

# **Circular Instead of Hierarchical**

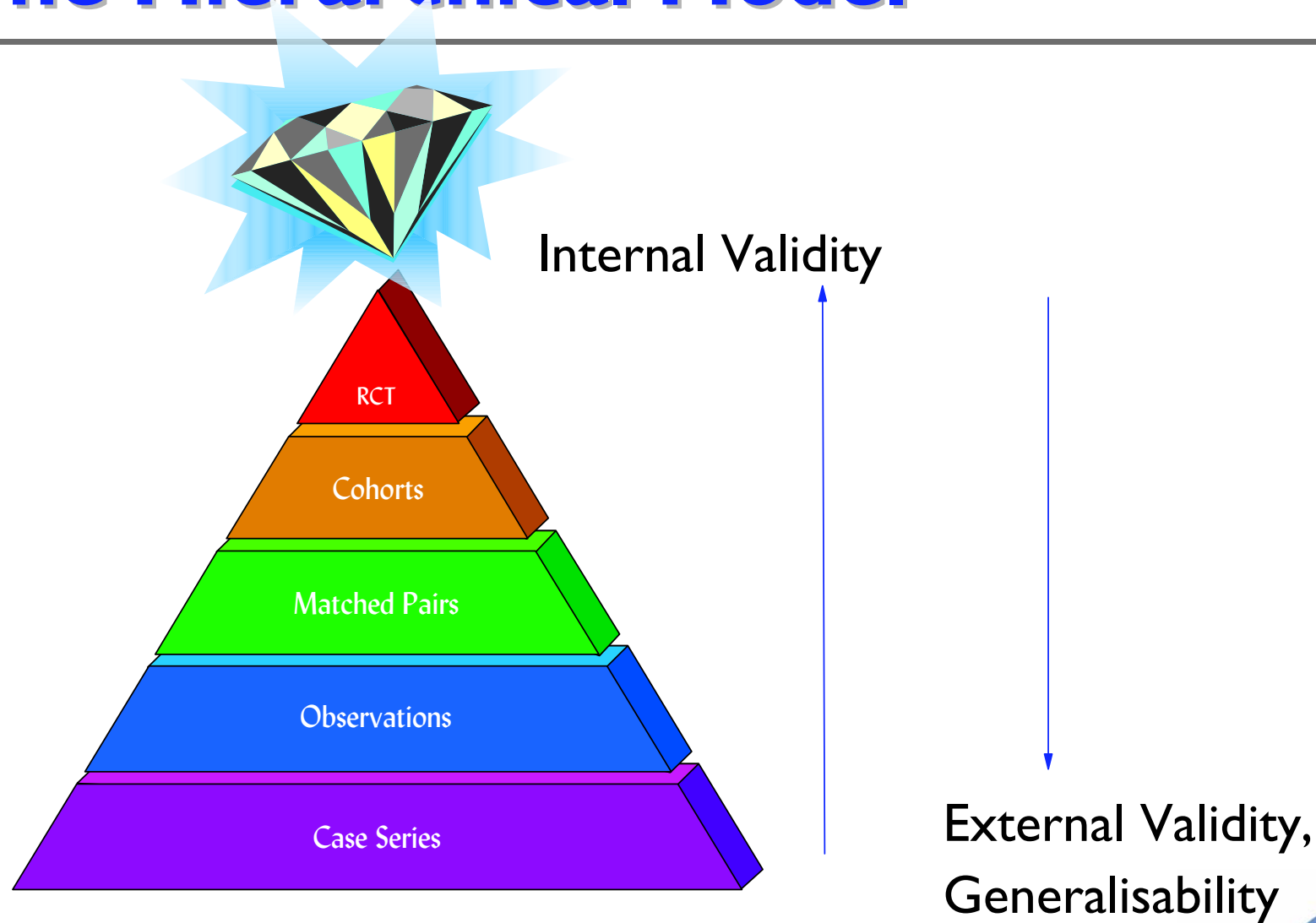
## **Challenges for Evaluating Complex Interventions**

**Harald Walach**



# The Hierarchical Model

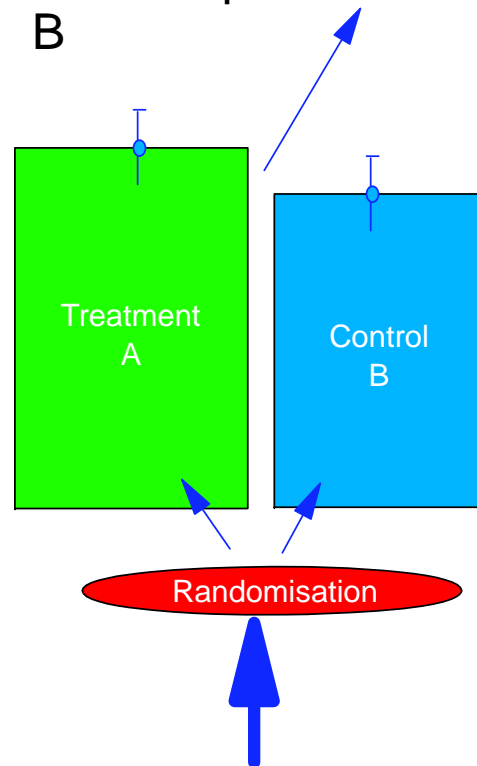
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# Received View: Randomised Controlled Trials are best because...

