
***Unsolved, forgotten, and /or
ignored features of the
placebo response in medicine***

Paul Enck & Sibylle Klosterhalfen

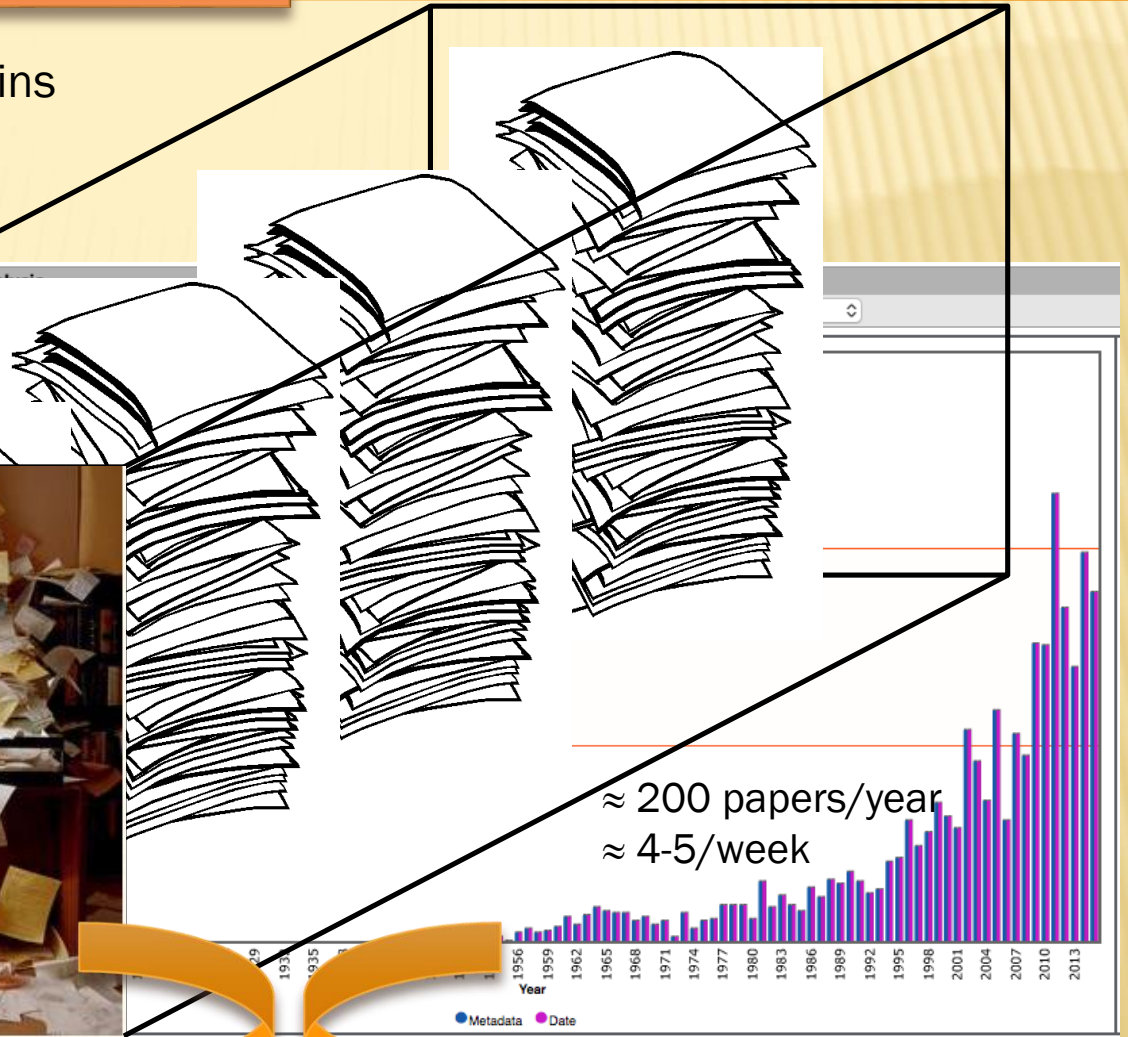
University Hospitals Tübingen, Germany

The "Placebo Box"

Currently (until 2015) contains
> 3000 papers on the
placebo/nocebo effect or
response



