1,18) = 6.2$, $p = 0.023$) and a nonsignificant trend with a similar pattern at Fp2 ($F(1,18) = 2.7$, $p = 0.12$). When the analysis was restricted only to those patients who were on one "remedy" at both laboratory sessions 1 and 2, rather than changing "remedies" (verum or placebo, as dictated by original random group assignment), the Fp1 main effect findings remained significant, and the main effect trend at Fp2 again persisted (Fp1: $F(1,21) = 9.1$, $p = 0.006$; Fp2: $F(1,21) = 4.0$, $p = 0.06$).

Rest (nonsniff) findings for laboratory sessions 1 and 2. Analyses of cordance by prefrontal electrode at eyes-closed rest revealed no significant differences for clinical responder groups for either baseline (Fp1 exceptional responders: 1.8 SE 0.7; all others: 1.9 SE 0.2, $p = 0.95$; Fp2 exceptional responders: 1.0 SE 0.6; all others: 1.3 SE 0.2, $p = 0.6$) or 3-month laboratory sessions (Fp1 exceptional responders:

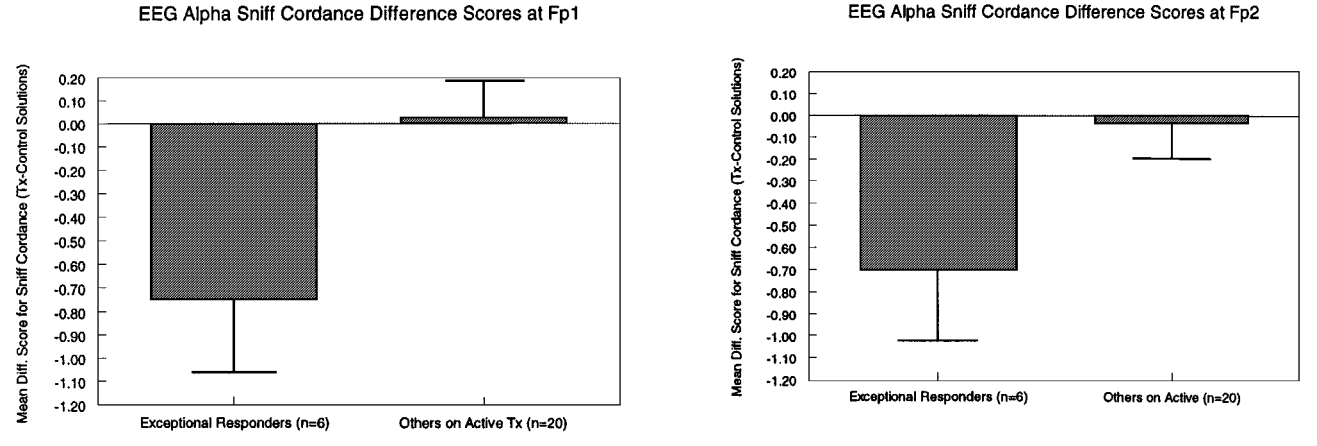

FIG. 3. Electroencephalographic (EEG) cordance difference scores at the first laboratory session between sniffs of treatment and control solutions at prefrontal electrode sites for exceptional responders to active remedies ($n = 6$) and lesser responders to active remedies ($n = 20$). Means (standard error) adjusted for covariates of education and presence of criteria for chronic fatigue syndrome diagnosis. Fp1 (left prefrontal): $F(1,22) = 4.4$, $p = 0.048$; Fp2 (right prefrontal): $F(1,22) = 3.1$, $p = 0.09$.

2.5 SE 0.8; all others: 2.0 SE 0.3, $p = 0.5$; Fp2 exceptional responders: 2.0 SE 0.7; all others: 1.3 SE 0.2, $p = 0.4$).

