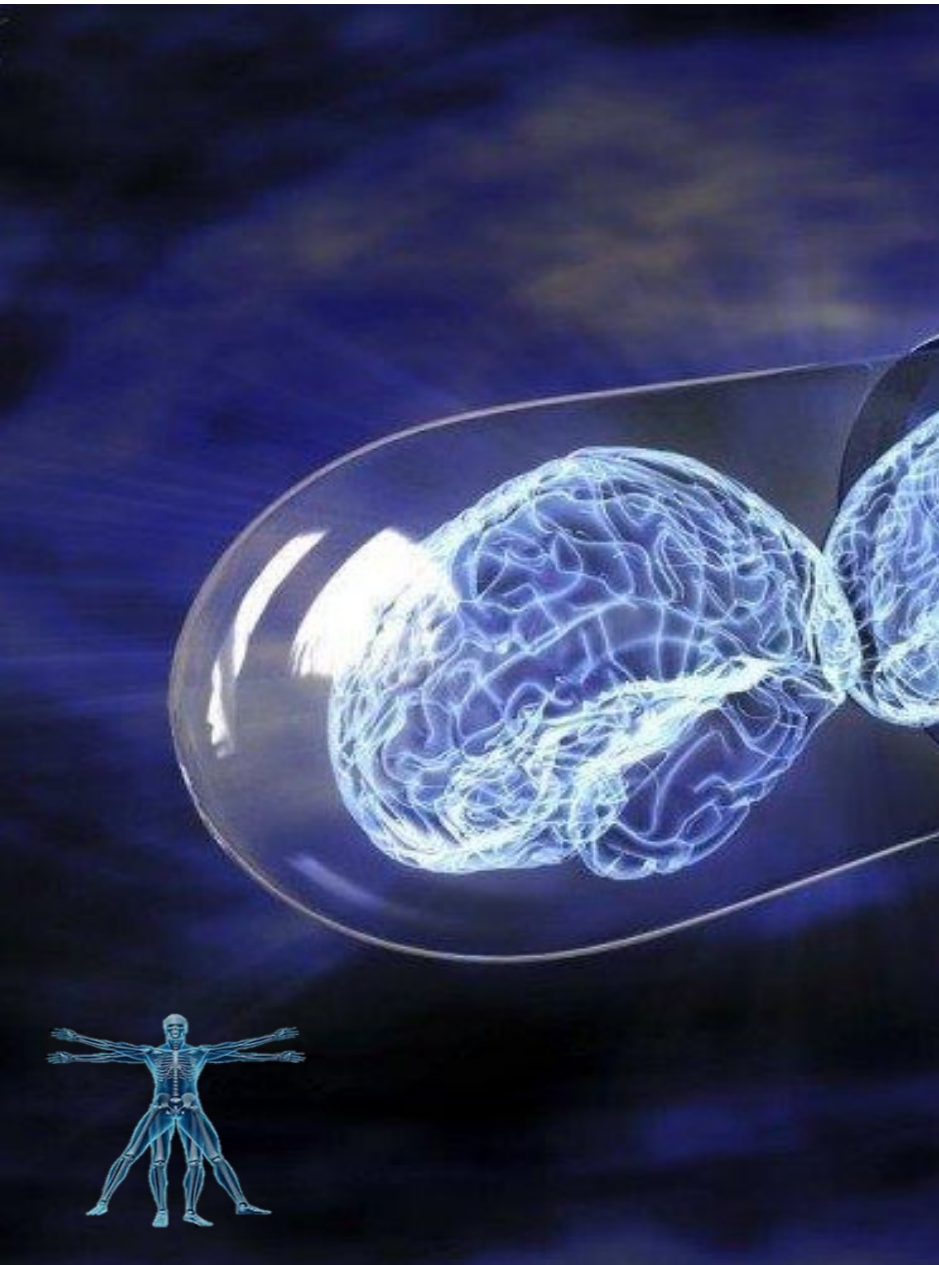




Woorden als Medicijn

Hoe het placebo effect kan
bijdragen aan betere zorg

Andrea Evers



De rol van de context in je behandeling...

Artsen die een **warme, vriendelijke** en **geruststellende houding** aannemen, zijn effectiever dan degenen die het consult formeel houden

Influence of context effects on health outcomes: a systematic review

[Z Di Blasi](#) ¹, [E Harkness](#), [E Ernst](#), [A Georgiou](#), [J Kleijnen](#)

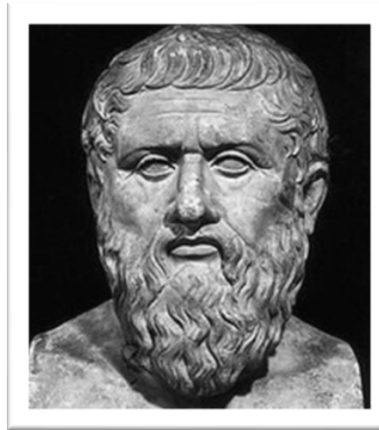
Affiliations + expand

PMID: 11253970 DOI: [10.1016/s0140-6736\(00\)04169-6](https://doi.org/10.1016/s0140-6736(00)04169-6)



De rol van de context in je behandeling...

Placebo mechanismen =
hoe contextfactoren invloed hebben
op behandelresultaat



Plato 428 - 347 v. Chr.



Descartes 1596-1656

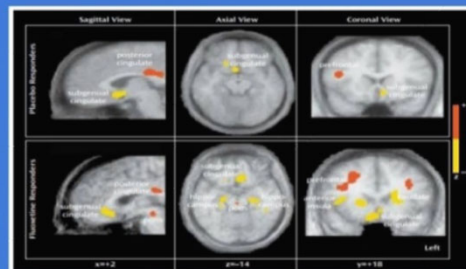


De rol van de context in je behandeling...

Placebo effecten even groot als
effecten antidepressiva...

Placebos as Effective Antidepressants

Administration of placebos can result in physiological and biochemical changes that are indistinguishable from a drug with an active ingredient. Placebos have been shown to have significant antidepressant effects when tested against active drugs. In addition, administration of a placebo results in activation of areas of the brain similar to that of the active selective serotonin reuptake inhibitor (SSRI) drug fluoxetine. Placebos therefore not only are effective antidepressants, but are also able to somehow activate similar parts of the brain as active drugs. But no one knows how.



Activation of glucose metabolism in response to placebo (top) and the SSRI fluoxetine (bottom). Activated areas are coloured.

See: Mayberg, H. S., Silva, J. A., Brannan, S. K., Tekell, J. L., Mahurin, R. K., McGinnis, S. and Jerabek, P. A. 2002. The functional neuroanatomy of the placebo effect. *American Journal of Psychiatry*. 159: 728-733





De rol van de context in je behandeling...

Placebo effecten even groot als
effecten pijnstillers...





De rol van de context in je behandeling...

Placebo effecten even groot als
effecten operaties artrose...

he clinical effects of
eopathy placebo
ts? Comparative
r of
bo-controlled trials
roduction

ethods

Literature search
and data sources

Study selection

Procedures

Graphical and
statistical analysis

Role of the funding

Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy

Aijing Shang, Karin Huxwiler-Muntenier, Linda Nartey, Peter Juni, Stephan Dörig, Jonathan A C Sterne, Daniel Pewsner, Matthias Egger

Summary
Background Homoeopathy is widely used, but specific effects of homoeopathic remedies seem implausible. The conduct and reporting of trials is a possible explanation for positive findings of trials of both homoeopathy and conventional medicine. We analysed trials of homoeopathy and conventional medicine and estimated effects in trials least likely to be affected by bias.

Methods Placebo-controlled trials of homoeopathy were identified by a comprehensive literature search covering 19 electronic databases, reference lists of relevant papers, and contacts with experts. Trials in conventional medicine matched to homoeopathy trials for disorder and type of outcome were randomly selected from the Cochrane Controlled Trials Register (issue 1, 2003). Data were extracted in duplicate and outcomes were pooled using random-effects meta-analysis. Odds ratios below 1 indicated benefit. Trials described as double-blind, with adequate randomisation, were to be of higher methodological quality. Bias effects were examined in funnel plots and meta-regression.

Findings 110 homoeopathy trials and 110 matched conventional-medicine trials were analysed. The median size was 65 participants (range ten to 1573). 21 homoeopathy trials (19%) and nine (8%) conventional-medicine trials were of higher quality. In both groups, smaller trials and those of lower quality showed more beneficial effects than larger and higher-quality trials. When the analysis was restricted to large trials of higher quality, the odds ratio was 0.88 (95% CI 0.65–1.19) for homoeopathy (eight trials) and 0.58 (0.39–0.85) for conventional medicine (four trials).

Annals of Internal Medicine

Relative Efficacy of Knee Osteoarthritis Treatments: Are All Placebos Created Equal?

EDITORIAL

Almost 40% of the U.S. population older than 45 years has some degree of knee osteoarthritis (OA), and the estimated lifetime risk for knee OA is 14% (1). This number is likely to rise even further. Obesity is skyrocketing, with an estimated 65 million more obese U.S. adults by 2030 (2). Greater participation in sports has led to high rates of anterior cruciate ligament rupture, and up to half of persons with this injury will develop symptomatic knee OA (3). Most important, the burden of knee OA is increasing globally, with an estimated \$2.5 billion by 2017, and the market for glucosamine is estimated to be \$12 billion by 2020 (8, 9).

Why this dichotomy? Perhaps despite our best efforts, patients with knee OA who enroll in randomized controlled trials are simply not representative of the world patients. Perhaps comparing interventions for OA pain with placebo—the gold standard for proving efficacy—fails to fully incorporate effects on central pain, which may be similar between stu...

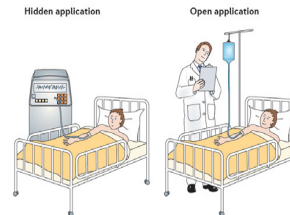
hritis is a chronic disease, and results from short particularly ... when large trials comparing multipl

Placebo effect = gunstige verwachting tav behandeluitkomst

- Gunstige behandel-effecten, niet toegeschreven aan het behandelmechanisme
- Ontstaan door verwachtingen tov de gunstige effecten

Bijv. minder pijn alleen maar bij het zien van de pijnstiller

'Behandeling'

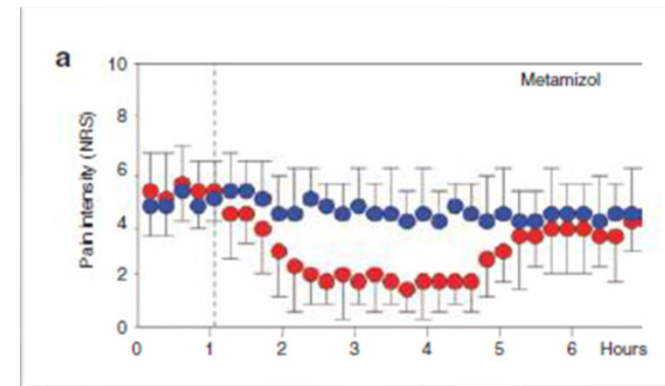
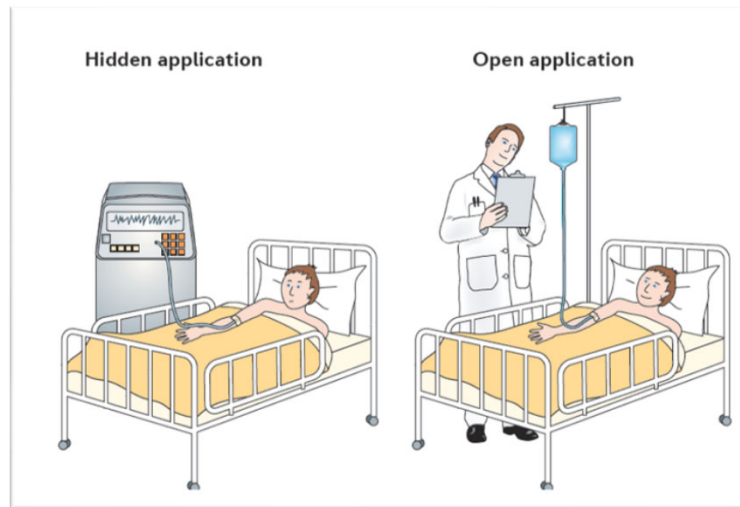


'Minder klachten'