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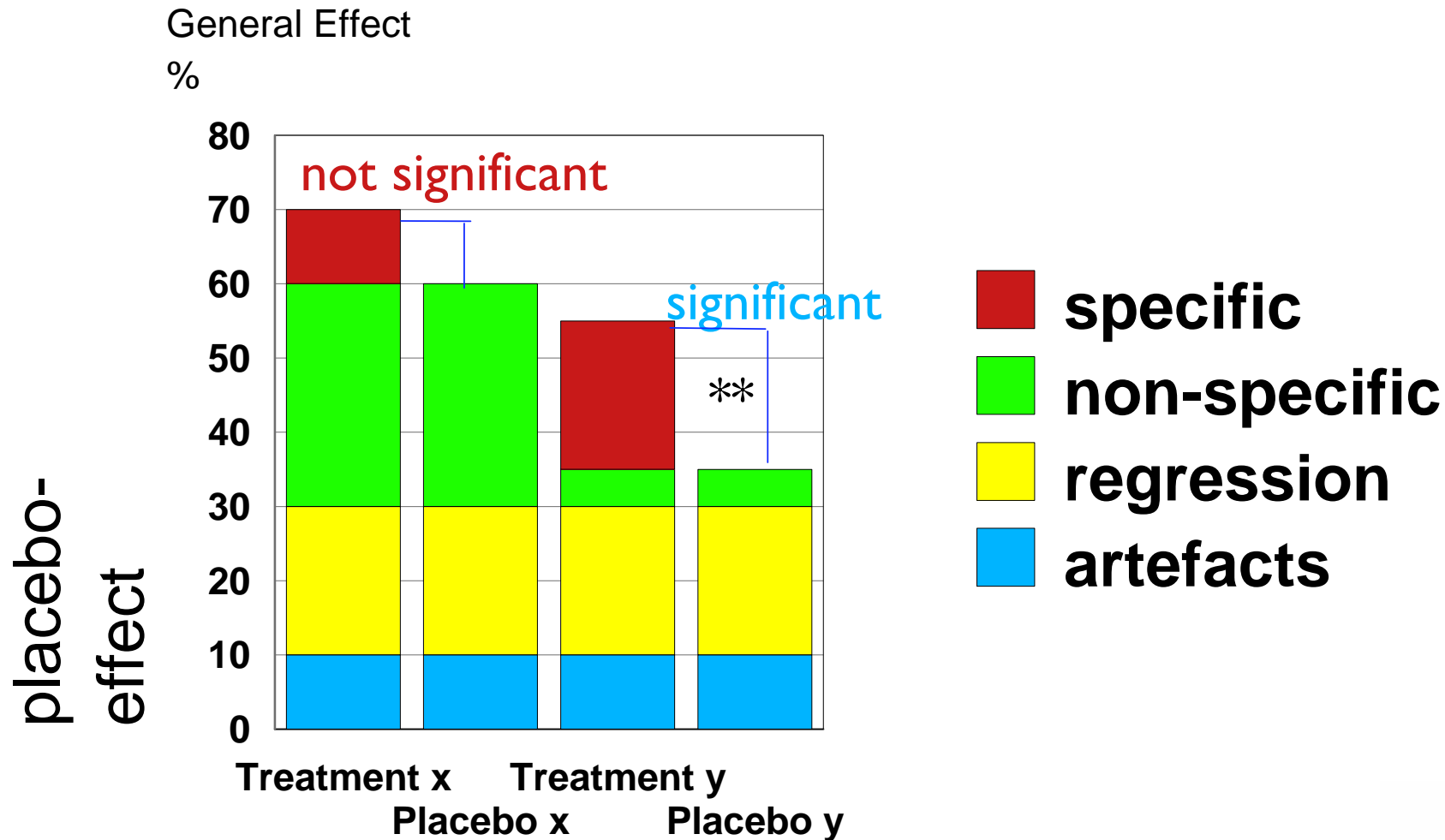
Information:  
mean improvement in A vs.  
B



- they eliminate bias
- control for unwanted confounders
- allow application of simple statistics
- make groups homogenous
- allow for causal inference

