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Short-Term Effects of Repeated Olfactory Administration of Homeopathic Sulphur or Pulsatilla on Electroencephalographic Alpha Power in Healthy Young Adults

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Abstract

Introduction—Homeopathic pathogenetic trials usually rely on symptom self report measures. Adding objective biomarkers could enhance detection of subtle initial remedy effects. The present feasibility study examined electroencephalographic (EEG) effects of repeated olfactory administration of two polycrest remedies.

Methods—College student volunteers (ages 18–30, both sexes) from an introductory psychology course were screened for good health and relatively elevated Sulphur OR Pulsatilla symptom scores on the Homeopathic Constitutional Type Questionnaire. Subjects underwent a series of 3 once-weekly double-blind sessions during which they repeatedly sniffed the remedy matched to their CTQ type and solvent controls. Each remedy was given in a 6c, 12c, and 30c potency, one potency per week, in randomly assigned order. Solvent controls included both plain distilled water and a water-ethanol (95%) solution. All sniff test solutions were further diluted just prior to laboratory sessions (0.5 ml test solution in 150 ml distilled water). Within a session, remedies and control solvents were administered via 2-second sniffs (8 sniffs of each of 4 different succussion levels for the potency in randomized order). Primary outcome variable was relative EEG power (alpha 1 8–10 hertz; alpha 2 10–12 hertz) averaged over 19 electrode sites, including all succussions for a given potency.

Results—Mixed-effect models revealed significant main effects for remedy type (Sulphur>Pulsatilla) in both alpha bands, controlling for gender, baseline resting EEG alpha, and solvent control responses. Additional analyses showed significant non-linear interactions between dilution and time (weekly session) in alpha 2 for both remedies and alpha 1 for Sulphur.

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Conflicts of interest

Drs. Bell and Brooks consult for Standard Homeopathic/Hyland's Inc. However, the present study did not test any products made by this company; and Standard Homeopathic/Hyland's Inc. did not provide financial support for this study.

Conclusion—EEG alpha offers an objective biomarker of remedy effects for future studies and potential method for distinguishing time-dependent effects of specific remedies and remedy potencies from one another.

Keywords

Electroencephalography; Homeopathy; Sulphur; Pulsatilla; EEG alpha; repeated measures; sniffing; olfactory administration

Introduction

Research on homeopathic provings or pathogenetic trials,[12] as well as clinical studies,[34] has revealed limitations in the reliability and reproducibility of the mainly subjective symptom findings reported. Despite recent advances in study design,[5] physiological markers such as quantitative electroencephalography (EEG) offer a possible objective indicator of subtle effects, especially in the early period after remedy administration when the evolution of the response is most ambiguous.[6]

Remedies exert detectable effects not only on self rated mood,[7] but also on sleep EEG patterns[8] in relatively healthy young adults with a history of coffee-induced insomnia, given either Nux Vomica or Coffea Cruda 30c pellets under the tongue at bedtime. Earlier animal studies also showed complex, nonlinear effects of remedies on sleep EEG.[910] Moreover, Bell et al previously demonstrated significant differences over time in waking EEG responses to repeated olfactory administration of individually-prescribed LM potency remedies versus placebo solvent in fibromyalgia patients.[11] No studies in human subjects have as yet reported waking EEG effects of specific remedies in the centesimal dilution series, in the context of a pathogenetic trial.

Another challenge for preclinical and clinical research in homeopathy is the apparent nonlinearity of the dose-response relationship. Multiple studies[12–16] in plants, animals, and human subjects suggest that remedies may trigger bidirectional and nonlinear changes in outcome measures, depending in part on (a) passage of time after the last remedy administration; (b) the dilution or potency given; (c) the point in time relative to the injury or last remedy dose when the host system is assessed; (d) variations in baseline host traits and states.

The state of the recipient (host) at the time of remedy administration and at the point of follow-up assessments matters. For example, Lewith et al[17] found an oscillatory pattern of change over 16 weeks in multiple outcome variables after initially administering dust mite 30c to asthmatics, a pattern not seen in the comparison group who received placebo. In terms of time dependency of remedy administration, Bertani et al[16] demonstrated in an animal model for edema that pre-injury treatment with remedy worsened, whereas post-injury remedy treatment lessened, paw edema caused by an inflammatory agent (carrageenan). The latter study is consistent with a fundamental tenet of homeopathic philosophy, i.e., an agent that can cause illness in a healthy person can relieve similar symptoms in a sick person.

Finally, the same potency in basic science studies may lead to significant effects, but in opposite directions during different attempted replication studies.[12] Factors that may contribute to such confusing results could include differences in the state of the test system (i.e., plant seedling) in its immediate environmental context at the moment of remedy administration, differences in remedy preparation between batches and manufacturers, and/or differences in effective dose received (i.e., differential uptake or absorption). Various

observers[1518–21] have proposed that homeopathic remedies act by modifying the complex nonlinear dynamics of the recipient host system, i.e., its variability per se, based on the recent history and momentary state of the organism, as well as the specific salience of the remedy for the host.[7]

Furthermore, plant seedling development studies have also indicated that a series of adjacent potencies, e.g., 24×, 25×, 26×, can produce a nonlinear dose-response pattern of, respectively, increases, decreases, and increases in the outcome variable.[14] Baumgartner[12] recently wrote an excellent review and discussion of these issues with reliability and reproducibility. Taken together, prior research suggests the need for additional examination of interactions between the momentary state of the host, remedy potency, timing of repeated dosing, and timing of assessments.

