SIPS society for interdisciplinary placebo studies

2nd
OFFICIAL SIPS CONFERENCE
ON PLACEBO STUDIES

Program & Abstract book

July 7 - 9, 2019
Leiden, the Netherlands

Welcome

Dear attendee of the 2019 SIPS conference,

It is our great pleasure to welcome you to the 2nd official Society for Interdisciplinary Placebo Studies (SIPS) conference on placebo studies. The conference venue is the beautiful historic Stadsgehoorzaal in Leiden, the Netherlands. This second edition of the SIPS conference promises to be very inspiring. We highly appreciate that so many researchers contributed to the rich and varied conference program and made their way to attend the conference.

The SIPS conference is devoted to the interdisciplinary study of placebo effects. It focuses on medical, psychosocial, philosophical, and neurobiological research on placebo and nocebo effects, and also addresses ethical dilemmas and treatment options. The range of topics mirrors the efforts of SIPS to advance research on knowledge of placebo and nocebo effects and to eventually improve clinical care. Next to the keynote speakers and the invited speakers, we are pleased to offer a diverse scientific program due to the many submitted contributions, with different parallel sessions to choose from. We are also very pleased to invite you to the conference dinner which will take place on Monday evening July 8, at beachclub BAIT in Wassenaar. The busses for the dinner will leave at 7 PM from the Stadsgehoorzaal in Leiden and will return to the conference location at 11 PM.

We hope that this conference will foster the exchange of new ideas and promote new contacts between researchers on the placebo effect. We wish you an inspirational and fruitful conference, and hope that you will enjoy everything the conference and the beautiful city of Leiden has to offer!

Sincerely,

On behalf of the SIPS conference and steering committees,

Andrea W.M. Evers
Chair SIPS conference 2019

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The SIPS Conference Committee


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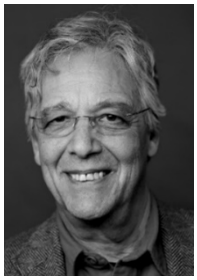
Irving Kirsch


Bruce Wampold

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Conference Day 1: Sunday July 7, 2019

Conference venue: Stadsgehoorzaal, Leiden

Time	Activity	Location
03:00 PM	**Registration**	Entree Foyer
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	Special Welcome Henri Lenferink (Mayor Leiden)	
	Short welcome Andrea Evers (Chair conference committee)	
	Keynote Lecture Jet Bussemaker - Breaking the boundaries	
	Keynote Lecture Luana Colloca - Mechanisms of observationally-induced pain modulation: From placebo effects to virtual reality	
	Travel awards ceremony	
06.00 - 07.30 PM	**Opening reception and selected poster presentations**	Catharina Foyer

Conference Day 2: Monday July 8, 2019

Conference venue: Stadsgehoorzaal, Leiden

Time	Activity	Location
08:00 AM	Registration and welcome with coffee and tea	Entree Foyer
08:30 AM	**Keynote Lecture** Tor Wager - Placebos, therapy, and self-fulfilling prophecies	Grote Zaal
09:15 AM	**Plenary session 1** How to use placebos in clinical practice?	Grote Zaal
11:00 AM	*Coffee break*	Catharina Foyer
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12:30 PM	*Lunch*	Catharina Foyer
1:00 PM	**Poster presentations** */ Lunch*	Catharina Foyer
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03:45 PM	*Coffee break*	Catharina Foyer
04:15 PM	**Plenary session 3** Nocebo: Expecting harmful effects will make you ill	Grote Zaal
06:00 PM	**Keynote Lecture** Ionica Smeets - This study will change your life – health news in the media	Grote Zaal
06:45 PM	*Short break*	
07:00 PM	Busses depart from conference location	
07:30 PM	***Conference dinner***	Beachclub BAIT Wassenaar
11:00 PM	Busses return to conference location	

Conference Day 3: Tuesday July 9, 2019

Conference venue: Stadsgehoorzaal, Leiden

Time	Activity	Location
08:00 AM	Registration and welcome with coffee and tea	Entree Foyer
08:30 AM	**Keynote Lecture** Irving Kirsch - Hypnosis as a non-deceptive extra-strength placebo	Grote Zaal
09:15 AM	**Plenary session 4** The future of placebo: Conceptualizations and beyond	Grote Zaal
11:00 AM	*Coffee break*	Catharina Foyer
11:30 AM	**Parallel sessions 2** 2.1 Open up about placebos: Open label placebo applications 2.2 From genes to expectancies: Predicting placebo effects 2.3 New applications of traditional conditioning paradigms 2.4 Placebo effects in psychotherapy and neurocognitive disorders 2.5 Placebo and nocebo effects on cognition	 Grote Zaal Aalmarktzaal Breezaal Jan Willem Schaap zaal Cornelis Schuytzaal
12:30 PM	*Lunch*	Catharina Foyer
1:00 PM	**Poster presentations** */ Lunch*	Catharina Foyer
02:00 PM	**Parallel sessions 3** 3.1 Neural mechanisms in placebo studies 3.2 Placebo effects in clinician-patient interactions 3.3 Placebo effects in children and adolescents 3.4 Innovative ways to enhance placebo analgesia 3.5 Novel perspectives on placebo effects	 Grote Zaal Aalmarktzaal Breezaal Jan Willem Schaap zaal Cornelis Schuytzaal
03:00 PM	*Coffee break*	Catharina Foyer
03:30 PM	**Plenary session 5** Novel neuroimaging findings: How do placebo effects work?	Grote Zaal
05:15 PM	**Presentation & poster award ceremony**	Grote Zaal
05:30 PM	**Conference closure**	Grote Zaal

Sunday July 7

Keynote lecture: Jet Bussemaker

Time:	Sunday, July 7, ~04:35 PM
Location:	Grote Zaal
Chair:	Andrea Evers

About Jet Bussemaker

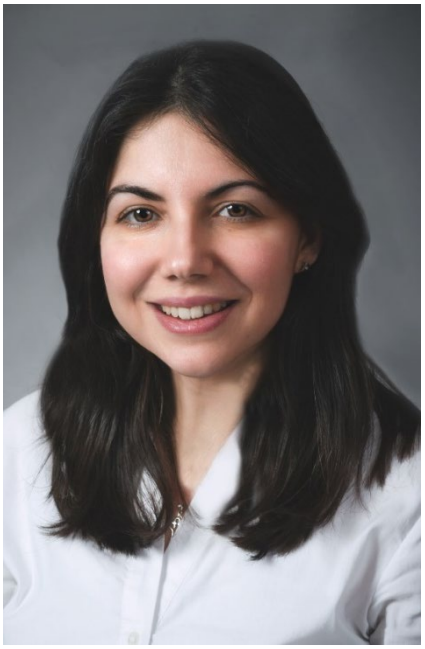
Prof. dr. Jet Bussemaker is a professor of Governance, Science and Societal Impact, especially concerning Health Care at Leiden University Medical Center and the Governance Faculty of Leiden University. Starting from June 2019, she is also the President of the Dutch Council for Public Health and Society.
Bussemaker is a political scientist with both an academic and political career. She served as Minister of Education, Science and Culture from 2012 till the end of 2017. Previously, she served as the State Secretary for Health, Welfare and Sports from 2007 to 2010. In the 1998 elections, Bussemaker was elected into the House of Representatives for the social-democratic Party (Partij van de Arbeid).
She started her career as a lecturer and a researcher at both the University of Amsterdam and the Vrije Universiteit Amsterdam between 1993 and 2007. In 1997 she was a visiting fellow at the Center for European Studies at Harvard University. She returned to academic life from 2010 till 2012 as a dean at the University of Applied Sciences in Amsterdam, also joining the board of the University of Amsterdam.

Keynote abstract
Breaking the boundaries

The Dutch health care system belongs to the best of the world. We have highly educated doctors and nurses, we use the newest technologies, we have very specialized treatments and accessible medicine. So, nothing to complain, no problems to be solved yet? Unfortunately not.
Despite - or maybe also as a result of - the high complexity of the system, we are losing sight of where it all started with; the improvement of health and quality of life of citizens.
In my presentation, I will argue that health care is not only a matter of knowledge and technology but also – and maybe in the first place - an issue of normativity and social in- and exclusion.
Many health care issues are wicked problems, i.e. problems that are difficult to solve because they are highly complex in itself (knowledge), and, consequently, demand effort from many different parties and professionals who usually are inclined to think from different normative and moral frameworks. Moreover, these wicked problems are becoming more complex in a world showing a growing tendency towards indifference and inequality. In an indifferent and unequal world it becomes increasingly difficult to listen and to understand. It is all too easy to stick to your own narrow view. And for professionals, it is not enough to repeat your knowledge, e.g. for a doctor to explain the diagnosis and the treatment. We have to find new ways to communicate, to listen, to reflect upon our own scientific and societal assumptions and to look beyond the borders of disciplines and social communities, in order to come to a shared understanding. In short, we have to rethink the genuine concept of healthcare and what it is for. Maybe we should talk more about good health instead of sickness and healthcare; more on wellbeing and positive health, than on fighting diseases, more about people, less about patients.

Keynote lecture: Luana Colloca

Time:	Sunday, July 7, ~04:50 PM
Location:	Grote Zaal
Chair:	Jens Gaab



About Luana Colloca

Dr. Luana Colloca has conducted pioneering groundbreaking studies that have advanced scientific understanding of the psychoneurobiological bases of endogenous systems for pain modulation in humans including the discovery that social learning shapes placebo effects and that the vasopressin system is involved in the enhancement of placebo effects with a dimorphic effect. Currently, Luana leads an NIH-funded team at University of Maryland investigating the placebo/nocebo effect, how expectancy shapes pain response, social learning and pain. More recently, Colloca team has been working with virtual reality technology and clinical pain care to develop better management plans for acute post-operative pain.
Dr. Colloca holds an MD, a master degree in Bioethics and a PhD in Neuroscience. She completed a post-doc training at the Karolinska Institute in Stockholm, Sweden and a senior research fellowship at the National Institutes of Health in Bethesda, USA. Dr. Colloca received several prestigious awards including the Wall Patrick International Award for basic research on pain mechanisms by the International Association for the Study of Pain (IASP).
Dr. Colloca uses an integrative approach including psychopharmacological, psychobiological, brain mapping and behavioral approaches. Her research has been published in top-ranked international journals including Biological Psychiatry, Pain, JAMA, and Lancet Neurology. Her research has been also featured on The National Geographic, The New Scientist, Washington Post, Science daily, Boston Globe, The New Yorker, Nature, The Guardian, The Wall Street Journal, News and World Reports and USA Today.

Keynote abstract
Mechanisms of observationally-induced pain modulation: From placebo effects to virtual reality

The capacity to activate endogenous opioid and nonopioid systems in concomitance with the administration of an intervention represents a fascinating phenomenon that is capturing the attention of scientists from different disciplines. This Lecture focuses on the neurobiology of placebo effects and virtual reality with an emphasis on relevant discoveries, new insights and developments.

Selected Poster Session 1

Sunday, July 7
6:00 PM - 7.30 PM

P1.01 The development and evaluation of a new model of an active placebo

1. Christoph Werner. *University of Sydney, Sydney, NSW, Australia.*
2. Kate Faasse. *University of New South Wales, Sydney, NSW, Australia.*
3. Louise Sharpe. *University of Sydney, Sydney, NSW, Australia.*
4. Ben Colagiuri. *University of Sydney, Sydney, NSW, Australia.*

Double-blind randomised placebo-controlled trials (RCTs) usually compare an active drug eliciting side effects with an inactive placebo that has no such inherent effects. A lack of side effects in the placebo group could result in unblinding, which may bias the estimate of the treatment effect, therefore jeopardising the validity of the current gold standard in drug evaluation.
In order to examine this problem, we aimed to develop a new active placebo using treatment of sleep difficulty as model. The active placebo was beetroot extract, which causes urine colouration, a noticeable but harmless side effect. Seventy-one healthy participants were recruited under the guise of receiving a new sleep remedy. After one week of baseline measures participants were randomised to either the new active placebo group, conventional placebo (lactose), or no-treatment for one week.
During the treatment week, 50% of participants in the active placebo group reported changed urine colouration compared with 23% in the conventional placebo and 0% in the no-treatment group. While, both types of placebo treatment improved sleep relative to no-treatment, the active placebo did not significantly improve sleep relative to the conventional placebo.
The active placebo successfully increased the target side effect (i.e. urine colouration) relative to both the conventional placebo and the no-treatment group, but did not enhance the placebo effect for sleep in healthy participants under full deception. Next, we aim to evaluate the active placebo in a double-blind RCT using a sample of sleep-impaired people.

P1.02 Momentary mood as a moderator of verbally-induced placebo analgesia in an experimental pain paradigm

1. Kelly Clemens. *University of Toledo, Toledo, OH, United States.*
2. Stephanie Fowler. *National Institutes of Health, Washington, DC, United States.*
3. Suzanne Helfer. *Adrian College, Adrian, MI, United States.*
4. Andrew Geers. *University of Toledo, Toledo, OH, United States.*

Despite acting as a primary mechanism of placebo effects, expectation alone is not always enough to cause placebo effects. It has been theorized that other variables, including momentary mood states, modulate the influence of expectations (Geers, Briñol, & Petty, 2019). This study tested the possibility that mood states moderate verbally-induced expectation on placebo analgesia. A sample of 107 healthy student volunteers first completed the Brief Mood Introspection Scale (Mayer & Gaschke, 1988) in order to assess pre-task positive/negative mood states. Expectations for pain relief were subsequently manipulated by randomly assigning participants to one of two conditions. Specifically, half of the participants were told a placebo cream would reduce their pain during an upcoming cold pressor task, whereas the other half were told the cream was a hand cleanser. Participants then completed the cold pressor task, in which they submerged their hand in an ice bath for 75 seconds, reporting their pain every 15 seconds on a 10-point scale. Participants also reported their pain relief expectations. A hierarchical linear regression was used to predict in-task pain reports from pre-task mood, expectation condition, and their two-way interaction. A significant Pre-Task Mood × Expectation-Condition interaction was found, $F(3,101)=1.88$, $p=.046$, $R2=.05$, such that placebo analgesia occurred more for participants in a more positive mood than participants in a more negative mood. Self-reported expectations suggested that the expectation manipulation was most effective for participants currently in a positive mood. These findings suggest that pre-existing moods moderate the effect of verbally-induced expectations on placebo analgesia.

P1.03 Serotonergic neurons in the rostral midline medulla are activated by placebo-induced analgesia in rats with chronic neuropathic pain

1. Damien Boorman. *University of Sydney, Sydney, NSW, Australia.*
2. Kevin Keay. *University of Sydney, Sydney, NSW, Australia.*

Introduction: Several recent studies have developed rodent models of placebo analgesia (PA) to investigate its underlying neural circuitry. However, PA in a rodent model of chronic pain has yet to be demonstrated. This study investigated whether rats with a neuropathic injury can show PA and whether neurons in medullary regions previously shown to modulate noxious inputs, are activated during PA.
Methods: Male Sprague-Dawley rats (n=40) received unilateral sciatic nerve constriction injuries and hind paw withdrawals on a cold-plate (5°C) were measured. Rats that developed cold allodynia (n=35) underwent 4 days of pharmacological conditioning followed by a test day. Rats given morphine during conditioning and saline on test day (placebo condition; n=14) were classified

as either placebo 'responders' (n=5/14) or 'non-responders' (n=9/14). These rats were compared to: saline/saline rats (n=8), saline/morphine rats (n=6), and morphine/morphine rats (n=7). Neuronal activity in medullary serotonergic cells was determined using double-label c-Fos/TpH immunohistochemistry and five 'responders' and five 'non-responders' were compared to the three control groups.
Results: Rats given morphine on test day showed increased c-Fos expression in the rostral midline medulla (RMM) compared to rats given saline. However, only placebo 'responders' showed similar numbers of double-labelled c-Fos/TpH-IR cells to rats receiving morphine on test day. The double-labelled c-Fos/TpH cells were located primarily in the nucleus raphe magnus.
Conclusions: This study presents some of the first evidence of PA in rodents with a chronic neuropathic injury and direct evidence that the serotonergic cells in the RMM are differentially activated in placebo analgesic responders versus non-responders.

P1.04 Active effects and placebo effects of a mindfulness based psychological intervention

1. Karina Hansen. *Aarhus University, Aarhus, Denmark.*
2. Mette Kold. *Aalborg University, Aalborg, Denmark.*
3. Ulrik Kesmodel. *Copenhagen University, Copenhagen, Denmark.*
4. Rikke Pristed. *Aarhus, Denmark.*
5. Axel Forman. *Aarhus University, Aarhus, Denmark.*
6. Lene Vase. *Aarhus University, Aarhus, Denmark.*

Background: It is unknown whether mindfulness-based psychological intervention for chronic pain has an effect beyond the placebo effect, since previous studies primarily have compared mindfulness-based psychological interventions to other psychological treatments, support groups or waiting lists. The aim of this study was therefore to test the active effect and the placebo effect of mindfulness-based psychological intervention in women with endometriosis.
Methods: A total of 58 women with endometriosis-related chronic pelvic pain where included in the study and randomized to one of three groups; 1) mindfulness-based psychological intervention, 2) placebo-controlled psychological intervention and 3) a waiting list. Both interventions consisted of 3-hour sessions on a weekly basis over a period of ten weeks. The interventions were carefully matched on significant parameters and were managed by two trained psychologists in a cross-over design. Participants filled out a pain diary measuring pain intensity and pain unpleasantness on a numeric rating scale on a daily basis from pre- to post intervention. Patients also answered questionnaires before and after intervention on quality of life, work ability, mindfulness, treatment expectations and the quality of the relation with the therapist.
Results: Blinded data analysis is still ongoing and indicates interesting results for pain ratings and quality of life between the groups. Final results, on the effects of mindfulness-based psychological intervention and placebo mechanisms will be presented at the conference.
Conclusions: Results of this study will answer some of the questions about the active effects and the placebo effects of mindfulness-based psychological intervention in women with endometriosis.

P1.05 Relieving sad mood - Can a placebo be of help?

1. Annelie Göhler. *Justus-Liebig-University, Gießen, Germany.*
2. Alexander Winkler. *Justus-Liebig-University, Gießen, Germany.*
3. Julia Wittkowski. *Philipps-University Marburg, Marburg, Germany.*
4. Christiane Hermann. *Justus-Liebig-University, Gießen, Germany.*

Background: Expectations play a crucial role in placebo effects observed in antidepressant clinical trials. In a first experimental study entailing mood induction by film clips, we showed that an expectation manipulation combined with an active placebo attenuated induced sadness. Here, we aimed at replicating and extending these findings by inducing sadness using self-deprecating statements (Velten method) and psychophysiological responses in addition to mere self-report.
Method: 113 healthy female students were randomly (2:1:1) assigned to a deceptive placebo group (active placebo, positive treatment expectation), an open label placebo group (active placebo, no treatment expectation) or a natural history group (no placebo, no treatment expectation). Sadness was induced using the Velten method including a rumination phase. Sadness was measured using the Positive and Negative Affect Schedule Expanded Form (PANAS-X). Autonomous arousal (heart rate, skin conductance) was assessed continuously.
Results: After mood induction and during rumination, sadness was significantly higher in the natural history than in the deceptive placebo group. There was no significant difference between the open label and the deceptive placebo and natural history groups. In none of the three groups, the level of depressive symptoms correlated with the change in sadness. The results for the subjective report will be complemented by psychophysiological data.
Conclusion: Manipulation of treatment expectation protects against induced sadness. An active placebo, even when no explicit expectations are induced, might trigger a positive treatment expectation. Whether active placebo (with/without deception) might alter mood in individuals with elevated depressive symptoms needs to be investigated.

P1.06 Ergogenic placebo and social support effects on muscle work and fatigue in an fMRI-compatible experiment

1. Arran Davis. *University of Oxford, Oxford, United Kingdom.*
2. Emma Cohen. *University of Oxford, Oxford, United Kingdom.*
3. Ben Crittenden. *University of Oxford, Oxford, United Kingdom.*

Performance-enhancing (ergogenic) placebo effects are well documented in sport and exercise, and recent research suggests that enhanced physical outputs are underpinned by activity in endogenous pain modulation systems, which reduces perceptions of pain, fatigue, and difficulty. Cues to social support, such as photos of a romantic partner, have also been shown to have analgesic effects, and these effects may share neurobiological pathways with analgesic placebo effects. While placebo analgesia has been associated with enhanced physical performance, research is yet to establish a similar link between social support based analgesia and physical outputs. This study tested ergogenic social support and placebo effects on hand grip outputs in an fMRI-compatible, within-subjects experiment. During hand grip trials, participants saw photos of either a support figure or stranger, while in a placebo or control condition. It was hypothesised that both social support and placebo would enhance hand grip performance by increasing outputs and/or reducing perceptions of difficulty, and that these effects would be stronger in trials with more difficult target outputs. Results revealed significant main effects of social support and non-significant main effects of placebo on hand grips. Further, ergogenic social support effects increased in size along with trial difficulty. Despite producing greater outputs during the social support condition, participants did not perceive these trials as more difficult. These findings extend previous research on social support based endogenous analgesia, suggesting that social support may alter the self-regulatory processes that govern physical outputs, and that these effects are comparable to (relatively more established) ergogenic placebo effects.

P1.07 Leveraging patient mindsets to harness the clinical utility of the placebo effect in modern medicine

1. Sean Zion. *Stanford University, Stanford, CA, United States.*

In this talk, I will present a framework for understanding the clinical utility of the placebo effect in modern medicine. This framework has three underlying principles: (1) the placebo effect is a critical component of all active medical treatments and is not limited to sham treatments, (2) the placebo effect is driven by both conscious and non-conscious psychological processes, and (3) by leveraging these processes we can improve patient health and well-being while enhancing treatment efficacy.
In outlining this framework, I will focus on the importance of one key psychological process: the mindsets patients have about illness and the body. In Study 1 (N=400), the development and validation of a novel tool (The Illness Mindset Inventory; IMI) to measure these mindsets will be presented. Results indicate that two mindsets about illness (illness is a catastrophe and illness is an opportunity) and two mindsets about the body (the body is an adversary and the body is capable) are particularly important in clinical populations and predict health and wellbeing above and beyond disease status alone ($\Delta R2=0.01\text{-}0.12$; $p<0.01$). In Study 2 (N=120), pilot data will be presented from an ongoing clinical trial of an interactive web-based mindset intervention designed to shape these mindsets in patients with cancer. Preliminary results indicate that this intervention facilitates the adoption of more adaptive mindsets, and these mindsets are causally related to both psychological and physiological health outcomes. The implications and future directions of this work will be discussed.

P1.08 Can oxytocin influence placebo and nocebo effects?

1. Aleksandrina Skvortsova. *Leiden University, Leiden, Netherlands.*
2. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
3. Omer Van den Bergh. *KU Leuven, Leuven, Belgium.*
4. Luana Colloca. *University of Maryland, Baltimore, MD, United States.*
5. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Placebo effects relieve pain but it is yet unclear how they can be enhanced to maximize positive treatment outcomes. Oxytocin may potentially be a mediator of the placebo effect due to its trust enhancing and stress relieving actions. In two studies, we investigated the influence of oxytocin on placebo analgesia and hyperalgesia. In the first study, 108 female participants were allocated to one of four groups: oxytocin with positive verbal suggestions, placebo with positive verbal suggestions, oxytocin without suggestions, and placebo without suggestions. The administration of 24 IU oxytocin or a placebo spray was preceded by positive verbal suggestions regarding the pain-relieving properties of the spray or no suggestions. Pain was assessed with a cold pressor test. In the second study, 80 male participants were allocated to an oxytocin or a control group. After the administration of 40 IU of oxytocin, they received verbal suggestions regarding a sham electrode that was said to increase or decrease their pain sensitivity depending on the mode indicated by a visual cue. To induce and test placebo analgesia and hyperalgesia, a conditioning task was used in which visual cues indicated low, medium or high heat pain. Positive verbal suggestions and a combination of suggestions and conditioning induced significant placebo analgesia and hyperalgesia. No evidence was found that oxytocin influences placebo effect, using female and male samples and also different dosages of oxytocin. Future research should focus on other possible mediators of the placebo effect such as, for example, vasopressin or other pharmacological agents.

P1.09 Minimizing drug adverse events by informing about the nocebo effect - An experimental proof-of-concept study with headache patients

1. Yiqi Pan. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
2. Timm Kinitz. *University of Hamburg, Hamburg, Germany.*
3. Marin Stapic. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
4. Yvonne Nestoriuc. *Helmut-Schmidt-University/University of the Federal Armed Forces Hamburg, Hamburg, Germany.*

Background: Informing patients about potential adverse events may facilitate the development of nocebo-driven drug adverse events. We investigate whether knowledge about the expectation-related mechanisms of these nocebo side effects can reduce nocebo effects.
Methods: A total of N = 44 participants with weekly headaches for 6 months were recruited by using the cover story of a clinical trial for a headache medication. In reality, all participants took a placebo pill. All participants read a bogus medication leaflet entailing side effects information shortly before pill intake. The nocebo group additionally received a written explanation about the nocebo effect. Questionnaires were completed at baseline, 2 minutes, and 4 days after the pill intake.
Results: Most participants (70.5%) reported nocebo side effects at 2 minutes. Participants who received the nocebo information reported less nocebo symptoms than the control group (estimated difference: 3.3, BCa 95% CI [1.14; 5.15], p = .01). Baseline symptoms, perceived sensitivity to medicine, and side effect expectations each moderated the group effect (estimated difference in slope: 0.47 [0.19; 0.73], p = .001; 1.07 [0.27; 1.61], p = .006; 1.57 [0.38; 2.76], p = .02). No group differences were found at 4-day follow-up.
Conclusions: Results provide the first evidence that informing patients about the nocebo effect can reduce nocebo side effects and that patients who are severely burdened by symptoms, or report high sensitivity to medicine, or have unfavorable side effect expectations at treatment start may profit from the nocebo information to a larger extent.

P1.10 Open-label placebo treatment for women suffering from premenstrual syndrome: Study protocol and first results of a randomized controlled trial

1. Antje Frey Nascimento. *University of Basel, Basel, Switzerland.*
2. Cosima Locher. *University of Basel, Basel, Switzerland.*
3. Jens Gaab. *University of Basel, Basel, Switzerland.*

Background: Premenstrual syndrome (PMS) is highly prevalent among reproductive women worldwide and entails a considerable symptom burden. An array of treatments is described for PMS, indicating partly mixed-evidence and side-effects. Importantly, also a high placebo susceptibility is described for PMS. To date, there exists no study examining the efficacy of open-label placebos (OLPs) on PMS. This talk presents the study protocol and first results of a randomized controlled clinical trial (NCT03547661), investigating the effect of an OLP intervention on PMS.
Methods: The study started in spring 2018 and 150 women suffering from moderate to severe PMS will be included in a randomized controlled trial with three study groups: a treatment as usual group (TAU; n=50) and two intervention groups: an open-label placebo with treatment rationale (OLP+; n=50) and an open-label placebo without treatment rationale group (OLP-; n=50). I.e., one intervention group (OLP+) will obtain a treatment rationale, explaining why placebos may help with PMS complaints, whereas the other group (OLP-) will not obtain any further explanations. Both intervention groups obtain open-label placebo pills for 6 weeks twice a day. Primary endpoints are PMS symptom severity, intensity, and interference which are collected prospectively by means of a symptom diary.
Results: Until June 2019, 100 participants are expected to be enrolled. Preliminary findings will be reported and subjective reports of participants are conveyed.
Conclusions: This study aims to examine whether an OLP intervention is effective for PMS and investigates the importance of a plausible and comprehensive treatment rationale for OLP treatment.

Monday July 8

Keynote lecture: Tor Wager

Time: Monday, July 8, 8:30 AM - 09:15 AM
Location: Grote Zaal
Chair: John Kelley

About Tor Wager

Tor Wager is Professor of Psychology, Neuroscience, and Cognitive Science at the University of Colorado, Boulder. As of July 2019, he is joining the faculty of Dartmouth College as the Diana L. Taylor Distinguished Professor in Neuroscience. He received his Ph.D. from the University of Michigan in Cognitive Psychology in 2003, and served as an Assistant and Associate Professor at Columbia University from 2004-2009. Since 2004, he has directed the Cognitive and Affective Neuroscience laboratory, a research lab devoted to work on the neurophysiology of affective processes—pain, emotion, stress, and empathy—and how they are shaped by cognitive and social influences. Dr. Wager and his lab are also dedicated to developing analysis methods for functional neuroimaging and sharing ideas, tools, and scientific data with the scientific community and public. See http://wagerlab.colorado.edu and http://canlab.github.io for papers, data, tools, and code.

Keynote abstract
Placebos, therapy, and self-fulfilling prophecies

Placebo effects are improvements in signs and symptoms caused by the context in which a treatment is delivered. They are a natural part of the way our brains work; their mechanisms include learning and neuroplasticity, emotion, social cognition, and future-oriented cognition (i.e., prospection and expectation). Clinically, placebo treatments tap into psychological “common factors” that are harnessed by wise therapists across many psychotherapeutic traditions. However, not all placebo effects are equally efficacious. Though it is relatively easy to influence patients’ symptom reports, demonstrations of placebo effects on pathophysiology with meaningfully large effect sizes are rare. Our work over the last years has explored some of the factors that create large and durable placebo effects on symptom-related brain physiology. A working hypothesis is that strong placebo effects arise from the interaction between expectations and lived experience (i.e., reinforcement). Reinforcement induces learning and neuroplasticity in the brain systems that govern motivation and control over bodily physiology, and expectations guide what is learned from experience. During this process, two mechanisms are crucial for creating durable effects. First, symptoms assimilate towards learned expectations; and (2) there is a confirmation bias in learning, such that symptoms congruent with expectations have more influence on learning that incongruent symptoms. Together, these two mechanisms can create self-reinforcing placebo effects that are resistant to extinction. Psychological and biobehavioral therapies are not yet designed with these principles in mind. Advances in the science of placebo effects thus provides an opportunity to design a new generation of more effective forms of therapy.

Plenary Session 1

How to use placebos in clinical practice?

Monday, July 8, 09.15 AM - 11.00 AM
Grote zaal
Chair: Cláudia Carvalho

From good to bad to good: Why the placebo is necessary for treatment

Jens Gaab

University of Basel, Basel, Switzerland

About Jens Gaab
Jens Gaab is Full Professor for Clinical Psychology and Psychotherapy at the Faculty of Psychology of the University of Basel, Switzerland, where he and his team are determined and eager to examine the placebo and its effects in different settings, populations and interventions, to explore the relationship between placebo and psychotherapy and to test ethically acceptable ways to harness the placebo and its effects.

Plenary Abstract
The placebo has experienced a turbulent career in the past 500 years. Since then, it has been employed to find truth (usually defined as the absence of untruth), calm the restless, ease the pain, make money and gain influence. Interestingly, its connotation shifted according to the aims, while the driving force – the effects of placebos – remained the same. However and regardless to its connotation, the placebo – or more precisely: the forces that are operationalized by placebos – are inherent components of treatments and thus should be part of the understanding of a „good treatment“. Furthermore, the placebo and its effects not only exemplify the importance of contextual factors and processes, but also serve as a reminder of the ethical dimension of a good treatment. This not only has important repercussions on what to do, but also on who defines a treatment to be good. Thus, the placebo and its effects are not per se „something to control for“ or „sham, fake and deceit“, but they mark and define the space for necessary and basic (and sometimes even sufficient) components of what could be considered a „good treatment“. This understanding of the placebo and its function for good treatment will be exemplified empirically and theoretical for psychotherapy.

Efficacy of open-label placebos in RCTs, and possible clinical applications in mainstream medicine

John Kelley

Endicott College, Beverly, MA, United States

About John Kelley
John Kelley, PhD, is a Distinguished Professor of Psychology at Endicott College, the Deputy Director of the Program in Placebo Studies and the Therapeutic Encounter at Harvard Medical School, and a licensed clinical psychologist. His research interests include investigating the placebo effect in medical and psychiatric disorders, and understanding how the patient-clinician relationship affects healthcare outcomes in medicine and psychiatry. Dr. Kelley has served as a co-investigator or consultant on 10 National Institutes of Health research grants, and he is the author or co-author of more than 50 peer-reviewed scientific publications.

Plenary Abstract
I will review several recent randomized controlled trials that suggest that open-label placebos can be effective in treating a variety of conditions, including irritable bowel syndrome, migraine headaches, cancer-related fatigue, and chronic low back pain. In addition to discussing how open-label placebos might be used in mainstream medical care, I will also discuss the possibility of using "authorized concealment" as a method for reducing the dosage of pain medication

necessary to produce effective analgesia. In the potential clinical applications of both open-label placebo and authorized concealment, I will pay particular attention to the critical role of the patient-clinician relationship in producing beneficial effects. Finally, and perhaps most importantly, open-label placebo and authorized concealment both have the potential to reduce the incidence of addiction to pain medications, which is of particular concern given the ongoing opioid crisis.

Why changing dysfunctional expectations in clinical practice is challenging

Winfried Rief

Philipps University of Marburg, Marburg, Germany

About Windfried Rief

Rief, Winfried, Professor of Clinical Psychology and Psychotherapy, Philipps University of Marburg, Germany. Head of the Clinic for Psychological Interventions. License for psychotherapy and supervision. Dr. Rief worked for many years in hospital settings (e.g., Roseneck Hospital for Psychosomatic Medicine, Prien a. Ch.). He is specialized in placebo- and nocebo effects, perception and coping with somatic symptoms, optimization of clinical studies and interventions. He was guest professor at Harvard Medical School, Boston (2004/2005), University of Auckland Medical School (2002), and University of California San Diego (2009/2010). Additionally, he was nominated for the expert committee of WHO/APA for the revision of the classification of mental disorders according to DSM-5, and he is co-chairing the WHO working group on chronic pain diagnoses in ICD-11. Dr. Rief is elected coordinator for grant applications to the German Research Foundation and he is spokesperson of the DFG-research unit on placebo and nocebo mechanisms. His publication record summarizes more than 450 articles, in particular in the field of behavioral medicine and somatoform disorders. He received the Distinguished Researchers award in Behavioral Medicine in 2014.

Plenary Abstract

During the last decade, psychological and neurobiological mechanisms that are involved in the development of placebo and nocebo responses have been identified. While clinical trials used to reduce placebo mechanisms, clinical practice should try to make use of them for the benefit of the patient. Expectation and learning mechanisms are the major psychological factors contributing to placebo and nocebo effects. Examples will be presented how optimizing patients' expectations leads to improved outcome in different clinical conditions. However, to better understand the persistence of dysfunctional expectations in patients, we need a model for understanding mediators of expectation change in the case of expectation violation. We introduce the concept of "cognitive immunization" to understand expectation persistence, and we will present examples how dysfunctional expectations can be changed in patients, even if they have a tendency for persistence of negative expectations.
Finally, implications for optimizing psychological interventions in general will be highlighted, and first examples confirm the clinical potential of successfully applying our model of expectation change.

Clinical practice: implications for the study of placebo

Damien Finniss

Royal North Shore Hospital, Sydney, Australia; Griffith University School of Allied Health Sciences, Gold Coast, Queensland, Australia.

About Damien Finniss

Professor Finniss is a clinician and researcher at the Department of Anaesthesia and the University of Sydney Pain Management Research Institute, Royal North Shore Hospital. He has published numerous papers in International peer reviewed journals and contributed several book chapters in the field of placebo analgesia, particularly on clinical implications. He served as the Chair of the International Association for the Study of Pain (IASP) group on Placebo for 15 years and regularly presents his work at International meetings. He has held and continues to hold leadership positions in Pain Management in Australia and Internationally.

Plenary Abstract

Harnessing placebo effects in clinical practice is one of the key goals in the field of research, yet the majority of the literature is either conducted in experimental populations or in short-term, well controlled clinical settings. Clinical practice is dynamic, with disease processes and symptomatology changing over time according to the natural history of the conditions or responses to treatment of them. Even a brief journey into a health care encounter can be shaped by pre-treatment factors (both individual and societal), the treatment ritual including the many people involved in the process, and the post-treatment care be this an acute or chronic disease process. A longitudinal approach is needed at both individual, system and societal levels to better understand how placebo effects operate and how they may be sustainably harnessed in routine care.

Deliberate application of placebo effects: Use of placebo effects in clinical practice by modulating expectancies

Regine Klinger

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

About Regine Klinger

Regine is the head psychologist of the section „Pain Medicine and Pain Psychology“, University Medical Hospital Hamburg-Eppendorf (UKE), Center for Anesthesiology and Intensive Care Medicine, Department of Anesthesiology . In her working field the research models „Placeboanalgesia“, „Nocebohyperalgesia“ and „Placeboresponses in Itching” play an important role. Regine is head of several placebo research projects which are part of the DFG-Research group „Expectation and Conditioning as Basic Processes of the Placebo and Nocebo Response: From Neurobiology to Clinical Applications”. The transfer of research results to clinical application in ethical borders is one of her utmost aims: she describes and proposes several approaches how to exploit placebo mechanisms to improve pharmacological and nonpharmacological pain interventions in a more systematic manner than what naturally occurs in clinical settings. Her current projects focus on placeboeffects in acute pain therapy, e.g. postoperative knee pain, postoperative pain after sectio caeseare.

Plenary Abstract

Clinical work must be a comprehensible process—random positive results are a pleasant benefit but are not usable and therefore not helpful for clinical practice. Accordingly, patient care relies on reliable and predictable results. Research on placebo effects offers a variety of possibilities to use placebo effects in ethical acceptable ways. One key finding of previous research is that the pharmacological effect of pain medication can be enhanced by the additive effect of analgesic placebo effect.

The application of placebo effects in clinical settings does not mean that pain medication should be substituted with placebos. It rather stands for increasing the effectiveness of pain medication by amplifying their inherent placebo component. Every effective pain medication has a pharmacological active component and a psychological (placebo) component.

In clinical practice, it is possible to boost an analgesic therapy by supporting it with the placebo component. The principles are to modulate expectancies by a targeted use of verbal instructions, cues, associations, and social learning models in the healing context of pain treatment. Accordingly, the open application of medication is an ethically way of using placebo effects in a clinical context. In this approach, physicians and other providers of pain treatment draw patients’ attention to the positive aspects of analgesics or other treatments. They give supporting information about the medication, take care of the patients, and try to establish a positive patient–clinician atmosphere.

On the basis of current studies with patients the potential of using placebo effects in pain therapy will be presented.

Parallel Session 1.1

The power of nocebo: From mechanisms to clinical application

Monday, July 8, 11:30 AM - 12.30 PM
Grote zaal
Chair: Ben Colagiuri

1.1a Changing patient mindsets about non-life-threatening symptoms during oral immunotherapy: A randomized clinical trial

1. Lauren Howe. *University of Zurich, Zurich, Switzerland.*
2. Kari Leibowitz. *Stanford University, Stanford, CA, United States.*
3. Margaret Perry. *Stanford University, Stanford, CA, United States.*
4. Julie Bitler. *Sean N. Parker Center for Allergy and Asthma Research, Mountain View, CA, United States.*
5. Whitney Block. *Sean N. Parker Center for Allergy and Asthma Research, Mountain View, CA, United States.*
6. Ted Kaptchuk. *Harvard Medical School, Cambridge, MA, United States.*
7. Kari Nadeau. *Sean N. Parker Center for Allergy and Asthma Research, Mountain View, CA, United States.*
8. Alia Crum. *Stanford University, Stanford, CA, United States.*

Background: How can we help physicians inform patients of treatment side effects without causing nocebo effects? Our intervention tested whether informing patients undergoing oral immunotherapy (OIT) for food allergies that non-life-threatening treatment-related symptoms can signal treatment efficacy improves treatment outcomes and experience.
Methods: In a randomized, blinded, controlled phase II study, 50 children/adolescents (28% girls, aged 7-17, M=10.82, SD=3.01) completed OIT for peanut allergies. Patients and their parent(s) had monthly clinic visits at the Sean N. Parker Center for Allergy & Asthma Research between 1/5/2017-8/3/2017. All families received the same safety training regarding symptom management. In a 1:1 approach, 24 control patients were informed that non-life-threatening symptoms during OIT were unfortunate side effects of treatment, and 26 intervention patients were informed that non-life-threatening symptoms could signal desensitization. Families completed activities to reinforce these mindsets about symptoms.
Results: Compared to families informed that symptoms are side effects, families informed that symptoms can signal desensitization were less anxious (B=-0.45, 95% CI (-0.75 to -0.15), p=0.005), less likely to contact staff about symptoms (5/24[9.4%] vs. 27/154[17.5%] instances, p=0.036), less likely to skip/reduce doses (1/26[4%] vs. 5/24[21%] patients, p=0.065), experienced fewer non-life-threatening symptoms as doses increased (BInteraction=-0.54(-0.83 to -0.27), p<0.001), and showed greater increase in patient peanut-specific blood IgG4 levels, a biomarker of allergic tolerance (BInteraction=13.53(7.28 to 19.79), SE=3.04, t(26)=4.45, p<0.001).
Conclusion: Fostering the mindset that symptoms can signal desensitization improves OIT experience and outcomes. Changing how providers inform patients about non-life-threatening symptoms is a promising avenue for reducing nocebo effects during treatment.

1.1b Evidence of a media-induced nocebo response following a national antidepressant brand switch

1. Kate MacKrill. *University of Auckland, Auckland, New-Zealand.*
2. Greg Gamble. *University of Auckland, Auckland, New-Zealand.*
3. Debbie Bean. *University of Auckland, Auckland, New-Zealand.*
4. Tim Cundy. *University of Auckland, Auckland, New-Zealand.*
5. Keith Petrie. *University of Auckland, Auckland, New-Zealand.*

Background: In 2017, New Zealanders taking the funded antidepressant venlafaxine (generic or branded) were switched to a different generic medication. Following the switch, print and television media ran stories about the new generic being less effective and causing side effects including fatigue, nausea and suicidal thoughts. We examined the impact of media coverage on side effects reported to the New Zealand Centre for Adverse Reactions Monitoring, specifically symptoms mentioned in the media compared to other side effects not reported. We also compared the effect of newspaper versus television reporting.
Method: The study analysed 402 adverse reaction reports over 13 months, comparing total adverse reports, complaints of decreased therapeutic effect and specific symptom reports before and after the media coverage.
Results: Following the media exposure, there was a significant increase in both side effect reporting (interruption effect = 41.83, p = .003) and complaints of reduced therapeutic effect (interruption effect = 15.49, p = .012). The specific side effects discussed

in the media, particularly suicidal thoughts, increased significantly compared to those not mentioned. Further, side effect reporting was more than 600% greater following the television coverage compared to print.
Conclusion: Media coverage of side effects during this medicine switch appears to have caused a strong nocebo response, increasing reporting of both the overall rate of side effects and those specifically mentioned in the media. The research has implications for understanding how media influences the nocebo response and for managing national medication changes.

1.1c Learning mechanisms in nocebo hyperalgesia: The role of conditioning and extinction processes

1. Mia Thomaïdou. *Leiden University, Leiden, Netherlands.*
2. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
3. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
4. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Nocebo hyperalgesia refers to adverse health or treatment outcomes on pain, putatively induced by patients' expectations. Nocebo effects have been studied in experimental models by use of learning-based methods. To date, few studies focus on bridging the gap between experimental and clinical settings, an important step towards understanding and counteracting these effects. In the present study we aim to test 140 healthy participants; we compare sham-conditioning to two distinct nocebo induction methods: conditioning with continuous reinforcement (CRF) and conditioning with only partial reinforcement (PRF). We also compare counterconditioning to extinction for the attenuation of nocebo hyperalgesia. During the induction phase, in the CRF group the activation of a sham TENS device is always paired with a surreptitious increase in thermal pain stimulation, whereas the PRF group experiences this increase during only 70% of nocebo trials. In the evocation phase, pain stimulation is equivalent across nocebo and control trials. Thereafter, pain is surreptitiously decreased on nocebo trials relative to control trials for the counterconditioning group, while pain stimulation remains equivalent across all trials for the extinction group. Preliminary results indicate that while PRF is sufficient to induce nocebo hyperalgesia, this is weaker than CRF. Moreover, counterconditioning is more effective than extinction in attenuating the nocebo effect. Nocebo hyperalgesia is more resistant to attenuation when induced with PRF, as compared to CRF. Overall, these findings suggest that the more ambiguous and clinically relevant learning method of PRF can induce nocebo hyperalgesia and can also potentially explain treatment resistance and chronification of symptoms.

1.1d Preventing adverse events of chemotherapy by educating patients about the nocebo effect – A randomized controlled trial with gastrointestinal cancer patients

1. Twyla Michnevich. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
2. Yiqi Pan. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
3. Armin Hendi. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
4. Julia Mann. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
5. Yvonne Nestoriuc. *Helmut-Schmidt-University, Hamburg, Germany.*

Background: Side-effects of chemotherapy are severely burdening to patients. They may be caused by pharmacodynamics or psychological factors such as negative expectations, which constitute nocebo effects. In this study, we examined whether educating patients about the nocebo effect is efficacious in reducing the intensity of perceived side-effects.
Methods: In this proof-of-concept study, N=106 outpatients starting first-line, de novo chemotherapy for gastrointestinal cancers were randomized 1:1 to a nocebo education session or an attention control group with matching interaction times. Primary outcome was patient-rated intensity of adverse events adverse events at 10-days and 12-weeks after first course of chemotherapy. Secondary outcomes included perceived control of side-effects and tendency to misattribute symptoms.
Results: N = 52 and n = 54 patients (mean age: 60.7y, 66.0% male, 50.9% UICC tumor staging IV) were allocated to the nocebo education and attention control group, respectively. ANCOVA indicated that after adjusting for tumor staging and distress, intensity of side-effects did not differ between groups at 10-days follow up ($F(1,102) = 0.62$, $p = .44$), yet it did differ at 12 weeks ($F(1,102) = 5.26$, $p = .02$, $\eta p^2 = 0.05$). Intensity of unspecific side-effects differed at both time points (10 days: $F(1,102) = 3.98$, $p = .049$, $\eta p^2 = 0.04$; 12 weeks: $F(1,102) = 5.19$, $p = .03$, $\eta p^2 = 0.05$), whereas for intensity of specific side-effects, no differences were found.
Discussion: Informing patients about the nocebo effect may be an innovative and clinically feasible intervention for reducing the burden of side-effects.

