SIPS society for interdisciplinary placebo studies

FIRST OFFICIAL SIPS CONFERENCE

Program & Abstract book

APRIL 2 - 4, 2017
Leiden, the Netherlands

Content

Welcome

Dear attendee of the SIPS conference 2017,

It is a great pleasure and honor for the organizing committee of this first official Society for Interdisciplinary Placebo Studies (SIPS) conference on placebo studies to welcome you at the conference. The conference venue is Stadsgehoorzaal in Leiden, the Netherlands. This first edition of the SIPS conference promises to be very inspiring and we highly appreciate that so many researchers contributed to the rich and varied conference program and made their way to attend the conference.

The range of topics mirrors the efforts of SIPS to advance research on knowledge of placebo effects to eventually improve clinical care. Next to the keynote speakers and the invited speaker sessions, we are pleased to offer a scientific program with different sessions to choose from each time due to the many submitted contributions. This may serve you to make the most out of the program. We are also very pleased to invite you to the conference dinner which will take place on Monday evening April 3, at the Scheltema restaurant.

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 have to offer!

Sincerely,

On behalf of the local and international conference committee,

Andrea W.M. Evers
Chair SIPS conference 2017

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Conference Day 1: Sunday April 2, 2017

Conference venue: Stadsgehoorzaal, Leiden

Time	Activity	Location
03:00 PM	Registration	Entree Foyer
04:00 PM	Special welcome *Henri Lenferink (Mayor Leiden)*	Aalmarktzaal
	Conference opening *John Kelley & Andrea Evers*	
	Keynote Lecture *Ted Kaptchuk*	
	Travel awards	
06:00 PM	Opening reception	Aalmarkt Foyer

Conference Day 2: Monday April 3, 2017

Conference venue: Stadsgehoorzaal, Leiden

Time	Activity	Location
08:00 AM	Registration and welcome with coffee and tea	Entree Foyer
08:30 AM	Keynote Lecture *Fabrizio Benedetti*	Grote Zaal
09:15 AM	Plenary session 1: Ethical aspects and challenges of trial design in placebo research	Grote Zaal
11:00 AM	Coffee break	Catharina Foyer
11:30 AM	Parallel sessions 1.1 Neuroimaging of placebo effects 1.2 Learning mechanisms of placebo and nocebo effects 1.3 Doctor-patient communication and placebo effects 1.4 How we think about placebo effects	 Grote Zaal Breezaal Jan Willem Schaap zaal Cornelis Schuytzaal
01:00 PM	Lunch and poster presentations	Catharina Foyer
02:00 PM	Plenary session 2: Clinical applications of placebo effects	Grote Zaal
03:45 PM	Coffee break	Catharina Foyer
04:15 PM	Plenary session 3: Learning and brain plasticity in placebo effects	Grote Zaal
06:00 PM	Keynote Lecture *Katja Wiech*	Grote Zaal
06:45 PM	Break	
07:30 PM	Conference dinner	Scheltema restaurant

Conference Day 3: Tuesday April 4, 2017

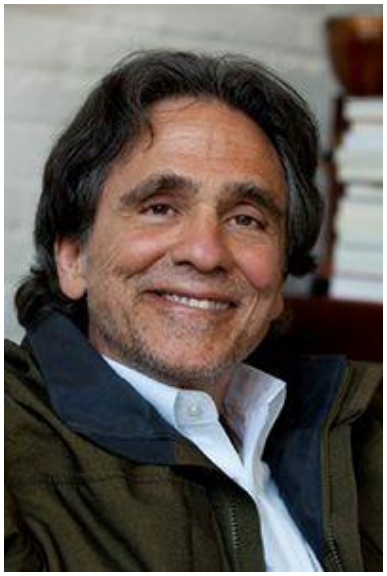
Conference venue: Stadsgehoorzaal, Leiden

Time	Activity	Location
08:00 AM	Registration and welcome with coffee and tea	Entree Foyer
08:30 AM	Keynote Lecture *John Kelley*	Grote Zaal
09:15 AM	Plenary session 4: Placebo effects: mediators and moderators	Grote Zaal
11:00 AM	Coffee break	Catharina Foyer
11:30 AM	Parallel sessions 2.1 Nocebo effects 2.2 Biological predictors of placebo effects 2.3 Placebo effects in psychology and psychiatry 2.4 Concepts in placebo research	 Grote Zaal Breezaal Jan Willem Schaap zaal Cornelis Schuytzaal
01:00 PM	Lunch and poster presentations	Catharina Foyer
02:00 PM	Plenary session 5: The neurobiology of placebo and nocebo effects	Grote Zaal
03:45 PM	Coffee break	Catharina Foyer
04:15 PM	Parallel sessions 3.1 Towards applications of placebo effects in clinical practice 3.2 Neurobiological & pharmacological placebo effects 3.3 Generalization of placebo effects 3.4 Placebos in RCTs	 Grote Zaal Breezaal Jan Willem Schaap zaal Cornelis Schuytzaal
05:45 PM	Keynote Lecture *Christian Büchel*	Grote Zaal
06:30 PM	Presentation & poster award ceremony	Grote Zaal
06:45 PM	Conference closure	Grote Zaal

Keynote speakers
Biosketches and Abstracts

Keynote speaker: Ted Kaptchuk

Time: Sunday, April 2 04:45 PM - 05:30 PM
Location: Aalmarktzaal
Chair: Andrea Evers



About Ted Kaptchuk

Ted is a Professor of Medicine and Professor of Global Health and Social Medicine at Harvard Medical School. He is the director of the Program in Placebo Studies and Therapeutic Encounter (PiPS) hosted at the Beth Israel Deaconess Medical Center. PiPS is a multi-disciplinary network of Harvard-wide researchers from a broad range of disciplines. Ted's over 200 publications have made significant contributions to what we know (or think we know) about placebo effects.

Keynote abstract
Things not usually said: Unorthodox views about placebo

When we SIPS people give talks they are designed either to persuade the medical community we have something important to contribute (public talks) or share experimental details and new findings with our colleagues (intra-professional). For this talk, Ted will share some of his private ruminations, emergent thoughts and percolating ideas. His talk will touch on overlooked aspects of his studies, unconventional ideas about placebo mechanisms, qualitative data that dramatically changed his research models and overlooked differences between clinical and laboratory studies. The talk will be deliberately provocative to foster our community's self-examination and foster open discussion and innovative approaches especially with young researchers as they join our community.

Keynote speaker: Fabrizio Benedetti

Time: Monday, April 3 08:30 AM - 09:15 AM
Location: Grote Zaal
Chair: Lene Vase

About Fabrizio Benedetti

Fabrizio Benedetti, M.D. is Professor of Neurophysiology and Human Physiology at the University of Turin Medical School, Turin (Italy), and Director of the Center for Hypoxia at the Plateau Rosà Labs, Plateau Rosà (Italy/Switzerland). He has been nominated member of The Academy of Europe and of the European Dana Alliance for the Brain. He identified some basic mechanisms of placebo responses across a variety of medical conditions.
Recent books: Placebo Effects (Oxford, 2nd Edition, 2014), The Patient's Brain (Oxford 2010), Placebo (Springer 2014).
Recent awards: Highly Commended Book Award of the British Medical Association in 2009, Seymour Solomon Award of the American Headache Society in 2012, William S. Kroger Award of the American Society of Clinical Hypnosis in 2015.

Keynote abstract
Placebo effects at great heights

Placebo effects have been found and described in a variety of systems, ranging from sensory and motor systems to immune and endocrine systems. What has emerged from these studies is that placebos induce powerful psychological effects that can change the physiology of different body functions, and that these changes are very similar to those induced by drugs. However, it is not surprising that there are some limits of these psychological effects in a variety of conditions. For example, can placebo effects occur for functions that are crucial for survival? For instance, can a placebo replace oxygen during respiration? Or, in other words, is it possible to breathe without oxygen by merely using a placebo procedure? Although the answers to these questions may seem quite obvious at first sight, several years ago we started a project to assess the role of placebo effects for critical physiological functions in extreme environmental conditions, where survival is at stake. Indeed, we have investigated the role of placebo effects at high altitudes (3500 m), where oxygen pressure drops to 102 mmHg (159 mmHg at sea level). This corresponds to an oxygen concentration in the air of only 12%, compared to 21% at the sea level. In these extreme conditions, where both physical and cognitive performance deteriorate very quickly, we found that a conditioned placebo procedure can mimic the effects of oxygen, including ventilation, blood pH, heart activity and cyclooxygenase activity, and these effects are still present, albeit to a lesser extent, at altitudes as high as 4500 and 5500 m, where oxygen pressure drops to 92 and 81 mmHg, respectively. Interestingly, opposite effects (nocebo effects) can be elicited as well. A crucial question is to understand the limits of these effects, at altitudes of 8000 m and beyond, where oxygen pressure and concentration approach zero.

Keynote speaker: Katja Wiech

Time: Monday, April 3 06:00 PM - 06:45 PM
Location: Grote Zaal
Chair: Tor Wager

About Katja Wiech

Katja Wiech studied Psychology at the Universities of Kiel and Düsseldorf (Germany) and completed her PhD on neurobiological processes underlying phantom limb pain in Tübingen (Germany) under the supervision of Prof. Niels Birbaumer. In 2003 she joined the group of Prof. Ray Dolan at the Wellcome Trust Centre for Neuroimaging in London (UK) to investigate neural mechanisms of psychological pain modulation using functional magnetic resonance imaging. In 2005, she became a member of the Pain Imaging Neuroscience Group at the University of Oxford (headed by Prof. Irene Tracey) where she established her own group ("pain & mind") in 2014. Katja's work focuses on the influence of beliefs on the perception and neural processing of pain. Using a multi-methods approach, her research aims to characterize the processes that integrate beliefs with incoming sensory information and the failure of optimal integration in biased perception.

Keynote abstract
Neurobiology of beliefs and placebo effects

Research into placebo effects has shown that treatment success is critically determined by the beliefs we hold. These beliefs can relate to the disease we seek treatment for (e.g., progression, treatability) and the treatment itself (e.g., tolerability, potency). Although the influence of beliefs has extensively been described for various health conditions, we still know little about their formation, maintenance and revision and the neural basis of their impact on treatment outcome.
Studies combining brain imaging with computational modelling have begun to explore these processes in more detail. In my presentation, I will give an overview on our current understanding of the neurobiological basis of beliefs and their role in placebo effects. In particular, I will focus on how beliefs as a cognitive process interface with physical symptoms and how they are incorporated into the perceptual process. Furthermore, I will discuss how these insights could be used to challenge and revise maladaptive beliefs and how a therapeutic contact could be used to foster helpful expectations.