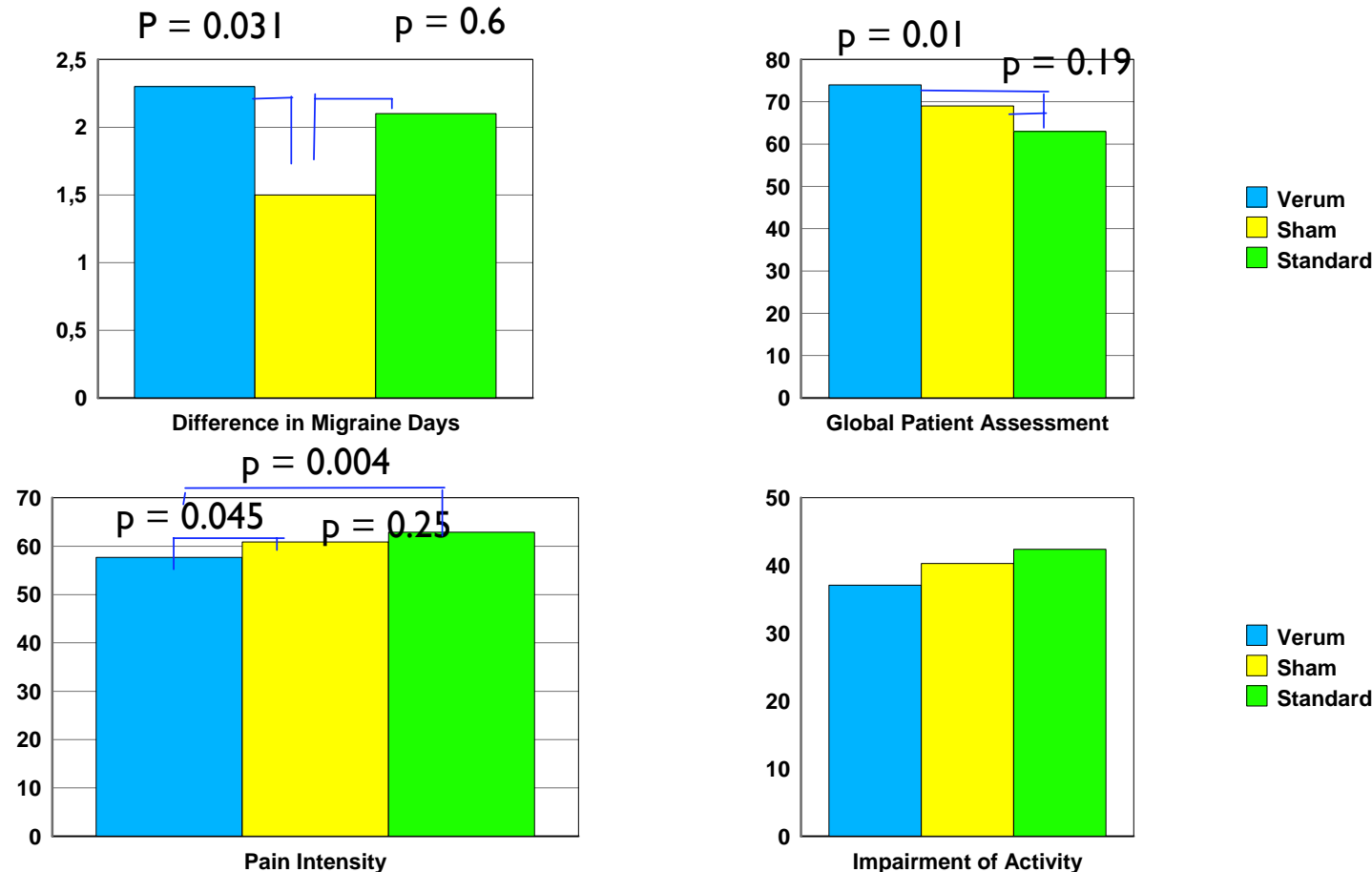
# Problem: Efficacy Paradox

Walach (2001) Forsch Komplementärmedizin 8:193



# The Efficacy Paradox Come True

Diener et al (2006) Lancet Neurology 5: 310



GERAC: RCT of Acupuncture vs. Sham vs. Standard Prophylaxis in Migraine  
n = 960; 26 weeks follow-up

# Peconditions of RCTs in general

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- Equipoise between treatment options
  - lack of knowledge
- Small effects anticipated that are not immediately obvious
- Lack of preference in providers and consumers
- **Normally met in new interventions**

# Peconditions of RCTs in general

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- Rarely met in CAM and other complex interventions
  - no equipoise
  - no lack of preference
  - often strong experiential knowledge

# Preconditions - Specific to Placebo Controlled Trials

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- Effects of therapies are additive and separable
- Specific effects are most important
- Non-specific effects are negligible
- Effects of context are unimportant
  - non-specific/placebo effects are constant

# Preconditions - Specific to Placebo Controlled Trials

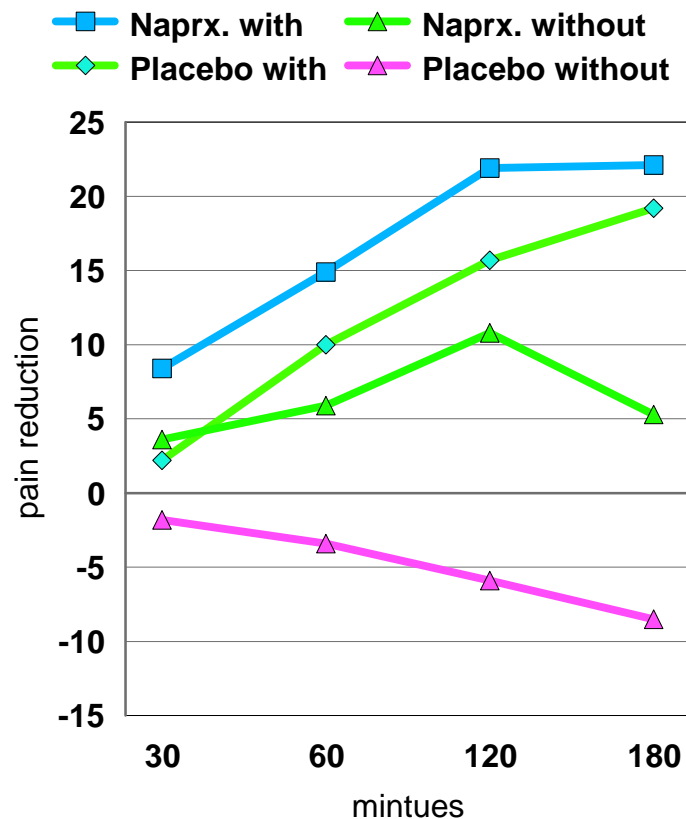
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## ■ Nearly all wrong:

- strong context effects
- non-specific effects are very important
- additivity not warranted
- non-specific effects not constant

# Context Dependence

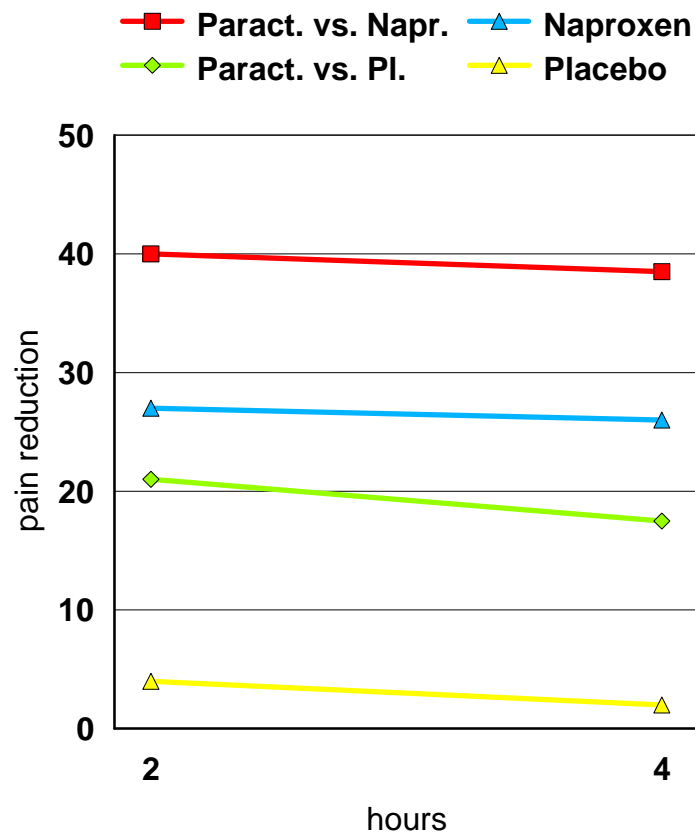
Bergmann et al. (1994) Clin Trial Meta-Anal 29:41



- 43 patients with cancer pain
- randomised to "consent" or none
- Naproxen or placebo
- VAS pain
- Placebo in RCT context better than Naproxen under normal conditions

# Expectation of Treatment I

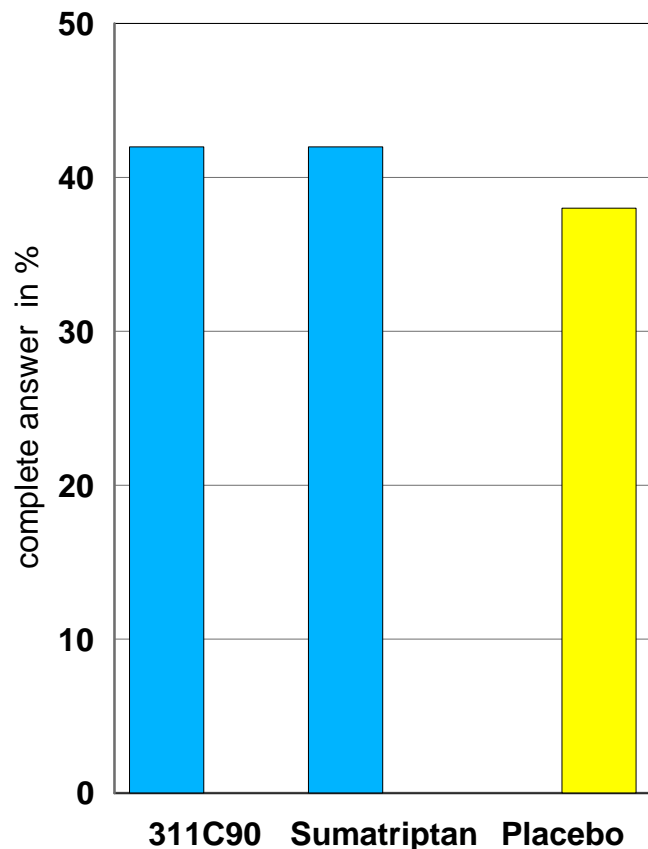
Skovlund et al. (1991) *Eur J Clin Pharmacol* 40: 343; 539



- 2 studies in women with post-partum pain
- Paracetamol vs. Placebo
- Paracetamol vs. Naproxen
- Reduction of pain much less if placebo is expected

