In Search of Responders: Using Individual Differences To Improve Homeopathic Clinical Research

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Overview of Challenges

- Recent reviews of homeopathic research raise key issues:
  - Basic and preclinical studies overall demonstrate homeopathic remedy effects, but …
  - Findings vary in directionality and consistency from study to study: that is, **increased variability**
  - **Individual differences in prescribed treatment and in response patterns**: Difficulties in determining the true simillimum remedy result in “verum” groups that include varying proportions of patients receiving active AND inactive remedies in clinical studies

Individualized Homeopathic Treatment Improves Global Behavior Patterns in ADHD

(Frei et al, 2007)

- First confirm with open label pre-screening trial that "verum" homeopathic remedy is really active *in a given individual* under study conditions
- Then enroll responders in the double-blind RCT study, using global behavior as outcome
  - Clinically needed 5 months and open trials of 3 different sequential single remedies (median) to find a truly active individualized treatment for most ADHD children, prior to enrolling in double-blind placebo-controlled trial
- Frei's modified design RCT was positive (external validity: clinical practice is iterative), vs Jacobs et al's unmodified RCT (no pre-screening for correct remedy) was negative

Issues To Consider For Research

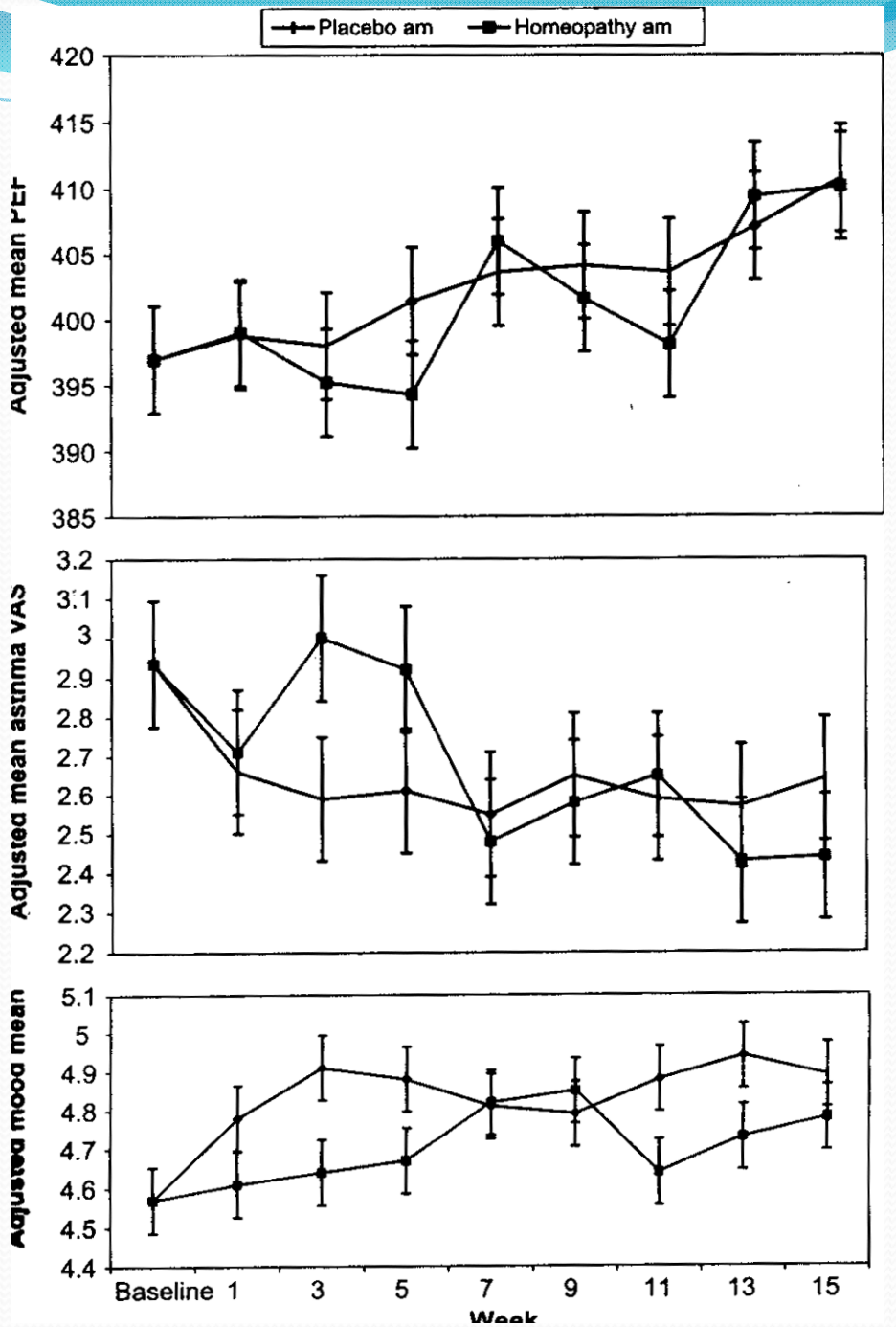
- Reliance on only self-report or even observer rated data is limited and out of step with mainstream medical research standards
- Multiple biological/physiological markers are available to improve sensitivity to detect effects of homeopathic remedies in human subjects
- Animal studies have already shown measurable remedy effects on objective measures such as EEG sleep, laboratory blood tests, experimental markers
- It is essential to include objective measures in future clinical and preclinical human subjects studies of homeopathy together with subjective data

Nonlinear Effects of Non-Individualized Homeopathic Verum vs. Placebo

- Isopathic Dust Mite, but not Placebo, in Asthmatics
  Perturbed System into Biphasic, Oscillating Dynamical Behavior

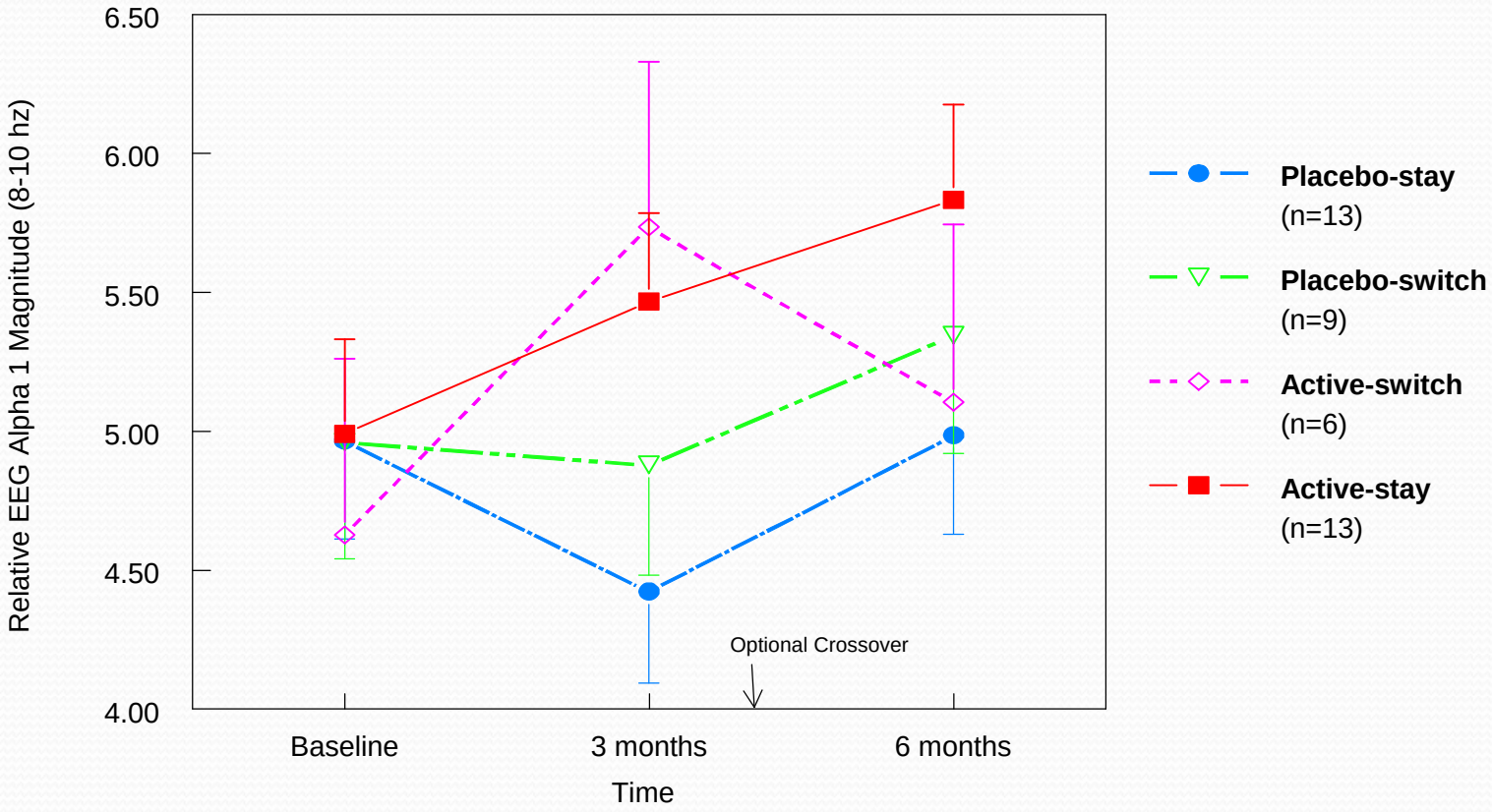
- Yet, No Net Differences in Clinical Endpoints at 16 weeks between Verum & Placebo

(Lewith et al. BMJ 2002; Hyland & Lewith Homeopathy 2002)