Keynote speaker: John Kelley

Time: Tuesday, April 4 08:30 AM - 09:15 AM
Location: Grote Zaal
Chair: Jens Gaab

About John Kelley

John M. Kelley, Ph.D. is Professor of Psychology at Endicott College and the Deputy Director of the Program in Placebo Studies and the Therapeutic Encounter at Harvard Medical School. He is the president of the Society for Interdisciplinary Placebo Studies (SIPS). In addition, he is a licensed psychologist in the Psychiatry Service at Massachusetts General Hospital, and he has a private practice in psychotherapy. His research interests include: (1) investigating the placebo effect in medical and psychiatric disorders, and (2) understanding how the patient-clinician relationship affects healthcare outcomes in medicine and psychiatry. Professor Kelley has served on ten US National Institutes of Health (NIH) research grants. His research has also been funded by the Robert Wood Johnson Foundation, the Arnold P. Gold Foundation, the David Judah Fund, the Josiah Macy, Jr. Foundation, and the Risk Management Foundation.

Keynote abstract
Lumping and splitting: Toward a taxonomy of placebo and related effects

The placebo effect is closely related to many other constructs, including most prominently, conditioning and expectancy, but also natural history, regression to the mean, priming, mindset, context effects, the meaning response, specific and non-specific clinical effects, placebo-related effects, the patient-clinician relationship, and the common factors in psychotherapy. How are these various constructs related to one another? To what degree do they overlap, and to what degree do they diverge?
To form a better theoretical understanding of these constructs and to foster improved empirical research, is it better to lump these constructs together in some fashion? Or will progress best be served by maintaining the splits between the constructs? Or would it perhaps be most effective to employ some mixture of lumping and splitting? In this talk, I will address these and related questions with two major goals: (1) to delineate and clarify the relationship between these constructs; and (2) to suggest some possible re-alignments in the way in which we conceptualize the relationships among these constructs that might prove useful in fostering research on placebo and related effects. In addition, clarifying the interconnections between the placebo effect and other related constructs has the potential to spark innovative cross-fertilizations between related areas of research.

Keynote speaker: Christian Büchel

Time: Tuesday, April 4 05:45 PM - 06:30 PM
Location: Grote Zaal
Chair: Paul Enck

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 current director of the Neuroimaging Center NeuroImage Nord and holder of major research grants from the European Research Council, German Research Foundation (DFG), and German Ministry for Science and Volkswagen Foundation. His main scientific interests are the interplay of cognition, pain and emotion with an emphasis on emotional learning in health and disease. He is a member of the Hamburg Academy of Science. Christian Büchel has published more than 150 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.

Keynote abstract
How expectations shape pain perception

Expectation and experience can shape pain perception in a powerful way. However, the neurobiological mechanisms underlying these effects are still unknown. This talk will focus on potential mechanisms of how expectations can increase (nocebo hyperalgesia) or decrease (placebo hypoalgesia) pain perception. The focus will be on a conceptual framework which posits that pain perception can be seen as the integration (in a Bayesian sense) of expectation (i.e. prior) and incoming data (i.e. stimulus). Importantly, this framework leads to testable hypotheses (e.g., the variance of the expectation should reduce the influence of expectation)**.**

Monday April 3
Oral presentation abstracts

Plenary Session 1

Ethical aspects and challenges of trial design in placebo research

Monday, April 3 09:15 AM - 11:00 AM
Grote Zaal
Chair: Serge Marchand

Plenary Session 1: Ethical aspects and challenges of trial design in placebo research

1. 

The ethics of deception in placebo and nocebo research

Marco Annoni[1]
1) Research Fellow, National Research Council of Italy, Italy

About Marco Annoni

Marco Annoni is a Research Fellow in bioethics at the National Research Council of Italy (CNR). He owns a Ph.D. in "philosophy of science" (University of Pisa) and a Ph.D. in "foundations and ethics of the life sciences" (University of Milan and European School of Molecular Medicine). In 2014 he has been Research Fellow at the Program in Placebo Studies and the Therapeutic Encounter (Harvard Medical School and Beth Israel Deaconess Center).
His main research interests concern biomedical ethics, with a particular focus on the ethics of the doctor-patient communication, placebo effects, and clinical trials. He works as ethic consultant for the national Research Ethics and Bioethics Advisory Committee and for the Fondazione Umberto Veronesi, a leading Italian institution devoted to the public engagement of science and the promotion of human rights. He is the editor in chief of The Future of Science and Ethics a new, open-access, peer-reviewed, scientific journal dedicated to bioethics, biolaw and biopolitics.

Plenary abstract

Empirical research on placebo and nocebo effects raises a host of ethical quandaries. On the one hand, investigating placebo and nocebo mechanisms is necessary to better harness such effects in clinical and research settings. On the other hand, these studies often require the use of strategic concealment, partial disclosure or deception in order to preserve their internal validity. Yet, the use of deceptive techniques for scientific purposes is morally problematic because it infringes on the autonomy of trial participants, violates their right to informed consent, and jeopardizes public trust. Against this backdrop, in this talk I will explore the ethics of deceptive and concealing techniques in scientific contexts, identifying under which conditions they can be morally utilized in placebo and nocebo research.

2. 

Informed Consent and Clinical Trials: WHERE IS THE PLACEBO EFFECT? - The ethical imperative to disclose information about placebo effects in research contexts

C.R. Blease[1,2], F.L Bishop[3], T.J. Kaptchuk[2]
1) School of Philosophy, University College Dublin, Dublin, Ireland
2) Program in Placebo Studies, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts, United States
3) Department of Psychology, University of Southampton, Southampton, United Kingdom

About Charlotte Blease

Dr. Charlotte Blease is Research Fellow in Philosophy at University College Dublin, and Dublin Institute of Advanced Studies. Her research is interdisciplinary. She has published on the ethics of placebo, and the role of placebo in psychotherapy.

Plenary abstract

The Declaration of Helsinki states that researchers are obliged to provide accurate and understandable information to participants prior to enrolment in clinical trials. Recent research analysing the content of written patient information in clinical trials reveals factual inaccuracies, and routine omissions of detail about placebos and placebo effects. In this paper I argue that the provision of adequate evidence-based information about placebos and placebo effects would help to improve participant understanding of fundamental aspects of clinical trials. Inadequate information about placebo may contribute to already well-known persistent misunderstandings about the methodology and primary goals of clinical trials among research participants ("therapeutic misconception"). Truthful information is also required to uphold transparency and genuine informed consent. I close by providing practical recommendations for clinical researchers on the disclosure of placebo effects to trial participants.

Plenary Session 1: Ethical aspects and challenges of trial design in placebo research

3.

What´s in the placebo research box? Past achievements and future tasks!

Paul Enck[1]
1) Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Tübingen, Germany

About Paul Enck

Prof. Dr. Paul Enck, Director of Research, Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Germany. His main interests are gut functions in health and disease, including functional and inflammatory bowel disorders, the role of the gut microbiota, regulation of eating and food intake and its disorders, of nausea, vomiting and motion sickness, and the psychophysiology and neurobiology of the placebo response, with specific emphasis on gender differences. He has published more than 220 original data papers in scientific, peer-reviewed journals, and more than 250 review articles and book chapters. He is board member/treasurer of the European Society of Neurogastroenterology and Motility, the German Society of Neurogastroenterology and Motility, and The Society of Interdisciplinary Placebo Studies, and has served as reviewer for many national and international journals and grant agencies.

Plenary abstract

To identify topics of research that have been neglected, undervalued or overseen in the past two decades of placebo/nocebo research, a highly specialized literature database containing more than 3,500 papers on the placebo or nocebo effects or response was screened for papers covering placebo effects in nutrition, sports medicine, physical therapy and psychotherapy, for papers covering gender, age, and culture as influencing factors, for articles dealing with long-term outcome, multi-modality, and for papers related to technical (eHealth, mHealth) aspects of placebo effects.
Results: While placebo research has gained substantial progress over the last two decades, it has not resolved all its puzzles, it has ignored some obvious and some less obvious facets of the placebo topic, and it has overlooked that during these years, medicine has further developed and progressed, as has the doctor-patient relationship and the social environment in which this communication happens.
Conclusion: The biggest threat for placebo research is that it may outdate itself by declaring all and everything as a placebo effect even if there may be better terms and concepts (e.g. patient expectations, doctor-patient communication, empathy), and by ignoring that medicine continuously changes its face, for patients as well as for clinical researchers. Its biggest opportunity is the fact that it - as no other topic in medicine - requires both medical and psychological experts for its exploration, and to stay updated.

4.

Effects of placebos without deception compared with no treatment: a systematic review and meta-analysis

James E.G. Charlesworth[1*], Grace Petkovic[1*], John M. Kelley[2], Monika Hunter[3], Igho Onakpoya[1], Nia Roberts[4], Franklin G. Miller[5], Jeremy Howick[1*]
* These authors contributed equally to this work
1) Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom.
2) Psychiatry Department, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts, United States & Psychology Department, Endicott College, Beverly, Massachusetts, United States
3) Salomons Centre for Applied Psychology, Canterbury Christ Church University, Canterbury, Kent, United Kingdom4) Bodleian Libraries, University of Oxford, Oxford, United Kingdom
5) Weill Cornell Medical College, New York, New York, United States

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 a forthcoming 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

Aim: Our aim was to address the clinical efficacy of open-label placebos compared with no treatment by systematic review, and meta-analysis where possible.
Methods: We searched the Cochrane Injuries Group's Specialised Register, The Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (OvidSP), EMBASE

(OvidSP), and clinical trials registers and screened reference lists. We ran the most recent search on April 27 2015. All randomised controlled trials of any medical condition, which had both open-label placebo and no-treatment or treatment as usual groups were included. Two authors independently applied the selection criteria and extracted data. The risk of bias of included studies was assessed using the Cochrane criteria. We used random-effects model for meta-analysis.
Results: After removing duplicates we screened 348 publications, assessed 24 articles for eligibility and identified 5 trials (260 participants) that met our inclusion criteria. The clinical conditions were: irritable bowel syndrome (IBS), depression, allergic rhinitis, back pain and attention deficit hyperactivity disorder (ADHD). The overall risk of bias was moderate. All 5 trials were eligible for meta-analysis. We found a positive effect for non-deceptive placebos (standardized mean difference (SMD) 0.88, 95% CI 0.62 to 1.14, P<0.00001, I^2= 1%).
Conclusions: Open-label placebos appear to have favorable clinical outcomes, compared to no treatment or no additional treatment. Caution is warranted when interpreting the results due to the limitations including the small number of trials and lack of blinding. Larger definitive trials are now warranted to explore the potential patient benefit of open-label placebos..