DISCUSSION

The finding of 23% exceptional responders among patients randomized to active treatment in the present study is consistent with clinical reports for rates of simillimum-like responses. Anecdotally, apart from observational data showing at least some degree of improvement in 60%–80% of primary care patients on homeopathy (Riley et al., 2001; Walach and Guthlin, 2000), experienced homeopaths also report that approximately 20%–30% of consecutive patients in their clinical practices undergo transformational, system-wide enhancements in multiple dimensions of health and biopsychosocial well-being. Master homeopaths claim much higher rates of transformational outcomes, but no systematic studies have ever evaluated these claims (Bell et al., 2003a). In terms of individual difference factors, the patients in this study who showed a marked positive local and global outcome after only 3 months of treatment began the study with trends toward a greater amount of tender point pain on examination, but less comorbidity with CFS, as well as higher levels of the personality trait absorption.

Cordance sniff findings. The exceptional responders exhibited significantly different prefrontal alpha cordance responses to sniffs of treatment solution versus control solution bottles in the first exposure to the remedy compared with all other patients in the study. One could argue that the exceptional responders simply had more time on one remedy, thereby giving them the opportunity for a better outcome than the other patients, whose remedies changed during the study. However, the main reason behind a remedy change during treatment would have been the homeopaths' assessment of a suboptimal or absent clinical change on the double-blinded follow-up contacts or visits. To determine with greater clarity whether the stability of remedy treatment was a cause or an effect of an exceptional clinical outcome, future studies should compare a larger number of patients who start and end treatment on the same individualized remedy regardless of interim homeopathic assessments. Nonetheless, the present findings remained significant when the analyses were re-run only on persons receiving one "remedy" (i.e., treatment solution—verum or placebo) throughout the study.

The cordance sniff findings were bilateral, but statistically most robust at Fp1, the left prefrontal electrode site. As noted in the Methods section, blink and movement artifacts were removed before analysis, making artifact a highly unlikely explanation for the findings, even though the prefrontal sites are potentially vulnerable to such confounds, given their proximity to muscles surrounding the eyes. Left dorsolateral prefrontal cortex shows decreases in metabolic activity or blood flow in a range of disorders characterized by depression (Dunkin et al., 2000). Other CAM interventions, such as mindfulness meditation training, can raise left anterior activation as measured in EEG alpha power asymmetry, improve immune system reasponsivity, and elevate depressed affect after 4 months (Davidson et al., 2003). However, responder types in the current analysis did not differ for Profile of Mood State (POMS) depression when the Laboratory Session 1 EEG-C alpha findings occurred.

Painful stimuli can activate the thalamus and anterior cingulate bilaterally (Peyron et al., 2000), although the right thalamus, among certain other brain regions, also normally responds to both painful and nonpainful somatosensory stimulus information (Coghill et al., 2001; Pauli et al., 1999). The right prefrontal cordance sniff difference scores were highly correlated with the subsequent clinical improvements only in the exceptional responders to active remedies, but not in the other patients on active treatment with lesser clinical responses. Earlier studies have found a lateralized association of right frontal hyperactivity with heightened pain sensitivity and negative affect (Pauli et al., 1999). The present cordance findings for exceptional responders add to evidence from other studies showing that active homeopathic remedies exert dynamical psychophysiological effects different from those of placebo (Bell et al., 2004b; Hyland and Lewith, 2002; Lewith et al., 2002). The current correlational findings raise the possibility that EEG-C may offer a quantitative as well as qualitative predictor of clinical outcomes in FM.

The finding of early prefrontal cordance differences between exceptional and lesser responders to active individualized homeopathic remedies in FM within the present study is analogous to that of Cook and colleagues (Cook and Leuchter, 2001; Cook et al., 2002) with multiple different conventional antidepressants in major depression. The prefrontal cordance data converge with neuropsychologic evidence that better baseline executive function predicts better response to conventional antidepressants in major depressives (Dunkin et al., 2000), better occupational outcomes in traumatic brain injury patients (Hanks et al., 1999), recently detoxified alcoholics (Moriyama et al., 2002), and better functional capacities in schizophrenics (Hoff et al., 1992; Martinez-Aran et al., 2002; Reed et al., 2002). Notably, abuse histories are extremely common among patients with FM (Walker et al., 1997). Children with abuse-related post-traumatic stress disorder (Beers and De Bellis, 2002) and women with a history of intimate partner violence (Stein et al., 2002), with or without post-traumatic stress disorder, exhibit impairments in executive function.