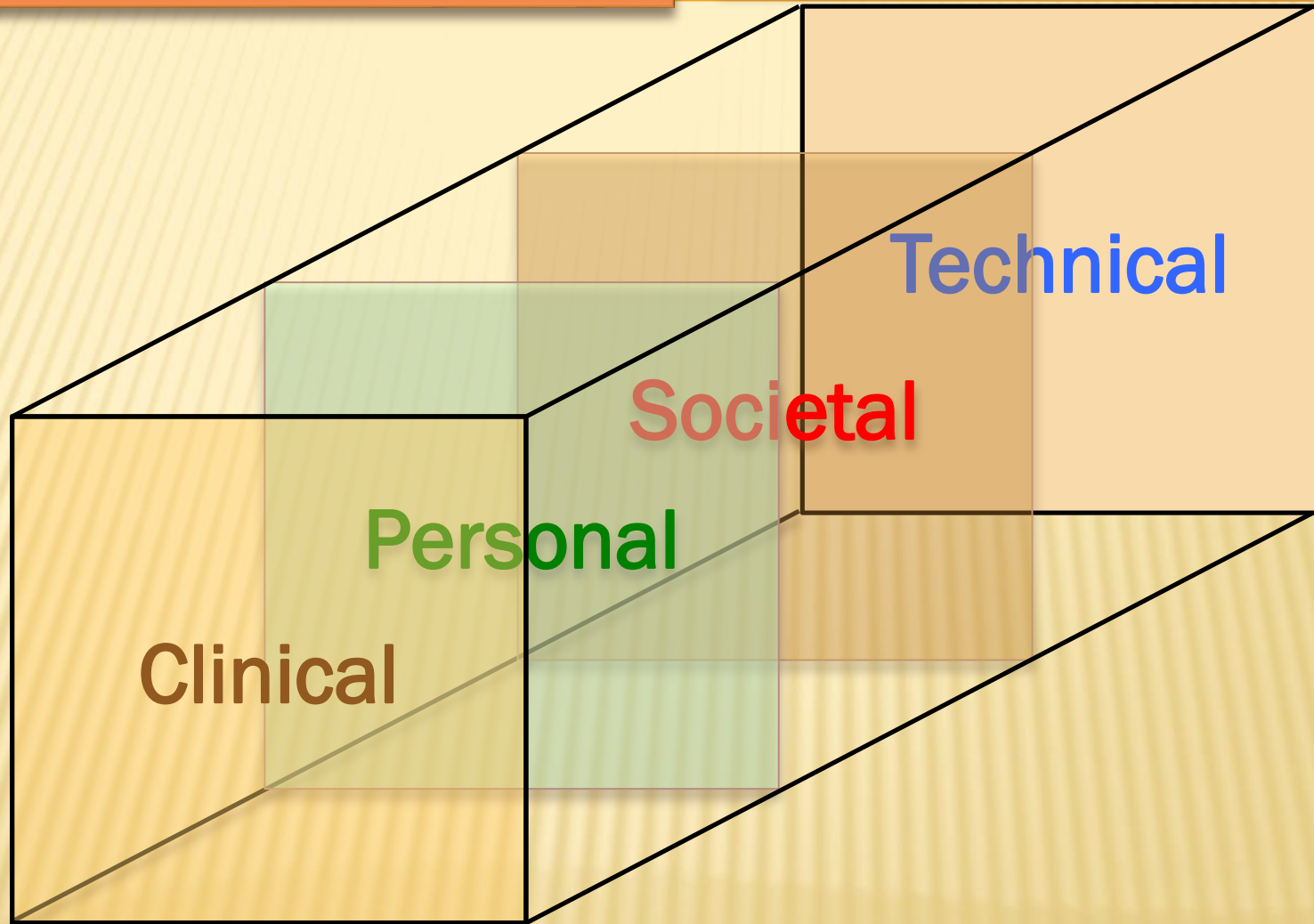
The heuristic approach



The empirical approach

The "Placebo Box"

: The heuristic approach

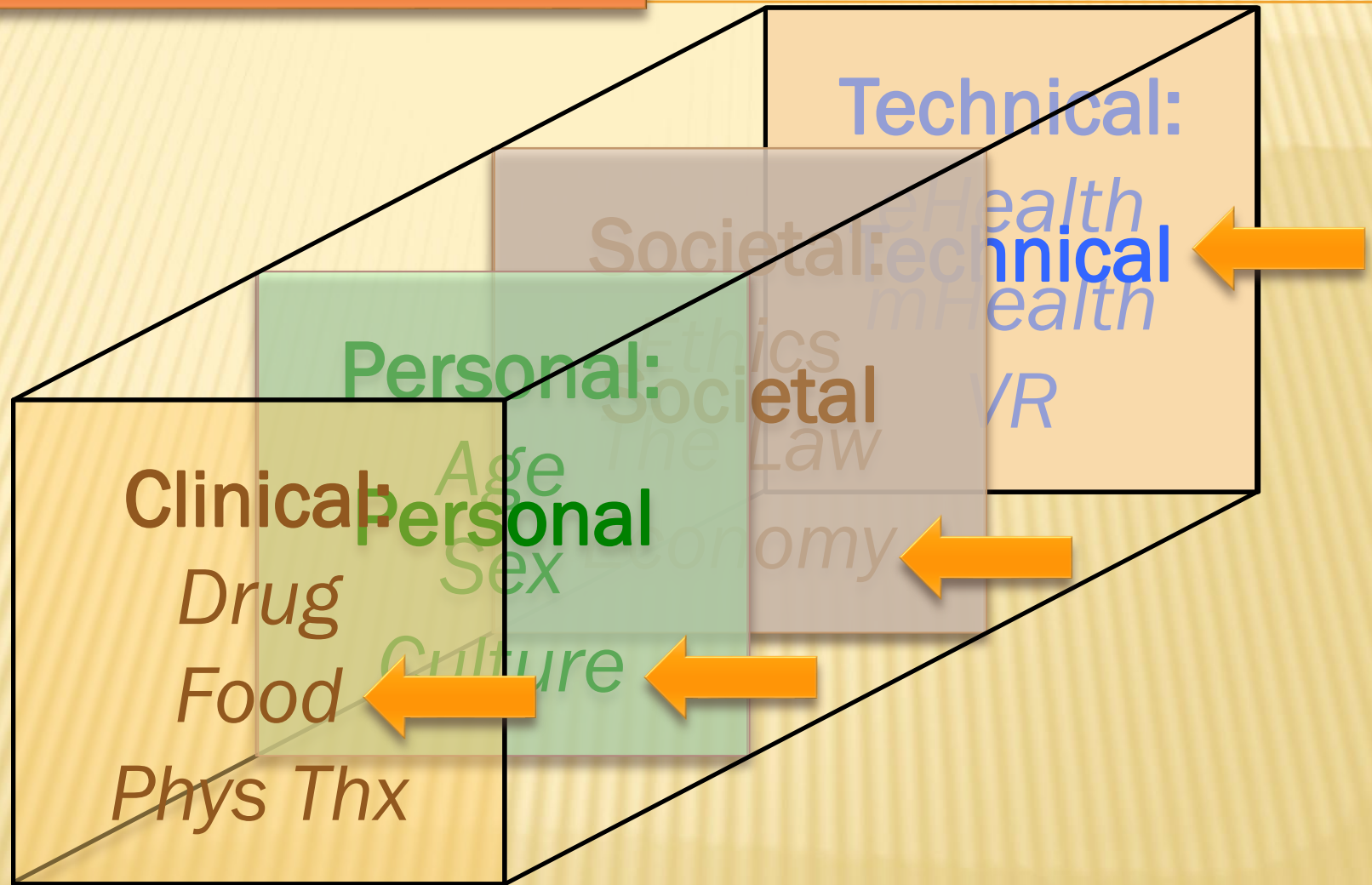


The "Placebo Box"