5.

Can knowledge of placebo and nocebo mechanisms help improve the RCT?

Lene Vase[1]
1) Department of Psychology and Behavioural Sciences, School of Business and Social Sciences, Aarhus University, Aarhus, Denmark

About Lene Vase
Lene Vase received her PhD in experimental psychology in 2006 and she currently holds a position as professor at the Department of Psychology and Behavioural Sciences, School of Business and Social Sciences, Aarhus University, Aarhus, Denmark. Her research focuses on how psychological interventions or dispositions may enhance or decrease the experience of pain with a special focus on placebo analgesia and nocebo hyperalgesia effects. Recently, she has investigated how knowledge of placebo and nocebo mechanisms may improve the test of new treatments in Randomized Controlled Trials. She has published more than 60 papers and book chapters and has given several presentations at conferences world-wide. She has numerous international collaborations, and she was awarded the EU Innovative Medicines Initiative grant EUROPAIN together with leading pain laboratories in Europe. She is currently Associate Editor on PAIN and member of the steering committee for the Society for Interdisciplinary Placebo Studies.

Plenary abstract

The RCT is currently facing several challenges. One of these challenges is that the placebo response appears to be increasing in RCTs, thereby making it difficult to prove a putative effect of new treatments over placebo. This problem has primarily been approached by using stable factors to predict the magnitude of the placebo response and by developing complex designs aimed at reducing the placebo response, in the hope that it would improve the test of the active treatment. Still, the success of this approach has so far been limited.
Based on placebo mechanism studies, a new approach is proposed. The magnitude of placebo effects is large and highly variable. Pharmacological and non-pharmacological treatments, patients' perception of the treatment, verbal suggestions given for pain relief, as well as patients' expectations towards pain relief contribute, across different types of chronic pain, to the magnitude of the placebo effect. A recent study has shown that it is possible to make approximations of patients' expectations towards the treatment and hence predict the magnitude of the placebo response in RCTs. Also, by directly asking patients, in future studies about their perceptions and expectations towards the treatment it may be possible to account for the contribution of the placebo component to the overall treatment.
Thus, by interfacing insights from placebo and nocebo mechanism studies, it may be possible to enhance the information that can be obtained from RCTs and to account for the variability in the placebo component of the overall treatment effect in ethically appropriate ways. This approach has the potential to improve the scientific test of treatments as well as to illustrate how the effect of treatments can be optimized in clinical practice.

Parallel Session 1.1

Neuroimaging of placebo effects

Monday, April 3 11:30 AM - 01:00 PM
Grote Zaal
Chair: Peter Hagoort

Parallel Session 1.1: Neuroimaging of placebo effects

1. **When opposites lead to the same: A direct comparison of explicit and implicit disgust regulation via fMRI**

Anne Schienle[1]
1) University of Graz, Graz, Styria, Austria

Cognitive reappraisal and placebo administration constitute two different approaches for modulating one's own emotional state. Whereas reappraisal is an explicit (effortful) type of self-regulation, placebo treatment initiates implicit processes of affective control. The brain mechanisms underlying these processes have not been directly compared with each other up until now.
We conducted a functional magnetic resonance imaging study with forty-five women, who were presented with disgusting and neutral images in a block design, at three experimental sessions, over three consecutive days. They were asked to passively view the images in one session, engage in reappraisal in another, and in another session they received a placebo pill: a disgust-reducing 'anti-nausea drug'.
Relative to passive viewing, both reappraisal and placebo treatment effectively reduced the experienced disgust intensity. In the placebo condition, this reduction was associated with decreased activation of the insula and the dorsolateral prefrontal cortex (DLPFC). In contrast, reappraisal induced increased activation in both regions. Furthermore, both regulation strategies were associated with opposite patterns of connectivity in a network encompassing the amygdala, the insula, and the DLPFC. Only placebo administration led to a reduced coupling in this network.

2. **Neural correlates of treatment variability and placebo effects - better be certain**

Arvina Grahl[1], Christian Büchel[1]
1) University Medical Center Hamburg-Eppendorf, Department of Systems Neuroscience, Hamburg, Germany

This study investigates the substantial influence of variability in prior experience and expectations on placebo effects and treatment outcomes. By using a Bayesian-like manipulation and fMRI, we contribute to a better understanding of individual placebo effect magnitudes and corresponding neural processing experimentally induced by experienced treatment variability. 63 healthy male participants (N_group1/N_group2=31/32) underwent a heat pain conditioning procedure experiencing either a constantly effective (certain group, SD=0°C) or variable treatment (uncertain group, SD=0.57°C). In both groups, the placebo condition was compared to an untreated more painful control condition. Transcutaneous electrical nerve stimulation (TENS) was introduced as the putative hypoanalgesic pain treatment. During test phase, identical pain stimuli were delivered for both groups (certain/uncertain) and conditions (placebo/control) respectively. Only in the certain group pain ratings were significantly lower in the placebo compared to the control condition. On the neural level, experimentally induced treatment variability was investigated by modeling and controlling for subject specific rating inaccuracies (assessed prior to experiment). Activation increase for placebo treatment in the uncertain compared to the certain group was observed in brain areas such as anterior cingulate cortex (ACC) and substantia nigra (SN). Dopaminoceptive structures such as the SN have been linked to appetitive prediction error coding. Supported by our neural findings, we propose that treatment variability influences the effect of expectation on pain perception and the magnitude of individual placebo effects. Higher uncertainty about treatment effectiveness can lead to decreased placebo effects mediated by differences in avoidance value coding and prediction error signaling.

3. **The functional role of large-scale brain network coordination in placebo anxiolysis**

Benjamin Meyer[1], Raffael Kalisch[1]
1) Neuroimaging Center (NIC), Johannes Gutenberg University Medical Center Mainz, Mainz, Rheinland-Pfalz, Germany

Anxiety reduction through expectation of anxiolytic treatment effects (placebo anxiolysis) is of enormous clinical importance, but the underlying mechanisms have hardly been examined. Recent data suggest that placebo anxiolysis involves reduced vigilance for salient external stimuli coupled with heightened cognitive control and internalization of attention.
We here investigate the neural bases of these cognitive changes, by introducing a systemic neural-network approach to the study of placebo effects. We show down-regulation of external stimulus-related activity in the salience network (SN) under placebo, in line with reduced vigilance. Recent studies have indicated that coordinated switching between task-positive and task-negative networks, such as the SN and the default mode network (DMN), respectively, is a prerequisite for cognitive control. We therefore also wanted to know whether the placebo effect induces more coordinated inverse (more anti-correlated) SN and DMN responses to aversive experimental cues, that is, cue-related network switches that would be indicative of a state of heightened cognitive control. We found a precise temporal coordination of stimulus-related SN and DMN activities, showing pronounced anti-correlation. These phasic stimulus-related activity patterns are embedded in a sustained brain state of enhanced stimulus-unrelated intra-DMN functional connectivity (FC), congruent with internalized attention, and inter-SN-DMN FC, orchestrated by the rostral anterior cingulate cortex (rACC). A highly organized, well-coordinated brain state thus supports expectation-induced anxiolysis.

4. **First results from the placebo imaging collaboration**

Matthias Zunhammer[1], Tor Wager[2], Ulrike Bingel[1], The Placebo Neuroimaging Consortium Collaboration Author[2]
1) Universitätsklinikum Essen, Essen, Germany
2) University of Colorado at Boulder, Boulder, Colorado, United States

Ten research groups from around the world have teamed up to pool their data from functional imaging studies on placebo analgesia. Over the last two years, the placebo neuroimaging collaboration has gathered single-subject behavioral and imaging data from 20 studies comprising 603 healthy individuals. The size and methodological diversity of this dataset has allowed us to investigate cerebral mechanisms of placebo analgesia with unprecedented statistical power and generalizability.
Here, we present results from an initial, focused meta-analysis of these data. We present a summary map localizing cerebral correlates of placebo analgesia across studies and experimental approaches. Moreover, we address the question whether and how placebos alter pain processing in the brain by testing for placebo effects on the Neurologic Pain Signature (NPS), a multi-voxel pattern that predicts acute pain intensity from fMRI images with high sensitivity and specificity (Wager et al. 2013). We found that the NPS is sensitive to multiple types of acute pain and responds to active analgesic medication. However, placebo treatment has little effect on the NPS. These findings are consistent with the emerging multiple-systems view of pain, in which the NPS reflects one component of the cerebral processing of pain, among others.

5. **Toward the motivational side of placebo effects: Placebo enhances wanting and liking.**

Liane Schmidt[1], Vasilisa Skvortsova[2], Christina Walz[3], Claus Kullen[3], Pierre Chandon[4], Mathias Pessiglione[5], Bernd Weber[3], Hilke Plassmann[4]
1) Centre Multidisciplinaire de Sciences Comportementales Sorbonne-Universités-INSEAD, Paris, France
2) INSERM, U960 Laboratoire de Neuroscience Cognitive, Economic Decision-Making Group, Ecole Normale Supérieure, Paris, France
3) NeuroCognition Group, Imaging Life&Brain Center, Department of Epileptology, University Bonn, Bonn, Germany

Background: Evidence from neuroscience suggests that placebo responses recruit neural pathways linked to reward and motivation. If so, positive expectancies induced by a placebo (i.e. labels, informational cues) should enhance incentive motivation reflected by behavioral components of reward, such as wanting and liking, and be mediated by brain regions sensitive to reward.
Methods: We conducted two independent studies using behavioral testing (study 1, N=88) and functional magnetic resonance imaging (fMRI, study 2, N=30) in healthy participants. First, we crossed expected and actual consumption of an energy drink (EnD) and measured wanting - the allocation of mental effort according to the magnitude of by trial-by-trial incentives. Then, we used a well-known wine tasting paradigm to search with whole brain moderated-multilevel mediation for brain mediators and moderators of wine price cue effects on taste liking.
Results:We found that expected, but not actual EnD consumption, translated into enhanced wanting, which implied a facilitation of cognitive performances in high incentive trials only. FMRI revealed that the brain's valuation system formally mediated the effect of price cue on taste liking reports, and was moderated by reward responses in a common motivational node - the ventral striatum.
Conclusion:These findings provide convergent, direct behavioral and neural evidence for enhanced incentive motivation under expectancy-based placebos. Paralleling findings from placebo analgesia, our results suggest that enhanced motivational processes in brain and behavior constitute an elementary neurocognitive mechanism for placebo effects.