# Expectation of Treatment 2

Diener et al (1999) Cephalalgia 19:699

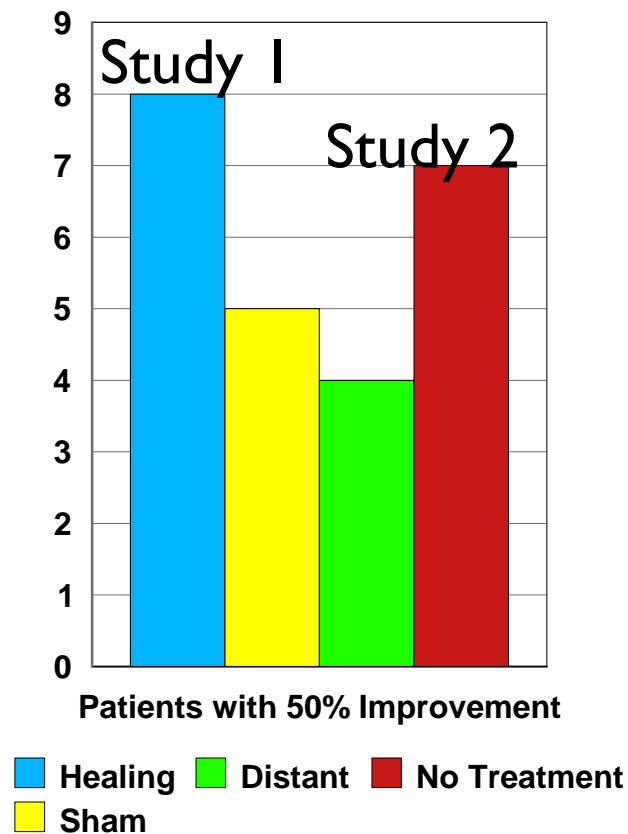


- Migraine therapy in attack
- Zolmitriptan vs. Sumatriptan vs. Placebo
- Randomisation in ratio 8:8:1
- $n = 491:492:56$
- "complete answer": reduction of pain/pain free after 2 hours
- no difference

Studies with **unequal** ratio of placebo and treatment show larger placebo-effects: **effect of expectation**

# Spiritual Healing in Chronic Pain

Abbot et al. 2001; Pain 91:79



- 2 studies 30:30 patients with chronic pain (n = 120)
- Healing or "sham", distant healing or none
- "no significant differences"
- But: rather big non-specific effects
  - significant improvement for **ALL** patients pre-post
  - more than 50% improvement
    - Total: 24 of 105

# Spiritual Healing in Chronic Pain - 2

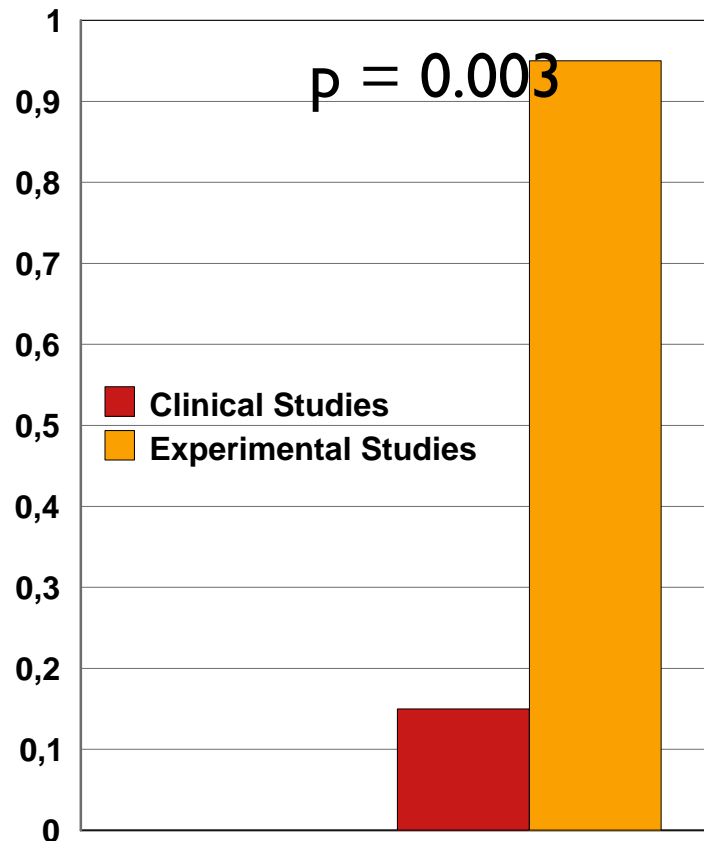
Walach et al. 2002, Pain 96:403

## Effect size pre-post per group and between groups

Measure	d pre-post healing	d pre-post sham	d between
PRIT	1,12	0,83	0,29
VAS	0,21	0,26	-0,05
SF36-bod.F	0,62	0,01	0,63
- role f.	0,05	0,23	-0,19
- pain	0,47	0,62	-0,15
HAD-anxiety	0,18	0,29	-0,12
HAD-depr.	0,29	0,58	-0,29
MYMOP	0,62	0,34	0,28