The purpose of the present feasibility study was to explore the short term waking EEG effects of repeated sniffs of the homeopathic polycrest remedies, Sulphur and Pulsatilla, on relatively healthy human subjects. Hypotheses included: (a) remedies would differ from one another in their overall effects on EEG alpha responses to sniffing (i.e., remedy specificity); (b) the point in time in the study when a given dilution was administered would lead to differential effects of the same remedy dilution (i.e., time sensitivity interacting with host state and recent remedy history).

Material and methods

Subjects

Subjects were undergraduate college student volunteers between ages 18 and 30 enrolled in the introductory psychology course at the University of Arizona. Eligibility criteria included good global health (rating of 3 out of 5 on a single item screening question [22]) and either a score ≥25 for the remedy Sulphur on the Homeopathic Constitutional Type Questionnaire (CTQ)[23], together with a score ≤21 on the CTQ for the remedy Pulsatilla, OR a score ≥24 for the remedy Pulsatilla, together with a score ≤24 for the remedy Sulphur. The original selection criteria were based on previously-observed cut-offs in a similar subject population for top and bottom 40% of sample scores. After screening participants for five additional semesters, we reexamined the population and determined new cut-offs to maintain representation of the top and bottom 40% of the sample.

The CTQ is a validated 160-item 5-point Likert self-rating scale for assessing 21 commonly-used, clinically-documented homeopathic remedies (polycrests). The CTQ subscales for each remedy include 8 symptom items self-rated on a 5-point Likert scale. A previous survey study using the CTQ in a sample of over 100 college students had revealed the likelihood of finding an adequate pool of potential subjects who would meet these screening cut-offs for one or the other of the remedies.[24]

Exclusion criteria were pregnancy or planning to become pregnant, major psychiatric or serious medical conditions, chronic use of medications other than contraceptives, a history of anaphylactic shock, epilepsy, asthma and/or migraine headaches.

Study Design and Procedures

The design was a repeated measure study in which each subject was tested in a psychophysiology laboratory at the same time of day, once per week for 3 weeks.

Homeopathic remedy preparation involves two discrete procedures, i.e., serial dilution and succussion. In this study, three dilutions (6c, 12c, or 30c, where c potencies were diluted at a ratio of 1/100 parts over 6, 12, or 30 steps) and four succussion levels (no succussion

(stirred), 20 succussions, 40 succussions, and 100 succussions) were selected for testing. Due to practical and budgetary limitations, each subject received one dilution per week (in a randomized order) at all of the four different succussion levels. For example, a subject may be randomized to receive 6c in week 1, then 30c and 12c on the following visits. During week 1, the subject would sniff vials of 6c (and two different control solutions) prepared with no succussions, 20, 40 and 100 succussions presented in a randomized order.

The four different succussion level vials were also randomized and presented in 8 complete blocks for the three types of vial contents evaluated (test verum remedy [Sulphur or Pulsatilla, see below], distilled water control, and distilled water-ethanol [95% v/v] control). In short, there were 8 randomized presentations of 4 different succussion levels for each of 3 different vial contents on a given day on which a specific dilution was tested.

The repeated measure design was based on specific methods used in two previous studies, one on homeopathy in fibromyalgia patients [6] and one on women with environmental chemical sensitivity [25]. The mode of administration was olfactory, using 2 second sniffs. In a sense, the design generated a type of average evoked EEG response to repeated sniffs of the same material, controlled for the effects of simply sniffing remedy-free solvent (distilled water control and the distilled water-ethanol control).

The rationale for use of the EEG is that EEG is a dynamical biomarker of physiological brain activity that can be sampled repeatedly and frequently over short time scales.[21] The variability and complexity of the EEG changes with the state of the organism as a whole. Advantages of the olfactory method of administration are that it permits greater certainty of the momentary point in time when the host receives a dose of remedy and therefore a clearer time window for assessing and possibly detecting subtle, even transient, post-dose effects.

Both research staff and subjects were blinded to the contents of the vials during the laboratory procedures. We purchased the remedies and solvents from an FDA-regulated homeopathic pharmacy with experience in preparing materials for research purposes (Hahnemann Laboratories, San Rafael, CA). Although the pharmacy prepared the original remedy and water-ethanol solutions in accord with their usual procedures using a 95% ethanol in distilled water solvent, the test solutions that subjects sniffed were markedly diluted in distilled water in a final local preparation step (0.5 ml of test solution was placed in a cup with 150 ml of distilled water and stirred, followed by pouring 10 ml of this final water-diluted solution into the sniff vials). Each vial contained 10 ml of test liquid in 60 cc amber glass vial (E.D. Luce Packing, CA).

Subjects were instructed not to consume beverage alcohol, caffeinated beverages, and/or tobacco for six hours prior to the recording. Subjects also were instructed not to wear strong perfumes or lotions the day of the recording.