6. **Using placebo analgesia as a tool for investigating the neural mechanisms of empathy**

Markus Rütgen[1], Eva-Maria Seidel[1], Giorgia Silani[2], Igor Riecansky[1], Allan Hummer[3], Christian Windischberger[3], Predrag Petrovic[4], Claus Lamm[1]
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2) Department of Applied Psychology: Health, Development, Enhancement and Intervention, Faculty of Psychology, University of Vienna, Vienna, Austria
3) MR Center of Excellence, Medical University of Vienna, Vienna, Austria
4) Cognitive Neurophysiology Research Group, Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

Background: Partially overlapping neural responses to painful experiences and empathy for pain were previously taken as evidence for theories of shared representations of emotions. But due to methodological limitations of previous studies and technical limitations of neuroscientific measures, it is unclear whether such shared activations imply that pain empathy engages similar neural functions as first-hand pain experiences. To overcome these limitations, we pursued a conceptually novel approach: we used the phenomenon of placebo analgesia to experimentally reduce the first-hand experience of pain, and assessed whether this results in a concomitant reduction of empathy for pain.
Methods: We applied a placebo analgesia manipulation consisting of both verbal suggestion and conditioning in a series of multimethod studies (using event-related potentials, functional magnetic resonance imaging, and psychopharmacology). In a pain and empathy for pain paradigm, we then measured subjective ratings and neural correlates of pain processing.
Results: We found significant placebo-induced reductions of ratings and different neural measures in response to

both pain and empathy for pain. These reductions were pain-specific, as comparison to non-painful control conditions showed. Moreover, we were able to block these placebo-induced changes in both experiences with an opioid receptor antagonist, showing a link to the endogenous opioid system.
Conclusions: Taken together, these findings suggest that pain empathy may be associated with neural responses and neurotransmitter activity engaged during first-hand pain, and thus might indeed be grounded in our own pain experiences. Placebo analgesia proved to be a useful tool that had a very specific impact without evoking side-effects.

Parallel Session 1.2

Learning mechanisms of placebo and nocebo effects

Monday, April 3 11:30 AM - 01:00 PM
Breezaal
Chair: Ursula Stockhorst

Parallel Session 1.2: Learning mechanisms of placebo and nocebo effects

1. **Reversing nocebo effects on itch by conditioning with verbal suggestion**

Danielle Bartels[1], Antoinette van Laarhoven[1], Michiel Stroo[1], Kim Hijne[1], Kaya Peerdeman[1], Rogier Donders[2], Peter van de Kerkhof[2], Andrea Evers[1]
1) Leiden University, Leiden, Netherlands
2) Radboud university medical center, Nijmegen, Netherlands

Background: Nocebo effects are known to contribute to the experience of physical symptoms such as pain or itch, however, it has not yet been investigated if nocebo effects can be diminished by positive expectations. In this study, we examined whether nocebo effects can be reduced by positive expectation induction with respect to electrical itch stimuli 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: Positive expectation induction resulted in a significantly smaller nocebo effect on itch in comparison with both control groups. Mean levels of itch showed that the nocebo effect was even reversed, signifying a placebo effect. Discussion: The current study is the first to demonstrate that nocebo effects can be reversed by conditioning with verbal suggestion. A better understanding how to diminish and reverse nocebo responses might eventually contribute to increased treatment effectiveness and improved quality of life for patients suffering from chronic itch conditions and potentially also other somatosensory conditions.

2. **Is classical conditioning a distinct mechanism producing placebo and nocebo effects?**

Przemysław Bąbel[1], Elżbieta Anita Bajcar[1], Wacław Adamczyk[1], Paweł Kicman[1], Natalia Lisińska[1], Karolina Świder[1], Karolina Wiercioch[1]
1) Jagiellonian University, Institute of Psychology, Pain Research Group, Kraków, Poland

Background: Classical conditioning can enhance placebo analgesia induced by verbal suggestions and these effects are likely to be mediated by expectancies. However, little is known about the role of expectancy in placebo analgesia and nocebo hyperalgesia induced by classical conditioning without verbal suggestions. The aim of a series of studies was to induce placebo analgesia and nocebo hyperalgesia by classical conditioning without verbal suggestions, and to investigate the influence of expectancy, fear of pain (trait) and fear (state) on the effects of conditioning.
Methods: Participants received electrical stimuli, preceded by either orange or blue lights. In the conditioning phase, light of one colour was paired with pain stimuli of moderate intensity (control stimuli), and light of the other colour was paired with either nonpainful stimuli (placebo groups) or painful stimuli of high intensity (nocebo groups). Only participants in the open conditioning groups were informed about this association. In the control groups, both colour lights were followed by control stimuli of moderate intensity without any conditioning procedure. In the testing phase, both of the coloured lights were followed by identical control pain stimuli.
Results: It was found that placebo analgesia and nocebo hyperalgesia can be induced by hidden rather than open classical conditioning, and that these effects are not necessarily predicted by expectancy or fear. However, the effects of hidden conditioning may be limited to the participants with high or low fear of pain.
Conclusions: It is concluded that there is a distinct classical conditioning mechanism for placebo and nocebo effects.

Parallel Session 1.2: Learning mechanisms of placebo and nocebo effects

3. **Placebo-like analgesia via response imagery: two experiments**

Kaya Peerdeman[1], Antoinette van Laarhoven[1], Danielle Bartels[1], Madelon Peters[2], Andrea Evers[1]
1) Health, Medical and Neuropsychology unit, Leiden University, Leiden, Netherlands
2) Department of Clinical Psychological Science, Maastricht University, Maastricht, Netherlands

Background: Placebo effects on pain are reliably observed in the literature. A core mechanism of these effects are response expectancies. Response expectancies are commonly considered to be formed by instructions (verbal suggestion), prior experiences (conditioning), and observation of others (observational learning). Possibly also mental imagery of a response can induce comparable, placebo-like, expectancy effects on pain. This is suggested by previous observations of the effects of imagery on expectations, pain, and brain activation, but has not yet been studied systematically.
Methods: In Study 1, 80 healthy participants were randomly allocated to 1) response imagery or 2) control imagery. In Study 2, 135 healthy participants were randomly allocated to 1) response imagery with an added verbal suggestion regarding its effectiveness, 2) response imagery only, or 3) no intervention. In both studies, expected and experienced pain during cold pressor tests were measured pre- and post-intervention.
Results: In Study 1, participants rated pain as less intense after response imagery than after control imagery. In Study 2, participants rated pain as less intense after response imagery (with or without verbal suggestion) than after no intervention. Verbal suggestion did not significantly reduce experienced pain further (Study 2). In both studies, the effects of response imagery on pain were mediated by pain expectancies.
Conclusions: In line with research on placebo effects, the current results indicate that response imagery, like verbal suggestion, conditioning, and observational learning, can reduce pain, via its effects on response expectancies.

4. **Placebo and nocebo responses induced by free-operant conditioning**

Thomas Janssens[1], Bien Cuyvers[1], Luana Colloca[2], Johan Vlaeyen[1]
1) KU Leuven (University of Leuven), Leuven, Belgium
2) University of Maryland, Baltimore, MD, United States

Background: Learning plays a major part in placebo and nocebo effects, and most of the research investigating this has used Pavlovian conditioning procedures. However, free-operant conditioning designs - in which behaviors chosen by participants are punished or rewarded - may match more closely to real-life situations in which placebo/nocebo effects can occur (e.g. taking medication, avoiding painful movements). In this study, we therefore developed a novel task to investigate the occurrence and persistence of placebo/nocebo effects after free-operant learning.
Methods: Participants (n=60) performed 3 different movements (straight ahead, small diversion, large diversion) which were punished by a painful electrical stimulus of low, medium, or high intensity respectively. During acquisition, contingencies between movement and punishment were cued by environmental features, signaling either increasing or decreasing pain intensity with larger diversions from the straight path. During test, each movement was followed by the same (medium) intensity stimulus.
Results:During acquisition, pain intensity sensitized for the high intensity stimulus and habituated for the low intensity stimulus. Furthermore, participants avoided the most painful movement more than other movements. After acquisition, this movement preference diminished, and disappeared by the end of the test phase. For pain ratings, we observed a placebo effect, but only for the condition in which deviations from the straight path (more effort) had previously signaled an increase in pain intensity.
Conclusions: Our findings suggest that placebo/nocebo induced experiences of movement-pain contingencies during free-operant learning both changes perception of pain intensities and shapes avoidance behavior.

Parallel Session 1.2: Learning mechanisms of placebo and nocebo effects

5. **Mismatch cues attenuate placebo hypoalgesia and nocebo hyperalgesia**

Lieven Schenk[1], Luana Colloca[1]
1) University of Maryland, Baltimore, Baltimore, MD, United States

Background: During treatment, patients often experience a mismatch between what they expected and what actually happens (1). This has been shown to decrease treatment compliance (2), however it remains unclear how this influences endogenous pain modulation like placebo hypoalgesia and nocebo hyperalgesia. Here we explored for the first time the influences of mismatch processing on placebo and nocebo effects.
Methods: 25 healthy volunteers (12M) received heat pain preceded by 3 cues (red, yellow, green) during a conditioning and test session. During conditioning on day 1, the cues were followed by three pain levels and a congruent second cue was presented during the pain delivery (red: fearful face-high pain; yellow: neutral face-medium pain; green: happy face-low pain). During test on day 2, all cues were followed by medium pain and congruent (i.e. red: fearful) or incongruent second cues (i.e. red: neutral or happy) and fMRI measurements were performed.
Results: Placebo and nocebo modulated pain in the congruent conditions (placebo: $F(1,24)=30.5$, $p<0.001$; nocebo: $F(1,24)=13.9$, $p<0.005$), while a mismatch between the anticipatory and pain-related cues significantly attenuated placebo and nocebo effects (congruent vs incongruent placebo: $F(1,24)=9.6$, $p<0.005$; congruent vs incongruent nocebo: $F(1,24)=12.9$, $p<0.005$). On the neural level, we observed a stronger activation of the inferior parietal lobe during the incongruent compared to the congruent condition.
Conclusions: Our data supports that if expectations are not met, placebo and nocebo effects are reduced. Our data further reveals a new mechanism in the inferior parietal cortex underlying placebo and nocebo effects during mismatch processing.