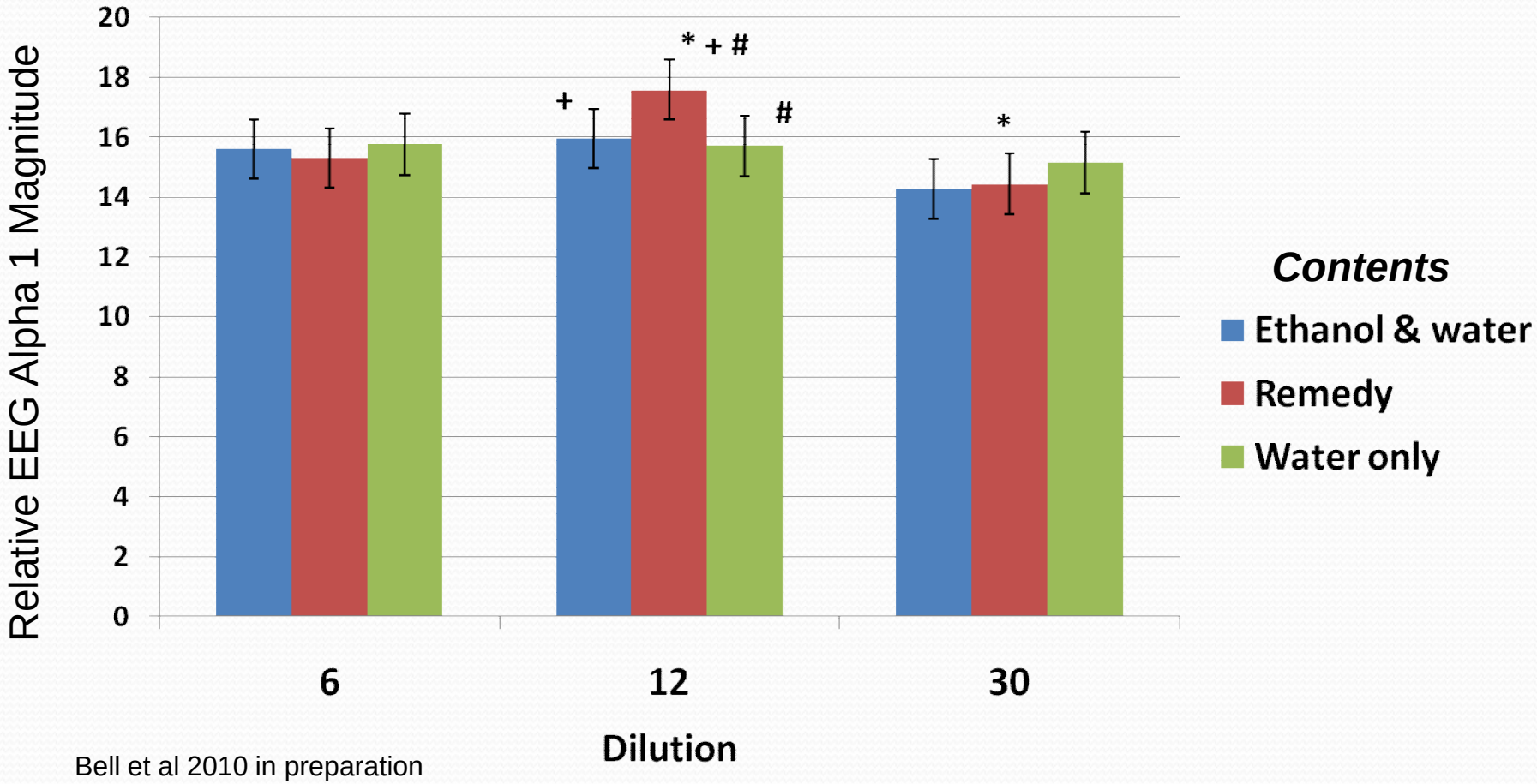
Individualized Homeopathic Treatment in Fibromyalgia Patients Produces Differential Changes in Waking qEEG over Time vs Placebo

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



(Bell et al 2004)

Contents by Dilution Interaction – Relative qEEG Alpha 1 (8-10 Hz)



Bell et al 2010 in preparation

***p=0.0223; +p=0027; #p=0.0005**

2-way interaction F(4,549)=3.67; p=0.0058

Key Guiding Principles

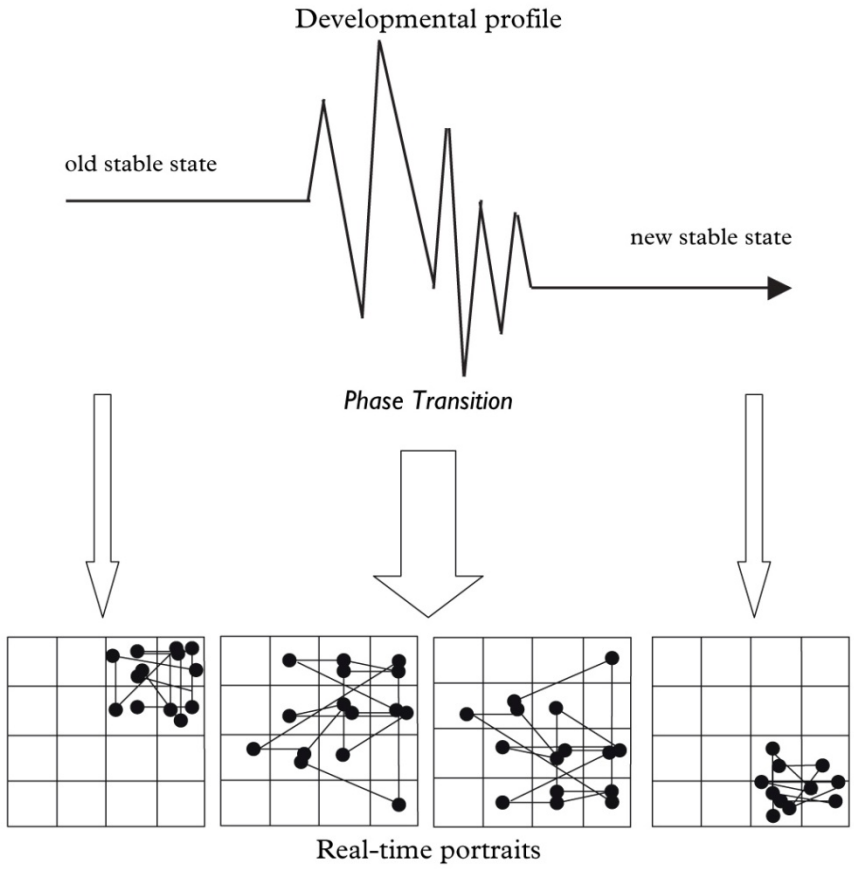
- **Bidirectionality and variability in reproducibility** are hallmarks of a **nonlinear dynamical system** (**NDS**)
  - Overlap with homeopathic basic research findings points to the need for NDS theory-driven research in homeopathy
- Clinical practice is an iterative, empirical process resulting in responders and non-responders
  - Points to the need for **individual difference research**
  - Points to the need for **highly sensitive outcome measures**
  - Points to the need to capture the ***process of change***, not just the endpoints

Nonlinear Complex Systems Model for Remedy Action in Living Systems

- Living systems are complex adaptive systems, i.e., indivisible interactive, interdependent networks
- Life occurs in the delicate dynamic balance between excess order and excess disorder (chaos): optimum complexity
- Age and disease lead to loss of complexity of system dynamics
- Healing/recovery leads to more complexity (resilience, adaptability to change)

Complexity Model for Homeopathic Effects on Living Systems

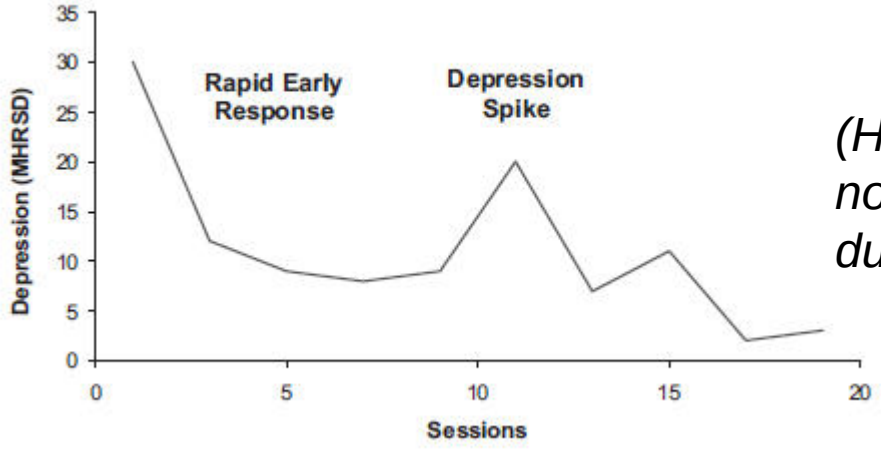
- A remedy triggers **dynamic destabilization** of the person as a complex system far from equilibrium (↑ variability)
- Effects depend on **sensitivity to initial conditions**
- If remedy therapeutic, system restabilizes into a new & healthier dynamic pattern
- If remedy not therapeutic, system returns to previous dysfunctional dynamic pattern



(Hollenstein 2007)

What Is Needed?