Parallel Session 1.2

Psychopharmacology and psychophysiology in placebo studies

Monday, July 8, 11:30 AM - 12.30 PM
Aalmaktzaal
Chair: Ursula Stockhorst

1.2a Opioid-mediated mechanisms of antidepressant placebo effects

1. Marta Pecina. *University of Pittsburgh, Pittsburgh, PA, United States.*

Background: Two theories of the placebo effect have emerged, mostly from work on placebo analgesia. The first emphasizes expectations of improvement as the main driver, whereas the second stresses learning mechanisms. Experimental models of placebo analgesia under these theories have linked placebo effects to activity in cortical areas, as well as the descending pain-modulating system. Neuropharmacological studies have further implicated the opioid system, as indicated by the effects of μ-opioid antagonists' and in vivo μ-opioid receptor binding studies. Here, we implemented conceptual and methodological advances from the field of placebo analgesia to understand the mechanisms underlying antidepressant placebo effects.
Methods: 32 patients with Major Depressive Disorder were enrolled in a randomized double-blinded counterbalance crossover trial of one single dose of naltrexone 50mg or placebo in two consecutive days. After each administration patients completed a functional MRI (fMRI) paradigm aimed at inducing fast-acting antidepressant effects, while isolating the expectancy- and reinforcement-driven components of the placebo response.
Results: Treatment expectancy ratings were significantly higher during the infusion compared to the no-infusion condition (Estimate=0.7, S.E.=0.1, p=6.7*E-12), especially during the positive sham neurofeedback condition (Estimate=0.84, S.E.=0.15, p=1.5*E-08). Mood ratings during the task were significantly higher during the positive sham neurofeedback condition, compared to baseline (Estimate=1.3, S.E.=0.1, p=2*E-16), especially during the infusion condition (Estimate=0.5, S.E.=0.15, p=0.001). These effects were significantly reduced after the administration of naltrexone.
Conclusions: In patients with depression, antidepressant treatment expectancies interact with unfolding reinforcement. Specifically, mood improves when positive expectancies are confirmed by positive reinforcement and these effects are modulated by μ-opioid receptors.

1.2b Effects of positive and negative verbal suggestions on the psychophysiological response to stress

1. Judith Tekampe. *1) Leiden University, Leiden, Netherlands; 2) Radboud university medical center, Nijmegen, Netherlands*
2. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
3. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Placebo and nocebo effects are known to affect a variety of psychological and physiological health parameters. Whether placebo and nocebo effects on the subjective and physiological responses to stress can be induced by verbal suggestions is currently unclear.
Method: To investigate whether verbal suggestions affect subjective and physiological responses to stress, a randomized single-blind experiment was conducted in healthy volunteers. After receiving either a positive, negative or no verbal suggestion about their stress responsiveness, participants were exposed to the Trier Social Stress Test (TSST). Subjective self-report, autonomous and HPA-axis parameters were measured at baseline and several times after stress. An emotional Stroop task was administered to investigate effects on implicit cognitive processing after stress.
Results: Preliminary analysis indicated that the negative verbal suggestion was significantly more convincing than the positive verbal suggestion but both suggestions did not have a significant effect on expected stressfulness of the TSST. In response to stress, the positive and negative suggestion lead to smaller decreases compared to the control group in self-reported feeling of "clam" measured on a visual analog scale. No significant effects of the verbal suggestions were found on the other self-report outcomes, cognitive bias or on cortisol, alpha-amylase, heart rate and skin conductance.
Discussion: The verbal suggestions directed at stress responsiveness used in this study did not affect expectations about the stressfulness of the TSST and the subjective and physiological responses to stress. This is in contrast to other studies finding effects of verbal manipulations directed at stress appraisal and mindset.

1.2c Conditioning of the neuroendocrine system: Learned oxytocin responses

1. Aleksandrina Skvortsova. *Leiden University, Leiden, Netherlands.*
2. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
3. Gustavo Pacheco-Lopez. *Metropolitan Autonomous University, Lerma, Mexico.*
4. Marian Bakermans-Kranenburg. *Leiden University, Leiden, Netherlands.*
5. Marinus van IJzendoorn. *Erasmus University Rotterdam, Rotterdam, Netherlands.*
6. Monique Smeets. *Utrecht University, Utrecht, Netherlands.*
7. Tom Wilderjans. *Leiden University, Leiden, Netherlands.*
8. Albert Dahan. *Leiden University Medical Center, Leiden, Netherlands.*
9. Omer Van den Bergh. *KU Leuven, Leuven, Belgium.*
10. Niels Chavannes. *Leiden University Medical Center, Leiden, Netherlands.*
11. Nic van der Wee. *Leiden University Medical Center, Leiden, Netherlands.*
12. Karen Grewen. *University of North Carolina, Charlotte, NC, United States.*
13. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
14. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Even though the possibility to influence hormone secretion with a behavioral manipulation has widespread clinical implications, only few studies examined classical conditioning of hormonal responses in humans, particularly not oxytocin responses. In this trial, we investigated conditioning of oxytocin in ninety-nine healthy females who were assigned to conditioned, placebo or drug-control group. In the two-phase conditioning paradigm, participants in the conditioned and drug-control groups received an oxytocin nasal spray combined with a distinctive smell (conditioned stimulus, CS) during three acquisition days, while the placebo group received placebo nasal spray. Subsequently, the conditioned and placebo groups received placebo spray with the CS and the drug-control group- oxytocin spray during three evocation days. Salivary oxytocin levels were measured at baseline and at different points after the spray administration. Pain sensitivity and facial evaluation tests previously used in oxytocin research were also administered. A significant increase of oxytocin levels in the conditioned group at 5, 20, and 50 minutes after the CS on evocation day 1 was demonstrated. On evocation day 2, a trend for increased oxytocin levels was found at 5 and 20 minutes after the CS. No conditioned responses were found on evocation day 3. Neither exogenous nor conditioned oxytocin affected pain or facial task outcomes. Our results indicate for the first time that endogenous oxytocin release can be conditioned and that this conditioned response extinguishes over time. Conditioning of hormonal responses offers various clinical possibilities, e.g., enhancing effects of pharmacological treatments or reducing dosages of medications.

1.2d Naltrexone during pain conditioning - A double-blind placebo-controlled experimental trial

1. Moa Pontén. *Karolinska Institute, Stockholm, Sweden.*
2. Jens Fust. *Karolinska Institute, Stockholm, Sweden.*
3. Eva Kosek. *Karolinska Institute, Stockholm, Sweden.*
4. Joar Guterstam. *Karolinska Institute, Stockholm, Sweden.*
5. Karin Jensen. *Karolinska Institute, Stockholm, Sweden.*

Aim of investigation: Naltrexone reversibly blocks the effects of opioids and has been shown to decrease placebo analgesia in a treatment context. However, pain relief can also be induced through classical conditioning and it is not clear to what extent naltrexone affects the pain modulation through stimulus intensity cues. The aim of this study was to investigate if naltrexone given already during the learning sequence may have effect on conditioned pain responses.
Methods: A classical conditioning paradigm, using pressure pain in combination with naltrexone/sugar pill administration was performed in healthy controls. In a double-blind procedure prior to the conditioning 27 healthy participants were randomized to receive an acute, oral dose of either naltrexone (50 mg, n=14) or sugar pill (n=13). A pressure pain stimulator was placed on participants' left thumb, and a response-device in the right hand allowed for pain ratings (0 to 20 Numeric Rating Scale). The procedure included a conditioning procedure (learning sequence), followed by a test-sequence. Painful and non-painful pressures were paired with two different visual cues. During the test-sequence, a medium level of pressure was used for both visual cues. Difference in subjective pain ratings between the painful- and non-painful visual cue during the test-sequence (paired with the same medium pressure) was calculated.
Results: Results showed significant conditioned pain responses across groups ($P < 0.001$), however there was no significant difference between subjects receiving naltrexone or placebo ($P=.193$). There was a significant correlation between the difference in high pain / low pain ratings during the learning sequence and the painful cue / non-painful cue ratings during the test-sequence ($r=0.575$, $P=0.002$).
Conclusions: Here we demonstrate comparable conditioned pain responses in participants with naltrexone or sugar pill. These findings indicate that full function of the endogenous opioid system during the learning sequence of pain conditioning is not necessary for conditional responding. To the best of our knowledge, previous studies that used opioid antagonists in order to investigate its effects on placebo analgesia were performed in a treatment context, and not in a stimulus context. Therefore, our study may add important information about the role of opioids during pain conditioning.
Acknowledgments/Disclosures: This study was supported by the Swedish Research Council and The Swedish Brain Foundation. The authors have no financial disclosure

Parallel Session 1.3

Placebo response and treatment expectations in clinical populations

Monday, July 8, 11:30 AM - 12.30 PM
Breezaal
Chair: Chantal Berna

1.3a The potency of placebo: A meta-analysis on placebo effects of PDE5Is for erectile dysfunction

1. Alexander Stridh. *Karolinska Institute, Stockholm, Sweden.*
2. Christoph Abé. *Karolinska Institute, Stockholm, Sweden.*
3. Moa Pontén. *Karolinska Institute, Stockholm, Sweden.*
4. Stefan Arver. *Karolinska Institute, Stockholm, Sweden.*
5. Irving Kirsch. *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States.*
6. Karin Jensen. *Karolinska Institute, Stockholm, Sweden.*

Background: To date no thorough meta-analysis on the magnitude of the placebo response on improving erectile dysfunction (ED) has been conducted. Here, the treatment response of phosphodiesterase 5 inhibitors (PDE5I) and the corresponding placebo arm in clinical trials on ED was assessed.
Methods: A statistical meta-analysis on within-group and between group effect sizes (Hedge's g) was performed for both drug and placebo response, as assessed on the International Index of Erectile function (IIEF) questionnaire. A total of 63 studies were included in this meta-analysis.
Results: The response to the study drug showed a large effect size (g=1.249) and there was a low to medium placebo response (g=0.346). There was a low placebo effect as compared with natural history (g=0.135). The difference in effect size between drug and placebo response was statistically significant (p=0,0001). The placebo effect was larger in studies with psychogenic ED (g=0.774) with no significant difference between outcomes in drug and placebo arm. No significant difference in effect size was seen between drug and placebo in treatment with PDE5Is for recovery of ED after prostate surgery.
Conclusions: This meta-analysis shows a placebo effect in improvement of ED that cannot be attributed to regression to the mean, reporting bias etc. The impact of the placebo effect is larger in psychogenic causes for ED. Previous research with PDE5Is for treatment of ED after prostate surgery has been conflicting. This meta-analysis suggests that there is no additional effect of PDE5I in addition to the placebo response in this patient group.

1.3b Patients' expectations of therapeutic outcome affect the clinical response in myasthenia gravis

1. Elisa Frisaldi. *University of Turin Medical School, Turin, Italy.*
2. Bruno Ferrero. *University of Turin Medical School, Turin, Italy.*
3. Aziz Shaibani. *Nerve & Muscle Center, Houston, TX, United States.*
4. Alessandro Piedimonte. *University of Turin Medical School, Turin, Italy.*
5. Diletta Barbiani. *University of Turin Medical School, Turin, Italy.*
6. Eleonora Camerone. *1) University of Genoa, Genoa, Italy; 2) University of Turin Medical School, Turin, Italy.*
7. Alessandra Di Liberto. *University of Turin Medical School, Turin, Italy.*
8. Roberto Cavallo. *University of Turin Medical School, Turin, Italy.*
9. Leonardo Lopiano. *University of Turin Medical School, Turin, Italy.*
10. Fabrizio Benedetti. *1) University of Turin Medical School, Turin, Italy; 2) Plateau Rosà Laboratories, Plateau Rosà, Italy/Switzerland.*

Background: This prospective, multicenter, and ethically approved study was aimed at assessing the impact of patients' expectations on the management of myasthenia gravis (MG) symptoms.
Methods: Eighteen MG patients starting a new treatment with immunosuppressants (N=13) or corticosteroids (N=5) and assessed for their expectations were studied for 6 or 3 months, respectively. A control group of 18 MG patients starting the same treatments, but not evaluated for their expectations, was also investigated. A correlation analysis was performed between a set of expectations' questionnaires (for a total of 8 variables) and clinical improvements assessed by means of the Quantitative Myasthenia Gravis (QMG) Test (both as total score and through 6 selected subscores). Bonferroni correction was then applied for multiple comparisons. Finally, clinical improvement in the experimental group was compared to the control group.
Results: Patients treated with the immunosuppressant azathioprine (N=10) showed strong correlations between half of the expectations' variables and the QMG improvement specific for swallowing and right arm outstretched subscores ($p<0.00001$). The role of patients' expectations was substantial in modulating the QMG improvement in the whole experimental group compared to

the control group [-36,13 (CI95%: -58,61 to -13,65) p = 0.002] and also in the azathioprine group compared to its respective control group [-45,08 (CI95%: -68,09 to -22,07) p = 0.001].
Conclusions: Patients' expectations about the immunosuppressant azathioprine strongly improved the clinical response, as assessed by means of QMG scores. We are now analyzing other outcome measures, such as single-fiber electromyography, repetitive nerve stimulation, fatigue and quality of life.

1.3c How response expectancies of sexual toxicity experiences interact early in radiotherapy: A mediation analysis of prostate cancer patient reports

1. Elise Devlin. *University of Adelaide, Adelaide, SA, Australia.*
2. Hayley Whitford. *for University of South Australia Cancer Research Institute, Adelaide, SA, Australia.*
3. Linley Denson. *University of Adelaide, Adelaide, SA, Australia.*
4. Andrew Potter. *GenesisCare Radiation Oncology, Adelaide, SA, Australia.*

Background: Response expectancies (REs) of cancer treatment toxicities often predict subsequent experiences, and patients frequently report such side effects before they are medically anticipated. Both findings indicate a nocebo component to patients' experiences. However, it is unclear whether pre-treatment REs remain consistent, or whether patients update their baseline REs throughout treatment. This study investigated whether pre-treatment REs of side effects predicted the strength of REs assessed during early radiotherapy, and if this relationship was mediated by reported toxicity experiences.
Methods: A multi-site, prospective, longitudinal design followed a homogeneous group of men (N=41) treated with radiotherapy (74-78Gy) for prostate cancer. Four-weeks pre-treatment (baseline), patients reported their REs of sexual side effects; 'lack of desire', 'problems with erection', and 'inability to reach orgasm'. Two-weeks into treatment, before radiotherapy toxicities are medically expected, patients recorded the severity of their toxicities, and their REs for the remaining 5 weeks of treatment.
Results: Simple mediation analyses, using ordinal least squares regression and bootstrapping with 5000 samples, indicated the severity of the side effect 'lack of desire' fully mediated the association between REs of 'lack of desire' at baseline and 2-weeks into treatment. Experiences of 'problems with erection' and 'inability to reach orgasm' partially mediated associations between REs.
Conclusions: Patients appear to update their initial REs following treatment experiences supporting early intervention during radiotherapy. Preventing early toxicities that likely have a large nocebo component, may reduce subsequent REs, which could in turn prevent severe toxicity experiences.

1.3d Odors as asthma triggers: The role of information, worry and arousal. A replication and extension of Jaen and Dalton (2014), Journal of Psychosomatic Research, 77: 302-308.

1. Thomas Janssens. *KU Leuven, Leuven, Belgium.*
2. Lieven Dupont. *1) KU Leuven; Leuven, Belgium; 2) UZ Leuven, Leuven, Belgium.*
3. Omer Van den Bergh. *KU Leuven, Leuven, Belgium.*

Background: Individuals with asthma often report odors as a symptom trigger, but the mechanisms of odor-induced asthma symptoms remain unclear. Jaen and Dalton (2014), demonstrated that Phenyl Ethylalcohol (PEA) in combination with placebo vs. nocebo information changed airway inflammation in a small sample of individuals with moderate asthma. In this study, we aimed to replicate these findings and investigated arousal and worry as potential moderators and mediators of this effect.
Methods: Individuals with mild or moderate asthma (n=39) received information about PEA as either having an asthmogenic (nocebo) or therapeutic (placebo) effect. Participants underwent a 15-minute odor provocation and rated odor intensity, irritation and annoyance. Asthma symptoms, arousal, lung function (FEV1) and exhaled nitric oxide (FeNO) were measured at baseline, after provocation, and 2 and 24 hours after baseline. Worry was measured at each time point after provocation.
Results: During PEA provocation ratings of odor intensity, irritancy and annoyance changed over time, showing increased sensitization in the nocebo group and increased habituation in the placebo group. 24h after baseline, we observed significant differences in FeNO (nocebo 120%BL; placebo 89%BL, p=.005). Changes in FEV1 and asthma symptoms did not reach significance. Increased worry about the odor was associated with stronger FeNO nocebo responses (Condition x Worry interaction= F(1,42)=4.69 , p=.036). FeNO response was not associated with arousal or worry unrelated to the odor.
Conclusion: Our findings confirm previous results by Jaen and Dalton (2014) and suggest that worry about odor exposure may help us understand odor-related symptoms in individuals with asthma.

Parallel Session 1.4

What's in a definition: Conceptualizing placebo

Monday, July 8, 11:30 AM - 12.30 PM
Jan Willem Schaap zaal
Chair: Jeremy Howick

1.4a Placebo effects and the healing power of the subjunctive

1. Doug Hardman. *University of Southampton, Southampton, United Kingdom.*
2. Adam Geraghty. *University of Southampton, Southampton, United Kingdom.*
3. Mark Lown. *University of Southampton, Southampton, United Kingdom.*
4. Felicity Bishop. *University of Southampton, Southampton, United Kingdom.*

Background: There is evidence that 'placebos' might be useful for treating some medical conditions. Despite such evidence there is significant disagreement on the definition, ethics, and clinical viability of placebo treatment; these issues cannot be resolved exclusively in laboratory or trial settings.
Methods: To explore these issues we conducted an ethnography of a general practice surgery in southern England, including participant observation, interviews, and focus groups with patients, clinicians, and support staff over the course of a year.
Results: Clinicians and patients in our study did not make use of 'placebo pills' or even placebo terminology. Despite some claims that the term 'placebo' is pervasive in biomedical discourse, we suggest this pervasiveness may be restricted to research not clinical settings. Instead our findings broadly support modern accounts of the placebo phenomenon grounded in the therapeutic encounter. These accounts often foreground the autonomous, authentic individual and the value of sincere engagement with patients. In our study, however, clinicians often explicitly adapted their approach to the particular patient, condition, and situation, utilising, we suggest, a framework of performance. In so doing they were successful not by being 'genuinely' themselves, but by exploiting the transitory, shared social environment each unique consultation creates: practising what we term 'subjunctive medicine'.
Conclusion: Our findings suggest that the dominant focus in placebo research on autonomy, deception, and the potential open administration of substances is misplaced. Here we will explicate an alternative focus on the healing power of the subjunctive.

1.4b Placebo responses as a class of medically significant responses to the lifeworld and how to explain them: ethnomethodology & ecological psychology

1. Phil Hutchinson. *Manchester University, Manchester, United Kingdom.*

There are two currently dominant explanatory frameworks employed for the phenomenon that goes by the name of the placebo response: Conditioned Response (e.g. Ader 1988) and Response-Expectancy (see Kirsch 1985, 1997). Drawing on work already published (2018), I will argue that both these explanatory frameworks fail. Having rejected Conditioning and Response-Expectancy, I suggest that the data from randomised controlled trials, from anthropological fieldwork, and from the historical record show that humans (and perhaps also some non-human animals) exhibit medically significant responses to meaningful loci of significance in their lifeworld, which we might call, following Moerman, meaning responses. Rather than being a third candidate explanation, the proposal of meaning responses instead serves as an invitation to reorient and refocus one's gaze away from postulating underlying causes, mechanisms and models and to the meaning the world and social practices have for members of societies and how some of these meanings have medical significance. Understand this and we'll understand the nature of the responses in which we're here interested, in ways which might help us predict them, harness them, facilitate and maintain them. To explicate the Meaning Response there are a number of explanatory paradigms we might explore. In this talk I will advocate and say a little about Ethnomethodology (Garfinkel 1967; Heritage 1991), while also proposing that we might make use of the analytic tools afforded us by Ecological Psychology (Gibson (1979) 2014; Costall 1995). I end by proposing ways of integrating these methods into placebo studies.

1.4c The placebo effect as a family resemblance concept

1. Ryan van Nood. *Purdue University, West Lafayette, IN, United States.*

Conceptual debates regarding the placebo effect, even debate about the very existence of such debate (Blease 2018), remains fervent. No modern reconceptualization of the placebo effect can contain the entire set of placebo phenomena (Miller 2018) and some prefer eliminating placebo language altogether (Turner 2018).

Rather than airbrush cases of the placebo effect to fit under one concept or forego conceptual bridges among instances placebo phenomena, we might more helpfully understand the concept of the placebo effect as having a family resemblance structure, whereby no one member-sense goes proxy for the rest but which hangs together with fellow senses through intermediate cases. This strategy simultaneously enables sensitivity to the specificity of placebic events and alertness to new features of the clinical context and mindsets that may prove placebic. Aims identified by the field's consensus (Evers et al. 2018), namely, the translation of placebo research to clinical practice and the exploitation of open-label placebos, are used to show the limits of common strategies for addressing conceptual issues regarding the placebo effect relative to these goals. The family resemblance approach reminds us that definitions are relative to their contexts of deployment and helps to articulate which criteria need to be satisfied by a vision of placebo effects that does justice to the open-label placebo phenomenon and the deeply particular realities of placebo effects in the clinical encounter.

1.4d The participation effect: The power of the powerless placebo

1. Michael Sauder. *University of Pennsylvania, Lancaster, PA, United States.*

Placebos were first considered a harmless medicine which pleases rather than cures. William Cullen, who introduced the term to clinical medicine, thought that any power a placebo has is mediated through its effect of pleasing the patient. Cullen was not confused about why patients could improve after receiving a sugar pill. But in the 20th century, randomized trials employed inert control substances that were termed placebos. A placebo was now, by definition, powerless. Yet, a recent headline in the New York Times declared “A placebo can make you run faster.” We seem confused—are placebos powerless, or powerful? In this paper I present a novel framework to help us think and talk clearly about placebos. I start by shifting our focus away from the substance itself. Since not every sugar pill is a placebo, we must consider how a pill (or any intervention) is used. To decide if something is a placebo, we must consider the doctor’s beliefs about its efficacy in a particular situation, the patient’s beliefs about the doctor’s beliefs, and the patient’s belief about the intervention’s efficacy. This framework, rooted in the clinical context in which placebo use arose, clarifies when it is appropriate to term something a placebo intervention. It also helps us think clearly about control substances in clinical trials and the ethics of placebo use. I apply my framework to recent studies involving “open label placebo,” arguing that the term “participation effect” would be useful in describing the improvement of these trial participants.

Parallel Session 1.5

Context matters! Contextual factors in placebo effects

Monday, July 8, 11:30 AM - 12.30 PM
Cornelis Schuyt zaal
Chair: Przemyslaw Babel

1.5a Physical therapists' perspectives on using contextual factors in clinical practice: Findings from an Italian national survey

1. Marco Testa. *University of Genoa, Genoa, Italy.*
2. Giacomo Rossettini. *University of Genoa, Genoa, Italy.*
3. Alvisa Palese. *University of Udine, Udine, Italy.*
4. Mirta Fiorio. *University of Verona, Verona, Italy.*
5. Luana Colloca. *University of Maryland, Baltimore, MD, United States.*
6. Tommaso Geri. *University of Genoa, Genoa, Italy.*

Background: Contextual factors (CFs) represent a potential therapeutic tool to boost physiotherapy outcomes, triggering placebo effects. Nevertheless, no evidence about the use of CFs among physical therapists is currently available. Our aim was to investigate the use of CFs and the opinion of Italian physical therapists specialized in Orthopaedic Manual Therapy (OMTs) on their therapeutic benefits.
Methods: An exploratory cross-sectional online survey was performed. A national sample of 906 Italian OMTs was recruited. Survey Monkey software was used to deliver the survey. The questionnaire was self-reported and composed by open, closed questions and clinical vignettes. Data were analyzed by descriptive and inferential statistics.
Results: 558 OMTs participated. Half of the participants claimed to use CFs frequently in their practice. More of 50% of OMTs valued the therapeutic significance of CFs for different health problems as determined by a combined psychological and physiological effect. OMTs considered the use of CFs ethically acceptable when they exert beneficial therapeutic effects and their effectiveness has emerged in previous clinical experiences. They disagreed on the adoption of CFs when they are deceptive. Moreover, OMTs did not communicate the adoption of CFs to patients, and CFs were usually used in addition to other interventions to optimize clinical responses. Psychological mechanisms, patient's expectation and conditioning were believed to be the main components behind CFs.
Conclusion: OMTs used CFs in their clinical practice and believed in their therapeutic effect. The knowledge of CFs, placebo and nocebo mechanisms and their clinical effects should be included in physiotherapists' university studies.

1.5b Does the concordance between actual treatment and patient preferred-administration-route interact with analgesic placebo mechanisms? Preference study among acute-low-back-pain patients

1. Adi Shani. *1) Haifa University, Haifa, Israel; 2) Galilee medical center, Hanita, Israel.*
2. Michal Granot. *Haifa University, Haifa, Israel.*
3. Nimrod Rahamimov. *Galilee Medical Center, Israel.*

Background: Consideration of the patient's-preference regarding treatment allows greater responsiveness and better clinical outcomes. This may be attributes to cognitive process, beliefs, expectations and learning that induce analgesic placebo-response. The effect of administration-route-preference (ARP) on the individual analgesic response has not been extensively examined to date. The aim of this study was to explore whether ARP matching treatment i.e. intramuscular- or oral administration, will increase the analgesic effect.
Methods: 38 patients with Acute-low-back-pain (ALBP) reported their ARP for analgesics, and regardless their initial desire, randomly assigned to receive either PO or IM diclofenac. Pain intensity was measured before and during the first hour after drug administration.
Results: Both groups of PO and IM administration reported severe initial pain, (VAS 8.63±1.5 and 8.74±1.6 respectively(. While both PO and IM groups reported a similar magnitude of pain reduction, patients who received the drug in their desired route (oral treatment or injection) had a significantly greater reduction in pain levels (4.05±2.8) compared with patients who received the undesired route (2.08±1.8) $p<0.05$.
Conclusions: These findings support our hypothesis that individualized ARP matching treatment in ALBP improves therapeutic outcomes, although larger studies are needed.

We suggest that in addition to the direct pharmacological effect of analgesics, ARP is linked to previous experience, belief in the efficacy of the treatment given, and expectation of pain relief. Hence when ARP matches the given treatment, it may trigger an analgesic placebo reaction.

1.5c Are the clinical effects of invasive procedures for chronic pain all placebo effects? Implications for practice and research

1. Wayne Jonas. *Samueli Integrative Health Programs, Alexandria, VA, United States.*
2. Cindy Crawford. *Uniformed Services University, Bethesda, MD, United States.*
3. Luana Colloca. *University of Maryland, Baltimore, MD, United States.*
4. Levente Kriston. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
5. Karin Meissner. *1) Coburg University, Coburg, Germany 2) LMU Munich, Munich, Germany.*

Background: Surgery and invasive procedures involve rituals and expectations that likely maximize the placebo effect, but they are rarely studied in placebo-controlled trials.
Methods: In this session, a team of researchers from a recently published systematic review and meta-analysis of sham controlled studies of surgery and invasive procedures for chronic pain will summarize the findings and discuss the methodological, clinical and ethical challenges of doing sham surgery studies - and the consequences of not doing them. Discussion of the GRADE methodology for advancing the clinical utility of SR and MA methods will be illustrated.
Results: Twenty-five trials (2,000 participants) were included in the systematic review on a variety of pain conditions with low back pain and knee arthritis the most common. The risk of any adverse event was significantly higher for invasive procedures (12%) than sham (4%) (RD 0.05, 95% CI, 0.01 to 0.09, p=0.01; I2=65%). The SMD for reduction of low back pain in seven studies (N=445) was 0.18 (95% CI,.-0.14 to 0.51; p=0.26; I2=62%); for knee pain in three studies (N=496) was 0.04 (95% CI,.-0.11 to 0.19; p=0.63; I2=36%). The relative contribution of within-group improvement in sham treatments accounted for 87% of the effect compared to active treatment across all conditions.
Conclusions: The current evidence indicates that invasive procedures are no better than sham procedures for chronic back or knee pain and may be more harmful. The presenters will discuss the implications of this evidence for pain treatment and for research using invasive placebo (sham) procedures.

1.5d How colours shape pain perception. Implications for studies on placebo effects involving colour stimuli paradigm

1. Karolina Wiercioch-Kuzianik. *Jagiellonian University, Kraków, Poland.*
2. Elżbieta A. Bajcar. *Jagiellonian University, Kraków, Poland.*
3. Wacław M. Adamczyk. *1) Jagiellonian University, Kraków, Poland; 2) The Jerzy Kukuczka Academy of Physical Education, Kraków, Poland.*
4. Ewa Buglewicz. *Jagiellonian University, Kraków, Poland.*
5. Jakub Nastaj. *Jagiellonian University, Kraków, Poland.*
6. Przemysław Bąbel. *Jagiellonian University, Kraków, Poland.*

Background: Placebo analgesia and nocebo hyperalgesia can be elicited by several methods, including classical conditioning, verbal suggestions and observational learning. However, they are affected by many other factors as well. Other studies focused on such aspects as: sex, personality or ethnicity of participants; role and sex of the experimentator, or the type of placebos used. However, still little is known about the role of colours. It is especially important, since colours are commonly used in a popular experimental paradigm to study placebo effects. The aim of the described series of studies was to explore possible influence of colours on pain perception.
Methods: Participants received electrocutaneous stimuli of one, individually adjusted intensity preceded by different colours. In the six subsequent experiments, colours differed by the following parameters: hue, saturation, and lightness. In the first study, participants rated experienced pain intensity, whereas in the subsequent experiments they rated both experienced and expected pain intensity. Additionally, participants were asked if colour can affect pain perception, to control for possible prior expectations.
Results: It was found that the red colour especially enhanced pain perception compared to other colours. Moreover, the more saturated the colour and the closer the lightness is to the value of 50, the higher is the experienced pain. This effect was observed regardless of either short term expectations or consciously declared beliefs.
Conclusions: Colours can alter pain perception and their effects should therefore be taken into account when designing either experimental or clinical studies on placebo and nocebo effects.

Poster Session 2

Monday, July 8
1:00 PM - 2.00 PM

P2.01 Open-label placebos for elderly patients with chronic knee pain: Effects on pain, functionality, and quality of life

1. Elisabeth Olliges. *1) LMU Munich, Munich, Germany; 2) Coburg University, Coburg, Germany.*
2. Sabine Stroppe. *LMU Munich, Munich, Germany.*
3. Anja Haile. *LMU Munich, Munich, Germany.*
4. Marwa Malhis. *Coburg University, Coburg, Germany.*
5. Susanne Aileen Funke. *Coburg University, Coburg, Germany.*
6. Karin Meissner. *1) Coburg University, Coburg, Germany; 2) LMU Munich, Munich, Germany.*

Recent trials indicate that open-label placebos (OLP) can have beneficial effects in various medical conditions. The aim of this study was to examine the effects of OLP on pain, functionality, and quality of life in patients with painful knee osteoarthritis. Sixty participants (mean age: 67 years, 55% female) were randomized to either an untreated control group (n = 19) or to one of two OLP groups targeting either pain (n = 21) or mood (n = 20). Patients randomized to OLP knowingly received placebos for 3 weeks. At baseline and after 21 days, pain, function and stiffness (WOMAC), quality of life (SF-12), anxiety (STAI), and self-efficacy (SWE) were assessed, and saliva probes for diurnal cortisol profiles were collected. Furthermore, patients filled in a diary to rate pain at start, rest, load as well as mood for 21 days. Results showed no differential effects between the 2 OLP groups, which were therefore combined. From week 1 to 3, pain at rest decreased significantly in the OLP group as compared to the control group ($F(1,55)=4.5$, $p=0.038$). Furthermore, interactions with sex were observed for pain at start ($F(1,55)=4.1$, $p=0.048$) and WOMAC-pain ($F(1,56)=4.7$, $p=0.035$), with placebo effects in women only (p's < 0.05). Finally, self-efficacy scores increased significantly in the control group ($F(1,57)=9.2$, $p=0.004$). No further main or interaction effects were significant. In conclusion, OLP improved pain in elderly patients with knee osteoarthritis, with women benefiting more than men. The effect of OLP on pain was not accompanied by stress reduction.

P2.02 Knowledge of contextual factors, placebo and nocebo effects in patients with musculoskeletal pain: A national survey

1. Giacomo Rossettini. *University of Genoa, Genoa, Italy.*
2. Alvisa Palese. *University of Udine, Udine, Italy.*
3. Marco Testa. *University of Genoa, Genoa, Italy.*
4. Mattia Mirandola. *University of Genoa, Genoa, Italy.*
5. Fabio Tortella. *University of Genoa, Genoa, Italy.*
6. Tommaso Geri. *University of Genoa, Genoa, Italy.*

Background: Contextual factors (CFs) have been recently proposed as triggers of placebo and nocebo effects in musculoskeletal pain. To date the Italian patients' knowledge about CFs role in musculoskeletal pain treatment is lacking. The aim of this study was to investigate attitudes and beliefs of Italian patients with musculoskeletal pain, regarding the use of CFs in clinical practice.
Methods: A national sample of 1112 Italian patients with musculoskeletal pain was recruited from 12 outpatients' private clinics in Italy presenting: 18-75 years; valid e-mail account; understanding of Italian language. Survey Monkey software was used to deliver the online survey. The questionnaire was self-reported and composed by open, closed questions and clinical vignettes.
Results: 574 participants were female. Patients' mean age was 41.7 ± 15.2 years. Patients defined CFs as an intervention with an aspecific effect, but they believed in their clinical effectiveness. They identified several therapeutic effects of CFs for different health problems. Patients perceived as ethical the adoption of CFs in clinical practice. They considered as non-ethical the deceptive use of CFs. During clinical practice patients desired a direct communication about the use of CFs. They mostly had positive beliefs and attitudes towards their use and effectiveness when associated with evidence-based therapy. Patients explained the power of CFs through body-mind connections
Conclusion: According to our findings, clinicians, educators, managers and policy makers should consider an aware adoption of CFs at multiple levels of healthcare systems aimed at enhancing patients' therapeutic outcomes.

P2.03 Knowledge, beliefs, use, and ethical and communicational issues of placebo and nocebo effects among nursing students: A national survey

1. Alvisa Palese. *University of Udine, Udine, Italy.*
2. Giacomo Rossettini. *University of Genoa, Genoa, Italy.*
3. Marco Testa. *University of Genoa, Genoa, Italy.*
4. Tommaso Geri. *University of Genoa, Genoa, Italy.*
5. Lucia Cadorin. *CRO Aviano National Cancer Institute, Aviano, Italy.*

Background: Placebo/nocebo effects have been documented as those positive and/or negative psychosomatic responses to a nursing intervention. Recently, a set of contextual factors (CFs) has been identified that triggers placebo/nocebo responses capable of influencing patients' outcomes. This study explored the way nursing students perceive the use of CFs in their clinical practice.
Methods: A cross-sectional survey was adopted in two Italian nursing programmes using a self-administered questionnaire. Survey was delivered using a paper-and-pencil, self-administered approach. The questionnaire was self-reported and composed by open, closed questions.
Results: A total of 510 students participated in the survey; 415 were female, and their average age was 23.2 years. Students defined the CFs as an intervention with a possible aspecific effect, believing in their effects. They identified mainly physiological and psychological therapeutic effects of CFs for different health problems. Students perceived as ethical the adoption of CFs in clinical practice. During clinical practice students communicated the use of CFs. They mostly had positive beliefs and attitudes towards their use and effectiveness when associated with evidence-based therapy to optimize outcomes and to calm patient.
Conclusion: Nurses are aware of CFs as elements to increase the placebo and prevent the nocebo responses in concomitance with evidence-based nursing interventions.

P2.04 Contextual factors triggering placebo and nocebo effects in Italian nursing practice: A national cross-sectional study

1. Marco Testa. *University of Genoa, Campus of Savona, Savona, Italy.*
2. Lucia Cadorin. *CRO Aviano National Cancer Institute, Pordenone, Italy.*
3. Tommaso Geri. *University of Genoa, Campus of Savona, Savona, Italy.*
4. Luana Colloca. *University of Maryland, Baltimora, MD, United States.*
5. Giacomo Rossettini. *University of Genoa, Campus of Savona, Savona, Italy.*
6. Alvisa Palese. *University of Udine, Udine, Italy.*

Background: Placebo effects have been studied in the nursing discipline, but nocebo effects still remain unexplored. Recently, a set of Contextual Factors (CFs) functioning as triggers of placebo/nocebo responses has been described; however, its use in daily care has never been documented to date. The aim of this study was to describe CFs used by nurses to increase placebo and to prevent nocebo responses.
Methods: A national cross-sectional survey was performed on 2016. A nation-wide sample of Italian nurses belonging to four national associations was involved. Survey Monkey software was used to deliver the online survey. The questionnaire was self-reported and composed by open, closed questions.
Results: Out of 1411 eligible nurses, 455 answered, and 425 questionnaires were valid for the analysis. Nurses defined the CFs as an intervention with a possible aspecific effect, believing in their effects. They identified several therapeutic effects of CFs for different health problems. Nurses perceived as ethical the adoption of CFs in clinical practice. They considered as non-ethical the deceptive use of CFs. During clinical practice nurses communicated the use of CFs. They mostly had positive beliefs and attitudes towards their use and effectiveness when associated with evidence-based therapy.
Conclusion: Nurses are aware of CFs as elements to increase the placebo and prevent the nocebo responses in concomitance with evidence-based nursing interventions.

P2.05 A taste of the (un)expected

1. Lotte van Dillen. *Leiden University, Leiden, Netherlands.*
2. Marieke Jepma. *University of Amsterdam, Amsterdam, Netherlands.*
3. Marret Noordewier. *Leiden University, Leiden, Netherlands.*

Background: Expectations often drive perception, such that sensations are assimilated towards them. An interesting question is how far this influence extends, and when it shifts towards surprise. In two studies, we tested this in the domain of taste perception. Taste can be considered a core affective stimulus, as it often has a clear aversive or rewarding nature, but contrary to most other affective stimuli, its intensity can be tightly controlled, lending itself well to examine how expectations and surprise shape sensory perception.
Methods: We examined how expectations about intensity and flavor shape taste perception in two studies, either between (Study 1) or within participants (Study 2), by (mis)labeling high and low intensity sweet (rewarding) and sour (aversive) tastants (Study 1) and by (repeatedly) pairing these tastants with distinct cues in a training phase and examining their effect on taste intensity ratings of medium intensity tastants during a subsequent test phase (Study 2).
Results: Participants assimilated their taste intensity ratings to expectations (Study 1) or previously learned associations (Study 2). However, this effect was more pronounced when expectations about taste intensity were assessed within a taste modality (i.e. within sweet or sour) than across modalities (i.e. across sweet and sour), and especially when rewarding sweetness cues were next paired with an aversive sour flavor, their influence was reduced.
Conclusion: Together, the findings shed new light on the role of expectations in taste perception, and the potential asymmetry in expectancy violations. Implications for placebo research will be discussed.

P2.06 Incidence and characteristics of the nocebo response from meta-analyses of the placebo arms of clinical trials

1. Seetal Dodd. *Deakin University, Geelong, Vic., Australia.*

Background: The nocebo phenomenon is an unwanted treatment response in a situation in which conditioning from previous treatment exposure and/or expectations of sickness or symptoms lead to sickness and symptoms in a conditioned or expectant individual. The nocebo response may be a confounder in clinical treatment and clinical research. There is a need to know how to predict if an individual is likely to be a nocebo responder, and how significant and commonplace the nocebo effect might be.
Methods: An analysis was conducted on nine placebo-controlled, randomised clinical trials of olanzapine for the treatment of bipolar disorder using data from placebo-treated study participants only. Data were analysed to identify participant or study characteristics associated with a nocebo event, defined as any treatment-emergent adverse event (TEAE) or an increase in score from baseline to endpoint for primary measures of clinical symptoms.
Results: A total of 1185 participants were randomised to placebo, of whom 806 (68%) reported a TEAE. Hamilton Depression Rating Scale (HDRS) data were only available for 649 placebo-treated participants, of whom 321 (49.5%) demonstrated worsening. Nocebo events were significantly associated with: not being treatment-naïve, younger age, being located in the USA, being a participant in an earlier study, and being classified as obese compared with normal weight.
Conclusions: A pattern to identify nocebo responders did not emerge, although some prognostic variables were associated with a greater probability of nocebo response. There was some evidence to support the role of expectancy as a cause of nocebo reactions.

P2.07 The influence of personality traits on the placebo/nocebo response: A systematic review

1. Alexandra Kern. *1) Institute for Complementary and Integrative Medicine University Hospital Zurich; 2) University of Zurich, Zurich, Switzerland.*
2. Christoph Kramm. *1) Institute for Complementary and Integrative Medicine University Hospital Zurich; 2) University of Zurich, Zurich, Switzerland.*
3. Claudia Witt. *1) Institute for Complementary and Integrative Medicine University Hospital Zurich; 2) University of Zurich, Zurich, Switzerland.*
4. Jürgen Barth. *1) Institute for Complementary and Integrative Medicine University Hospital Zurich; 2) University of Zurich, Zurich, Switzerland.*

Background: Some people might be more prone to placebo responses than others depending on their personality characteristics. We aimed to identify the established personality traits with predictive power and explore reasons to explain heterogeneity of findings.
Methods: We identified primary studies from reviews related to this topic (k = 10) and subsequently conducted a systematic literature search in the databases of EBSCO (CINAHL, AMED, PsycINFO) and EMBASE for publications published between January 1997 and March 2018. For all included papers we conducted an additional forward search.
Results: After the screening of 392 references, 21 studies were identified. The results indicate that studies covering this topic are scarce and widely heterogeneous in terms of study design, investigated personality traits, the assessment thereof and outcomes. The Big Five (i.e. neuroticism, extraversion, openness to experience, agreeableness and conscientiousness) and Optimism were the most frequently investigated traits. Several studies found a positive association between optimism and the placebo response. Furthermore, we found that higher anxiety was in general associated with elevated nocebo responses.
Conclusion: Since there is no clear-cut pattern in the findings it is difficult to conclude which personality trait is most predictive for placebo/nocebo responses. However, optimism is likely to be associated with placebo responses. For clinical practice the impact of anxiety on the nocebo response might be important to identify patients at risk for side effects.

P2.08 The placebo diet: How suggestion affects cognitive regulation, and through it hunger perception

1. Solene Frileux. *Institute du Cerevau et de la Moelle épinière (ICM), Paris, France.*
2. Philippe Fossati. *APHP, ICM, Paris, France.*
3. Liane Schmidt. *Inserm, ICM, Paris, France.*

Background: Brain imaging studies across domains suggest that placebo effects are underpinned by the activation of a set of frontal cortex regions associated to the cognitive regulation of affective states. Here we aim at providing direct behavioral evidence for the contribution of cognitive regulation to suggestion-based placebo effects.
Methods: We used hunger and its perception as a model in 126 participants who had fasted for 12 hours. Participants were administered a glass of water that was either labeled as enhancing or diminishing appetite. A food choice paradigm from decision neuroscience quantified cognitive regulation propensities in form of regulatory success such as the ability to devalue unhealthy, tasty and to value healthy, untasty food during decision-making.
Results: Suggestion about appetite significantly influenced hunger ratings (β=0.75, p=0.01) with more hunger reported by participants in the enhanced compared to the diminished appetite group. Participants under the diminished appetite suggestion displayed more regulatory success than participants under the enhanced appetite suggestion (β=-0.11, p=0.03), and irrespective of appetite suggestion more regulatory success generated lesser hunger (β=-1.7, p=0.001). Importantly, regulatory success mediated the effect of appetite suggestion on hunger ratings (β=0.2, p=0.02), controlling for baseline hunger and BMI.
Conclusion: These findings indicate that suggestion about appetite engendered cognitive regulation processes that shaped participants' hunger perception. These results provide insights into how suggestions get translated into an effect on behaviour, and contribute to a better understanding of the psychological processes that give rise to placebo effects.

P2.09 Open-label placebos improve test anxiety and self-management abilities and resources

1. Michael Schaefer. *Medical School Berlin, Berlin, Germany.*
2. Rebecca Harke. *Medical School Berlin, Berlin, Germany.*
3. Claudia Denke. *Universitätsmedizin Charite Berlin, Berlin, Germany.*
4. Sören Enge. *Medical School Berlin, Berlin, Germany.*

Background: Test anxiety is a condition in which people experience extreme distress and anxiety before and in test situations. It affects between 25 and 40 percent of all students. Conventional treatment includes both medication and psychotherapy, but studies also demonstrated that placebos affect anxiety symptoms. While in the traditional view concealment of the placebo is essential, recent studies report intriguing evidence that placebos may work even without deception (open-label placebos). This has been shown, for example, in patients with irritable bowel syndrome, chronic low back pain, and allergic rhinitis. Since prescription of fake pills involve ethical problems, open-label placebos may provide important new treatment possibilities. Here we report results of a pilot study examining if open-label placebos may reduce test anxiety and improve self-management skills.
Methods: We conducted a two-group randomized controlled trial including 58 students. The participants received either placebos without deception or no pills at all before an exam at the university. After two weeks we tested whether anxiety symptoms and self-management skills had changed.
Results: After two weeks test anxiety was reduced and self-management abilities (skills and resources) were improved more than in the control group. In addition, improvement in resource motivation predicted performance in the exam in the open-label placebo group.
Conclusions: We conclude that open label placebos seem to improve test anxiety better than a control group with comparable patient-adviser contact. Thus, we argue that open-label placebos might be a possible treatment for students to reduce test anxiety and improve self-management abilities.

P2.10 Therapeutic landscapes and atmospheres: Important components of context effects in healthcare

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2. Louise Sandal. *University of Southern Denmark, Odense, Denmark.*
3. Andrew Moore. *University of Bristol, Bristol, United Kingdom.*

Background: Context effects involve different interacting factors, including those relating to the space in which healthcare interventions are delivered, and their 'atmosphere'. We examined the hypothesis that enhancing the environment in which physiotherapy is delivered would result in a better treatment responses.
Methods: Patients requiring physiotherapy for knee pain were randomised to physiotherapy in an enhanced environment (42), a standard environment (n = 40), or a waiting list control group (n = 21). Focus groups were carried out with 25 participants, and 2 of the 3 therapists involved were interviewed. We have also examined relevant literature.
Results: Contrary to expectations, the treatment response was significantly greater in those treated in the standard environment than in the enhanced environment. Qualitative work identified three main themes: 1) fellowship and 'at homeness', 2) reflection, and 3) transitions. The standard environment appeared to result in a greater sense of safety, belonging and 'at homeness'. The literature suggests that theoretical frameworks from social sciences, such as 'therapeutic landscapes' (the physical and psychological environment), 'sense of place' and 'atmospheres' need to be incorporated into our thinking about context (placebo) effects.
Conclusions: Conventional medicine pays little attention to the places in which patients are treated, and how they may become landscapes and atmospheres, in spite of a plethora of literature on these subjects in other disciplines. From our study and literature reviews we conclude that such factors contribute greatly to the context (placebo) effects of group physiotherapy, and probably most other healthcare interventions.