6. **Comparing placebo and nocebo effects in a large sample study**

Mari Feldhaus[1], Christian Büchel[1]
1) University Medical Center Hamburg-Eppendorf, Institute of Systems Neuroscience, Hamburg, Hamburg, Germany

Background: Placebo and nocebo effects are not always evoked successfully. To investigate possible factors which can predict placebo and/or nocebo effects, we conducted a large within-subject study (N=717), which allowed a systematic comparison of the evoked treatment effects.
Methods :Treatment expectations were elicited by applying an inert ointment with different labels, suggesting either hypoalgesia (placebo), hyperalgesia (nocebo) or no change (control) in a within-subject design. Both, placebo and nocebo effects were tested without conditioning (pure expectation manipulation) and with conditioning (expectation manipulation and prior conditioning with either heightened or lowered temperatures for control and treatment). Placebo and nocebo effects were defined as the difference of mean pain ratings between treatment and control.
Results: All treatments but placebo without conditioning showed significant effects. Nocebo with conditioning evoked the most pronounced effect (13.84% pain increase), followed by nocebo without conditioning (8.60% pain increase) and placebo with conditioning (3.72% pain relieve). Overall, only 17% of the volunteers showed placebo and nocebo effects in all four conditions. A repeated measures ANOVA determined that nocebo effects were more pronounced than placebo effects, which was independent of conditioning. Moreover, conditioning enhanced the effect in placebo and nocebo conditions compared to exclusive manipulation of the volunteer's expectation.
Conclusion: This study is the first to compare placebo and nocebo effects in an exceptionally large sample. The data suggests that nocebo effects are easier to evoke than placebo effects and conditioning boosts both, placebo and nocebo effects.

Parallel Session 1.3

Doctor-patient communication and placebo effects

Monday, April 3 11:30 AM - 01:00 PM
Jan Willem Schaap zaal
Chair: Willem van der Does

Parallel Session 1.3: Doctor-patient communication and placebo effects

1. **What general practitioners (do not) say during consultations with patients with medically unexplained symptoms: A quantitative multilevel analysis**

Inge Stortenbeker[1], Juul Houwen[2], Peter Lucassen[2], Hugo Stappers[2], Pim Assendelft[2], Sandra van Dulmen[2], Tim Olde Hartman[2], Enny Das[1]
1) Radboud University, Nijmegen, Netherlands
2) Radboud University Medical Centre, Nijmegen, Netherlands

Background: General practitioners (GPs) experience difficulties during communication with patients presenting symptoms that do not have a specific underlying disease, and patients with these medically unexplained symptoms (MUS) feel anxious and not taken seriously. Experts on MUS suggest beneficial health effects of positive communication but it remains unclear what positive communication entails; empirical evidence supporting a relationship between communication and medical outcomes is scarce and poorly operationalised. The current study introduces linguistic methods to assess differences in message formulations in GP consultations with patients with MUS versus patients with explained symptoms (MES), and examines how message formulations relate to patient anxiety.
Methods: Coders systematically identified and categorised GPs' judgmental expressions about patients based on the content and formulation of the message (N = 2590, 21% double-coded) of 82 transcribed recorded consultations (50% MUS) of 18 Dutch GPs. Patient anxiety was assessed with an abbreviated State Trait Anxiety Inventory (STAI) before and after the consultation.
Results: Multilevel models showed that, compared to patients with MES, patients with MUS were more likely to receive negatively loaded messages, i.e. positive messages in an indirect ("not bad") rather than direct manner ("good"), or direct negative messages ("bad") rather than indirect ones ("not good"). Negatively loaded messages predicted increased patient anxiety after the consultation.
Conclusions: GPs tend to use negative wordings to explain symptoms and give treatment advice for patients with MUS, but patients in general would benefit from hearing more positively loaded messages. GP message formulations may partially explain a placebo effect of communication.

2. **Language as placebo - A litterature study**

Roel Gaymans[1]
1) Private, Made, Netherlands

Language is considered to be one of the first tools in the evolutionary course of the human brain and behavior. Not just conscious words or sentences. Also, within a subconscious field , signs symbols, rituals and body language. Language is capable of translating subconscious elements into the conscious domain. And a helpful system by transforming mental processes into organic action.
Now where does our language affect the placebo action?
One of the frequent sentences in placebo studies is:" ..patients have been told..."
However ,how the patient self translates the verbal information, may be more influential than the words "the therapist has told". Verbal entanglement between talker and listener seems prerequisite to create the activation of placebo processes.
Looking for the origins of placebo has proceded from the "pill with nothing in it" to the various determinants we now know ? It seems worth while to consider and study language as an even deeper layer of functioning of the placebo construct . The placebo path can be seen as: naming the need state (P.D.Wall) of the organism, followed by a associate thinking search for culturally determined appropriate healing connectivity. Leading towards an intended, expected formulated"Better". The caregiver can have the chance to be a guide within this healing process in a narrative dance with the patient.
The well known placebo determinants are discussed from the viewpoint of language.

3. **The influence of social modelling, gender, and empathy on nocebo effects and symptom misattribution**

Kate Faasse[1]
1) University of New South Wales, Sydney, NSW, Australia

Objective: This study investigated the influence of social modelling of treatment side effects, gender, and empathy, on nocebo effects.
Methods: 96 participants (48 female) completed the experimental session purportedly investigating the influence of modafinil on alertness and cognitive performance. Participants were randomly assigned to be seated with either a male or female confederate, and then to see this confederate report experiencing side effects (headache and dizziness) or no side effects after using the same spray. Participant empathy was assessed at baseline, and changes in symptom reporting (both modelled and other non-modelled symptoms), attribution of symptoms as side effects, heart rate, blood pressure, fatigue, and alertness were assessed. Symptoms and attribution were assessed again at 24-hour follow-up.
Results: During the experimental session, seeing either confederate report side effects significantly increased

modelled symptoms, but not non-modelled or misattributed symptoms. Female participants seated with a female confederate during the experimental session reported significantly more non-modelled symptoms than females seated with a male, or males seated with the same female confederate. At follow-up, social modelling of side effects resulted in significantly higher rates of modelled, non-modelled, and misattributed symptoms. The experience of nocebo effects in response to social modelling was significantly positively correlated with participant empathy.
Conclusions: Social modelling of symptoms can increase reported side effects following a placebo treatment, and this effect appears to generalise to a broader range of symptoms over time. Participants higher in empathy showed stronger responses to social modelling.

4. **Placebo responses created on the Internet**

Moa Pontén[1], Brjánn Ljótsson[1], Martin Ingvar[1], Karin Jensen[1]
1) Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Background: eHealth has started to replace traditional face-to-face therapy in various clinical domains. However, little is known about placebo effects created online and patients' perception of online therapeutic relationships.
Aims: The aim of this study was to investigate if placebo analgesia could be induced through online communication, and if "enhanced" versus "limited" online therapeutic relationships had differential placebo effects.
Methods: In this double-blind experiment, healthy participants (n=30) were randomized to an enhanced (empathetic) or neutral (non-personalized) pre-experimental interaction online. After completing two online modules (on 2 consecutive days) a placebo analgesia experiment was performed in our lab. An independent experimenter (blinded as to online condition) performed the placebo experiment, using thermal pain and a sham analgesic device. Verbal communication during the experiment was minimal, as the online modules were designed to provide all information.
Results: There was a significant overall placebo effect across groups (p=.003) as pain was lower when the sham device was turned on compared to off. Participants in the enhanced condition rated the online communication as more positive (p=.006) and had higher compliance in completing the online modules (p=.040), yet, there was no significant difference in placebo responses between the two conditions.
Conclusion: The results in this study suggest that placebo responses can be created even when information about the analgesic treatment is delivered online rather than face-to-face. This is the first indication of a novel research line, using the Internet to mediate expectations about a treatment intervention.

5. **Trust in the health care professional and health outcome: A meta-analysis**

Heike Gerger[1], Johanna Birkhäuer[1], Jens Gaab[1]
1) University of Basel, Basel, Switzerland

Objective: To examine whether patients' trust in the health care professional is associated with health outcomes.
Study Selection: We searched 4 major electronic databases for studies that reported quantitative data on the association between trust in the health care professional and health-outcome. We screened the full-texts of 400 publications and included 47 studies in our meta-analysis.
Data Extraction and Data Synthesis: We conducted random effects meta-analyses and meta-regressions and calculated correlation coefficients with corresponding 95% confidence intervals. Two interdependent researchers assessed the quality of the included studies using the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.
Results: Overall, we found a small to moderate correlation between trust and health outcomes (r = 0.24, 95% CI: 0.19 - 0.29). Subgroup analyses revealed a moderate correlation between trust and self-rated subjective health outcomes (r = 0.30, 0.24 - 0.35). Correlations between trust and objective (r = -0.02, -0.08 - 0.03) as well as observer-rated outcomes (r = 0.10, -0.16 - 0.36) were non-significant. Exploratory analyses showed a large correlation between trust and patient satisfaction and somewhat smaller correlations with health behaviours, quality of life and symptom severity. Heterogeneity was small to moderate across the analyses.
Conclusions: From a clinical perspective, patients reported more beneficial health behaviours, less symptoms, higher quality of life and more treatment satisfaction, when they had higher trust in their health care professional. There was evidence for an upward bias in the summarized results. Prospective studies are required to deepen our understanding of the complex interplay between trust and outcome.

Parallel Session 1.4

How we think about placebo effects

Monday, April 3 11:30 AM - 01:00 PM
Cornelis Schuytzaal
Chair: Daniel Moerman

Parallel Session 1.4: How we think about placebo effects

1. **Diagnosis itself as treatment: ethnographic insights from Akha indigenous medicine.**

Giulio Ongaro[1]
1) London School of Economics and Political Sciences, London, United Kingdom

The Akha - an ethnic group of non-literate subsistence farmers living in highland Laos - have maintained to the present a remarkably elaborate system of healing practices, largely unusurped by biomedicine and heavily infused with animistic elements. Based on fifteen months of ethnographic fieldwork, the paper examines these therapeutic practices from the point of view of the science of placebo effects. It reveals that the factors that are most well known to enhance healing responses in the placebo literature - empathic patient-healer interaction; value, novelty and perceived potency of the treatment; heightened sensory experience, among others - are virtually absent in Akha shamanic cures for spiritual illnesses. Akha healing rituals, while rich in drama and symbolism, seldom require the involvement of the patient, who is usually asleep or elsewhere during the performance. Akha themselves insist that healing efficacy does not lie in the intrinsic power of the ritual but in the identification of the right afflicting spirit, which must be then accordingly propitiated. This suggests that the factor most likely to elicit “placebo responses”, if any, resides in the meaning of the diagnostic process occurring prior to the ritual. The paper examines in detail this process, both in the form of indigenous divination techniques and in the reasoning and cogitations Akha engage in while linking past misbehaviors with the possible instigation of afflicting spirits. Drawing parallels to the more familiar Western biomedical context, it calls for additional attention to the healing potential of medical diagnoses and suggests possible ways to experimentally investigate their effects.