Executive function, homeopathic case analysis, and systems theory. Executive function encompasses complex problem-solving ability, including the flexibility to shift response set, to inhibit habitual behaviors and redirect attention, and to make goals, plans, and decisions, all regulated by prefrontal cortex (Lezak, 1995). In neuropsychology, Lezak

(1995) describes executive functions as: "[T]hose capacities that enable a person to engage successfully in independent, purposive, self-serving behavior." She further distinguishes executive functions from cognitive functions in that the former involve questions of: "[H]ow or whether a person goes about doing something" whereas the latter involve questions of: "[W]hat or how much [can the person do]?"

Notably, in homeopathic case analysis for identifying the single correct individualized remedy (simillimum), Sherr (2002) points out the importance of characterizing the dynamics, change, or "motion" of each patient's case. Homeopaths generally believe that greater adaptability to change reflects better health in homeopathy; rigidity and stasis indicate disease (Bell et al., 2003a). Sherr (2002) suggests the need to match the words for a patient's pathology to characteristics of the remedy along a descriptive hierarchy, in order of emphasis from verbs to adverbs to adjectives to nouns (i.e., whether and how a person does things in the world, for example, "hold on" or "explode" or "withdraw"; "circularly" or "slowly" or "violently"—examples of diagnostic words in homeopathy) versus reaching static endpoints in his or her life (e.g., nouns such as "tumor" or "fibromyalgia" or "cirrhosis"—examples of diagnostic words in conventional medicine). Lezak's description of the "doing," or not doing, inherent in executive functions, which are modulated by prefrontal areas of the brain, suggests that the current prefrontal cordance findings may have particular clinical significance and relevance to how homeopaths evaluate health and disease in dynamical terms.

Perseveration, the persistence of a behavior beyond what is expected or needed, is a clinical symptom of poor executive function in neuropsychology. Consequences of perseveration would include (1) within homeopathic terms, a loss of freedom (Vithoulkas, 1980) or living under a central delusion (nonpsychotic, false perception of one's personal reality, leading to repetitive, dysfunctional reactions to life events, for example, victim stance) (Sankaran, 2000) or (2) within nonlinear complex systems theory, systemic "stuckness" in a bio-psycho-social-spiritual pattern of chronic disease (Bell et al., 2003a; Bellavite, 2003; Hyland and Lewith, 2002). In short, chronic disease in this model reflects an inability to shift, without the assistance of an intervention, from a sick to a healthy response set (Torres, 2002).

Although speculative, a testable neuropsychologic hypothesis is that individuals who experience exceptional healing responses will have better baseline executive function than will lesser responders, thereby leading to a better capacity to respond to homeopathic remedies with a shift in the person's bio-psycho-social-spiritual functioning as a system out of old, repetitive, dysfunctional patterns into new, healthier patterns (Bell et al., 2003a; Hyland, 2003; Hyland and Lewith, 2002). The shifts in symptom patterns would be manifestations of moving from one "attractor" to another in systems theory terms (i.e., an equilibrium state on which a dynamic system converges) (Bell et al., 2002a). Higher levels of executive function (capacity to redirect attention), in combination greater trait absorption (capacity to attend selectively and fully) (Bell et al., pp. 269–283; Neff et al., 1983), would constitute individual difference factors capable of interacting with an active CAM treatment such as homeopathy to generate optimal outcomes. Early shifts in prefrontal cortical function should correlate with the postulated mobilization of executive function and absorption.

This model postulates that the prefrontal cortex is a higher order network controller, a translator of the arrival of the homeopathic remedy information at the physical level of organization and perhaps a mediator of the initiation of changes at a bifurcation point in the system's dynamics, but not the highest order network controller in the person–system or even an ongoing participant in the evolution of the change process. The model predicts that better pre-existing executive function as a trait makes it easier to initiate changes system-wide in response to homeopathic, or other forms of, treatment, not that executive function necessarily changes as a result of homeopathic treatment. These ideas suggest processes, although not specific mechanisms, for the changes.