P2.11 Placebo effects in spider phobia: An eye-tracking experiment

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4. Andreas Gremsl. *University of Graz, Graz, Austria.*

Background: Several eye-tracking studies have revealed that spider phobic patients show a typical hypervigilance-avoidance pattern when confronted with images of spiders. The present experiment investigated if this pattern can be changed via placebo treatment.
Method: We conducted an eye-tracking experiment with 37 women with spider phobia. They looked at picture pairs (a spider paired with a neutral picture) for 7 s each in a retest design: once with and once without a placebo pill presented along with the verbal suggestion that it can reduce phobic symptoms. The placebo was labeled as Propranolol, a beta-blocker that has been successfully used to treat spider phobia.
Results: In the placebo condition, both the fixation count and the dwell time on the spider pictures increased, especially in the second half of the experiment. This was associated with a slight decrease in self-reported symptom severity.
Conclusions: We were able to show that a placebo was able to reduce visual avoidance and experienced fear in spider phobia. This effect might help to overcome apprehension about engaging in exposure therapy, which is present in many phobic patients.

P2.12 Placebo- and nocebo- effects in cognitive neuroenhancement: Expectation affects perceived but not actual cognitive performance

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Background: The number of students using prescription drugs to improve cognitive performance has increased. The actual improvements in cognitive functions due to such drugs do not fully match the subjectively perceived improvements. There is first evidence, that the expectation to receive a performance-enhancing drug alone can result in improved perceived and actual cognitive performance. In addition, expecting a placebo may result in lower perceived and actual cognitive performance. The aim of our study was to investigate whether the expectation of receiving a performance-modulating drug leads to changes in actual and perceived cognitive performance.
Methods: 75 healthy adults were randomly assigned to either receiving a sham performance-increasing nasal spray (placebo) or a sham performance-impairing nasal spray (nocebo) or no nasal spray. Participant's actual cognitive performance (TAP) as well as their performance expectation were assessed before and after nasal spray administration. Subsequent to the second assessment, participants rated the perceived change in cognitive performance, as well as adverse symptoms.
Results: Positive or negative performance expectation did not result in changes in actual performance. The placebo-group rated their performance in the second TAP test as better and the nocebo-group as worse as compared to their performance in the first assessment. Additionally, participants in the placebo-group felt less tired than participants in the nocebo-group did.
Conclusions: Manipulation of performance expectation affects the perceived change in performance and tiredness, but not the actual cognitive performance in healthy adults. This may explain why college students use such drugs despite their little impact on actual cognitive functioning.

P2.13 The role of placebo effects in immune-related conditions: Mechanisms and clinical considerations

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Introduction : Placebo effects are powerful modulators in clinical outcomes and can either result in treatment benefits or harms, known as placebo and nocebo effects. To harness these outcomes, it is important to focus on the underlying processes that steer these effects, namely by learning through expectations and conditioning. In this review, we focus on the influence of placebo effects on subjective and physiological levels of immune-related conditions (e.g. lymphocyte proliferation, cytokine production or other inflammatory markers).
Methods: A literature search was conducted in the databases PubMed and PsychInfo by making use of keywords such as 'expectations', 'classical conditioning', 'cytokines', 'immune system', 'learned immunosuppression', and covers studies done in animals, experimental studies in healthy controls as well as studies performed in immune-related patient populations.
Results and Discussion: We report on the presence of placebo effects in RCTs in immune-related conditions and review findings that demonstrate the ability to learn immune responses in both experimental animal and human placebo studies making use of conditioning paradigms with immunomodulating drug agents. We also discuss results to utilize placebo effects by means of classical conditioning principles in medication regimens for patient populations and elaborate on promising findings of preliminary studies focusing on this topic.

P2.14 Investigating placebo responses in preschoolers (≤ 6 y): Challenging but possible?

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2. Christiane Hermann. *Justus-Liebig-University, Gießen, Germany.*

Background: Unlike in adults, the placebo effect and its mechanisms has not yet been systematically investigated in very young children (≤ 6 y) despite considerable clinical implications, probably due to methodological challenges related to reliability, validity and safety. We aimed at examining verbally induced placebo hypoalgesia in children aged 3-12 using the hand-withdrawal-method, which is a modified version of the method-of-limits providing maximal control and safety which we first validated in adults.
Methods: 21 children (3-6 y) and 39 children (7-12 y) were assigned to either a placebo ("magical pain killer") or a control condition (moisturizer described as such). Placebo responses were determined as change from baseline to post-treatment for heat pain threshold, tolerance and subjective pain ratings.
Results: There were no significant group differences regarding the change score for pain threshold, tolerance and subjective pain rating, neither in the younger (3-6y) nor the older children (7-12y). In the older children, the group difference (placebo vs. control) with regard to the change scores for pain threshold and tolerance were in the expected direction (small to medium effect size). However, in the younger children the group differences in the change scores were contrary to the hypothesis.
Discussion: Considering, that verbally induced placebo effects have previously been successfully induced in children > six years and our successful validation of the hand-withdrawal-method in adults, methodological difficulties of placebo research in very young children (e.g. duration of testing, high interindividual variability in children´s responding, unintended context-induced placebo effects in the controls) will be outlined.

P2.15 Investigating parents' approaches of how to shape their children's mind: A pilot study on harnessing placebo effects in day-to-day life

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3. Ella Weik. *University of British Columbia, Vancouver, BC, Canada.*
4. Tim Oberlander. *University of British Columbia, Vancouver, BC, Canada.*

Background: Children's high degree of suggestibility may offer helpful ways to cope with pain in ways that harness key elements underlying the analgesic properties of placebo effects. In this study we explore parental approaches aiming to shape a child's experience of social or physical pain.
Methods: We conducted semi-structured interviews with parents of 4-12-year-olds. We asked two closed-ended questions ("How well does a placebo work for you/ your child?" [10-point Likert scale]) and several open-ended questions: "Tell me about a situation within the past 12 months where your child was physically injured or ill/ had to deal with a difficult social situation; what did you do? What other approaches do you usually apply?" Interviews were transcribed and qualitative-content-analysis was applied to cluster parental approaches.
Results: Parents (N=17) from various socio-economic backgrounds were interviewed (2 fathers, 15 mothers; 9 girls, 8 boys). Preliminary analyses indicate that parents used more diverse approaches (e.g., distraction, suggestions, providing loving care and/or food/drinks) if their child experienced physical pain compared to social pain (e.g., giving advice, talking about it). Furthermore, parents believed that a placebo is more efficacious for their child (M=8.1, SD=1) compared to themselves (M=5.8, SD=1.9), $p<.001$.
Conclusions: Our findings suggest the use of different strategies in social and physical pain: regarding children's socio-emotional pain parents seem to use more cognitive-based strategies, whereas when dealing with their child's physical pain, they rely on more hands-on, physical approaches. With this project we aim to understand how placebos can be harnessed in children's day-to-day life.

P2.16 I'm trying to tell you: Open label placebo effects in GVS and VR-induced nausea

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2. Alice Yu. *Western Sydney University, Sydney, NSW, Australia.*
3. Judith Josupeit. *Heinrich-Heine University, Düsseldorf, Germany.*
4. Ben Colagiuri. *University of Sydney, Sydney, NSW, Australia.*

Background: Nausea is a common complaint, responsive to the placebo effect. Existing placebo research in nausea has employed deception, limiting therapeutic translation on ethical grounds. Open-label placebos (OLPs) may circumvent these ethical barriers. The effect, however, has yet to be applied to nausea.
Method: Galvanic Vestibular Stimulation (GVS: Exp. 1) and Virtual Reality (VR: Exp. 2) were employed to model nausea in healthy volunteers. Experiments comprised two sessions, where nausea was elicited with and without sham treatment (peppermint vapour / brain stimulation). In Exp. 1, participants (n = 60) were randomly assigned to four conditions: natural history; deceptive placebo; semi-open placebo; fully-open placebo. In Exp. 2 (n = 91), fully and semi-open groups were collapsed into one OLP condition. Self-report nausea and postural stability (Exp. 2) formed outcome variables.
Results: Relative to natural history, Exp. 1 found limited evidence for a placebo effect across all conditions ($p = .24$, $\eta p2 = .03$). The largest effect was observed in the deceptive condition ($p = .09$, $\eta p2 = .05$). In Exp. 2, deceptive placebo differed from natural history ($p = .02$, $\eta p2 = .06$) and OLP ($p = .05$, $\eta p2 = .05$). The latter were numerically similar. Bayesian analysis concerning the OLP favoured the null. No difference in postural stability was observed.
Conclusion: Evidence for a deceptive placebo effect in VR-induced nausea was observed. Openly informing participants resulted in limited symptom improvement, however, raising questions regarding the efficacy of OLPs in nausea. Results are discussed in light of treatment novelty and expectancy.

P2.17 An exploration of the role of context effects in acupuncture practice: A qualitative study based on semi-structured interviews with acupuncturists in private practice in three different locations

1. Sarah Theiss. *Private practice, Munchen, Germany*.

Introduction: Acupuncture can be considered a complex treatment intervention which includes different components leading to an overall treatment effect. Among these are various factors, evoking specific effects and context effects. It has been argued that context effects might be especially potent in acupuncture. Therefore, this study aims to explore practitioner perceptions of the role of context effects, and contributing contextual factors, in clinical practice.
Methods: This qualitative study draws on data obtained in semi-structured interviews with acupuncturists in private practice. Maximum variation sampling was utilised, and a total of 18 participants from 3 different locations were sampled (Seoul, London and Munich). Thematic data analysis was implemented.
Findings: The majority of acupuncturists considered contextual factors, and resulting context effects, to be a fundamental aspect of their treatments. Participants reported they actively implement contextual factors in relation to patients, practitioners, therapeutic relationship, therapeutic ritual, clinical environment and touch. The overarching aim for implementation, however, was to induce patient relaxation. Further, acupuncturists highlighted a close link between contextual and specific treatment factors.
Discussion: Context effects seem to have significant potential in acupuncture. Moreover, they may be understood as deeply imbedded in the overarching framework of acupuncture. This becomes evident through contextual factors providing the particular supportive structure to treatments, and through their intimate link to East-Asian medical theory. In particular, being mainly

implemented to enhance patient relaxation, a state that is considered to powerfully support treatments in acupuncture, context effects seem to be inseparable from the specific treatment effects in clinical practice.

P2.18 Positive treatment expectancies reduce clinical pain and perceived motor disability despite increased pain experience: A randomized controlled trial on sham opioid infusion in patients with chronic back pain

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2. Maike Müller. *University Hospital of Würzburg, Würzburg, Germany.*
3. Christian Zoellner. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
4. Herta Flor. *Heidelberg University, Mannheim, Germany.*
5. Regine Klinger. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: Increasing evidence for the efficacy of analgesic placebo effects in experimental studies with healthy controls raises the question whether their underlying mechanisms could be used to improve clinical pain treatment. Expectancies play a central role in shaping analgesic placebo-/nocebo effects. Objectives: We investigated to what extend a sham opioid infusion (NaCl) can result in sustained clinically relevant placebo and nocebo effects in chronic back pain patients.
Method: Fifty-nine patients received the sham opioid infusion applied via a large drain dressing compared to 14 patients in the control group (no intervention, natural history, NH). We shaped treatment expectancies by suggestion and conditioning (infusion coupled with pain decrease (n=17: placebo conditioning), pain increase (n=21: nocebo conditioning), no conditioning (n=21: constant pain levels).
Results: Compared to NH, all infusion groups showed improved clinical back pain (primary outcome) and pain-related disability (secondary outcome). The pharmacologically inactive Infusion (NaCl), when presented as an effective treatment (sham “opioid” Infusion), induced positive expectancy in patients and placebo analgesia as evident in significantly lower back pain ratings ($p < .001$), increased self-reported functional capacity ($p < .001$) and less perceived impairment of mobility ($p < .001$). Even the nocebo conditioned group developed positive treatment expectancies followed by reduced pain experience. Over all participants we found a significant positive correlation between positive treatment expectancies and back pain relief ($r= .72$, $p < .01$).
Conclusions: These findings have consequences for clinical pain treatment, suggesting that it may be beneficial to explicitly shape and integrate treatment expectancies into pain management.

P2.19 An animal model of placebo analgesia in inflammatory pain rats

1. Jianyou Guo. *Chinese Academy of Sciences, Beijing, China.*

Background: The placebo effect is a topic of interest to psychologists and health practitioners in a wide variety of areas, and the question of the mechanisms underlying this effect is gaining increasing attention. Recent researches on placebo in human showed an urgent need for placebo animal models to investigate the neural mechanisms of the placebo effect.
Method: We have previously evoked placebo responses in normal rodent. In the present study, we tried to develop a placebo analgesia animal model in inflammatory pain rats. Complete Freund’s adjuvant-treated rats were given 4 days of morphine conditioning with the conditioned cue stimulus and the unconditioned drug stimulus, then mechanical paw withdrawal was measured after saline injection with the cue at day 5. The morphine conditioning was divided into two experimental procedures.
Results: As morphine was injected and received with mechanical paw withdrawal test each day, it did not produce placebo analgesia in rats at day 5. In contrast, when morphine was injected and the mechanical paw withdrawal test was not performed, it produces a strong placebo effect that was blocked by naloxone.
Conclusion: These findings suggest that placebo analgesia can also be observed in inflammatory pain animals. The present procedure of rats may serve as a model for further understanding of mechanisms underlying placebo responses.

P2.20 Open-label placebo for the treatment of depression – A randomized controlled trial

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2. Ted Kaptchuk. *Harvard Medical School, Boston, MA, United States.*
3. Irving Kirsch. *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States.*
4. Dafna Shefet. *Tel Aviv University, Hod-Hasharon, Israel.*
5. Israel Krieger. *Tel Aviv University, Hod-Hasharon, Israel.*
6. Yoram Braw. *Ariel University, Ariel, Israel.*
7. Yuval Bloch. *Tel Aviv University, Hod-Hasharon, Israel.*
8. Pesach Lichtenberg. *Hebrew University, Jerusalem, Israel.*

Background: In studies of anti-depressant treatment of various sorts, the response to placebo is robust. The strong placebo response combined with the absence of side-effects has prompted suggestions to use open-label placebo as a treatment for depression. The aim of the present study was to assess the efficacy of open-label placebo in treating patients suffering from unipolar depression.
Methods: Participants were randomized to one of two possible interventions: either 8 weeks of open label placebo, or 4 weeks of treatment as usual (TAU) followed by four weeks of open label placebo. Clinical response to treatment was determined using the Quick Inventory of Depressive Symptomatology (QIDS SR-16).
Results: Thirty-eight patients (28 females, 73.7%) participated in the study (n=18 in the placebo group, n=20 in the TAU group). There was significant decrease in depression levels over time among our entire study sample (i.e., main effect of time) [$F(2,35)=3.98$, $p=.028$]. A significant interaction between the placebo group and the TAU group was evident only among young

adults (age<65y) with early onset of the disorder (<50y) [F(2,22)=3.89, p=.036]. Post-hoc paired-samples t-tests, performed separately for each group, indicated a significant decrease during the first 4 weeks only in the placebo group [T0-T1: t(11)=2.29, p=.043].
Conclusions: Our results support the possibility that open label placebo is an effective treatment for young patients with a relatively early onset of the depressive disorder. Additional studies are warranted in order to explore the implementation of open label placebo in the clinical work.

P2.21 How placebo needles differ from placebo pills?

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2. Paul Enck. *University Hospital Tübingen, Tübingen, Germany.*

Acupuncture treatment is defined by the process of needles penetrating the body. Placebo needles were originally developed with non-penetrating mechanisms. However, whether placebo needles are valid controls in acupuncture research is subject of an ongoing debate. I will provide an overview of the characteristics of placebo needles and how they differ from placebo pills in two aspects: (1) physiological response and (2) blinding efficacy. Placebo needles elicit physiological responses similar to real acupuncture and therefore provide similar clinical efficacy. This efficacy is further supported by ineffective blinding (even in acupuncture-naïve patients) which may lead to opposite guesses that will further enhances efficacy, as compared to no-treatment, e.g., with waiting list controls. Additionally, the manner in which placebo needles can exhibit therapeutic effects relative to placebo pills include enhanced touch sensations, direct stimulation of the somatosensory system and activation of multiple brain systems.

P2.22 Aiming for placebo and (partly) observing nocebo: A pilot study on open-label placebo

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2. Michael Witthöft. *University of Mainz, Mainz, Germany.*

Background: A non-deceptive administration of placebos is called “open-label placebo (OLP)" and has been shown to be effective for various conditions. In healthy participants, as well, OLP can improve well-being and reduce physical symptoms. The present study aimed to replicate OLP effects in healthy participants using a within-subjects design and to assess the role of labeling, personality traits, suggestibility, and expectation.
Methods: Healthy participants (N = 26) were informed about OLP effects in a face-to-face appointment. Personality traits were assessed with the NEO-FFI and suggestibility with the Creative Imagination Scale. Subsequently, participants filled in daily questionnaires concerning their well-being (WEMWBS) and health complaints (SHC) on five subsequent days with and without taking placebo pills (randomized sequence). Half of the participants received placebos with a label, the remaining without.
Results: Contrary to our hypotheses, participants reported more health complaints during the placebo condition (when the placebo condition appeared before the control condition). This effect was positively associated with neuroticism and the presence of a label. Consistent with the hypotheses, participants tended to report increased well-being during the placebo condition (when the control condition appeared before the placebo condition). Interactions of expectations, label, suggestibility, conscientiousness, openness, and extraversion influenced this effect.
Conclusions: In healthy participants with a low rate of health complaints, intake of placebos possibly leads to nocebo effects due to increased attention and symptom-focused perception. The OLP effect for well-being was small and moderated by various factors. Larger samples are necessary to validate these preliminary results.

P2.23 The blind leading the not-so-blind: A meta-analysis of blinding in pharmacological trials for chronic pain

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2. Louise Sharpe. *University of Sydney, Sydney, NSW, Australia.*
3. Ben Colagiuri. *University of Sydney, Sydney, NSW, Australia.*

Background: Patient blinding is a critical feature of double-blind placebo-controlled RCTs. It aims to evenly distribute patient beliefs about treatment allocation across active and placebo arms of these trials. Successful blinding indicates that observed differences between treatment arms cannot reflect differences in expectations and beliefs, which may bias a trial’s outcomes via processes such as the placebo effect. Little is known about blinding practices and outcomes in chronic pain trials, while evidence from other disciplines indicates that blinding is rarely assessed and often fails. Our aim was to determine rates and predictors of assessing blinding and its success or failure in chronic pain.
Methods: We systematically reviewed and meta-analysed double-blind placebo-controlled RCTs of pharmacological interventions for chronic pain between 2006 and 2016. Logistic regression, meta-analysis, and meta-regression using random effects models were employed.
Results: A systematic search identified 408 trials representing over 100,000 participants. Of these, only 23 RCTs reported assessing patient blinding. Study characteristics, including pharmaceutical sponsorship, were associated with lower rates of assessing blinding. Meta-analysis indicated that blinding was not successful when combined across studies (g = 1.12, 95% CI 0.92−2.01). Higher rates of adverse events and larger treatment effect sizes were associated with worse blinding outcomes.
Conclusion: We found that blinding is rarely reported and often fails in pharmacological RCTs for chronic pain. Importantly, a number of trial characteristics (e.g. pharmaceutical sponsorship and adverse events) appear to bias blinding assessment and its outcomes. Recommendations for assessing and analyzing blinding in RCTs for chronic pain will be discussed.

P2.24 The placebo response in migraine treatment trials: Comparing oral preventives, botulinum toxin, and anti-CGRP treatments

1. Sandhya Ravikumar. *University of Southern California, Los Angeles, CA, United States.*

Background: Oral migraine treatment trials have an estimated placebo response rate of 21%, with placebo groups showing an 18% reduction in monthly migraine days, according to a 2007 meta-analysis by Macedo. Since then, two treatment classes for migraines have emerged: botulinum toxin injections and the anti-CGRP (calcitonin gene related peptide) subcutaneous medications, including erenumab, fremanezumab, and galcanezumab. This analysis aims to compare the placebo responses in these treatments.
Methods: A Medline literature search was performed to identify double-blind, placebo-controlled trials for migraine prevention for botulinum toxin, erenumab, fremanezumab, and galcanezumab. A total of 10 articles were included in the analysis. The trial's end points, including change in monthly migraine days and responder rates, were collected, and weighted means and standard deviations were calculated.
Results: The analysis included 6491 patients, with 3116 from the placebo group. The average decrease in monthly migraine days was 32.8 ± 1.27% in the botulinum toxin placebo group (vs. 42.5 ± 3.89% in the active group), 26.7 ± 14.7% in the placebo group for anti-CGRP episodic migraine trials (vs. 45.7 ± 14.8% in the active group), and 17.7 ± 4.69% in the placebo group for anti-CGRP chronic migraine trials (vs. 30.4 ± 6.16% in the active group). The placebo responder rates for the anti-CGRP trials were 32.0 ± 15.0% for episodic and 18.0 ± 3.86% for chronic migraine, compared to 50.7 ± 14.5% for episodic and 36.4 ± 7.46% for chronic migraine in the active group.
Conclusions: Compared to previous studies of migraine oral preventives, the improvement in monthly migraine days in the placebo group was higher in the botulinum toxin trials and anti-CGRP episodic migraine trials. The placebo responder rates for the anti-CGRP trials were higher in the episodic compared to the chronic migraine trials. Overall, the placebo response in trials for new migraine treatments is higher compared to the response in previous trials.

P2.25 Expecting the worst: Investigating the effects of trigger warnings on reactions to ambiguously themed photos

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2. Melanie Takarangi. *Flinders University, Adelaide, SA, Australia.*

Background: Trigger warnings are messages alerting people to content containing themes that could cause distressing emotional reactions. Advocates claim that warnings allow people to prepare themselves and subsequently reduce negative reactions towards content, while critics insist warnings may increase negative reactions. Indeed, early research suggests that trigger warnings may act as a nocebo; when negative expectancies (e.g., expecting material to be distressing) lead to the exacerbation of negative outcomes (e.g., greater anxiety while viewing the material; Bellet, Jones, & McNally, 2018). However, other findings (e.g., Sanson, Strange, & Garry, 2018) suggest that the effects of trigger warnings are trivial; neither helpful nor harmful.
Methods: Here, we investigated (a) the emotional impact of viewing a warning message, (b) if a warning message would increase or decrease participants' negative reactions towards a set of ambiguous photos, and (c) how participants evaluated overall study participation.
Results: We meta-analyzed the results of 5 experiments conducted online, and found that trigger warnings did not cause participants to interpret the photos in a more negative manner than participants who were unwarned. However, warned participants experienced a negative anticipatory period prior to photo viewing that did little to mitigate subsequent negative reactions.
Conclusions: Trigger warnings may provide little when used in the real world. We are currently investigating if the effect of an optimism and nocebo instruction, asking participants to imagine their best and worst (respectively) possible reaction towards a set of threatening photos, differs (or does not differ) from a traditional trigger warning message.

P2.26 The role of expectations in placebo analgesia: A meta-analysis

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2. Susan Tomczak Matthiesen. *Aarhus University, Aarhus, Denmark.*
3. Lene Vase. *Aarhus University, Aarhus, Denmark.*

Background: Some studies have found that expected pain levels contribute to placebo analgesia whereas others have not. The aim of the current meta-analysis is to provide a systematic overview of the extent to which expectations contribute to placebo analgesia effects. The meta-analysis will consider potential effects of expectations regarding patients and healthy controls and various ways of inducing expectations and placebo.
Methods: Studies are identified through searching the databases PubMed, PsycINFO, Embase, and Web of Science for the following keywords: expectation AND ("placebo analgesia" OR "placebo effects"). Two researchers will independently screen abstracts, full-text articles, and references of included articles. Experts in the field of placebo studies will be contacted to identify other potential studies.
Results: Placebo analgesia mechanism studies including numerical measures of pain and expectations will be analyzed. The results will be presented at the 2nd official SIPS conference in Leiden, The Netherlands, July 2019.
Conclusions (preliminary): This meta-analysis is expected to estimate effects of expectations in placebo analgesia effects and thereby the extent to which expectations induce placebo effects. These findings will have implications for treatment optimization in research and clinical practice through effects of expectations.

P2.27 Selfhealing and the placebo effect

1. Roel Gaymans, *Made, Netherlands.*

Literature on placebo subjects is searched for the items selfhealing, self-efficacy and selfhelp methods.
The outcome of this study will be presented.
The way the placebo effect is defined and understood varies substantially due to the multiple disciplines that show their scientific interest. Accordingly the concepts of selfhealing show variation.
Placebo effect and selfhealing share the activity of similar endogenous systems. Such as dopamine-, endorfine-, hormonal-, immune-system, and emotional regulation.
As a consequence there arises a picture in which selfhealing and placebo effect overlap one another. Placebo effect occurs as part of regular treatments and, on the other hand, within selfhealing approaches.
By some authors it is suggested that application of strategies, showing positive placebo treatment outcomes, can actively be used in the doctor patient encounter.
This concerns mostly aspects of doctor behaviour and treatment modalities. At the same time various writers pay attention to an action of the patient as participant in selfhealing behavior and selfhelp methods.
The patient-doctor contact is accepted as a major contribution in any therapeutical situation.
When both parties share mutual ideas on healing, placebo effect, and selfhealing, this should improve the quality of this contact; With sharing similar language as a basic tool.
Implications for future studies will be suggested.

P2.28 How to administer deceptive and open-label placebos? A five-armed experimental study on sadness

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2. Winfried Rief. *Philipps-University Marburg, Marburg, Germany.*
3. Julia Anna Glombiewski. *University of Koblenz-Landau, Landau, Germany.*
4. Julia Wittkowski. *Philipps-University Marburg, Marburg, Germany.*
5. Tobias Kube. *1) University of Koblenz-Landau, Landau, Germany; 2) Philipps-University Marburg, Marburg, Germany.*

Background: Placebo effects have been shown to play a major role in drug treatments of depressive disorders (Kirsch & Sapirstein, 1998). To increase the overall drug treatment effectiveness, placebo effects might be utilised clinically (Finniss et al., 2010). This relies upon a thorough understanding of underlying mechanisms and their interplay (Rief et al., 2011). The present study aims to examine the effectiveness of two different placebo administration styles and how they interact with the type of placebo being administered (deceptive (DP) vs. open-label (OP)).
Methods: Healthy participants were randomly assigned to one of five groups. In this ”2x2+1” design, two factors were varied: The type of placebo (DP vs. OP) and the expectation induction style (personal-emotional (PES) vs. scientific-matter-of-fact style (SMS)). In addition, there was a no-treatment control group (CG). This design allows to differentiate between main and interaction effects and to compare them to CG. The primary outcome was pre-post change in sadness, as a major component of depression.
Results: Preliminary results indicate that DP was superior in its effect to OP and CG. PES was the strongest expectation induction style, although in DP, SMS might be a feasible option as well. Full results can be provided until the conference.
Conclusions: This study might provide insights into the interplay between placebo mechanisms in the context of depression. Furthermore, the design of the expectation induction styles might be used to optimise the induction of positive treatment expectations in both clinical practice and placebo research.
Keywords: Open-label, Expectation, Depression, Sadness, Mechanism

P2.29 Do we learn pain better from people like us? Observational learning in inducing placebo analgesia

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Background: Effectiveness of observational learning can be influenced by the characteristics of both the model and the observer. The aim of our study was to investigate whether information that the observed model is either another participant of the study or a coworker of the experimenter may affect the magnitude of observationally induced placebo analgesia.
Methods: 97 healthy volunteers were randomly assigned to: 1) demonstrator, 2) co-participant and 3) control groups. Participants in the two experimental groups observed a female model. The model in the first group was introduced as a coworker of the experimenter. The same model in the second group was introduced as another participant. The model rated the intensity of pain induced by electrocutaneous stimuli preceded by either blue or orange colours presented on the computer screen. One half of all participants observed the model rate stimuli preceded by orange colour higher than stimuli preceded by blue colour. For the other half, the ratings were reversed. There was no observation in the control group. Then all groups experienced 16 pain stimuli of the same intensity.
Results: Participants in both experimental groups rated pain stimuli preceded by the colour that was rated low by the model as significantly less painful than the stimuli preceded by the colour rated high by the model.

Conclusions: Observational learning was effective in inducing placebo analgesia regardless of what information about the role played by the model was given to the participants.

P2.30 Positive verbal suggestions optimize postural control

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Balance is a very important function that allows maintaining a stable stance needed for many daily life activities and for preventing falls. Here, we investigated whether balance control could be improved by a placebo procedure consisting of verbal suggestion. Thirty healthy volunteers were randomized in two groups (placebo and control) and asked to perform a single-leg stance task in which they had to stand as steadily as possible on the dominant leg for 30 seconds. The task was repeated for 10 trials in three sessions (T0, T1, T2). At T1 and T2 an inert treatment was applied on the leg, by informing the placebo group that it was effective in improving balance. The control group, instead, was overtly told that treatment was inert. Accelerometers applied on participants' leg allowed to derive two indexes of balance: relative leg angle and normalized hip displacement. These indexes were calculated as mean value of maximum body sways in the three-dimensional space, in the medial-lateral direction and in the anterior-posterior direction. Subjective parameters, like perception of stability, sense of effort, expectation of improvement and perception of treatment efficacy were also collected. Results showed that the placebo group had less body sways than the control group at T2, both in the three-dimensional space and in the medial-lateral direction. Furthermore, the placebo group perceived to be more stable than the control group. This study represents the first evidence that a placebo procedure can optimize posture, with a translational impact for patients with postural deficits and gait disturbances.

P2.31 Is pain contagious? The effect of observation on pain induction and its influence on placebo studies

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Research indicates that pain can be learned through classical and operant conditioning. Very few studies have investigated the role of the third learning process, i.e., observational learning, in pain induction. Due to serious methodological shortcomings, their results do not allow to draw any definite conclusions.On the other hand, the results of a few recent studies indicate that observational learning may modulate pain experience and induce both placebo analgesia and nocebo hyperalgesia. Thus, the aim of the present study was to investigate whether pain can be induced by observational learning and what factors moderate its effects. Pain-free, healthy volunteers rated the intensity of identical electrocutaneous stimuli, previously assessed by them as nonpainful. In the three experimental groups, a male model rated all of the stimuli as painful. Specifically, in Group 1, participants and the model were rating stimuli by turns, while in Groups 2 and 3 participants rated stimuli after having observed the model. While in Group 2 the model was present when participants were rating the stimuli, in Group 3 he was absent. There was no observation phase in the control group. Agreeableness and the need for cognitive closure were measured. The poster will present the results of the study, which may have important implications for the observational learning paradigm applied in studies on the placebo effects, the development of chronic pain as well as the management of chronic pain.

P2.32 The use of empathy and expectancy manipulations to counter nocebo-effects of information provision in palliative cancer care; An observational study of clinician-patient consultations

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Background: Oncologists are legally obliged to inform advanced cancer patients about treatment aims, options and side-effects. Information-provision, however, also entails overlooked risks such as increased patient anxiety and experienced side-effects. To counter potential detrimental effects, communication-strategies based on nocebo- and placebo-effect mechanisms might be promising. This study aimed to examine if and how oncologists use empathy and expectancy manipulations in consultations with advanced cancer patients.
Methods: We conducted a multi-center observational study of interactions between 12 oncologists and 45 incurably ill breast cancer patients. Consultations were audiotaped and transcribed. Using a self-created coding scheme (based on communication

and placebo-effect studies, clinical expertise, observations) we determined the occurrence of and manner in which empathy- and expectancy manipulations were employed. Two researchers independently scored all transcripts, discrepancies were resolved through discussion. 10% were rated by a third researcher.
Results: Preliminary results (full results available in July) show that expectancy manipulations were used in all consultations. Oncologists mainly stress possible positive treatment effects, while often omitting negative expectations regarding side-effects, but do confirm the side-effect nature of experienced complaints. Empathy-manipulations were used in 85% of consultations. Oncologists frequently express an understanding towards patients' emotions and sometimes offer supporting statements, while omitting to explicitly name emotions.
Conclusion: Several positive expectancy- and to a lesser extent empathy- manipulations occur in palliative care consultations. Follow-up studies should test the effect of specific manipulations on patients' outcomes. Ultimately, specific nocebo- and placebo effect inspired communication-strategies can be harnessed in clinical care to counter negative effects of information-provision.

P2.33 Factors influencing patient outcome expectations in daily clinical practice

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Background: Patient expectations are considered a key mechanism of placebo effects, but little is known about what drives expectations in daily clinical practice. The present study investigates the relative contribution of treatment and patient characteristics to outcome expectations regarding treatments for hand- and wrist conditions.
Methods: A total of 2571 patients received a treatment for their diagnosed hand or wrist problem at one of 18 specialized hand treatment centers, and prior to treatment they filled out a validated generic outcome expectation questionnaire. Multilevel hierarchical regression analysis was used to assess the relative contribution of treatment characteristic (e.g. surgical vs. non-surgical) and patient characteristics (e.g. sociodemographic, perceived physical and mental health, illness perceptions) to treatment outcome expectations.
Results: Mean age of the patients was 53 (SD 15), 66% were female and 66% employed. Sociodemographic factors explained 2% of the variance in outcome expectations. An additional 2% was explained by patients' perceived physical and mental health, 6% by illness perceptions and 14% by treatment characteristics. The strongest independent predictors of outcome expectations were the type of treatment (surgical vs. nonsurgical, $\beta = .587$, $p < .001$) and the perceived chronicity of the disease ($\beta = -.201$, $p < .001$).
Conclusions: Outcome expectations were mainly driven by the invasiveness of the treatment and by patients' illness perceptions. Interventions aimed at optimizing positive expectations to improve treatment outcomes may be more relevant for less invasive treatment options, and addressing illness perceptions may be a useful strategy.

P2.34 Common factors in the treatment of chronic primary pain in children and adolescents: Protocol for a network meta-analysis

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Background: Chronic primary pain (CPP) is a new and pragmatic classification in the upcoming ICD-11. CPP describes pain in one or more anatomic regions that persists or recurs for 3 months or more and is associated with significant emotional distress or functional disability. Previous randomized-controlled trials (RCTs) in the field of chronic pain have shown substantial placebo effects and provide evidence that active control groups (such as education or discussion forums) show better effects than passive control groups (such as waitlist control). Compared to passive controls, active controls leave room for common factors such as patient-clinician relationship or a convincing rationale. This project aims to examine the role of common factors in published RCTs of interventions for CPP in children and adolescents.
Method: Network meta-analytic methods will be used to make direct and indirect comparisons of various control groups across CPP syndromes. Systematic searches in electronic databases will be conducted and RCTs comparing any intervention with a control group for pediatric patients with CPP will be included. We will explore the role of moderators such as demographic factors.
Results: We expect active controls to show better effects compared to passive controls. We expect relative effects of interventions to be smaller when compared to an active control group than when compared to a passive control group.
Conclusion: To our knowledge, this is the first comprehensive network meta-analysis to summarize all available evidence and estimate the proportion of treatment success that results from common factors. Our findings have the potential to inform existing treatment models.

P2.35 Placebo economics – The economic potential of utilizing the placebo effect in drug therapy

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During the last 20 years, placebo research investigated intensively the mechanisms by which placebo and nocebo effects occur, but their utilization to optimize medical treatments is still in its infancy. Particularly ethical and legal concerns have been raised, but recent research shows that placebo mechanisms can be used without deception of patients, such as in open-label conditions for the treatment of irritable bowel syndrome (IBS), low back pain, and depression, and conditioning of drug effects in attention-deficit/hyperactivity disorder (ADHD) and psoriasis. Furthermore, empathic practitioner-patient interactions have been shown to reduce the duration of the common cold by one whole day which is a considerable economic factor. However, a health economics evaluation of the utilization of placebo mechanisms has yet not been performed.
In a systematic review, we review the placebo literature by means of a database of nearly 4,000 articles (https://jips.online) comprising placebo research articles only, and literature research databases such as PubMed and Web of Science. Databases are searched for economically relevant outcome measures which have already been shown to be affected by placebo mechanisms, such as savings of drugs when drug effects were conditioned, higher quality of life, or fewer sick days.
The health economic potential of utilizing placebo mechanisms in patient treatments are analyzed for the first time, and results will be discussed from the point of view of different stakeholders involved in the health care system, such as patients, practitioners and hospitals, and health insurance companies. Results of this review will be presented at the conference.

P2.36 Marketing placebo effects on taste perception are not related to the level of trust in marketers and not affected by oxytocin

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Background: Past research showed that marketing actions that create quality expectations in consumers, such as pricing or branding, influence the subjective experience of taste pleasantness. This phenomenon has been coined marketing placebo effects (MPEs). As yet, the neurobiological mechanisms mediating MPEs are still unclear. The neuropeptide oxytocin has been found to promote interpersonal trust and enhance pain placebo effects. Against this background, we hypothesized that oxytocin may also boost MPEs by increasing trust in marketers.
Methods: In a randomized, double-blind, and pre-registered between-group study, 202 male participants performed a tasting task after intranasally receiving oxytocin (24 IU) or placebo. The participants reported experienced taste pleasantness of identical but differently labelled (marketing-label vs. non-marketing label) and packaged (superior vs. inferior packaging) products. Questionnaires were used to assess participants' trust in marketers and expectations of quality and taste of marketing products.
Results: Our results showed no significant effect of oxytocin on marketing-induced taste preference, the level of trust in marketers or expectations of marketing products. The strength of MPEs was not associated with the level of trust in marketers but with taste expectation of marketing products.
Conclusions: Our study suggests that oxytocin does not affect MPEs on subjective experiences of consumers and provides preliminary evidence for distinct mechanisms of MPEs and placebo analgesia.

P2.37 No1likesu – An experimental paradigm to investigate social expectations and their adjustment

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Background: Expectations have been shown to be a crucial mechanism in the development, maintenance and treatment of mental disorders. However, there is little experimental research on how (negative) expectations in mental disorders can be adjusted through contradictory experiences. Social expectations play an important role in several mental disorders, e.g. social anxiety disorder or major depression. We developed a new paradigm to manipulate expectations in social interactions.
Methods: In this paradigm, participants experience either social rejection or inclusion after answering personal questions. Participants present answers to other individuals in supposed webcam conferences. Then, they are asked whether they expect interest for further contact from their webcam partners, and receive deceptive feedback about the "actual" interest. Thus, participants either predominantly experience social rejection or social inclusion. We applied a sequential paradigm, in which healthy participants first experienced a period of social rejection followed by a period of social inclusion. Next, we omitted the feedback and only asked for expectations.
Results: Until now, we included 89 participants in the paradigm. First results confirm that this paradigm can modify social expectations. That is, participants adjust their expectations according to the predominant feedback they receive. Without feedback, expectations remain stable.

Conclusion: Our results indicate that this paradigm can be used to investigate expectations and their adjustments in social interactions. The paradigm has a high ecological validity and is easy to administer and adjust. Thus, it can be used to investigate a wide range of hypotheses regarding social expectations and their change in various mental disorders.

P2.38 Prediction of placebo responsiveness in motion sickness by the cognitive reflection test – Are placebo responders more intuitive?

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Background: In the framework of dual-process theories, concepts of placebo responses (e.g., expectation, hope, meaning, interpersonal healing and belief) are related to System-1 based processes. In this exploratory study, we investigated whether System-1 dominance predicts placebo responsiveness in an experimental motion sickness paradigm.
Methods: Nested within another experiment, 80 motion-sickness-susceptible women were exposed to a vection stimulus for 20 minutes on 2 separate days. On day 2, participants were randomized to either placebo (sham acupuncture-point-stimulation) or no treatment and completed the Cognitive Reflection Test (CRT). Symptom severity was assessed by the Motion Sickness Questionnaire (MSQ) on both days.
Results: MSQ scores decreased significantly from day 1 to day 2 in the placebo group compared to controls ($F=19.9$, $p<.001$). The number of incorrect intuitive answers (IIAs) in the CRT representative of System-1 dominance did not differ between groups ($\chi^2=4.5$, $p>.20$). Higher numbers of IIAs were inversely related to reduction of MSQ scores (difference day 2 minus day 1) in the placebo group (Spearman's $r=-.524$, $p<.01$), but not in the control group (Spearman's $r=-.023$, $p=.876$). Linear regression analysis confirmed IIAs as an independent predictor of symptom reduction in the placebo group (ß=-0.537, $p<.01$; $R^2=0.29$), but not in the control group (ß=-0.05, $p=.980$).
Conclusions: Results suggest that System-1 dominance, i.e. intuitive thinking, contributes to greater placebo responsiveness in motion sickness. This is in line with previous conceptualizations of the placebo response in the realm of hope, belief and symbols, highlighting the importance of nonconscious, associative, and experience-based processes.

P2.39 The time component of expectation in placebo analgesia

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While it has repeatedly been shown that positive expectations represent a core mechanism in placebo analgesia, as of yet no attempt has been made to explore the time component of such beliefs. The present study investigates whether manipulation of temporal information associated with a placebo cream treatment modulates its onset of action.
Healthy subjects (N=30) underwent the same pain paradigm at baseline, after 10, 20 and 35 minutes. The pain paradigm consisted in eleven electric shocks of 500 ms duration, each delivered on participants' dominant hand forearm. Placebo cream was applied after the baseline trial. Some participants were told that the cream would be effective in 5 minutes (Group 1), and others in 15 minutes (Group 2). Natural history group was also present, no analgesic expectations were induced (Group 0). Pain perception was assessed by means of Numeric Rating Scale (NRS) ranging from 0 = no pain to 10 = maximum pain.
The onset of placebo cream analgesia varied accordingly with the given temporal suggestions.
Analgesic response was present after 10 minutes from cream application in Group 1, this effect persisted after 20 and 35 minutes. Differently, in Group 2, there was no pain reduction in the trial after 10 minutes, but only in the trial after 20 minutes.
These findings show that the time component of expectation is finely tuned with the onset of placebo analgesia. Further research is required to explore how to modulate temporal suggestions in order to maximise placebo analgesia efficacy.

P2.40 Belief about group allocation predicts placebo response in the 7.5% carbon dioxide inhalational model of anxiety

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Placebo-controlled studies are necessary to test novel anxiolytic treatments, but placebo 'treatment' can also produce clinical improvement. The placebo response is thought to result from interactions between prior expectations and learning. A participant's 'belief' in whether they were allocated to active medication or placebo may be influenced by their expectations and experience of a clinical trial. We investigated whether belief correlates with the magnitude of the anxiolytic response to placebo in the 7.5% CO2 experimental medicine model of anxiety. We pooled data from healthy volunteers randomised to the placebo arms of 2-week double-blind trials (n = 51, 27 males, mean age 22.9 years). On day 14, participants completed 20-minute inhalations of normal air and air enriched with 7.5% CO2 (CO2-challenge) in randomised order. Following testing, participants recorded whether they

thought they were taking drug or placebo, and their confidence in this decision, on two visual analogue scales. These measures were combined to produce a single interaction term we called 'belief'. Mixed model ANOVAs showed that CO2-challenge significantly increased blood pressure and heart rate (F's > 4.10, p < 0.05), and subjective peak anxiety, fearfulness, and worry (F's > 35.1, p < 0.001). Linear regression analyses showed that belief significantly predicted peak fearfulness (R2 = 0.063, F(1,47) = 3.08, B = -0.384, p < 0.05) and worry (R2 = 0.077, F(1,47) = 3.84, B = -0.443, p < 0.05). More studies are needed to understand the link between beliefs about group allocation and outcomes in experimental medicine studies and clinical trials.

P2.41 Can verbal suggestions strengthen the effects of a relaxation intervention?

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3. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
4. Meriem Manaï. *Leiden University, Leiden, Netherlands.*
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Short stress management interventions such as relaxation therapy have demonstrated preliminary effectiveness in reducing stress-related problems. Verbal suggestions are suggested to be a promising tool to strengthen the effectiveness of relaxation-based interventions, as placebo research on optimizing outcome expectancies showed that verbal suggestions can facilitate adaptive responses to stress and improve health outcomes. The present proof-of-concept study aimed to investigate the effects of a brief relaxation intervention and specifically the role of verbal suggestions on stress-related outcomes as assessed by self-report questionnaires and psychophysiological data. In this study, 120 participants were randomized to one of four intervention conditions: a brief relaxation intervention plus verbal suggestions condition, a brief relaxation intervention only condition, a verbal suggestions only condition, and a control condition (completing word finding puzzles). Afterwards, participants were subjected to a psychosocial stress challenge to assess reactivity to a stressful event. Immediately after both relaxation interventions (with and without verbal suggestions), lower self-reported state anxiety was found compared to the control condition, but no differences were observed in response to the stressor. The verbal suggestions only condition did not impact state anxiety. No significant effects were found for the interventions on psychophysiological data. This is the first study investigating the role of verbal suggestions in the effectiveness of a brief relaxation intervention. The effectiveness of brief relaxation interventions and verbal suggestions on stress responses should be investigated further in future research by incorporating interventions that are tailored to the specific needs of the participants and various types of verbal suggestions.

P2.42 Inducing placebo psychedelic experiences by manipulating contextual factors

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Background: Both placebos and psychedelics are known to be heavily influenced by mindset (e.g., expectations) and context (social and physical). Although controlled psychedelic studies emphasize the importance of these factors, researchers rarely focus on the placebo effects reported by participants. We explored whether we could induce placebo psychedelic experiences by influencing expectations and context.
Methods: Thirty-three university students enrolled in a study ostensibly examining the impact of psychedelics on creativity. Participants were told that they would ingest 4 mg of iprocin, a homologue of psilocybin—the active ingredient in magic mushrooms. They were then given a list of common drug effects including emotional sensitivity and hallucinations. The experimental context resembled a psychedelic party: a group setting with music, paintings, projections, and colourful lighting. Six confederates also enacted the drug effects throughout the study to promote social contagion. After obtaining consent, we collected measures of personality, mood, and consciousness (i.e., 5-Dimensional Altered States of Consciousness Rating Scale) before and after participants ingested the placebo pill.
Results: Participants experienced alterations in consciousness (Cohen's d = 0.57 [0.33, 0.81]), particularly in the following subscales: altered meaning of percepts, insightfulness, bliss, and audio-visual synesthesia. Interpolating from available dose-response curves, participants reported effects comparable to ingesting a low dose of psilocybin (M = 36 ug/kg, range: 17–144).
Conclusions: By establishing a specific mindset and context, we were able to elicit psychedelic-like experiences with a placebo. This study demonstrates the importance of considering these factors when investigating the effects of both placebos and psychedelic drugs.