: The empirical approach

The screenshot displays the Luxid web interface for document analysis. At the top, navigation tabs include Overview, Dashboards, Search, Discoveries, Knowledge Browser, and X-Match. The main content area shows 3006 documents with search and analysis options. On the left, the 'Analysis parameters' panel is open, showing a list of descriptors such as Entity, Metadata, and Relationship. The central part of the interface features a 'Clustering' view with a network graph of 12 nodes and a bar chart. The nodes represent clusters of terms, with node 12 being the largest and most central. Below the clustering view, a 'Proximity' panel is open, displaying a list of 10 documents related to the selected cluster. The documents are filtered by 'Digestive System Diseases' and include titles such as 'Neuronal correlates in the modulation of placebo analgesia...' and 'Enhanced affect/cognition-related brain responses during visceral placebo analgesia...'. The interface also includes a search bar, user profile information, and various utility icons.

The "Placebo Box"



Box Dimension

Papers in Box

Important Questions

Clinical:

Drug

Food

Phys Thx

about
2400

100

100

Are the mechanisms operating (conditioning, expectation) the same than with drugs ?

Published in final edited form as:

J Evid Based Complementary Altern Med. ; 19(3): 181-188. doi:10.1177/2156587214528513.

Expectancy, self-efficacy, and placebo effect of a sham supplement for weight loss in obese subjects

Kimberly M Tippens, ND, MSAOM, MPH¹, Jonathan Q Purnell, MD², William L Gregory, PhD, Erin Connelly, MA, Douglas Hanes, PhD¹, Barry Oken, MD³, and Carlo Calabrese, ND, MPH

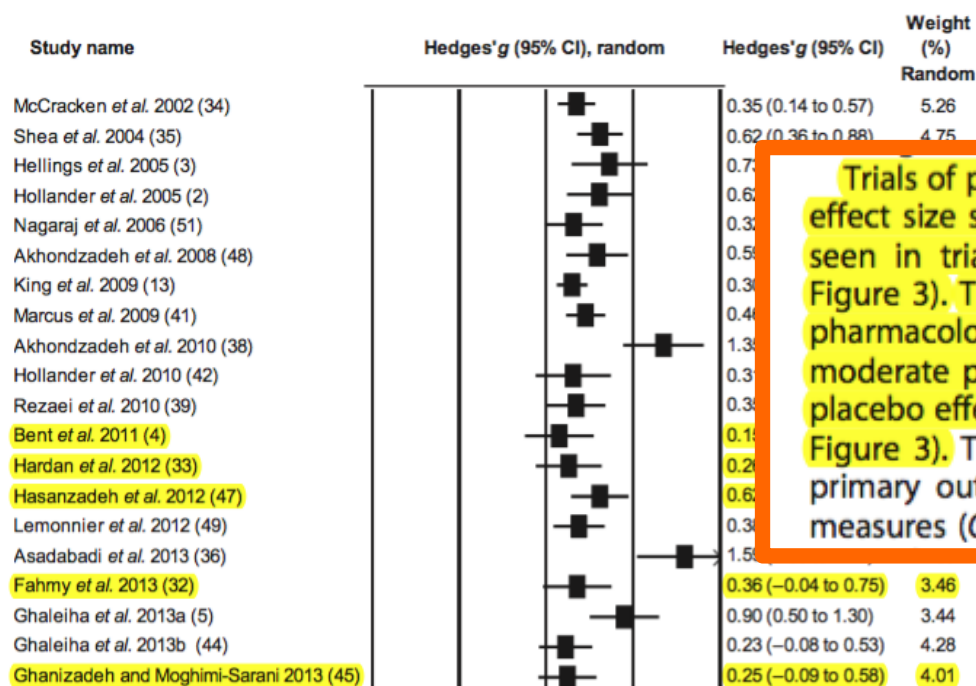
In our study, participants with stronger beliefs in supplements tended to lose a smaller proportion of weight. Participants with 100% expectancy of receiving the active supplement tended to report a decline in self-efficacy over the course of the study and to increase their beliefs in the supplement's effects. The group with 50% expectancy of active supplement remained somewhat stable in self-efficacy scores and did not change in their level of belief in the supplements, while those taking no capsules increased in self-efficacy and tended to reduce their belief in the value of supplements.

Predictors of placebo response in pharmacological and dietary supplement treatment trials in pediatric autism spectrum disorder: a meta-analysis

Citation: *Transl Psychiatry* (2015) **5**, e640; doi:10.1038/tp.2015.143

A Masi¹, A Lampit², N Glozier¹, IB Hickie¹ and AJ Guastella¹

www.nature.com/tp



Trials of pharmacological interventions had a moderate placebo effect size significantly greater than the small placebo effect size seen in trials of dietary supplements ($Q=5.02$, $df=1$, $P=0.03$; Figure 3). Trials of adjunctive interventions, which included both pharmacological and dietary supplement treatments, also had a moderate placebo effect size significantly greater than the small placebo effect size in monotherapy trials ($Q=5.26$, $df=1$, $P=0.02$; Figure 3). There was no difference in the placebo effect size for primary outcome measures compared with secondary outcome measures ($Q=3.20$, $df=1$, $P=0.07$).