2. **The placebo as a philosophical concept: A historical approach**

Jean-Félix Gross[1]
1) Université Lyon 3 Jean Moulin, Lyon, France

Defining the concept of placebo has often been referred to as a challenging task and has been the source of much confusion. One possible way of meeting this challenge would be to provide a clearer definition of what the placebo and the placebo effect are, starting from the contemporary attempts made in the 20th century (as Jeremy Howick is trying to do). Another way to clarify the definition could take the form of an enquiry about the history of the concept itself. Standard histories show that the placebo has been used since the Bible until the latest medical trials. This narrative has been repeatedly found not only in the work of English-speaking authors (e.g. Kaptchuk and Shapiro), but in that of French-speaking authors as well (e.g. Lemoine, Maire and Boussageon). I will argue that this narrative has been taken for granted too many times although in-depth analysis may reveal a full meaning network which may in turn be useful for our global comprehension. Why has the word “placebo” been chosen and for what purpose? What did it describe at the time? The answers will provide us with the tools for clarifying the meaning of the concept. Our enhanced history of the word will also help us explain why pejorative connotations still exist. By analysing the “Scottish connection” centred on W.Cullen in the 18th century, I will fill in the historical gaps and provide a fresh eye on the word as we know it today.

3. **Evolutionary psychology of the placebo effect**

Leander Steinkopf[1]
1) Ludwig-Maximilians-Universität München, Freie Universität Berlin, Munich, Bavaria, Germany

Empirical research sussesfully finds cognitive, neurological, and neuroendocrine mechanisms underlying the placebo effect. However, this research does not answer the question why there are such mechanisms. Why should symptoms be changed by the patient's expectation? Why should fake treatments and compassionate care improve the patient's physical well-being? An evolutionary approach allows reformulating these questions: Why have placebo mechanisms not been sorted out by natural selection? Thus: What advantage does the placebo response bring for biological fitness? Answers come from two distinct but complementary evolutionary approaches to the placebo effect. On the one hand, Humphrey's theory of the „health governor“ suggests that self-healing capacities are regulated based on relevant contextual information. On the other hand, Steinkopf's „Signaling Theory of Symptoms“ suggests that symptoms are shaped by evolution for a communicative purpose. Both approaches regard pain and sickness as socially embedded. First, patients communicate their sick state through symptoms to observers. Once observers acknowledge the sick state and act upon it, the „signaling symptoms“ can diminish - one kind of context effect on symptoms. Second, the „health governor“ should take into account external information, like a harsh environment or generous support, when regulating self-healing capacities - another kind of context effect on symptoms. Receiving support in case of sickness was a crucial and recurrent part of human evolutionary history, therefore humans developed specific adaptations for healing encounters. An evolutionary approach to the placbo effect emphasizes the social nature of humans and, in this way, offers biological arguments for a more humane healhcare.

Parallel Session 1.4: How we think about placebo effects

4. **The Meaning Response: A (post-analytic) philosophical defence**

Phil Hutchinson[1]
1) Manchester Metropolitan University, Crewe, Cheshire, United Kingdom

In this paper I offer a philosophical argument in defence of Dan Moerman's Meaning Response. I draw on recent arguments in anti-representationalist conceptions of cognition, emerging from the Enactivitist and Ecological traditions. I further support these arguments, by discussing recent work defending radical contextualist accounts of meaning, in the philosophy of language (such as those advanced by Avner Baz and Charles Travis). In conclusion, I draw parallels between the Meaning Response and current philosophical work on emotions.

5. **Conditioned, cognitive, and network placebo responses**

Phoebe Friesen[1]
1) CUNY Graduate Center, New York, New York, United States

Several unifying accounts of the placebo effect have been put forward, conceptualizing the phenomenon as primarily inert, non-specific, psychological, or incidental. A critical exposition of these accounts is offered, demonstrating that each is either theoretically inconsistent or incapable of accounting for the diverse instantiations of the placebo phenomenon. It is argued that rather than thinking of the placebo effect as one phenomenon, we should conceive of it as encompassing three types of responses: conditioned placebo responses, cognitive placebo responses, and network placebo responses. Conditioned placebo responses are deeply engrained responses that operate through classical conditioning and primarily impact immune and endocrine functions. These responses have been observed across many species and are likely to have evolved long ago. Cognitive placebo responses are likely to have developed much later, and are mediated by expectations and beliefs. These responses impact many types of pain as well as particular symptoms such as inflammation, anxiety, and bradykinesia. A third type of placebo response that has received much less attention can be thought of as a network placebo response, and may involve a combination of conditioned and cognitive placebo responses. This third type of response appears in conditions that are maintained through complex symptom networks, such as depression, irritable bowel syndrome, and sexual dysfunction. It is argued that in comparison to previous accounts, this conception of placebo phenomena covers more explanatory ground, illuminates more avenues for intervention, and requires more stringent measures for investigation. Implications for psychosomatic medicine, pain management, and psychiatry are briefly discussed.

6. **Mindsets as medicine: understanding mindsets about illness, medication, and the body**

Sean Zion[1], Alia Crum[1]
1) Stanford University, Stanford, California, United States

Decades of research on placebo effects have demonstrated the significance of context, beliefs, rituals, expectations, and conscious and non-conscious processes in affecting response to treatment (e.g., Kaptchuk, 2002; Miller & Kaptchuk, 2008). However there is limited understanding of how mindsets - the lens through which information is perceived and interpreted - relate to the placebo effect and, more critically, the trajectory of illness and the response to treatment. While recent work indicates the importance of mindsets in driving both psychological and physiological processes (Crum & Langer, 2007; Crum, et al., 2011), we have a poor understanding of the mindsets individuals hold about their bodies, illnesses, and medications. To understand the relationships between these mindsets and how they impact illness and the treatment outcomes, 200 participants were questioned about their mindsets relating to three critical domains: the capability and effectiveness of the body, the normality and progression of illness, and the mechanisms and meaning of medication. These relationships were used to construct models of adaptive and maladaptive health mindsets. This work offers a unique approach to understanding mindsets as a component of the placebo effect and provides a means to disentangle the factors that contribute to disease progression and treatment efficacy. Further, it offers a framework for the design of novel interventions aimed at shifting maladaptive mindsets. Understanding health mindsets may be simple and effective strategy for harnessing the components underlying placebo effects to improve treatment outcomes and quality of life.

Plenary Session 2

Clinical applications of placebo effects

Monday, April 3 02:00 PM - 03:45 PM
Grote Zaal
Chair: Yvonne Nestoriuc

Plenary Session 2: Clinical applications of placebo effects

1.

Open-label placebo treatment in chronic low back pain: A randomized controlled trial

Cláudia Carvalho[1]
1) Instituto Superior de Psicologia Aplicada - Instituto Universitário, Lisbon, Portugal

About Cláudia Carvalho
Cláudia Ferreira de Carvalho, PhD, is a faculty member of ISPA-Instituto Universitário and a licensed clinical psychologist and psychotherapist in private practice in Lisbon, Portugal. Claudia received her graduation in Psychology from Oporto University, her MS on Clinical Psychology and Psychopathology from ISPA and her PhD in Health Psychology from Nova University of Lisbon. Her research and clinical interests include placebo effects, clinician-patient communication and empathy and how it affects health outcomes, hypnosis, and suggestibility. Claudia's recent research focused on open-label placebo and its effect on chronic low back pain, research that has been featured in numerous magazine articles, including Nature, The New York Times and The Times.

Plenary abstract

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 (OLP) treatment to treatment as usual (TAU) for 3 weeks. Pain severity was assessed on three 0- to 10-point Numeric Rating Scales, scoring maximum pain, minimum pain, and usual pain, and a composite, primary outcome, total pain score. Our other primary outcome was back-related dysfunction, assessed on the Roland-Morris Disability Questionnaire. In an exploratory follow-up, participants on TAU received placebo pills for 3 additional weeks. We randomized 97 adults reporting persistent low back pain for more than 3 months duration and diagnosed by a board-certified pain specialist. Eighty-three adults completed the trial. Compared to TAU, OLP elicited greater pain reduction on each of the three 0- to 10-point Numeric Rating Scales and on the 0- to 10-point composite pain scale ($p < 0.001$), with moderate to large effect sizes. Open label placebo treatment also reduced disability compared to TAU ($p < 0.001$), with a large effect size. Our findings suggest that OLP pills presented in a positive context may be helpful in chronic low back pain. Implications of the findings for the clinical practice are discussed.

2.

Placebo and psychotherapy

Jens Gaab[1]
1) Department of Psychology, University of Basel, Basel, Switzerland

About Jens Gaab
Jens Gaab is a psychologist and psychotherapist. After completing his studies in psychology at the University of Trier, he enjoyed his PhD and Postdoc at the University of Zurich, Switzerland. Since 2011, he is Associate Professor for Clinical Psychology and Psychotherapy at the Department 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

Psychotherapy is a psychological intervention, which has a long track record and which has been shown to have proven and clinically significant effects in a multitude of psychological disorders and problems. But let's face it: The same can be said about the placebo. But does this resemblance suffice to equal both interventions? On the basis of conceptual, empirical and ethical arguments and findings I will argue that the aforementioned interventions share many features and processes (and thus psychotherapy can of course be a placebo!), but that it is possible for psychotherapy to be anything but placebo. However and therefore, the current reciprocal non-consideration of both interventions should best be ended, which would have important consequences on psychotherapy practice and research.

3.

Clinical application of analgetic placebo effects?

Regine Klinger[1]
1) Center for Anesthesiology and Intensive Care Medicine & Department of Anesthesiology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

About Regine Klinger

Regine is the head psychologist of the section „Pain Medicine and Pain Psychology“ at 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 non-pharmacological pain interventions in a more systematic manner than what naturally occurs in clinical settings.

Plenary abstract

A number of meta-analyses have demonstrated the efficacy of placebo analgesia, however, high variance is apparent in different study designs. The placebo phenomenon is a complex psychobiological process consisting of learning and expectancy components acting on neurophysiological systems, and its efficacy has been confirmed empirically in a range of fields such as pain and the immune system. Inert substances such as sugar pills can trigger placebo analgesia, and these effects can also enhance the response to active treatments. In the lecture different research approaches to placebo analgesia, different facets of the placebo phenomenon and the underlying mechanisms will be described. The central question will be: Does clinical application of placebo effects make sense? To answer this question two presumptions are necessary: (1) placebo research results must be transferable to patients; (2) that placebo effects must be deliberately applied, so that we can boost the efficacy of pain treatment. These 2 presumptions will be explicated. Proposals of clinical application will be discussed to make better use of placebo analgesia in clinical practice to optimize treatment outcome and to provide patients with an additional placebo-based benefit. The discussion will focus on ways of effectively translating these findings from laboratory to clinical settings and daily clinical practice.