# Effects in Control Groups Different According to Context

Vase, Riley & Price (2002) Pain 99:443



Effect size of difference between placebo groups and natural course of disease control groups

- Meta-analysis of effects of placebo groups in
  - clinical pain studies (n = 23) compared with
  - experimental pain studies (n = 14)
  - vs. natural course

# Consequence

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- Non-specific effects of prime importance
  - Expectation, trust
  - Conditioning
  - Possibly other factors
- Isolated test for specific components"  
only marginally useful
- circular model
  - for all complex therapeutic interventions,  
including CAM

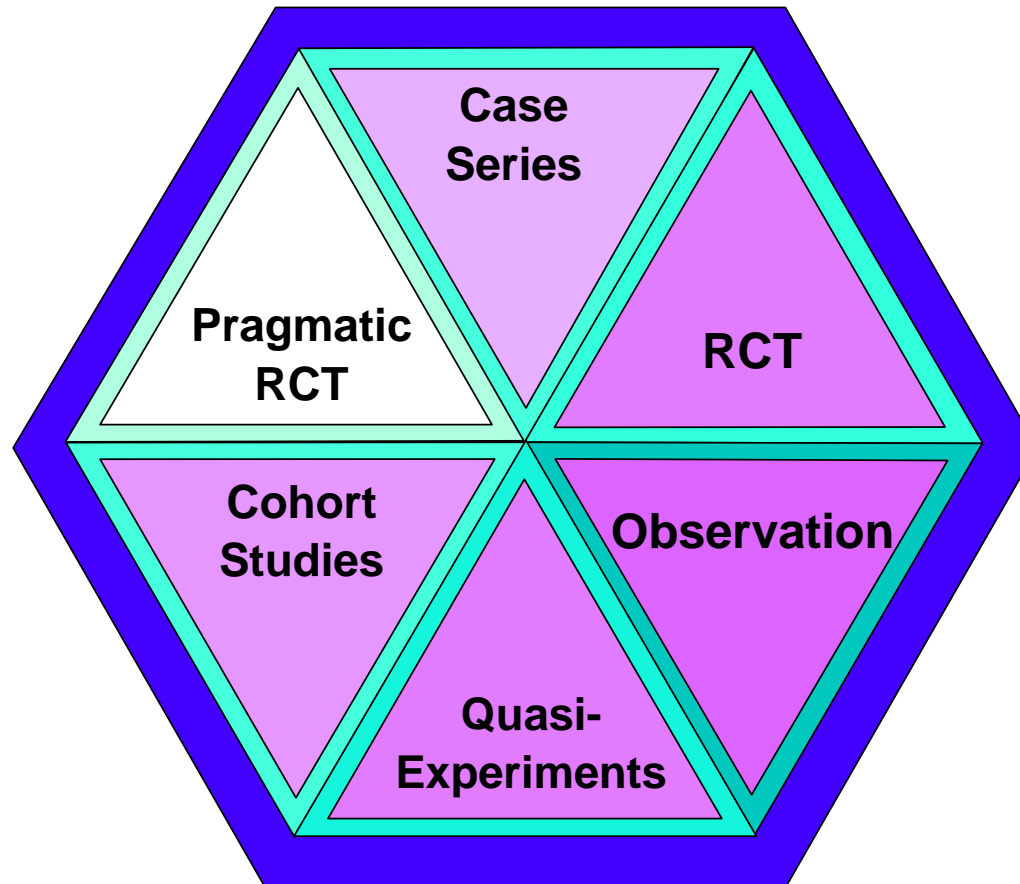
# Question and Method of Choice

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- specific efficacy
- comparative effectiveness
- general effectiveness, safety
- therapeutic effect as distinct from natural history
- blinded RCT
- pragmatic, comparative RCT
- cohort study, observational study
- wait-list controlled, open RCT