Type of intervention

Dietary supplement	7	20.68 (0.00 to 64.1)	0.26 (0.07 to 0.45)	0.025
Pharmacological	18	65.38 (42.98 to 78.99)	0.52 (0.40 to 0.63)	

Box Dimension

Papers in Box

Important Questions

Clinical:

Drug

Food

Phys Thx

about
2400

500

300

Are the mechanisms operating (conditioning, expectation) the same than with drugs ?

Are placebo effects larger or smaller with nutrients & foods than with drugs ?

To the best of our knowledge, no direct comparison has yet been made testing the difference experimentally

Using the Placebo Effect to Isolate Control Mechanisms of Athletic Performance: A Research Protocol

Ellen K. Broelz¹, Paul Enck^{1*}, Andreas M. Niess², Patrick Schneeweiß² and Katja Weimer¹

SPORTS AND EXERCISE MEDICINE 2015; 1(2): 54-63.

Food over Drugs:
Salience Hypothesis

Drugs over Food:
Conditioning Hypothesis

Box Dimension

Papers in Box

Important Questions

Personal:

Age

Sex

Culture

about

1100

450

150

Does no difference in RCTs imply no differences at all ?

If in clinical routine the placebo effects is a mixture of expectancy and conditioning, women and men may utilize both these mechanisms to a different degree.

Neurogastroenterology & Motility

Neurogastroenterol Motil (2014) 26, 1743–1753

doi: 10.1111/nmo.12454

Are there sex differences in placebo analgesia during visceral pain processing? A fMRI study in healthy subjects

N. THEYSOHN,* J. SCHMID,† A. ICENHOUR,† C. MEWES,† M. FORSTING,* E. R. GIZEWSKI,‡ M. SCHEDLOWSKI,† S. ELSENBRUCH† & S. BENSON†

At
On
an
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ons.

Box Dimension

Papers in Box

Important Questions

Personal:

Age

Sex

Culture

about

1100

450

150

Does no difference in RCTs imply no differences at all ?

Are there differences in utilization of mechanisms ?

But what about "culture", race, ethnic background, nationality, migration status, social status ?

There is very little beyond occasional reports of differences in the placebo response in RCTs between Europe and the US, Canada, Japan ...

RESEARCH ARTICLE

Placebo Trends across the Border: US versus Canada

Cory S. Harris¹, Natasha K. J. Campbell², Amir Raz^{2,3*}

PLOS ONE | DOI:10.1371/journal.pone.0142804 November 25, 2015

Acta Psychiatr Scand 2015; 1-4
All rights reserved
DOI: 10.1111/acps.12422

Editorial

Do cultures influence placebo response?

Colour, culture and placebo response

Dinesh Bhugra^{1,2}, Antonio Ventrigo^{3,4}, Alex Till⁵ and Gin Malhi⁶

International Journal of
Social Psychiatry
2015, Vol. 61(6) 615-617
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0020764015591492
isp.sagepub.com
SAGE

Box Dimension

Papers in Box

Important Questions

Societal:
Ethics
The Law
Economy

about
800
450
100

Do the ethics of placebo use in patients cover the ethics of placebo research in science ?

How do the different legal systems handle placebo use ?

Does the placebo effect help saving money ?

A: Is utilizing the placebo response ("harnessing") in medicine in conflict with better patient education and "shared decision making" ?

B: Is partial reinforcement ("dose extension") a strategy that not only benefits the patient but also the society, for instance by saving drugs and money ?

A: Is utilizing the placebo response ("harnessing") in medicine in conflict with better patient education and "shared decision making" ?

In our study, participants with stronger beliefs in supplements tended to lose a smaller proportion of weight. Participants with 100% expectancy of receiving the active supplement tended to report a decline in self-efficacy over the course of the study and to increase their beliefs in the supplement's effects. The group with 50% expectancy of active supplement remained somewhat stable in self-efficacy scores and did not change in their level of belief in the supplements, while those taking no capsules increased in self-efficacy and tended to reduce their belief in the value of supplements.

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Self-efficacy and placebo response are inversely related !

High self-efficacy = internal Locus of Control (LoC)

Low self-efficacy = external LoC = Placebo responder

frontiers in
PSYCHOLOGY

REVIEW ARTICLE
published: 01 October 2014
doi: 10.3389/fpsyg.2014.01079



Prediction of placebo responses: a systematic review of the literature

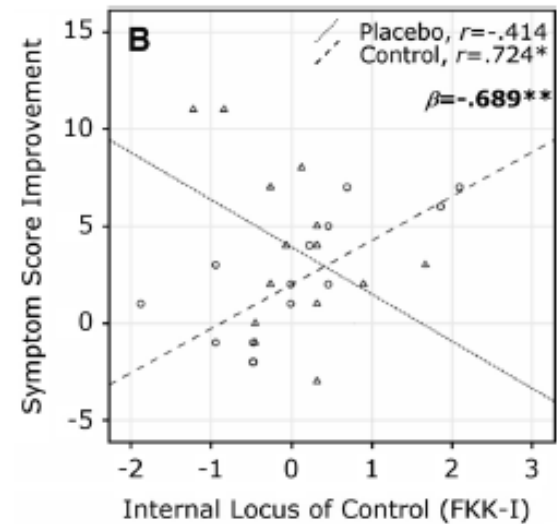
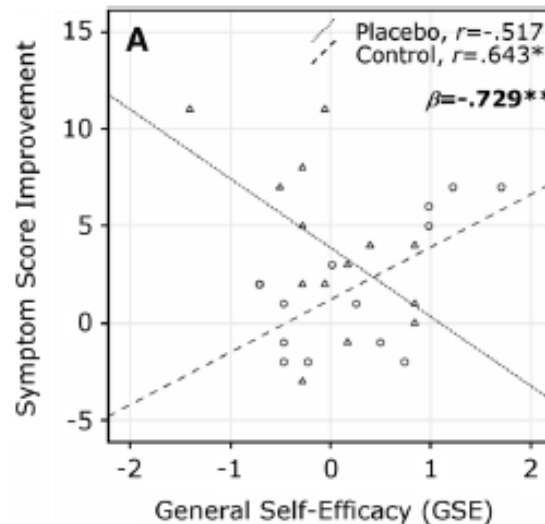
Bjoern Horing^{1,2*}, *Katja Weimer*¹, *Eric R. Muth*² and *Paul Enck*¹