Trait absorption, cordance, and exceptional responders. The personality trait of absorption, which correlated highly with right prefrontal cordance findings in this study, might facilitate the ability to lock into a healthier functional pattern or attractor (metastable state) during and after a shift in attractor patterns. Other investigators have shown that high absorbers are more responsive than low absorbers to both relaxing and aversive situations in autonomic (Zachariae et al., 2000) and immune responses (Gregerson et al., 1996). Once in a state, high absorbers can put their full attention selectively into an experience and ignore potentially distracting stimuli (Barnier and McConkey, 1999; Gliskey et al., 1991; Tellegen and Atkinson, 1974). Davidson et al. (1976) showed that high absorbers can inhibit alpha EEG activity in a task-irrelevant brain region better than can low absorbers.

Taken together, the data in the exceptional responders could indicate the possibility that the acute cordance changes reflect prefrontal registration of a higher order neural network signal from the remedy for the host to begin attenuating pain and other adverse physiologic responses over time. Lesser responders might exhibit responses in lower order networks, but not at the systemic organizational level of higher order controller networks (Hyland, 2003; Hyland and Lewith, 2002).

Limitations. Limitations of the study include a small sample of exceptional responders, the use of the olfactory rather than more common oral route of remedy administration, and reliance on a less well-known form of neuroimaging (i.e., EEG cordance). The above hypotheses will require replication of the cordance sniff findings in a much larger sample of patients, extension to the more common oral mode of remedy administration (Cerf-Ducastel and Murphy, 2001), and

more specific evaluation of responses to individualized homeopathic remedies with better known forms of functional neuroimaging (e.g., SPECT, PET, functional magnetic resonance imaging [MRI]). In view of the history of replication difficulties in homeopathic research (Walach and Jonas, 2002) and the current small sample of exceptional responders, it is imperative for our own and independent laboratories to repeat this study before fully accepting the present findings, or attempting to extend the work to other disorders.

Skeptics assert that homeopathy is no more than a placebo (Langman, 1997; Vickers, 2000), and homeopaths report that it is difficult to find the correct simillimum in clinical practice, let alone under double-blinded placebo-controlled randomized trial conditions (Chapman, 2002). In the least, the current findings raise the possibility that cordance responses may provide an objective biomarker for confirming highly individually salient remedy activity beyond that of nonspecific or placebo effects or the natural history of the disease. Whether or not cordance will lead to new research on neural network mechanisms for individualized remedy responses is an open question.

Alternatively, the high correlation between absorption and right prefrontal cordance difference scores could reflect merely a host characteristic (i.e., high absorbers can selectively increase blood flow in prefrontal regions when asked to pay attention to any subtle olfactory/sniffing-related stimuli, not just homeopathic remedies, better than low absorbers can. In the latter situation, the electrophysiologic findings would reflect simply individual differences in attentional function abilities of the host (Davidson et al., 1976), rather than a healing signal property of the remedy *per se*. If so, then in homeopathy studies, persons who later exhibit the capacity for exceptional clinical responses to individualized remedy treatment should show the same prefrontal cordance changes during sniffs of the correct or incorrect remedy versus plain solvent. Furthermore, persons who later exhibit the capacity for exceptional clinical responses to non-homeopathic treatments should show the same kinds of prefrontal changes to any subthreshold olfactory sniffing task involving an odorant versus plain solvent.

The objective findings in cordance would have no inherent therapeutic implications for the specific agent that is sniffed, but rather, for the broad healing potential of the host. In such circumstances, the capacity to shift attention selectively might contribute much more to the ability to heal across broad domains than would the specific treatment. One study showed that chronic pain patients who failed conventional medical care had lower levels of trait absorption (Kermit et al., 2000). Conversely, in the present study, even averaged over active and placebo group assignments, higher absorbers had better clinical outcomes than did lower absorbers (although those on verum did have the best outcomes) (Bell et al., pp. 269–283).