Laboratory recordings were performed using the Compumedics E-Series equipment (El Paso, TX) and a 20 channel Quik-Cap. Electrodes on the Quik-Cap are situated according to the International 10–20 System. Recordings include 19 unipolar EEG channels referenced to contralateral mastoids, bilateral electrooculograms (EOG), a two-lead electrocardiogram (bilateral sub-clavicle electrode placement), and a nasal pressure flow signal to detect sniff effort (Salter Labs Nasal ETCO2 Cannula). Electrode impedance levels were kept below 5 KΩ. Equipment settings for data acquisition included an EEG sampling rate of 512 Hz and a high pass filter set at 0.50 Hz. A 60 cycle notch filter was used to eliminate ambient electrical noise.

After hookup and completion of session questionnaires, each laboratory visit included a resting 5-minute, eyes-closed EEG recording performed before and after the sniffing period.

The pre-session resting EEG power was used as a baseline covariate for this study. Subjects then were asked to take a series of two-second sniffs from the 96 vials containing the test solutions in randomized order, one vial at a time. The contents were one of two well-documented, widely-used homeopathic remedies, Sulphur (mineral) or Pulsatilla (plant) and associated control solvents (water or a water-ethanol mixture prepared with stirring, 20 succussions, 40 succussions, or 100 succussions).

Research staff opened each vial and presented the open vial 2 cm below the nose and 2 cm from face. The subject's chin was stabilized relative to the vial by using a height-adjustable table stand with a padded chin rest adjusted for their comfort. Each vial was re-sealed before the next was opened. Subjects were instructed to exhale for 2-seconds, inhale for 2-seconds, then exhale for 2-seconds. The manual method of administration was chosen rather than a continuous flow olfactometer to mimic clinical administration methods, repeat previously successful exposure techniques from prior studies,[61126] and to avoid cross-contamination of delivery apparatus for the control substances by trace remedy.

The technicians electronically marked the recording as the subject began the exhalation-inhalation pattern, but sniffs were also confirmed as described below (see Spectral Computation). An Austin Healthmate Junior air filter with 4-stage filtration (including pre-filters for medium and large particles, an activated carbon/zeolite filter for volatile organic chemicals, and a medical grade HEPA filter) ran on the low setting throughout each session to clear the air of trace residual odors and volatile organic chemicals.

Spectral Computation

The EEG data samples were identified by the use of an automated algorithm detecting sniffing and verified by the research technician. The algorithm was designed to capture the positive upward, then rapid downward negative excursion from the recorded tracing of respiratory effort at the nose measured using a nasal cannula (Salter Labs). A technician blinded to bottle contents and outcomes reviewed each sniff identified by the algorithm, verified it as a 2-second artifact-free EEG segment (e.g., excluding epochs with eyeblink and muscle movement artifacts defined as amplitudes > 50 mV). Sniffs with artifact or an algorithm detection problem (e.g., research subject did not inhale deeply enough) were eliminated from analysis. On average, 6.8% of sniffs were removed for Pulsatilla and 6.1% were removed for Sulfur.

The 2-second EEG data were then analyzed into quantitative EEG spectral bands using fast Fourier transform, converted to relative power values (using the ratio of the power of each frequency band/total power within the range of 0.5–55 hertz). An additional 1% of outlier values were also eliminated from the analyses. Because of the previous empirical findings on changes in alpha band frequency during the homeopathy study in fibromyalgia and prior studies of EEG alpha changes as biomarkers of sub-olfactory and olfactory threshold levels of various odors in young adults[6112627], the current study focused on the alpha 1 (8 – 10 hertz) and alpha 2 (10 – 12 hertz) power averaged over the entire head. Relative EEG power was calculated by summing EEG power across all bands and calculating the percent of the total EEG power for each of the alpha bands.

Statistical Approach

A series of linear mixed-effect models using SAS Proc Mixed were conducted to examine the main effect of remedy, dilution, succussion, and time (visit week number) on EEG relative alpha power. Each model controlled for baseline resting EEG, effects from the water and water-ethanol controls, and gender, with person as the random effect. In each of the models, the independent variables were treated as class variables. Linear mixed effects

models have several advantages over traditional repeated measures analyses including the ability to generate slopes and estimate intercepts despite missing data, and varied time intervals, improved estimation of individual effects (esp. important in homeopathic research), and the ability to model cross-level interactions and partition variance/covariance components.[28]

The remedy model compared Sulphur versus Pulsatilla. The dilution model compared 6c, 12c, and 30c. The succussion model compared 0, 20, 40, and 100 succussions. The time model compared visit weeks 1, 2, and 3. Pair-wise comparisons of means were examined in the models with statistically significant main effects. Separate models were run within each band, alpha 1 and alpha 2. In order to test for dilution carry-over effects, we also conducted a linear mixed-effects model that included the main effects of dilution and visit week as well as their interaction.

Results

Fifty-one people were fully eligible, volunteered, and started the Sulphur arm; and 45 people were eligible, volunteered, and started the Pulsatilla arm. The Sulphur arm had 45 subjects with 3 complete laboratory sessions and the Pulsatilla arm had 43 subjects with 3 complete laboratory sessions. Table 1 summarizes the demographic and baseline trait characteristics of the study sample. All participants are included in the analysis.