Prediction of Symptom Change in Placebo Versus No-Treatment Group in Experimentally Induced Motion Sickness

Bjoern Horing^{1,2} · Katja Weimer¹ · Eric R. Muth² · Paul Enck¹

... if this holds true for all conditions and not only for nausea and for healthy volunteers

Fig. 1 Scatter plots for prediction of symptom score improvement (ASRmax). The regression slopes indicate differential effects of standardized predictors (z -scores) in placebo group (*dotted lines on triangles*) versus control group (*dashed lines on circles*). Correlation coefficients r and standardized regression coefficients β provided for context (cf. Table 3). **a** GSE, **b** FKK-I, **c** FKK-SK, **d** PTS 2. * $p < .05$; ** $p < .01$



... then the current approach in health economics, to educate the patients and train them to engage and participate in "shared decision making" may result in higher self-esteem and self-efficacy and in lower placebo responses ...

.... which is the opposite of "harnessing the placebo response".

B: Is partial reinforcement ("dose extension") a strategy that not only benefits the patient but also the society, for instance by saving drugs and money ?

from: Rief/Bingel/Schedlowski/Enck, CPT 2011

Table 2 Systematic use of placebo pills

Acquisition period														Maintenance treatment													
Day of treatment																											
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	P	D	D	P	D	P	D	D	P	P	D	D	

This example shows a drug administration regimen with a 2-week acquisition period, followed by drug administrations with interspersed placebo administrations (likelihood of placebo administration in 3rd week: 0.33).

D, drug; P, placebo.

Training

Test

Colloca, Enck, DeGrazia: Relieving pain using dose-extending placebos: A scoping review. Pain (in press)

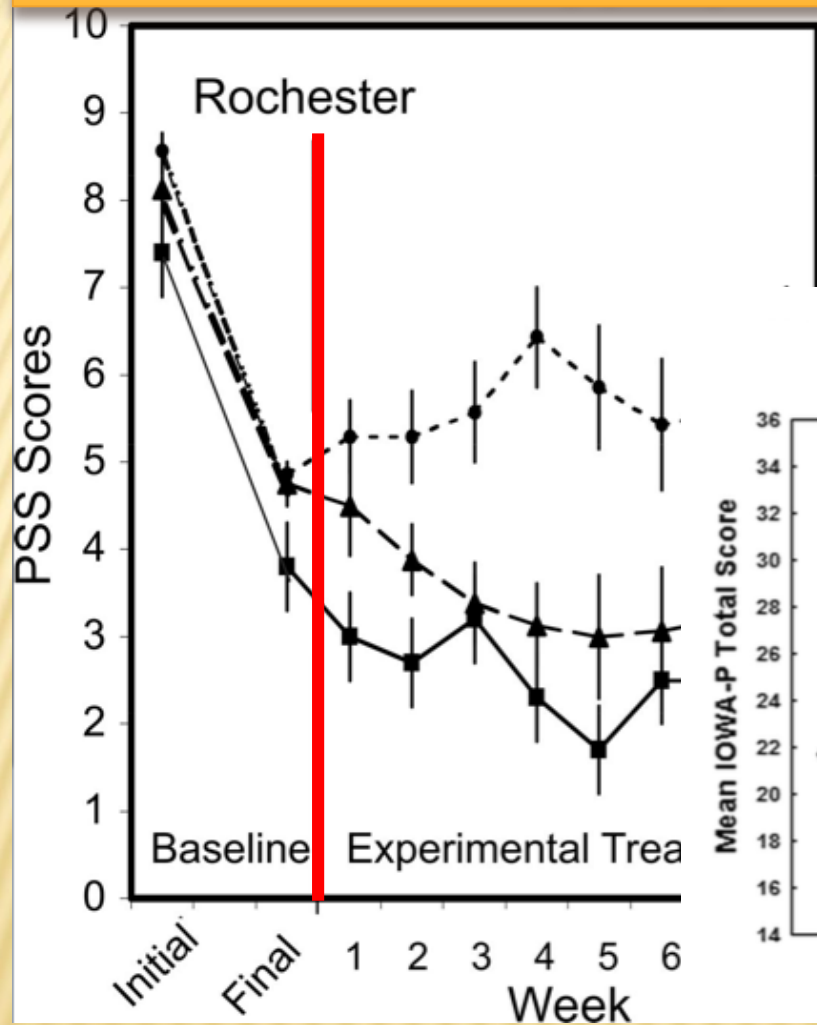
Conditioned Pharmacotherapeutic Effects: A Preliminary Study