4.

Expectancy focused psychotherapy

Winfried Rief[1]
1) Clinical Psychology and Psychotherapy, University of Marburg, Marburg, Germany

About Winfried Rief

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 400 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

Placebo research has shown that patient’s expectancies are one of the most potent predictors of treatment outcome in various medical conditions. Therefore interventions focusing on the change of expectations might be most effective. However, this could be of relevance not only for outcome expectations, but also for disease-specific, problem-specific and treatment-specific expectations.
I will present latest results on disorder-specific expectations, e.g. in depression. Psychotherapy will be reformulated as an intervention that should target expectation violation of disorder- and treatment specific expectations. Patient strategies how to devalue learning effects in expectation violation situations are exemplified, and ways how to optimize expectation-violating effects are highlighted.

As a practical example, data from a large RCT (n=126) are shown confirming the effect of a presurgery optimization of expectations in patients scheduled for heart surgery (CABG). Disability scores 6 months later confirmed best outcome for heart surgery patients who participated in preoperative psychological interventions optimizing expectations. Practical aspects of the intervention will be presented, and perspectives how to implement these procedures to optimize outcome in medical interventions will be discussed.

5.

The role of the therapeutic relationship in the placebo effect

Bruce E. Wampold[1]

1) Research Institute, Modum Bad Psychiatric Center, Vikersund, Norway & Counseling Psychology, University of Wisconsin, Madison, Wisconsin, United States

About Bruce Wampold

Bruce E. Wampold Ph.D., ABPP, is Director of the Research Institute at Modum Bad Psychiatric Center in Vikersund, Norway, Emeritus Professor of Counseling Psychology at the University of Wisconsin - Madison, and Chief Scientist, Theravue.com. He is a Fellow of the American Psychological Association (Divisions 12, 17, 29, 45), is Board Certified in Counseling Psychology by the American Board of Professional Psychology, and is the recipient of the 2007 Distinguished Professional Contributions to Applied Research Award from the American Psychological Association. Currently his work, summarized in The Great Psychotherapy Debate: The Evidence for What Makes Psychotherapy Work (with Z. Imel, Routledge, 2015), involves understanding psychotherapy from empirical, historical, and anthropological perspectives.

Plenary abstract

Ultrasocial species have evolved to heal socially. For example, bees and ants have social healing processes analogous to endogenous healing mechanisms of single organisms. As social organisms, it is not surprising that human civilizations have been characterized by socially mediated healing practices. Humans have evolved to be influenced by conspecifics, particularly those who are trusted and who are believed to have the expertise to be of assistance. Clearly, socially sanctioned healers have appeared in civilizations to provide health benefits. Therefore, it is not surprising that the therapeutic relationship is an important aspect of medical and psychosocial healing practices and that the relationship is intimately involved in the placebo response. Strictly speaking a placebo response can be elicited without a relationship, but as expected interactions with a healer are responsible for much of observed placebo effects. Evidence for the importance of the relationship from placebo studies, psychopharmacology, and psychotherapy is presented. Implications for clinical practice and research are discussed

Plenary Session 3

Learning and brain plasticity in placebo effects

Monday, April 3 04:15 PM - 06:00 PM
Grote Zaal
Chair: Gustavo Pacheco López

Plenary Session 3: Learning and brain plasticity in placebo effects

1.

Using learning mechanisms to inhibit the development of nocebo nausea.

Ben Colagiuri[1] & Veronica Quinn[1]
1) School of Psychology, University of Sydney, Sydney, Australia

About Ben Colagiuri

Dr. Ben Colagiuri received his PhD in Psychology from the University of Sydney, Australia in 2010. He currently holds a Senior Lectureship and Australian Research Council Discovery Early Career Research Award in the same School. His research aims to understand how expectancies shape human behavior, with a specific interest in placebo and nocebo effects. To date, he has developed a number of novel experimental models to uncover the mechanisms of the placebo and nocebo effect for pain, sleep, nausea, and other conditions. He has published over 40 scientific papers and received state and national recognition for his research, including the Australian Psychological Society Early Career Research Award 2014. His current research is exploring how the placebo effect can be used to improve clinical trial design and clinical practice, with the ultimate aim of enhancing patients' health and wellbeing.

Plenary abstract

Nausea is a prevalent and debilitating side effect of many medical treatments. While pharmacological factors undoubtedly contribute to nausea, there is increasing evidence that the nocebo effect also plays a critical role in the development of nausea. In particular, the formation of associations between the treatment context and the pharmacological agent can lead the treatment context to exacerbate or even induce nausea in and of itself via learning mechanisms. To attempt to combat this, we tested whether pre-exposure to the treatment context prior to treatment could reduce nocebo nausea via latent inhibition. Across two experiments, healthy volunteers underwent nocebo nausea conditioning with Galvanic Vestibular Stimulation (GVS). Critically, some of the participants were randomized to receive pre-exposure to placebo GVS prior to their conditioning in either a deceptive (Experiment 1) or open manner (Experiment 2). In Experiment 1 there was clear evidence of conditioned nocebo nausea that was entirely blocked by pre-exposure to placebo GVS, indicating a latent inhibition effect. In Experiment 2, we replicated the latent inhibition effect for deceptive pre-exposure and found that open pre-exposure was just as successful at blocking the development of nocebo nausea as deceptive pre-exposure. As such, pre-exposure may be an effective method of reducing the development of nocebo nausea and other nocebo effects to reduce the overall burden that side effects cause patients. To this end, the fact that open pre-exposure is as effective as deceptive pre-exposure indicates that latent inhibition can be deployed ethically in clinical practice without violating informed consent.

2.

From learning to expectancy violation: Understanding placebo effects to harness them

Luana Colloca[1]
1) University of Maryland, College Park, Maryland, United States & School of Psychology, University of Sydney, Sydney, Australia

About Luana Colloca

Dr. Luana Colloca is an NIH-funded associate professor at the University of Maryland and a honorary professor at the University of Sydney School of Psychology. Dr. Colloca holds an MD, a master degree in Bioethics and a PhD in Neuroscience. In addition, Dr. Colloca 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 has conducted several ground-breaking studies that have advanced scientific understanding of the psychoneurobiological bases of endogenous systems for pain modulation in humans. As a result, she has developed an international reputation as a leading scientist for advancing knowledge of the neurobiological mechanisms of placebo effects with an integrative approach including psychopharmacological, neurobiological and behavioral approaches publishing in top-ranked international journals including, Biological Psychiatry, Pain, JAMA, among others. The impact of her creative work is clear from her impressive citation rate and more than 100 invited lectures.

Plenary abstract

Expectancies produce positive outcomes and placebo effects in individuals by virtue of anticipations of a benefit and activation of specific endogenous modulatory systems. Based on a well-established proposed conceptual framework, placebo effects are presented as the product of expectancy mechanisms in which conditioned, verbal, and observational cues are centrally integrated to change behaviors and outcomes. Neuroimaging studies that

have capitalized on well-established behavioral paradigms within this framework implicate the dorsolateral prefrontal cortex as a key region in producing these effects. However, expectancies of improvements in real-world settings are often violated. The effects of expectancy violation are presented along with the brain mechanism implicated with mismatch processing and abolishment of placebo effects. Finally, strategies to harness placebo effects are discussed including the use of dose-extending placebos as well as vasopressin and oxytocin as promising adjuvants contributing to the enhancement of placebo effects.

3.

Conditioning as a higher-order cognitive phenomenon: Implications for placebo research

Jan de Houwer[1]
1) Ghent University, Ghent, Belgium

About Jan de Houwer

Jan De Houwer is a Professor at Ghent University (Belgium) where he heads the Learning and Implicit Processes Laboratory. His research is related to the manner in which spontaneous (automatic) preferences are learned and can be measured. Regarding the learning of preferences, he focuses on the role of stimulus pairings (associative learning). With regard to the measurement of preferences, he developed new reaction time measures and examined the processes underlying various measures. Jan De Houwer (co-)authored more than 250 publications in international journals including “Psychological Bulletin” and “Behavioral and Brain Sciences”. He was co-editor of the journal “Cognition and Emotion” and is a member of the editorial board of several journals including “Journal of Experimental Psychology: General”, “Psychological Bulletin”, and “Personality and Social Psychology Review”.

Plenary abstract

Contrary to the available evidence, conditioning is often conceptualized as “as a kind of low-level mechanical process in which control over a response is passed from one stimulus to another.” (Rescorla, 1988, p. 152). More modern views on conditioning, however, do attribute a crucial role to cognitive processes. Most learning researchers endorse the idea that cognitive processes moderate the formation of associations between stimulus representations. More recently, it has been argued that conditioning is mediated by the non-automatic formation of propositional beliefs about the relation between stimuli. Conditioning in verbal humans has even been described as a symbolic phenomenon in which stimulus pairings function as a symbolic cue for the way in which the stimuli are related. These modern views on conditioning imply that the relevance of conditioning for placebo research is not restricted to providing a non-cognitive mechanism for the emergence of placebo effects. Instead, stimulus pairings can function in ways similar to instructions, not only in shaping expectancies about the effects of drugs but also in allowing people to build models of the way in which drugs have their effects.

4.

What is minimally required to elicit placebo effects?

Karin Jensen[1]
1) Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden & Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, United States

About Karin Jensen

I am a clinical psychologist and neuroscientist specializing in brain imaging and pain. My studies have focused on the learning aspects of placebo analgesia, such as associative learning, and included psychophysical measurements as well as neuroimaging experiments. My research line includes studies of on the non-conscious aspects of treatment expectations.

Plenary abstract

Today, little is known about the placebo response in patients with limited cognitive abilities, such as intellectual disability (ID). The aim of this talk is to discuss recent data on placebo mechanisms in patients with impaired cognitive function, as well as experimental studies investigating how implicit cognitive processes may shape placebo responses.

Plenary Session 3: Learning and brain plasticity in placebo effects

5.

When perception is reality: How nocebos mimic real pruritogens in brain processing of itch

Vitaly Napadow[1]
1) Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, Massachusetts, United States & Center for Integrative Pain Neuroimaging, Harvard Medical School, Boston, Massachusetts, 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). He received his Ph.D. in biomedical engineering from the Harvard-MIT Health Sciences and Technology program and Dr. Napadow's laboratory has pioneered the application of non-invasive neuroimaging techniques to better understand the brain circuitry underlying aversive perceptual states, such as pain, itch, and nausea, and to better understand how neuromodulatory mind-body therapies such as acupuncture and placebo interventions ameliorate these states. Dr. Napadow has more than 100 publications in leading peer-reviewed journals, and serves on review panels for the National Institutes of Health and leading journals in the field.