Remedy

The results for remedy are presented in Figure 1. A significant main effect for remedy was found in both bands, alpha 1 ($F(1,7923)=15.48$, $p<0.001$) and alpha 2 ($F(1,7923)=18.58$, $p<0.001$). In both bands, relative alpha EEG was greater in Sulphur participants than Pulsatilla participants. Given the significant difference in EEG response between the two remedies, all subsequent models were also run separately for each remedy.

Dilution

A statistically significant dilution finding was found for alpha 1 relative EEG in Pulsatilla. The pair-wise comparisons revealed that relative EEG alpha 1 power was greater in dilution 6c than both dilutions 12c and 30c. A trend was also found for alpha 2 relative EEG in Sulphur. In contrast to the Pulsatilla findings, relative EEG alpha 2 power was greater in Sulphur dilution 12c than dilution 30c. No other differences in dilution were found. These results are presented in Table 2.

Succussion

Succussion was non-significant in both of the Sulphur models and in the Pulsatilla model for alpha 2. However, a statistically significant effect for succussion was found in the alpha 1 relative EEG band for Pulsatilla. Alpha 1 relative EEG was significantly lower in the 40 succussions level than the no succussion, 20 succussions, and 100 succussions (see Table 3).

Time (Visit Week)

Visit week was a statistically significant for Sulphur in the alpha 1 relative EEG band only. Alpha 1 relative EEG was greater at visit week 2 than visit week 1 or visit week 3. The results are presented in Table 4.

Dilution by Visit-Week Interaction

The dilution by visit interaction was statistically significant for the Sulphur remedy for both the alpha 1 and alpha 2 relative EEG bands. In the Pulsatilla model, the dilution by visit

interaction was statistically significant only in the alpha 2 relative EEG band. The dilution by visit week interaction results are presented in Table 5.

Sulphur Relative Alpha 1 EEG comparisons

In the within-visit week pair-wise comparisons for relative alpha 1 EEG power with Sulphur, on the first visit week, relative EEG power in alpha 1 was greater for participants receiving the 30c dilution than 6c. On the third visit week, there was less relative EEG in alpha 1 for participants given 30c than participants given 12c. In the within dilution pair-wise comparisons, alpha 1 relative EEG was greater when dilution 6c was given at visit week 2 than when it was given at visit week 1 or visit week 3. The relative EEG in alpha 1 was less when the dilution 30c was given at visit week 3 than visit weeks 1 or 2 (see Figure 2).

Sulphur Relative Alpha 2 EEG comparisons

In the within visit week pair-wise comparisons for alpha 2 relative EEG in Sulphur, participants who received 12c on the first visit week showed the greatest relative EEG power in alpha 2 than participants receiving either 6c or 30c at the first visit week. At the second visit week participants receiving 6c showed greater relative EEG power in alpha 2 than participants receiving 12c at that visit. For the within dilution pair-wise comparisons, alpha 2 relative EEG was greater when dilution 6c was given at visit week 2 than when it was given at visit week 1. For dilution 12c, alpha 2 relative EEG power was greater when it was given at visit week 1 than visit weeks 2 and 3.

Pulsatilla Relative Alpha 2 EEG power comparisons

Participants who received 6c on the first visit week showed greater relative EEG power in alpha 2 than participants receiving 12c at the first visit. At the third visit week participants receiving Pulsatilla 12c showed greater relative EEG power in alpha 2 than participants receiving 30c at that visit. For the within dilution comparisons, relative EEG in alpha 2 was greatest at when dilution 6c was given at visit week 1 than when it was given at visit 2 or 3.

Discussion

The present data support the homeopathic theory-based prediction of a differential remedy response when individuals are given their respective constitutional remedy. In this study Sulphur CTQ “types” exhibited greater relative EEG power remedy effects for both alpha 1 and alpha 2 than their Pulsatilla CTQ counterparts. The interaction between dilution and visit week was also more evident in the Sulphur CTQ types. Whether or not such findings would be replicable with subjects identified using individualized homeopathic case taking interviews rather than the CTQ is a valid, but as yet unanswered, question. These data in human subjects extend findings from controlled animal studies that previously demonstrated the short-term ability of single or combination homeopathic remedies to alter waking EEG alpha and delta[29] and sleeping EEG delta wave activity.[930] Although it would be preferable to have comparable proportions of men and women in subsequent studies with larger samples, the current analyses were controlled for gender differences between groups.

Future studies should also examine other designs, such as testing for differential effects of giving the constitutional remedy versus non-constitutional remedy to persons of a specific constitutional type. In a recent study of mood effects on sleep in which it was possible to evaluate the interaction of personality type and remedy received, Brooks et al.[7] reported different effects of two remedies (Nux Vomica 30c and Coffea Cruda 30c), based on an interaction between the specific remedy given and the baseline personality type. In the

present study, the design did not allow parsing the remedy effects apart from the baseline CTQ type.

The predictions concerning different main effects for dilution level and succussion level were, in general, minimally confirmed in this study. Dilution main effects were found only for Sulphur, with relative alpha 1 EEG power greater for the 6c dilution than either the 12c or 30c dilution. A contrasting trend was also observed in alpha 2, where dilution 12c produced greater effects than did 30c. An oscillatory response was observed for time, with relative alpha 1 EEG power greater at the second visit week than the first or third visit week for Sulphur only. These findings are additional examples of the nonlinear dose-response phenomena previously reported in a variety of living systems with homeopathic remedies.[1231]

The effect of succussion level was found for alpha 2 relative EEG power in Pulsatilla only. In this case relative EEG power was significantly lower at 40 succussions than the other succussion levels. Subsequent studies using larger samples and focusing only on different levels of succussion for a single dilution, may clarify whether or not the Pulsatilla finding was a statistical anomaly or a hint of more meaningful succussion-related findings, also nonlinear in nature.