ROBERT ADER, PhD, MARY GAIL MERCURIO, MD, JAMES WALTON, BS, DEBORRA JAMES, RN, MICHAEL DAVIS, PhD, VALERIE OJHA, RN, ALEXA BOER KIMBALL, MD, MPH, AND DAVID FIORENTINO, MD, PhD *Psychosomatic Medicine* 72;2010:192-7

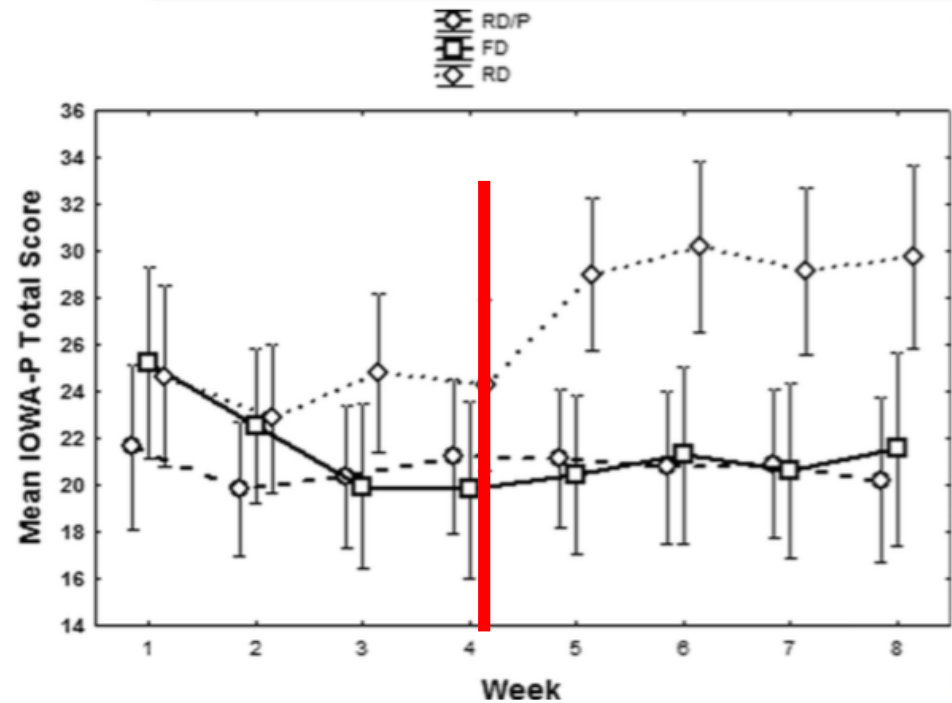
Conditioned Placebo Dose Reduction: A New Treatment in Attention-Deficit Hyperactivity Disorder?

Adrian D. Sandler, MD,* Corrine E. Glesne, PhD,* James W. Bodfish, PhD†‡ *(J Dev Behav Pediatr 31:369-375, 2010)*

Corticosteroid therapy in psoriasis



Amphetamine therapy in ADHD



Box Dimension

Papers in Box

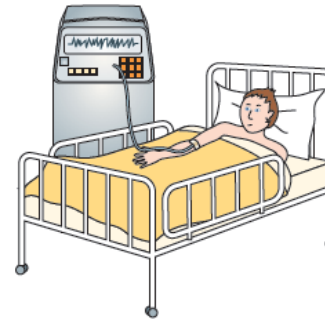
Important Questions

Technical:
eHealth
mHealth
VR

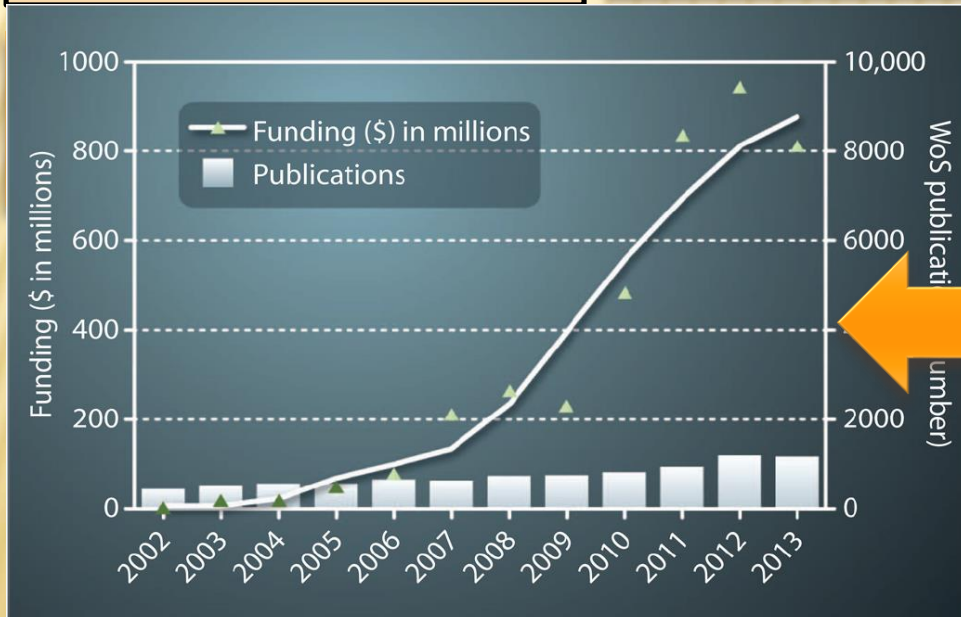
about
100
(internet)
2
(eHealth)