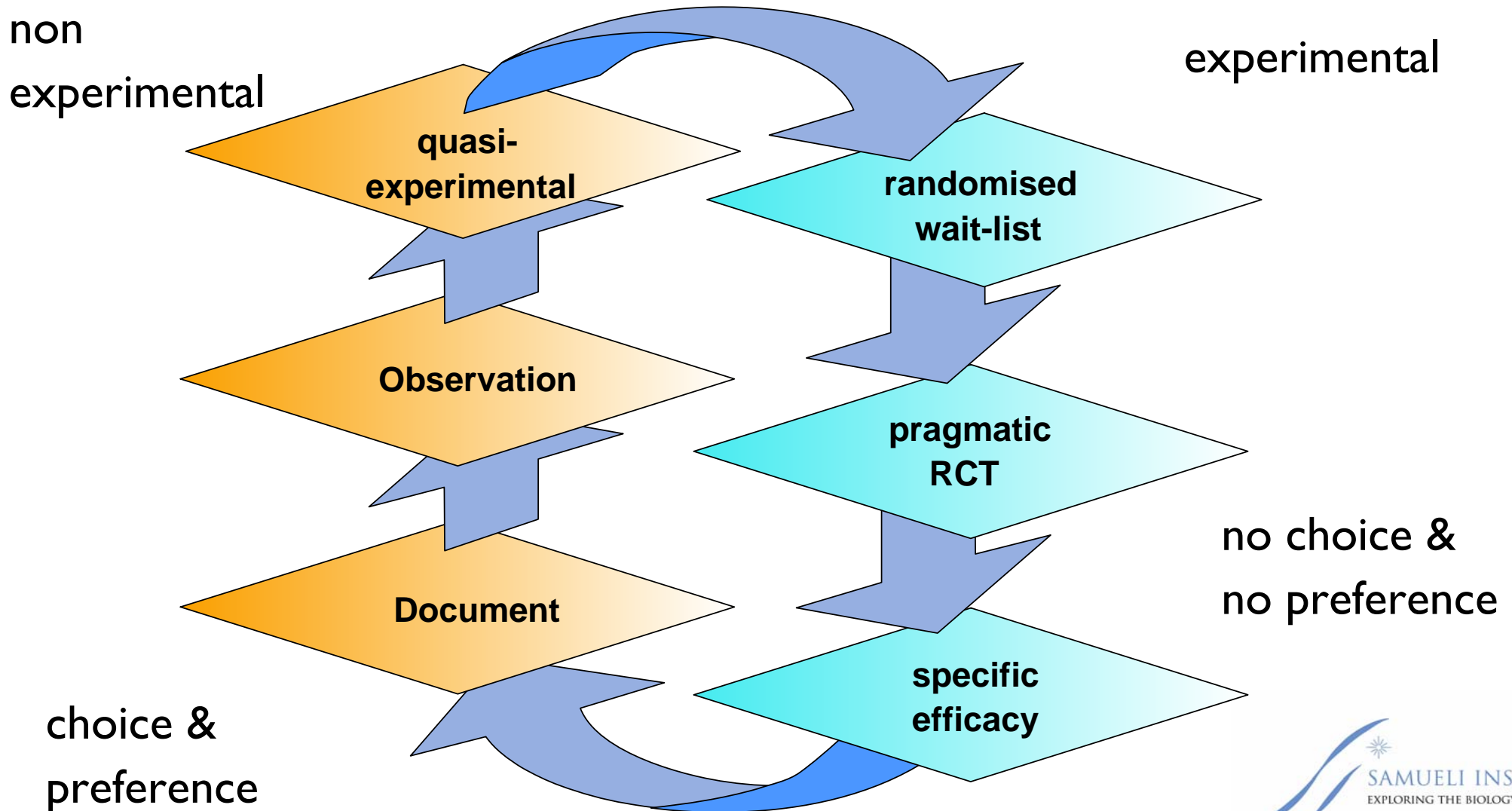
# Alternative View: Circular Model

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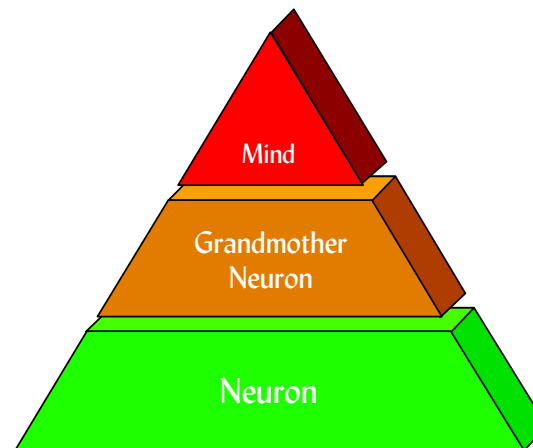
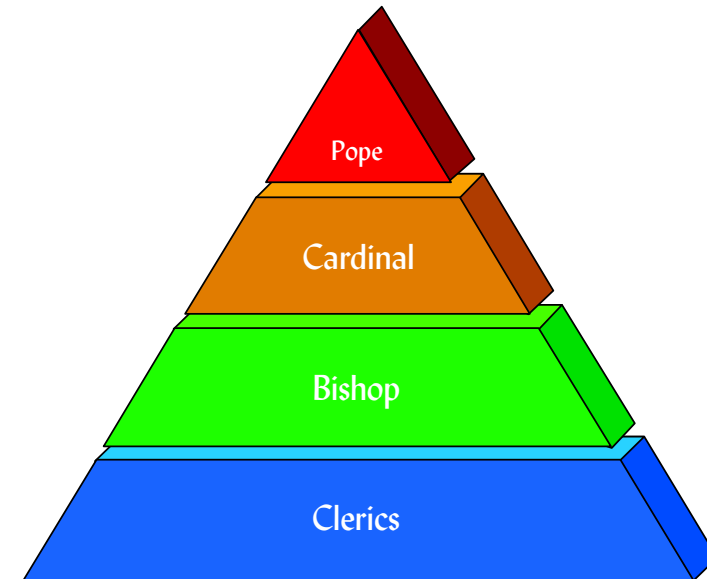
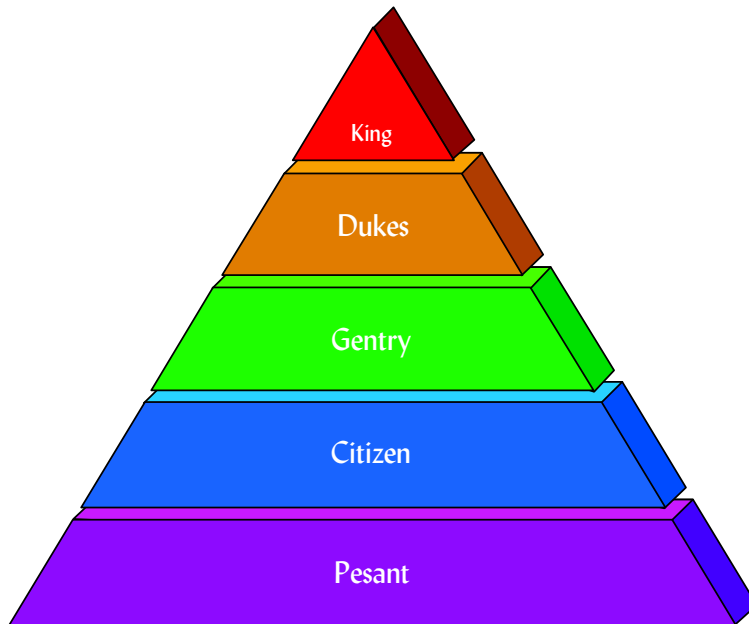
Complementarity  
of  
methods to  
balance  
respective  
strengths and  
weaknesses