More notably, the minimal main effects for dilution or time were superseded by the significant interaction within subjects between dilution and time (visit week), significant in both bands in Sulphur and in the alpha 2 band in Pulsatilla. No consistent pattern emerged across the two remedies or the alpha frequency bands. The EEG response to a 6c dilution was greater at the second visit than at the first visit for both bands in Sulphur participants; while the reverse was true for the Pulsatilla participants, i.e., the 6c dilution response was greater at the first visit than the second visit. During the first visit week a 30c dilution produced a stronger alpha1 EEG response than 6c dilution, while the 12c dilution produced the strongest EEG response in alpha 2 that same visit week for Sulphur participants. In contrast, the 6c dilution produced a stronger response than the 12c dilution in alpha 2 for the Pulsatilla participants during the first visit week. Similarly, during the third visit week a 12c dilution was associated with a greater alpha 1 EEG response than 30c in Sulphur participants and alpha 2 EEG response for Pulsatilla participants. However, there was no difference in EEG response to dilution level during that same visit week in alpha 1 for the Sulphur participants.

Taken together, the findings suggest that remedy effects on relative EEG alpha power are complex, nonlinear, and dynamical, dependent on the nature of the specific remedy, dilution, and time, including the individual's recent past history of remedy exposure in previous study week visits. Such data may relate to clinical claims that the same remedy at the same potency may act very differently in the same patient when administered under seemingly similar circumstances on two or more separate occasions over time.[32] Articulating relevant hypotheses based on this conceptualization should assist in generating innovative and novel study designs. New study designs will need to accommodate the hypothesis that homeopathic remedies may modulate system dynamics at global and local levels of scale,[33] rather than act like pharmaceutical drugs to consistently and linearly suppress local symptoms.[18]

The complexity of the findings is consistent with convergent models for homeopathic remedy effects that invoke complex adaptive systems and nonlinear dynamical systems (NDS) concepts. NDS may help account for the altered variability and response patterning within the host found in the current study and in previous research summarized above. Such models suggest that different remedies will mobilize changes in the host system not seen

with placebos, but that the direction, magnitude, and time pattern of effects will not necessarily be reproducible or consistent over time for subjective or objective measures. Using research methods adapted from the field of complexity science[18,33–36] could allow much better characterization of how remedies act in living systems. One example would be computer modeling of evolving systemic global and local changes during homeopathic remedy testing in pathogenetic trials or clinical treatment in patient care.

The findings require several caveats. This study is preliminary and mainly indicates the feasibility of using quantitative EEG as a biomarker for early remedy effects in human subjects participating in pathogenetic types of trials. The study extends findings from this laboratory's prior investigation of EEG alpha changes during individualized homeopathy treatment in patients with fibromyalgia.[6,11] The current data are not definitive in characterizing the nature of the EEG response to remedies.

On the one hand, the present study design may have captured some of the time-dependent and host state-dependent phenomenological processes underlying the variability of results from laboratory to laboratory or study to study. If remedies can set an initial destabilization of system dynamics into motion,[34,37] the hypothesized result of remedy administration would be a transient period of less predictable nonlinear dynamical bidirectional fluctuations (oscillations[31]), perhaps of greater than "usual" amplitude and irregular frequency. Eventually, without further external perturbation, e.g., from another remedy dose, a living system should restabilize into another dynamical pattern (i.e., an attractor). The nature of the evolving change over time would depend, in part, on sensitivity of the living system to small and subtle differences in initial conditions at the moment of remedy administration, i.e., the "butterfly" effect well-known from chaos theory and research.[38,39]

In such a model, if the remedy acted therapeutically, the net clinical outcome would be a healthier dynamical state characterized by greater resilience, flexibility, and adaptability to environmental change, i.e., flourishing.[34,36] If the remedy did not exert a therapeutic benefit even though it initiated a temporary disturbance in system behavior, i.e., an active but therapeutically poorly-matched remedy for the individual, the outcome would end up manifesting as a return to roughly the same rigid and maladaptive dynamics (attractor) as before the remedy.[36]

The current data demonstrate, as have many previous studies, that specific verum homeopathic remedies trigger changes in outcome variables different in pattern from those seen with placebo. The paradoxical feature of such effects is their inherent variability and even bidirectionality. These observations would be consistent with NDS phenomena such as bifurcations of system dynamics at critical moments, along with unstable phase transitions in the evolutionary or developmental shift from one relatively stable pattern to a different stable pattern of dynamics.[34,37]

On the other hand, the study design was a trade off between scientific and practical considerations. The design was admittedly complicated and confounded by potential carryover effects between verum and controls within a given session. However, it permitted evaluation of timing and dilution effects within budgetary constraints, despite losing experimental sensitivity to detecting succussion effects and a thorough examination of possible dilution presentation order effects. These practical limitations precluded adding more arms to the study to parse out more factors in the variable outcomes. However, future research, informed by the preliminary findings of the current investigation, can pursue some of these additional questions.