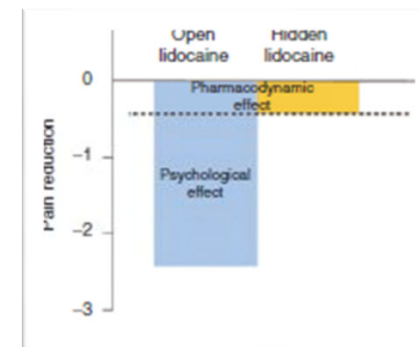


Placebo effect



Hidden Administration of Drugs

F Benedetti^{1,2}, E Carlino^{1,2} and A Pollo^{1,2}





Placebo effect

J. Jubb, J.M. Bensing / Neuroscience and Biobehavioral Reviews 37 (2013) 2709–2720

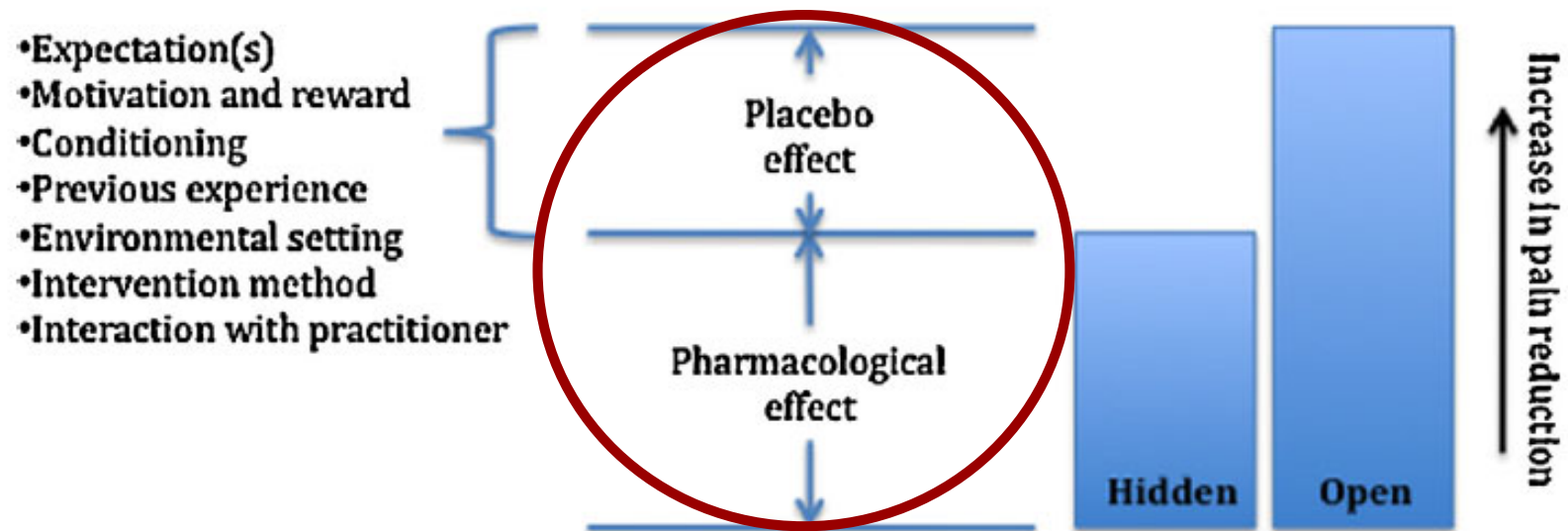
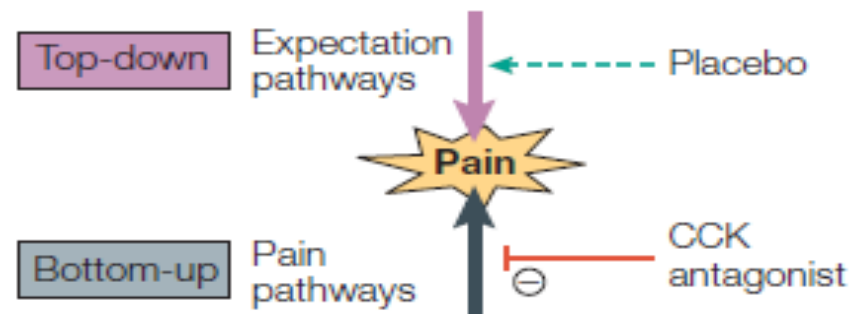
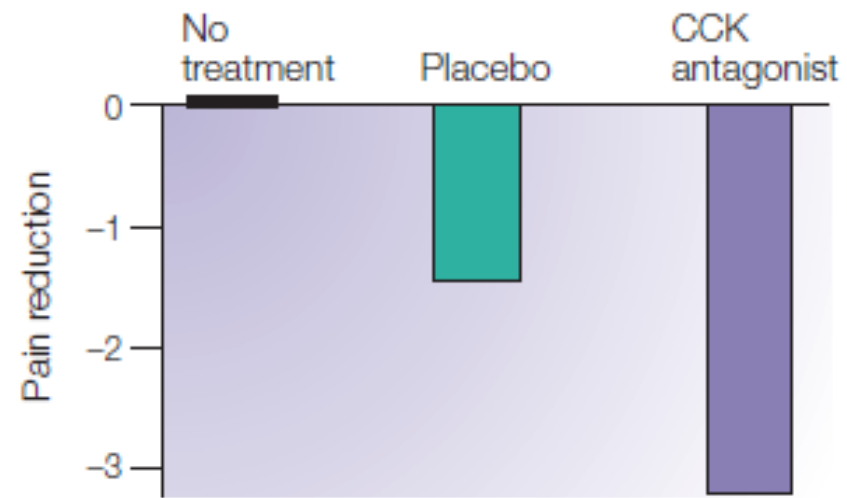


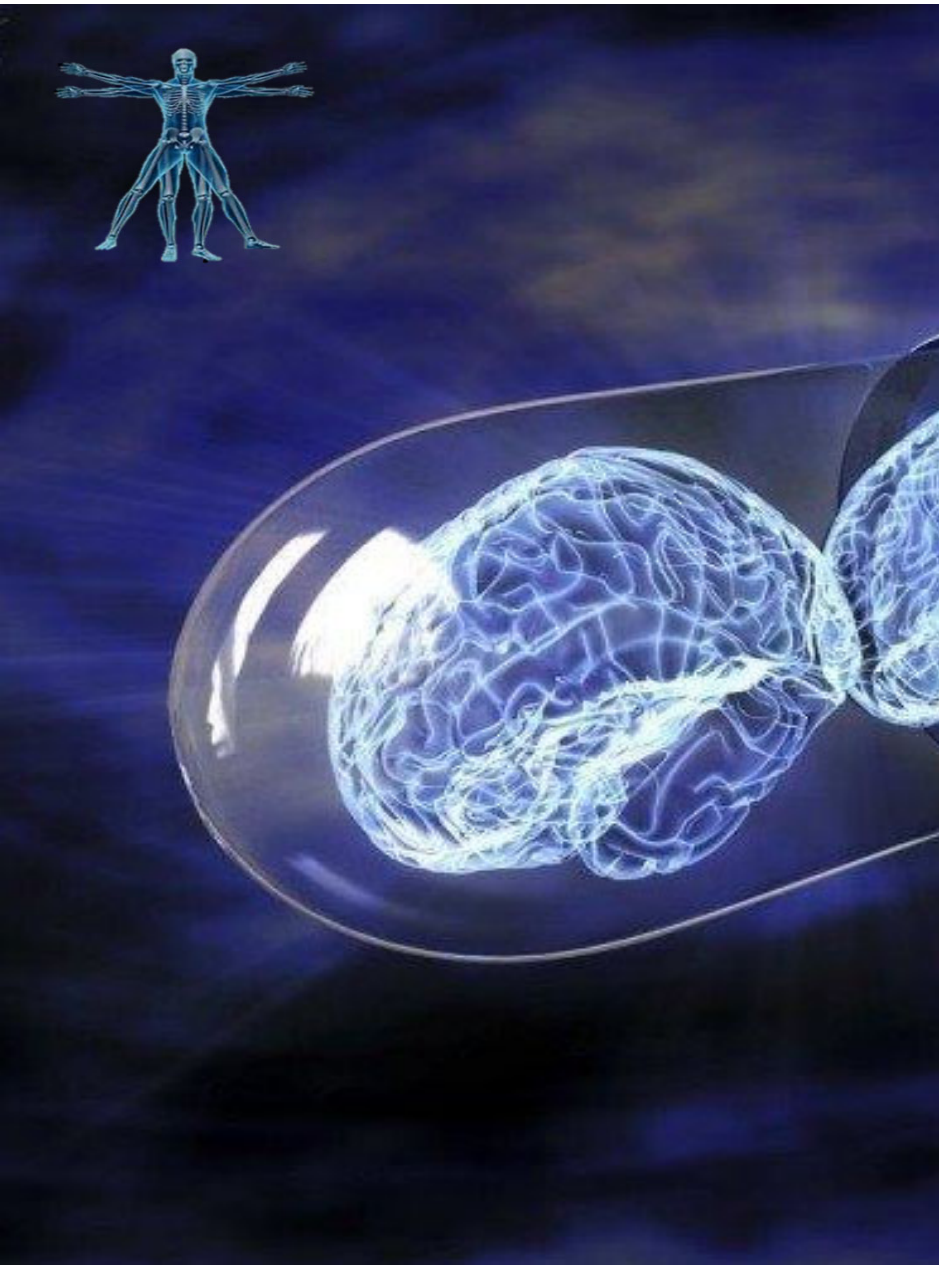
Fig. 1. The part of the change attributable to the context in placebo effects.



Placebo effect

Effect grootte





Quiz

Placebo effecten zijn doorgaans
groter bij kinderen dan bij
volwassenen ?



Placebo effecten **groter** bij kinderen dan bij volwassenen

Placebo effects in children

“...placebo effects in medicine in children do follow similar rules than in adults and may – even if not larger in effect size – be easier to elicit and may have long-lasting effects throughout life.”

The Journal of Pain
OFFICIAL JOURNAL OF THE AMERICAN PAIN SOCIETY

The Journal of Pain, Vol 15, No 12 (December), 2014; pp 1282-1293

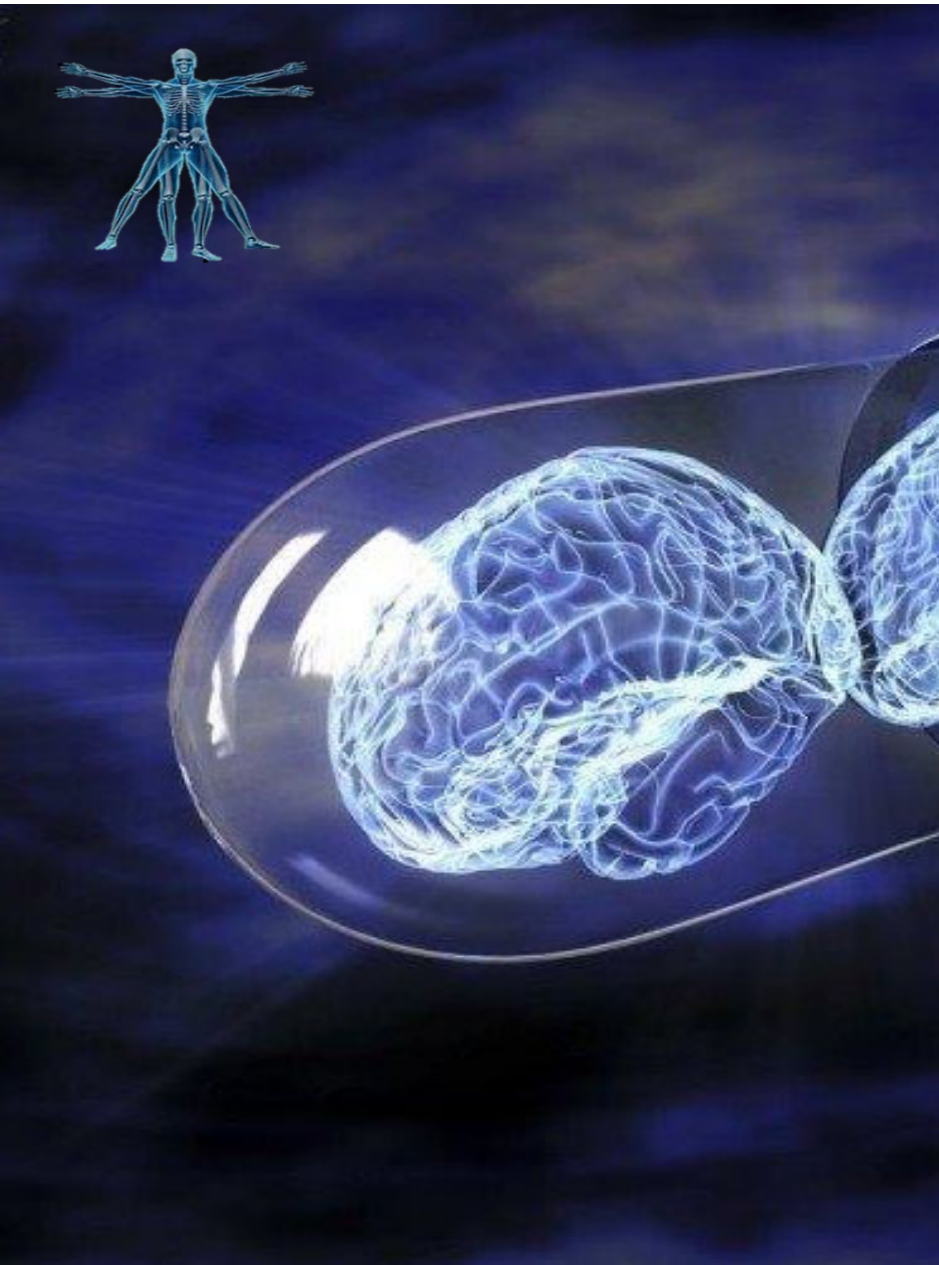
Expectancy-Induced Placebo Analgesia in Children and the Role of Magical Thinking

Peter Krummenacher,^{*,†,‡} Joe Kossowsky,^{*,§,||} Caroline Schwarz,^{*} Peter Brugger,[¶] John M. Kelley,^{||,*,*,††} Andrea Meyer,^{‡‡} and Jens Gaab^{*}

The Journal of Pain
OFFICIAL JOURNAL OF THE AMERICAN PAIN SOCIETY

Are Children the Better Placebo Analgesia Responders? An Experimental Approach

Nathalie Wrobel,^{*,†} Tahmine Fadaei,[‡] Christian Sprenger,^{†,‡} Johannes Hebebrand,[§] Katja Wiech,^{¶,||} and Ulrike Bingel^{*}



Quiz

Placebo effecten ook bij dieren ?



Placebo effecten ook bij dieren



The Placebo Effect Might Work for Your Pet, Too

By Cari Romm



Is There a Placebo Effect for Animals?

David Ramey on October 25, 2008



Placebo effecten ook bij dieren

“Ratten kunnen beter tegen pijn met een placeboprik”

Blootstelling aan pijn aan 2 groepen met en zonder pijnstiller,
gevolgd door placebo behandeling:

Minder pijngedrag bij de groep die eerder pijnstiller kreeg



NIH Public Access

Author Manuscript

Pain. Author manuscript; available in PMC 2013 October 01.