# Circular



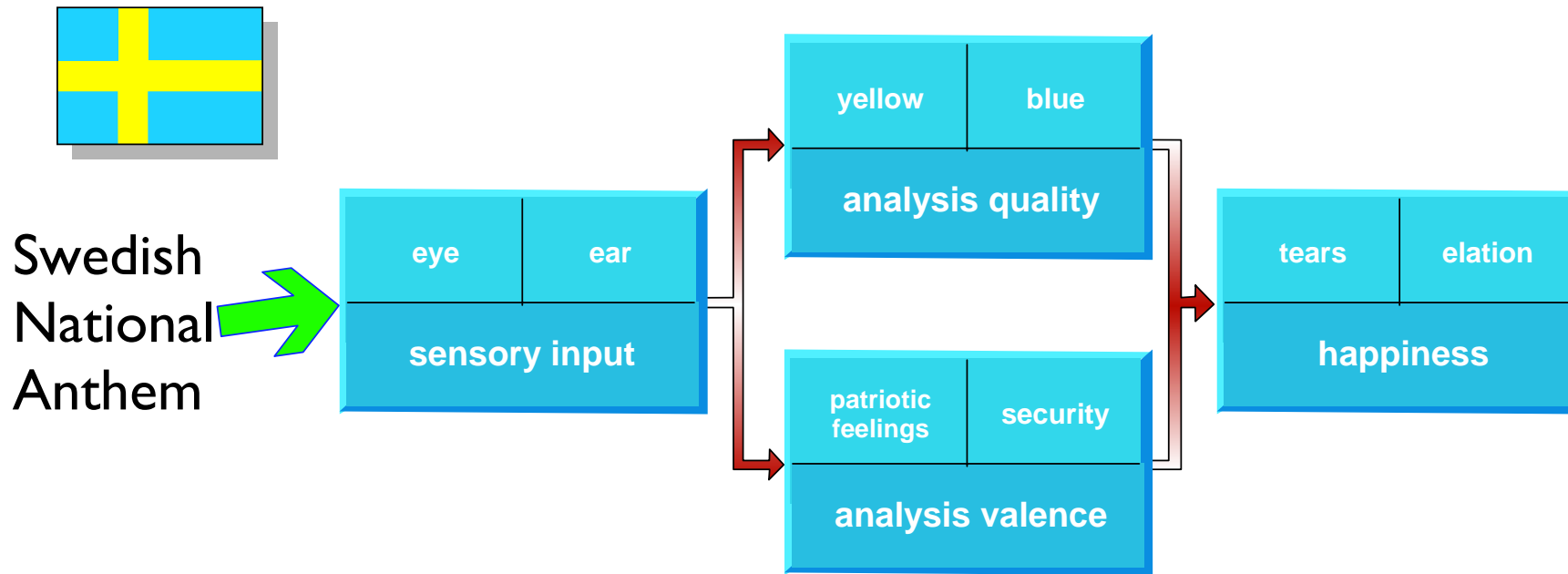
# Our Preference for Hierarchies...

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# ... is outdated

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neuro- and cognitive architecture are circular!

"re-entry loops"

"cortico-thalamic-cortical circuits"

....



# Suggestion and Non-specific Effects

Vase et al. (2003) Pain 105:17

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- 13 patients with "irritable bowel syndrome"
- experimental pain induction (distention of rectum and heat)
- balanced one of 4 interventions
  - natural course
  - lidocain rectal and oral
  - gel with pain reducing and pain inducing suggestion
- expectation and desire measured
- pain as outcome

## Effects:

## Results

Vase et al. (2003) Pain 105:17

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- no difference between
  - lidocain rectally, orally, placebo, nocebo
- big difference between all experimental interventions and natural course (NC)
  - placebo vs. NC:  $d = 2.0$
  - placebo vs. nocebo:  $d = 2.23$
  - placebo vs. lidocain: no difference
- big difference between experiment and clinical trial:
  - placebo and natural course (clin. trial):  $d = 0.89$
  - placebo vs. lidocain (clin trial):  $d = .89$