Also, the primary outcome variable in this study was EEG alpha power. In contrast with typical pathogenetic trials, the current study did not ask participants for ratings of self

reported symptoms after each sniff. The reason for this methodological choice was to minimize the otherwise high risk of confounding EEG changes with set shifting, mood, and motor task-related effects of giving symptom or mood ratings 96 times per session. In the future, researchers may be able to use other types of designs that would keep the duration of each session visit to an acceptable length and collect both moment-to-moment subjective and EEG data.[4041]

The study examined only 3 weeks of effects during an unusually intensive regimen of olfactory remedy administration per session. Clinically, most chronically ill patients only sniff a remedy once per day, if they take their treatment via olfactory administration. In order to obtain averaged EEG effects, we gave the olfactory sniffs 8 times per experimental condition (where condition = a given dilution at a given succussion level). The methodological choice to use such an approach stemmed from empirical data and experience in earlier studies[1126] indicating that any single remedy exposure may or may not produce effects, but repeated exposures will generate a measurable average effect on a system.

In addition, future studies will need to explore the issue of succussion in greater detail. While the data hint at an isolated effect of 40 succussions for Pulsatilla, the present study cannot provide clarification of an important question, e.g., is there a threshold number of succussions above which effects plateau, with further succussion producing no additional change in the capacity of a remedy to alter the function or health of the host? Anecdotal statements by basic scientists suggest the possibility of a threshold and plateau process, rather than a progressive increase in remedy effects with a greater number of succussions. However, a proper design to assess succussion effects would require a larger sample testing only one dilution prepared with different numbers of succussions and tested on separate occasions and/or within separate arms of a study.

In conclusion, this study opens the door to further research on the nonlinear dynamical effects of homeopathic remedies on human EEG response patterns.[42] It raises many questions that merit specific systematic study. Notably, these findings are consistent with the hypothesis that homeopathic remedy effects depend not only on the nature of the remedy, but also on the interaction of remedy with the continuously changing/evolving (dynamical) host system over time.[18] Re-focusing research attention away from the remedy per se and over to the interaction of the remedy with the host and to the factor of time may be a key step toward advancing understanding of variability in remedy effects on living systems.[43]

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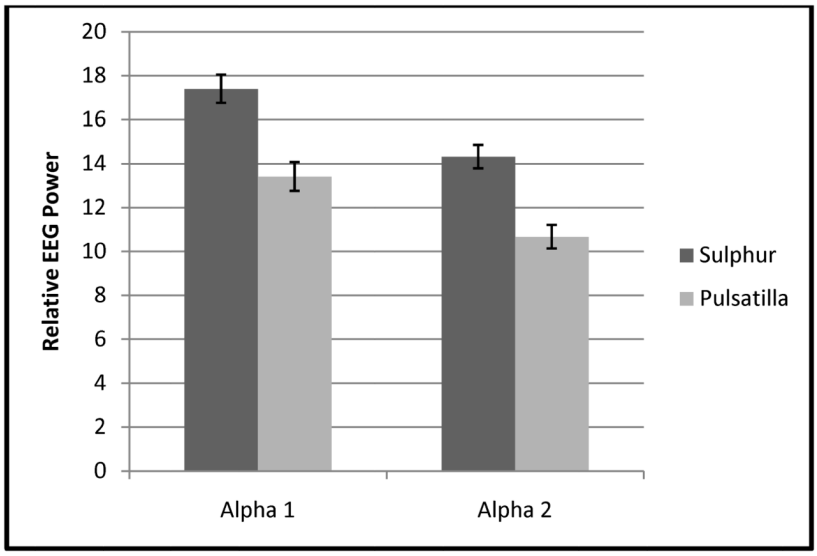

Figure 1.
Relative EEG Power for Alpha 1 and Alpha 2 Means and Standard Error by Remedy*
*Controlling for baseline resting EEG, ethanol and water controls, and gender

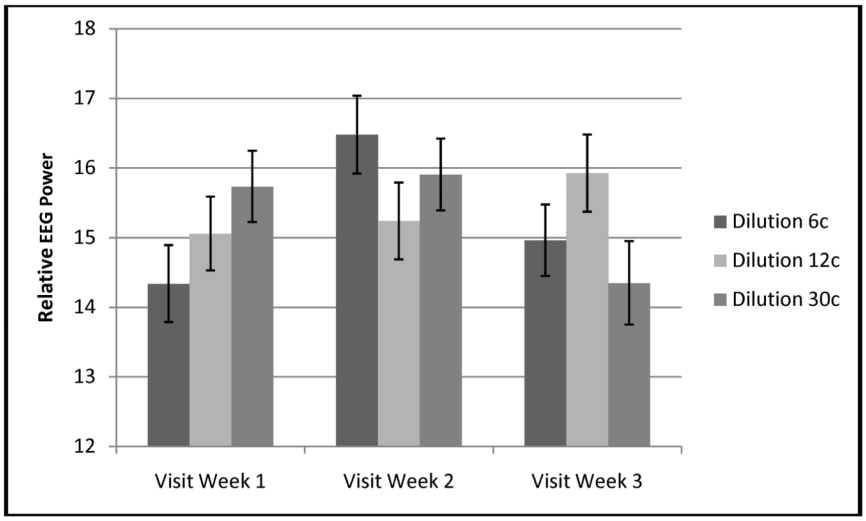

Figure 2.