- Methods to capture **<u>increased variability</u>** (**unstuckness**) early in homeopathic treatment before the development of persistent change, cf., psychotherapy:



(Hayes et al 2007 – nonlinear change during treatment)

- **Conclusion**: We need better ways both to choose remedies AND to assess treatment effects

Qualitative Findings

- Patterns of homeopathic remedy responses in exceptional responders reveal nonlinear, often sudden, discontinuous changes (cf. psychotherapy research – Hayes et al; Tang et al)
  - Stuckness (Sherr 2002) – fixed verb of the case, repeated pattern on every level
  - Unstuckness (Bell et al. 2003; Koithan et al 2007) – disruption of "ruts"
  - Aggravations (Vithoulkas 1980): worsening prior to improvement
- Homeopathic treatment responses involve persistent multi-dimensional person-wide changes rather than just resolution of chief complaint
  - Transformations (Vithoulkas 1980; Oberbaum et al 2005): qualitative multidimensional shift in whole person
- Such findings point to the need for modified designs and innovative measures for outcome studies

Nonlinear Dynamics of Business Teams with Low and High Productivity (Phase Space Plots of Interpersonal Behaviors) *(Losada et al 1999)*

Low-Functioning Pattern

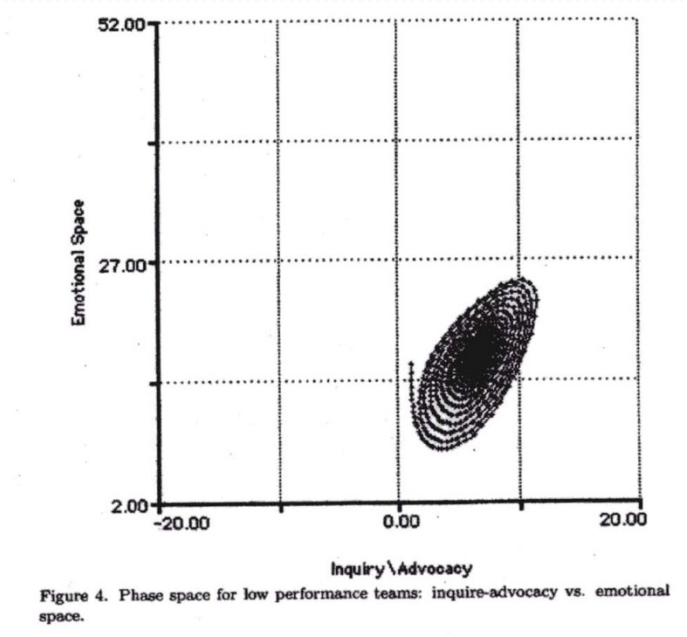


Figure 4. Phase space for low performance teams: inquire-advocacy vs. emotional space.

Excessive Order

High-Functioning Pattern

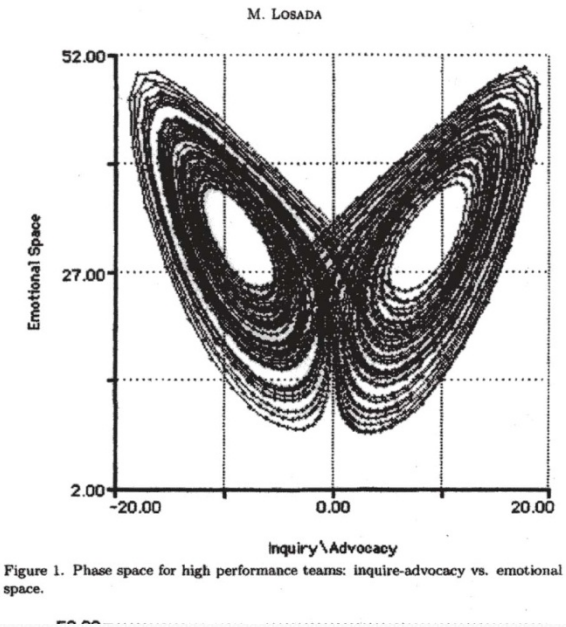
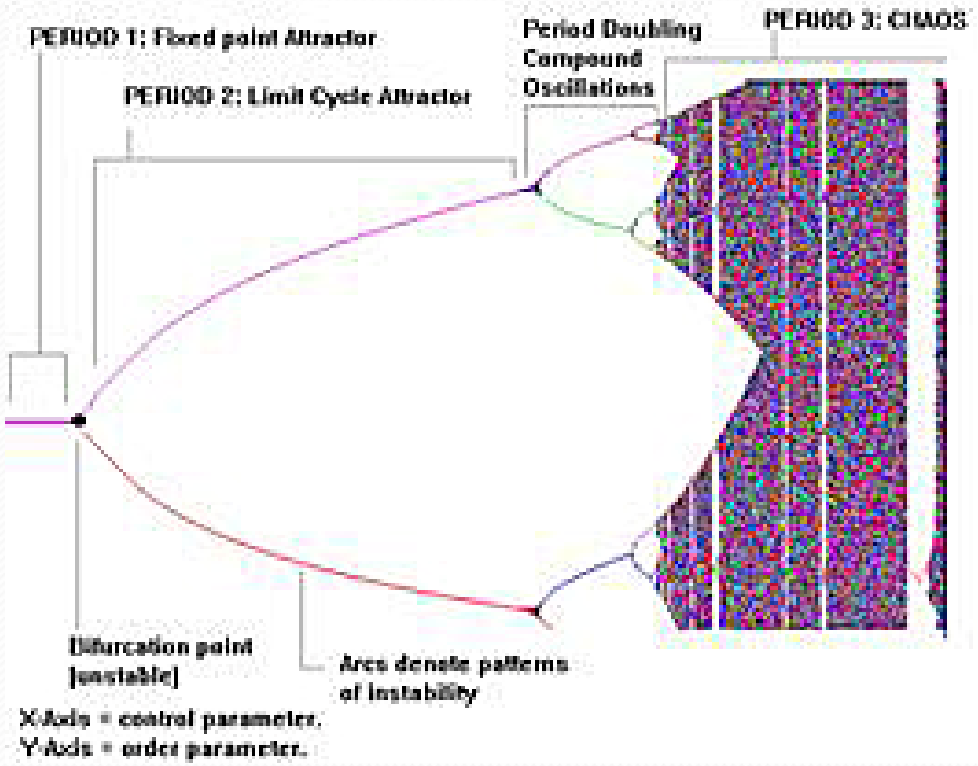


Figure 1. Phase space for high performance teams: inquire-advocacy vs. emotional space.

Balanced Adaptive Complexity

Dynamics of Bifurcation

(http://www.societyforchaostheory.org/tutorials/)



Excessive Order ⟶ Chaos

Flourishers With Losada's High Positive to Negative Affect Ratio Group (>2.9) Represent Only 15% of "Healthy" Young Adults *(Bell et al. 2007)*

- 15% of over 4,400 young adult college students had ratio of positive to negative affect greater than 2.9 (Losada line cut-off for flourishing human dynamics)
- Approximately 85% of the sample had suboptimal P:N ratio (< 2.9), in the "normal" to "languishing" range (see also Keyes 2002)

- Conclusion: Data consistent with homeopathic claims that general population's overall health and well being is not optimal

Resilience, Global Health, and Ratio of Positive To Negative Affect (P:N) Each Contribute to Variance in AIOS Scale Well Being Ratings *(Menk Otto et al 2010)*

Table 2.

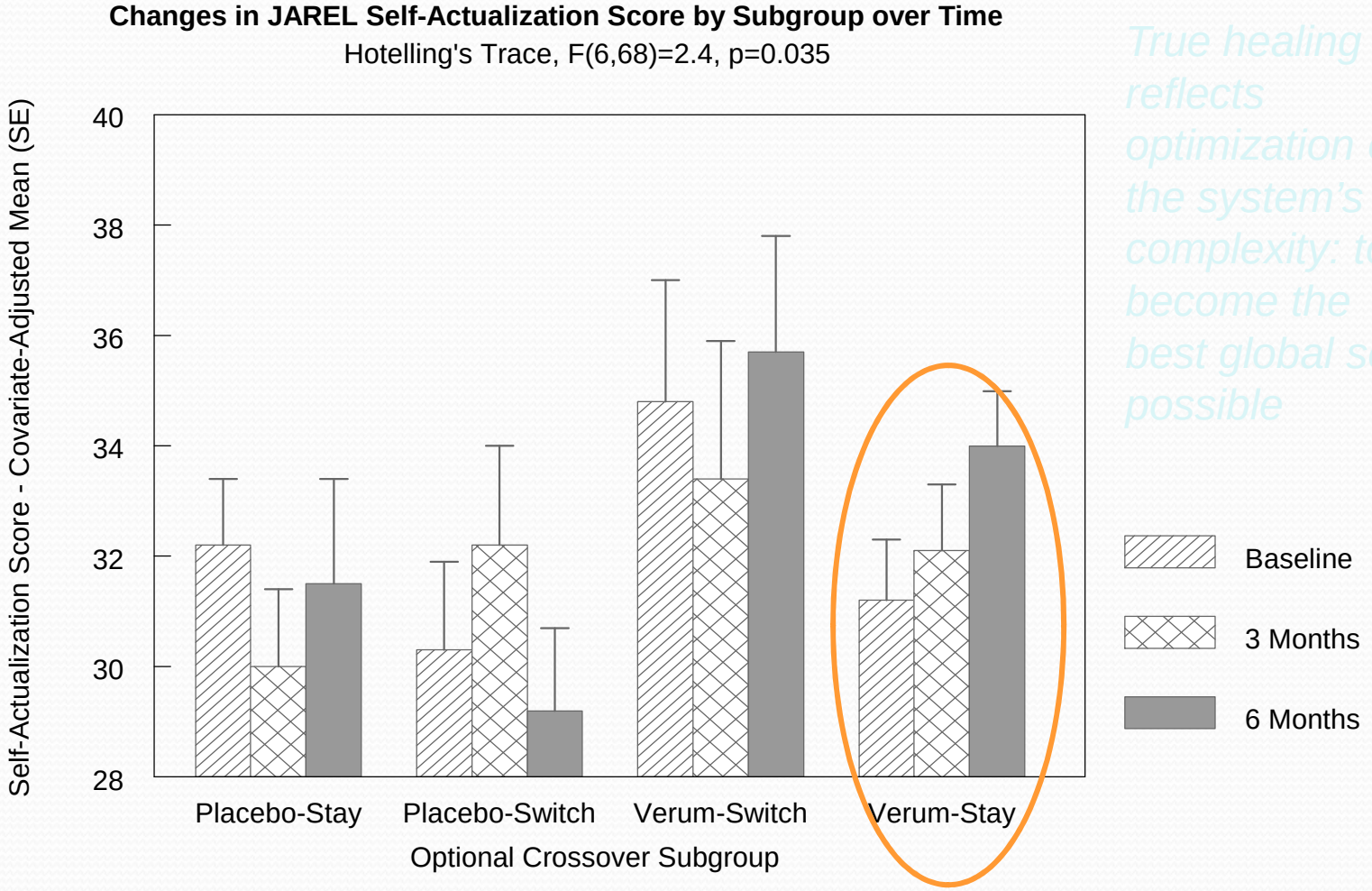
Regression Findings Predicting AIOS ratings

	β	Std. Error	t	R^2
Model with separate affect				
Constant	31.92	8.694		
Age	-.41	.42	-.96	.000
Sex	1.62	1.16	1.40	.008
MCSD	.396	.22	1.85	.050
PANAS Negative Affect	-.78	.09	-8.63**	.082
PANAS Positive Affect	.51	.07	7.22**	.129
GPH	4.82	.65	7.45**	.061
Resilience	.24	.05	5.21**	.023
Model with affect ratio				
Constant	21.24	8.61		
Age	-.54	.43	-1.27	.000
Sex	1.32	1.17	1.13	.008
MCSD	.36	.22	1.63	.050
P:N	7.14	.79	9.10**	.189
GPH	4.79	.65	7.36**	.063
Resilience	.27	.05	5.73**	.028

*P<0.05, **P<0.001.