P2.43 Expectation effects on surgery outcome in hip and knee arthroplasty: A meta-analysis

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Background: Total hip and total knee arthroplasty (THA/TKA) is one of the most frequently performed major surgery procedure. Although effective, patients do not always benefit from surgery the way doctors would predict from a medical point of view. Several prospective studies have linked positive preoperative expectations to improved outcome in orthopedic surgery patients, while other studies did not find evidence for such an association. Therefore, this study aims to provide meta-analytic evidence to determine the robustness and magnitude of expectation effects in THA/TKA.
Methods: We searched EMBASE, PsychINFO, and CINAHL for prospective studies reporting an association of preoperative expectations with surgery outcome in THA or TKA until August 2017. (ROSPERO ID: CRD42017079746)
Results: We identified 3803 references (after de-duplication) of which 201 references remained after the abstract screening. 71 studies were ultimately included after full-text evaluation of inclusion and exclusion criteria. 50 out of the 71 included studies report statistically significant associations indicating that positive preoperative expectations lead to improved surgery outcome. Data extraction, quality assessment and pooling of the effect sizes will be completed until May 2019. Pooled effect sizes will be presented on a) the overall effect of preoperative expectations on THA/TKA outcome, b) differential effects between THA and TKA, c) effects of different expectation constructs (i.e. value vs. probability expectations, behavioral vs. treatment expectations, …).
Conclusions: If there is a robust and sufficient association between preoperative expectations and outcome in THA/TKA surgery, psychological expectation interventions might be beneficial to enhance outcome in this surgery population.

P2.44 Predicting placebo analgesia – New approaches combining personality, brain and genetics in large-scale samples

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Placebo responses are reliably caused by active neurobiological processes, including prefrontal-striatal-brainstem interactions and involvement of endogenous neurochemicals. Placebo analgesia is the best-studied type of placebo effect. Definitive studies of the brain and genetic predictors of individual differences in the strength of the placebo effect remain to be performed. Such studies are crucial for harnessing placebo effects and placebo responses in clinical trials.
Here we summarize existing research on placebo analgesia and present promising new approaches. Placebo responses have been associated with genetic polymorphisms in several neurotransmitter systems, primarily opioids, dopamine, cannabinoids, and serotonin. However, these studies have generally been small and underpowered, and have focused on a few candidate genes, raising questions about their replicability and clinical utility.
We are here discussing a novel approach that combines systems-level fMRI-based signatures (potential endophenotypes) and GWAS in a large sample of N=600 twins, with data collection in process. The twin design provides heritability estimates and permits genetic correlation analyses. In a data fusion approach, brain features with the highest genetic overlap can be examined using large-scale consortium data—including the ENIGMA and UK Biobank samples—to investigate phenotype-relevant brain-genetic associations at scale. New results using this approach can identify new, replicable genetic associations.

P2.45 Can placebo effects be learned for histamine-induced itch? Conditioning the effects of antihistamines

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7. Nic van der Wee. *Leiden University Medical Center, Leiden, Netherlands.*
8. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Previous studies have demonstrated that it may be possible to elicit learned placebo effects for symptoms of allergic rhinitis through conditioning of antihistamines. These findings may extend to histamine-induced itch specifically. Moreover, the effects of conditioning under open-label conditions (i.e. telling subjects about the learning mechanisms involved) are not yet clear. Demonstrating the efficacy of (open-label) conditioning may lead towards new treatment possibilities. In the current study, a two-phase randomized conditioning paradigm was used, consisting of a learning phase, in which a conditioned stimulus (CS; distinctively-tasting beverage) was repeatedly combined with an unconditioned stimulus (UCS; the antihistamine levocetirizine) or placebo, and a testing phase, where the CS was presented with a placebo. Participants were assigned to 1) an open-label conditioned group, 2) a closed-label conditioned group, 3) a conditioned-not-evoked control group, or 4) a placebo control group. At baseline and on the final testing day, itch was induced through histamine iontophoresis. Participants in the combined conditioned groups tended to report marginal lower itch than participants in the combined control groups ($p=.076$), but no differences between separate groups were found ($p\geq.23$). Groups did not differ in physiological data with the exception of heart rate, which reduced significantly over time in the control groups, whereas reductions over time were less consistent for the conditioned groups. Overall, limited evidence is provided for conditioning of antihistamine effects for itch. More research is needed to examine how and under which circumstances placebo effects elicited by (open-label) conditioning may influence itch.

P2.46 Open label placebo in chronic low back pain: A follow up study

1. Cláudia Carvalho. *ISPA, Lisbon, Portugal.*
2. Lidia Cunha. *Hospital Egas Moniz, Lisbon, Portugal.*
3. Paula Rebouta. *Hospital Egas Moniz, Lisbon, Portugal.*
4. Ted Kaptchuk. *Harvard Medical School, Boston, MA, United States.*
5. Irving Kirsch. *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States.*

In this study we present the results of a quantitative and qualitative follow up of an open label placebo (OLP) RCT performed on chronic low back pain patients (Carvalho et al.2016). In the previous study, we performed a randomized controlled trial designed to investigate whether placebo effects in chronic low back pain could be harnessed ethically by adding open-label placebo treatment to treatment as usual (TAU) for 3 weeks. Compared to TAU, OLP elicited greater pain and disability reduction with moderate to large effect sizes. In this study, using a questionnaire performed by email and telephone, we examined their current pain and disability complaints as well as any relevant changes in treatment options for back pain after OLP, allowing us to learn about the midterm effect of open label placebo. We also examine the perceived factors that might have contributed to the observed results, and their opinions about the acceptability of taking open label prescribed placebos. Given the scarcity of OLP trials as well as follow up studies, we believe that bringing patients' perspective will help contribute to explain some of the mechanisms of OLP, as well as contribute to shed light on how placebo effects may be harnessed in clinical practice, in particular in chronic low back pain, respecting patients' values and interests and the ethics of medical practice.

P2.47 Nocebo effects on pressure pain: Their induction and reduction via learning

1. Merve Karacaoglu. *Leiden University, Leiden, Netherlands.*
2. Simone Meijer. *Leiden University, Leiden, Netherlands.*
3. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
4. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
5. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Nocebo effects (i.e. negative outcomes not attributable to active treatment components) are known to adversely affect the experience of various physical symptoms, such as pain and itch. Recent studies have shown that nocebo effects can be experimentally induced and reduced by associative learning mechanisms of conditioning and counterconditioning, respectively, especially when combined with verbal suggestions. Prior pain conditioning studies have used experimental heat or electrical pain to test nocebo pain manipulations. Nocebo conditioning and counterconditioning have, however, not been investigated for other pain modalities, such as pressure pain, that are more relevant to disorders affecting the musculoskeletal system.
Methods: In the current study, we are investigating in 124 healthy participants whether nocebo effects on pressure pain can be 1) induced via conditioning and 2) reduced via counterconditioning, both combined with open-label verbal suggestions. Furthermore, learning procedures of counterconditioning and extinction are also being investigated in their efficacy in reducing nocebo effects. It is expected that nocebo effects on pressure pain can be induced via conditioning and reduced via counterconditioning. Additionally, counterconditioning is expected to more effectively reduce nocebo effects than extinction.
Results: Data collection is ongoing and results are expected in the upcoming months.
Discussion: The current study offers insight into the effects of different learning strategies to manipulate nocebo effects on a pain modality relevant to musculoskeletal disorders.

P2.48 Randomized controlled trial on conditioning cortisol and its psychophysiological effects

1. Judith Tekampe. *1) Leiden University, Leiden, Netherlands; 2) Radboud university medical center, Nijmegen, Netherlands.*
2. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
3. Nienke Biermasz. *Leiden University Medical Center, Leiden, Netherlands.*
4. Fred Sweep. *Radboud University Medical Center, Nijmegen, Netherlands.*
5. Onno Meijer. *Leiden University Medical Center, Leiden, Netherlands.*
6. Alberto Pereira. *Leiden University Medical Center, Leiden, Netherlands.*
7. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Conditioning of physiological responses by repeatedly pairing a previously neutral conditioned stimulus with the administration of a pharmacologically salient unconditioned stimulus has been effective for specific immune and endocrine responses, but results with regard to conditioning of the key stress-regulatory parameter cortisol are currently unclear. This study builds on previous cortisol conditioning studies by investigating effects of cortisol conditioning under basal conditions as well as in response to stress.
Methods: A double-blind randomized controlled trial was conducted in 48 healthy female volunteers. During the acquisition phase, a gustatory stimulus (conditioned stimulus) was paired with hydrocortisone (100 mg, capsulated, unconditioned stimulus) three times before being administered with placebo during three evocation sessions. To investigate possible effects of cortisol conditioning in response to stress, participants were exposed to the Trier Social Stress Test during the third evocation session. Primary outcome measure was salivary cortisol. As secondary outcomes, self-reported affect and stress as well as alpha-amylase, heart rate and skin conductance were investigated.
Results: Data collection for this study has been finalized and data analysis is currently underway. Pilot data showed preliminary indications for conditioned effects with lower cortisol under basal conditions and lower levels of negative affect in response to stress compared to the placebo-control group.
Discussion: Successful conditioning of cortisol would be of conceptual relevance, showing that HPA-axis regulation can be influenced by associative learning processes. Eventually, this could also have important clinical implications for understanding and treating stress-related disorders in which HPA-axis dysregulation might play a role.

P2.49 The role of conditioning for pharmacological treatments in rheumatoid arthritis: A pilot study

1. Meriem Manaï. *Leiden University, Leiden, Netherlands.*
2. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
3. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
4. Renée Allaart. *Leiden University Medical Center, Leiden, Netherlands.*
5. Tom Huizinga. *Leiden University Medical Center, Leiden, Netherlands.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Introduction. Medication regimens using conditioning via variable reinforcement have led to similar or improved therapeutic effects as full pharmacological treatment. The study aim is to pilot-test whether treatment effects in rheumatoid arthritis (RA) can be optimized through pharmacological conditioning.
Methods: A randomized controlled pilot trial was conducted in patients with recent-onset RA. After four months of standardized treatment, patients in clinical remission were randomized to the C-group continuing standardized treatment (n=8, 2 dropouts) or the PC-group receiving variable treatment according to a conditioning principle (n=11, 7 dropouts). When in clinical remission after eight months, treatment was tapered and discontinued linearly (C) or variably (PC). Due to the low number of patients, no formal statistics were conducted, but Cohen's d effect sizes of group differences from baseline to 12 months after treatment start were calculated.
Findings: In the PC-group compared to the C-group, indications were found for a medium-sized more improved objective (Disease Activity Score; d=0.56; C 1.06±0.63; PC 1.65±0.72) and large-sized more improved self-reported (Rheumatoid Arthritis Disease Activity Index [RADAI]; d=0.86; C 2.29±2.07; PC 1.20±0.68;) disease activity, as well as a medium-sized- greater reduction in pain (RADAI) (d = 0,71; C 1.70±2.56; PC 0.52±0.79). Cytokines and quality of life changes will be investigated and presented as well.
Discussion: This pilot study provides first indications that offering medication regimens on a pharmacological variable reinforcement schedule may potentially result in stronger clinical treatment effects. However, high drop-out is a concern and research should be done in larger groups.

PP2.50 Hospital clowning – A psychological placebo intervention?

1. Heike Gerger. *University of Basel, Basel, Switzerland.*
2. Thea Zander-Schellenberg. *University of Basel, Basel, Switzerland.*
3. Janina Weber. *University of Basel, Basel, Switzerland.*
4. Helen Köchlin. *University of Basel, Basel, Switzerland.*

Background: Positive health-related effects of laughter have been demonstrated in several studies. Besides such direct effects on health caused by laughter, hospital clowning may have additional effects on patients' health and well-being, despite the fact that the clown visits do not actively or explicitly address the patients' health problems. In this sense, clowning interventions could be considered placebo interventions, i.e. interventions that are inert with respect to targeting the patients' health issue. The question arises whether hospital clowning may have additional health-related beneficial effects on patients, besides the proven benefits associated with laughter.
Methods: 28 hospital clowns, 40 nurses and 28 parents of hospitalized children filled in an online survey on the potential benefits of hospital clown visits in pediatric wards in 6 Swiss hospitals.
Results: All three subsamples reported that hospital clown visits positively impacted psychological health-related outcomes, such as for instance children's self-efficacy, fantasy, stress levels, anxiety, and mood. In addition, the establishment of a positive relationship with the patient was reported to be one of the main mechanisms of the clowns' work.
Discussion: Our study highlights the presence of positive health-related outcomes in the aftermath of hospital clown visits, besides the well-known positive effects of laughter alone. We will discuss possible implications of the view that the mechanisms at work in hospital clowning may partly be overlapping with those that have been described to cause placebo effects, such as the relationship between the clown and the patient.

P2.51 Manipulating NMDA-dependent learning to alter nocebo effects on itch: Experimental design

1. Joseph Blythe. *Leiden University, Leiden, Netherlands.*
2. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
3. Mia Thomaïdou. *Leiden University, Leiden, Netherlands.*
4. Antoinette van Laarhoven. *Leiden University, Leiden, Netherlands.*
5. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Nocebo effects describe the negative treatment effects putatively caused by negative outcome expectancies, and these effects can have a significant impact on the experience of itch and its treatment in chronic dermatological and systemic disorders. One potential process for developing nocebo effects is classical conditioning. Across repeated experiences, individuals are believed to develop a conditioned nocebo effect on itch by forming an association between factors in their environment such as the treatment setting, or even the treatment itself, with a worsening of their pruritic symptoms. Learning processes such as conditioning depend upon neural plasticity to adapt to repeated patterns of stimuli with changes in expectancies and behaviour. While neural plasticity may be influenced by numerous factors, N-methyl D-aspartate (NMDA) receptor activity has been shown to be crucial for mediating plasticity and learning. NMDA receptors can be agonized and antagonized with pharmacological interventions to augment or perturb neural plasticity. The primary objective of this fMRI experiment is to test the role of NMDA receptor-dependent

learning in conditioned nocebo effects on itch in 100 healthy subjects. After administering a NMDA receptor agonist (D-cycloserine) or NMDA receptor antagonist (ketamine), we will condition a nocebo effect on histamine-evoked itch by repeatedly pairing the activation of a sham transcutaneous electric nerve stimulation (TENS) device with increased histamine-induced itch stimulation. Outcomes will be measured with subjects' self-reported itch intensity and functional magnetic resonance imaging (fMRI). With this study, we aim to demonstrate the role of NMDA receptor-dependant learning for classically conditioned nocebo effects on itch.

Plenary Session 2

Neurobiological and pharmacological underpinnings of placebo effects

Monday, July 8, 02.00 PM – 03.45 PM
Grote zaal
Chair: Kathryn Hall

Placebo effects in the gut: how expectancies shape nausea and appetite

Karin Meissner

Coburg University, Coburg, Germany and Ludwig Maximilian University of Munich, Munich, Germany

About Karin Meissner
Karin Meissner, MD, is a professor of Integrative Medicine at the Division of Health Promotion, Coburg University, and director of the Placebo research group at the Institute of Medical Psychology, LMU Munich. She has been studying placebo effects for more than 20 years, focusing on the peripheral mechanisms of placebo effects and the modulation of placebo effects by treatment characteristics. Dr. Meissner's extensive experimental and clinical research on the placebo effect is reflected in more than 50 publications.

Plenary Abstract
Placebo effects are not limited to the central nervous system, but may also affect peripheral body systems such as the heart and the gut. In a series of experiments, we recently investigated the mechanisms and correlates of placebo effects on perceptions related to the stomach, namely nausea and appetite. In addition to behavioral outcomes (symptom ratings, questionnaires) we assessed a variety of psychophysiological correlates (EKG, EEG, EGG) and humoral outcomes (cortisol, ghrelin, plasma proteomics). The results of these extensive analyses provide new and intriguing insights into the peripheral correlates of placebo effects in the gut, spanning from the release of the gut hormone ghrelin to the identification of the first proteomic signature of the placebo effect in peripheral blood.

Teach the T cells: Learned immunosuppressive placebo responses

Manfred Schedlowski

University of Duisburg-Essen, Essen, Germany and Karolinska Institute, Stockholm, Sweden

About Manfred Schedlowski
Manfred Schedlowski is Professor and Director of the Institute of Medical Psychology and Behavioral Immunobiology at the Medical Faculty, University of Duisburg-Essen, Germany. Born 1957 in Hannover, Germany, he obtained his degree in Psychology and his PhD at the Department of Medical Psychology, Hannover Medical School, Germany. Since October 1997, Manfred Schedlowski is Full Professor and Director of the Institute of Medical Psychology and Behavioral Immunobiology at the Medical Faculty, University Essen-Duisburg interrupted by a research stay as Professor of Psychology and Behavioral Immunobiology at the Swiss Federal Institute of Technology (ETH) in Zürich, Switzerland (2004-2007). Manfred Schedlowski's current primary focus of research is the neurobiology of placebo and nocebo responses, in particular the mechanisms and clinical relevance of behavioral or Pavlovian conditioning of immune and neuroendocrine functions.

Plenary Abstract

Akin to other physiological responses, immune functions can be modified in humans through associative conditioning procedures as part of learned placebo responses. The potential clinical applicability of learned immunosuppressive responses has been convincingly demonstrated in rodents, where conditioned immune responses significantly reduced the mortality in animals with inflammatory autoimmune disease, significantly reduced allergic responses or prolonged the survival time of transplanted vascularized organs. In an established taste-immune learning paradigm in rodents and humans, the calcineurin-inhibitor and immunosuppressant cyclosporine A (CsA) as an unconditioned stimulus (US) is paired with a gustatory stimulus as a conditioned stimulus (CS) during acquisition. Subjects are re-exposed to the CS during evocation, inducing immunosuppressive responses similar to the drug effects. However, it is unclear so far, whether learned immune responses can be produced in patient populations already on immunosuppressive regimen. In a recent study, we demonstrated in renal transplant patients who were already on immunosuppressive treatment that learned immunosuppressive placebo responses increased efficacy of immunosuppressive medication reflected by significant reduction of T cell proliferative capacity. These data demonstrate, that behavioral conditioning of drug responses may be a promising tool that could be used as a placebo-based dose reduction strategy in ongoing immunopharmacological regimen the aim being to limit unwanted drug side effects and to improve treatment efficacy. Why changing dysfunctional expectations in clinical practice is challenging.

Use of pharmacological conditioning for innovative treatment strategies in somatic conditions

Andrea Evers

Leiden University, Leiden, Netherlands

About Andrea Evers

Evers is full professor of Health Psychology at Leiden University and chair of the unit of Health, Medical and Neuropsychology. Evers graduated (PhD) Cum Laude and obtained several personal awards and highly prestigious grants for her innovative, interdisciplinary and translational research on psychoneurobiological mechanisms and treatments for somatic conditions. In 2019, she received the Stevin award, the highest award in the Netherlands for research with significant societal impact. She was also elected as a member of the Academy of the Royal Netherlands Academy of Sciences (KNAW). Evers has diverse clinical registrations: she is registered as Clinical Psychologist (BIG) and supervisor Cognitive Behavioral Therapist. Evers is board member of the international Board IASP (International Association for the Study of Pain) SIG (Special Interest Group) on PLACEBO. She is scientific chair of the first and second official world conferences of the SIPS in Leiden.

Plenary Abstract

By altering physiological mechanisms independent of pharmacological agents, pharmacological conditioning can be used as a model to unravel neurobiological mechanisms of placebo effects and has high clinical relevance. Recent studies on conditioned pharmacological effects on immune and endocrine responses in humans are discussed during the presentation. Specifically, these studies show some evidence for pharmacological conditioning of immune (antihistamines) as well as endocrine (cortisol and oxytocin) responses in healthy subjects. Results also suggest that these effects even occur when people know that they are conditioned. Moreover, patient studies have been used to explore the possible therapeutic applications of pharmacological conditioning for dose reductions. A recently finished pilot study in patients with rheumatoid arthritis adds to this evidence, by showing beneficial treatment outcomes for the patients who were exposed to the pharmacological conditioning scheme. The results of pharmacological conditioning to unravel neurobiological mechanisms and offering innovative treatment options for reduced medication use are discussed.

Citius, Altius, Fortius: How placebos make humans run faster

Chris Beedie

University of Kent, Canterbury, United Kingdom

About Chris Beedie
Chris is Honorary Professor in Psychology (Cognition & Neuroscience) at the University of Kent, UK, and Science Director of CHX Performance in Chamonix, France. He has authored over 100 papers, many focussing on the physiology and psychology of self-regulatory processes such as emotion, mood and placebo effects. He was worked extensively in sports science laboratories, a setting in which he has found allows unique access to many aspects of placebo effects.

Plenary Abstract
During the last decade, Placebo and nocebo effects have been widely reported in the sports science literature. Significant placebo induced improvement in performance can occur in the absence of significant increase in physiological stress (i.e., effort); athletes can experience a dose:response placebo effect to different 'doses' of placebo, larger placebo effects are evident when athletes are led to believe they have been given banned drugs, athletes often perform below baseline when they correctly believe that they have ingested a placebo, and athletes who intend to use a real sport supplement are more likely to respond to a placebo.
A number of neurobiological systems, notably opioid, endocannabinoid and dopamine, are theoretically implicated, but systematic neurobiological research into placebo effects in sports science is as yet not happening. However, given that the type of placebo treatment appears to mediate the magnitude of effects (e.g., small in caffeine and large in steroids), it is likely that in sport, as has been reported elsewhere, placebo mechanism mimic drug mechanisms.
Placebos in sport, as is the case elsewhere, are catalysed by positive cues. It would be reasonable to assume therefore that a placebo effect that improves sports performance is the result of expectation driven improvements in 'positive' variables such as energy availability, motivation, confidence or motor coordination. However, there are many negative cues in sport, anxiety, pain and fatigue notable amongst them. Importantly, athletes often report that placebo effects they have experienced are the result of reductions in these negative cues. It is also relevant that these cues each have a substantial subjective component.
Previously we proposed the concept of headroom, a 'gap' between an athlete's current level of performance and what that athlete is ultimately capable of. We have speculated that the placebo effect operates in this headroom. Headroom is however by definition a deficit. Further, it is likely that this gap between current and optimum performance results at least in part from the subjective negative cues above; anxiety, pain and fatigue. The magnitude of any headroom might therefore be a function of subjective negative cues, therefore theoretically, also a function of nocebo effects. In this context, it is possible that in sport, a placebo treatment works by reducing the magnitude of nocebo effects.

Towards understanding the neural mechanisms of clinical fMRI neurofeedback

Rainer Goebel

Maastricht University, Maastricht, Netherlands

About Rainer Goebel
Rainer Goebel studied psychology and computer science in Marburg, Germany (1983-1988) and completed his PhD in 1994 at the Technical University Braunschweig, Germany. He received the Heinz Maier Leibnitz Advancement award in cognitive science in 1993 sponsored by the German minister of science and education, and the Heinz Billing award from the Max Planck society in 1994 for developing a software package for the creation and simulation of deep neural network models. From 1995-1999 he was a postdoctoral fellow at the Max Planck Institute for Brain Research in Frankfurt/Main in the department of Wolf Singer where he founded the functional neuroimaging group. Since January 2000, he is a full professor for Cognitive Neuroscience at Maastricht University, Netherlands. He is founding director of the Maastricht Brain Imaging Centre (M-BIC) and the driving force of the recently established ultra-high field imaging center housing 3, 7 and 9.4 Tesla human MRI scanners. From 2008-2017 he was team leader of the "Modeling and Neuroimaging" group at the Netherlands Institute for Neuroscience in Amsterdam. He has served as chair of the Organization for Human Brain Mapping (2006-2008). In 2014, he became member of the Royal Netherlands Academy of Arts and Sciences. In 2017 he became member of the German National Academy of Science (Leopoldina). He received funding for basic and applied neuroscience research including an ERC Advanced Investigators Grant (2011 - 2016) and funding from the EU flagship "Human Brain Project".

Plenary Abstract
In real-time fMRI neurofeedback studies, subjects observe and learn to modulate their own brain activity during ongoing fMRI measurements. Because of its high spatial resolution, fMRI allows to provide content-specific feedback information from circumscribed cortical and subcortical regions. We have recently shown that fMRI neurofeedback training not only enhances voluntary control over brain regions but that it also has a significant therapeutic effect for patients suffering from Parkinson's disease and patients with mood disorders such as major depression. At present it is not clear how much of the obtained therapeutic effects can be attributed to a "high-tech" placebo effect. Using conventional (3 Tesla) as well as ultra-high field MRI (7 Tesla), we currently investigate the neural mechanisms of fMRI neurofeedback and discuss new findings related to activity in reward networks as well as structural connectivity changes between engaged brain areas.

Plenary Session 3

Nocebo: Expecting harmful effects will make you ill

Monday, July 8, 4.15 PM – 06.00 PM
Grote zaal
Chair: Katja Weimer

Nocebo and the psychogenic generation of illness

Fabrizio Benedetti

University of Turin, Turin, Italy; Plateau Rosà Laboratories, Plateau Rosà, Italy/Switzerland

About Fabrizio Benedetti

Fabrizio Benedetti, MD is Professor of Neurophysiology and Human Physiology at the University of Turin Medical School, Turin, Italy, and Director of Medicine & Physiology of Hypoxia at the Plateau Rosà Laboratories, Plateau Rosà, Switzerland. He has been nominated member of The Academy of Europe and of the European Dana Alliance for the Brain. He is now a member of the Council of Scientists of the Human Frontiers Science Program Organization. He is author of the book Placebo Effects (Oxford University Press, 2nd Edition, 2014), which received the Medical Book Award of the British Medical Association, and The Patient's Brain (Oxford University Press 2010). He received the Seymour Solomon Award of the American Headache Society in 2012, the Herlitzka Prize for Physiology in 2012, the William S Kroger Award of the American Society of Clinical Hypnosis in 2015, the EFIC-IBSA Award in 2015, the ARNO Award from the Neurological Research Association in 2018.

Plenary Abstract

The biopsychosocial model claims that illness is generated by both biological and psychosocial factors. The nocebo response is an excellent model and approach to understand these effects and their psychophysiological underpinnings, as nocebos are made of negative psychological and social factors, such as negative expectations and social interactions. There is today experimental evidence that nocebos can create symptoms and illness from nothing, whereby a combination of biological, psychological and social factors interact with each other in the generation of symptoms and illness. Several biochemical pathways have been identified, e.g. cholecystokinin and cyclooxygenase, and the activation of these mechanisms have been found to take place in adulthood and as early as in prenatal life. The study of placebo and nocebo oxygen has been crucial to unravel these mechanisms. Therefore, the investigation of oxygen-related conditions, such as hypoxia, represents today an excellent approach to understand how nocebos can generate illness from nothing.

What's in a frame? Using positive attribute framing to inhibit nocebo side effects

Ben Colagiuri

University of Sydney, Sydney, Australia

About Ben Colagiuri

Ben Colagiuri is an Associate Professor in the School of Psychology, University of Sydney. He received his PhD in Psychology in 2010 from the same School. His research aims to understand how expectancies shape health outcomes via placebo and nocebo effects. To date, he has developed a number of novel experimental models to uncover the mechanisms of placebo and nocebo effects for pain, sleep, nausea, and related conditions. He has been awarded multiple Australian Research Council Discovery Grants, published over 60 scientific papers, and received national and international recognition for his research, including the Australian Psychological Society Early Career Research Award 2014 and the International Society for Behavioural Medicine Early Career Award 2016. His current research is exploring how knowledge about placebo and nocebo effects could be used ethically to improve patient outcomes.

Plenary Abstract

Side effect warnings are essential for informed consent. Yet, these warnings often lead to poorer patient outcomes via the nocebo effect. Communication strategies that impede the development of nocebo effects whilst providing accurate side effect information are critical for addressing this paradox. Positive framing is one such promising technique. Side effect information typically has a negative attribute frame, with the likelihood presented to patients as the risk of experiencing the side effect (e.g. 30% of patients will experience nausea). Positive attribute framing involves presenting the inverse likelihood, i.e. that of not experiencing the side effect (e.g. 70% of patients will not experience nausea). Critically, both frames provide statistically equivalent information, thus maintaining informed consent. Across a series of experiments, we found that positive framing was capable of reducing nocebo side effects. Importantly, this was when compared with both negative and generally framed side effect warnings and appropriate natural history controls. Interestingly, however, there was no evidence that expectancy mediated the framing effect, suggesting that other factors must underlie its efficacy. Irrespective of the mechanisms/s at play, the findings are encouraging and suggest that positive attribute framing may be an ethical and cost-effective method of reducing the burden of nocebo side effects in clinical settings.

Review on adverse events in trial placebo groups

Jeremy Howick

University of Oxford, Oxford, United Kingdom

About Jeremy Howick

I investigate medical questions that require input from philosophy and clinical epidemiology. These include: the ontology, effects, and ethics of placebo treatments in clinical trials and clinical practice, the benefits and harms of informed consent, the extent to which basic science and mechanism research is required for clinical advancements, and the problem of too much medicine. With over 60 academic publications (including two books), I have been funded by the Medical Research Council and the National Institutes of Health Research (both in the United Kingdom) and my research has been used to shape policy. I am also a dedicated teacher who has won four teaching awards. More recently I have expanded my public engagement activities and give regular talks to lay audiences, my social media platform has over 5000 followers, and I have written a popular science book (April 2017) called Doctor You, which explains the science behind the problem of too much medicine for a lay audience.

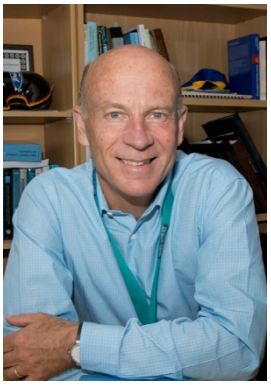
Plenary Abstract

Background: Trial participants in placebo groups experience adverse events (AEs). Existing systematic reviews have not been synthesized, leaving questions about why these events occur as well as their the prevalence of AEs across different conditions unanswered.
Objectives: (1) To synthesize the evidence of prevalence of AEs in trial placebo groups across different conditions. (2) To compare adverse events in trial placebo groups with adverse events reported in untreated groups within randomized trials.
Search methods: We searched PubMed for records with the word ‘nocebo’ in the title and ‘systematic’ in any field. We also contacted experts and hand-searched references of included studies.
Study eligibility: We included any systematic review of randomized trials where nocebo effects were reported. We excluded systematic reviews of non-randomised studies.
Participants and interventions: We included studies in any disease area.
Study appraisal and synthesis methods: We appraised the quality of the studies using a shortened version of the Assessment of Multiple Systematic Reviews tool (AMSTAR) tool. We reported medians and interquartile ranges of AEs. Among the trials within the review that included untreated groups, we compared the prevalence of adverse events in untreated groups with the prevalence of adverse events in placebo groups.
Results: We identified 20 systematic reviews. These included 1271 randomized trials and 250,726 placebo-treated patients. The median prevalence of adverse events in trial placebo groups 49.1% (interquartile range 25.7%-64.4%). The median rate of dropouts due to adverse events was 5% (interquartile range 2.28%-8.4%). Within the 15 of trials that reported adverse events in untreated groups, we found that the adverse event rate in placebo groups (6.51%) was higher than that reported in untreated groups (4.25%).
Limitations: This study was limited by the quality of included reviews, and the small number of trials that included untreated groups.
Conclusions and implications of key findings: Adverse events in trial placebo groups are common and cannot be attributed to natural history. Trial methodologies that reduce AEs in placebo groups while satisfying the requirement of informed consent should be developed and implemented.

Handle with care: The nocebo response in the clinical environment

Keith Petrie

Auckland University, Auckland, New Zealand



About Keith Petrie

Keith Petrie, PhD is Professor of Health Psychology at Auckland University Medical School in New Zealand. His research group does work on patients' perceptions of illness, treatment adherence, as well as the placebo and nocebo response. Keith Petrie and his colleague John Weinman developed the Illness Perception Questionnaire, which is widely used internationally. Professor Petrie's research in the placebo and nocebo area has recently focused on improving patient expectations about treatment and reducing the nocebo response. Keith Petrie has been awarded numerous prizes and fellowships for his research, including a Fulbright Fellowship to Harvard University, the Gluckman Medal and a Distinguished International Scholar Award from the American Psychological Association. He has been elected as a Fellow of the Association of Psychological Science and the Academy of Behavioural Medicine Research. In 2015, he was made a Fellow of the Royal Society and was the recipient of the Durie Medal, which is awarded to New Zealand's pre-eminent social scientist.

Plenary Abstract

The nocebo effect has a major influence on the outcome of medical treatment but it is relatively understudied and unrecognized, compared to its more glamorous counterpart, the placebo effect. Understanding the mechanisms involved in the nocebo response is key to reducing its negative outcomes in clinical settings, which include increased symptom burden, unnecessary hospitalization and treatment, non-adherence and impaired patient quality of life. The misattribution of physical symptoms is at the heart of the nocebo response and I will discuss the key factors involved in this process. I will also present some of our recent studies in different clinical areas focused on understanding the development and reduction of the nocebo response. These include the role of the media in intensifying the nocebo response following a recent nationwide medication switch. I will also discuss how subtle differences in clinician framing of drug information and response can influence patient expectations and willingness to change to new treatment. New research on the role of the internet and technology in promoting nocebo responding will be presented. The talk will also cover some new work on how the nocebo response can be reduced in clinical investigations and treatments.

An analysis of cognitive and affective factors involved in nocebo effects

Andrew Geers

University of Toledo, Toledo, OH, United States

About Andrew Geers

Andrew L. Geers, Ph.D. is a Professor of Psychology at the University of Toledo (USA) and completed his degree at Ohio University. His research focuses on the advancement and application of social psychology theory within health and medical contexts. This research typically concerns (1) how beliefs/expectations shape the outcome of medical treatments and interventions (placebo/nocebo effects), (2) the causes and consequences of optimistic or pessimistic evaluations of future events, (3) the effects of involving individuals in their own health care decision making and (4) how to increase the initiation and maintenance of healthy behavior. He has published numerous empirical and conceptual review articles and his research has been funded by the National Institutes of Health.

Plenary Abstract

Nocebo effects refers to unpleasant treatment responses or worsening of treatment outcomes that arise from medical procedures/contexts, but are not caused by the treatment itself. Research finds that nocebo effects can be caused by expecting adverse treatment responses. Laboratory and clinical research has demonstrated that nocebo expectations can originate from the verbal delivery of information, such as physician warnings, as well as by non-verbal indicators of adverse treatment effects, such as social observations. This situation poses a challenge for clinical care: There is an ethical obligation to notify individuals about possible adverse effects of treatment, however, supplying this information risks inducing these harmful responses due to the generation of nocebo expectations. Currently, little is known regarding the variables that reduce the likelihood that negative expectations cause nocebo effects in clinical care. Uncovering such information would aid our understanding of nocebo effects and provide practical tools for reducing these adverse outcomes. In this presentation, a distinction is made between cognitive and affective processes in nocebo effects. Following this distinction, it is suggested that there are both cognitive and affective approaches for reducing nocebo effects. To date, approaches for curtailing nocebo effects have used a cognitive approach, such as changing how adverse symptom information is communicated to patients. In this presentation, the merits of using affective and emotional approaches to mitigating nocebo effects will be discussed. Additionally, several experiments will be presented that tested the hypothesis that nocebo effects can be lessened through affective modulation.

Keynote lecture: Ionica Smeets

Time:	Monday, July 8, 06:00 PM - 06:45 PM
Location:	Grote Zaal
Chair:	Charlotte Blease

About Ionica Smeets

Ionica Smeets is professor of Science Communication at Leiden University since 2015. Her research focuses on bridging the gap between experts and the general public. Her work is very interdisciplinary with collaborations ranging from journalism scholars and psychologists to geoscientists and general practitioners. One of her particular interests is exaggerated health news in the media. Where does it come from and what are its effects? Before coming back to the university, she worked as an independent journalist and she still writes popular-scientific columns and actively participates in the public debate about science. She wrote three popular-scientific books, which are all bestsellers, and a handbook on science communication that is used in several courses in The Netherlands.

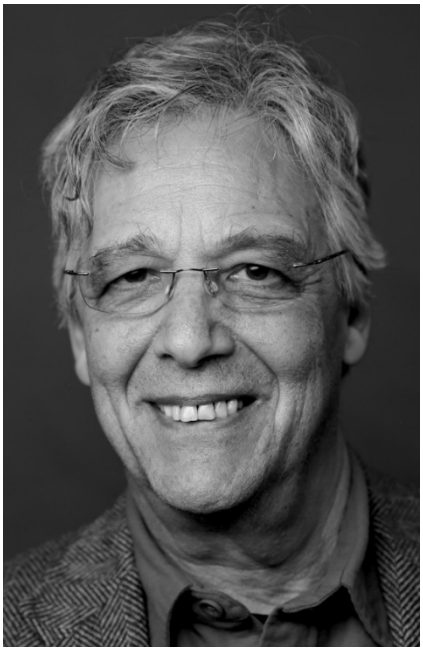
Keynote abstract
This study will change your life – health news in the media

Results from health research are regularly exaggerated in the media. For instance, a newspaper recently reported ‘Creative person has a lower risk of getting Parkinson’s disease’, while the original research paper claimed that ‘Artistic occupations are associated with a reduced risk of Parkinson’s disease.’ The correlation from the study is presented in the media as a causal relation, as if becoming a painter will protect you against Parkinson’s disease.
For many people the general media form an important source of health information and misrepresentations of medical research can have serious consequences. In our paper, we track how research is translated from scientific publications to news articles via press releases. We focus on the exaggeration of causal relations.
Methods: We collected press releases on biomedical research, published by 15 Dutch universities and university medical centers in 2015, their associated peer reviewed research papers and associated news articles. Two independent coders did a quantitative content analysis on these materials.
Results: We found that 20% of press releases and 29% of news articles contain exaggerated causal claims. So we see that a lot of the exaggeration happens on the academic side and not just in the journalists work. Furthermore, there was a strong correlation between exaggeration in press releases and news articles. When the press releases contained an exaggeration of a causal claim, 92% of associated news articles was exaggerated as well. On the other hand: when the causal claim in press releases was correct, so were those in 94% of the news articles. These results are in line with previous British studies.
We discuss the implications of our work and how science communication via press releases and media could be improved.

Tuesday July 9

Keynote lecture: Irving Kirsch

Time:	Monday, July 8, 08:30 AM - 09:15 AM
Location:	Grote Zaal
Chair:	Lene Vase



About Irving Kirsch

Irving Kirsch is Associate Director of the Program in Placebo Studies and a lecturer in medicine at the Harvard Medical School (Beth Israel Deaconess Medical Center). He is also Emeritus Professor of Psychology at the Plymouth University (UK), University of Hull (UK) and the University of Connecticut (USA). He has published 10 books, more than 250 scientific journal articles and 40 book chapters on placebo effects, antidepressant medication, hypnosis, and suggestion. He originated the concept of response expectancy. His 2002 meta-analysis on the efficacy of antidepressants influenced official guidelines for the treatment of depression in the United Kingdom. His 2008 meta-analysis was covered extensively in the international media and listed by the British Psychological Society as one of the “10 most controversial psychology studies ever published.” His book, The Emperor’s New Drugs: Exploding the Antidepressant Myth, has been published in English, French, Italian, Japanese, Turkish, and Polish, and was shortlisted for the prestigious Mind Book of the Year award. It was the topic of 60 Minutes segment on CBS and a 5-page cover story in Newsweek. In 2015, the University of Basel (Switzerland) awarded Irving Kirsch an Honorary Doctorate in Psychology.

Keynote abstract
Hypnosis as a non-deceptive extra-strength placebo

Placebos have been shown to be effective for many clinical conditions, but the assumption that deception is needed is a barrier to its use. Recently, studies have shown that placebos can be effective even when presented openly and honestly as placebos. However, clinicians report being uncomfortable asking clients or patients to take “sugar pills.” Hypnosis can provide an alternative means of generating a placebo effect without deception. Similarities between hypnotic suggestions and placebos include the following:

1. Both affect the same clinical conditions
2. Expectancy manipulations can enhance both placebo and hypnotic responding
3. Neither requires the presence of a trance state
4. Hypnotic inductions have no specific components
5. Suggestion is the active ingredient of both

Differences include the greater role of stable individual differences in hypnotic responding than placebo responding and findings showing that hypnotic suggestions can be more effective than placebo pills. Finally, Niels Bagge has developed an intervention in which clients or patients are asked to imagine taking imaginary pills, a procedure that can be implemented with or without inducing hypnosis and that blends open-label placebos with clinical hypnosis.

Plenary Session 4

The future of placebo: Conceptualizations and beyond

Tuesday, July 9, 09.15 AM - 11.00 AM
Grote zaal
Chair: Marco Annoni

Open Label Placebos: Reflections on a Research Program

Charlotte Blease

Program in Placebo Studies, Harvard Medical School, Cambridge, MA, United States

About Charlotte Blease
Dr. Charlotte Blease is a philosopher of medicine currently based at the Program in Placebo Studies, Harvard Medical School where she is a Fulbright Scholar and Irish Research Council/Marie Curie Awardee. Dr. Blease has published extensively on ethics and philosophy of science in relation to placebo studies in the BMJ, Journal of Medical Ethics, Perspectives in Biology and Medicine, etc. More broadly, she researchers philosophical issues relating to patient-doctor encounters.

Plenary Abstract
National surveys of primary care physicians demonstrate that placebo use is prevalent. A new program of research in placebo studies indicates that it may be possible to harness placebo effects in clinical practice via ethical, non-deceptively prescribed 'open label placebos' ('OLPs'). To date, there have been 14 small scale clinical and experimental studies into OLPs. Results suggest therapeutic potential of these treatments for a range of conditions and symptoms. In this talk I identify conceptual and empirical issues that, if not given due consideration, risk undermining research methodologies in OLP trials. Counterintuitively, owing to the nuances posed by placebo terminology, and the difficulties of designing placebos controls in OLP studies, experimentalists must reflect deeply when formulating adequate 'placebo' comparison groups. Further research is needed to disentangle which specific components of OLPs are effective. There may yet be potential to use OLPs in medical practice but clinical translation depends on rigorously controlled research.

The knife and the word: Surgeons' attitudes and usage of placebo effects in clinical practice

Karin Jensen

Karolinska Institute, Stockholm, Sweden

About Karin Jensen
Karin Jensen is an Assistant Professor of Clinical Neuroscience at the Karolinska Institute, Stockholm, Sweden. She is the leader of the Pain Neuroimaging Lab at Karolinska Institute - a research group focusing on brain mechanisms involved in pain control. Her team uses laboratory pain testing and brain scans in order to study the neural correlates of pain, and has specific focus on finding early predictors and biomarkers of chronic pain, as well as cognitive modulation of pain. Her lab also investigates placebo effects and has a research line that focuses on placebo effects in individuals with limited cognitive abilities, for example intellectual disability and dementia. In 2018, she was awarded the prestigious Pro Futura Fellowship from the Swedish Collegium & Foundation for Humanities and Social Sciences for her interdisciplinary placebo studies. The fellowship provides Jensen with resources to pursue curiosity-driven placebo research during five years.

Plenary Abstract

In a series of studies we are exploring the possible mechanisms of placebo effects in surgical treatments. Information on surgeons' attitudes towards non-specific treatment effects and placebo (sham) surgery is scarce. In a nationwide survey among Swedish surgeons, we asked questions about attitudes and clinical practices. The results suggest that surgeons have a strong belief that non-specific treatment factors, such as the doctor-patient relationship, has an impact on treatment outcomes in surgery. These beliefs have impact on the way surgical treatments are delivered. 97% of Swedish surgeons believe that non-specific treatment factors affect outcomes in surgery. When asked about placebo effects, 91% of surgeons believe that the placebo effect is genuine, has a scientific explanation and therapeutic benefits. When asked if they believe there are surgical treatments where the entire treatment effect is due to placebo, 78% said yes. While a majority of surgeons believe that sham surgery should be performed when there is uncertainty of the mechanism of an established surgical procedure (71%), they were more reluctant to refer patients to sham controlled trials (46%), mainly due to ethical considerations. In sum, surgeons believe that their words and behaviors are important components of their professional competence. We are now exploring the neural mechanisms of sham surgery among patients with chronic back pain in a multicenter trial in Sweden and Norway. The increased awareness about placebo effects in surgery has stimulated new collaborations that allow for systematic investigation of placebo mechanisms.frames provide statistically equivalent information, thus maintaining informed consent. Across a series of experiments, we found that positive framing was capable of reducing nocebo side effects. Importantly, this was when compared with both negative and generally framed side effect warnings and appropriate natural history controls. Interestingly, however, there was no evidence that expectancy mediated the framing effect, suggesting that other factors must underlie its efficacy. Irrespective of the mechanisms/s at play, the findings are encouraging and suggest that positive attribute framing may be an ethical and cost-effective method of reducing the burden of nocebo side effects in clinical settings.

Placebo effects across pharmacological, complementary and psychological interventions

Lene Vase

Aarhus University, Aarhus, Denmark

About Lene Vase

Lene Vase received her PhD in psychology in 2006 and her DMsc in Medicine in 2018. She is currently professor and head of the Neuroscientific Division at the Department of Psychology and Behavioural Sciences, School of Business and Social Sciences, Aarhus University, Aarhus, Denmark. Her research focuses on placebo effects across Central Nervous Diseases including Pain, Alzheimer's and Parkinson's disease and span across pharmacological, complementary, psychological and surgical interventions. She has a special interest in how expectancy and reward influence treatment outcomes and she heads an international initiative on how to account for this in test methodology. She has published more than 70 articles and book chapters and given multiple presentations world-wide. She is currently Associate Editor on PAIN and part of the steering committee for the Society for Interdisciplinary Placebo Studies.