Dilution by Visit Interaction* for Sulphur in Alpha 1 Relative EEG Power – Means and Standard Errors[+]

*Controlling for baseline resting EEG, ethanol and water controls, and gender

[+]Significant pair-wise comparisons:

at visit week 1: 30c dilution > 6c dilution ($t(3742)= 2.31$, $p=0.0209$);

at visit week 3: 12c dilution > 30c dilution ($t(3742)= 2.31$, $p=0.0212$);

dilution 6c at visit week 2 > dilution 6c at visit week 1 ($t(3742)= -3.3$, $p=0.001$);

dilution 30c at visit week 3 < visit week 1 ($t(3742)= -2.17$, $p=0.0302$);

dilution 30c at visit week 3 < visit week 2 ($t(3742) = -2.40$, $p=0.0165$).

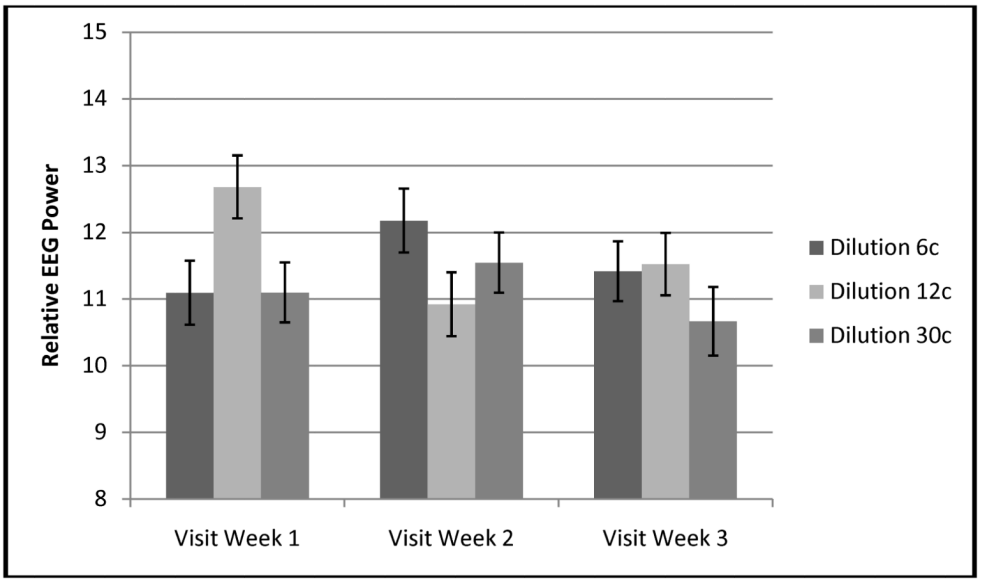

Figure 3.

Dilution by Visit Interaction for Sulphur* in Alpha 2 Relative EEG Power – Means and Standard Errors[+]

*Controlling for baseline resting EEG, ethanol and water controls, and gender

[+]Significant pair-wise comparisons:

at visit week 1: 12c dilution > 6c dilution (t(3742)= 3.20, p=0.0014);

at visit week 1: 12c dilution > 30c dilution (t(3742)= 3.22, p=0.0013);

at visit week 2: 6c dilution > 12c dilution (t(3742)= 2.48, p=0.0132);

dilution 6c at visit week 2 > dilution 6c at visit week 1 (t(3742)= 2.10, p=0.0358);

dilution 12c at visit week 1 > visit week 2 (t(3742)= 3.45, p=0.0006);

dilution 12c at visit week 1 > visit week 3 (t(3742)= 2.33, p=0.0201).

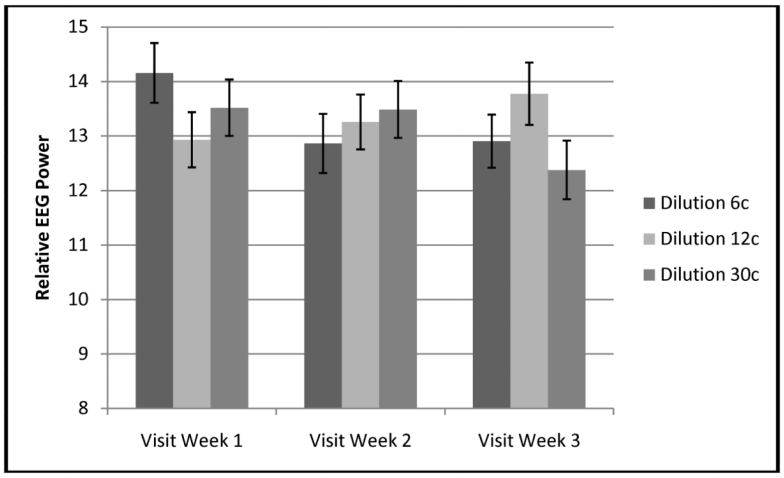

Figure 4.