AIOS= Arizona Integrative Outcomes Scale; MCSD = Marlowe Crowne Social Desirability; GPH= Global Physical Health; P:N = Positive to Negative Affect ratio.

Homeopathic Treatment Can Trigger Progressive Whole-Person Level Change on an Individual Self-Actualization Scale *(Bell et al. JACM 2004)*



True healing reflects optimization of the system's complexity: to become the best global self possible

Complexity of the Self-Report Response Pattern Over 90 Days *(Woyshville et al 1999)*

- Self report state 1-item visual analogue scales (VAS) recorded daily and/or multiple times per day to generate time series
- Compute nonlinear parameters (e.g., fractal dimension)
- Finding: patients have less complexity in mood variations than do normals, even though raw mood values appear to fluctuate more extremely in patients

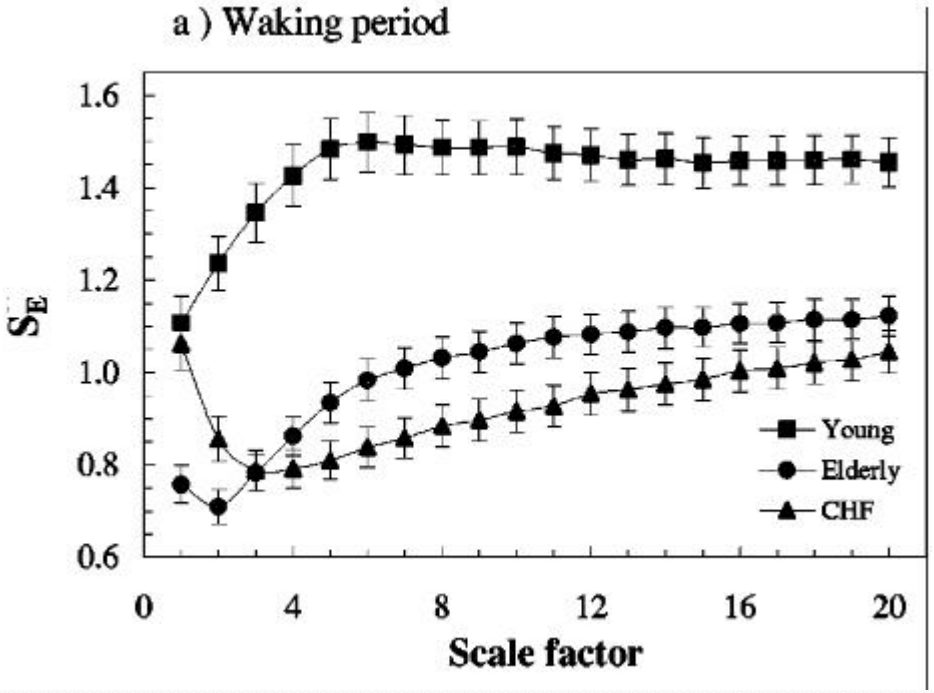
Table 3. Measures on the Time Series Data (MSSD and FD), and PSD (Raw Total Power and Percent Power)

	MSSD[a]	FD[a]	Raw total power[a]	Percent power[a]
Patients[b]	232.62 ± 190.70	1.359 ± 0.116	7878.67 ± 6237.71	1.54 ± 0.975
Controls[c]	123.27 ± 96.77	1.455 ± 0.166	3504.33 ± 2573.39	1.54 ± 0.533
p value	<.001[d]	<.001[d]	<.001[d]	.02[e]

[a]Mean ± SD.
[b]Patient $n = 108$.
[c]Control $n = 81$.
[d]Mann–Whitney rank sum test.
[e]Wilcoxon signed rank test.

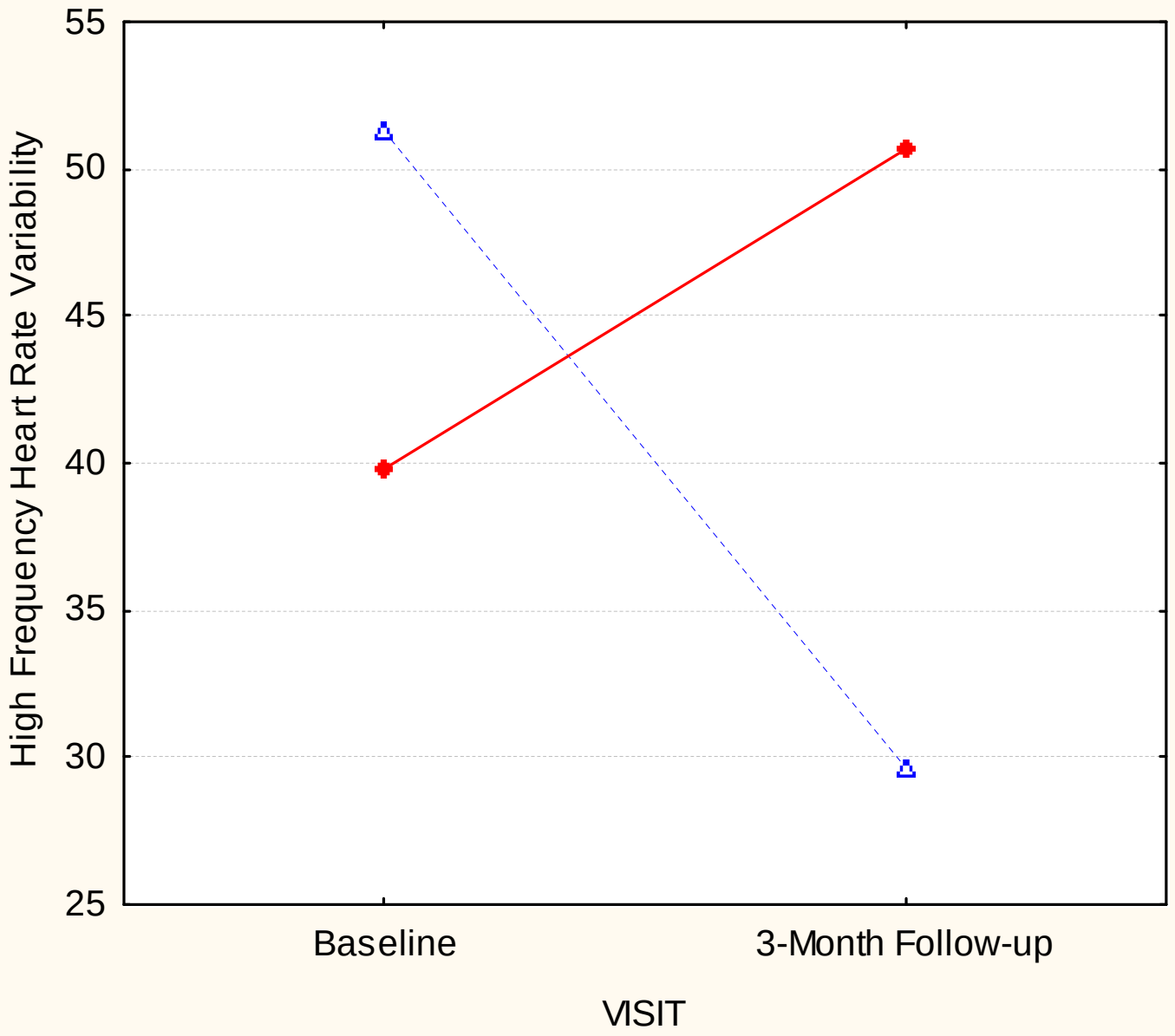
Loss of Physiological Complexity with Aging & Disease *(Costa et al 2005)*

- Multiscale entropy computation for heart rate variability of healthy young, healthy elderly, congestive heart failure patients



Improved Orthostatic High Frequency HR Variability during Individualized Homeopathic Treatment in Fibromyalgia *(Bell et al. 2006)*

(Averaged over Supine to Standing Values: F(1, 21)=5.5490, p=.02829)



ΔHRV was uncorrelated with ΔLocal Tender Point Pain (r=-0.01, ns)

ΔHRV did correlate with ΔGlobal Health (r=0.49, p=0.01)

Short-Term Effects of Homeopathic Remedy (Coffea Cruda 30c) on Multiscale Entropy of Sleep EEG in Young Adults *(Bell et al, submitted 2010)*

Table 1a. Regression Findings for Within-Subject Analyses on Multiscale Entropy for Subjects Receiving COFFEA CRUDA.

	Stage 3				Stage 4			
	REM Cycle 1		REM Cycle 2		REM Cycle 1		REM Cycle 2	
Electrode Site	Remedy Night	Post-Remedy Change	Remedy Night	Post-Remedy Change	Remedy Night	Post-Remedy Change	Remedy Night	Post-Remedy Change
C3	.54(.42)	-.52(.59)	.69(.44)	-1.3(.62)*	.55(.43)	-.11(.61)	.74(.4) †	-.97(.68)
C4	.47(.44)	-.42(.6)	.44(.46)	-1.4(.53)*	.89(.38)*	-.74(.54)	.87(.32)**	-1.7(.62)**
CZ	.98(.35)**	-1(.49)*	.69(.49)	-1.5(.51)**	.67(.39) †	-.49(.52)	.95(.38)*	-1.5(.62)*
PZ	.57(.4)	-.33(.56)	1.1(.46)*	-1.8(.55)**	.83(.42)*	-.66(.56)	.8(.41)*	-1.4(.59)*
O1	.63(.42)	-.53(.61)	.72(.52)	-1.2(.66) †	.03(.44)	.41(.51)	.9(.25)***	-1.1(.53)*
O2	.61(.4)	-.43(.65)	.97(.46)*	-1.4(.54)*	.84(.35)*	-.55(.5)	.79(.31)*	-1.6(.63)*

†P<0.10, *P<0.05, **P<0.01, ***P<0.001.