Plenary Abstract

Only pharmacological treatments are obliged to show an effect beyond placebo to be approved for use in clinical practice. Yet, there is a pushing demand for complementary treatments, neuro-stimulating techniques and psychological interventions to demonstrate efficacy in rigorous ways.
In a series of studies, carefully matched placebo control for the pain relieving effect of acupuncture, religious prayer, musical intervention, deep brain stimulation and mindfulness therapy was develop. Across interventions, patients rated expectations and emotional feelings and the involvement of endogenous opioid and dopamine was tested.
Results: The majority of the interventions showed large placebo effects with no or small effects of the active intervention. Across interventions, expected pain levels accounted for increasingly larger amounts of the variance in pain levels over time and the involvement of endogenous opioids and dopamine was not demonstrated
Discussion: Based on the knowledge of placebo mechanisms it is possible to develop precise and adequate placebo control for a range of interventions yielding new information about the placebo mechanisms that are distinct and similar across interventions.

Beyond placebos: Harnessing mindset in 21st century healthcare

Alia Crum

Stanford University, Stanford, CA, United States

About Alia Crum

Dr. Alia Crum is an Assistant Professor of Psychology at Stanford University. She received her PhD from Yale University and BA degree from Harvard University. Dr. Crum's research focuses on how changes in subjective mindsets—the lenses through which information is perceived, organized, and interpreted—can alter objective reality through behavioral, psychological, and physiological mechanisms. Her work is, in part, inspired by research on the placebo effect, a robust demonstration of the ability of the mindset to elicit healing properties in the body. She is interested in understanding how mindsets affect important outcomes outside the realm of medicine, in domains such as exercise, diet and stress. More specifically, Dr. Crum aims to understand how mindsets can be consciously and deliberately changed through intervention to affect physiological and psychological well-beings. To date, her research has won several awards, most recently, the NIH New Innovator Award. In addition to her academic research and teaching, Dr. Crum has worked as a clinical psychologist for the VA healthcare system and an organizational trainer and consultant, creating, delivering, and evaluating workshops on mindset change and stress management for organizations including UBS, Colgate Palmolive and the United States Navy.

Plenary Abstract

Mindsets are lenses or frames of mind that orient an individual to a particular set of associations and expectations. Our research aims to move beyond the limited notion of the placebo effect as a mysterious response to an inert substance and toward a recognition that ultimately our mindsets (conscious or embodied) are responsible for these physiological responses. This talk will explore the role of mindsets in three stages of chronic disease progression: genetic predisposition, behavioral prevention, and clinical treatment. I will discuss the mechanisms through which mindsets influence health as well as the myriad ways that mindsets can be more effectively leveraged to improve 21st century healthcare.

Harnessing placebo effects in clinical care: Lessons learned from placebo research

Ulrike Bingel

University Hospital Essen, Essen, Germany

About Ulrike Bingel

Ulrike Bingel is a neurologist by background and Professor of Clinical Neuroscience at the Medical Faculty, University of Duisburg-Essen, Germany. Her research focuses on pain processing and -modulation in health and disease and interactions between pain and analgesic treatments and cognitive factors. Her work has revealed critical insights into the neurobiological basis of placebo and nocebo responses, their interaction with active pharmacological treatments and implications of these findings for clinical practice.

Plenary Abstract

In this presentation I will highlight what we have learned from experimental and clinical placebo studies over the past decades and provide suggestions how the gained insights could be translated in clinical care to optimize treatment outcomes.

Parallel Session 2.1

Open up about placebos: Open label placebo applications

Tuesday, July 9, 11:30 AM - 12.30 PM
Grote zaal
Chair: Robert Jütte

2.1a Mechanisms of open-label placebos in pain and sadness

1. Tobias Kube. *University of Koblenz-Landau, Landau, Germany.*

Background: Although there is evidence of the efficacy of open-label placebos (OLPs), knowledge of their specific mechanisms is limited compared to deceptive placebos (DPs).
Methods: In Study 1 (N = 117), an experimental heat pain paradigm was used to examine hopes and expectancies as possible mechanisms of OLPs. Participants were randomly assigned to OLP with hope induction, OLP with expectancy induction, DP, or no treatment (NT). In Study 2 (N = 150), we used a five-group design to examine mechanisms of OLPs and DPs in experimentally induced sadness. In particular, we examined the effects of two different communication styles in the administration of placebos (personal-emotional vs. scientific-objective), the effects of type of placebo (OLP vs. DP), and their interactions.
Results: In Study 1, results indicate that increase in pain tolerance was larger in the three treatment groups compared to NT, while the treatment groups did not differ from each other. The largest reduction of the pain intensity and unpleasantness was found in DP. In Study 2, DP and, to a lesser extent, OLP were superior to NT in providing protection against sadness. The communication style interacted with the type of placebo to the extent that DPs were more effective when provided in a personal-emotional manner than in a scientific-objective manner.
Conclusions: Both studies provide evidence for the efficacy of OLPs. The interaction effect from Study 2 raises the idea that OLP and DP may differ in terms of the communication style with which they are most effectively administered.

2.1b Open-placebo improves exercise performance in female cyclists

1. Bryan Saunders. *University of São Paulo, São Paulo, Brazil.*
2. Tiemi Saito. *University of São Paulo, Sao Paulo, Brazil.*
3. Rafael Klosterhoff. *University of São Paulo, São Paulo, Brazil.*
4. Luana Farias de Oliveira. *University of São Paulo, São Paulo, Brazil.*
5. Gabriel Barreto. *University of São Paulo, São Paulo, Brazil.*
6. Pedro Perim. *University of São Paulo, São Paulo, Brazil.*
7. Ana Jessica Pinto. *University of São Paulo, São Paulo, Brazil.*
8. Fernanda Lima. *University of São Paulo, São Paulo, Brazil.*
9. Ana Lucia Pinto. *University of São Paulo, São Paulo, Brazil.*
10. Bruno Gualano. *University of São Paulo, São Paulo, Brazil.*

Background: Administration of open-placebo has shown benefits in several clinical conditions although no study has investigated its effect on exercise performance. Aim: To investigate the effect of open-placebo on exercise performance.
Methods: Twenty-eight trained female cyclists completed a 1-km cycling TT following a control session or an open-placebo intervention. The intervention was provided by a medic, in which the concept of open-placebo was explained to the participant, before ingesting two red and white capsules containing flour; 15 min later they performed the TT. In the control session, the participant sat quietly for 20 min. Heart rate and ratings of perceived exertion (RPE) were monitored throughout exercise, while blood lactate was determined pre- and post-exercise. Post-exercise questionnaires were employed to gain insight into the perceived influence of the supplement on performance.
Results: Open-placebo improved time-to-completion (P=0.039, 103.6±5.0 vs. 104.4±5.1 s) and mean power output (P=0.01, 244.8±34.7 vs. 239.7±33.2 W). Individual analysis showed that 11 individuals improved, 13 remained unchanged and 4 worsened their performance with open-placebo. Heart rate, RPE and blood lactate were not different between sessions (all P>0.05).
Conclusions: Open-placebo improved 1-km cycling TT performance in trained female cyclists. Positive expectation did not appear necessary to induce performance improvements, suggesting non-cognitive processes occurred, although a lack of an improvement appeared to be associated with a lack of belief. Although the intervention was successful for some individuals, some athletes may not respond or even perform worse. Open-placebo interventions should be carefully considered by coaches and practitioners, while further studies are warranted.

2.1c Acceptance of open-label placebo treatments in the lay population

1. Julia Wittkowski. *Philipps-University Marburg, Marburg, Germany.*
2. Winfried Rief. *Philipps-University Marburg, Marburg, Germany.*
3. Bettina Doering. *Catholic University of Eichstaett-Ingolstadt, Eichstaett, Germany.*

Background: Although patients tend to endorse placebo treatments in clinical practice deception is still an ethical problem. Open-label placebos (OLPs) might be a promising approach to solve this dilemma. This study compared general acceptance and outcome expectations of OLPs and deceptive placebos (DPs).
Methods: In an online survey, 808 participants read a vignette of a person with insomnia. They were then allocated randomly into two groups: the second part of the vignette described either a deceptive placebo treatment (DP group) or an open-label placebo treatment (OLP group). The Credibility Expectancy Questionnaire (CEQ) assessed treatment expectations after the first (T1) and the second part (T2) of the vignette. Treatment acceptance was measured via two 5-point-likert-scale items at T2. Data were analysed by a MANOVA, t-tests and Mann-Whitney U tests.
Results: The MANOVA revealed a significant group main effect ($F[2,805]=55.73$, $p<.001$) and a significant time*group interaction effect ($F[2,805]=27.17$, $p<.001$). After the second part of the case vignette, both treatment expectancy ($t[806]=-10.12$, $p<.001$) and credibility ($t[806]=-5.59$, $p<.001$) were higher in the DP group than in the OLP group. Acceptance of the placebo treatment was higher in the DP group than in the OLP group (item 1: $z=-2.42$, $p=.016$; item 2: $z=-4.20$, $p<.001$).
Conclusions: Treatment expectations towards DPs are higher than towards OLPs. Interestingly, applying placebos with deception was rated as more acceptable than applying OLPs. Future research needs to investigate the replicability of these results across samples with more heterogeneous demographic characteristics and both patient and healthy samples.

2.1d The influence of treatment information on expectations and open-label placebo effects

1. Marco Valerio. *UNSW, Sydney, NSW, Australia.*
2. Emily Babbage. *UNSW, Sydney, NSW, Australia.*
3. Natasha Jain. *UNSW, Sydney, NSW, Australia.*
4. Kate Faasse. *UNSW, Sydney, NSW, Australia.*

Background: Open-label placebos (OLPs; i.e. placebos that are administered without deception) may allow placebo effects to be utilised by healthcare professionals without infringing on the patient's right to informed consent. Understanding the mechanisms by which OLPs work may enhance their effects in clinical applications. Therefore, the proposed study aims to investigate the role of information provision in OLP effects to improve physical and psychological wellbeing.
Methods: The study used a one-way between-subjects design involving 108 university students, to assess the effects of OLP given with positive information about placebos (PI) or neutral information (NI). Expectations of placebo (for PI and NI groups) or no treatment (for NTC), positive mental wellbeing, psychological distress, physical symptoms, and sleep quality were assessed at the baseline session and after the treatment.
Results: The PI group had significantly more positive treatment expectations than the NI group. A significant OLP effect was seen in the positive information group (relative to the NTC group) in psychological distress, positive mental wellbeing, physical symptoms, and sleep quality. No OLP effects were seen in participants given placebo tablets with neutral information.
Conclusions: The study suggests that OLPs associated with information that does not enhance treatment expectation do not improve physical and psychological wellbeing. When expectation enhancing information rationale is provided, however, OLP treatment improves negative emotions, mental wellbeing, physical symptoms and sleep quality. These findings suggest that information provision is critical to OLP effects.

Parallel Session 2.2

From genes to expectancies: Predicting placebo effects

Tuesday, July 9, 11:30 AM - 12.30 PM.
Aalmarktzaal
Chair: Andrew Geers

2.2a Do patients' treatment expectations change over time?

1. Anja Zieger. *1) University Hospital Zurich, Zurich, Switzerland; 2) University of Zurich, Zurich, Switzerland.*
2. Alexandra Kern. *1) University Hospital Zurich, Zurich, Switzerland; 2) University of Zurich, Zurich, Switzerland.*
3. Jürgen Barth. *1) University Hospital Zurich, Zurich, Switzerland; 2) University of Zurich, Zurich, Switzerland.*
4. Claudia Witt. *1) University Hospital Zurich, Zurich, Switzerland; 2) University of Zurich, Zurich, Switzerland.*

Background: Little is known about the course of expectations during treatments. We aimed to identify clusters with similar change patterns in expectations in patients with chronic low back pain (CLBP) and describe differences in patient characteristics between the clusters.
Methods: A total of 140 patients (40.1□12.5 years; 66.4% female) reported their expectations about acupuncture treatment on the Expectation for Treatment Scale (ETS) at baseline, after inclusion, and after four sessions of acupuncture treatment. Pain intensity and bothersomeness (NRS 0-10) and self-reported health (PROMIS-29) were measured at baseline, after four treatment sessions and at end of treatment. Optimism and pessimism (LOT-R) were measured at baseline.
Results: Cluster analysis revealed four clusters: 44.3% of patients showed a pattern of low stable expectations (n=62), whereas 55.7 % of patients showed changes in expectations over time (pre-treatment increased expectations (n=12); treatment increased expectations (n = 52); treatment decreased expectations (n=14)). Significant differences between the stable and treatment increased expectation cluster were found for pain intensity at baseline (p=0.002), change in pain intensity after session 4 (p<0.001) and change in pain intensity after treatment (p=0.032), with lower values in the stable expectation cluster. Anxiety (p=0.022) and sleep disturbance (p=0.032) at baseline were the highest in the treatment decreased expectations cluster.
Conclusion: This analysis revealed that treatment expectations can change over time.
Interventions targeting at expectations to optimize a treatment outcome should therefore not only target at pre-treatment expectations but also at expectations during the course of treatment.

2.2b Placebo-pharmacogenomic effects in clinical trials and precision medicine

1. Kathryn Hall. *Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States.*
2. Ted Kaptchuk. *Harvard Medical School, Boston, MA, United States.*

Background: Through the randomized-clinical trial (RCT), drugs and placebos are linked to disease. Still pharmacogenomics, the study of how individual genetic variation modifies drug response, focuses on genes-drug relationships, overlooking gene-disease effects, while placebo response is ignored. The placebome is a group of genome-related mediators implicated in placebo response in RCTs. Genetic variation in catechol-O-methyltransferase, COMT, a placebome gene, can have main and combinatorial effects on disease, drug and placebo response, and thereby influence outcomes in RCTs.
Methods: Using a systematic literature review, we created a candidate list of placebome genes. We mapped these placebome genes to the interactome, the comprehensive network of protein-protein interactions, and derived characteristics of the placebome from the interactome network. We then preformed retrospective analyses of RCTs to understand main and combinatorial effects in drug and placebo arms of COMT and other placebome genes.
Results: We determined that the placebome is enriched for proteins implicated in disease and targeted by a wide cross-section of drugs e.g. analgesics, antidepressants, and anti-oxidants. Using COMT as a case study, we examine its association with psychiatric, neurological, cardiometabolic disease and cancer and gene-drug/placebo interaction effects. We identified recent RCTs which using genome-wide association studies or placebome candidate analyses found genes that mapped directly to the placebome in asthma, depression, and cancer.
Conclusions: These findings support our assertion that COMT is a placebo-pharmacogenomic hub which if perturbed can influence RCT outcomes. Further, findings of other placebome genetic effects reinforce the translational utility of the placebome in drug discovery and development.

2.2c COMT met/met genotype is associated with higher placebo response rates and pain tolerance in healthy men exposed to experimental pain

1. Efrat Czerniak. *Tel Aviv University, Tel Aviv, Israel.*
2. Roi Treister. *University of Haifa, Haifa, Israel.*
3. Atay Citron. *University of Haifa, Haifa, Israel.*
4. Amitai Ziv. *Tel Aviv University, Tel Aviv, Israel.*
5. Orit Karnieli-Miller. *Tel Aviv University, Tel Aviv, Israel.*
6. Mark Weiser. *Tel Aviv University, Tel Aviv, Israel.*
7. Uri Alon. *Weizmann Institute of Science, Rehovot, Israel.*
8. Elon Eisenberg. *Israel Institute of Technology, Haifa, Israel.*
9. Dorit Pud. *University of Haifa, Haifa, Israel.*
10. Anat Biegon. *State University of New York, Stony Brook, NY, United States.*

Background: Catechol-O-methyltransferase (COMT) met/met-genotype (AA) has been associated with greater placebo response in irritable bowel syndrome relative to the val/met and val/val genotypes (GA/GG). Here we studied the effect of COMT genotype on placebo response rate and size in experimental pain.
Methods: Healthy volunteers from two studies (N=257, 117 women) were given the cold pressor test before and after administration of placebo. Subjects displaying an increase in pain tolerance of 30% or more were considered placebo responders. All participants provided saliva samples for genotyping.
Results: Useful data were obtained from 193 participants (29 responders, 164 non-responders). The odds of being a responder were higher for AA-carriers ($\chi2(1,193)=4.61$, $p=.039$). This association was stronger in males ($\chi2(3,193)=16.85$, $p=.001$), with a 5.7-fold increase in AA-carriers compared to male GA/GG-carriers (95% CI: 1.95-16.8). Additionally, genotype ($F(1,192)=5.83$, $p=.017$, $\eta2=.030$) and sex ($F(1,192)=20.1$, $p<.011$, $\eta2=.096$) as well as their interaction ($F(1,192)=10.0$, $p=.002$, $\eta2=.050$) had a significant effect on the increase in tolerance size. Thus, male AA-carriers showed a larger increase in tolerance (35.4±14.3) compared to male GA/GG-carriers (-4.1±4.4; $p<.001$) and female of AA (-18.8±5.8; $p<.001$) and AG/GG genotypes (-13.4±5.0; $p<.001$; $F(3,192)=8.64$, $p<.001$).
Conclusions: Our research supports recent findings on the contribution of COMT met/met genotype to the placebo response, though this is the first study to suggest an interaction between genotype and sex. Since met/met-genotype is associated with higher levels of dopamine in the synapse, these results also support a role for dopamine in the placebo response which may, however be modulated by biological sex.

2.2d Using Bayesian integration in two independent studies to predict placebo treatment outcomes

1. Arvina Grahl. *1) Massachusetts General Hospital, Boston, MA, United States; 2) Harvard Medical School, Boston, MA, United States; 3) University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
2. Mari Feldhaus. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
3. Christian Büchel. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Pain perception and placebo effects are highly variable between individuals. To better understand these differences, we used a Bayesian framework not only accounting for the strength but also the precision levels of treatment expectations (“prior”) and new sensory inputs (“likelihood”) to predict placebo treatment outcomes, i.e. pain relief (“posterior”). In the sense of replicability, results from an fMRI study (N1=62), which already used this approach, were compared to an independent behavioral placebo study (N2=714). A random effects Bayesian model selection approach was applied to compare the Bayesian to a Null model which assumed no influence of prior treatment experience. Bayes factors were computed subject-wise reflecting a ratio of how much more likely the Bayesian model was compared to the Null model given the observed data. Both studies tested healthy participants with heat pain using a similar experimental procedure (putative treatments: TENS or ointments; conditioning with high pain for non-treated control and low pain for treated placebo condition; test phase with middle pain for both conditions). The observed data of the treatment outcome was better explained by the Bayesian framework compared to the Null model reflected in greater overall posterior model probabilities (Study 1: 0.913; Study 2: 0.877). A positive relationship was found between the predicted and observed placebo treatment outcome for both studies (Study 1: $r=0.441$, $p<0.001$; Study 2: $r=0.304$, $p<0.001$). Summarizing, by including the influence of precision levels, Bayesian integration highlights the importance of assessing detailed treatment expectations prior to new medical procedures to maximize potential placebo effects.

Parallel Session 2.3

New applications of traditional conditioning paradigms

Tuesday, July 9, 11:30 AM - 12.30 PM
Breezaal
Chair: Karin Jensen

2.3a Operant conditioning as a new mechanism of placebo effects

1. Przemysław Bąbel. *Jagiellonian University, Kraków, Poland.*

Placebo effects have been considered as learning phenomena since the 1950s when classical conditioning was suggested as their mechanism. In the 1980s, a second learning process was proposed as a mechanism of placebo effects, i.e. observational learning. There is a growing body of evidence supporting the role of both classical conditioning and observational learning in the induction of placebo effects. However, third learning process, operant conditioning, has not been previously considered as a mechanism of placebo effects. Unlike classically conditioned responses, which are induced by stimuli that precede the behavior, operant behaviors are shaped and maintained by their consequences. Thus, placebo effects may not only result from pairing an active intervention with stimuli accompanying its administration (placebo), but also positive consequences of placebo administration may increase the frequency of placebo application in the future. Those consequences include, for example, attention or feedback received from doctors or significant others, the ability to perform a desired activity or – on the contrary – the ability to avoid an undesired activity, among others. On the other hand, negative consequences of placebo administration may decrease the frequency of its application in the future. Recently, we have developed an operant conditioning paradigm to study placebo effects in the laboratory conditions. By using this paradigm, we provided the very first empirical support for the operant conditioning as a mechanism of placebo effects. The aim of the paper is to present and briefly discuss the operant conditioning account of placebo effects.

2.3b The influence of expectations and conditioning on apnea performance

1. Diletta Barbiani. *University of Turin, Turin, Italy.*
2. Elisa Carlino. *University of Turin, Turin, Italy.*
3. Alessandro Piedimonte. *University of Turin Medical School, Turin, Italy.*
4. Fabrizio Benedetti. *1) University of Turin Medical Schoo, Turin, Italy; 2) Plateau Rosà Laboratories, Plateau Rosà, Italy/Switzerland.*

Background: Besides being leveraged in the clinical context, placebo effects have been found to be crucial for critical physiological functions in extreme environmental conditions, whereby conditioned placebo procedures are capable of mimicking the effects of oxygen by affecting such parameters as fatigue and physical performance.
Objective: The aim of the present study is to investigate whether expectations of receiving real O2 combined with a conditioning paradigm with sham O2, is capable of affecting apnea performance.
Methods: A total of 50 healthy volunteers were subdivided into 2 groups and tested in our labs in Turin. Group 1 (natural history group) did not receive any manipulation and underwent 4 identical baseline trials. Subjects of Group 2 (placebo group), after a first baseline trial, breathed sham O2 in the two subsequent trials for 5 minutes before each apnea test. Importantly, in addition to the positive expectations of receiving real O2, these subjects underwent a conditioning procedure in which their perception of the time of apnea was manipulated so to make them believe that the perceived improvement was due to the previously inhaled O2. In the last trial, subjects breathed sham O2 albeit without any time manipulation.
Results: Compared to the natural history group, the placebo group (positive expectation + conditioning) exhibited a greater percentage improvement in total apnea time (41%) between the first and last session.
Conclusions: These findings indicate that psychological factors alone can account for the improvements in total apnea time, highlighting how placebo effects can also apply to apnea performance.

2.3c Generalization in placebo hypoalgesia

1. Lea Kampermann. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
2. Christian Büchel. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Placebo hypoalgesia refers to a perceived pain relief due to modulation induced by expectation and experience. Having experienced a substantial pain relief from one treatment in the past, one might expect similar outcomes - if the features of a novel treatment resemble the ones experienced before. We formally studied how previous experiences are transferred to future situations, controlling the similarity between original and novel situations. Using a placebo conditioning paradigm in N = 35 healthy humans during functional MRI, we treated heat induced tonic pain on capsaicin pretreated skin. We conditioned participants to expect better treatment from one 'doctor' (a human face cue, CS+) by pairing it with a stronger temperature decrease, i.e. pain relief, than another face cue (CS-), followed by a more subtle decrease. Following conditioning, participants were tested on a circular continuum of eight faces ranging from CS+ to CS, all followed by the subtle treatment. Pain relief ratings in the test phase showed that previous relief experiences carried over in form of a placebo effect, i.e. stronger relief ratings for the CS+ vs. CS-, accompanied by decaying placebo relief with increasing dissimilarity to the CS+. This gradient in the placebo effect was better explained by a Gaussian fit than a uniform null model. Furthermore, we identified Gaussian shaped generalization profiles on the neuronal level in prefrontal as well as subcortical regions. We conclude that learned analgesic associations are transferred to novel situations to the degree they resemble previous experiences, thus following the principle of generalization.

2.3d Hippocampus mediates conceptual generalization effects on pain

1. Leonie Koban. *1) Brain and Spine Institute; 2) INSEAD, Paris, France.*
2. Tor Wager. *University of Colorado, Boulder, CO, United States.*

Introduction: Placebo effects reflect the modulation of pain or other symptoms by contextual factors and conceptual appraisals that generate expectations of relief. Here, we used fMRI to test how conceptual generalization—i.e., the transfer of learned relationships to novel but conceptually related stimuli—influences the perception of experimental heat pain.
Methods: N=36 adults first learned to associate two conditioned cues (CS)—drawings of a vehicle and an animal— with lower (CSLOW) or higher (CSHIGH) heat pain intensities. Participants subsequently performed a generalization task, in which novel stimuli (words, photos, and drawings) preceded a series of painful stimuli (always 49□C). These stimuli could be conceptually related (i.e., belonging to the same category) to either the CSLOW or the CSHIGH.
Results: Participants who learned the contingency between cues and pain during the learning phase reported higher pain in the generalization phase when cues matched the conceptual category of the CSHIGH versus CSLOW. FMRI revealed increased activation for pain preceded by CSHIGH-category vs. CSLOW-category cues in amygdala, hippocampus, and temporal pole. Hippocampus, but not amygdala activity was modulated by the strength of explicit expectations and formally mediated the effects of cue-category on pain.
Conclusions: This study shows that conditioned influences on pain generalize to novel, conceptually related cues, demonstrating an important role of conscious expectations and brain areas related to conceptual inference on learned pain modulation. These results have implications for understanding the role of associative learning and conceptual thought in placebo and other expectation effects.

Parallel Session 2.4

Placebo effects in psychotherapy and neurocognitive disorders

Tuesday, July 9, 11:30 AM - 12.30 PM.
Jan Willem Schaap zaal
Chair: Liesbeth van Vliet

2.4a Placebo therapy – A randomized controlled trial

1. Luzius Heydrich. *University of Basel, Basel, Switzerland.*
2. Delfine d'Huart. *University of Basel, Basel, Switzerland.*
3. Süheyla Seker. *University of Basel, Basel, Switzerland.*
4. Kerstin Trachsel. *University of Basel, Basel, Switzerland.*
5. Julia Wagner. *University of Basel, Basel, Switzerland.*
6. Jens Gaab. *University of Basel, Basel, Switzerland.*

In 1973, Jefferson M. Fish proposed Placebo Therapy, which considered the context of therapy, the exploration of the participant's beliefs in order to provide an interpersonally valid rationale, and a healing ritual accepted by the participant as central mechanisms of psychotherapy. However, despite the potential of this approach, Placebo Therapy so far has not been evaluated empirically. Therefore, we set out to investigate the feasibility and efficacy of a manualized version of Placebo Therapy in healthy adults. For this purpose, 60 healthy participants were randomly assigned to either intervention or no-treatment control group. The intervention group underwent four weekly sessions of individual Placebo Therapy. Baseline, post-treatment and 1-month follow-up psychological outcome measurements were conducted. Results indicate that the intervention presented here was broadly accepted by participants and showed significant effects on well-being (group by time interaction: ASS-SYM-G; $F(1,58) = 3.81$, $p = .028$, $\eta p2 = .12$) in healthy adults. The results indicate that a psychological intervention solely based on placebo principles is both feasible and effective. This not only calls for replication in clinical population, but also highlights the importance of plausibility as a driving force in psychotherapy's effects as well as the need to caution the ethical implication of this finding.

2.4b Can the addition of placebo pills augment psychotherapy?

1. Heike Gerger. *University of Basel, Basel, Switzerland.*

Background: Previous meta-analyses demonstrated a small advantage of the combination between psychotherapy and pharmacotherapy over psychotherapy alone. In addition, the combination of psychotherapy and pharmacotherapy has outperformed the combination of psychotherapy and placebo in previous meta-analyses. But what about the comparison between psychotherapy and the combination of psychotherapy with placebo - can the addition of placebo pills improve psychotherapy's efficacy?
Methods: The talk present network meta-analytic data on the efficacy of the combined treatment approach of psychotherapy and pill placebos as compared with psychotherapy alone or the combination of psychotherapy and pharmacotherapy. On the example of comparative PTSD treatment studies, using a network of comparisons between psychotherapy and the combinations of psychotherapy with pharmacotherapy as well as with pill placebos the efficacy of the three treatment approaches will be compared within one network of evidence.
Results: Based on 12 randomised clinical trials indirect evidence suggests that the addition of placebo pills to psychotherapy does not increase psychotherapy's efficacy in adults with post-traumatic stress disorder.
Conclusions: The results will be interpreted in the context of partly contradicting previous findings, which suggest superiority of combining placebos with psychotherapy over psychotherapy alone. It is important to note a huge lack of research on the efficacy of adding placebo pills to psychotherapy.

2.4c Expectation-induced placebo responses in major depression: An experimental investigation

1. Bettina Doering. *Catholic University of Eichstaett-Ingolstadt, Eichstaett, Germany.*
2. Julia Anna Glombiewski. *University of Koblenz-Landau, Landau, Germany.*
3. Winfried Rief. *Philipps-University Marburg, Marburg, Germany.*
4. Alexander Winkler. *Justus-Liebig-University, Gießen, Germany.*
5. Julia Wittkowski. *Philipps-University Marburg, Marburg, Germany.*

Background: Expectations contribute to placebo responses in antidepressant treatments. In a previous experiment, we were able to demonstrate that an expectation manipulation combined with the intake of an active placebo ("fast-operating antidepressant") reduces the intensity of sadness after a sadness-inducing mood manipulation in healthy participants. In the present study, we aimed at investigating this placebo mechanism in clinically depressed participants.
Methods: 94 women who suffered from a current major depressive episode were allocated randomly (2:1:1) to the experimental group (active placebo, positive treatment expectation; EG), the expectation-control group (active placebo, no treatment expectation; ECG) and the control group (no placebo, no expectation; CG). All participants watched a sadness-inducing film sequence. A subscale of the Positive and Negative Affect Schedule-Expanded Form (PANAS-X) assessed sadness at baseline (T1), after randomisation (T2) and after placebo intake and mood-induction (T3). Data were analysed by a 3x3 analysis of variance.
Results: After the mood-induction, sadness was higher in the control groups than in the experimental group, indicated by a significant time*group interaction effect (Greenhouse-Geisser: F [2.86, 130.04]=13.61; $p<.001$) and significant post-hoc comparisons (ΔEG-ECG:
-8.65, $p=.007$; ΔEG-CG: -16.63, $p<.001$). Neither time (Greenhouse-Geisser: F [1.43, 130.04]=1.84; $p=.174$) nor group (F [2, 91]=2.18; $p=.119$) showed main effects.
Conclusions: Sadness represents a core symptom of depression. This experimental paradigm showed an expectation-induced placebo response on sadness in clinically depressed participants. Further research needs to investigate the stability of this effect and its applicability to longer treatment periods.

Parallel Session 2.5

Placebo and nocebo effects on cognition

Tuesday, July 9, 11:30 AM - 12.30 PM.
Cornelis Schuyt zaal
Chair: Enny Das

2.5a The effects of information about chemotherapy-induced cognitive decline, stigma consciousness, and framing on cognitive performance of breast cancer patients

1. Anne Janssen. *Radboud University, Nijmegen, Netherlands.*
2. Wendy Jacobs. *Radboud University, Nijmegen, Netherlands.*
3. Enny Das. *Radboud University, Nijmegen, Netherlands.*

Background: Informing patients about side effects may contribute to their occurrence, a phenomenon called Adverse information Effects (AIE). The objective of the current study was to assess whether systematic language variations in information about side effects of chemotherapy can reduce AIE on cognitive problem reporting (CPR) and cognitive performance of breast cancer patients. Additionally, we investigated whether patients with varying levels of stigma consciousness respond differently to these language variations.
Methods: 121 breast cancer patients participated in an online experiment with three conditions. Participants in the two experimental conditions were presented with information about cognitive side effects using either a direct negative frame (e.g. 'decreased speed of information processing), or an indirect positive frame ('changes in information processing speed'). The third group was a no-information control group. The main dependent variables were CPR and cognitive performance. Stigma consciousness was assessed as a moderator.
Results: An information effect was found on one of the cognitive performance tasks: when stigma consciousness was high, the no-information control group performed worse on recognition than the experimental groups. These effects were particularly pronounced for patients who reported high self-perceived cognitive problems. No framing effects were observed.
Conclusions: Contradicting earlier studies finding AIE, in the current study the information groups performed better than the control group. Future studies should examine if these effects reverse in the long term.

2.5b Placebo and nocebo effects on visuospatial attention: A direct comparison

1. Carina Höfler. *University of Graz, Graz, Austria.*
2. Jonas Potthoff. *University of Graz, Graz, Austria.*
3. Anne Schienle. *University of Graz, Graz, Austria.*

Recent findings indicate that placebos as well as nocebos are able to influence visual processing. In the present eye-tracking investigation effects of placebos and nocebos on visuospatial attention were directly compared in a healthy sample. A sham transcranial magnetic stimulation (sTMS) was administered along with the verbal suggestion that the treatment would either increase (placebo) or decrease (nocebo) left-sided visual attention. Twenty participants who had reported decreased attention (nocebo responders) and 20 participants who had reported increased attention (placebo responders) following sTMS completed a visual search task with three visual load levels. The task was performed once with, and once without the placebo or the nocebo. Left-sided fixation frequency and reaction times to left-sided targets (in comparison to right-sided targets) were analyzed. Contrary to the suggestion, the nocebo increased the number of left-sided fixations and decreased reaction times to left-sided targets in the high load condition, whereas the placebo had no effects. These findings indicate a more beneficial effect of nocebos relative to placebos in visual attention for the first time. Limits and possibilities of placebo and (paradoxical) nocebo interventions are discussed.

2.5c The placebo effect in motor skill learning: Comparing cognitive and motor placebos

1. Bernardo Villa-Sánchez. *University of Verona, Verona, Italy.*
2. Mehran Emadi Andani. *University of Verona, Verona, Italy.*
3. Paola Cesari. *University of Verona, Verona, Italy.*
4. Mirta Fiorio. *University of Verona, Verona, Italy.*

Motor learning is a key component of human motor functions that allows to acquire new skills, like playing an instrument. In this study, we tackled the differential role of two types of placebo treatments, one motor and one cognitive, in influencing the performance at an implicit motor learning task. Eighty-nine healthy participants performed a serial reaction time task in three sessions (baseline, learning, final). Before the learning and final session, a placebo procedure was applied in two experimental

groups. One group (placebo-TENS) received an inert treatment with transcutaneous electrical nerve stimulation (TENS) applied on the hand involved in the task together with the positive effect of TENS in increasing muscle activity (motor placebo). Another group (placebo-tDCS) received sham transcranial direct current stimulation (tDCS) on the supraorbital areas along with the positive effect of tDCS in increasing concentration and attention (cognitive placebo). A control group performed the same task without treatment. Reaction times were measured as index of performance and perception of mental and physical fatigue was measured as subjective variable. Results showed that the cognitive placebo (tDCS) reduced the perception of mental and physical fatigue, while motor placebo (TENS) reduced the perception of physical fatigue. Performance improved independently from the placebo procedure. This study shows for the first time that the perception of mental and physical fatigue in a repetitive motor task can be reduced by a cognitive placebo procedure.

2.5d Experimental research on expectancy effects in cognitive enhancement

1. Michiel van Elk. *University of Amsterdam, Amsterdam, Netherlands.*
2. Suzanne Hoogeveen. *University of Amsterdam, Amsterdam, Netherlands.*
3. Uffe Schjoedt. *Aarhus University, Aarhus, Denmark.*

Many people are mesmerized by the promises of novel brain technologies and express a remarkable faith in the potential of cognitive enhancement through transcranial stimulation devices. At the same time, the actual efficacy of these techniques (e.g., such as transcranial direct current stimulation, tDCS) is currently strongly debated. It has even been suggested that many of the effects observed may actually be related to participants' beliefs that brain stimulation can enhance or impair their performance. In this talk we discuss recent studies from our lab, in which we investigated the psychological and neurocognitive basis of expectancy effects about transcranial cognitive enhancement. We boosted participants' belief in the potential of a placebo-tDCS device to up- or down-regulate their performance on a cognitive task. Participants indeed subjectively experienced enhanced or impaired performance in line with our expectancy manipulations. Moreover, they were also more likely to attribute errors on a cognitive task to the transcranial device when expecting impaired performance. At a neural level we found that the expectancy manipulation also affected early and automatic brain responses in response to errors. We integrate our findings within the computational framework of predictive processing, which provides a unifying theory to account for the effects of expectancy manipulations on subjective experience and error processing. Our studies thus convincingly show that by inducing strong placebo-manipulations, people can externalize agency (e.g., ' they blame their brain') and that these effects exert a strong top-down influence on early neural markers of cognitive processing as well.

Poster Session 3

Tuesday, July 9
1:00 PM – 2:00 PM

PP3.01 Do placebos cause an aggravation response?

1. Paul Dieppe. *University of Exeter Medical School, Exeter, United Kingdom.*
2. Natalie Harriman. *Stellanbosch University Medical School, Stellenbosch, South Africa.*
3. Jeremy Swayne. *Exeter, United Kingdom.*

Background: Complementary therapies, such as homeopathy, are often dismissed as 'just a placebo'. But practitioners point out that they can cause a worsening of symptoms before improvement (the aggravation response) and suggest that this shows that they are not just placebos. We wanted to know if placebos cause an aggravation response.
Methods: We sent a survey out to all members of SIPS on the email circulation list (n=157). We asked four questions about the effects of placebos on symptoms, including whether they caused an aggravation response. The options for completion were 'often', 'sometimes' or 'never'.
Results: We only received 20 responses, respondents varying in age from 30 to 77, the majority saying that they were clinicians and/or researchers/academics. All respondents thought that placebos could relieve symptoms (15 sometimes, 5 often), and the majority thought that such symptom relief could be permanent (4 never, 14 sometimes, 2 often). The majority also thought that placebos could cause an aggravation response (3 never, 16 sometimes, 1 often), and that if this occurred it would be followed by symptom relief (16 sometimes, 2 often).
Conclusions: The 'sometimes' option was the most used, suggesting uncertainty, and 4 respondents noted that they did not really know the answers. However, the consensus was that placebo can cause an aggravation response. We conclude that further research on the 'if, how and why?' of such responses are warranted, and that the SIPS organisation needs to consider if it can be a vehicle for research.

P3.02 Placebo analgesia: The interplay between classical conditioning and verbal suggestions. Results from a comprehensive, multi-group study

1. Karolina Wiercioch-Kuzianik. *Jagiellonian University, Kraków, Poland.*
2. Elżbieta A. Bajcar. *Jagiellonian University, Kraków, Poland.*
3. Wacław M. Adamczyk. *1) Jagiellonian University, Kraków, Poland; 2) The Jerzy Kukuczka Academy of Physical Education, Kraków, Poland.*
4. Dominika Farley. *Jagiellonian University, Kraków, Poland.*
5. Ewa Buglewicz. *Jagiellonian University, Kraków, Poland.*
6. Jakub Nastaj. *Jagiellonian University, Kraków, Poland.*
7. Helena Bieniek. *Jagiellonian University, Kraków, Poland.*
8. Przemysław Bąbel. *Jagiellonian University, Kraków, Poland.*

Classical conditioning and expectancy are two mechanisms of eliciting placebo effects. However, the debate about their roles is still ongoing. Previous studies lack both a comprehensive design, covering all combinations of classical conditioning and verbal suggestions, as well as the measurement of expectancy. Therefore, we planned a multi-group study, investigating the importance of classical conditioning and verbal suggestion, and controlling for expectancies. Healthy volunteers were randomly assigned to six experimental groups: placebo conditioning, placebo suggestion, congruent placebo suggestion before conditioning, congruent placebo suggestion after conditioning, incongruent placebo suggestion before conditioning and incongruent placebo suggestion after conditioning, and two control groups: random placebo and natural history. Participants in all groups received electrocutaneous stimuli preceded by orange or blue colour stimuli and rated pain intensity and expected pain intensity. In congruent and incongruent groups both classical conditioning and verbal suggestions were used. Participants in these groups received information (either before or after conditioning) that one colour would precede more painful stimuli (control stimuli) and the other colour would precede less painful stimuli (placebo stimuli). In congruent groups this information was in line with the conditioning used, while in incongruent groups, it was the opposite. The placebo conditioning group received control and placebo stimuli paired with colour stimuli, while in the random placebo group there was no association between preceding colour stimuli and pain stimuli. Participants in the placebo suggestion and natural history groups received control stimuli only, regardless of the preceding colour stimuli. The poster presents the results of this study.

P3.03 Placebo by proxy: Parent's role in child's medical treatment

1. Efrat Czerniak. *University of British Columbia, Vancouver, BC, Canada.*
2. Katja Weimer. *Ulm University Medical Center, Ulm, Germany.*
3. Joe Kossowsky. *Harvard Medical School, Boston, MA, United States.*
4. Paul Enck. *University Hospital Tübingen, Tübingen, Germany.*
5. Tim Oberlander. *University of British Columbia, Vancouver, BC, Canada.*

Placebos may have an impact on an individual other than the person being treated. This complex phenomenon is known as "placebo by proxy" and may reflect an interaction between a patient's treatment and its effect on proxies such as parents, partners or caregivers. These complex reciprocal effects between placebo by proxy and placebo effects appear to occur when a proxy feels better and in turn behaves differently towards the patient who in turn experiences symptom improvement. Such symptom improvements may be due to placebo effects as they do not originate from the treatment but rather from contextual factors. Originally, the "placebo (effect) by proxy" concept as per Grelotti and Kaptchuk, describes the positive effects of a patient's treatment on persons in their surrounding such as family members or health care providers, who themselves feel better because the patient is being treated. Negative effects which can also occur when an ineffective treatment is given, suggesting the possibility of a "nocebo by proxy" when a proxy feels worse following a patient's treatment, has also yet to be systematically studied. While this has been reported in children and their parents in studies of temper tantrums, acupuncture, and preterm infants, to date there is limited understanding about how children respond to the proxy experience. This presentation will discuss the placebo/nocebo by proxy phenomena in children, review the current state of research, elucidate the nocebo by proxy concept and provide a broader discussion of the implications of these findings for placebo/nocebo research and clinical care.

P3.04 The placebo response in myasthenia gravis: A meta-analysis

1. Elisa Frisaldi. *University of Turin Medical School, Turin, Italy.*
2. Aziz Shaibani. *Nerve & Muscle Center, Houston, TX, United States.*
3. Jan Vollert. *1) Imperial College London, London, United Kingdom; 2) Center of Biomedicine and Medical Technology Mannheim, Mannheim, Germany.*
4. Bruno Ferrero. *University of Turin Medical School, Turin, Italy.*
5. Roberta Carrino. *University of Turin Medical School, Turin, Italy.*
6. Hayan Dhamer Ibraheem. *Nerve & Muscle Center, Houston, TX, United States.*
7. Lene Vase. *Aarhus University, Aarhus, Denmark.*
8. Fabrizio Benedetti. *1) University of Turin Medical Schoo, Turin, Italy; 2) Plateau Rosà Laboratories, Plateau Rosà, Italy/Switzerland.*

Background: This meta-analysis investigates the placebo response in generalized Myasthenia Gravis (MG) trials by means of Quantitative myasthenia gravis (QMG) scores.
Methods: PubMed, Scopus, Web of Science, Cochrane Controlled Trial Register, and EMBASE were searched. QMG scores, dropouts rate, adverse events (AEs), and AEs responsible for dropouts were examined, together with treatment moderators.
Results: The magnitude of placebo response showed an effect size of 0.24, which was significantly lower than 0.67 of the drug response. Furthermore, the forest plot revealed that, overall, active treatments did show a significantly higher impact on QMG scores compared to placebos.
Conclusions: Expressed as a change in the QMG scores, placebo and drug responses in MG trials are small and moderate, respectively. The lack of MG trials with pure placebo arm and no-treatment control arm made it impossible to disentangle improvements due to the real placebo psychological effect from other effects such as natural history and/or regression to the mean.

P3.05 Studying a possible placebo effect of an imaginary low-calorie diet

1. Valentin Panayotov. *Bulgarian National Sports Academy, Sofia, Bulgaria.*

Background: In recent years the prevalence of obesity has increased to the point that some authorities pinned the term "obesity epidemics". The most effective approach in addressing this problem proved to be that of combining energy intake control measures (via diet) with protocols for increasing energy expenditure (predominantly via low to medium intensity aerobic exercise).
Methods: In this experiment we studied the possible placebo effect of an isocaloric diet combined with regular physical activity on changes in body mass and fat tissue in healthy overweight or obese people. 14 adults of both sexes aged between 19 and 45 with Body Mass Index (BMI) > 27 participated in the study. They were randomly assigned to 2 groups – one experimental and one control. The subjects in the experimental group followed an isocaloric diet, but were told they were put on a calorie-deficient regimen. The subjects in the control group knew they were following an energy balanced diet. All participants exercised regularly (energy cost of approximately 750-900 kcal/week), which was taken into account in energy balance calculations. We measured post hoc within-group differences of body mass, percentage of fat tissue and BMI.
Results: All 3 variables reduced significantly their values in the experimental group: body mass 9.25 ± 5.26 kg, percentage of fat tissue 3.4 ± 0.97 % and BMI 2.88 ± 1.50.
Conclusions: Despite some methodological biases of the study construct, in our opinion there is evidence for the existence of a placebo effect on body parameters in the experimental group.

P3.06 Do placebo and nocebo effects generalize across somatosensory sensations?

1. LingLing Weng. *Leiden University, Leiden, Netherlands.*
2. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
3. Hjalte Andersen. *Aalborg University, Aalborg, Denmark.*
4. Antoinette van Laarhoven. *Leiden University, Leiden, Netherlands.*
5. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Abstract: Both pain and itch are associated with reduced quality of life, particularly when chronic. Through induction of positive expectations, they can be effectively reduced by placebo effects and through the induction of negative expectations they can be increased by nocebo effects. Generalization of nocebo effects from one sensation to another may play a role in comorbidity across conditions, whereas generalization of placebo effects across sensations can be beneficial in treatment. It is barely known whether placebo and nocebo effects generalize across physical sensations. The aim of the present study is to investigate whether placebo and nocebo effects can generalize from pain to a different type of pain and to itch, in healthy participants. Participants will be randomized to a placebo group or a nocebo group. First, in the learning phase, expectations will be induced by verbal suggestion ("heat pain intensity will decrease/increase") and conditioning (by decreasing/increasing heat stimulus intensity when a TENS device is supposedly switched on). To test generalization to pressure pain and itch, pressure stimuli and cowhage spicules will be applied with the TENS device supposedly on or off. Placebo and nocebo effects on heat pain are expected to generalize to pressure pain and cowhage-induced itch. This study could provide a novel perspective on the role that generalization may play in clinical treatments of patients with chronic somatosensory symptoms.