Published in final edited form as:

Pain. 2012 October ; 153(10): 2009–2016. doi:10.1016/j.pain.2012.04.026.

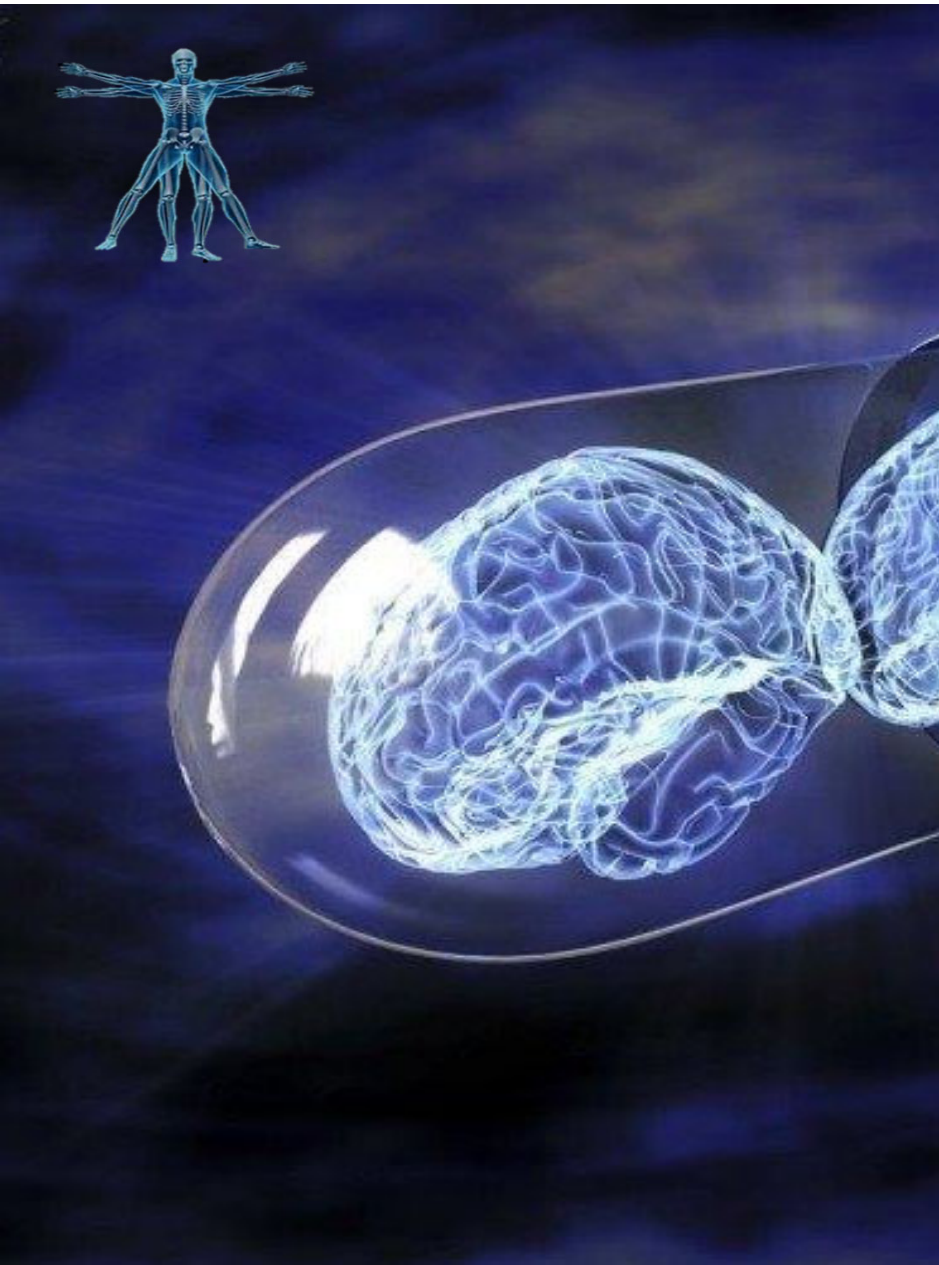
Placebo-induced analgesia in an operant pain model in rats

Todd A. Nolan¹, Donald D. Price², Robert Caudle², Niall P. Murphy³, and John K. Neubert^{1,*}

¹ College of Dentistry, Department of Orthodontics, University of Florida, Gainesville, FL

² Department of Oral Surgery, University of Florida, Gainesville, FL

³ Department of Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA



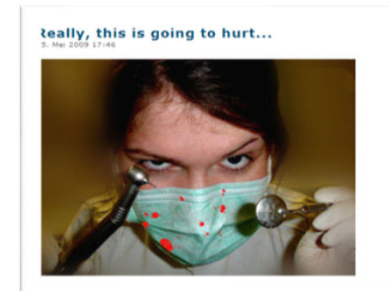
Quiz

Kan het placebo effect ook negatief werken?

Nocebo effect = ongunstige verwachting tav behandeluitkomst

- Ongunstige behandel-effecten, niet toegeschreven aan het behandelmechanisme
- Ontstaan door verwachtingen tov de ongunstige effecten

Bijv. “ik reageer altijd overgevoelig op alle medicijnen”





Nocebo effect

Voorbeeld

Bijwerkingen in 73 klinische trials migraine (bv. NSAIDs)

- Vergelijkbaar *aantal* bijwerkingen in behandel- en placebocondities
- Vergelijkbaar *type* bijwerkingen in behandel- en placebo condities bv. misselijkheid



Amanzio, Corazzini, Vase, Benedetti 2009



Nocebo effect Vaccinaties

Rapportage van ziekte-specifieke bijwerkingen
bij actieve en niet-actieve vaccins

Vaccine 29 (2011) 6321–6326

Contents lists available at ScienceDirect

 **Vaccine**

journal homepage: www.elsevier.com/locate/vaccine

Disease-specific adverse events following nonlive vaccines: A paradoxical placebo effect or a nocebo phenomenon?

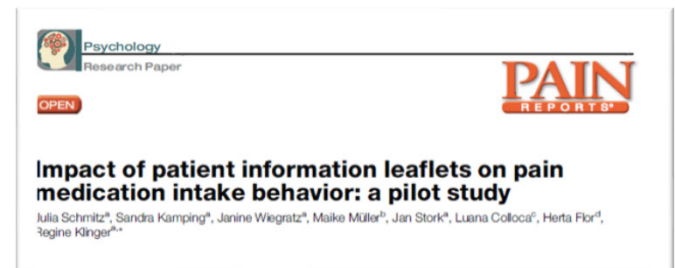
Claire Okaïs, Constance Gav, Fabrice Seon, Lvdie Buchaille, Emilie Charv, Benoît Soubeyrand *



Nocebo effect

Voorbeeld

Lezen van bijsluiter vermindert
de bereidwilligheid om
pijnmedicatie in te nemen



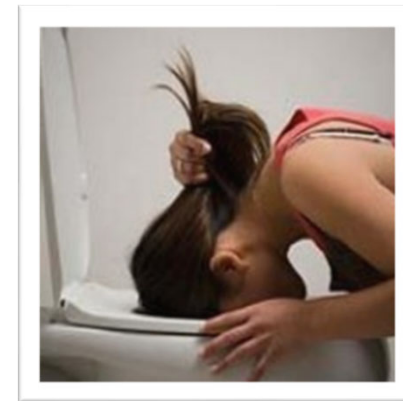


Nocebo effect

Voorbeeld

Sterke lichamelijke reacties op
chemotherapie

25-30% misselijkheid of braken
voor de behandeling of het
innemen medicatie



Jordan, Kasper & Schmoll, 2005



Nocebo effect

Media en internet

Verband tussen aandacht in de media of internet
en het rapporteren van meer klachten

Media Warnings About Environmental Pollution Facilitate the Acquisition of Symptoms in Response to Chemical Substances

WINNIE WINTERS, PhD, STEPHAN DEVRIESE, PhD, ILSE VAN DIEST, MA, BENOIT NEMERY, MD,
HENDRIK VEULEMANS, PhD, PAUL EELLEN, PhD, KAREL VAN DE WOESTIJNE, MD, AND OMER VAN DEN BERGH, PhD



Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Bad news: The influence of news coverage and Google searches on
Gardasil adverse event reporting

Kate Faasse^{a,*}, Jarry T. Porsius^{b,c,d}, Jonathan Faasse, Leslie R. Martin^e

Are media warnings about the adverse health effects of modern life self-fulfilling? An
experimental study on idiopathic environmental intolerance attributed to
electromagnetic fields (IEI-EMF)

Michael Witthöft^{a,b,*,1}, G. James Rubin^a



Placebo and Nocebo effecten hebben een significante impact

Therapietrouw
medicatie



Rapportage van
bijwerkingen

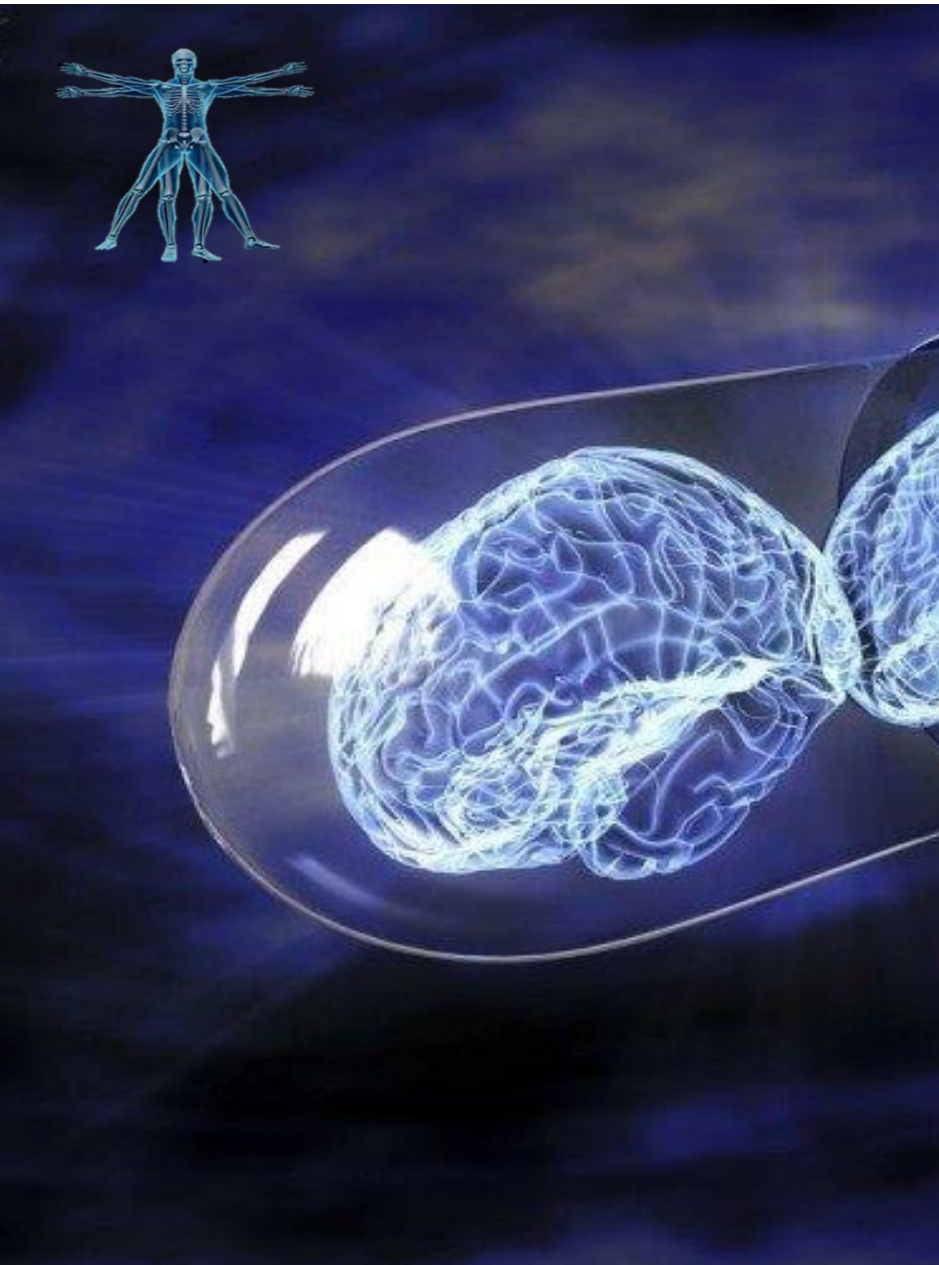


Herstel na
operaties



Mortaliteit en
morbiditeit





Neurobiologische basis

Placebo effecten



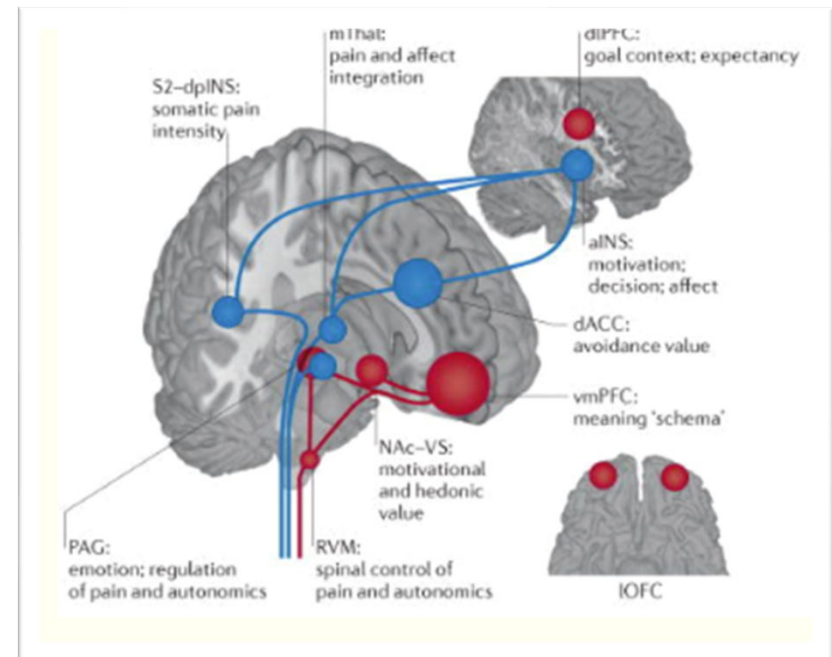
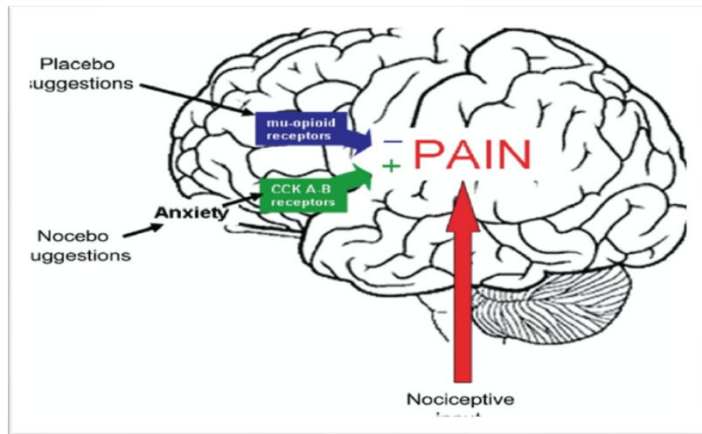
Quiz

Placebo effecten hebben vooral effecten op subjectieve klachten (bv. pijn), maar niet op neurobiologische markers, zoals het immuunsysteem ?