The future

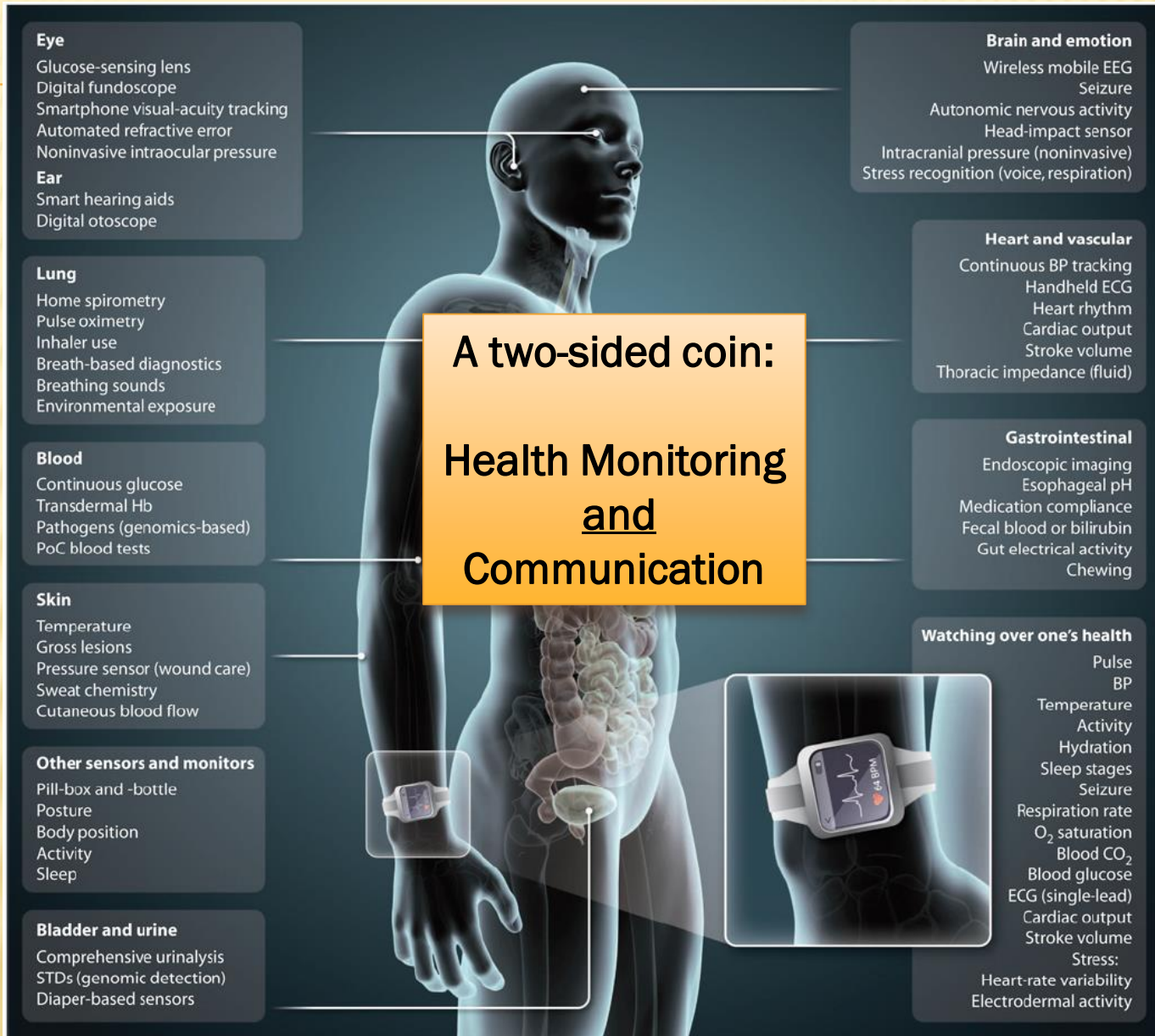
The presence



How contemporary is placebo and nocebo research?



This growth is much faster than the growth of knowledge in placebo research



The digital placebo effect: mobile mental health meets clinical psychiatry

Torous J, Firth J. In: Lancet Psychiatry 3;2016:1000-103

There are more than 165.000 medical apps Here, we introduce the concept of the digital placebo effect, referring to placebo-like effects seen from mobile health interventions, such as smartphone apps. Many people have a high level of affinity for their

J Med Internet Res. 2012 May-Jun; 14(3): e67.

Published online 2012 Jun 25. doi: [10.2196/jmir.1858](https://doi.org/10.2196/jmir.1858)

Self-monitoring Using Mobile Phones in the Early Stages of Adolescent Depression: Randomized Controlled Trial

JMIR MHEALTH AND UHEALTH

JMIR mHealth uHealth 2015 | vol. 3 | iss. 3 | e82 | p.1
(page number not for citation purposes) Mani et al

Original Paper

Review and Evaluation of Mindfulness-Based iPhone Apps

Madhavan Mani, BTech, MSc (Applied Psychology); David J Kavanagh, PhD; Leanne Hides, PhD (Psych); Stoyan R Stoyanov, MRes (Psych)

Results: The “mindfulness” search identified 700 apps. However, 94 were duplicates, 6 were not accessible and 40 were not in English. Of the remaining 560, 23 apps met inclusion criteria and were reviewed. The median MARS score was 3.2 (out of 5.0), which exceeded the minimum acceptable score (3.0). The Headspace app had the highest average score (4.0), followed by Smiling Mind (3.7), iMindfulness (3.5) and Mindfulness Daily (3.5). There was a high level of inter-rater reliability between the two MARS raters.

Conclusions: Though many apps claim to be mindfulness-related, most were guided meditation apps, timers, or reminders. Very few had high ratings on the MARS subscales of visual aesthetics, engagement, functionality or information quality. Little evidence is available on the efficacy of the apps in developing mindfulness.

Can a "virtual doctor" elicit reliable placebo responses ?