P3.07 The Treatment Expectation Questionnaire (TEX-Q) – A generic multidimensional scale measuring patients' treatment expectations

1. Meike Shedden-Mora. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
2. Jannis Alberts. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
3. Keith Petrie. *University of Auckland, Auckland, New Zealand.*
4. Johannes Laferton. *Philipps-University Marburg, Marburg, Germany.*
5. Yvonne Nestoriuc. *Helmut-Schmidt University, Hamburg, Germany.*
6. Bernd Löwe. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: While patient expectations are a relevant predictor for health outcomes and a central mechanism of placebo and nocebo effects, the lack of conceptual clarity and generic assessment tools impedes an integrated understanding of expectations across treatments. The aim of this study was to develop and validate a generic, multidimensional scale measuring patient expectations of medical and psychological treatments.
Methods: The Treatment Expectation Questionnaire (TEX-Q) was developed based on the integrative model of expectations (Laferton, Kube, Salzmann, Auer & Shedden-Mora, 2017). Its multidimensional structure assesses three expectation constructs (probabilistic expectations, value-based expectations, process expectations) across three outcome domains (benefit, adverse events, impact). The development steps include systematic literature review, expert ratings, and cognitive patient interviews. Item characteristics, factor structure, internal consistency and construct validity are examined in 300 individuals prior to receiving different medical and psychological treatments.
Results: After systematically reviewing the literature, content validity of 78 preliminary items was rated by 13 experts according to item fit, comprehensibility, and clarity. The best 53 items where evaluated for comprehensibility, acceptability, phrasing preference and consistence of understanding by interviewing 11 patients prior to treatment using the "think aloud"-technique. Psychometric properties of a 35-item pilot-version developed from this analysis and the validated final version of the TEX-Q will be presented.
Conclusions: The TEX-Q is a generic, multidimensional self-report scale measuring patient expectations of medical and psychological treatments. Overcoming the constraints of ad-hoc scales and disease-specific assessment methods for expectations, it allows comparing the impact of expectations across different conditions and treatments.

P3.08 Nocebo hyperalgesia: The interplay between classical conditioning and verbal suggestions. Results from a comprehensive, multi-group study

1. Dominika Farley. *Jagiellonian University, Krakow, Poland.*
2. Wacław Adamczyk. *1) Jagiellonian University, Krakow, Poland; 2) The Jerzy Kukuczka Academy of Physical Education, Krakow, Poland.*
3. Karolina Wiercioch-Kuzianik. *Jagiellonian University, Krakow, Poland.*
4. Elżbieta Bajcar. *Jagiellonian University, Krakow, Poland.*
5. Jakub Nastaj. *Jagiellonian University, Krakow, Poland.*
6. Ewa Buglewicz. *Jagiellonian University, Krakow, Poland.*
7. Helena Bieniek. *Jagiellonian University, Krakow, Poland.*
8. Przemysław Bąbel. *Jagiellonian University, Krakow, Poland.*

The debate on the role of classical conditioning versus expectancy in induction of placebo effects has still not been fully resolved for at least two reasons. First, no previous study designs included all possible combinations of classical conditioning and verbal suggestions. Second, in most of the previous studies expectancy was not measured. Therefore, we aimed to thoroughly investigate which mechanism of nocebo hyperalgesia would prove superior to the other, the classical conditioning or verbal suggestions, while controlling for expectancies. Healthy participants were randomly assigned to six experimental and two control groups: random nocebo and natural history. Experimental groups included: nocebo conditioning, nocebo suggestion, congruent nocebo suggestion after conditioning, congruent nocebo suggestion before conditioning, incongruent nocebo suggestion after conditioning, incongruent nocebo suggestion before conditioning. Participants in all groups received electrocutaneous stimuli preceded by either orange or blue colour stimuli and rated pain intensity and expected pain intensity. In experimental groups

(except the nocebo suggestion group) colours were paired with two painful stimuli (nocebo or control). In congruent and incongruent groups both conditioning and verbal suggestions were used. Participants in those groups received information about the association between colours and painful stimuli consistent ('congruent' groups) or inconsistent ('incongruent' groups) with the conditioning applied. The information was given either before or after the conditioning. The nocebo conditioning group did not receive any additional information. Participants in the nocebo suggestion and natural history groups received control stimuli only. The poster presents the results of this study.

P3.09 An educational placebo effect intervention reduces the likelihood of athletes using performance enhancing drugs

1. Philip Hurst. *Canterbury Christ Church University, Canterbury, United Kingdom.*
2. Abby Foad. *Canterbury Christ Church University, Canterbury, United Kingdom.*
3. Damian Coleman. *Canterbury Christ Church University, Canterbury, United Kingdom.*
4. Chris Beedie. *University of Kent, Kent, United Kingdom.*

Background: Recent research has reported that placebo effects can significantly improve sport performance. However, while research has generated knowledge about placebo effects on sport performance, there is limited research devoted to how this can support applied practice. In light of this, it has been suggested that placebo effect research could be harnessed and used as a tool to prevent drug use in sport. The aim of this study was to investigate the effect of an educational placebo effect intervention on an athlete's decision to use performance enhancing drugs.
Method: Elite athletes (N=169; 56% male, age=18.2±0.4yrs) attended a one-hour educational placebo effect intervention. The session was delivered by a facilitator using Power-point in a university classroom. The session introduced participants to placebo effects, the role expectations and prior experiences can have on the effectiveness of performance enhancing drugs and placebo effect research on sport performance. Throughout the session, participants were encouraged to critically examine the need to use performance enhancing drugs and to consider the role of placebo effects. Participants completed measures of performance enhancing drug use pre and one-week post intervention.
Results : Data indicated that participants were less likely to use performance enhancing drugs following the intervention ($p<.001$, $d=0.42$).
Conclusion: The results of this study provide novel evidence to suggest that an educational placebo effect intervention may be an effective in preventing drug use in sport. Future research should aim to harness knowledge of placebo effects to prevent other drug use behaviours.

P3.10 Faces and masks of the placebo effect: Open-label placebos and the mind-body problem

1. Ryan van Nood. *Purdue University, West Lafayette, IN, United States.*

Some modern reconceptualizations of the placebo effect frame the "placebo puzzle" as a matter of accounting for how meaning and physiology touch (Ongaro and Ward 2017; Miller and Colloca 2010). Most modern strategies for approaching conceptual issues regarding the placebo effect shy away from this problem and emphasize treatment context. I argue that two aims identified in the field's consensus paper, namely, the translation of placebo research into clinical practice and the exploration of open-label placebos (OLP) (Evers et al. 2018), are only partially approached by emphasizing context effects.
The meaning-physiology problem is not of mere abstract philosophical interest but ramifies for how clinicians, prone to misunderstanding or underestimating the frequency of placebo effects in practice (Fent 2011; Hardman 2018), may better spot and exploit the phenomenon. Furthermore, a convincing and clear approach to the problem may go toward more robustly informing patients receiving OLP's. My approach endeavors to collapse the gap in the meaning-physiology problem by invoking philosophical approaches together with the insights of scientists in disciplines neighboring placebo studies. At the level of everyday human interaction, spontaneous physiognomic responses that display and express experiences of meaning and which may be continuous with certain placebic responses may be seen as manifesting both aspects of the meaning-physiology dichotomy in those gestural phenomena. This ordinary language approach may fruitfully converse with more abstract theoretical constructs recently proposed to account for OLP effects, including embodied cognition (Colloca and Howick 2018) and prediction and error processing (Kaptchuk 2018).

P3.11 Animal-assisted placebo intervention: Can the presence of a dog affect placebo analgesia?

1. Cora Wagner. *University of Basel, Basel, Switzerland.*

Background: An increased interest of animal-assisted interventions (AAI) within clinical practice can be observed, even though it is still not entirely clear how the presence of an animal contributes to the outcome of a treatment. One theory maintains that the presence of an animal influences the relationship between health-provider and patient, which then in turn affects the outcome of the treatment. To investigate this theory, this study will combine AAI with a placebo intervention, as placebo interventions offer the basic form of intervention working through relationship and expectancy.
Methods: The effects of the presence of a dog will be assessed with a standardized experimental heat pain paradigm (TSA-II) in a randomized controlled trial in healthy participants (N=128). After a baseline measurements of heat pain threshold and tolerance, participants will be randomly assigned to one of the following four conditions: a) analgesia-expectation, no dog present, b) analgesia-expectation, dog present, c) no-expectation, no dog present and d) no-expectation, dog present.

The dog will be introduced after randomization. Expectancy will be induced by a deceptive cream which is said to helps against pain. Afterwards, post-treatment measurements will be conducted and participants fill in questionnaires about their perceptions of the experimenter.
Results: The results are still in process. Primary outcomes are the comparison of heat pain tolerance and the perception of the experimenter.
Conclusions: This is the first study combining AAI and placebo intervention. The results will help to better understand if animal-assisted interventions also operate through similar mechanisms as placebo interventions, such as relationship.

P3.12 Explaining the placebo effect: Does 'Pavlov' ring a bell?

1. Rosanne Smits. *Leiden University, Leiden, Netherlands.*
2. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
3. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Expectations play a significant role in steering the placebo effect. One of the most important expectations about the placebo effect is based on the notion that individuals have of the placebo effect itself. Because there is a large variability in how placebo effects are explained in (clinical) trials, it remains unclear how the placebo effect is explained best. This study will compare the different types of explanations based on underlying placebo mechanisms from placebo studies and investigate how this information is received by healthy controls.
Methods: 200 healthy controls will fill out a placebo questionnaire online, consisting of questions about placebo knowledge, attitude and preference for placebo explanations. Placebo explanations are based on the different mechanisms steering the placebo effect (e.g. expectations, clinical conditioning, clinician-patient communication). Demographic factors (e.g. sex, age, and education), personality factors, and medication use will be taken into account as potential predictors for the outcomes of the placebo questionnaire.
Results: Expected in July 2019.
Conclusion: This is the first study that provides insight in how placebo information is received by healthy controls and what kind of explanations about the placebo effect is preferred. With these results, we aim to contribute in developing guidelines for placebo instructions applicable for clinical practice.

P3.13 Counterconditioning as treatment for chronic pain symptoms: A study design

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2. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
3. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
4. Niels Chavannes. *Leiden University Medical Center, Leiden, Netherlands.*
5. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Treatment opportunities for chronic physical symptoms are currently limited due to incomplete knowledge on the underlying mechanisms. It is suggested that physical symptoms sensitize due to negative learning experiences (e.g., previous treatment experiences) leading to nocebo effects (i.e., adverse outcomes not attributable to an active treatment). Nocebo effects can be induced by classical conditioning. Furthermore, fear and evaluative conditioning paradigms have shown that conditioned effects can be changed by counterconditioning. This suggests counterconditioning could potentially be a promising method for reducing conditioned nocebo effects including sensitized physical symptoms in patients, such as in fibromyalgia. In the current study, we aim to investigate the effects of an open-label counterconditioning intervention on pain in patients with fibromyalgia. The intervention group will participate in a 6-week intervention using counterconditioning in the laboratory and at home. In the control group, we will use a sham counterconditioning paradigm, combined with neutral homework exercises. The primary outcome is experimentally-induced pressure pain at post-intervention; secondary outcomes include these effects at follow-up (3 and 6 months post-treatment) and generalizability of the effects to clinical pain symptoms. Additionally, the possible influence of individual characteristics and patients' expectations towards the intervention on the outcome will be explored. This study design contributes to a better understanding of mechanisms involved in sensitization and desensitization of chronic symptoms and offers an innovative treatment approach.

P3.14 Does social status matter when it comes to learning pain from others? A study on observational learning in inducing placebo analgesia

1. Helena Bieniek. *Jagiellonian University, Kraków, Poland.*
2. Przemysław Bąbel. *Jagiellonian University, Kraków, Poland.*

Research indicates that pain behaviour can be learned not only through classical and operant conditioning but also through observational learning. Many factors influence the process of learning about pain by observing the reactions of others, or the characteristics of the model. There are more and more studies researching those factors but the influence of some of them remains unexplored. Thus, the study was aimed at investigating the role of one of the still unexamined factors: the perceived social status of the model in inducing placebo analgesia through observational learning.
Healthy volunteers were randomly assigned to three groups: 1) professor as a model, 2) janitor as a model and 3) control group. Participants in the two experimental groups watched a video with the same person as a model, presented as a professor (higher social status) in group 1 and as a janitor in group 2 (lower social status). In each group, half of participants watched the video where the model rated 'blue' stimuli higher and 'orange' stimuli lower, while the other half of participants watched the video where

the model rated 'orange' stimuli higher and 'blue' stimuli lower. In the control group no video was showed. Then all groups experienced 16 pain stimuli of the same intensity preceded by the blue and orange stimuli and rated their intensity. The poster presents the results of the study.

P3.15 Evoking placebo and nocebo effects on mental fatigue

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2. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
3. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Several studies in sports psychology have demonstrated placebo or nocebo effects on muscle fatigue. It is unknown whether this also holds for other kinds of fatigue, such as mental fatigue. Mental fatigue is a common feature of chronic fatigue and leads to reduced quality of life and productivity in patients as well as healthy individuals. It has been shown to be affected by conditioning, making it a valuable potential target.
Methods: Participants performed a two-back task designed to induce mental fatigue in 4 sessions. The first session served as baseline. In sessions 2, 3 and 4, participants received a saline nasal spray (placebo) described as a stimulant (placebo group), a sedative (nocebo group) or a placebo (control group). In the second and third sessions, experimental groups were conditioned by performing a shorter and easier version of the task (placebo group) or a longer and more difficult version (nocebo group). In session 4, the test session, all participants performed the same, baseline version of the task.
Results: Results from sessions 2 and 3 suggest the manipulation was more effective for the placebo group than for the nocebo group. Fatigue scores did not differ significantly between groups in session 4. Control for session 1 fatigue did not affect the results.
Conclusions: No placebo or nocebo effects on mental fatigue were demonstrated. Results may have been influenced by practice effects and a sense of relief. Future methods should control for these factors.

P3.16 Shifting the balance: The role of context in shaping metacontrol policies.

1. Roel van Dooren. *Leiden University, Leiden, Netherlands.*
2. Roberta Sellaro. *Leiden University, Leiden, Netherlands.*
3. Bernhard Hommel. *Leiden University, Leiden, Netherlands.*

According to the Metacontrol State Model, human behavior can be described in terms of two counteracting systems: one promoting persistence, the other promoting flexibility. The ability to shift the balance between these two opposing systems is referred to as metacontrol. Within recent years, an abundance of literature has demonstrated that metacontrol states are relatively flexible and can change as a function of both long-term (e.g., genetic profile, cultural background) and short-term factors (e.g., mood, meditation). The aim of the current project was to extend previous observations by investigating whether such states, once established, can be bound to environmental cues. In order to test this prediction, we designed four experiments (N > 55 for each study), each comprising an induction- and a test phase. Within the induction phase, participants were led to believe that stimulus processing, as measured in terms of performance on conflict tasks (e.g., Simon task), was modulated by the presence of contextual information. Herafter, participants were presented with a test phase, which was designed to test whether the mere presentation of previously shown cues allowed for a re-activation of the associated metacontrol state. Three out of four experiments provided converging evidence, showing that metacontrol states can be bound to contextual information. More specifically, the results indicated that the level of experienced conflict in the test phase was modulated by the associations formed within the induction phase. These results highlight the importance of contextual cues in shifting the persistence-flexibility balance towards one or the other cognitive control dimension.

P3.17 Nocebo effect in experimental paraesthesia

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2. Piotr Wodarski. *Silesian University of Technology, Gliwice, Poland.*
3. Aleksandra Budzisz. *The Jerzy Kukuczka Academy of Physical Education, Katowice, Poland.*
4. Andrzej Bieniek. *Silesian University of Technology, Gliwice, Poland.*
5. Tibor Szikszay. *University of Lübeck, Lübeck, Germany.*
6. Kerstin Luedtke. *1) University of Lübeck, Lübeck, Germany; 2) The Jerzy Kukuczka Academy of Physical Education, Katowice, Poland.*

Mechanisms of nocebo hyperalgesia are relatively well understood. For example, it has been demonstrated that classical conditioning or verbal suggestion of increased pain intensity can elicit a strong nocebo effect. Little is known about the nocebo effect in other bodily symptoms such as paraesthesia. This neurological symptom described as a tingling sensation is often reported by patients with dysfunctions in the peripheral or central nervous system. In this study, for the first time, we aim to induce paraesthesia experimentally and test the effect of nocebo manipulation on paraesthesia and investigate if this manipulation generalizes to altered pain perception. Healthy volunteers were randomly allocated into one of two groups. They were exposed to a series of ischemic stimuli delivered by an electronic sphygmomanometer to their non-dominant arm. In the pretest and posttest phase -the same for each subject in both groups- they received a series of two identical stimuli (80mmHG). Pain and paraesthesia were measured continuously by two computerized Visual Analogue Scales. Physiological correlates of bodily symptoms were measured by skin conductance. After the pretest phase, subjects in the experimental group received a nocebo cream and verbal suggestion on its effectiveness (tingling intensification). Then, they underwent a conditioning procedure (surreptitious increase of pressure) to make them believe that tingling is enhanced. In the control group, subjects were exposed to the same stimuli without

cream and no verbal suggestion was applied. Results of this experiment extend our understanding of the mechanisms of the nocebo effect and will be presented on the poster.

P3.18 Discontinuing antidepressants and antipsychotics: An online survey of consumers' experiences and expectations

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2. Anika Schulze. *Helmut-Schmidt University, Hamburg, Germany.*
3. Tony Kendrick. *University of Southampton, Southampton, United Kingdom.*
4. Tania Lincoln. *University of Hamburg, Hamburg, Germany.*

Background: Long-term intake of antidepressants and antipsychotics is rising, while knowledge about patients' perspectives on continued use and experiences with discontinuation is largely missing.
Methods: A cross-sectional online survey was conducted to determine and compare consumer experiences (n=474) with discontinuing antidepressants and antipsychotics. Participants included 338 adults taking antidepressants and 136 adults taking antipsychotics. Medication discontinuation experiences and expectations, illness and medication characteristics were assessed and compared between medication type and intake duration.
Results: Most participants (78.1%) attempted to discontinue medication one or more times (M = 2.00, SD = 1.70). Prior discontinuation attempts where rated rather negatively (0 very negative – 10 very positive, M = 3.17, SD = 2.88). Nearly half of the participants (45.3%) experienced severe discontinuation symptoms (0 none – 10 very severe, M = 5.10, SD = 3.60). Antidepressant consumers reported more severe discontinuation symptoms during past discontinuation attempts than antipsychotic consumers (t368 = 3.14, Padj = .008). Antipsychotic consumers demonstrated a greater wish to discontinue current medication (t265.65 = -6.13, Padj = .004), resulting from negative expectations about long-term effects (Chi21, 241 = 42.60, Padj = .01), higher expectations of side-effects of medication (Chi21, 241 = 32.52, Padj = .01) and impression that medication was never needed (Chi21, 241 = 8.12, Padj = .04), than antidepressant consumers.
Conclusions: Negative discontinuation experiences and associated negative expectations are highly prevalent and show consumers struggles during medication discontinuation. Yet, the systematic analysis of predictors and mechanisms with regard to expectation management remains untapped.

P3.19 The influences of observational learning on pain perception and its neural correlates

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2. Nandini Raghuraman. *University of Maryland, Baltimore, MD, United States.*
3. Lieven Schenk. *University of Maryland, Baltimore, MD, United States.*
4. Andrew Furman. *University of Maryland, Baltimore, MD, United States.*
5. Christina Tricou. *University of Maryland, Baltimore, MD, United States.*
6. David Semiowicz. *University of Maryland, Baltimore, MD, United States.*
7. Luana Colloca. *University of Maryland, Baltimore, MD, United States.*

Humans are social beings and often learn about their environment by observing others. A growing number of research has supported that observational learning does induce placebo hypoalgesia, and expectation is a crux for this analgesia. Here we plan to use electroencephalography (EEG) to provide a neurophysiological basis for observationally-induced placebo hypoalgesia.
31 participants completed observation and test phase during EEG acquisitions. Volunteers viewed pictures of a demonstrator experiencing heat pain on his forearm. Two creams described as treatment and control were applied and linked to different color cues (blue and green). The demonstrator showed painful and non-painful facial expressions for control and treatment cues, respectively. Subsequently, participants received the same creams and a series of heat stimuli of the same intensity for both treatment and control cues. Pain intensity ratings of placebo and control trials were recorded to determine the observationally-induced placebo hypoalgesia.
Behavioral pain intensity ratings of placebo trials were lower than control trials ($F1,23=5.70$, $p=0.026$). Neurophysiological measurements indicated placebo anticipatory cues elicited smaller P300 than control cues ($F1,24=4.67$, $p=0.041$). The heat pain-induced P2 was also smaller for placebo than control condition ($F1,27=5.41$, $p=0.028$). The amplitude of peak alpha frequency (APAF) during resting state was negatively correlated with placebo hypoalgesia in electrodes P3 ($r =-0.591$, $p=0.0004$), PO3 ($r=-0.631$, $p=0.000142$) and C1($r=-0.607$, $p=0.000298$).
Placebo anticipatory cues inhibit frontal attention mechanism while placebo hypoalgesia is associated with decreased neutral activities encoding pain intensity. Neurophysiological measurements APAF in resting state may serve as a predictor of the magnitude of observationally-induced placebo hypoalgesia.

P3.20 Pain reporting accuracy and the placebo response

1. Liat Honigman. *University of Haifa, Haifa, Israel.*
2. Israa Asaad. *University of Haifa, Haifa, Israel.*
3. Roi Treister. *University of Haifa, Haifa, Israel.*

Background: Good clinical care relies on precise evaluation of patients' conditions. We have recently developed the Focused Analgesia Selection Task (FAST), a method aimed to assess pain-reporting accuracy. Preliminary results suggest that pain reporting accuracy relates to the placebo response. The aim of this study is to further characterize this relation in healthy population using experimental placebo manipulation.

Methods: Seventy-five healthy subjects (18-53 YO, 39 F) completed the FAST and a placebo manipulation. The FAST is based on recording subjects' pain reports in response to repeated administration of thermal noxious stimuli of various blinded intensities. Performance in the FAST is based on relations between stimuli intensities and pain reports, quantified by R2, Inter-class-correlations (ICC), and coefficient of variance (CoV). The placebo response was assessed based one-minute-long supra-threshold heat-stimuli, at fixed temperatures of 44, 46.5, and 48°C delivered before and after receiving a placebo pill. The placebo response (Δ) was calculated as the difference between the mean reported numerical pain scores.
Results: All pain intensities significantly responded to the placebo manipulation. FAST R2 trended to negatively correlated with the placebo effect produced by the severe pain (Spearman's r= - 0.203, P=0.08). When splitting the group by R2 median, focusing only on the low accuracy group (low R2), this association became significant (Spearman's r= -0.447, P=0.025).
Conclusions: This is an ongoing study. Preliminary results partly support that accuracy of pain reports is associated with the placebo response, such that the less accurate the person is, the higher the placebo response is.

P3.21 Can training aimed to increase pain-reporting accuracy diminish the placebo response?

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2. Liat Honigman. *University of Haifa, Haifa, Israel.*
3. Israa Asaad. *University of Haifa, Haifa, Israel.*
4. Roi Treister. *University of Haifa, Haifa, Israel.*

Background: In previous studies, we developed the Focused Analgesia Selection Test (FAST), a method to assess pain-reporting accuracy and the Evoked Pain Training (EPT), aimed to improve pain-reporting accuracy. The objectives of the current project are to determine if training (1) increases pain reporting accuracy and (2) reduces the placebo response.
Methods: This is a two-stage, experimental-pain study in healthy subjects. After baseline assessment (visit #1), subjects are randomly assigned to three in-clinic visits of either EPT or control. Thereafter, all subjects enter an experimental cross-over study design (second study stage) comprised of two in-clinic visits (visits # 5 and 6) in which the effects of one-of two pills (either Ibuprofen 400mg or identical sugar pill) are tested on battery of experimental pain tests. The calculated changes between the pre-treatment and post-treatment assessments serve as model for drug/placebo effects. Treatment difference (between drug and placebo) is calculated by subtracting the "change in placebo" from the "change in drug".
Results: Until now, 37 subjects completed the entire study. Out of the 15 subjects who completed EPT, 86% exhibited improvement in pain reporting accuracy ($p<0.001$). Pain reporting accuracy (R2 linear) significantly correlated with the placebo response, as assessed by the heat-pain-threshold model (r= -0.312, P=0.047, spearman's correlation). Other pain models showed similar, but not yet significant trends.
Conclusion: Our preliminary results supports that EPT does improve pain-reporting accuracy, and perhaps also reduces the placebo response. Data collection is ongoing, with a target of 100 subject, which will be achieved at spring 2019.

P3.22 Patient–clinician relationship as an “add-on” to drugs? Empathic clinician visits impacts the success of the perioperative pain therapy (RCT)

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2. Christian Roder. *Schoen Clinic Hamburg Eilbek, Hamburg, Germany.*
3. Christian Zöllner. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
4. Florian Krug. *Schoen Clinic Hamburg Eilbek, Hamburg, Germany.*
5. Regine Klinger. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: The patient–clinician relationship plays a crucial role within pain treatment. However, the question about its influence and clinical relevance to the acute pain therapy has been neglected so far. Experimental studies show, that “open medication of analgesics” is superior to “hidden medication”. The aim of our study was to investigate in a clinical postoperative setting, if the efficacy of analgesics can be improved through empathic clinician interactions. We hypothesized that the patients, who have empathic clinician visits perceive pain treatment as more successful.
Methods: The results are partial results of the DFG-Study KL 1350/3-1 within the FOR 1328 transregional DFGResearch Unit. Patients (n = 32) who received a knee endoprothesis were included. The patients were distributed randomly to either the treatment group which had increased contact to the physician or the control group. The preoperative expectations with respect to treatment success of the pain medication and the actual treatment success were assessed with the modified Stanford Expectations of Treatment Scale (SETS).
Results: A significant interaction between the success estimation and the actual treatment success and the groups was shown ($F(1,30) = 4.69$, $p = .038$, $d = 0.63$). Both groups had the same expectations with respect to effectiveness of their pain medication before surgery. However, the group with empathic visits evaluated their treatment as more successful at discharge.
Conclusions: The results show, that the patient–clinician relationship is a crucial component of the pain treatment in a clinical postoperative setting. It enhances subjective estimation of the medical treatment success.

P3.23 The role of nocebo effects in identifying patients at risk for pain sensitization in fibromyalgia: A study design

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2. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
3. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
4. Mattijs Numans. *Leiden University Medical Center, Leiden, Netherlands.*
5. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Physical symptoms (e.g., pain) may become chronic due to sensitization processes, such as by amplification and generalization of symptoms. Sensitization could result from negative learning experiences induced by classical conditioning and verbal suggestions, leading to nocebo effects, i.e., adverse outcomes not attributable to an active treatment. Especially in patients with persistent physical symptoms, who frequently experience adverse treatment outcomes in daily life, nocebo effects could play a role in pain progression. With this prospective study, we will investigate whether individual differences in susceptibility to nocebo effects in patients with fibromyalgia predict pain progression at one year and we explore differences in nocebo learning processes between patients and healthy controls.
Methods: In the lab, nocebo effects to pressure stimuli will be induced via a conditioning paradigm with verbal suggestions, followed by an extinction procedure to reduce these effects. Individual susceptibility to nocebo effects (primary) and extinction (secondary) will be examined as predictors of change at one-year follow-up in self-reported clinical pain levels (primary outcome), as well as changes in self-reported fibromyalgia symptomatology, and daily pain fluctuations via Experience Sampling Method (secondary outcomes). In an intertwined study, nocebo learning processes and the stability thereof is explored in a subsample of patients and matched healthy controls via lab experiments at baseline and after one year.
Discussion: Examining the role of nocebo effects offers insight into the mechanisms of sensitization of physical symptoms and provides knowledge to enable early identification of patients at risk for adverse symptom prognosis.

P3.24 Neurophysiological underpinnings of nocebo hyperalgesia: Current findings and future directions.

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3. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
4. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Nocebo hyperalgesia is an adverse effect on pain that is not physiologically attributable to health conditions or active treatments. Nocebo effects can influence the results of placebo-controlled clinical trials, are thought to contribute to the chronification of pain symptoms, and can affect the tolerability of medical treatments. A better understanding of the neurophysiological and learning mechanisms underlying nocebo effects could be an important step towards minimizing or counteracting these effects. This review aims to comprehensively summarize the currently known neurophysiological correlates of nocebo hyperalgesia. All studies that experimentally induced nocebo hyperalgesia in humans were identified by searching PubMed and PsychInfo. Studies that did not utilize at least one physiological measure were excluded. The final selection included 20 articles. Functional imaging studies suggest an involvement of areas related to pain, learning, and cognitive-affective processes. These include spinal cord areas, the periaqueductal gray, thalamus, basal ganglia, insula, amygdala, hippocampus, as well as areas within the prefrontal and cingulate cortices. Electroencephalography studies also point to a potential involvement of cognitive-affective processes, through findings related to low alpha brain activity, as well as the N2/P2 and stimulus-preceding negativity components. Studies that included neurochemical measures have indicated increased cortisol levels, as well as a deactivation of μ-opioid and dopaminergic neurotransmission in specific subcortical systems. These findings are discussed in relation to established findings in the fields of learning research, as neurophysiological components of nocebo hyperalgesia seem to overlap with those involved in learning and expectation processes.

P3.25 Novel race effects on expectancy-induced analgesia in temporomandibular joint disorder

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4. Sharon Thomas. *University of Maryland, Baltimore, MD, United States.*
5. Nicole Corsi. *University of Maryland, Baltimore, MD, United States.*
6. Lieven Schenk. *University of Maryland, Baltimore, MD, United States.*
7. Ria Patel. *University of Maryland, Baltimore, MD, United States.*
8. Maxie Blasini. *University of Maryland, Baltimore, MD, United States.*
9. Jane Phillips. *University of Maryland, Baltimore, MD, United States.*
10. Luana Colloca. *University of Maryland, Baltimore, MD, United States.*

Background: Temporomandibular Join Disorder (TMD) is the 2nd most common cause of chronic orofacial pain, affecting >20% of adults. Differences in pain sensitivity and treatment effectiveness continually pose a challenge to chronic pain treatment. Studies show that ethnic minorities experience more pain, less pain relief and conditioned pain modulation than Whites. Racial differences in endogenous pain modulation (EPM) may influence responses to treatment. Expectancy-Induced Analgesia (EIA) is a form of EPM that depends on the activation of descending pain inhibitory systems. Here we examine the effect of race on pain sensitivity and EIA in TMD patients and healthy controls.
Methods: 152 TMD, 338 healthy controls were recruited and race was measured via self-report. Baseline pain sensitivity measures were assessed to identify two levels of pain intensity for the conditioning paradigm used to reinforce expectation. EIA

was established through a behavioral pain modulation task in which participants underwent a 2-trial conditioning paradigm to learn to associate visual cues with high and low-pain heat stimulations. A final test-session was performed to determine the levels of EIA to equal levels of pain.
Results: Race influenced pain tolerance and EIA in both healthy and TMD participants. Whites showed significantly higher pain tolerance than Asians (p=0.001) and African Americans (p=0.018) in healthy participants and significantly higher pain tolerance levels than African Americans (p<0.001) but not Asians in the TMD cohort. Asians showed a larger EIA than African-Americans (p=0.038) and Whites (p=0.001) in healthy controls and significantly higher EIA than African Americans (p=0.019) but not whites in the TMD cohort. Pearson correlation showed negative correlations between pain tolerance and EIA in the races.
Conclusions: These findings suggest, for the first time, that race may affect EIA and pain sensitivity in TMD. Further research with larger databases is needed to fully understand how ethnicity, race and cultural elements affect the formation of placebo effects.

P3.26 Association of information disclosure on placebo control with blinding and trial outcomes - A case study of participant information leaflets of randomised placebo-controlled trials of acupuncture

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2. Jiyoon Won. *Kyung Hee University, Seoul, South Korea.*
3. Hyangsook Lee. *Kyung Hee University, Seoul, South Korea.*

Background: There have been concerns regarding complete information on placebo control in participant information leaflets (PILs) of a clinical trial may breach blinding or induce nocebo responses thus modulate trial outcomes. Taking an example of acupuncture studies, we aimed to examine what participants are told about placebo controls in randomised, placebo-controlled trials, and how it may affect blinding and trial outcomes.
Methods: PILs of randomised, placebo-controlled trials of acupuncture published in recent 10 years were obtained from authors. They were subjected to content analysis and categorised based on degree of information disclosure on placebo. Blinding index (BI) was calculated and its association with different information disclosure was examined. The impact of information disclosure on primary outcomes was estimated using a random effects model.
Results: In 65 obtained PILs, approximately 57% of them fully disclosed placebo control, i.e. full disclosure, while the others gave deceptive or no information on placebo, i.e. no disclosure. Placebo groups in the studies with no disclosure tended to make more opposite guesses on the type of received intervention than those with full disclosure (BI −0.21 vs. −0.16; p = 0.38). Studies with no disclosure significantly favoured acupuncture than those with full disclosure (standardised mean difference − 0.43 vs. −0.12; p = 0.03).
Conclusions: Pre-trial suggestions on placebos may influence participant blinding and study outcomes by possibly modulating patient expectation. As we have few empirical findings on this issue, future studies are needed to determine whether the present findings are relevant to other medical disciplines.

P3.27 Blinding in physical intervention research: A framework for sham development

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2. Julie Walters. *University of South Australia, Adelaide, SA, Australia.*
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4. Marie Williams. *University of South Australia, Adelaide, SA, Australia.*
5. Maureen McEvoy. *University of South Australia, Adelaide, SA, Australia.*

Background: While there are internationally recommended processes for designing and reporting clinical trials of various designs, no such recognised processes exist for developing sham protocols. Based on published guidance for developing health research reporting guidelines, we prospectively designed a four-stage framework for sham development for physical interventions that can blind both participants and therapists. We tested the framework using the model of dry needling.
Methods: Stage 1 involved systematic reviews of dry needling trials to synthesise evidence on previously used blinding strategies. Stage 2 involved Delphi surveying experts in research methodology, dry needling, and deceptive/hypnotic techniques (including magic) on how to enhance sham believability. Stage 3 was a workshop with invited experts where information from Stages 1 and 2 was synthesised and tested in a series of practical experiments. Stage 4 was a randomised experiment that empirically evaluated the final sham protocol.
Results: Stage 1 revealed that a variety of blinding strategies had been used to blind participants, but no trials attempted to blind therapists. In Stages 2 and 3, experts agreed that cognitive/multisensory cues beyond direct tactile simulation are important for effective blinding. In Stage 4, proportions of correct guesses about intervention allocation (active or sham) were no different from random chance (50%) for participants (48.9%; p=0.916) or therapists (40.8%; p=0.055), indicating effective blinding.
Conclusions: Our framework led to the first sham dry needling protocol that successfully blinded participants and therapists simultaneously. These studies yielded important discoveries about factors that contribute to effective blinding of therapist administered physical interventions.

P3.28 Nocebo effects on cowhage-evoked itch: The role of conditioning and observational learning

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3. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
4. Antoinette van Laarhoven. *Leiden University, Leiden, Netherlands.*
5. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Nocebo effects on itch are putatively caused by negative outcome expectancies. Expectancies can be learned, and previous experiments have modeled this learning process for itch with verbal suggestion and conditioning. Observational learning is also believed to induce expectancies. For example, patients who observe treatment outcomes of fellow patients in support groups or online may develop negative outcome expectancies based on these observations. However, observational learning of nocebo effects on itch has not been assessed. Furthermore, nocebo research using models of itch that more closely resemble the pruritic symptoms which arise in chronic dermatological conditions than the commonly used pruritic stimuli (e.g. histamine) is warranted. Cowhage may evoke itch through peripheral mechanisms that resemble chronic pruritic symptoms in atopic dermatitis. In this experimental study, we aim to induce nocebo effects on cowhage-evoked itch, using either a neutral (control) or reinforced with increased itch (nocebo) inert cream applied prior to cowhage as the nocebo, and compare the efficacy of conditioning and observational learning as methods for inducing nocebo effects on itch. Using a 3x2 mixed model design, expectancy induction methods will vary between 3 groups: 1) conditioning, 2) observational learning through a video of the itch conditioning procedure, and 3) sham conditioning. Nocebo effects will be measured by comparing itch between neutral and reinforced trials within groups. Preliminary results will be presented. These results will provide new insights into the effects of both observational learning and conditioning on cowhage-evoked itch, utilizing a model of itch with greater clinical transferability than previous studies.

P3.29 Open/hidden administration of exposure training in spider phobia

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In order to gain deeper understanding of the mechanisms behind psychotherapy, this study assessed the impact of treatment outcome expectations on exposure training in participants with spider fear. For this purpose we implemented a study design from placebo research. Adult participants with spider fear were randomly allocated to open and hidden administration of exposure training (Öst, 2012). The impact of the administration condition (open vs. hidden) on subjective spider fear was measured by a questionnaire (FAS, Rinck et al. 2002). Secondary outcomes were anxiety and treatment expectation, both measured by questionnaires administered before and after the exposure training. Heart rate, heart rate variability and skin conductance were continuously assessed before, during and after the exposure training.
Results of the study will be presented at the conference.

P3.30 The role of expectations in conditioned pain modulation

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2. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
3. Antoinette van Laarhoven. *Leiden University, Leiden, Netherlands.*
4. Andrea Evers. *Leiden University, Netherlands.*

Background: Conditioned Pain Modulation (CPM) dysfunction has been proposed to be an important mechanism in chronic pain. The present study aimed to investigate the role of expectations in the CPM effect. Potential sex differences in these effects were also examined.
Methods: In total 114 (57 of each sex) healthy participants were randomly assigned over three groups in which different expectations were induced regarding the application of a second stimulus on the first stimulus in a CPM paradigm: 1) an analgesia group, 2) a hyperalgesia group, and 3) a no verbal suggestion control group. Pain expectations were assessed following verbal suggestion administration. CPM was measured by determining the pressure pain threshold with and without a cold water bath immersion procedure.
Results: Verbal suggestion manipulation resulted in altered pain expectations ($F(2,108) = 15.27$, $p < .001$). A mixed repeated measures ANOVA furthermore demonstrated an interaction effect between group and CPM ($F(2,111) = 5.45$, $p = .006$). Posthoc analyses, however, showed no significant group differences. Although males overall had a larger CPM effect than females ($F(1,108) = 10.68$, $p = .001$), no interaction effect with group allocation was found.
Conclusions: Positive or negative verbal suggestions can result in differential pain expectations which in turn may influence the CPM-effect, but relatively small effects were found. The influence of expectations on CPM was not dependent on sex. Altered CPM efficacy, such as observed in patients with chronic pain, may possibly reflect differential pain expectations in addition to descending pain inhibitory deficits.

P3.31 Moderators and mediators of a preoperative psychological intervention aiming at improving heart surgery outcomes – the PSY-HEART I trial

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3. Johannes Laferton. *Philipps-University Marburg, Marburg, Germany.*
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5. Winfried Rief. *Philipps-University Marburg, Marburg, Germany.*

Background: The PSY-HEART I RCT examined whether a brief preoperative psychological intervention aiming at optimizing expectations in heart surgery patients is capable of improving long-term surgery outcomes. In a prospective three-arm randomized clinical trial with a 6 months follow-up, 124 patients scheduled for heart surgery were randomized to either a psychological preoperative intervention to optimize expectations (EXPECT); or a psychological control intervention focusing on emotional support and general advice, but not on expectations (SUPPORT); or to standard medical care (SMC) only. Patients in the EXPECT group showed significantly larger improvements in disability than the SMC group; patients in the SUPPORT group did not differ from the SMC group. However, the exact mechanisms of this intervention effect are not yet fully understood and need further examination.
Methods: In a secondary explorative analysis we examine several potential mediators and moderators (i.e., age, gender, different expectation constructs, illness beliefs, anxiety, depression, physical activity, sleep quality, biological parameters such as adrenaline) to better understand what worked best for whom and why.
Results: Cardiac anxiety was partially confirmed as a potential mediator. The role of postoperative adrenaline was also of significance. Results will be presented and discussed to optimize future expectation-focused interventions by focusing on the most effective mechanisms of change. The results of the discussion will also be considered for analyses of the multi-centered PSY-HEART II trial.
Conclusion: The identification of possible mediators and moderators is important to further optimize the effectiveness of expectation-focused treatments while reducing the resources necessary to deliver the treatment.

P3.32 Does expectancy increase analgesia during opioid treatment?

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3. Christian Büchel. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background and aims: Expectations can modulate a drug's efficacy. To investigate if the level of certainty about receiving a treatment increases opioid analgesia, participants received the opioid agonist remifentanil in either an open-label or a blind fashion. Furthermore, offset analgesia was studied under the influence of opioids and expectancy. To assess analgesic effects in the entire central pain system, we recorded BOLD responses from the spinal cord to the brain.
Methods: Eighty-five healthy, male volunteers were randomly assigned to one of three experimental groups. One group received remifentanil in an open-label manner (N = 28) whereas the other two groups received either saline solution (N = 28) or remifentanil (N = 29) in a blind manner. To assess neural correlates of opioid analgesia in the entire central pain system, BOLD responses were simultaneously recorded in the brain and spinal cord. The MRI experiment comprised a baseline and an infusion phase. Each phase consisted of 32 heat pain stimuli including constant and offset stimuli that were applied on the left volar forearm using a thermode. Individual pain ratings were assessed after every heat stimulus.
Results: Pain ratings in both remifentanil groups were significantly reduced compared to the saline group. However, analgesia in the open-label and blind remifentanil group did not differ significantly. Furthermore, the magnitude of offset analgesia was modulated neither by remifentanil nor by expectancy.
Conclusions: In this study, certainty about receiving an opioid treatment did not modulate opioid or offset analgesia suggesting that expectancies did not increase the drug's efficacy.

P3.33 Open-label placebo vs. conventional and alternative medicine – An online study on expected effectiveness

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3. Frank Euteneuer. *Medical School Berlin, Berlin, Germany.*

Background: Treatment expectations are a key mechanism in placebo effects. Optimizing these expectations is a main goal in placebo designs but is often based on deception. To address ethical concerns, open-label placebo treatments seem to be effective without deception, although the role of expectations for their effect is rather unclear.
Methods: Participants (N=253) who occasionally suffer from headaches were recruited online and randomized to receive one of three hypothetical descriptions of a doctor-patient-situation in which a certain headache treatment is prescribed: 1) conventional medicine, 2) open-label placebo, 3) alternative medicine (homeopathy). Subsequently, participants rated how strongly they expect that the given treatment can be effective.
Results: One-way ANOVA revealed differences in expected effectiveness between groups. The highest expected effectiveness occurred in the conventional medicine group, the lowest in the open-label placebo group as well as in the homeopathy group. Potential moderators are discussed, e.g., socioeconomic variables, health literacy, locus of control.
Conclusions: Participants expect lower effectiveness of treatment if they are truthfully informed about the inertness of a prescribed treatment (open-label placebo). While the descriptions were otherwise identical, the homeopathy group also scored lower levels of expectancy compared to conventional medicine. Homeopathy can be interpreted as a placebo prescription with deception as it does not contain pharmacologically active substances. The expected effectiveness in the homeopathy group did

not differ from open-label placebo. These results suggest that prescribing a placebo while truthfully informing about placebo effects seems to be as feasible as to prescribe homeopathy regarding the expected effectiveness.

P3.34 Expectancies as predictors of symptom improvement in patients with persistent symptoms attributed to Lyme disease

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4. Hadewych ter Hofstede. *Radboud University Medical Center, Nijmegen, Netherlands.*
5. Bart-Jan Kullberg. *Radboud University Medical Center, Nijmegen, Netherlands.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Expectancies about symptom changes are reliable predictors of symptom progression or treatment outcomes in a broad variety of (non-)pharmacological studies and treatments. Such expectancies thus offer potential new ways to improve patient outcomes. The current study examined the role of expectancies and other individual differences in predicting primary outcomes of symptom improvement after antimicrobial therapy for persistent symptoms attributed to Lyme disease.
Methods: A predictive study was conducted on data from a randomized placebo-controlled trial (PLEASE) comparing shorter- and longer-term antimicrobial treatments in 280 patients (190 at follow-up) with persistent symptoms (e.g., pain, fatigue) attributed to Lyme disease. Physical and mental health-related quality of life (HRQoL) was assessed before study treatment (pre-treatment functioning), at week 14 (end-of-treatment), and at week 52 (follow-up). Regression analyses predicting outcomes from pre-treatment characteristics, controlling for pre-treatment functioning, were performed.
Results: In addition to pre-treatment functioning, only expecting symptom improvement was consistently associated with stronger physical and mental HRQoL improvements at both end-of-treatment and follow-up (95% CI-range: 0.14-0.58, p = .002 to 0.46-1.06, p<.001). Post-treatment expectancies regarding having received antibiotics vs. placebo was also associated with more improvement on all outcome measures (95% CI-range: 0.13-5.38, p = .04 to 2.47-6.47, p<.001).
Conclusions: The present study shows how patients' expectancies regarding improvement of persistent Lyme-associated symptoms can explain a more beneficial symptom course, implying that optimization of expectancies might improve symptom course and treatment effectiveness in these patients.

P3.35 Conditioning the effects of a stress management intervention to a distinctive scent

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Introduction. Olfactory conditioning has been shown to be effective in positively influencing human behavior. This study investigates whether a distinctive scent, conditioned to the effects of a brief 1-session stress management intervention (SMI), can decrease stress-related outcomes after exposure to stress.
Methods: On day one (acquisition phase), 96 healthy participants, aged 18-35, were randomized to one of three groups. The No-treatment Control group (C1) performed a neutral filler task, the Treatment Control group (C2) and the Treatment Conditioned group (E1) underwent a SMI (21 minutes). Before and after the manipulations, participants were exposed to a distinctive scent. On day two (test phase), all groups underwent an acute social stress task, where only groups C1 and E1 were re-exposed to the scent. The primary outcome is state anxiety (Shortened State-Trait Anxiety Inventory-State version). Secondary outcomes include self-report questionnaires (Positive and Negative Affect Schedule) and psychophysiological data (cortisol).
Results: The SMI significantly lowered state anxiety ($F(1, 62)=27$, $p<.001$). However, no significant differences in state anxiety in response to the stressor were found between the combined control groups versus E1 ($t(90)=0.30$), $p=0.76$).
Discussion. This is the first study investigating the possibility of using olfactory conditioning to efficiently evoke feelings of relaxation to buffer psychophysiological responses to acute social stress. Although the brief SMI proved effective, no conditioned effects were observed in response to the stressor. Future research should focus on possible factors that might affect learning of stress-management methods, such as conditioning stress-management during stress exposure or the number of conditioning trials.