Neurobiologische basis Placebo and Nocebo effecten

Neurobiologie deels verschillend
voor placebo en nocebo effecten



Wager & Atlas, 2015, Thomaïdou et al, 2021

Pacheco-Lopez et al, Brain Beh Immun 2006



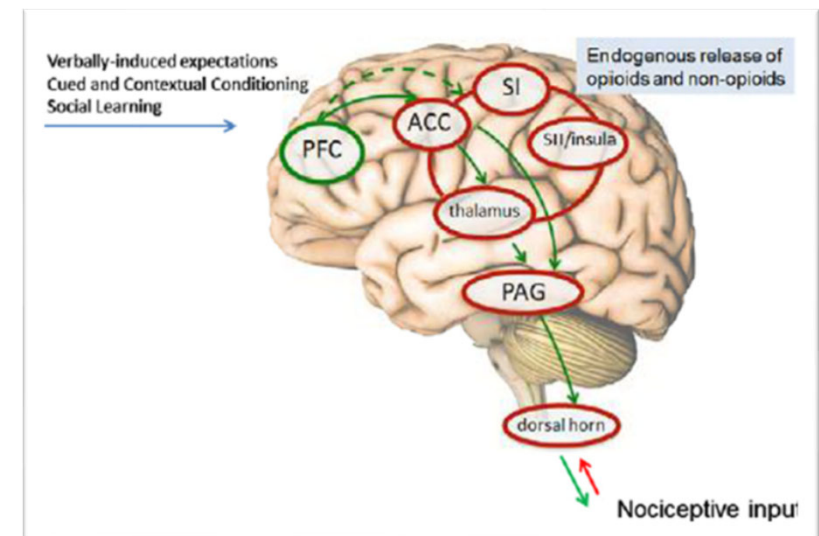
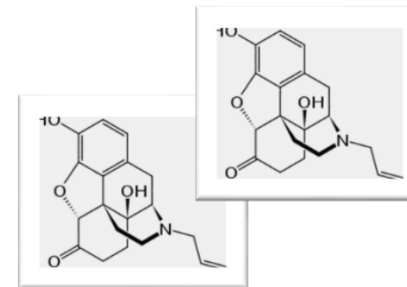
Neurobiologische basis

Placebo effecten bij pijn

Vrijkomen van endogene opioïden
(morfine-achtige pijnstillers)

→ Placebo effect bij pijn kan
geblokkeerd worden door opioïde
antagonisten

Zie voor review, bv. Colloca et al., Pain 2013

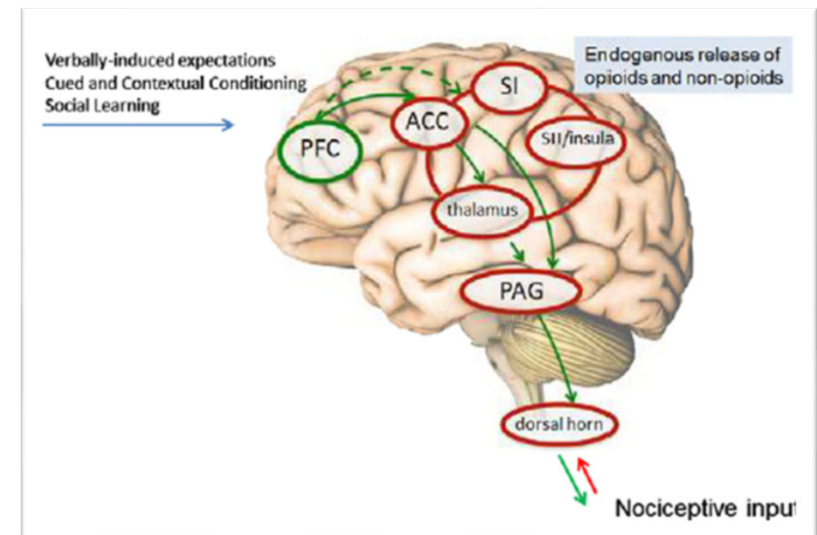
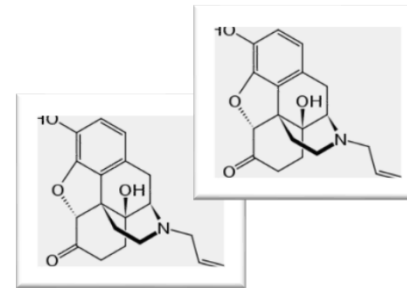




Neurobiologische basis

Placebo effecten bij pijn

- Naloxone
(opioïde antagonist)
remt placebo effecten
- Proglumide
(CCK- Cholecystokinin antagonist)
faciliteert placebo effecten
remt nocebo effecten



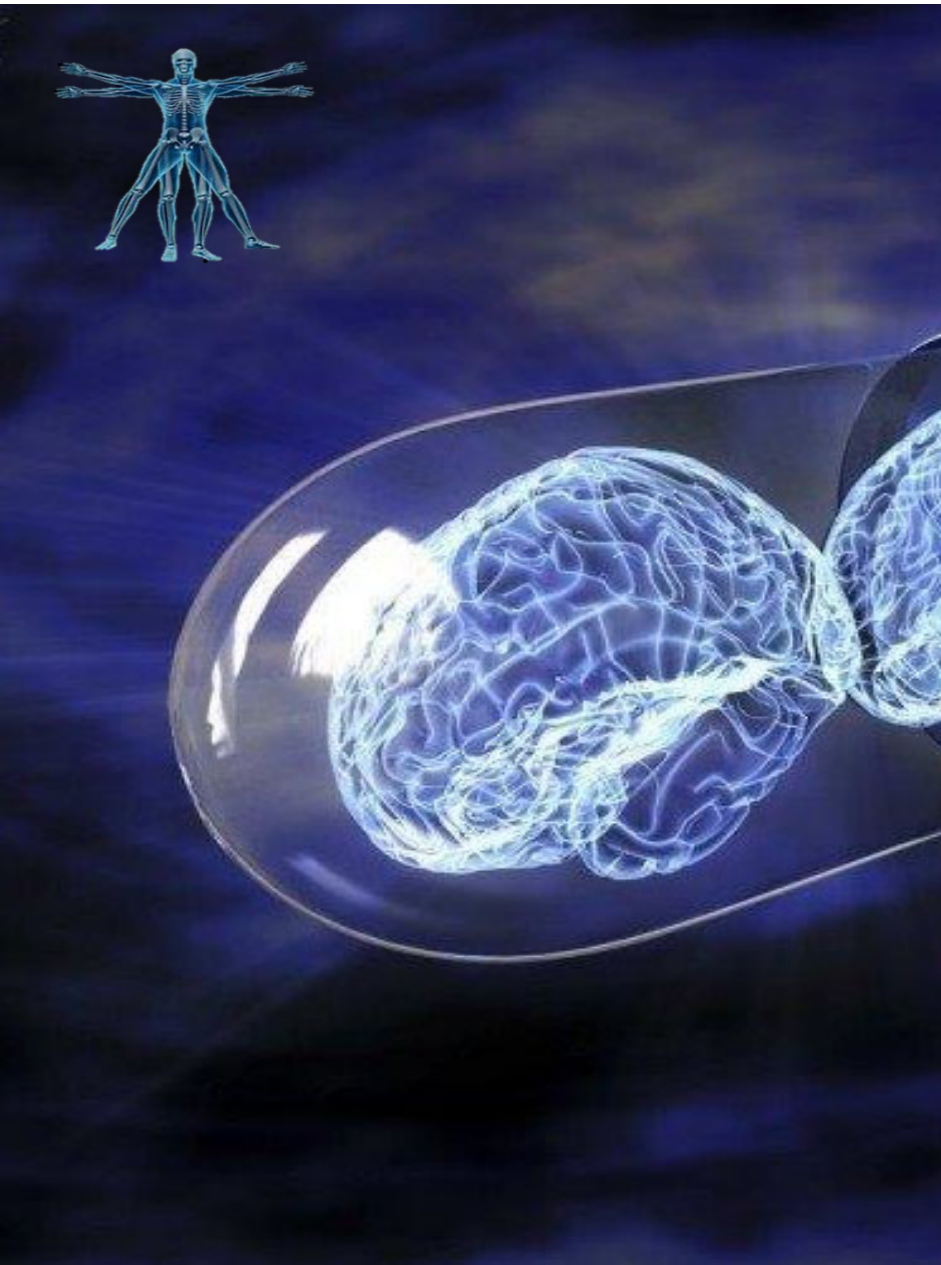


Neurobiologische basis Placebo effecten

Table 1 Summary of the mechanisms of placebo and placebo-related effects across diseases/systems and treatments

Disease/System	Treatment	Mechanism
Pain	Placebo administration Nocebo administration Verbal suggestions Open versus hidden administration	Expectation-induced activation of endogenous opioids and cholecystokinin as well as of several brain regions
Parkinson's disease	Placebo administration Nocebo administration Verbal suggestions Open versus hidden administration	Expectation-induced release of dopamine in the striatum and changes of firing pattern of subthalamic nucleus neurons
Depression	Placebo administration	Changes of metabolic responses in different brain regions (inhibition of serotonin reuptake?)
Anxiety	Placebo administration Open versus hidden diazepam	Change of activity of some brain regions
Addiction	Expected versus unexpected methylphenidate	Changes of metabolic activity in different brain regions
Autonomic responses to deep brain stimulation	Open versus hidden deep brain stimulation	Change of neuronal excitability in associative/limbic regions
Cardiovascular system	Placebo administration	Reduction of β -adrenergic activity of the heart
Respiratory system	Pharmacological preconditioning with buprenorphine	Conditioning of opioid receptors in the respiratory centers
Immune system	Pharmacological preconditioning with immunosuppressive drugs (e.g., cyclophosphamide and cyclosporin A)	Conditioning of some immune mediators (e.g., IL-2, IFN- γ , lymphocytes)
Endocrine system	Pharmacological preconditioning with 5-HT _{1B-1D} receptor agonists (sumatriptan)	Conditioning of some hormones (e.g., growth hormone, cortisol)

Benedetti, 2008



Placebo effect

Het lerende lichaam

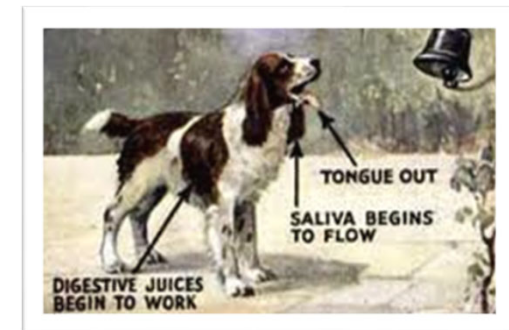
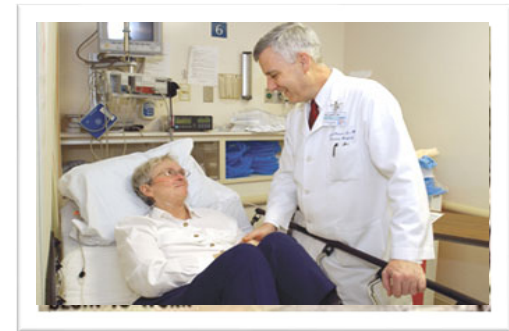


Placebo effect

Het lerende lichaam

Leerprincipes

- Verbale suggesties
 - Korte-termijn effecten, vooral in nocebo
- Conditionering
 - Meer stabiele, lange-termijn effecten
 - Effecten op het fysiologische responsysteem



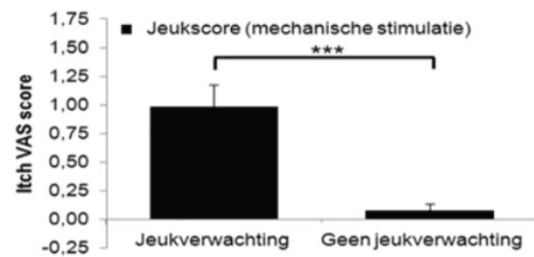


Rol van verbale suggesties Placebo effecten

Hoge verwachting



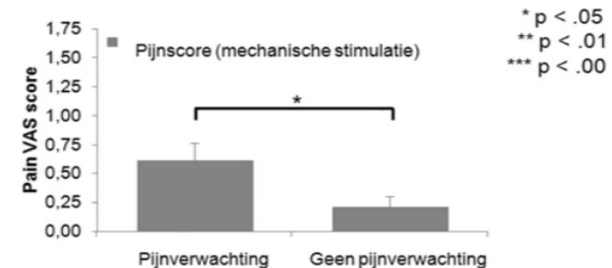
95% ervaart jeuk
(pijn) bij deze stimuli