Dilution by Visit Interaction* for Pulsatilla in Alpha 2 Relative EEG Power – Means and Standard Errors[+]

*Controlling for baseline resting EEG, ethanol and water controls, and gender

[+]Significant pair-wise comparisons:

at visit week 1: 6c dilution > 12c dilution ($t(4162)= 2.04$, $p=0.0418$);

at visit week 3: 12c dilution > 30c dilution ($t(4162)= 2.19$, $p=0.0238$);

dilution 6c at visit week 1 > visit week 2 ($t(4162)= 2.07$, $p=0.0382$);

dilution 6c at visit week 1 > visit week 3 ($t(4162)= 2.16$, $p=0.031$).

Table 1

Baseline Comparisons between remedy groups – Means ±Standard Deviation

Variable	Sulphur group (*n*=51)	Pulsatilla group (*n*=45)
Age	19.2±2.0	19.0±0.98
Gender (% female)	31%	82%**
CTQ- Sulfur	27.4±1.9	22.4±1.5**
CTQ- Pulsatilla	18.8±2.1	25.8±1.8**

* p<.05,

** p<.01; CTQ = Constitutional Type Questionnaire

Table 2

Relative EEG Power Means (Standard Error) for Dilution by Remedy and EEG Band

Remedy	Band	Dilution 6c	Dilution 12c	Dilution 30c	F	P-value
Sulphur	alpha 1	15.215 (0.42)	15.399 (0.42)	15.477 (0.41)	F(2,3748)= 0.47	0.63
Sulphur	alpha 2	11.535 (0.38)	11.743 (0.38)[a]	11.201 (0.38)[b]	F(2,3748)= 2.86	0.0576
Pulsatilla	alpha 1	15.800 (0.46)[c]	14.876 (0.46)[d]	15.020 (0.46)[e]	F(2,4168)= 8.55	0.0002
Pulsatilla	alpha 2	13.248 (0.40)	13.256 (0.40)	13.175 (0.40)	F(2,4168)= 0.06	0.9452

a> b, t(3748)= 2.37, p<0.0179; c > d, t(4168)= 3.83, p<0.0001; c > e, t(4168)= 3.21, p<0.0013

Table 3

Relative EEG Power Means (Standard Error) for Succussion by Remedy and EEG Band

Remedy	Band	0 Succussions	20 Succussions	40 Succussions	100 Succussions	F	P-value
Sulphur	alpha 1	15.606 (0.43)	15.170 (0.43)	15.417 (0.43)	15.264 (0.43)	F(3,3747)=0.72	0.543
Sulphur	alpha 2	11.420 (0.38)	11.499 (0.38)	11.434 (0.38)	11.596 (0.38)	F(3,3747)=0.20	0.898
Pulsatilla	alpha 1	15.396 (0.48)[b]	15.522 (0.48)[c]	14.699 (0.48)[a]	15.341 (0.48)[d]	F(3,4167)=3.52	0.014
Pulsatilla	alpha 2	12.967 (0.41)	13.484 (0.41)	13.226 (0.41)	13.232 (0.41)	F(3, 4167)=0.99	0.395

a < b, t(4167)= 2.51, p=0.0121; a < c, t(4167)= 2.97, p=0.003; a < d, t(4167)= −2.31, p=0.0208

Table 4

Visit Week Means (Standard Error) by Remedy and EEG Band

Remedy	Band	Week 1	Week 2	Week 3	F	P-value
Sulphur	alpha 1	15.141[b]	15.859[a]	15.129[c]	F(2,3748)=4.38	0.0126
Sulphur	alpha 2	11.588	11.572	11.259	F(2,3748)=1.31	0.2695
Pulsatilla	alpha 1	15.137	15.269	15.319	F(2,4168)=0.3	0.7402
Pulsatilla	alpha 2	13.479	13.212	12.976	F(2,4168)=1.84	0.1594

a > b, t(3748)=2.52, p<0.0117; a > c, t(3748)=2.57, p<0.0103

Table 5

Relative EEG Power Means (Standard Error) for Dilution by Visit Week Interaction by Remedy and EEG Band

Remedy	Band	Dilution	Visit 1	Visit 2	Visit 3	F	Sig
Sulphur	alpha 1	6c	14.338 (0.55)	16.476 (0.56)	14.961 (0.51)	F(4,3742)= 2.86	0.022
		12c	15.057 (0.53)	15.239 (0.55)	15.924 (0.55)		
		30c	15.734 (0.51)	15.903 (0.52)	14.348 (0.60)		
Sulphur	alpha 2	6c	11.091 (0.48)	12.175 (0.48)	11.414 (0.45)	F(4,3742)= 3.97	0.0032
		12c	12.679 (0.47)	10.919 (0.48)	11.521 (0.47)		
		30c	11.096 (0.45)	11.543 (0.45)	10.664 (0.51)		
Pulsatilla	alpha 1	6c	15.834 (0.58)	15.836 (0.58)	15.751 (0.53)	F(4,4162)= 2.88	0.0213
		12c	14.797 (0.55)	14.683 (0.55)	15.320 (0.61)		
		30c	14.914 (0.56)	15.434 (0.57)	14.674 (0.58)		
Pulsatilla	alpha 2	6c	14.155 (0.55)	12.861 (0.54)	12.904 (0.49)	F(4,4162)= 0.83	0.5078
		12c	12.929 (0.50)	13.254 (0.50)	13.774 (0.57)		
		30c	13.515 (0.52)	13.483 (0.52)	12.376 (0.54)		