P3.36 'At face value': General practitioners' attitudes toward placebos and open-label placebos

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3. Oliver Frank. *University of Adelaide, Adelaide, SA, Australia.*

Introduction: Although medical practitioners often agree placebos can be effective in clinical practice, they commonly express concerns that the use of placebos requires deception. Because previous research has indicated that placebos remain effective when given without deceit (open-label placebos), we explored and compared general practitioners' (GPs) attitudes to traditional (placebos) and open-label placebos.
Method: GPs in Australia (n=51, 65% female) completed a cross-sectional online survey, containing study-specific questionnaires exploring their attitudes towards placebos and open-label placebos.
Results: Paired samples t-tests revealed GPs felt placebos were significantly more likely to be effective (d=0.48) and produce physical changes in the body (d=0.31) than open-label placebos, but were more likely to report open-label placebos could be

delivered ethically (d=0.35). No significant differences emerged around a willingness to prescribe (d=0.04) placebo or open-label placebos, or their acceptability in clinical practice (d=0.16). GPs with 30-40 years practice experience were significantly less likely to agree placebos and open label placebos have a place in clinical practice (η2=.24, η2=.23, respectively) and can be delivered ethically (η2=.20, η2= .41, respectively), compared to those practicing for longer or fewer years.
Discussion: Although this sample of GPs indicated traditional placebos were more effective, they felt placebos and open-label placebos are equally acceptable in clinical practice but open-label placebos were more ethical. Thus, the GPs were receptive to open-label placebos, but required more evidence of their efficacy, warranting further research. GPs with 30-40 years' experience were less accepting of placebos, highlighting a target group for further exploratory investigations, and information provision.

P3.37 Placebo effect and cognitive ability in children with attention deficit hyperactivity disorder

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Studies on children with attention deficit hyperactivity disorder (ADHD) have shown that they have a 2-3 years cortical maturation delay of the dorsolateral prefrontal cortex (DLPFC) and a deficient dopaminergic release (related to norepinephrine release). ADHD is associated to lower academic performance, which is modulated by students' expectations regarding their own abilities. Expectations are also involved in the placebo effect, as are the DLPFC and norepinephrine release.
The data will be collected from 44 children with and without ADHD. Placebo effect on cognitive tasks (Go/No-go and Attention Network Task) will be induced using placebo pills that "improve" or "reduce" the performance. Neurophysiological measurements will also be taken (cortical thickness of DLPFC with MRI, and norepinephrine blood concentration).
Children with ADHD should respond less to the placebo effect than healthy children. Neurophysiological measurements will be different in the two groups. T Tests will be used for the comparison between children with and without ADHD on placebo effect on cognitive ability. Simple and multiple regression analysis will be used to determine whether there is an association between the placebo effect on cognitive tasks and the neurophysiological measures.
This study will help to better understand the contribution of the DLPFC in the mechanism of the placebo effect. We will also be able to better understand the role of placebo in children with ADHD, in a school context. As a result, we will be able to improve the intervention strategies to be implemented, in order to guarantee better support for children with ADHD.

P3.38 The role of expectancy and adherence on open-label placebo effects in premenstrual syndrome: Preliminary results of a randomized controlled trial

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3. Jens Gaab. *University of Basel, Basel, Switzerland.*
4. Linda Kost. *University of Basel, Basel, Switzerland.*
5. Cosima Locher. *University of Basel, Basel, Switzerland.*

Background: Premenstrual Syndrome (PMS) is highly prevalent in women of reproductive age, leading to substantial distress and impairment. Current treatments are associated with considerable placebo effects, making PMS a suitable candidate to harness these effects with open-label placebo (OLP) administration. First evidence from an experimental study in healthy participants supports the importance of expectancy of relief (EoR) and treatment adherence (TA) in OLP administration (El Brihi, Horne, & Faasse, 2018). Therefore, we set out to test the role of these moderators in a clinical trial of OLP in PMS.
Methods: After a 4-week prospective PMS screening, eligible participants are randomized to either treatment as usual (TAU; n = 50), an OLP+ (receiving plausible treatment rationales; n = 50), or an OLP- group (receiving intake instructions only; n = 50). Over the course of two menstrual cycles symptom intensity (SI) and TA are daily assessed by means of a German PMS symptom diary. EoR and PMS-impact are measured at baseline, 3-weeks midpoint, and 6-weeks endpoint.
Results: So far, 50 of 150 women with PMS have been included in the trial. We hypothesize that EoR and TA will be significantly higher in the OLP+ group compared to the OLP- group. In addition, we hypothesize that TA adherence and EoR will predict improvements in SI and PMS-impact.
Conclusions: OLP administration - if found to be acceptable and efficacious – would offer a new approach for treatment in PMS and EoR and TA could be important mediators of OLP effects in women suffering from PMS.

P3.39 Open-label placebo in premenstrual syndrome: Preliminary results of a randomized controlled trial on psychological distress, functional interference and health-related quality of life

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3. Bojana Degen. *University of Basel, Basel, Switzerland.*
4. Jens Gaab. *University of Basel, Basel, Switzerland.*
5. Cosima Locher. *University of Basel, Basel, Switzerland.*

Background: Premenstrual Syndrome (PMS) is highly prevalent in women of reproductive age and leads to high psychological distress (PD), functional interference (FI) and subsequently reduces health-related quality of life (HR-QoL). Current PMS

treatments are associated with considerable placebo effects of up to 43% of observed improvements, making PMS a suitable candidate to harness these effects with open-label placebo (OLP) administration. Therefore, we set out to test the impact of OLP on PD, FI and HR-QoL in women with PMS.
Methods: After a 4-week prospective PMS screening, eligible participants are randomized to either treatment as usual (TAU; n = 50), an OLP+ (receiving plausible treatment rationales; n = 50), or an OLP- group (receiving intake instructions only; n = 50). Outcomes are measured using the PMS-Impact-Questionnaire and the Short-Form-12 Health-Survey completed at baseline, 3-weeks mid- and 6-weeks endpoint.
Results: So far, 50 out of 150 women with PMS have been included in the study, running until mid-2019. We hypothesize that subjects in the OLP intervention report higher improvements in PI, FI and HR-QoL compared to TAU at study endpoint, with the OLP+ group showing the strongest improvement.
Conclusions: Regarding the side effects of existing treatments, OLP treatment could be a suitable and effective intervention for women with PMS and thus be an example of an ethically acceptable clinical implementation of placebo treatment.

P3.40 Placebo manipulations influence the effectiveness of pain regulation

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Emotion regulation strategies such as Reappraisal were found to successfully modulate the perception of pain. However, the question arises to what degree regulation of pain is prone to placebo manipulations, similar to established analgesic medical interventions. To explore this potential interaction, we compared two experimental groups: participants were either instructed about the high effectiveness of Reappraisal in reducing pain as demonstrated in a serious of empirical studies (placebo group) or they received a standard instruction informing about the experimental procedure (control group). Afterwards, the placebo group underwent placebo conditioning (low pain + reappraisal; high pain + control trials), reinforcing the placebo instruction. The control group instead received high and low intensity pain stimuli during reappraisal and control trials in random order. Thereafter, participants of both groups entered the test phase and received identical paint stimuli during both, reappraisal and control trials. In addition to pain intensity and unpleasantness ratings, we recorded skin conductance and heartrate as physiological indicators of pain processing. Preliminary results suggest a successful pain modulation of reappraisal in both groups, however pain intensity ratings suggest a slightly more pronounced differentiation between reappraisal and control trials for the placebo group. Physiological indicators demonstrated only a moderate modulation by the experimental variations. In summary, the results lend further evidence for the effectiveness of pain regulation and suggest a moderate additional benefit by a placebo manipulation. Individual attitudes towards pain regulation might play a crucial role for placebo effects interacting with reappraisal strategies and thus taken into account carefully.

P3.41 Statin intolerance: Biological toxicity or nocebo-effect?

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Introduction: Statins are in the top 5 most prevalent used medical drugs on a life-long prescription. These medications are used for the treatment of hypercholesterolemia. Statin intolerance appears to play a major role in clinical practice, especially the associated muscle symptoms. Recently this is a highly debated subject in the context of the dilemma's in the balance between benefit and harm, and of the discrepancies in ascribed mechanisms of drug-toxicity versus nocebo-effects.
Methods: Data are collected from pharmacovigilance databases, epidemiological literature and case histories. Information is gathered about discontinuation protocols in medical drug treatment in perspective of personalized medicine.
Results and discussion: The reported adverse events of statins are many, both physical and psychological side effects: muscle complaints, diabetes mellitus, cognitive problems and other psychological complaints. Analysis is complicated by lacking data of patient-groups with comorbidity, multimorbidity and polypharmacy. Arguments for the plausibility of the biological-toxicity hypotheses for statin intolerance with the nocebo explanation for statin intolerance are validated and compared. Consequences for clinical practice and a personalized approach in individual cases are discussed.

P3.42 Nocebo effects and scratching behaviour on itch

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4. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Background: Nocebo effects are known to contribute to the experience of itch. Recent studies have shown that nocebo effects can experimentally be induced on itch and also subsequently be reversed. So far, it is not known whether these effects generalize to itch-associated scratching behaviour. Therefore, we examined whether induction and reversal of nocebo effects on itch evoked by electrical and histamine stimuli generalized to scratching in healthy subjects.
Methods: First, negative expectations about itch stimuli were induced in 99 participants by conditioning with verbal suggestion (part 1: induction of nocebo effect). Second, these participants were randomized to either the experimental group or one of the control groups (part 2: reversing nocebo effect). In the experimental group, positive expectations were induced by conditioning with verbal suggestion. In the control groups either the negative expectation induction was continued or an extinction procedure was applied.

Results: The manipulation was successful, as during the nocebo learning phase, increased scratching responses were found for higher intensity compared with lower intensity itch stimuli. During the testing phase of induction or reversal of the nocebo effects, however, no significant nocebo effects or reversed nocebo effects were found in scratching.
Conclusions: No straightforward generalization of nocebo effects from itch to scratching was found in this laboratory setting. Potential generalization of placebo and nocebo effects from itch to scratching should be further investigated in different settings and in patients with chronic itch.

P3.43 Improved affect and physical wellbeing after only three minutes: The power of an active- and a pure placebo pill

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Background: Expectancies shape human behavior. Initial drug use might be associated with information-based expectations and maintained through experience-based conditioning. The aim of this research was to examine the hypothesis that acute changes in positive- and negative affect and perceived physical wellbeing will be stronger after ingesting an active placebo than a pure placebo presented as a mood-enhancing 'super-pill'.
Methods: With the approval of the University's Research Ethics Committee, the work (doi:10.1080/00221309.2018.1459454) was conducted as a classroom-experiment at a large university. Eighty sports science students, were randomized into two groups. One group received an active placebo comprised by a white Tic-Tac mint, while the other group received a white placebo pill presented as a fast-acting legal mood enhancer. After baseline assessment of positive/negative affect and wellbeing, participants completed a treatment-expectancy scale, then ingested the mint/super-pill, then attended to the effects over 3-minutes. Subsequently, they completed again the psychological tests.
Results: Expectancy scores were positive and did not differ between the groups. The pure placebo group increased in physical wellbeing above the baseline, but less than the active placebo group, which also showed an increase in positive affect. Negative affect decreased in both groups. The Tic-Tac produced greater affective changes than the pure placebo.
Conclusions: Experience with an agent has greater effect than information-based trial. In non-volunteers this explanation may be linked to skepticism and fear of the unknown. This study is the first to suggest that a Tic-Tac and an inert placebo pill elicit changes in affect after only three minutes.

P3.44 Brain activations in the expectations of sensory experience for acupuncture stimulation

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The brain is known to actively interpret sensory inputs from the integration of top-down and bottom-up information. Humans can make inferences on somatosensation based on prior experiences and expectations even without the actual stimulation. We used fMRI and investigated the neural substrates to the expectations of sensory experience about acupuncture stimulation without invasive cutaneous stimuli. We included twenty-two participants who wore sticker type electrodes attached on three different acupoints on different body regions: CV17 (chest), CV23 (chin), and left PC6 (arm). Participants were asked to rate deqi sensations after they receive electrical stimulation on those points in random order, but there were no actual stimulation. All stimuli were presented with corresponding visual information of the stimulation sites, and control condition included similar visual information but outside the body. Expectations of acupuncture stimuli without actual stimulation on three acupoints resulted in greater deqi sensation compared to the control condition. Cognitive components of acupuncture stimulation exhibited greater brain activation in the anterior insula, dorsal mid-cingulate cortex and pre-supplementary motor area, and secondary somatosensory area. We demonstrated that expectations of acupuncture stimulation exhibited a distinct experience of somatosensation as well as activations in salience networks in the brain. Our findings imply the involvement of salience network in cognitively induced somatosensation from acupuncture stimulation, which is likely due to the predictive role of salience network in monitoring internal and external bodily state.

P3.45 The influence of caffeine expectancies on simulated soccer performance

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3. Andy Hooton. *University of Derby, Derby, United Kingdom.*
4. George Spencer. *University of Derby, Derby, United Kingdom.*
5. Mitch Storey. *University of Derby, Derby, United Kingdom.*
6. Laura Sandford. *University of Derby, Derby, United Kingdom.*
7. Olivia Ensor. *University of Derby, Derby, United Kingdom.*
8. Jason Tallis. *Coventry University, Coventry, United Kingdom.*
9. Bryan Saunders. *University of São Paulo, São Paulo, Brazil.*

Introduction: Caffeine (CAF) has been reported to improve various facets of soccer play, including gross motor skill performance, endurance capacity and cognitions. However, at present the associated benefits are primarily attributed to pharmacological mechanisms with no soccer specific studies accounting for any potential psychological impact.
Methods: Utilising a double-dissociation design, eight recreational soccer players consumed CAF (3 mg/kg/body mass) or placebo (PLA) capsules, 1 hour before performing the Loughborough Intermittent Shuttle Test (LIST) interspersed with collection of ratings of perceived exertion (RPE), blood glucose and lactate, heart rate and performing the Loughborough Soccer Passing

Test (LSPT). Whole body dynamic reaction time (DRT) was assessed pre and post and exercise capacity (TLIM) post, LIST. Subjective perceptions were explored using template analysis.
Results: Mean TLIM was ~ 45 s greater (7%; P=0.012) for given PLA/told CAF (psychology) vs. given CAF/told PLA (pharmacology) potentially, via reduced RPE. This appeared related to told CAF groups, irrespective of positive/negative perceptions for CAF ergogenicity. Although DRT performance was greater (P=0.024) post-ingestion (+5 hits) and post-exercise (+7 hits) for pharmacology vs. given PLA/told PLA (placebo), only given CAF/told CAF (synergism) and psychology appeared to improve LSPT performance. Interestingly, positive perceptions during psychology inhibited LSPT and DRT performance via potential CAF over-reliance, with the opposite occurring following negative perceptions. Thus, the mechanisms how CAF expectancies might influence exercise performance appear to be dependent on the task performed, with reduced RPE a potential key mediator during endurance capacity, whilst positive perceptions proved debilitative during LSPT and/or DRT. Subsequently, CAF expectancies may better suit tasks that require lesser cognitive/skill specific attributes.

P3.46 Patient attitudes towards adverse event disclosure

1. Mette Sieg. *Aarhus University, Aarhus, Denmark.*
2. Luana Colloca. *University of Maryland, Baltimora, MD, United States.*
3. Lene Vase. *Aarhus University, Aarhus, Denmark.*

Background: Receiving information about possible adverse events, in relation to a treatment, could increase the occurrence of these; thus questioning how much information health care professionals should give their patients. This has triggered an ethical debate, as health care professionals should ensure both patient autonomy and beneficence. The opinion of the patients themselves are important to consider in this debate. Therefore, the objective of this survey is to examine patient attitudes about information on adverse events.
Methods: Participants will be Danish and American hospital patients and healthy age/gender matched individuals. With a mixture of scenarios and statements, this survey will investigate attitudes towards adverse event information across different populations (US vs DK; patients vs healthy individuals), across different treatment paradigms (medication vs surgery), and across different degrees of relatability (“me” vs “others”).
Results: Template will be presented.
Conclusions and Implications: Results from this survey will bring the viewpoint of the patients themselves into the ethical debate about how health care professionals should inform patients about possible adverse events from treatments. Results will also show whether attitudes differ depending on population and context.

P3.47 Open- and closed-label verbal suggestions regarding a sham transdermal caffeine patch: Effects on itch

1. Stefanie Meeuwis. *Leiden University, Leiden, Netherlands.*
2. Henriët van Middendorp. *Leiden University, Leiden, Netherlands.*
3. Adriana Lavrijsen. *Leiden University Medical Center, Leiden, Netherlands.*
4. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
5. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Negative and positive verbal suggestions may influence psychosomatic symptoms such as itch, even when it is known that a treatment is inert (i.e. open-label). Few studies have investigated the efficacy of such suggestions for itch under comparable open-label and closed-label (i.e. concealed) conditions. A randomized controlled between-subjects design was applied in which healthy volunteers (n=112, 84% female) were randomized to 1) a closed-label negative verbal suggestions (VS) group, 2) an open-label negative VS group, 3) a closed-label positive VS group, or 4) an open-label positive VS group. Participants were told that a transdermal caffeine patch would be applied, which would influence cognitive functioning and moreover, would positively or negatively (depending on group allocation) influence itch. Participants in the open-label groups were given an explanation of the procedure. Itch was induced experimentally at baseline and following suggestions by histamine iontophoresis. As part of the cover story, the Stroop test was assessed twice as well. Open- and closed-label suggestions significantly influenced both itch expectations and itch experienced during iontophoresis (all $p<.008$). Within-group analyses of baseline-to-post-suggestions change demonstrated that itch reduced significantly in both positive VS groups (all $p<.001$), but did not change in the negative VS groups (all $p>.22$). The current study shows that open-label suggestions may be a promising method for utilizing placebo effect mechanisms in clinical practice.

P3.48 The self-confidence of a model – Can it modulate the strength of learning about pain? A study on placebo analgesia induced by observational learning.

1. Justyna Brączyk. *Jagiellonian University, Kraków, Poland.*
2. Przemysław Bąbel. *Jagiellonian University, Kraków, Poland.*

Previous research conducted in the field of pain has indicated that placebo analgesia may be evoked through the three mechanisms: classical conditioning, operant conditioning and social observational learning. The mechanism of observational learning may be moderated by various factors such as specific behaviour or characteristics of the model. Although the number of research aiming to reveal those factors grows, some of them seem to be undiscovered. The main aim of the study is to investigate whether the level of the trait of self-confidence influences the effectiveness of observational learning in inducing placebo analgesia.

Healthy volunteers were randomly assigned to one of three groups: 1) model with high self-confidence, 2) model with low self-confidence, 3) control group. In groups 1 and 2 participants watched a video with a model undergoing the same (planned also for participants) experimental procedure. In each group, half of participants watched the video where the model rated 'blue' stimuli higher and 'orange' stimuli lower, while the other half of participants watched the video where this rating trend was reversed. The only difference between experimental groups was that in the video 1 model showed self-confident behaviour, while in the video 2 he behaved insecure. In the control group no video was displayed. Then 16 electrical pain stimuli of the same intensity, preceded by the blue or orange colour, were applied to all groups. Participants rated each of them on the NRS scale. The poster presents the results of the study.

P3.49 Evaluating the feasibility of adjunctive open-placebos for acute pain: A pilot study

1. Michael Bernstein. *Brown University, Providence, RI, United States.*
2. Molly Magill. *Brown University, Providence, RI, United States.*
3. Arnold-Peter Weiss. *Brown University, Providence, RI, United States.*
4. Ted Kaptchuk. *Harvard Medical School, Cambridge, MA, United States.*
5. Charlotte Blease. *Harvard Medical School, Cambridge, MA, United States.*
6. Steven Mach. *University of Massachusetts School of Medicine, Boston, MA, United States.*
7. Josiah Rich. *Miriam Hospital, Providence, RI, United States.*
8. Sara Becker. *Brown University, Providence, RI, United States.*
9. Francesca Beaudoin. *Brown University, Providence, RI, United States.*

Open placebos have been successfully used to treat a wide range of medical conditions, including chronic lower back pain. The purpose of this ongoing pilot study is to examine the feasibility of using open placebos to treat acute pain (n=6) following hand surgery and Emergency Department discharge. All participants were given an opioid prescription by their physician to be taken as needed for pain. In addition, a research team member also asked participants to take one open placebo pill at the same time as they took their prescribed opioid pill prescription. Participants could take open placebos, not paired with opioids, as desired. A description of what the placebos were, and how they might work, was provided to participants consistent with prior studies (e.g. Kaptchuk et al., 2010). A follow-up assessment measuring the participant's subjective experience of the study procedures and with the placebo protocol was given approximately three weeks after enrollment. Study results showed than all participants took the placebos as instructed. Eighty percent of participants believed they were taking an inactive pill, 100% of participants understood the explanation for how placebos might work, and no one said the study was misleading. When asked how easy it was to take the placebos from 1 (very easy) to 5 (very difficult), all participants reported "1" or "2". Forty percent of participant's reported the placebos were helpful in relieving pain. This study suggests open placebos hold promise as a potential adjunctive treatment for pain, as a means of reducing long-term opioid prescribing.

P3.50 Order matters: Pain experience and expectation continuously shape perception

1. Davide Anchisi. *University of Udine, Udine, Italy.*

In placebo experiments it is common practice to randomize stimulation order between subjects, to average out additional but unintended effects specific to the sequence. Mixing collected results is appropriate when data follow a unimodal distribution. But if results are clustered according to stimulus ordering, or if the sequence has meaningful relations with them, averaging may not be the best choice; indeed, it can mask real effects.
Examining experimental results from different protocols, and with the support of a probabilistic theoretical framework, we show how the experimental procedure influences study outcomes and affects research conclusions. For example, we demonstrate how changing the first stimulus (high or low) in an acute pain experiment, significantly affects subsequent perception of the stimuli.
A theoretical model may help to explain and predict what happens. There is no such thing as a true or correct perception: pain is the result of a decision process based on past experience and sensory and cognitive/emotional contingencies. Each pain experience (e.g. a stimulus during an experimental session) updates the subject's (and it's nociceptive system) knowledge, changing the way the next stimulus is perceived.
This effect have seldom, if ever, been accounted for in the placebo literature, but slight differences in the procedure may produce drastically different results; to avoid misinterpretation or missing relevant outcomes it is thus mandatory to separately evaluate data from different stimulation settings and decide if, or not, mix them together; the benefit: to better understand the underlying phenomenon.

P3.51 Open-label placebo injection for chronic back pain: A randomized controlled trial

1. Jonathan Ashar. *University of Colorado, Boulder, CO, United States.*
2. Karen Knight. *Panorama Orthopedics and Spine Center, Golden, CO, United States.*
3. Alan Gordon. *The Pain Psychology Center, Beverly Hills, CO, United States.*
4. Mark Lumley. *Wayne State University, Detroit, MI, United States.*
5. Stephan Geuter. *University of Colorado, Boulder, CO, United States.*
6. Thomas Flood. *Mass General Imaging, Boston, MA, United States.*
7. Joe Clark. *University of Colorado, Boulder, CO, United States.*
8. Zachary Anderson. *University of Colorado, Boulder, CO, United States.*
9. Laurie Polisky. *University of Colorado, Boulder, CO, United States.*
10. Judith Carlisle. *University of Colorado, Boulder, CO, United States.*
11. Sona Dimidjian. *University of Colorado, Boulder, CO, United States.*
12. Tor Wager. *University of Colorado, Boulder, CO, United States.*

Background: Epidural steroid injections are one of the most commonly performed procedures for chronic back pain, yet they are no more effective than control (placebo) injections (Bicket et al., 2013). However, it is unknown whether placebo injections can be effective when both patients and providers know it is a placebo (i.e., “open label placebo”, OLP). Here, we tested the efficacy of a single OLP injection vs. waitlist in the context of a randomized controlled trial (NCT #03294148).
Methods: Patients with chronic back pain were randomized to either an OLP injection or to a waitlist control condition. The treatment consisted of a subcutaneous injection of saline into the back, in the context of an augmented patient-provider interaction in a orthopedic clinic setting. Functional MRI and a battery of patient reported outcomes were collected at pre- and post-treatment, with average pain over the past week (0 – 10, measured with the Brief Pain Inventory – Short Form) serving as the pre-registered primary outcome.
Results: There were N = 101 patients randomized, with N = 91 (90%) completing the study at post-treatment. Pre-treatment pain intensity was M = 4.03, SD = 1.29, with no significant differences between conditions at baseline, $T(99) = 0.96$, $p > .3$. There was a significant group by time interaction, $p < .05$, with an effect size of $g = -0.53$, 95% CI [-0.97 -0.13]. Patient interviews will be presented indicating that patients understood that the treatment was inert, and with patient reflections on possible treatment mechanisms.
Conclusions: Our results suggest that deception is not required for effective placebo treatment of chronic back pain.

P3.52 Sex influence on expectancy and placebo analgesia in chronic orofacial pain patients

1. Elizabeth Olson. *University of Maryland, Baltimore, MD, United States.*
2. Yang Wang. *University of Maryland, Baltimore, MD, United States.*
3. Titilola Akintola. *University of Maryland, Baltimore, MD, United States.*
4. Nathaniel Haycock. *University of Maryland, Baltimore, MD, United States.*
5. Jane Phillips. *University of Maryland, Baltimore, MD, United States.*
6. Nandini Raghuraman. *University of Maryland, Baltimore, MD, United States.*
7. Lievan Schenk. *University of Maryland, Baltimore, MD, United States.*
8. Maxie Blasini. *University of Maryland, Baltimore, MD, United States.*
9. Nicole Corsi. *University of Maryland, Baltimore, MD, United States.*
10. Sharon Thomas. *University of Maryland, Baltimore, MD, United States.*
11. Pedro Martinez. *National Institutes of Mental Health, National Institutes of Health, Bethesda, MD, United States.*
12. Luana Colloca. *University of Maryland, Baltimore, MD, United States.*

Temporomandibular pain disorder (TMD) is approximately three times as common in women as in men. Symptoms of TMD are also more severe in women and vary in intensity across the menstrual cycle. In pain studies reporting sex difference, women trend more sensitive to pain than men. Placebo studies are emerging to investigate influence of sex on expectancy-induced analgesia, though as in pain, sex- and gonadal hormone level-dependency is undetermined.
Between- and within-sex differences in placebo analgesia were assessed through a behavioral pain modulation task in 260 patients with at least a three-month history of TMD to evaluate sex differences, controlling for menstruation pattern and birth control regimen in women. Mediation analysis was conducted to explore if expectancy favors sex difference in placebo effects.
Among TMD patients, significant differences were observed in expectancy between men (mean=61.12) and women (mean=70.26, $t173=-2.60$, $p=0.010$), as were differences in placebo effect between men (mean=14.22) and women (mean=18.97, $t258=-1.91$, $p=0.050$). Among women with self-reported regular menses, no significant effects on expectancy or placebo were found based on menstrual pattern (expectancy: $p=0.47$; placebo: $p=0.99$) or birth control method (expectancy: $p=0.072$; placebo: $p=0.46$). Mediation analysis results underlined sex effects, indicating expectancy does not mediate dimorphic placebo effects (indirect=-1.00, SE=0.83, 95% CI [-3.01,0.18]).
We conclude strong sex differences in expectancy and placebo analgesia in TMD patients, controlling for menstrual pattern and birth control method. Our results emphasize the need to consider sex as a biological variable when expectancy and placebo effects are explored while taking into account hormonal factors.

P3.53 A research protocol for empathy and expectation management for patients in primary care: Methods for developing a new digital intervention for practitioners

1. Felicity Bishop. *University of Southampton, Southampton, United Kingdom.*
2. Hazel Everitt. *University of Southampton, Southampton, United Kingdom.*
3. Jeremy Howick. *Oxford University, Oxford, United Kingdom.*
4. Paul Little. *University of Southampton, Southampton, United Kingdom.*
5. Christian Mallen. *Keele University, Keele, United Kingdom.*
6. Leanne Morrison. *University of Southampton, Southampton, United Kingdom.*
7. Lucy Yardley. *University of Southampton, Southampton, United Kingdom.*
8. Stephanie Hughes. *University of Southampton, Southampton, United Kingdom.*
9. Kirsten Smith. *University of Southampton, Southampton, United Kingdom.*
10. Jane Vennik. *University of Southampton, Southampton, United Kingdom.*
11. Mohana Ratnapalan. *University of Southampton, Southampton, United Kingdom.*
12. Emily Lyness. *University of Southampton, Southampton, United Kingdom.*
13. Hajira Dambha-Miller. *University of Southampton, Southampton, United Kingdom.*

Osteoarthritis (OA) pain is prevalent, personally and economically costly. Large placebo effects have been documented in OA. Pharmacological and non-pharmacological treatments are recommended but patients report adverse effects and limited benefits. Regardless of which treatment patients receive, people in pain have better outcomes when practitioners communicate empathically and encourage realistic and positive expectations about treatment. However, this evidence remains to be implemented in practice in a pragmatic format that engages practitioners effectively, and practitioners vary widely in how much they express empathy to their patients. We will address this by developing a digital intervention to enhance primary care practitioners' skills in the context of managing OA pain, focusing on empathic communication and expectation management. We will combine person-based, theory-based and evidence-based approaches, using qualitative research, existing theories and evidence to plan, design, and build our intervention. This will entail conducting: a meta-ethnography of patients' and clinicians' views of OA consultations; components' analyses of existing empathy and expectation interventions; qualitative interview studies with patients and practitioners about empathy and expectations in practice; a behavioural analysis; and two think-aloud studies to capture practitioners' responses to intervention prototypes. These methods will ensure our intervention is engaging, pragmatic, relevant and likely effective at changing practitioners' communication behaviours and patients' pain, quality of life, and satisfaction. In a separate subsequent project, we will conduct a feasibility study to see how best to evaluate our intervention in a cluster randomised controlled trial in primary care. Our intervention will be called Empathica.

Parallel Session 3.1

Neural mechanisms in placebo studies

Tuesday, July 9, 2:00 PM - 3.00 PM
Grote zaal
Chair: Lauren Atlas

3.1a Neural mechanisms of expectancy-based placebo effects in antidepressant clinical trials

1. Sigal Zilcha-Mano. *University of Haifa, Haifa, Israel.*
2. Zhishun Wang. *Columbia University, New York, NY, United States.*
3. Bradley Peterson. *University of Southern California, Los Angeles, CA, United States.*
4. Melanie Wall. *Columbia University, New York, NY, United States.*
5. Ying Chen. *Columbia University, New York, NY, United States.*
6. Tor Wager. *University of Colorado, Boulder, CO, United States.*
7. Patrick Brown. *Columbia University, New York, NY, United States.*
8. Steven Roose. *Columbia University, New York, NY, United States.*
9. Bret Rutherford. *Columbia University, New York, NY, United States.*

Background: Patient expectancy of therapeutic improvement is a primary mediator of placebo effects in antidepressant clinical trials, but it mechanisms are poorly understood. This study employed a novel antidepressant trial design with integrated functional magnetic resonance imaging (fMRI) to manipulate patient expectancy and examine its neural mediators.
Method: Twenty-three depressed outpatients participated in a randomized controlled trial assigning them to either Open (high expectancy) or Placebo-controlled (low expectancy) treatment with citalopram for eight weeks. fMRI scans were acquired before and after the expectancy manipulation (before medication treatment) while participants performed a masked emotional face task. Focusing on an amygdala region-of-interest (ROI), we tested a model where amygdala activation mediated expectancy effects on the slope of change in depressive symptoms.
Results: Following the manipulation, significant differences between conditions were found in neural activation changes in the amygdala, as well as in the superior temporal gyrus, insula, and thalamus. Findings support the proposed mediation model according to which activation in the left amygdala ROI decreased significantly in the Open as opposed to the Placebo-controlled group following randomization (p=0.009) for sad vs. neutral face contrast. The reduced left amygdala activation in turn was a significant predictor of decreased depressive symptoms during the trial (p=0.007), and the mediation model was significant.
Conclusions: Results from this study, the first designed to identify the neural mechanisms of expectancy-based placebo effects in an antidepressant trial, suggest that therapeutic modulation of amygdala activity may be an important pathway by which patient expectancy influences depressive symptoms.

3.1b Clinical and neural effects of placebo and SSRIs in social anxiety disorder

1. Vanda Faria. *1) Uppsala University, Uppsala, Sweden; 2) Boston Children's Hospital Harvard Medical School, Boston, MA, United States.*
2. Malin Gingnell. *Uppsala University, Uppsala, Sweden.*
3. Johanna Hoppe. *Uppsala University, Uppsala, Sweden.*
4. Olof Hjorth. *Uppsala University, Uppsala, Sweden.*
5. Iman Alaie. *Uppsala University, Uppsala, Sweden.*
6. Andreas Frick. *Uppsala University, Uppsala, Sweden.*
7. Kurt Wahlstedt. *Uppsala University, Uppsala, Sweden.*
8. Kristoffer Månsson. *Uppsala University, Uppsala, Sweden.*
9. Per Carlbring. *Stockholm University, Stockholm, Sweden.*
10. Gerard Andersson. *Linköping University, Linköping, Sweden.*
11. Margareta Reis. *Linköping University, Linköping, Sweden.*
12. Elna-Marie Larsson. *Uppsala University, Uppsala, Sweden.*
13. Mats Fredrikson. *Uppsala University, Uppsala, Sweden.*
14. Tomas Furmark Furmark. *Uppsala University, Uppsala, Sweden.*

SSRIs are commonly prescribed for depression and anxiety but their superiority over placebo has been questioned, generating considerable controversy. It has been argued that the beneficial effects of SSRIs can be explained by differential expectancies induced in drug vs. placebo groups.
In previous studies we measured anxiety-related regional cerebral blood flow in 72 patients with social anxiety disorder (SAD) before and after 6-8 weeks of double-blind randomized placebo/SSRI treatment. Results showed:

a) No neural differences between responders to SSRIs and placebo.
b) Amygdala activity was attenuated with SSRI as well as placebo treatment. Amygdala attenuation correlated with reduced anxiety.
c) Responders to placebo and SSRIs shared top-down neuromodulatory paths that may underlie improved emotion regulation and reduced anxiety.

To further elucidate the role of expectancies in SSRI-treatment, 46 SAD patients were treated with the same clinical dosage of escitalopram for 9 weeks, but only one group was correctly informed about the drug. The other group was led to believe that they were treated with an ineffective active placebo, thereby lowering expectancies. The number of treatment responders was three times higher when correct information about the SSRI was given. This was accompanied by a differential neural response to treatment, as measured with fMRI during an emotional face-matching task, in the posterior cingulate cortex, mid temporal and inferior frontal gyri. Thus, the efficacy of SSRIs may be highly dependent on positive expectancies, traditionally associated with placebo response. The presentation of the treatment may be as important as the treatment itself.

3.1c Patient-clinician brain concordance supports therapeutic alliance, facial mirroring, and placebo analgesia during pain treatment: a fMRI hyperscanning study

1. Dan-Mikael Ellingsen. *University of Oslo, Oslo, Norway.*
2. Kylie Isenburg. *Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States.*
3. Changjin Jung. *Korea Institute of Oriental Medicine, Daejeon, South Korea.*
4. Jeungchan Lee. *Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States.*
5. Jess Gerber. *Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States.*
6. Ishtiaq Mawla. *University of Michigan Medical School, Ann Arbor, MI, United States.*
7. Roberta Sclocco. *Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States.*
8. Karin Jensen. *Karolinska Institute, Stockholm, Sweden.*
9. Robert Edwards. *Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States.*
10. John Kelley. *1) Endicott College, Beverly, MA, United States; 2) Harvard Medical School, Boston, MA, United States.*
11. Irving Kirsch. *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States.*
12. Ted Kaptchuk. *Harvard Medical School, Boston, MA, United States.*
13. Vitaly Napadow. *Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States.*

The patient-clinician relationship can powerfully shape pain and placebo response, but the brain mechanisms are unknown. We simultaneously recorded functional MRI in patient-clinician dyads, who interacted via on-line video, while clinicians treated patients' pain. We hypothesized that placebo analgesia and non-verbal communication would be supported by concordant activation of ventrolateral Prefrontal Cortex (vlPFC), anterior Insula (aINS), and Temporoparietal Junction (TPJ), which are implicated in social mirroring, empathy, and theory-of-mind.
We enrolled patients (fibromyalgia) and clinicians (acupuncturists). Each patient was matched with a clinician (n=37 dyads). During block-design fMRI, patients received 12 moderately painful cuff pressures to the left leg while the clinician applied (real/sham, double-blind) electro-acupuncture stimulation (EA) to reduce cuff pain. Facial expression was assessed using Affectiva software. While cuff pressure was identical for all stimuli, patients' pain was significantly decreased during both real ($t=2.89, p=0.01$) and sham ($t=2.70, p=0.01$) EA treatment compared to overt no-treatment. Correspondingly, clinicians rated vicarious pain as decreased with treatment (real/sham combined), relative to no-treatment ($t=4.88, p<0.0001$).
A conjunction analysis of patients' (evoked pain+treatment) and clinicians' (observing pain+treating) brain response demonstrated consistent activation of vlPFC, aINS, and TPJ. Furthermore, stronger patient-clinician concordance in right TPJ was associated with higher mirroring in facial expressions ($r=0.44, p=0.03$) and stronger patient-rated placebo analgesia (Treat–No-treat; $r=-0.45, p=0.005$). Finally, higher facial mirroring was associated with higher therapeutic alliance and stronger placebo analgesia ($r=-0.48, p=0.01$).
Consistent with TPJ as central in social mirroring and theory-of-mind, brain-to-brain coupling of TPJ activity between interacting patients and clinicians may underpin therapeutic alliance and psychosocially facilitated placebo analgesia.

3.1d Neural correlates of placebo analgesia – A meta-analysis of individual participant fMRI data

1. Matthias Zunhammer. *Essen University Hospital, Essen, Germany.*
2. Tamás Spisák. *Essen University Hospital, Essen, Germany.*
3. Tor Wager. *University of Colorado, Boulder, CO, United States.*
4. Ulrike Bingel. *Essen University Hospital, Essen, Germany.*

Background: Placebo effects can reduce pain and contribute to clinical analgesia. Our understanding of this phenomenon is insufficient, partly, since mapping the neural correlates of placebo effects is hampered by small sample sizes and the limitations of coordinate-based meta-analyses. We conducted a systematic, image-based meta-analysis of corresponding functional neuroimaging studies to map neuronal correlates of placebo analgesia in the human brain.
Methods: This is a secondary analysis of the sample obtained in (Zunhammer et al. 2018), and includes imaging data of 603 healthy individuals from 21 out of the 28 eligible functional neuroimaging studies on experimental placebo analgesia, published until 2015.
We assessed pain-related brain activity and its correlation with individual behavioral placebo analgesia under matched placebo and control conditions. Analyses included voxel-wise, whole-brain analyses and pattern-similarity analyses with an a-priory set of regions.
Results: Placebo vs. control treatment induced small but widespread reductions in pain-related activity, particularly in regions belonging to ventral attention (including mid-insula) and somatomotor networks (including posterior insula). Placebo treatment tended to increase fronto-parietal activity, though increases displayed a high between-study heterogeneity. Decreases in pain-related activity correlated with the reduction of pain ratings in the ventral attention and somatomotor networks, thalamus, posterior-insula, mid-cingulate and supplementary motor area.
Conclusions: Placebo treatments affect pain-related activity in multiple brain areas. These activity changes may only partly reflect changes in nociception and involve additional brain circuitry related to affective processing and decision-making surrounding pain. Heterogeneity across studies suggests that placebo analgesia is a multi-faceted phenomenon involving multiple cerebral mechanisms.

Parallel Session 3.2

Placebo effects in clinician-patient interactions

Tuesday, July 9, 2:00 PM - 3.00 PM
Aalmarktzaal
Chair: Sandra van Dulmen

3.2a Synchrony in clinician-patient movement mediates placebo effect on perceived pain and trust

1. Pavel Goldstein. *1) University of Haifa, Haifa, Israel; 2) University of Colorado, Boulder, CO, United States.*

Background: Pain is influenced by many 'nonspecific' factors, including placebo effects and social influences. The quality of the clinician-patient relationship is particularly important and also understudied. In this study, we tested whether movement synchrony, a nonverbal expression related to the clinician-patient relationship, mediated the relationship between perceived clinician-patient similarity and patients' pain and patients' trust toward clinicians in a simulated medical interaction.
Methods: Participants (N=66) were assigned 'clinician' and 'patient' roles, and we experimentally manipulated the perceived similarity between clinicians and patients. Each 'patient' was a part of two simulated clinical interactions: one with a 'clinician' partner who they were told shared their core beliefs and values (concordant) and one who did not (discordant). Clinicians administered painful thermal stimulation in a simulated painful medical procedure. Clinician-patient interactions were videotaped and movement synchrony was estimated from videos.
Results: Concordant dyads demonstrated a higher level of movement synchrony than discordant dyads, which was in turn negatively associated with the patients' pain ratings and positively related with trust toward the clinician. Moreover, movement synchrony mediated the group concordance effects on perceived pain and trust toward a clinician.
Conclusions: Movement synchrony in clinician-patient interactions may be a nonverbal measure related to the relationship quality between clinicians and their patients, which in turn affects patient pain perception and also is reflected in patients' trust toward a clinician. These findings increase our understanding of the role of nonverbal clinician-patient interactions on pain perception and pain-related outcomes and the mechanisms that may underlie this relationship.

3.2b Are sweet words enough? A randomized control trial of positive communication surrounding venous catheter insertion in the emergency room

1. Anne Beyeler. *University of Lausanne, Lausanne, Switzerland.*
2. Adélaïde Bonzon. *University of Lausanne, Lausanne, Switzerland.*
3. Hélène Gerhard-Donnet. *Lausanne University Hospital, Lausanne, Switzerland.*
4. Ariane Gonthier. *Lausanne University Hospital, Lausanne, Switzerland.*
5. Olivier Hügli. *Lausanne University Hospital, Lausanne, Switzerland.*
6. Chantal Berna. *Lausanne University Hospital, Lausanne, Switzerland.*

Background. Most prior studies showing that positive communication during procedural information had analgesic effects were not blinded, as the clinician delivering the standardized message was aware of its content. Hence, this study aimed to test positive vs. usual communication during a peripheral venous catheter (PVC) insertion, while keeping both nurses and investigators blinded to the message.
Methods. In the emergency room of a teaching hospital, 131 patients needing a PVC were randomized to a positive or usual (based on observed practices, containing "negative" words such as "needle", "sting", "hurt") message, delivered in a triple-blind through standardized audio-recordings. Intensity of pain and anxiety were measured with a visual analogue scale (0-100mm) after PVC insertion. Scores for non-verbal pain manifestations and for nurse empathic behavior were collected.
Results. 113 patients completed the study; mean age was 49 ± 19 years. Median pain and anxiety intensity in the positive and usual groups was 9.0 (2.0; 29.2) vs 16.0 (2.5; 27.5) (p= 0.75), and 19.0 (0; 58.7) and 22.0 (2.5; 51.0) (p= 0.85), respectively. Median pain behavior was not significantly different between groups. The median nurses empathic behavior score was low in both groups (Positive: 1/5 (1; 2); Usual 1/5 (1; 1.5), p= 0.07).
Conclusions. A positive message delivered blindly regarding a mildly painful procedure in the emergency room did not affect the pain nor the anxiety perceived by patients. Another arm of this study, where nurses deliver the same message, is ongoing and will allow further conclusions.

3.2c From placebo to practice: Insights from the medicine plus provider training program

1. Kari Leibowitz. *Stanford University, Palo Alto, CA, United States.*
2. Alia Crum. *Stanford University, Palo Alto, CA, United States.*

Placebo researchers and experts have long called for work helping clinical practitioners to recognize and utilize the tremendous power of placebo effects in clinical practice. But what would it take to do this? What might a program to help providers recognize and leverage the power of placebo in healthcare look like? This talk assesses the strategies and insights of one such training program. Developed by the Stanford Mind & Body Lab, the Medicine Plus training program teaches healthcare providers about the power and nature of placebo effects over the course of a two-hour, live group training and a one-hour follow-up session. By focusing on recognizing and shaping patient mindsets, the Medicine Plus program teaches providers how to consistently, effectively, and deliberately leverage the effects that produce placebo response alongside active medications and treatments in clinical practice. This talk will discuss insights from implementing this training program throughout Stanford University Primary Care, where over 100 healthcare providers – including physicians, medical assistants, nurse practitioners, and clinic staff – have received the training. Preliminary data analysis suggests that this training was well-received: 87% of providers gave the training the highest possible score for usefulness, 92% of providers gave the training the highest possible score for enjoyableness, and 93% of providers said they were maximally committed to using what they learned in the training in every day practice. Further effects of the training on provider burnout, job satisfaction, and utilization of strategies that boost placebo effects will also be discussed.