Lage verwachting

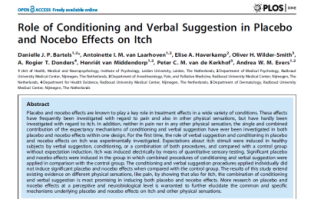


5% ervaart jeuk
(pijn) bij deze stimuli





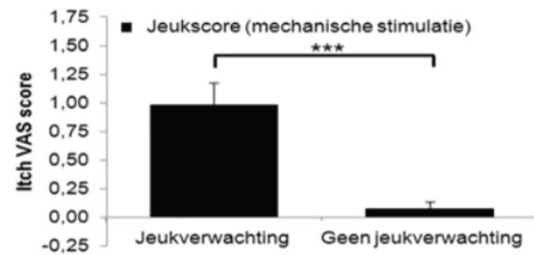
Combinatie van verbale suggesties en conditionering meest effectief



Hoge verwachting



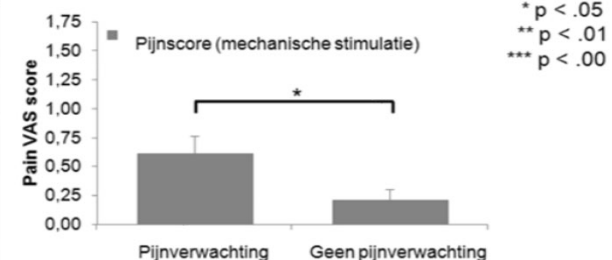
95% ervaart jeuk (pijn) bij deze stimuli



Lage verwachting



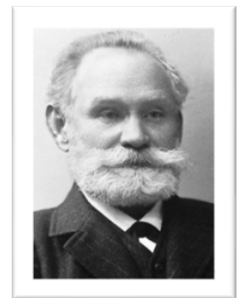
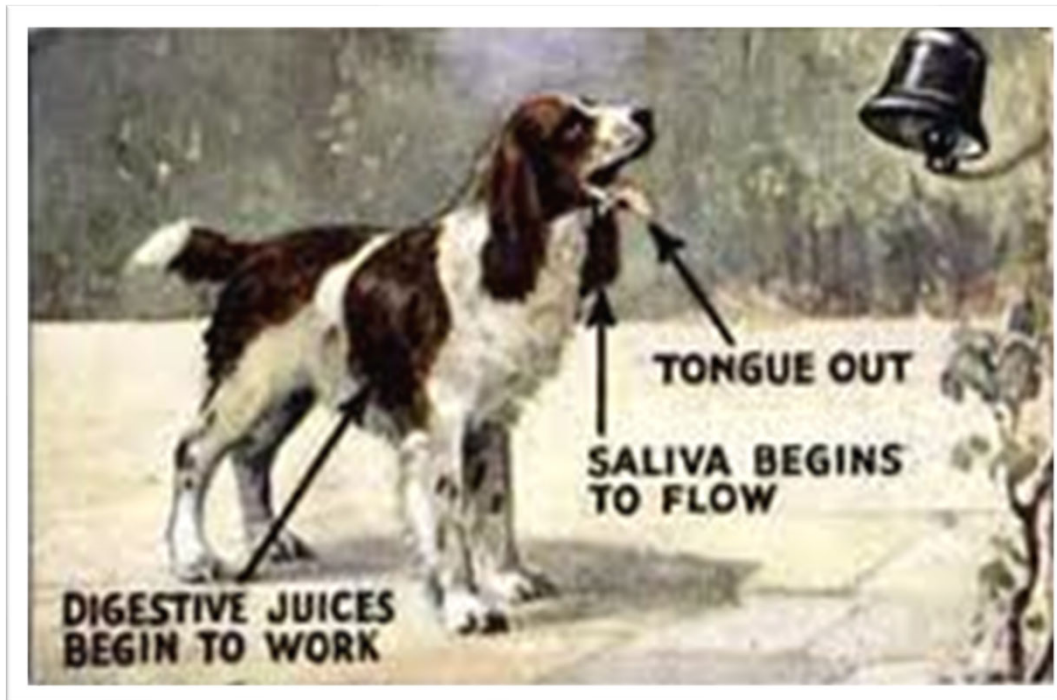
5% ervaart jeuk (pijn) bij deze stimuli





Rol van conditionering

Placebo effecten



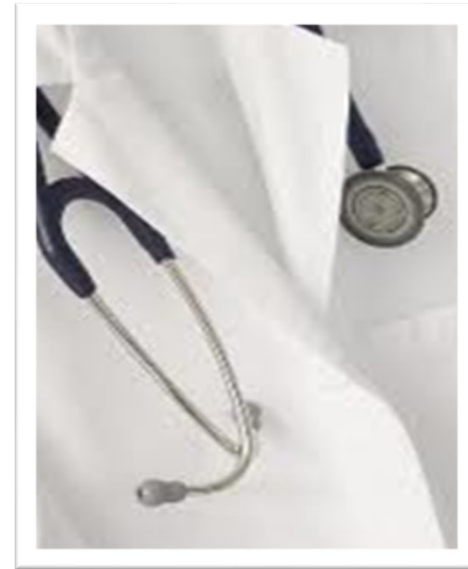


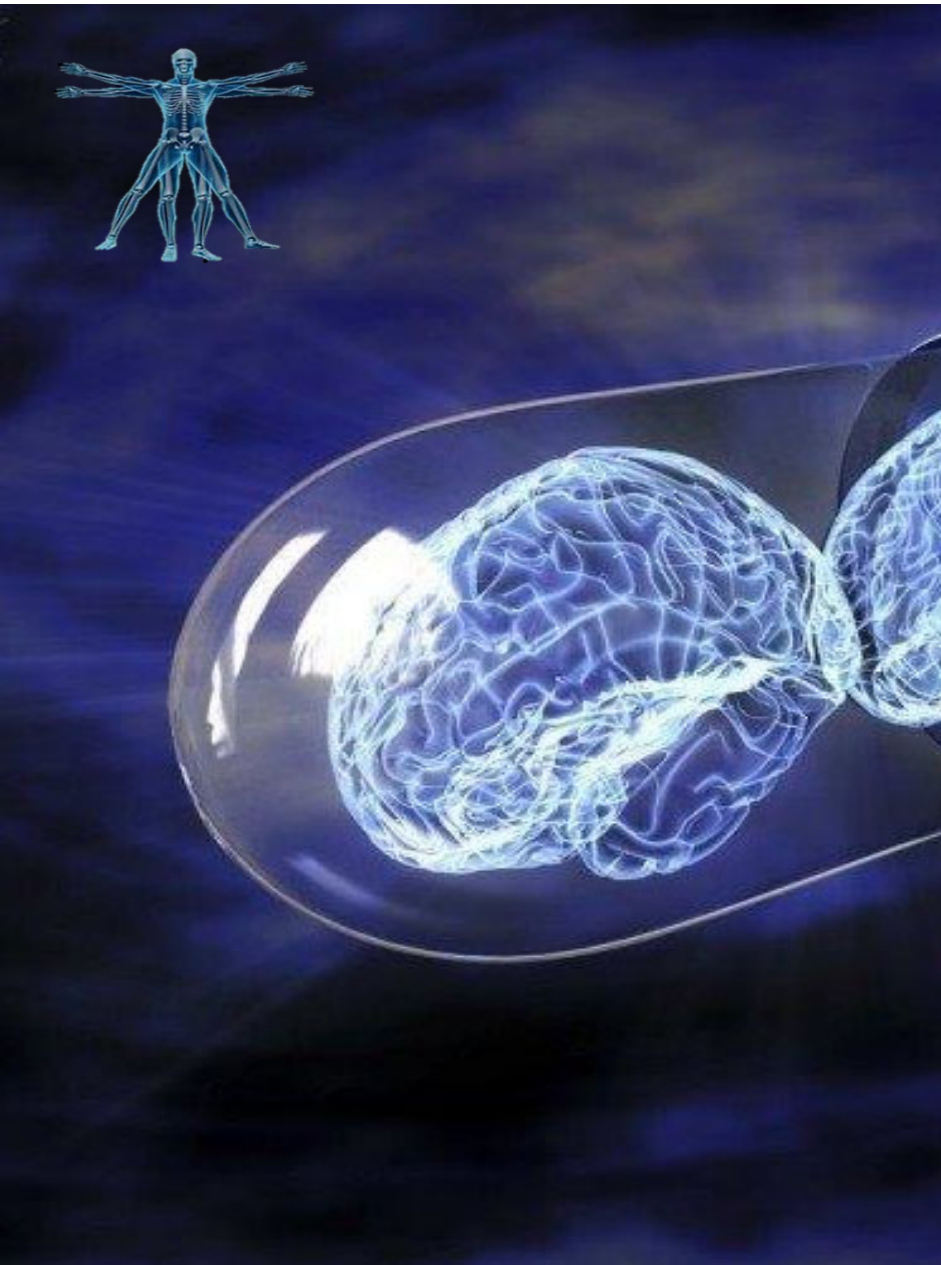
Rol van conditionering





Rol van conditionering





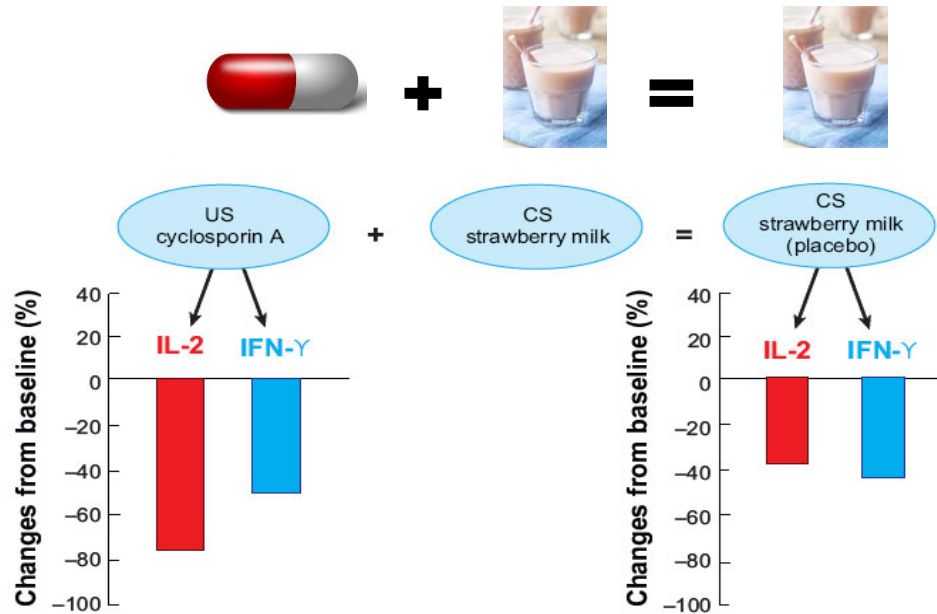
Placebo effect

Het lerende lichaam



Het lerende lichaam

Immuun conditionering



Benedetti, Ann Rev Pharma Tox, 2008



Het lerende lichaam

Immuun conditionering



Immunosuppressie



- Interleukin-2
- Interferon gamma

Immunostimulatie



- Natural killer cell activity
- Quinolinic acid
- CD14
- CD64

Allergieën





Het lerende lichaam

Endocriene conditionering



Frontiers in Neuroendocrinology
Volume 52, January 2019, Pages 206-218



Conditioned hormonal responses: A systematic review in animals and humans

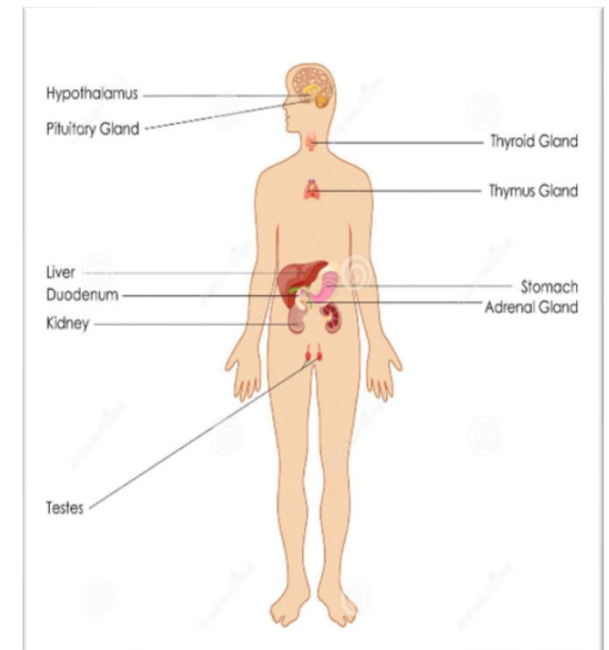
Dieronderzoek: Aleksandrina Skvortsova ^{a, b, d, e}, Dieuwke S. Veldhuijzen ^{a, b}, Iris E.M. Kloosterman ^a, Onno C. Meijer ^c, Henriët van Middendorp ^{a, b}, Gustavo Pacheco-Lopez ^{a, d}, Andrea W.M. Evers ^{a, b, e}

- Corticosterone
- Luteinizing hormone
- Testosterone
- Insulin
- Melatonin
- Oxytocin



Humane studies:

- Growth hormone
- Cortisol
- Insulin
- Oxytocin

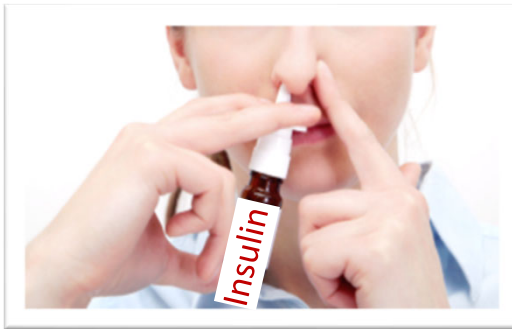




Het lerende lichaam

Insuline conditionering

Dag 1 (leerfase)



Dag 2 (testfase)

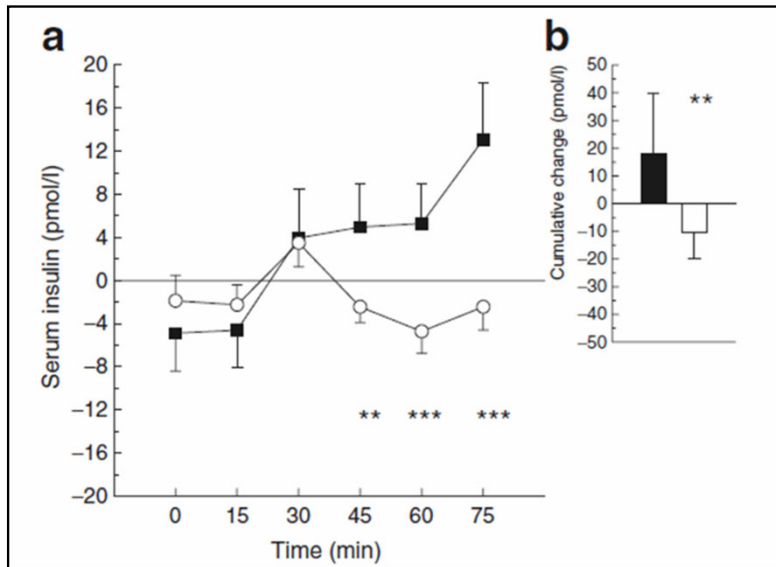




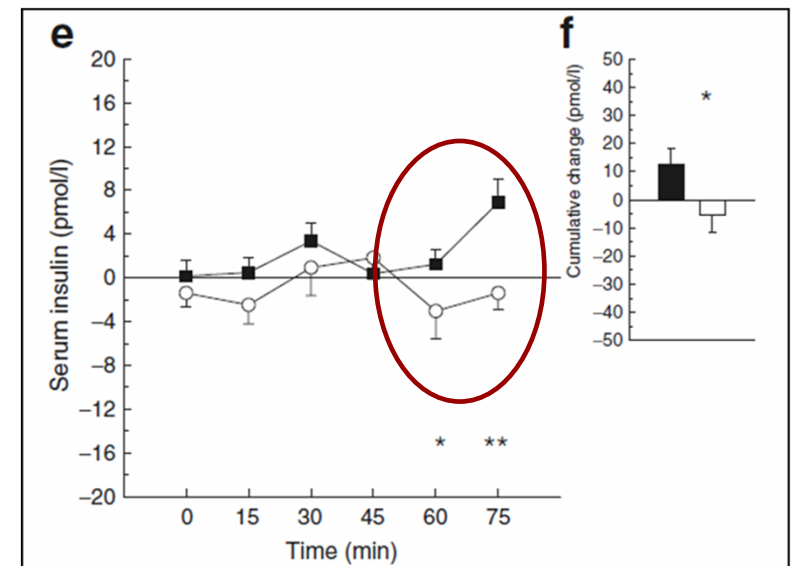
Het lerende lichaam

Insuline conditionering

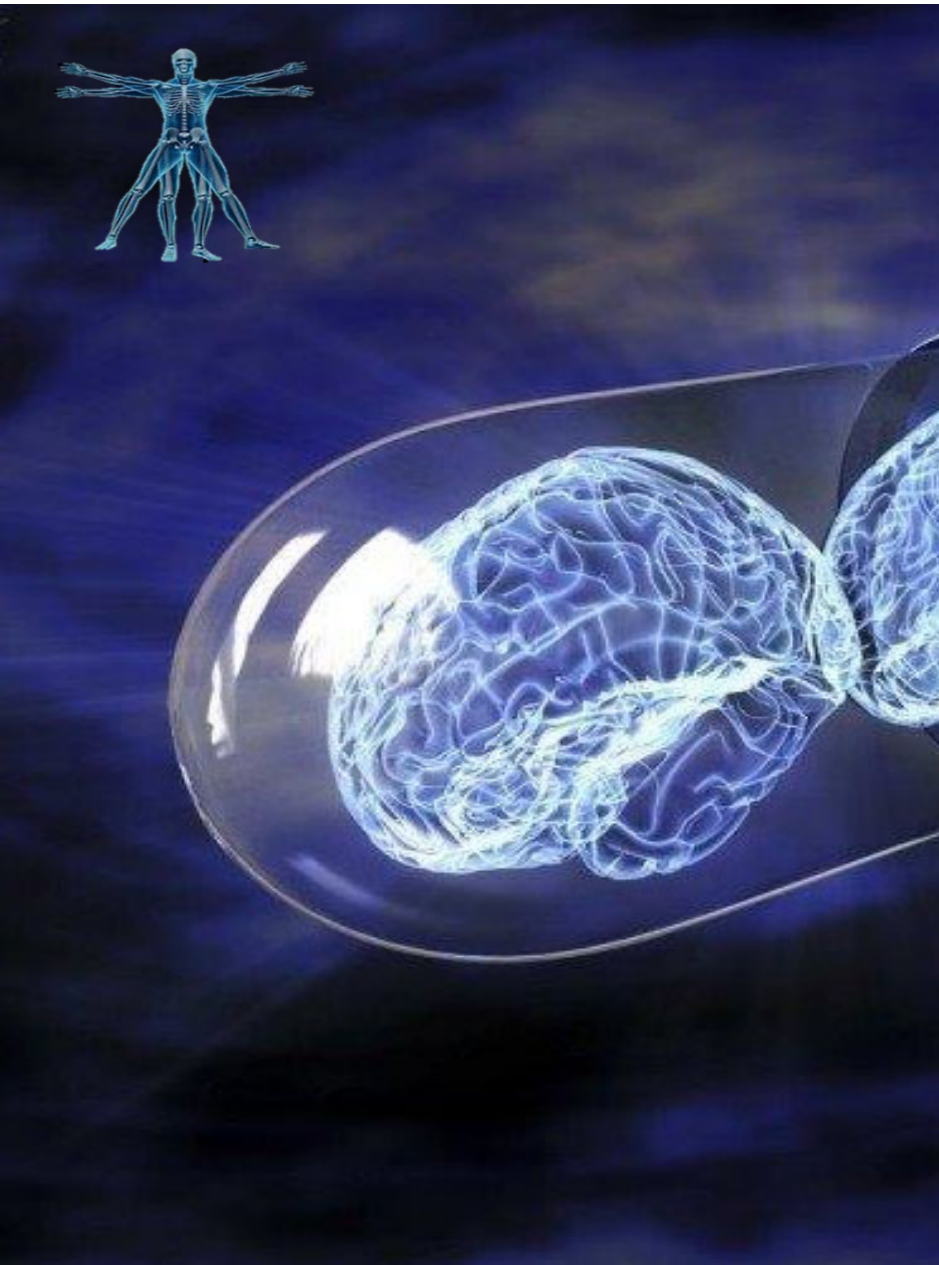
Dag 1 (leerfase)



Dag 2 (testfase)



■ Insuline-conditionering groep
□ Placebo groep

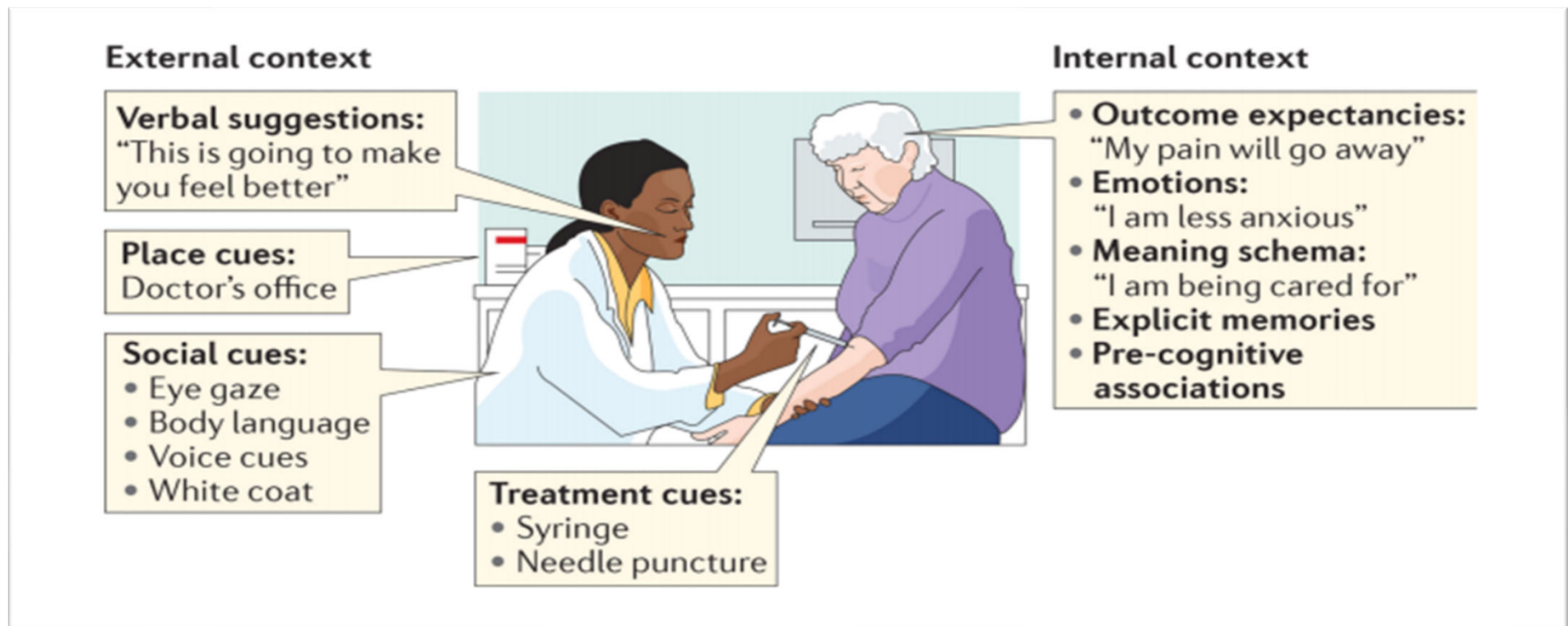


Klinische implicaties

De rol van de
behandelcontext



Klinische implicaties Behandelcontext

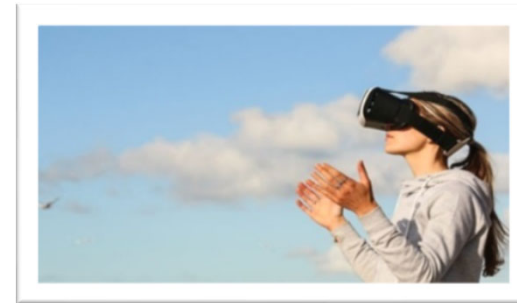




De rol van de behandelcontext

Patiënt

Expectation behandelingen



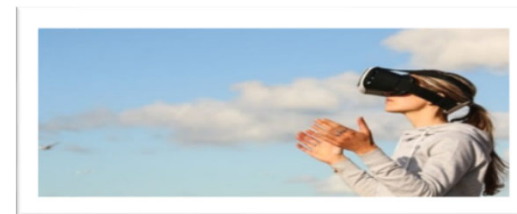
Professional

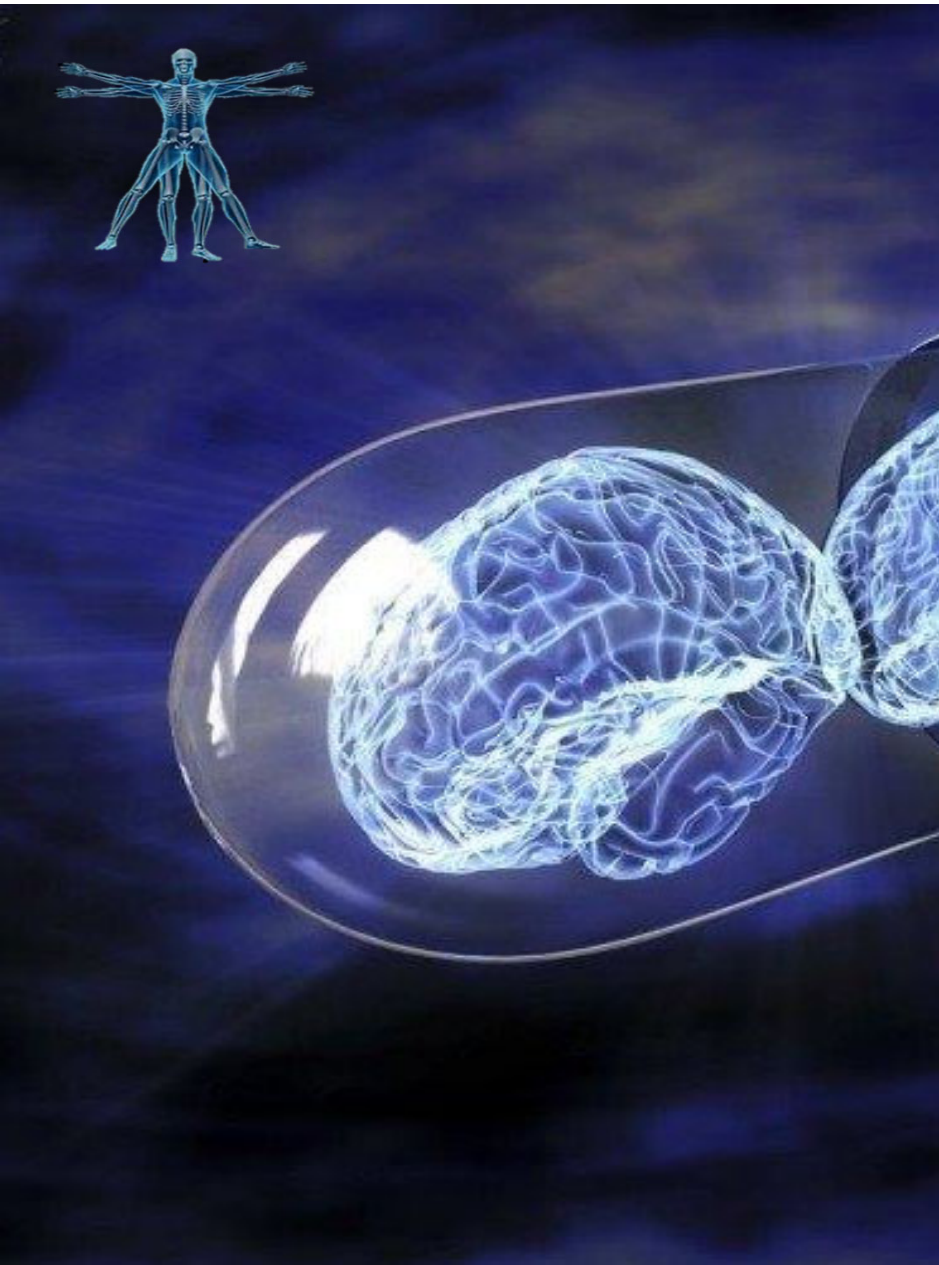
Arts-patiënt communicatie



Medicatie

Farmacotherapeutische conditionering





Quiz

Openheid over placebo effecten
vermindert het therapeutisch
effect ?