Reported effects are unstandardized beta coefficients and standard error for each of the two REM cycles of remedy night (night 22) and the change from night 22 to post-remedy night 23, after controlling for personality, baseline nights, placebo night, and change from placebo to post-placebo night.

Short-Term Effects of Homeopathic Remedy (Nux Vomica 30c) on Multiscale Entropy of Sleep EEG in Young Adults *(Bell et al, submitted 2010)*

Table 2a. Regression Findings for Within-Subject Analyses on Multiscale Entropy for Subjects Receiving NUX VOMICA.

	Stage 3				Stage 4			
	REM Cycle 1		REM Cycle 2		REM Cycle 1		REM Cycle 2	
Electrode Site	Remedy Night	Post-Remedy Change	Remedy Night	Post-Remedy Change	Remedy Night	Post-Remedy Change	Remedy Night	Post-Remedy Change
C3	-.32(.28)	.51(.54)	-.56(.41)	1.28(.55)*	-.29(.36)	.15(.38)	-.11(.52)	-.18(.69)
C4	-.54(.27)*	.24(.36)	-.98(.42)*	.85(.66)	-.71(.34)*	.56(.43)	-.32(.52)	-.24(.45)
CZ	-.16(.2)	-.21(.24)	-1.1(.37)**	1.3(.54)*	-.34(.3)	.02(.33)	-.63(.43)	-.06(.59)
PZ	-.31(.24)	.19(.39)	-.74(.45)	1.3(.56)*	-.41(.36)	.06(.39)	-.54(.67)	-.17(.64)
O1	-.09(.41)	.19(.57)	-.9(.45)*	1.4(.53)**	-.58(.42)	.21(.46)	-.43(.68)	.29(.6)
O2	-.22(.31)	.34(.65)	-0.4(.37)	.31(.55)	-.38(.39)	.08(.47)	-.25(.49)	-.07(.43)

†P<0.10, *P<0.05, **P<0.01, ***P<0.001.

Reported effects are unstandardized beta coefficients and standard error for each of the two REM cycles of remedy night (night 22) and the change from night 22 to post-remedy night 23, after controlling for personality, baseline nights, placebo night, and change from placebo to post-placebo night.

Clinical Significance of Patterns of Change: Responders With Early Sudden Gains Subsequently Relapse Much Less than Responders Without Sudden Gains in Psychotherapy

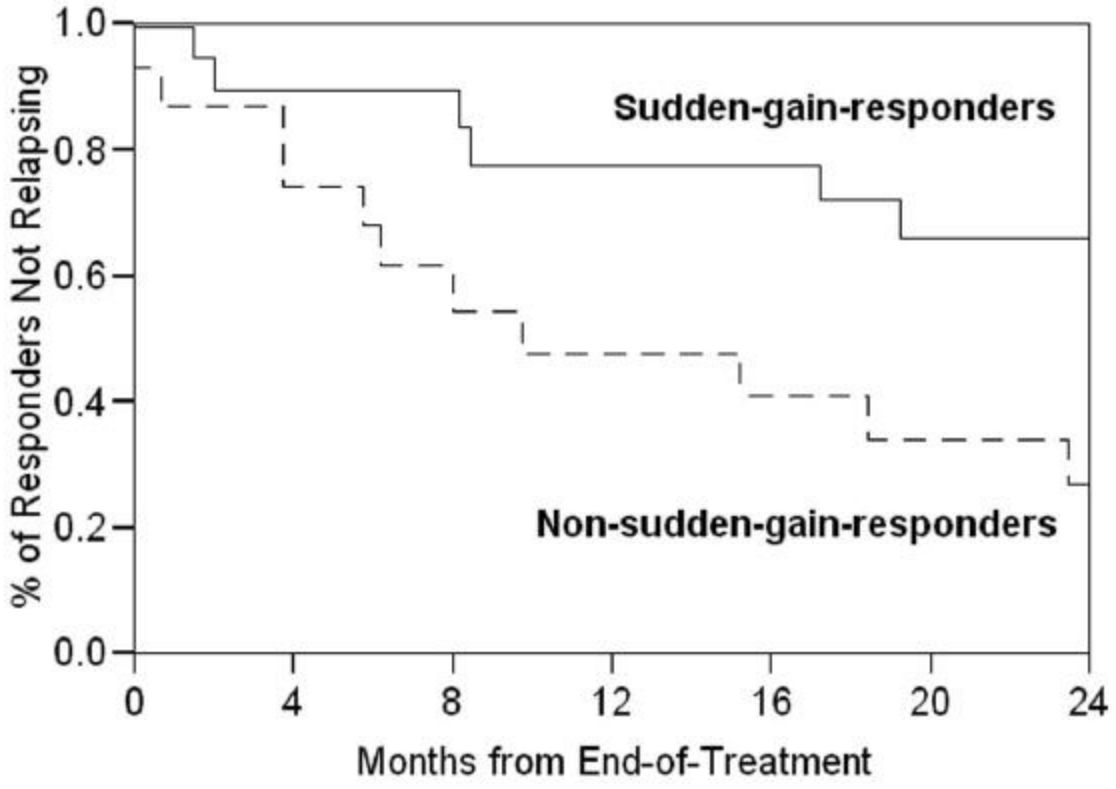
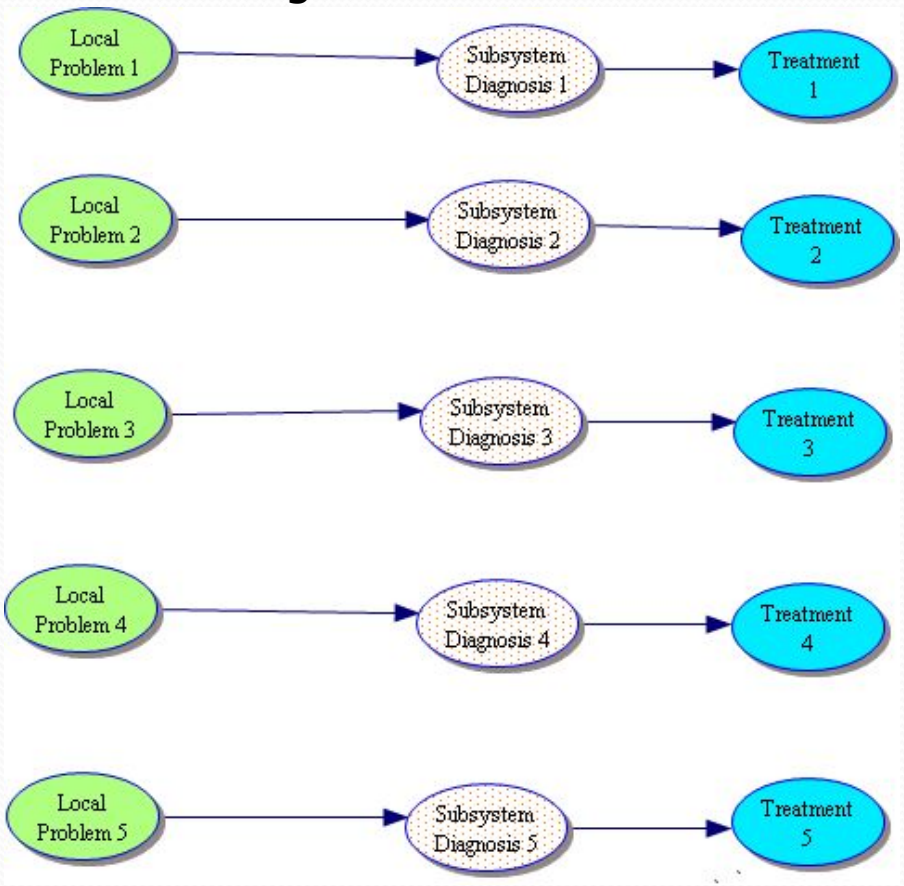


Figure 1. The CT responders who experienced sudden gains during treatment were much less likely to have depression relapse/recurrence than were the CT responders who did not experience sudden gains.