3.2d Underpredicting pain may help and harm

1. Kaya Peerdeman. *Leiden University, Leiden, Netherlands.*
2. Antoinette I.M. van Laarhoven. *Leiden University, Leiden, Netherlands.*
3. Dieuwke Veldhuijzen. *Leiden University, Leiden, Netherlands.*
4. Andrew Geers. *University of Toledo, Toledo, OH, United States.*
5. Irving Kirsch. *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States.*
6. Andrea Evers. *Leiden University, Leiden, Netherlands.*

Pain experiences can be shaped by expectancies. Generally, experiences change in the direction of what one expects, i.e., assimilation occurs. Under certain circumstances, however, experiences may change away from what is expected, referred to as contrast effects. Contrast effects have been observed on affective responses, judgements upon social priming, and other outcomes, but for pain only few indications exist. We investigated if contrast effects might occur on pain in cases of strong underprediction of pain.
In Study 1, healthy participants (n=82) received a verbal suggestion that subsequent heat stimuli would be non-painful (strong underprediction) or a suggestion that the stimuli would be moderate-high painful (correct prediction). All participants then received moderate-highly painful heat stimuli. Study 2 (n=123) replicated and extended this by, among others, adding a group who received a suggestion of mild pain (moderate underprediction).
In Study 1, participants who received the strong underprediction suggestion experienced significantly less intense heat pain than participants who received the correct suggestion, i.e., assimilation occurred. Expected pain, certainty of expectation, pain anxiety, pain unpleasantness, as well as trust in the experimenter were also lower after underprediction. Study 2 replicated these findings and additionally indicated that strong versus moderate underpredictions had largely comparable effects.
In conclusion, underpredicting pain can cause people to assimilate their pain experiences towards the instructed pain intensity, even when there is a salient discrepancy. However, it can harm trust and cause uncertainty. Thus, these findings suggest that underpredicting pain can be both helpful and harmful, which is relevant for understanding how painful medical procedures can best be introduced in clinical practice

Parallel Session 3.3

Placebo effects in children and adolescents

Tuesday, July 9, 2:00 PM - 3.00 PM
Breezaal
Chair: Henriet van Middendorp

3.3a Efficacy and safety of pharmacological treatments for migraine prophylaxis: A systematic review and network meta-analysis in children and adolescents

1. Cosima Locher. *1) University of Plymouth, Plymouth, United Kingdom; 2) University of Basel, Basel, Switzerland.*
2. Joe Kossowsky. *1) University of Basel, Basel, Switzerland; 2) Boston Children's Hospital, Harvard Medical School, Boston, MA, United States.*
3. Helen Koechlin. *1) University of Basel, Basel, Switzerland; 2) Boston Children's Hospital, Harvard Medical School, Boston, MA, United States.*
4. Thanh Lan Lam. *LMU Munich, Munich, Germany.*
5. Johannes Barthel. *LMU Munich, Munich, Germany.*
6. Guido Schwarzer. *IMBI Freiburg, Freiburg, Germany.*
7. Klaus Linde. *Technical University Munich, Munich, Germany.*
8. Karin Meissner. *1) Coburg University, Coburg, Germany; 2) LMU Munich, Munich, Germany.*

Background: Migraine is one of the most common neurological disorders in children and adolescents. Despite the high prevalence and burden of migraine, there is a lack of evidence for preventive pharmacological treatments in the pediatric population. The purpose of this study was to examine whether prophylactic pharmacological treatments are more effective than placebo and whether there are differences between substance classes regarding efficacy and safety.
Methods: MEDLINE, Cochrane, Embase, and PsycINFO were searched for studies published through July 2017. Randomized controlled trials of prophylactic pharmacological treatments in youth diagnosed with episodic migraine were included. Primary outcomes were efficacy (i.e., migraine frequency, number of migraine days, number of headache days, headache frequency, or headache index) and safety (i.e., treatment discontinuation due to adverse events and amount of adverse events). We estimated summary odds ratios (ORs) and risk ratios (RRs) using pairwise and network meta-analysis with random effects.
Results: We deemed 25 studies eligible, including 2257 participants. Prophylactic pharmacological treatments included antiepileptics, antidepressants, calcium channel blockers, antihypertensive agents, and food supplements. Preliminary results of the network meta-analysis indicated that migraine preventive treatments have only small effect sizes when compared to placebo. Further results will be presented.
Conclusions: Prophylactic pharmacological treatments have limited evidence supporting efficacy for pediatric migraine. Placebos are effective in reducing migraine frequency. The significant placebo response in migraine indicates that children and adolescents might benefit from innovative treatment modalities that harness the power of the placebo effect in an ethical way. Clinical implications will be discussed.

3.3b Social learning of placebo effects across the life span

1. Katja Weimer. *1) Ulm University Medical Center, Ulm, Germany; 2) University Medical Hospital Tübingen, Tübingen, Germany.*
2. Nazar Mazurak. *University Medical Hospital Tübingen, Tübingen, Germany.*
3. Marco Gulewitsch. *Eberhard-Karls-University Tübingen, Tübingen, Germany.*
4. Luana Colloca. *University of Maryland, Baltimore, MD, United States.*
5. Paul Enck. *University Medical Hospital Tübingen, Tübingen, Germany.*

To investigate whether placebo effects through social observational learning can be elicited in children and adolescents (C&A) and whether these effects are comparable to those in adults.
159 C&A (8-18 years, 46% girls) and their mothers, and 82 couples (CO) (19-67 years) were randomized to five groups. In four groups, participants observed a putative effective intervention either in a familiar (mother/partner) or unfamiliar (trained model) person, and either live or in a video. The control group received verbal suggestions only. Then, participants underwent the same intervention: an inert ointment was applied to two areas of the forearm together with the information that one is a control ointment and the other is an analgesic. Heat stimuli were applied on both areas and rated by the participants regarding their painfulness; difference was calculated as placebo analgesia.
In C&A, we found significant group and sex differences and a responder rate of 69%. Post-hoc tests showed placebo analgesia in all except the mother/video group in girls, whereas boys showed placebo analgesia in the control group only. In CO, there was significant placebo analgesia without group or sex differences, and a placebo responder rate of 62%. Post-hoc tests revealed significant placebo analgesia in the control group in women, and in the unknown model/live group in men only.
Overall, children, adolescents and adults are equally often placebo responders, but under different conditions and dependent on sex. Effects of explicit expectancies and other psychological variables will be further investigated and presented.
(Supported by Deutsche Forschungsgemeinschaft, WE5658/2-1).

3.3c Mind over medication: Using placebo machines and positive suggestion to treat behavioural disorders

1. Jay Olson. *McGill University, Montreal, QC, Canada.*
2. Michael Lifshitz. *Stanford University, Palo Alto, CA, United States.*
3. Michael Stevens. *Intellectual Property Corporation, Van Nuys, CA, United States.*
4. Amir Raz. *Chapman University, Orange, CA, United States.*
5. Samuel Veissiere. *McGill University, Montreal, QC, Canada.*

Background: Various studies have explored the social and situational factors that modulate the placebo response, but few have attempted to combine and maximise these factors. Leveraging research on placebos, suggestion, and persuasion, we tested a novel paradigm to maximise placebo effects in order to reduce the symptoms of behavioural disorders.
Methods: In this feasibility study, we recruited 11 children with various co-morbid conditions: Attention Deficit Hyperactivity Disorder (n=9), Tourette Syndrome (n=4), chronic skin picking (n=1), and migraines (n=1). After watching a celebrity endorsement video of the procedure, the children and families met a large team of researchers in lab coats at the Montreal Neurological Institute. To enhance expectations, a film crew and celebrity science communicator were documenting the procedure. We introduced the children to an elaborate sham fMRI scanner that we explained was inactive but could still help the brain heal itself through the power of suggestion. Over two to four sessions, children entered the scanner for 15 minutes as we gave them positive suggestions that the procedure would reduce their symptoms and improve their strengths. At one- and three-week follow-ups, we collected qualitative data from video-taped home visits, parent reports, and interviews.
Results: Ten of the eleven children showed improvements in symptoms and functioning. Two showed complete remission of symptoms (skin picking and migraines), one of whom remains symptom-free a year later. None reported any side effects.
Conclusion: Combining known factors to maximise placebo effects can offer a safe and effective treatment for chronic conditions.

Parallel Session 3.4

Innovative ways to enhance placebo analgesia

Tuesday, July 9, 2:00 PM - 3.00 PM
Jan Willem Schaap zaal
Chair: Judy Veldhuijzen

3.4a Testing if and when the mere possession of a placebo analgesic cream enhances pain resilience

1. Victoria Wai-lan Yeung. *Lingnan University, Tuen Mun, Hong Kong.*
2. Andrew Geers. *University of Toledo, Toledo, United States.*
3. Luana Colloca. *University of Maryland, Maryland, MD, United States.*

Background: Yeung et al. (2017) proposed that merely possessing a placebo analgesic may reduce pain. Study 1 directly compared the effect of using vs. possessing a placebo analgesic (compared to controls) on pain-resilience. Second, Geers et al. (2015) found that a placebo analgesic leads to greater pain-reduction for participants without a related prior pain experience. As such, Study 2 examined if mere-possession of a placebo analgesic affects pain with vs. without a related prior-pain-experience.
Methods: Study 1: Participants completed a marketing-survey. Some received a souvenir (a placebo analgesic cream vs. a pain-irrelevant sham cream), some did not (no-cream). Participants who received the placebo analgesic cream either used it or merely possessed it. All participants did a cold-pressor-test (CPT).
Study 2: Participants completed a marketing-survey. Some received a souvenir (a placebo analgesic cream), some did not (no-cream). All participants completed a CPT. In the with-prior-pain condition, participants did a practice-CPT before the marketing-survey to induce a prior-pain-experience. No practice-CPT in the without-prior-pain condition.
Results: Study 1: Participants using the placebo analgesic cream reported higher pain-tolerance and lower pain-intensity than participants in the two control-groups (no-cream, sham-cream). Surprisingly, participants merely possessing the placebo analgesic cream performed equally well as those actually using the cream.
Study 2: Upon possessing a placebo cream, participants without (vs. with) prior-pain-experience reported greater pain-efficacy. This effect was not observed when participants did not possess any cream.
Conclusions: Merely possessing a placebo can enhance pain-resilience to the same extent as applying it. Such mere-possession enhances pain-efficacy when one has no prior-pain-experience.

3.4b Instrumental control enhances placebo analgesia

1. Biya Tang. *University of Sydney, Sydney, NSW, Australia.*
2. Andrew Geers. *University of Toledo, Toledo, OH, United States.*
3. Kirsten Barnes. *University of Sydney, Sydney, NSW, Australia.*
4. Ben Colagiuri. *University of Sydney, Sydney, NSW, Australia.*

Placebo effects are often studied under passive conditions where participants have no control over their treatment. However, having instrumental control over if and when a treatment is administered may facilitate placebo learning and lead to stronger placebo effects. We tested this possibility for placebo analgesia using an electro-cutaneous pain paradigm. 87 healthy volunteers were recruited under the guise of a study investigating the effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS) on psychophysiological responses to pain but it was actually a placebo. Instead, participants were randomized to receive either placebo conditioning with instrumental control over treatment administration, standard passive placebo conditioning with no such control, or natural history. During training, the placebo was paired with a surreptitious reduction in shock intensity in placebo groups but not in the natural history group. At test, shock intensity remained equivalent regardless of the whether or not the placebo was applied. As expected, placebo analgesia was observed following standard passive conditioning. Importantly, however, we found that those given instrumental control exhibited larger and more durable placebo analgesia as well as reduced anticipatory autonomic arousal than their passive counterparts. As such, the study suggests that providing instrumental control facilitates placebo analgesia both in terms of its magnitude and resistance to extinction, and therefore could be used to improve clinical pain outcomes cheaply and ethically.

3.4c The imaginary placebo pill: Isolating psychological components of placebo pills for treatment in clinical practice

1. Niels Bagge. *Institute for Emotion Focused Therapy, Roskilde, Denmark.*

Received wisdom was that placebos had to be administered deceptively to have an effect in clinical practice. More recently, it has been shown that placebos can be effective even when patients know they are taking a placebo pill. This presentation moves one step further and looks a placebo effect without a physical pill. What would happen if you just imagined taking a placebo pill? Would that work? And how much? The presenter shares his clinical work as a psychologist in the treatment of pain and emotional problems with imaginary placebo pills (IPP). You will learn about the discovery and background of IPP, the procedure of administering the IPP, including a presentation of cases and a live demonstration of IPP. The method of the imaginary placebo pill offers a practical clinical use of placebo effects without the limitations of deception and physical pills, but still harnessing the placebo effects. The presentation will end with a discussion of theoretical, practical and research implications of the use of imaginary placebo pills.

3.4d Social learning influences the additive placebo effect of analgesic treatment in functional capacity in chronic pain patients

1. Marie Schwartz. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
2. Laura-Marie Fischer. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
3. Corinna Blaeute. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
4. Jan Storck. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
5. Christian Zöllner. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*
6. Regine Klinger. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: Research demonstrates that placebo effects enhance the effectiveness of analgesics. Hence the effectiveness of analgesics consist of the pharmacological and the (additive) placebo component. The placebo effect can be learned by instruction and classical conditioning. New studies suggest social learning as another learning mechanism. This has not been investigated in chronic pain patients, leading to our research question: Can social learning strengthen the additive placebo effect in chronic pain patients?
Methods: 44 patients with chronic back pain and amitriptyline medication encounter a model patient. The control group had a neutral interaction. The social learning group was told that he experiences less pain and was more mobile. He demonstrated his improved flexibility with short exercises. After 2 weeks the patients were interviewed via phone. The primary outcome was the NRS (numeric rating scale) and the secondary outcome was everyday mobility (FFbH-R).
Results: Both groups experienced significantly less pain on average ($F(1;42)=7.16$, $p<0.05$). There was no difference in improvement between groups ($F(1;42)=0,69$, $p=0,41$). Only the social learning group benefitted significantly from the encounter with improved everyday mobility ($F(1;42=4,22$, $p<0,05$).
Conclusions: The placebo effect on average pain was equal in both groups which we attribute to contextual factors (attention etc.). The social learning group could not observe directly the change in pain in their model which explains why no social learning took place. The results in functional capacity substantiate this theory further. Only the social learning group benefitted in functional capacity because they could observe the improvement in the model patient directly.

Parallel Session 3.5

Novel perspectives on placebo effects

Tuesday, July 9, 2:00 PM - 3.00 PM
Cornelis Schuyt zaal
Chair: Ann Meulders

3.5a Placebo-effects of communication alongside standard medical care: Results of a randomized controlled trial in clinical tonsillectomy care

1. Liesbeth van Vliet. *1) OLVG Hospital, Amsterdam, Netherlands; 2) NIVEL, Utrecht, Netherlands.*
2. Marc Godfried. *OLVG Hospital, Amsterdam, Netherlands.*
3. Gerard van Deelen. *OLVG Hospital, Amsterdam, Netherlands.*
4. Menno Kaunang. *NIVEL, Utrecht, Netherlands.*
5. Ted Kaptchuk. *Harvard Medical School, Boston, MA, United States.*
6. Sandra van Dulmen. *1) NIVEL, Utrecht, Netherlands; 2) Radboud University Medical Center, Nijmegen, Netherlands; 3) University of South-Eastern Norway, Drammen, Norway.*
7. Bram Thiel. *OLVG Hospital, Amsterdam, Netherlands.*
8. Jozien Bensing. *NIVEL, Utrecht, Netherlands.*

Background: Placebo effects of clinicians' communication can be attributed to several mechanisms including expectancy (about pain-relieving effects of medication) and empathy (displayed by clinicians). So far, such effects have primarily been studied in laboratory settings. To strengthen the clinical application of placebo-effects, we tested the separate and combined effects of expectancy- and empathy-manipulation alongside standard medical care via nurses' communication on clinical patients' (pain) outcomes.
Methods: 128 adult tonsillectomy patients were randomly assigned to one out of four conditions differing in the level of expectancy- and empathy-manipulation (standard vs enhanced, 2x2 design). Trained nurses delivered the intervention alongside standard (analgesic) hospital care. Outcome measures were, amongst others, pain-related (e.g. primary outcome (maximum) pain day 1-3, evaluation of pain) and psychological (e.g. anxiety). Audio-recordings of nurse–patient interactions verified the manipulations. Main and interaction effects of expectancy and empathy were assessed.
Results: Patients' experienced pain was unaffected by expectancy and empathy on day 1 ($p=0.43$, $p=0.34$), day 2 ($p=0.96$, $p=0.57$), day 3 ($p=0.33$, $p=0.23$). Following high expectancies, patients' evaluated their experienced pain ($p=0.02$) and experienced care ($p<0.10$, trend) more favorable. No effects on other outcomes were found. Nurses successfully performed expectancy- and empathy-manipulations (82% vs 68%), which was not consistently perceived as such by patients ($p>0.10$).
Discussion: Although our study found little significant effects of enhanced expectancy and empathy on patient (pain) outcomes compared to standard medical care, results were often in the expected direction. Described methodological complexities and limitations can be overcome by future studies in this important, yet fragile, research field.

3.5b Placebo algorithms: An ethical roadmap for the next revolution in medicine

1. Marco Annoni. *1) National Research Council (CNR - Italy), Rome, Italy; 2) Fondazione Umberto Veronesi, Milan, Italy.*

Medicine is about to face another revolution caused by rapid development and massive adoption of technologies based on the coalescence of artificial intelligence, machine learning, and big data. This algorithmic revolution is bound to dramatically transform both clinical and research practice. As I will argue, this paradigm shift has many relevant implications for placebo studies too. For instance, soon it may be possible to rapidly discriminate between placebo responders and non-responders with a degree of reliability that genetic and physiological data alone cannot presently match. Likewise, these new technologies may be able to identify in advance what is the intrinsic potential of each doctor to promote or inhibit placebo and nocebo effects, and thus how to pair a specific patient with a specific doctor in order to maximize positive clinical outcomes. In this talk, I shall explore the main ethical challenges that medicine in general – and placebo studies in particular – will face in the near future due to these new and algorithmically-driven innovations. As I will argue, identifying such challenges at this early stage is crucial in order to prepare for what is about to come, thus ensuring that these technologies will be used to promote the health and wellbeing of patients, doctors, and society, rather than to serve only corporative interests.

3.5c Music relieves pain – Especially if you expect it to

1. Sigrid Juhl Lunde. *Aarhus University, Aarhus, Denmark.*
2. Peter Vuust. *Aarhus University, Aarhus, Denmark.*
3. Eduardo A. Garza-Villarreal. *National Institute of Psychiatry "Ramon de la Fuente Muñiz", Mexico City, Mexico.*
4. Irving Kirsch. *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States.*
5. Arne Møller. *Aarhus University, Aarhus, Denmark.*
6. Lene Vase. *Aarhus University, Aarhus, Denmark.*

Background: Several studies have demonstrated an analgesic effect of music. Yet, whether this effect is induced by music itself or whether it reflects positive expectations for the analgesic capacity of music is largely unknown.
Methods: Forty-eight healthy participants were exposed to painful thermal stimuli while listening to three auditory conditions: classical music (active), nature sound (placebo) and pink noise (control). Participants were given verbal suggestions for pain relief prior to music and nature sound, and they rated their expected pain intensity (PI) and pain unpleasantness (PU) on 0-100 VAS prior to thermal stimuli. After each thermal stimulus participants rated their experienced PI and PU on VAS.
Results: Participants expected significantly lower PI and PU for music ($p < .001$) and nature sound ($p < .001$) compared with pink noise, and they expected significantly lower PI and PU for music ($p \leq .026$) compared with nature sound. Similarly, participants experienced significantly lower PI and PU during music ($p < .001$) and nature sound ($p < .001$) compared with pink noise, and they experienced significantly lower PI and PU during music ($p \leq .046$) compared with nature sound. Path regression analysis showed that expectations for PI and PU significantly predicted experienced PI and PU.
Conclusions: The results support an analgesic effect of music. Importantly, however, the study demonstrates that this effect may be explained by expectations rather than by an analgesic capacity of music per se.

3.5d The role of placebo effects in mindfulness-based analgesia

1. Jonathan Davies. *University of Sydney, Sydney, NSW, Australia.*
2. Louise Sharpe. *University of Sydney, Sydney, NSW, Australia.*
3. Melissa Day. *University of Queensland, Brisbane, QLD, Australia.*
4. Ben Colagiuri. *University of Sydney, Sydney, NSW, Australia.*

Background: Mindfulness meditation can reduce pain both in experimental and clinical settings, though it is not known to what extent mindfulness-specific vs placebo-like expectancy effects account for these changes. This study aimed to: 1. establish whether placebo effects contribute to mindfulness-mediated analgesia; and 2. identify putative cognitive mechanisms responsible for placebo- vs mindfulness-mediated analgesia.
Methods: We compared the effects of focussed-attention mindfulness training (6 x 20 min), sham mindfulness, and a no-treatment in a double-blind RCT for experimental heat pain. Sham mindfulness instructions lacked the 'active ingredients' of the real training but were matched on all other contextual factors.
Results: Both real and sham mindfulness training led to greater pain tolerance relative to no treatment, but there was no difference between the real and sham training. This was accompanied by increased expectancy, beliefs, and pain-related cognitive processes in the two mindfulness groups relative to no treatment, but again there were no differences between real and sham training on these outcomes. There were no effects on pain intensity, pleasantness or threshold.
Conclusion: These findings suggest that mindfulness training – at least those involving focused-attention – may lead to improved pain tolerance via the placebo effect rather than any specific mindfulness-related mechanisms. Potential mediators of these effects will be discussed.

Plenary Session 5

Novel neuroimaging findings: How do placebo effects work?

Tuesday, July 9, 03.30 PM - 05.15 PM
Grote zaal
Chair: Katja Weich

The role of the periaqueductal gray in placebo and nocebo

Christian Büchel

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

About Christian Büchel
Christian Büchel is a full professor of Systems Neuroscience and Head of the Department of Systems Neuroscience at the University Medical Center Hamburg-Eppendorf. He graduated from Heidelberg University as MD. His scientific career continued as a Wellcome Research Fellow at the Wellcome Department of Imaging Neuroscience at UCL in London. From there he moved to Hamburg and headed a research group funded by the Volkswagen Foundation. He is the holder of major research grants from the European Research Council, German Research Foundation (DFG), and German Ministry for Science. Christian Büchel has published more than 200 peer reviewed research articles and was awarded the Jung Award for Medicine, the Gottfried Wilhelm Leibniz-Preis by the German Research Foundation, and the Wiley Young Investigator Award of the Organization for Human Brain Mapping for recognition of his work on effective connectivity in neuroimaging.

Plenary Abstract
Expectation and experience can shape pain perception in a powerful way. The neurobiological mechanisms underlying these effects are slowly unfolding. Many studies have identified the periaqueductal gray (PAG) as a key area in modulating pain such as in offset analgesia. In addition, many studies have highlighted the PAG in placebo analgesia, but also in nocebo hyperalgesia. Based on these results and new data, we propose a specific role for the PAG in pain modulation emphasizing its role in dynamic aspects of pain.

Dissociating psychological and neural components of placebo and expectancy-based modulation

Lauren Atlas

National Institutes of Health, Bethesda, MD, United States

About Lauren Atlas
Lauren Atlas is a Tenure-Track Clinical Investigator at the National Institutes of Health. She is Chief of the Section on Affective Neuroscience and Pain in the National Center for Complementary and Integrative Health and holds a joint appointment with the National Institute on Drug Abuse. Her laboratory integrates experimental psychology, neuroimaging, psychophysiology, and computational approaches to understand how expectations and other cognitive and affective factors influence pain, emotional experience, and clinical outcomes. Current projects focus on dissociating components of expectancy, relating pain with other types of hedonic affective responses, and understanding social influences on pain. Long–term goals include revealing how specific features of the clinical context and interpersonal aspects influence patient outcomes, as well as determining whether expectancy–based processing is altered in specific patient populations. Dr. Atlas received her PhD in Psychology from Columbia University, and completed postdoctoral training at New York University.

Plenary Abstract
It has long been understood that placebo effects and expectancy-based modulation depend on a combination of factors, including cognitive beliefs, conditioning or associative learning, and contextual factors such as the patient-provider relationship. In this talk, I will present a series of studies that combine experimental psychology and cognitive neuroscience to dissociate these components. I will present work that directly compares stimulus expectancies and treatment expectancies, and isolates their underlying neural substrates. We find that both stimulus and expectancy effects influence acute pain, and that there are interactions between the two types of expectations. I will also address work dissociating instructions and conditioning, and new findings on patient-provider relationships. Together, this work demonstrates how we can systematically manipulate and measure the various factors that underlie placebo analgesia to better understand the placebo effect and how to maximize patient outcomes.

Brain concordance supports patient/clinician therapeutic alliance and modulates placebo analgesia: A hyperscan fMRI approach

Vitaly Napadow

Harvard Medical School, Boston, MA, United States

About Vitaly Napadow
Vitaly Napadow is an Associate Professor at the Martinos Center for Biomedical Imaging at Massachusetts General Hospital and Harvard Medical School in Boston, MA, where he is also the Director of the Center for Integrative Pain Neuroimaging (CiPNI). Vitaly received his Ph.D. in biomedical engineering from the Harvard-MIT Health Sciences and Technology program. Dr. Napadow's laboratory has pioneered the application of non-invasive neuroimaging techniques to better understand the brain circuitry underlying aversive perceptual states, particularly chronic pain, and to better understand how non-pharmacological therapies ameliorate these states. Specifically, somatosensory, cognitive, and affective factors all influence the malleable experience of pain, and the Napadow Lab has applied human functional and structural neuroimaging to localize and suggest mechanisms by which different brain circuitries modulate pain perception. Dr. Napadow has more than 130 publications in leading peer-reviewed scientific journals and serves on numerous conference, journal, and NIH review panels.

Plenary Abstract
The patient-clinician relationship and therapeutic alliance can significantly influence how the patient perceives pain. While this factor is acknowledged as significantly contributing (or even driving) analgesia for many clinical therapies, the neural mechanisms supporting this effect are unknown. We simultaneously recorded functional Magnetic Resonance Imaging (fMRI hyperscanning) in patient-clinician dyads, who interact via video transfer, during clinician-initiated treatment of evoked pain in chronic pain (fibromyalgia) patients. We hypothesized concordant activation of circuitry involved in social mirroring, such as ventrolateral Prefrontal Cortex (vlPFC) and anterior Insula (aINS) in both patients and clinicians during pain treatment. Patients' pain significantly decreased during acupuncture treatment compared to overt no-treatment, which corresponded with lower vicarious pain ratings by clinicians. Furthermore, patients' analgesia correlated with clinicians' estimation of patients' pain reduction. A conjunction analysis of patients' and clinicians' brain response during pain and treatment demonstrated overlapping activation of vlPFC, aINS, and temporoparietal junction (TPJ), all regions previously linked with social mirroring circuitry. Using ROI extraction from the group conjunction mask, we found that association in trial-to-trial variability in activation between patients and clinicians (i.e. the degree of brain concordance) correlated with patients' analgesia, within dyads. Thus, increased patient-clinician concordance in social mirror circuitry may support socially facilitated placebo analgesia. Our novel experimental design provides a viable framework by which brain-based mechanisms supporting therapeutic alliance can be evaluated in a systematic manner in future studies.

How are expectations and sensations combined in the sensory brain?

Floris de Lange

Radboud University, Nijmegen, Netherlands; 2) Donders Institute, Nijmegen, Netherlands

About Floris de Lange
I am full Professor at the Radboud University in Nijmegen, Netherlands and Principal Investigator of the Predictive Brain Lab at the Donders Institute. I obtained a Master's degree in Artificial Intelligence in 2003, and a PhD degree in Cognitive Neuroscience in 2008, both at Radboud University Nijmegen. From 2007-2009, I was a post-doctoral fellow in the lab of Prof. Stanislas Dehaene at Neurospin, Paris, France. From 2009, I established the Predictive Brain Lab at the Donders Institute, where we study how various forms of prior knowledge modify perception and decision-making, both in health and disease. I am currently supported by a ERC Starting grant, NWO Vidi grant and a James McDonnnell Foundation grant. I am member of the Young Academy of the Netherlands Royal Academy of Sciences (KNAW) and my work is internationally visible (>7,500 citations, h-index=49). I am a strong believer in and proponent of Open Science (e.g., all recent data and code of my lab can be freely downloaded) and Open Access (e.g., I'm an editorial board member at eLife).

Plenary Abstract
Perception and perceptual decision-making are strongly facilitated by prior knowledge about the probabilistic structure of the world. While the computational benefits of using prior expectation in perception are clear, there are myriad ways in which this computation can be realized. In my talk, I will discuss recent observations from my lab into how this process may be neurally implemented. Specifically, I will: 1) provide evidence for the separation of priors and likelihood in different layers of the cortex; 2) examine the integration of priors and likelihood in the context of the word superiority effect; 3) show that attention mediates this balance by increasing, rather than reducing, the effect of priors.

Placebo effects in RCTs: Emerging neuroimaging evidence and implications for the additivity model in RCTs

Vishivarani Wanigasekera

University of Oxford, Oxford, United Kingdom

About Vishivarani Wanigasekera
Dr. Wanigasekera is a Clinical Research fellow in the Anaesthesia, Pain and Analgesia Neuroimaging Group lead by Prof. Irene Tracey at the University of Oxford. She is also a practicing clinician at the Oxford University Hospitals Trust with clinical commitments as an intensivist in the Cardio Thoracic Critical Care Unit at the John Radcliffe Hospital.
Her research interests focus on understanding pain and analgesia mechanisms to optimize pain relief in chronic pain. These include validating neuroimaging as a biomarker for early analgesic drug development and characterising the placebo effects in a clinical trial setting. Dr. Wanigasekera received her D.Phil from University of Oxford for her work on the investigation of human brain mechanisms of opioid pharmacodynamics using neuroimaging. In this body of work, she explored the role of reward circuitry in predicting opioid analgesic efficacy and the interaction between expectation and opioid analgesic efficacy.

Plenary Abstract
Chronic pain is poorly managed, lack of effective analgesics being one of the key reasons. Inherent variability in subjective pain reports and the expectation driven effects on pain reports make assessment of analgesics efficacy challenging especially during early analgesic drug development. The current gold standard of demonstrating analgesic efficacy is by using RCTs that include a placebo arm. Here analgesic efficacy is assumed if the drug arm shows pain relief beyond that seen in the placebo arm. The validity of this additivity model is being currently questioned. I will present emerging evidence from neuroimaging studies that support this view.

Practicalities

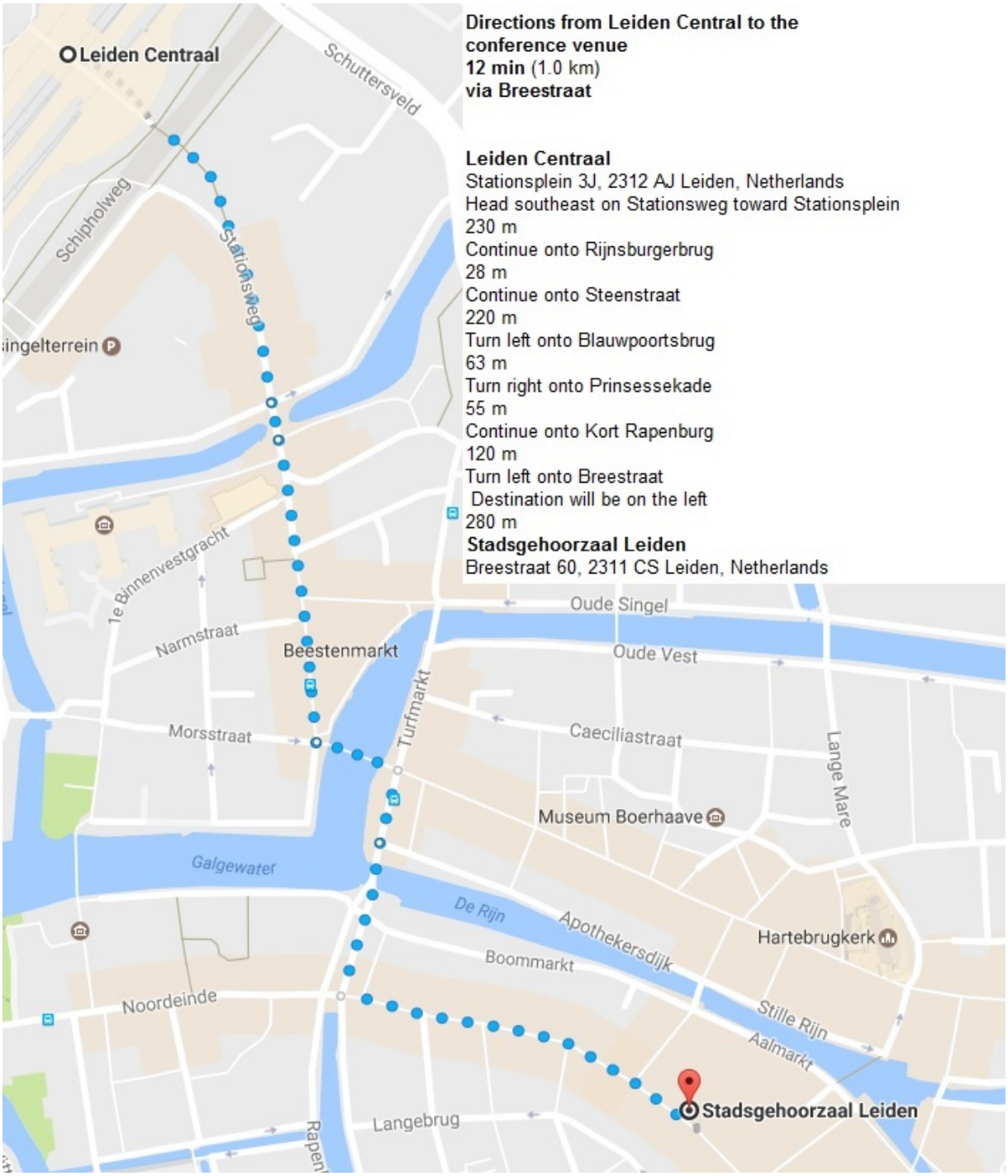
WiFi Passwords

WiFi Password	Address
Stadsgehoorzaal (conference venue)	Network name: leidseschouwburg-stadsgehoorzaal Password: Applaus!

Address overview

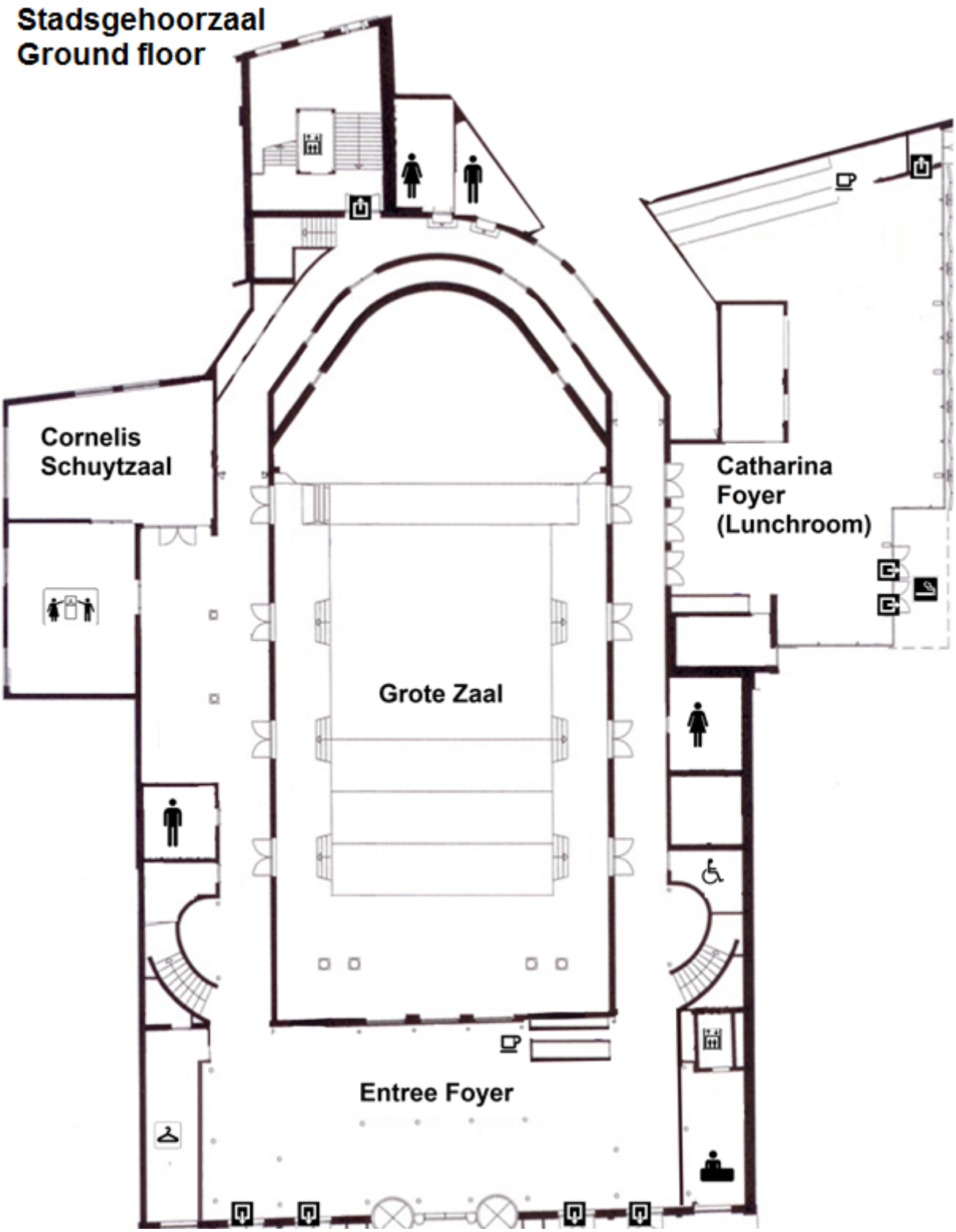
Location	Address
Stadsgehoorzaal (conference venue)	Breestraat 60 2311 CS Leiden
Beachclub Bait (dinner location)	Busses will take you from the conference venue to the restaurant Wassenaarse slag 31 2242 PG Wassenaar
Leiden Central Station	Stationsplein 3J 2312 AJ Leiden

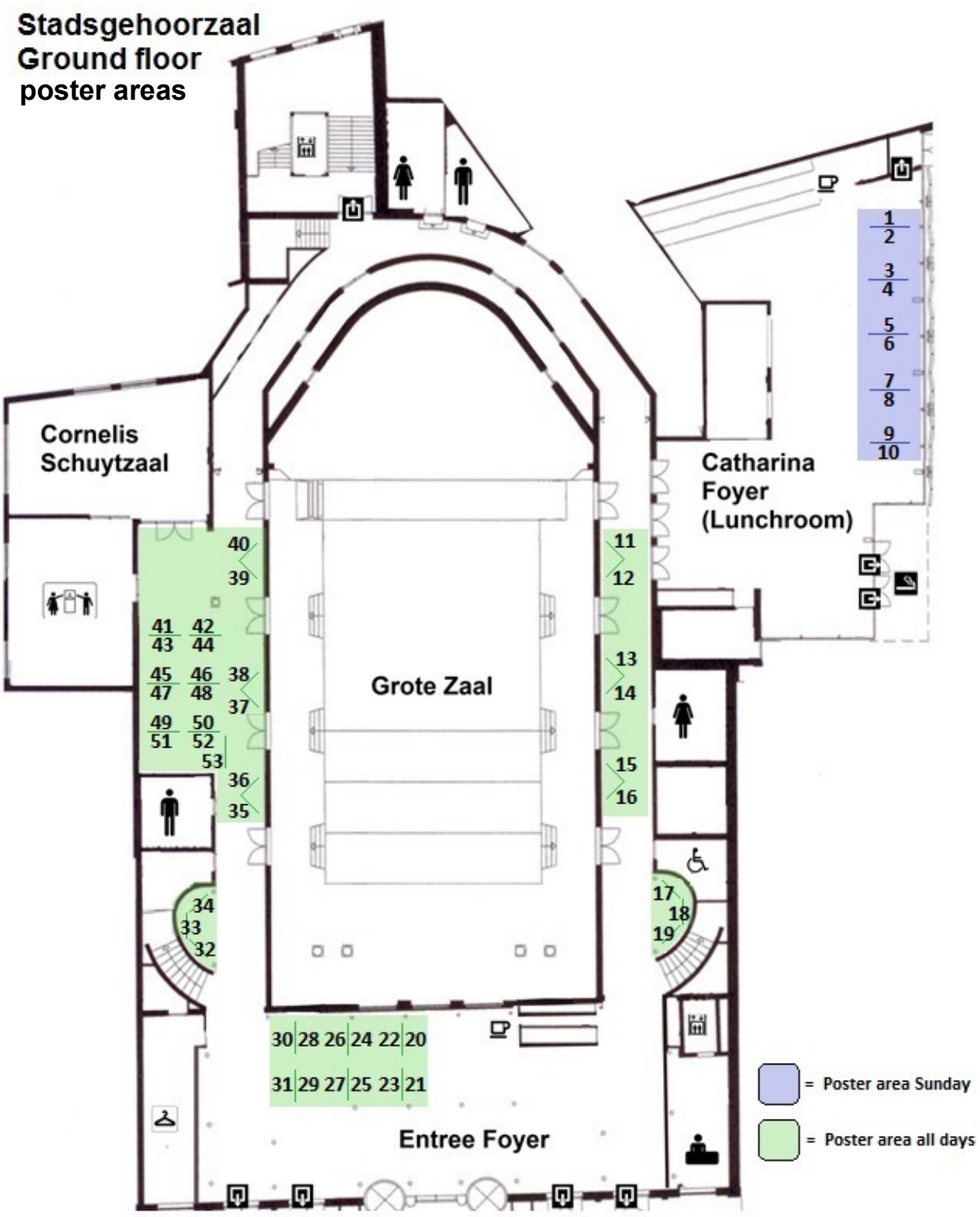
Leiden Central to Stadsgehoorzaal



Directions from Leiden Central to the conference venue
12 min (1.0 km)
via Breestraat

Leiden Centraal
Stationsplein 3J, 2312 AJ Leiden, Netherlands
Head southeast on Stationsweg toward Stationsplein
230 m
Continue onto Rijnsburgerbrug
28 m
Continue onto Steenstraat
220 m
Turn left onto Blauwpoortsbrug
63 m
Turn right onto Prinsessekade
55 m
Continue onto Kort Rapenburg
120 m
Turn left onto Breestraat
Destination will be on the left
280 m
Stadsgehoorzaal Leiden
Breestraat 60, 2311 CS Leiden, Netherlands


Stadsgehoorzaal
Ground floor
Cornelis
Schuytzaal
Catharina
Foyer
(Lunchroom)
Grote Zaal
Entree Foyer


Stadsgehoorzaal
Ground floor
poster areas
Cornelis
Schuytzaal
Catharina
Foyer
(Lunchroom)
Grote Zaal
Entree Foyer
1/2
3/4
5/6
7/8
9/10
40
39
41/43
42/44
45/47
46/48
38
37
49/51
50/52
53
36
35
11
12
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14
15
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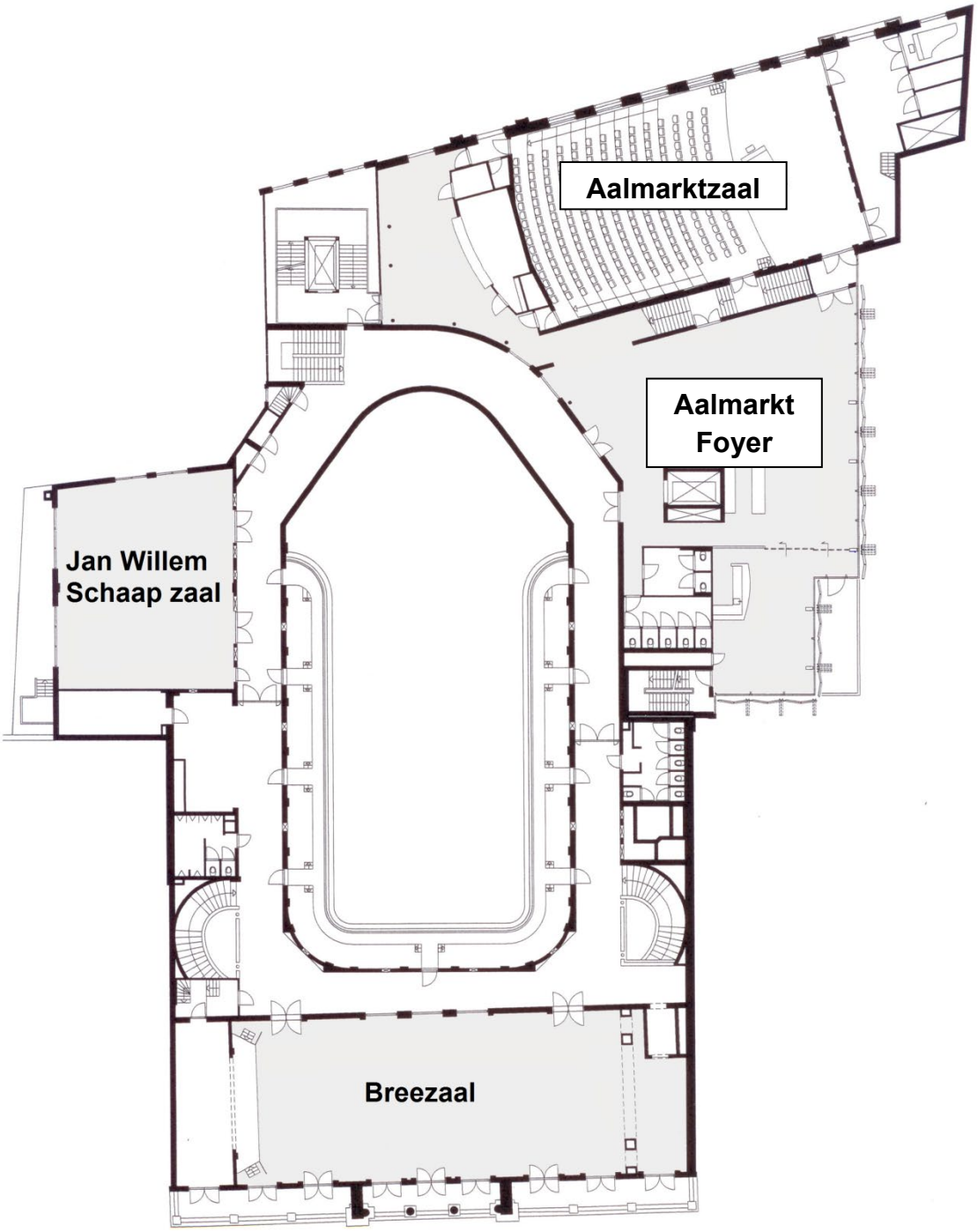
32
17
18
19
30 28 26 24 22 20
31 29 27 25 23 21
= Poster area Sunday
= Poster area all days

Stadsgehoorzaal
First floor



Accreditation

Accreditation was granted for Dutch general practitioners (huisartsen), medical specialists (medisch specialisten), health care psychologists (gezondheidszorgpsychologen), nurses (verpleegkundigen), nurse specialists (verpleegkundig specialisten), and physiotherapists (fysiotherapeuten).

- Accreditatie Bureau Algemene Nascholing (ABAN) Cluster 1, 2, and 3
  13 points
- Federatie van Gezondheidszorgpsychologen en Psychotherapeuten (FGzPt)
  14 points
- Accreditatiebureau Kwaliteitsregister V&V en Register Zorgprofessionals (V&V): Scholing Pijnverpleegkunde, Scholing Research & Scholing Researchprofessionals
  16 points
- Accreditatiebureau Verpleegkundig Specialisten Register (V&VN): Scholing verpleegkundig specialisten
  16 points
- Accreditatiebureau Nederlands Genootschap voor Fysiotherapie (KNGF): Kwaliteitsdeel van het Centraal Kwaliteitsregister voor Fysiotherapie
  17 points

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