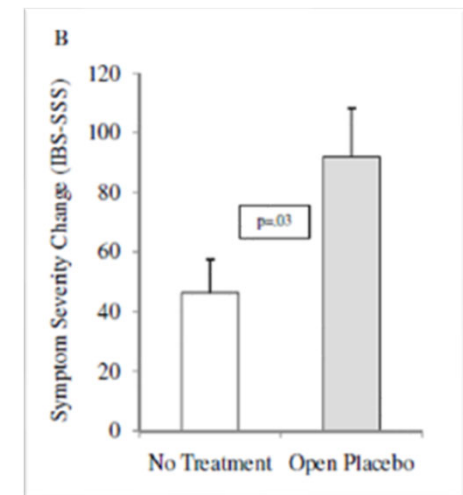
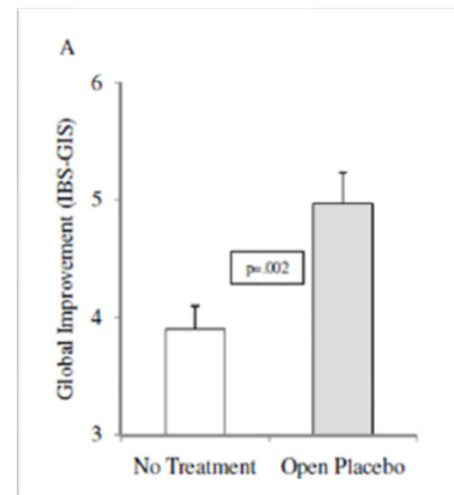


Klinische implicaties

Open label placebo

Voorschrijven placebo's na gedetailleerde informatie over placebo effect bij patiënten met prikkelbaar darmsyndroom

Verbeterde prikkelbare darm-symptomen (bijv. buikpijn) in vergelijking met geen behandeling



Kaptchuk et al., 2010

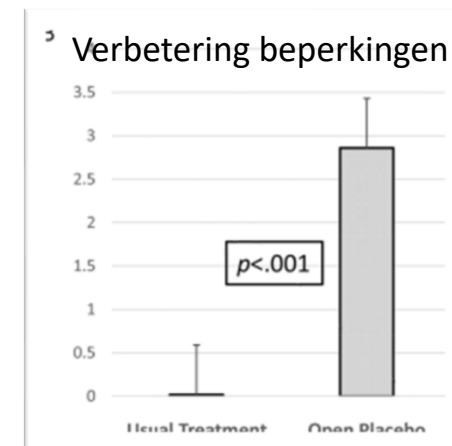
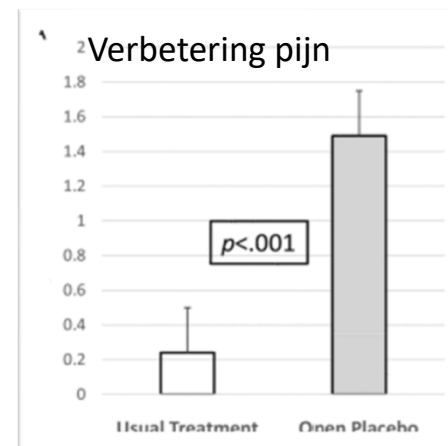


Klinische implicaties

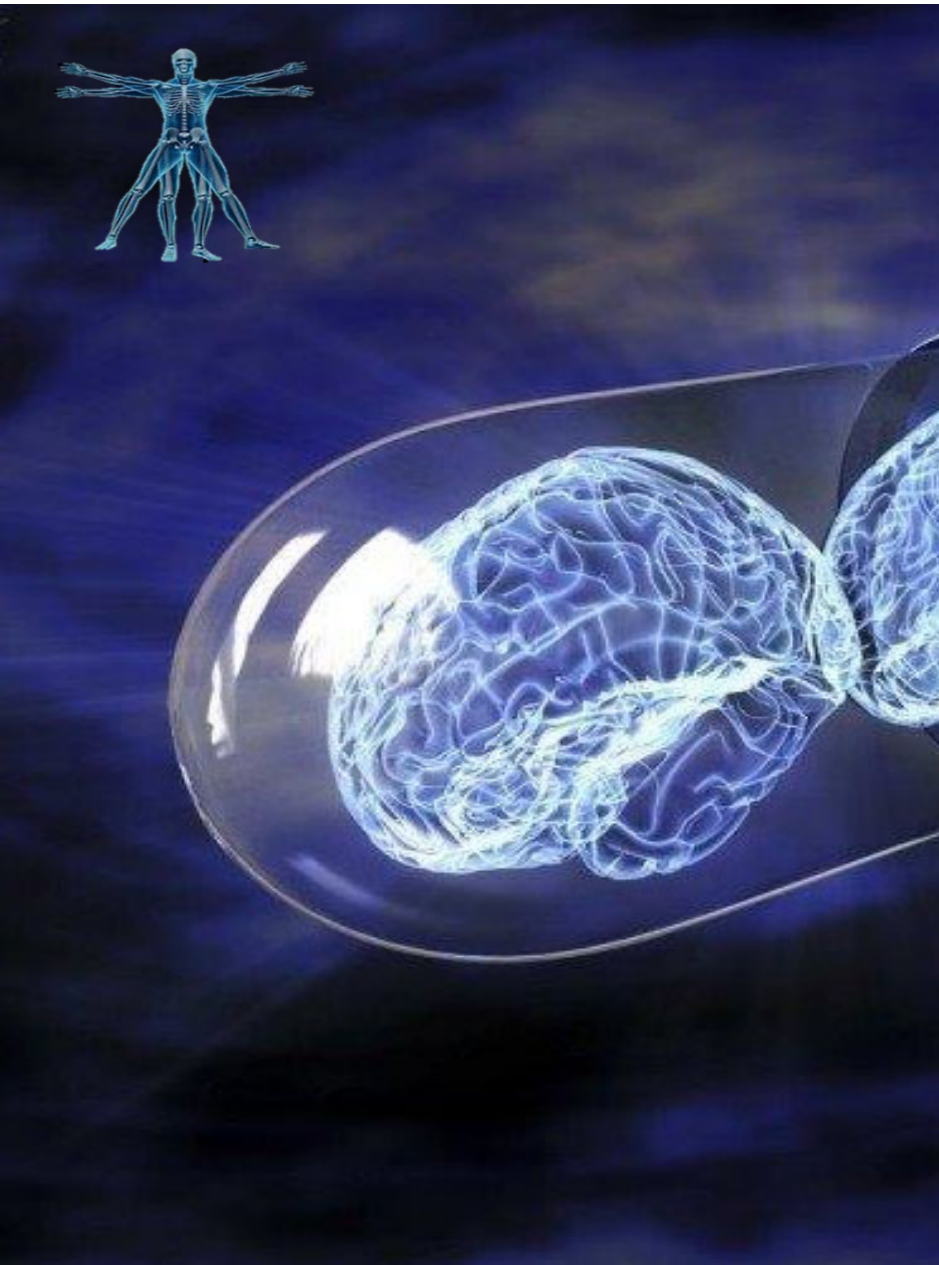
Open label placebo

Voorschrijven placebo's aan patiënten met chronische lage rugpijn

Minder pijn en dagelijkse beperkingen in vergelijking met patiënten met enkel de reguliere behandeling



Kaptchuk et al., 2010



Quiz

Patiënten moeten voor de start van een behandeling geïnformeerd worden over mogelijke placebo- en nocebo-effecten.

In de arts opleiding hoort daarom scholing over deze effecten.

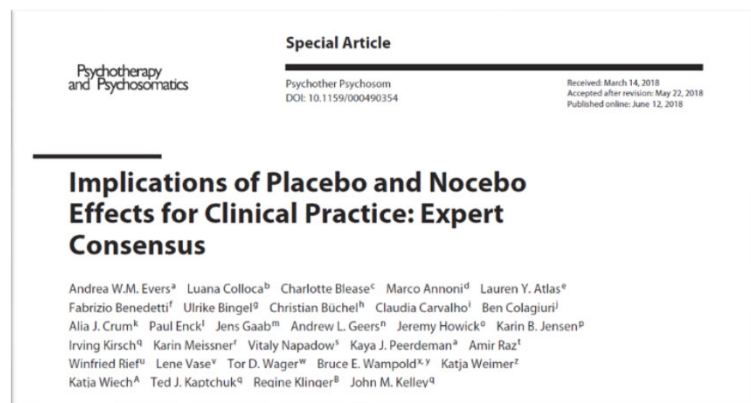


Expert consensus SIPS Conference 2017 en 2019

Consensus paper: Klinische aanbevelingen

1st and 2nd official SIPS conferences

- Informeer patiënten over placebo en nocebo effecten
- Train professionals in de communicatie over placebo en nocebo effecten



Evers et al, 2018 and 2020

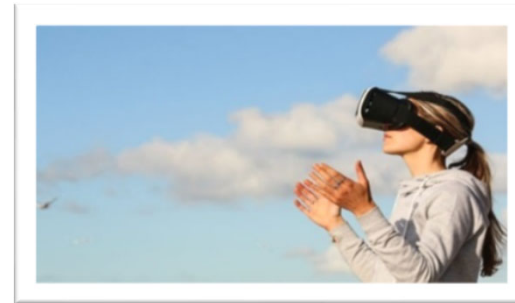




De rol van de behandelcontext

Patiënt

Werken met verwachtingen



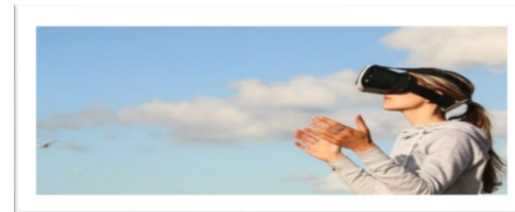
Professional

Arts-patiënt communicatie



Medicatie

Farmacotherapeutische conditionering





De rol van de behandelcontext Optimaliseren verwachtingen

Expectation-Focused Psychotherapy to Improve Clinical Outcomes

Bettina K. Doering*, Julia A. Glombiewski[†], Winfried Rief^{‡,1}

SYSTEMATIC REVIEW/META-ANALYSIS

**Using Different Expectation Mechanisms to Optimize
Treatment of Patients With Medical Conditions:
A Systematic Review**

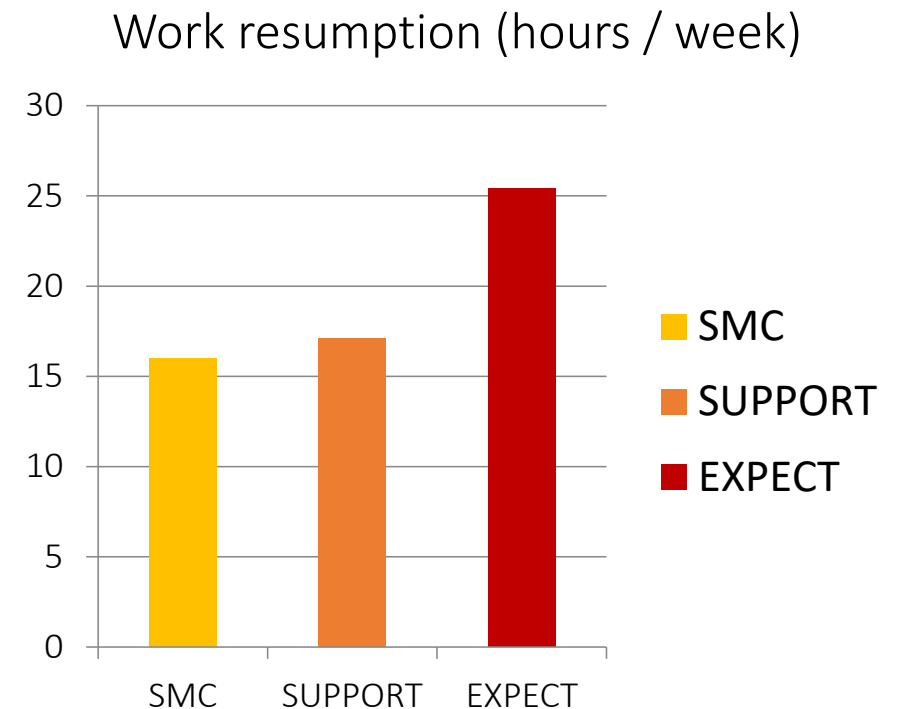
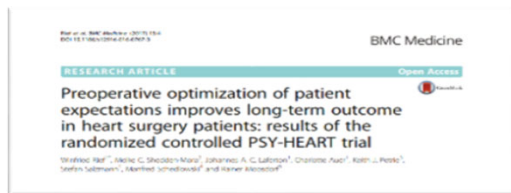
Tobias Kube, PhD, Julia Anna Glombiewski, PhD, and Winfried Rief, PhD