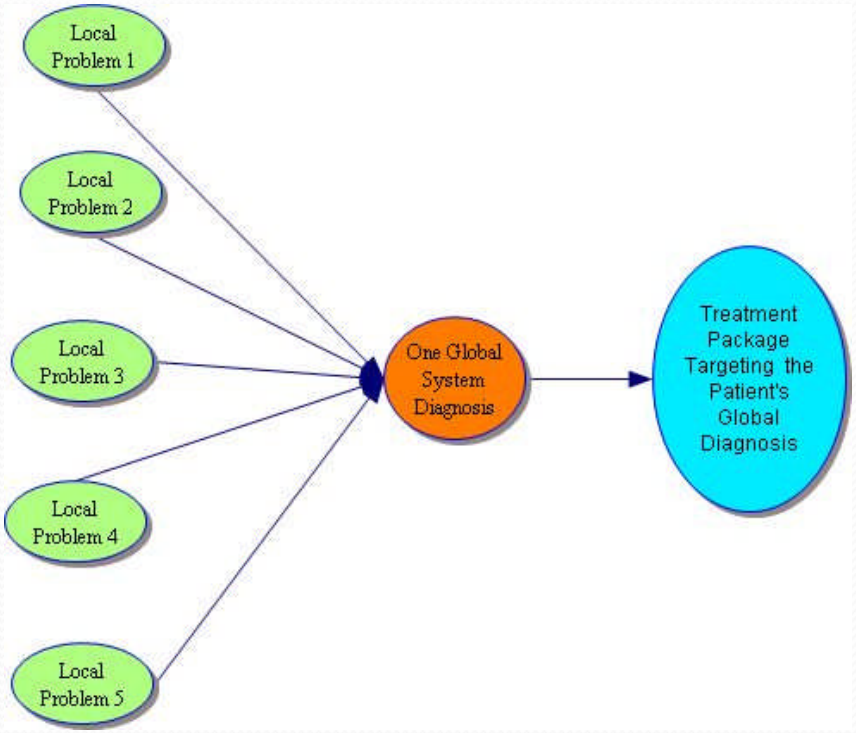
(Tang et al 2007)

Western Medical versus Homeopathic System: Local versus Global Diagnosis and Treatment

Western Medical Approach to Drugs or CAM Modalities



Individualized Homeopathic Approach to Multimodal Treatment



Real World Challenge: It Is Difficult For Homeopaths To Find the Right Remedy

- Frei et al (2007) study of individualized homeopathy in children with Attention Deficit-Hyperactivity Disorder
  - Open label pre-testing for individualized remedy required a median time of **5 months (range 1-18) and a median of 3 different medications (range 1-9)**
  - Most RCT-type clinical trials only run each patient for 3-4 months and require the same treatment throughout the trial
- **<u>Implication</u>: Verum groups in some clinical trials will have a lot of placebo-equivalent "verums" for individual patients, thus reducing treatment effect size**
  - Parallels: acupuncture research is plagued by active "shams" whereas homeopathy research is plagued by inactive "verums"

Possible Strategies

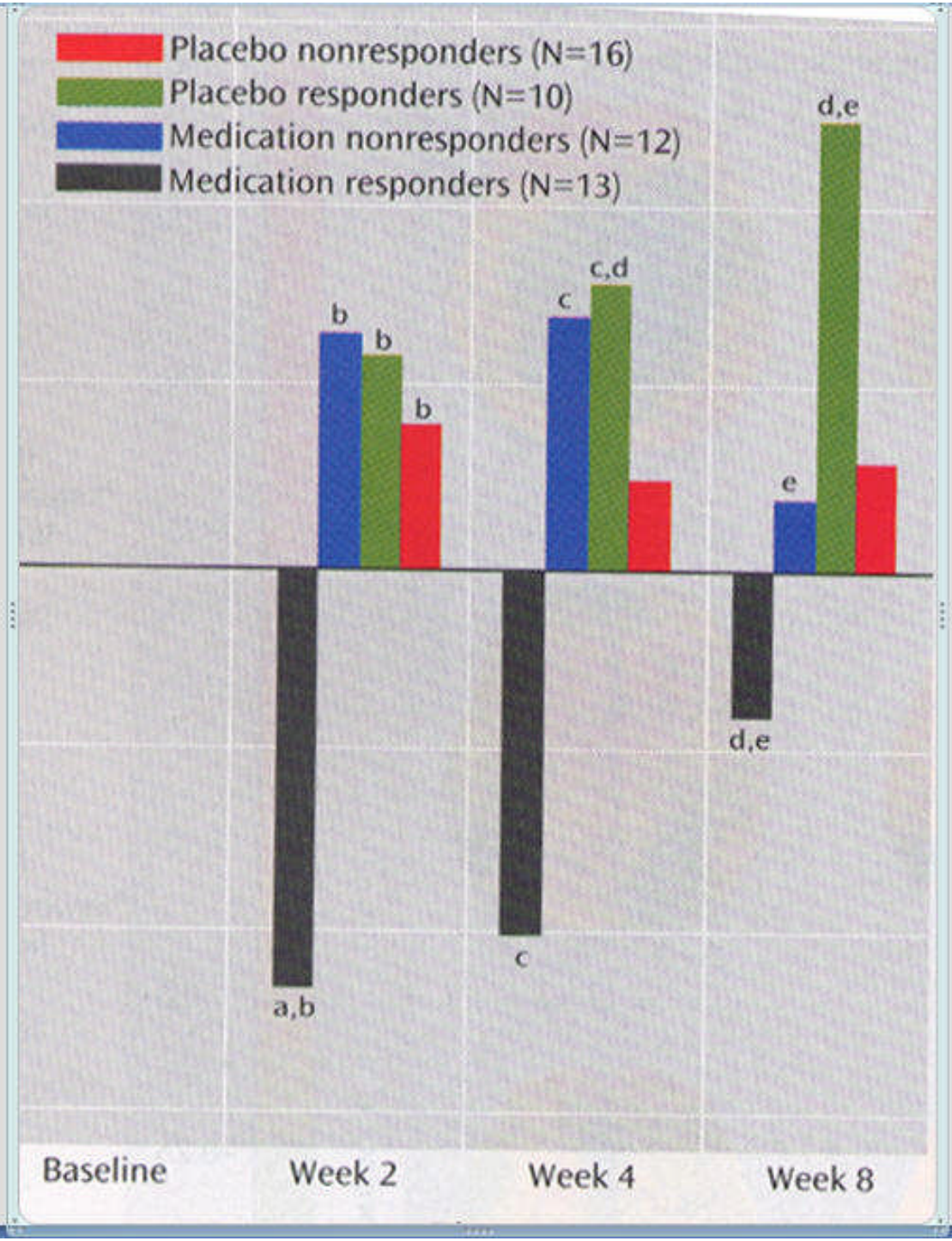
- Improve clinical diagnostic procedures to select remedy
  - e.g., Frei et al (2006) – polarity analysis of the case
- Improve capacity to identify potential responders early
  - Use validated, quantitative rating scales for assessment of baseline individual traits, states & outcomes, by both patient and provider
  - Evaluate patient comprehensively rather than on basis of chief complaint alone, given homeopathic practice theory's predictions of evolving multi-system local and emergent global changes in the patient as a whole
  - Adapt objective outcome state measures that can assess real time changes in repeated measure, time series datasets (behavioral and physiological variables)

EEG Cordance as Biomarker of Brain Function (Cook et al 2002; Leuchter et al 2002)

- Cordance derives from an algorithm that evaluates relative and absolute EEG in a given frequency band normalized at a specific electrode site compared with neighboring sites
- Previous studies showed that cordance values correlate with SPECT and PET findings for brain metabolic activity in specific regions
- The direction of EEG theta cordance changes early in treatment distinguishes verum responders from placebo responders in antidepressant research

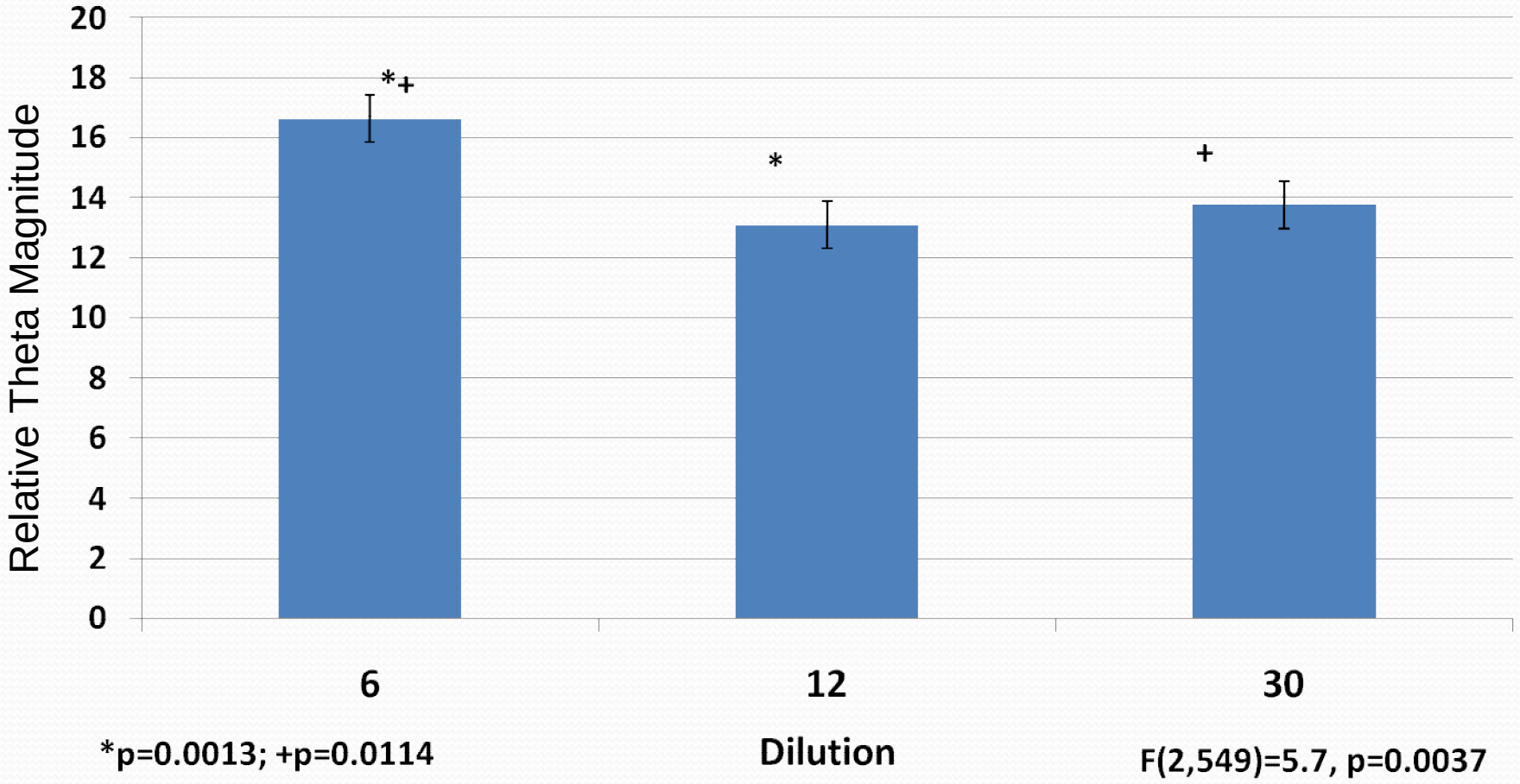
Changes in qEEG Theta Cordance from Baseline over 8 Weeks in Prefrontal Region of Responders and Non-Responders to Antidepressant Medication & to Placebo