The evidence to date, with relevance to the cordance findings, is more consistent with an interaction between patient characteristics (personality trait and diagnosis) and specific treatments than with certain persons' nonspecific capacity to heal. Previous research in non-FM chronic pain disorders has demonstrated that absorption influences treatment outcomes to specific treatments. For example, in vascular headache, higher absorption predicted better outcomes from mind–body interventions such as guided imagery and/or relaxation but not from biofeedback (Neff et al., 1983). Lower absorption in persons with vascular headache led to better outcomes from biofeedback but not relaxation. For low absorbers with tension headache, however, neither relaxation nor biofeedback was beneficial.

The strength of the absorption correlation with the cordance findings could represent an artifact of the small sample size. However, if reproducible, these observations raise another consideration (i.e., that high absorption is a marker of the individual's capacity for merging into a proposed macroentanglement between the larger patient-practitioner-remedy-symptom system; Hyland, 2003; Milgrom, 2002b; Walach, 2003). Entanglement is the quantum mechanical construct used to account for the reliable empirical observation of nonlocal effects demonstrated in physical science research at the subatomic level. Change in one element of a system occurs simultaneously in another part of the system independent of the distance between the parts. Some investigators have proposed that entanglement occurs at a macro- as well as microlevel of scale. Clinically, high absorption predicts increased numbers of reported experiences with nonlocal, anomalous phenomena (Kennedy et al., 1994; Thalbourne et al., 1997). Therefore, from an entanglement perspective, the cordance difference scores might mark the instantaneous perception of the simillimum or correct remedy by the whole system, as registered through the heightened receptivity of the high-absorbing patient who is part of a larger system.

CONCLUSIONS

In conclusion, given the growing basic science evidence that the physicochemical properties of homeopathic remedies differ from those of plain solvent (Bell et al., 2003b; Elia and Niccoli, 1999; Rey, 2003), it is feasible and warranted to study the objective nature of host response patterns to individually appropriate versus inappropriate active remedies and placebo (Bell et al., 2002a). Prefrontal cordance, in combination with psychologic/neuropsychologic assessments of executive function and trait absorption, may provide a way of identifying, at the beginning of homeopathic treatment, the subset of individuals with FM who will later experience the most favorable clinical responses over the long-term. For those patients without such initial CNS findings, homeopaths might elect to switch to a different remedy sooner rather than later.

Individualization of treatment is a hallmark feature of many CAM modalities (Levin et al., 1997). In integrative

medicine, a therapeutic goal is to develop a tailored package of care for each person (Bell et al., 2002b). However, little prior research has addressed empirical or theoretical considerations other than patient preferences (Ratcliffe et al., 2002) as to how to triage a given person to the most helpful treatment program for that person (Astin, 1998).

Evidence-based practice in integrative medicine must emerge not only from group averages showing efficacy and effectiveness of a given modality across large cohorts, but individual difference characteristics within patients that correlate with or predict positive outcomes (Bell and Caspi, 2004; Neff et al., 1983). The larger magnitude of the standard error terms for the cordance difference score findings in the exceptional responders compared with the error terms for the other patients in the study could reflect the inter-individual variability of the process for such a small subgroup of the total sample. Consequently, the findings must be viewed as preliminary. This study merits prospective replication in a larger sample of patients with FM entering treatment with classical homeopathy. Nevertheless, the present observations, in the context of the research literature, suggest directions for further investigation with relevance to classical homeopathy as well as to a number of other forms of CAM interventions that purport to act on the person as a whole (Hyland, 2003).

ACKNOWLEDGMENTS

This study was supported by National Institutes of Health (NIH) grants R21 AT00315 (I.R.B.), K24 AT00057 (I.R.B.), P20 AT00774 (G.E.S.), P50 AT00008 from the National Center for Complementary and Alternative Medicine (NCCAM) and NIH HL53938-07S1 (C.M.B.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCCAM or NIH. We thank Ian Cook, M.D., of the UCLA Quantitative EEG Research Laboratory for consultation in the use of cordance analysis software.

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