De rol van de behandelcontext

Optimaliseren verwachtingen

Gunstige effecten op herstel na
expectation-focused therapie
(5 sessies) in patiënten die een
hartoperatie ondergaan





De rol van de behandelcontext

Patiënt

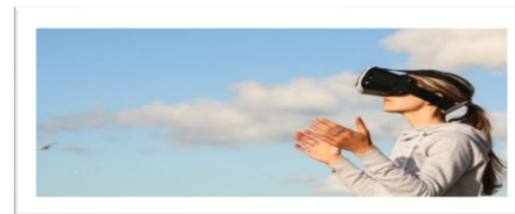
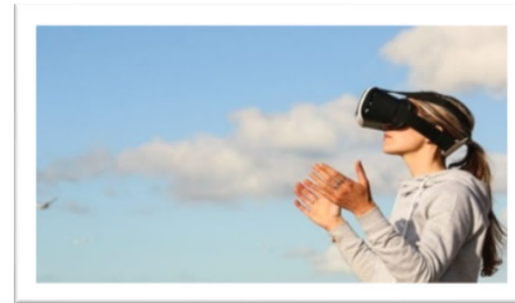
Werken met verwachtingen

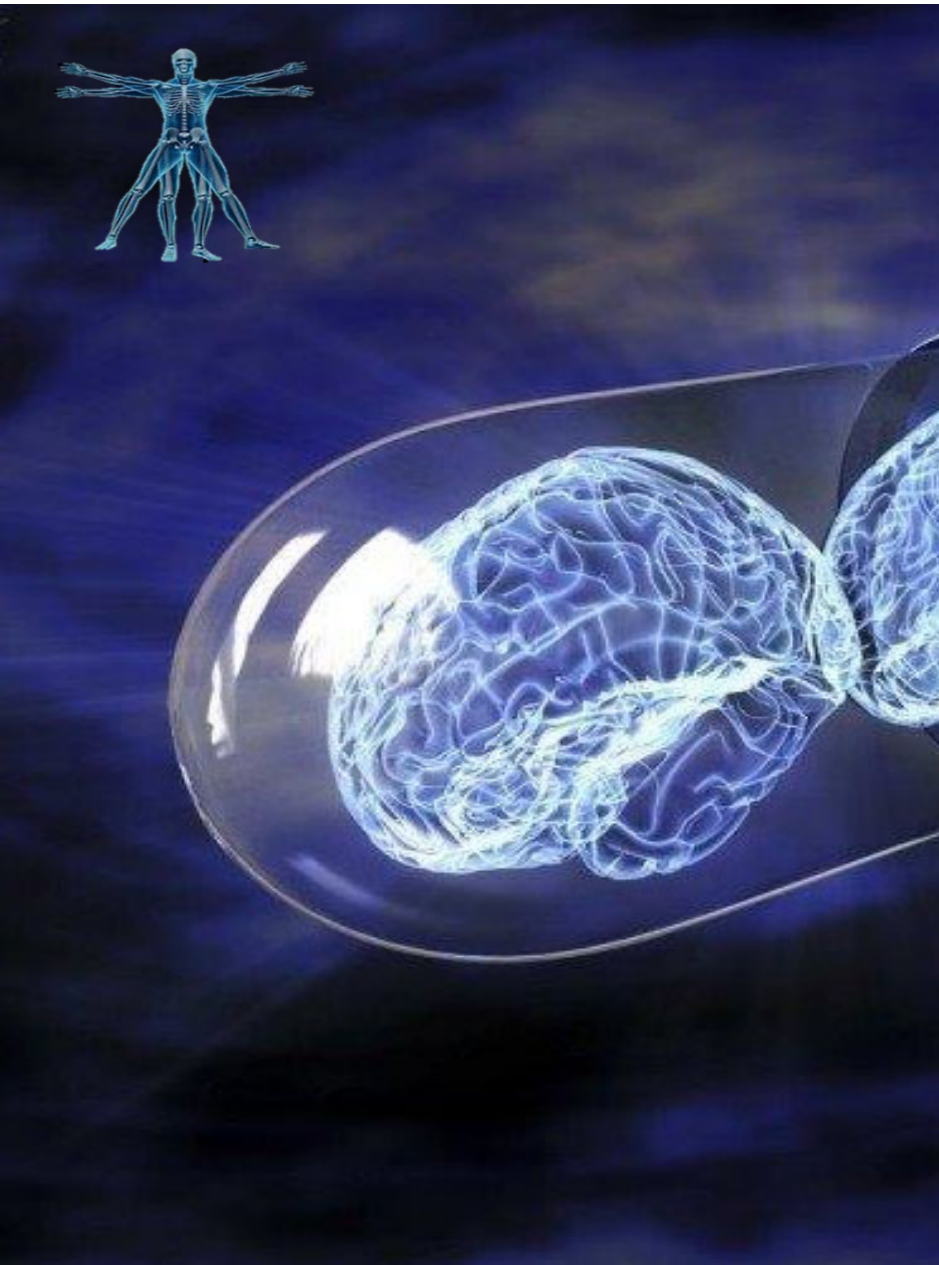
Professional

Arts-patiënt communicatie

Medicatie

Farmacotherapeutische conditionering





Quiz

Hoe communiceer je over risico's
en bijwerkingen om nocebo
effecten te voorkomen?



De rol van de behandelcontext

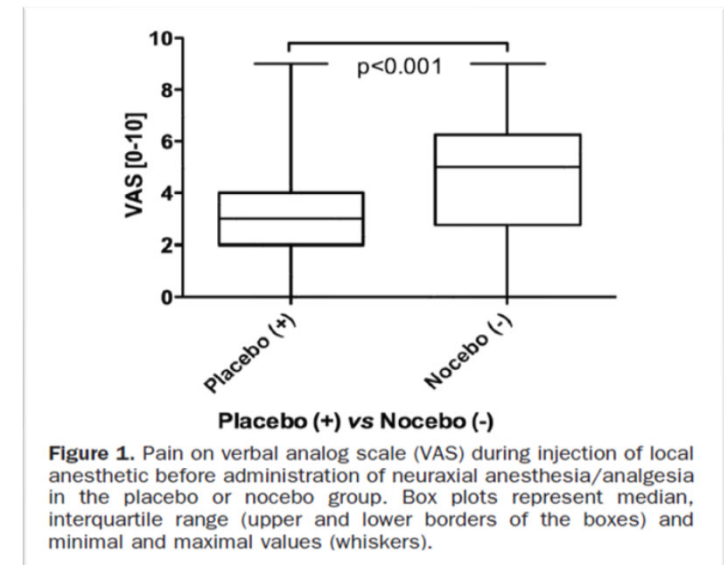
Informatie over procedures

Groep 1 (nocebo):

"Je zult een **harde steek** voelen; dit is de **ergste pijn** gedurende de ingreep. "

Groep 2 (placebo):

"We zullen je een **lokale pijnstiller** geven die het gebied zal verdoven en die je **comfortabel** laat voelen gedurende de hele ingreep."



Nocebo-Induced Hyperalgesia During Local Anesthetic Injection

Dirk Varelmann, MD, DESA,* Carlo Pancaro, MD,† Eric C. Cappiello, MD,* and William R. Camann, MD*
(Anesth Analg 2010;110:868-70)



De rol van de behandelcontext Informatie over nocebo

Waarschuwen voor specifieke
bijwerkingen verhoogt juist de kans op
het krijgen van deze bijwerkingen

Original Paper

Warning about side effects can increase their occurrence: an experimental model using placebo treatment for sleep difficulty

**Ben Colagiuri^{1,2}, Kari McGuinness², Robert A Boakes¹
and Phyllis N Butow^{1,3}**

Psychopharm

Journal of Psychopharmacology
26(12) 1540–1547
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DOI: 10.1177/0269881112458730
jop.sagepub.com

SAGE



De rol van de behandelcontext Informatie over nocebo

Klachten die mensen toeschreven aan
windmolen-syndroom verminderden
na uitleg over nocebo-effecten





De rol van de behandelcontext

Informatie over nocebo

1. **Informeer** patiënten over nocebo effecten (in je eigen woorden) bij een verhoogd risico op bijwerkingen
2. Vraag naar **voorkeur** om geïnformeerd te worden over risico's en bijwerkingen
3. Screening van patiënten met **hoog risico op nocebo effecten** met zorg op maat voor patiënten at risk

Tell Me the Truth and I Will Not Be Harmed: Informed Consents and Nocebo Effects

Luana Colloca¹
University of Maryland, Baltimore

Placebo and Pain Research: From Bench-to-Bedside and Beyond
Review

OPEN

PAIN
REPORTS

How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions

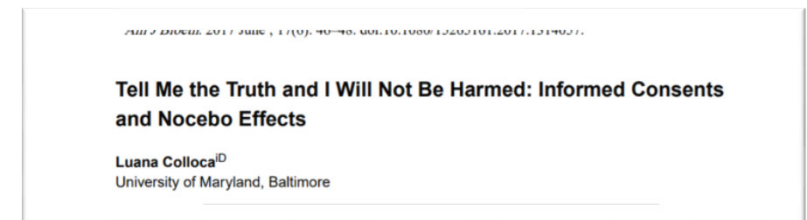
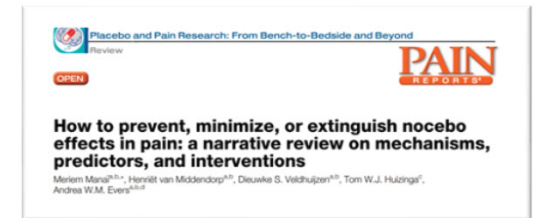
Meriem Manal^{1,2,*}, Henriëtte van Middendorp^{1,3}, Dieuwke S. Veldhuijzen^{1,3}, Tom W.J. Huzinga¹,
Andree W.M. Evers^{1,2,4}



De rol van de behandelcontext

Gebruik maken van placebo

1. Leg de **werking van het placebo effect** (in je eigen woorden) en **behandelmechanismen** begrijpelijk uit
2. Benadruk de mogelijke **lange-termijn voordelen** van de behandeling
3. Creëer een **open samenwerkende sfeer** gebaseerd op **transparantie**: Placebo effecten werken op basis van vertrouwen



Communicatietraining

artsen en andere zorgverleners



eLearning voor arts-patient communicatie
gericht op placebo – nocebo effecten

1. Praten over verwachtingen
2. Behandelrationale
3. Risico's en bijwerkingen
4. Therapeutische relatie

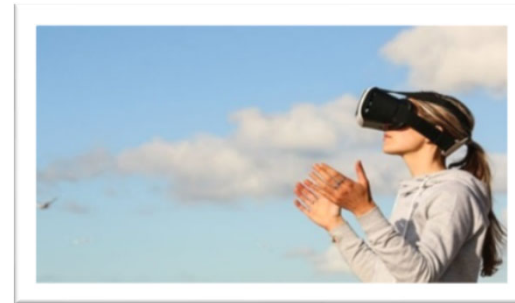




De rol van de behandelcontext

Patiënt

Werken aan verwachtingen



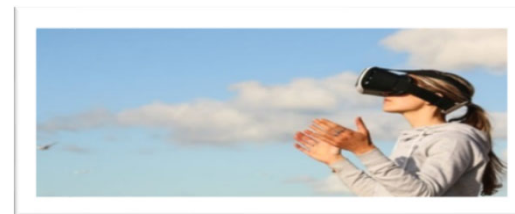
Professional

Arts-patiënt communicatie



Medicatie

Farmacotherapeutische conditionering





Farmacotherapeutische conditionering

Standaard dosering



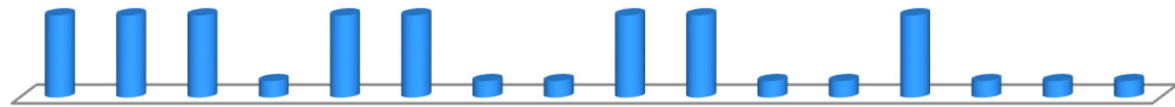


Farmacotherapeutische conditionering

Standaard dosering



Aangepaste dosering
conditionering schema



Gunstiger behandelbeloop en/of minder bijwerkingen
bij o.m. **depressie, ADHD, psoriasis, nierziekten**

Review Colloca et al., 2017, Smits et al 2020



Reguliere zorg:

Behandelingen effectiever
en doelgerichter inzetten

Patiënt:

Beter resultaat met minder bijwerkingen

Bijna 5 miljard Euro:

Jaarlijkse geneesmiddelen kosten
in Nederland

Woorden als medicijn:

It's magic?

The difference between medicine and magic is that magicians know what they are doing

Rodney J. Hicks

LU Leids Universitair
MC Medisch Centrum



Helpt u ons zieke kinderen hun behandeling
beter te laten doorstaan door magie & illusie?

Steun ons onderzoek



**Medicine as performance: what
can magicians teach doctors?**

Daniel K Sokol

Lecturer in Medical Ethics and Law, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK
E-mail: daniel.sokol@talk21.com



Woorden als medicijn: It's the placebo effect ...

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