(Leuchter et al Am J Psychiatry 2002)

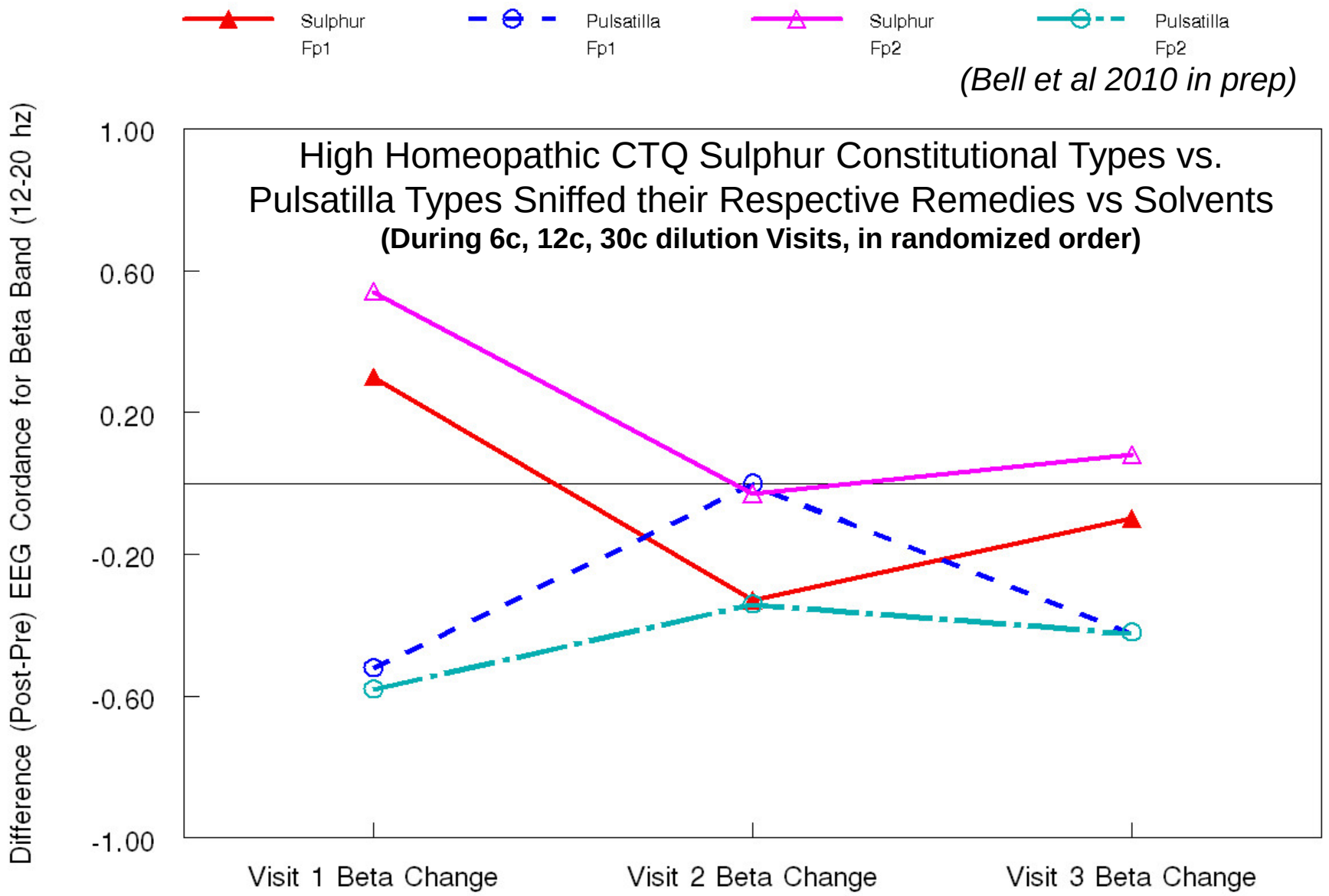


Relative EEG Theta (4-8 hertz) – Main Effect for Remedy Dilution Tested in Visit 1 (Bell et al 2010 in preparation)

*(Main Effect: **F(2,549)=5.7, p=0.0037)***



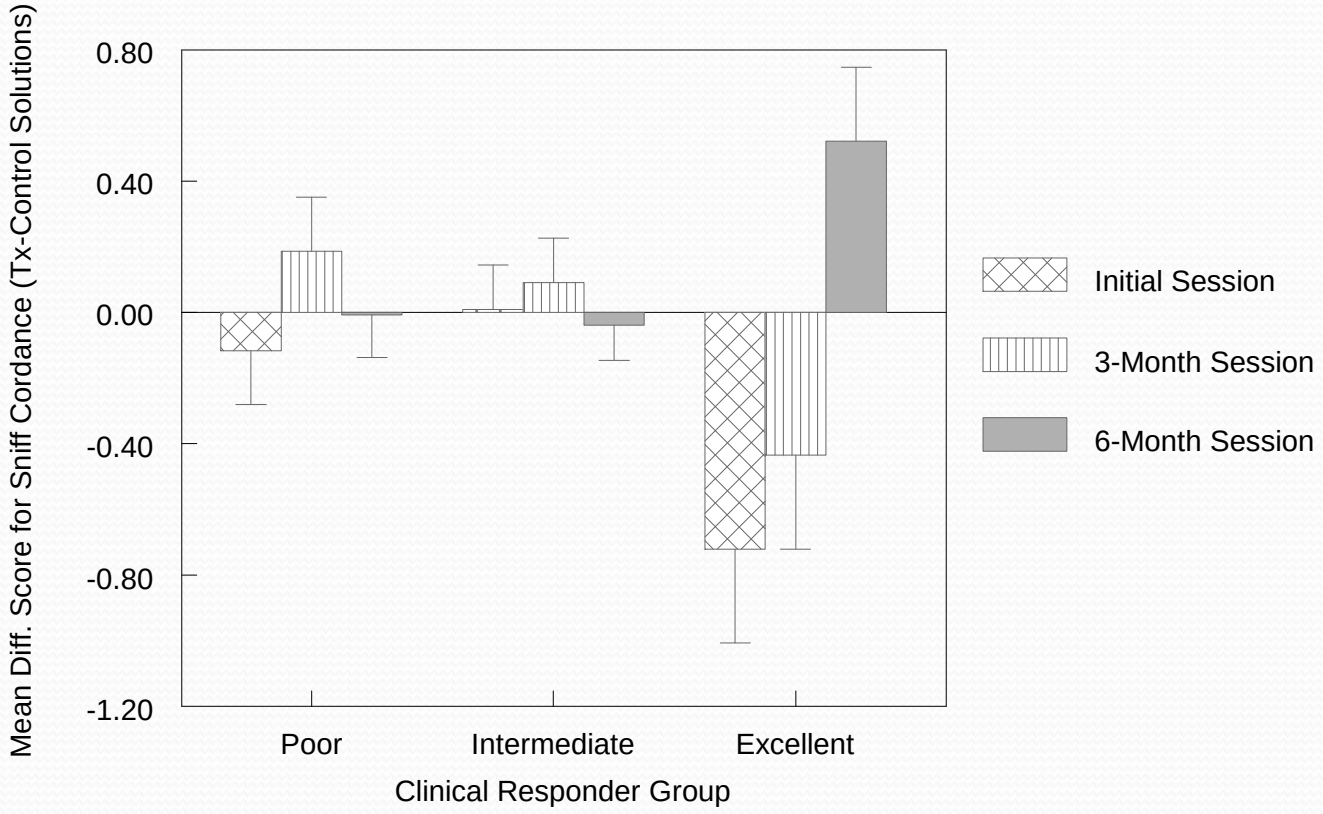
Sulphur & Pulsatilla Alter qEEG Beta Cordance Differently Over Visits



(Bell et al 2010 in prep)

Visit x Remedy Interaction: $F(2,443)=7.24$, $p=0.008$, controlled for gender, chemical sensitivity, dilution

qEEG Alpha Prefrontal Cordance on Initial Individualized Remedy Administration Distinguishes Subsequent Clinical Responders From Non-Responders With Fibromyalgia (Finding Also Changes With Time in Treatment)



(Bell et al 2004; Bell & Koithan 2006)

Implications of EEG Cordance Findings

- Homeopathic remedies appear to exert differential effects on EEG cordance (implying effects on brain metabolic activity)
  - Specific remedy
  - Specific individual receiving the remedy
- Note interaction patterns over time, not always just main effects
- Future Directions: Replicate and extend to functional brain imaging studies with fMRI, SPECT, PET