Dr. V

Horing, Newsome, Enck, Babu, Muth: A V for the investigation of placebo effects. B



Patient Education and Counseling 60 (2006) 136–141

Patient Education and Counseling

www.elsevier.com/locate/pateducou

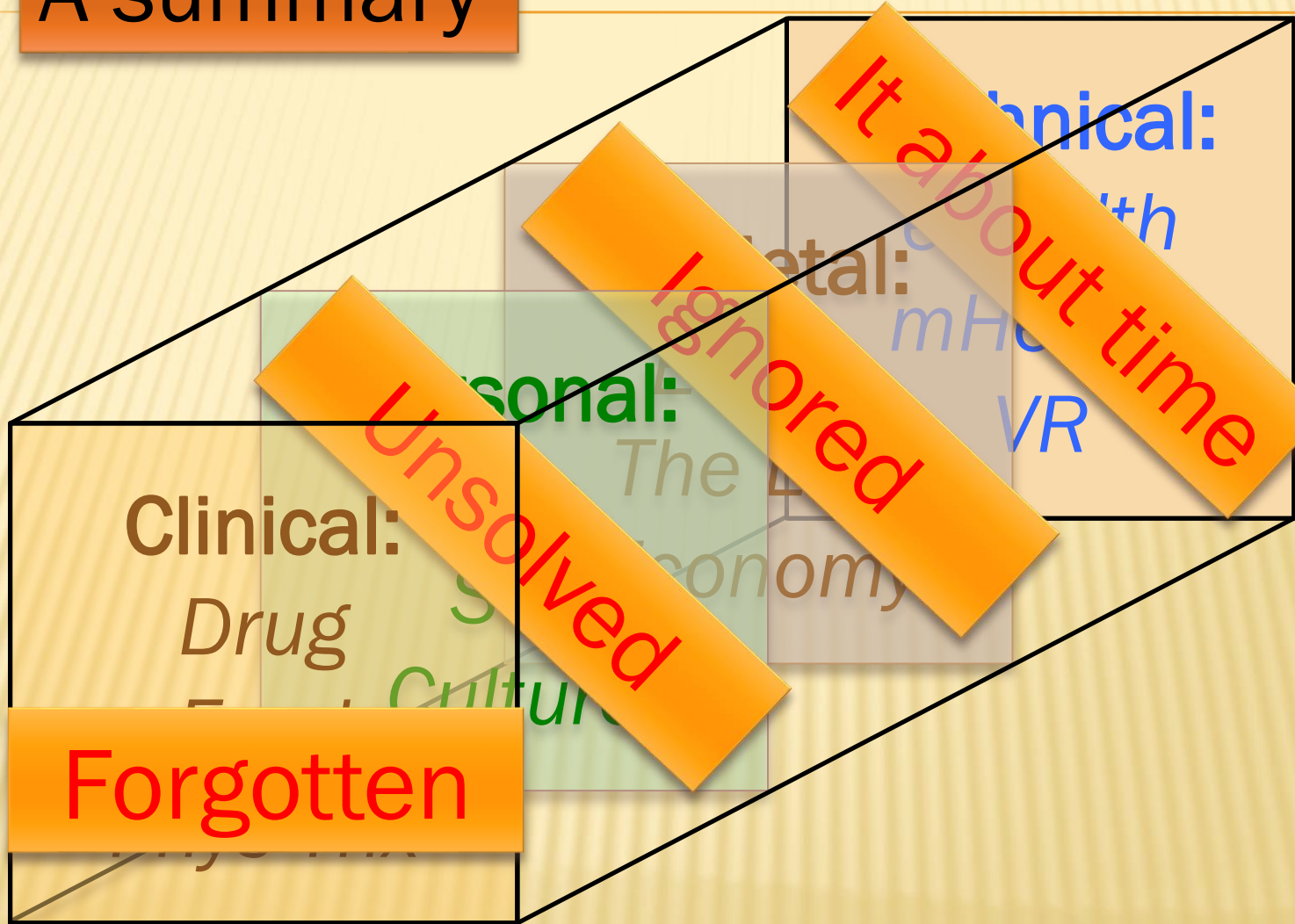
‘What’s in a face?’ The role of doctor ethnicity, age and gender in the formation of patients’ judgements: an experimental study

Reena Shah^a, Jane Ogden^{b,*}

Multivariate analysis

Variable	Main effect: ethnicity		Main effect: age		Main effect: gender		Interaction: ethnicity/age/gender	
	F	p	F	p	F	p	F	p
Expected behaviour of doctor								
Personal manner	2.67	0.10	10.56	0.001	22.7	0.0001	0.21	0.65
Technical skills	0.65	0.42	5.78	0.02	6.36	0.012	0.67	0.41
Explanation	1.49	0.224	8.93	0.003	8.94	0.003	0.01	0.91
Emotional	5.43	0.02	6.90	0.009	20.37	0.0001	0.24	0.62
Empowerment	1.61	0.20	7.20	0.008	19.09	0.0001	0.26	0.61
Management—prescription	0.36	0.55	0.68	0.412	3.68	0.06	0.39	0.53
Management—refer	1.93	0.166	8.20	0.004	1.89	0.17	0.11	0.74
Management—complementary	1.03	0.31	3.15	0.077	5.41	0.021	0.77	0.382
Expected behaviour of patient								
Patient behaviour	0.81	0.37	13.74	0.0001	8.39	0.004	0.35	0.555
Expected patient ease with doctor								
Physical examination	1.33	0.25	7.36	0.007	5.23	0.023	0.024	0.876
Health promotion	1.45	0.23	1.62	0.20	0.09	0.766	0.013	0.909
Psychosexual	2.37	0.12	1.87	0.17	3.39	0.067	0.306	0.581

A summary





Thanks for your attention !