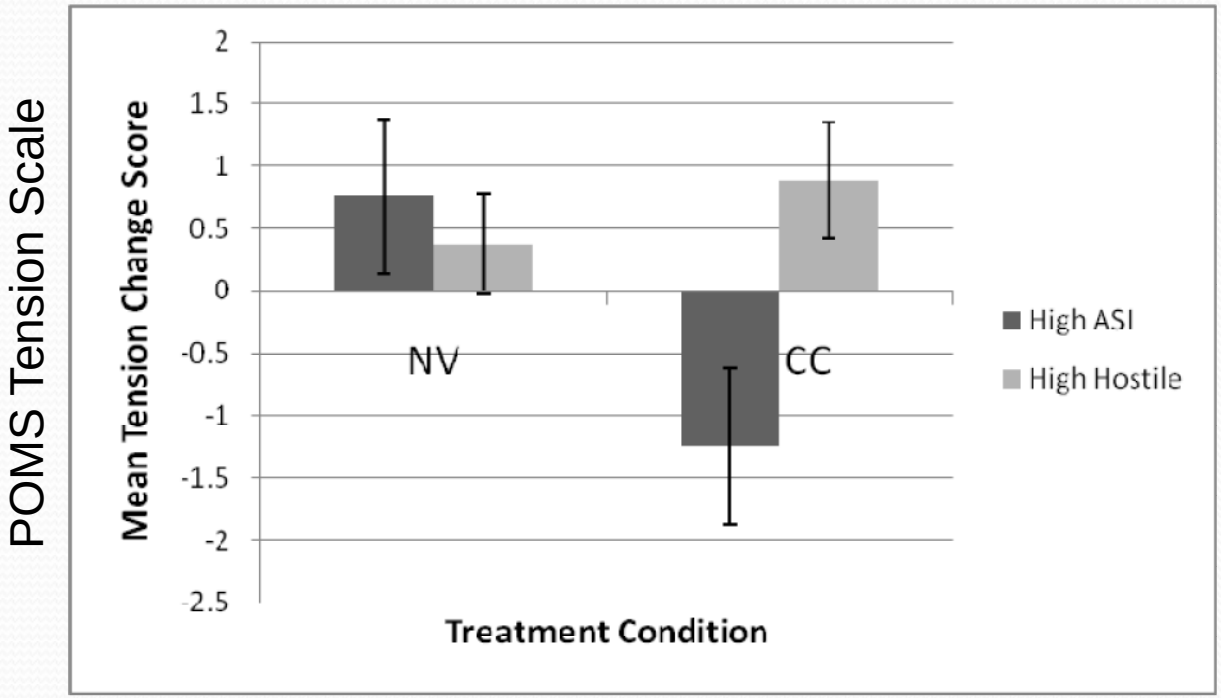
Individual Difference Traits

- **Chemical sensitivity** (Sherr 1994): High chemical sensitivity suggests universal provers with heightened general sensitivity reactivity to any remedy administered)
  - Bell Chemical Intolerance Index (Szarek et al 1997)
- **Absorption/Openness to Experience** (Honda & Jacobson 2005: Persons High in Openness Use Homeopathy, Acupuncture, and Energy Medicine modalities more than Persons Low in Openness)
  - NEO Personality Inventory Revised (Costa & McCrae 1995)
- **Resilience** (Vithoulkas (1980): Freedom from pain, passion, and selfishness, to recover from effects of stressors & challenges is an indicator of health at each level of system organization)
  - Connor-Davidson Resilience Scale (Connor & Davidson 2003)

Translating Concepts to Methods

- Baseline Individual Difference Traits
  - Chemical Intolerance Index, Connor-Davidson Resilience Scale, NEO 5-Factor Personality Inventory
- Use validated state scales assessed frequently to generate time series of self report data
  - Condition-Specific Scales
  - MYMOP – individualized symptoms
  - Global Health – overall physical health (5-point Likert)
  - AIOS – global well-being visual analogue scale
  - PANAS – ratio of positive to negative mood state (marker of flourishing, resilience)
  - JAREL Self Actualization – becoming the best "self" possible

External Validity: As In Clinical Practice, Who Gets the Remedy Interacts With the Specific Remedy Given (Brooks et al 2009)

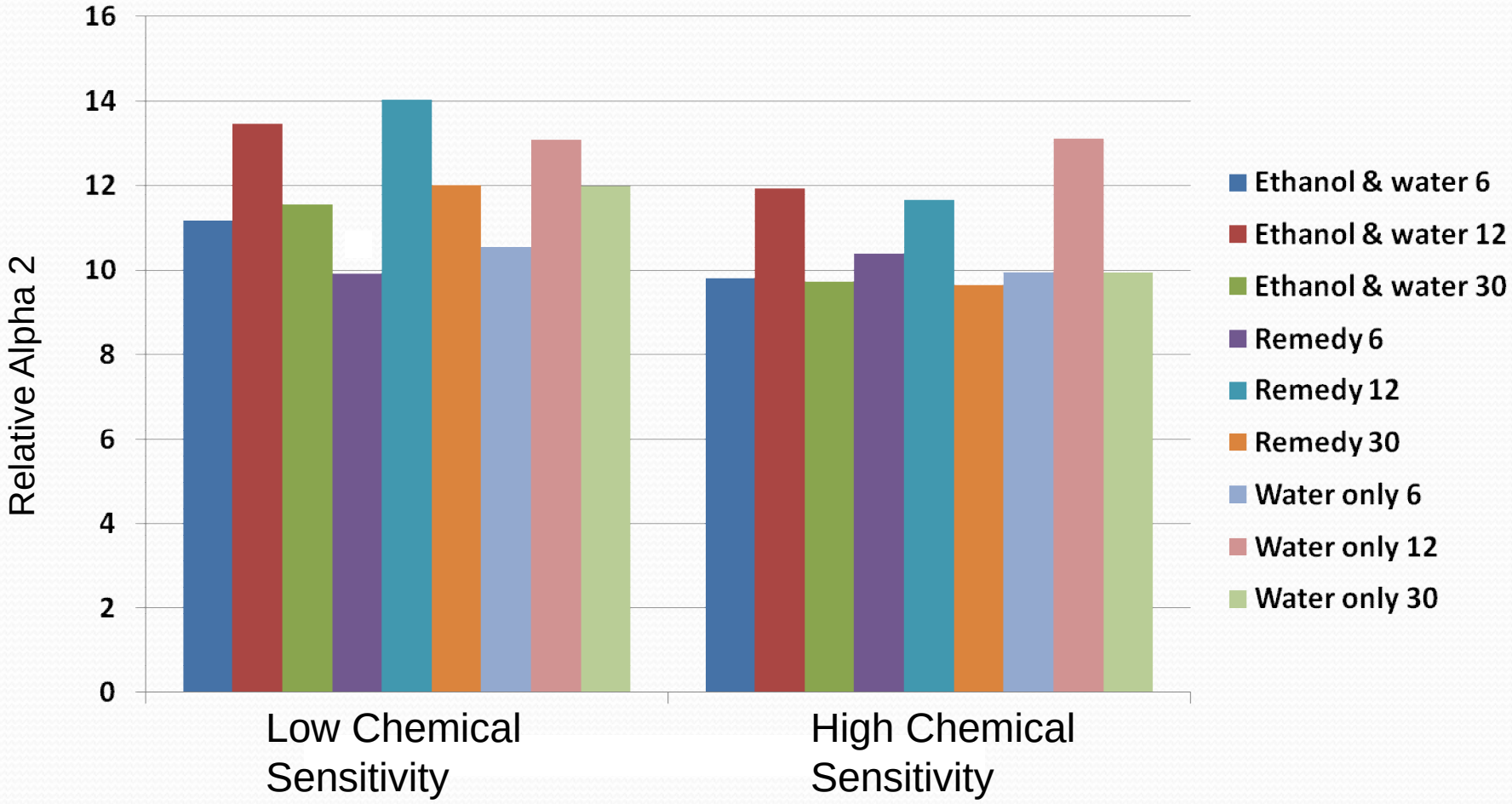


NV=Nux Vomica; CC=Coffea Cruda;
ASI=high Anxiety Sensitivity Index; Hostile=high Cook Medley Hostility

Openness Personality Trait Predicts Complementary & Alternative Medicine Use (N=3,032) *(Honda & Jacobson 2005)*

	Alternative Medical Systems	Energy Therapies	Any CAM
Agreeableness	1.69	2.41	1.06
Neuroticism	1.30	0.79	0.88
Openness	*3.55 (1.33-9.44)**	*15.77 (2.86-86.87)***	*1.65 (1.18-2.31)***
Extraversion	0.85	0.96	*0.65 (0.46-0.91)**
Conscientiousness	0.90	1.64	0.94

Interaction of [Contents by Dilution by Chemical Intolerance] for Relative EEG Alpha 2 (10-12 hertz) Magnitude During Sniffs (3-way interaction: **F(4,549)=2.47; p=0.0436)**



(Bell et al 2010 in preparation)

All between CS group comparisons Not Significant

Individual Differences: Responders vs. Non-Responders

- Compare baseline traits and pre-treatment states of eventual remedy responders versus non-responders
  - Look for self report and objective measures that could predict treatment responders
  - Advantages:
    - Change homeopathic remedy choice or potency or pace of dosing based on **early** indications
    - Improve quality and effectiveness of clinical practice in homeopathy
    - Triage patients to other modalities or other homeopaths sooner if no benefit

"Specific" and "Non-Specific" Effects *(Bootzin & Bailey, J Clin Psychol 2005)*

- Specific effects: Effects of treatment that are predicted *by the theory* about how the treatment produces change
- Nonspecific effects: Effects that are not related to the causal pathways specified in the theory about how the treatment produces change. Nonspecific effects can refer to broad psychological effects of a treatment as well as contextual factors present in the delivery of treatment.
  - Common Factors: The factors in the delivery of treatment that are common to different therapeutic endeavors such as the patient-therapist relationship and expectations of receiving help. Common factors are a subset of nonspecific effects.
- **Homeopathy's "specific" effects are "non-specific" to allopaths because of being global and diffusely local across multiple subsystems, but these effects are specific & in accord with homeopathic practice theory**

Variability of Findings in Homeopathy Research Is A Big Clue to Indirect Causality & the Nonlinear Dynamical Nature of the Process: Linear Causality Does Not Apply

- "One of the powerful ways of probing the behavior of a complex system is observing how it responds to a force applied to it, especially the "indirect" effects that take place at different places or at other times than the force.
- This is a way of probing the direct and **indirect relationships of cause and effect**."

i.e., Push here, observe effects over there…

(Bar-Yam www.necsi.org, 2006)

Conclusions

- Who gets the remedy does matter
  - Baseline traits – Constitutional Type, Chemical Sensitivity, Personality traits (Openness To Experience)
  - Baseline biobehavioral states
  - Dynamical patterns emerging from age and disease
- Which remedy he/she receives does matter
  - Specific remedy interacts with who gets the remedy
- Physiological data from EEG and EKG (Heart Rate Variability) may provide sensitive biomarkers of remedy effects in sleep and waking (at rest and under stress)
- Nonlinear Dynamical Systems models are promising to explore the variable interactions of individual with remedy over time: global AND local changes

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