Plenary abstract

When perception is reality: how nocebos mimic real pruritogens in brain processing of itch
Psychological factors are known to significantly modulate itch in patients suffering from chronic itch. Itch is also highly susceptible to both placebo and nocebo (negative placebo) effects. Moreover, brain activity likely supports nocebo-induced itch, but is currently unknown. We collected functional MRI (fMRI) data from atopic dermatitis (AD) patients, in a within-subject design, and contrast brain response to nocebo saline understood to be allergen vs open-label saline control. Analyses also compared results to real allergen itch response and placebo responsiveness, evaluated in the same patients. Nocebo saline produced greater itch than open saline control and compared to open saline, nocebo saline demonstrated greater fMRI response in caudate, dorsolateral prefrontal cortex (dlPFC), and intraparietal sulcus (iPS) - brain regions important for cognitive executive and motivational processing. Furthermore, we found that subjects with greater dlPFC and caudate activation to nocebo-induced itch also demonstrated greater dlPFC and caudate activation, respectively, for real allergen itch. Subjects reporting greater nocebo-induced itch also demonstrated greater placebo reduction of allergen-evoked itch, suggesting increased generalized modulation of itch perception. Our study demonstrates the capacity of nocebo saline to mimic both the sensory and neural effects of real allergens and provides an insight to the brain mechanisms supporting nocebo-induced itch in AD, thus aiding our understanding of the role that expectations and other psychological factors play in modulating itch perception in chronic itch patients. Our results show that our brains have an amazing capacity to recreate the world around them, even without the afferent stimulus we think is necessary to produce certain sensations.

Tuesday April 4
Oral presentation abstracts

Plenary Session 4

Placebo effects: mediators and moderators

Tuesday, April 4 09:15 AM - 11:00 AM
Grote Zaal
Chair: Joel Greenspan

Plenary Session 4: Placebo effects: mediators and moderators

1. 

Mindset matters

Alia Crum[1]
1) Stanford University, Stanford, California, 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

The placebo response has been recognized within western medicine for centuries. Yet -since the advent of the randomized control trial - it has been marginalized as an effect that should be ignored or controlled for. In this talk I will argue that placebo-like effects can be explained, in part, by the role of mindset - the psychological lens through which information is perceived, organized, and interpreted. First, I will present a selection of studies demonstrating how mindsets can affect health outcomes in various stages of disease including a) influencing the effects of genetic predisposition b) shaping the benefits of health behaviors such as diet, exercise and stress and c) improving the physiological effects of treatment. Second, I will discuss how elements of the social context such as the patient-provider interaction can moderate the effect of mindset on health outcomes. Finally, I will discuss how an improved understanding of mindsets and the social context can empower individuals and healthcare providers to harness the power of mindset to improve health and reduce unnecessary suffering.

2. 

A social psychological process approach for understanding placebo effects

Andrew Geers[1]
1) University of Toledo, Toledo, Ohio, 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

An underlying goal of research on placebo effects is to develop a deeper understanding of the phenomenon so as to strategically incorporate it into patient care. Because placebo effects are strongly influenced by a patient's subjective interpretation of the clinical encounter and the interpersonal context surrounding treatment, clarifying the various psychological processes at play should aid translation of research findings to clinical interventions that encourage placebo responses and discourage nocebo responses. In this talk, I will review and describe an empirically-supported multi-process model that can serve as a framework for research into the psychology of placebo effects. From this approach, the success or failure of treatment-relevant information in producing placebo effects depends to a large extend upon the specific communication variables at play, and most importantly, upon the processes by which those variables operate. This model leads to predictions regarding many facets of placebo effects, such as their directionality, durability, and likelihood to alter subsequent behaviors. The proposed conceptualization could help in synthesizing prior theoretical approaches regarding the occurrence of placebo

effects and in addressing several unanswered questions in the placebo literature. The model also suggests steps that practitioners might take to amplify the placebo component of medical treatments and interventions. Research relevant to the model will be described and directions for future research will be highlighted.

3.

Response expectancy and automaticity

Irving Kirsch[1]
1) Harvard Medical School, Boston, Massachusetts, United States

About Irving Kirsch

Irving Kirsch is Associate Director of the Program in Placebo Studies and a lecturer in medicine at the Harvard Medical School. He is also Emeritus Professor of Psychology at Plymouth University (UK), University of Hull (UK) and University of Connecticut (USA). He has published 10 books and more than 250 scientific journal articles and book chapters on placebo effects, antidepressant medication, hypnosis, and suggestion. He originated the concept of response expectancy. His 2008 meta-analyses on the efficacy of antidepressants 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 Newsweek. In 2015, the University of Basel (Switzerland) awarded Irving Kirsch an Honorary Doctorate in Psychology.

Plenary abstract

Response expectancies are anticipations of one's own automatic responses and can generate expected responses in the form of self-fulfilling prophecies. At the time of their influence on conscious experience, they can themselves be conscious, but once acquired, they can also operate quickly and automatically, without conscious awareness. Stimulus expectancies (i.e., expectancies about the external world) can also be self-confirming, although to a lesser degree. The degree to which an expectancy affects experience varies with the ambiguity of the stimulus and the confidence with which the expectancy is held. There are various dimensions of response expectancy that can be manipulated and measured. One is the magnitude of the expected change; another is the confidence with which the expectancy is held. Expectancies are fluid rather than static and have a reciprocal relationship with subjective outcomes. Best outcomes may be obtained by promoting very confident expectancies for initially small changes, thereby setting in motion a benign cycle. Conditioning and expectancy are not opposing processes. Instead, both classical and operant conditioning can function by influencing expectancies. This has been demonstrated both in humans and in other animals. Classical conditioning can also produce responses that are not mediated by expectancies, as has been shown with very primitive organisms and in humans with responses that are not consciously introspectable. The adaptive value of consciousness is that it provides flexibility in considering other sources of information and allowing the organism to override automatic conditioned responses.

4.

Differential effectiveness of placebo treatments

Karin Meissner[1]
1) Placebo Research Group, Institute of Medical Psychology, Ludwig-Maximilians-University Munich, Munich, Germany & Integrative Medicine, University of Applied Sciences and Arts Coburg, Coburg, Germany

About Karin Meissner

Karin Meissner, MD, is Head of the Placebo Research Group at the Institute of Medical Psychology at the Ludwig-Maximilians-University Munich and since 2016 also a full professor of Integrative Medicine at the University of Applied Sciences and Arts in Coburg. Her research interests include meta-analyses of placebo effects in clinical trials, psychobiological correlates of placebo effects in nausea and appetite regulation, and mechanisms of placebo effects on autonomic organ functions. She is also interested in the evaluation of CAM treatments to optimize the care of chronically ill patients. Her research has been funded by the German Ministry for Science and the German Research Foundation (DFG).

Plenary abstract

The size of placebo effects depends on various contextual factors, including the type and characteristics of the placebo intervention. Several systematic reviews provided evidence that more intense placebo interventions are associated with larger placebo effects than less intense ones. For example, sham acupuncture and sham surgery were associated with significantly higher placebo response rates than oral placebos in 79 randomized placebo-controlled studies of migraine prophylaxis (Meissner et al., JAMA Int Med 2013). Similarly, a review of 149 randomized trials on knee osteoarthritis showed intra-articular and topical placebo interventions to induce larger improvement than oral placebos (Bannuru et al., Ann Intern Med 2015). However, a systematic review of 12

studies allowing a direct comparison of different placebo treatment modalities within the same study did not reveal consistent evidence for greater effectiveness of more intense placebos (Fässler et al., J Clin Epidemiol 2015). Likewise, in an experimental paradigm we recently found no evidence for a differential effectiveness of more and less intensive placebo interventions in the treatment of nausea (Meissner et al., submitted). Thus, while there is accumulating evidence from indirect comparisons of placebo groups in clinical trials that the placebo effect size varies systematically according to type of intervention, evidence from studies allowing a direct comparison still challenges this view. Possibly, not only the type of treatment, but also other closely related contextual factors, such as treatment duration and the amount of attention provided by doctors and nurses, contribute to the observed differences of placebo effectiveness across treatment modalities. Implications of the results for the design and interpretation of clinical trials will be discussed.

5.

Social mediators and moderators of placebo effects in children and twins

Katja Weimer[1]
1) Department of Psychosomatic Medicine and Psychotherapy, Medical University Hospital Tübingen, Tübingen, Germany

About Katja Weimer

Katja Weimer is a postdoctoral researcher at the Department of Psychosomatic Medicine and Psychotherapy, Medical University Hospital Tübingen. She studied psychology at the University of Koblenz-Landau, and completed her PhD about placebo effects on motion sickness and gender differences under supervision of Prof. Paul Enck in Tübingen in 2012. Since then, she investigated mechanisms and aspects of placebo effects on cognitive performance and pain in adults and children. Her current work focuses on placebo effects in children, and social learning of placebo effects in children and adults which is funded by an own grant of the German Research Foundation. Currently, Paul Enck and Katja Weimer are establishing a German twin registry, “TwinHealth”, at the University Hospital Tübingen. Furthermore, she is interested in the impact of study designs on placebo effects, and is engaged in psychophysiological research in children with functional bowel disorders and obesity, and in adults with somatic symptom disorders.

Plenary abstract

Recent research has shown that placebo effects could be elicited through social observational learning in adults, and social mediators and moderators were repeatedly discussed to have an impact on placebo effects in children. Social observational learning as well as expectations of parents could be important in children as they have fewer own experiences in medical settings, but only few studies investigated such factors. Furthermore, studies with mono- and dizygotic twins could give further insights into effects of shared and individual learning experiences as well as into the impact of genetics on placebo effects.
In a series of studies, effects of social mediators and moderators on placebo effects in children, adolescents, and adult twins were investigated: 1) An experimental study tested the relationship between placebo effects on cognitive performance and expectations in children and their parents; 2) Impact of parents’ expectations, mood, and traits on children’s pain experience was investigated in a questionnaire-based study in the context of dental treatments; 3) In a 2x2 study design, children observed an effective intervention to reduce heat pain in their mother or an unfamiliar woman (a trained model), either live or in a video; 4) In the control group of the later study, placebo effects by verbal suggestions only were tested in children and their mothers; 5) Placebo analgesia was induced through conditioning in mono- and dizygotic adult twins to analyze effects of an individual learning experience, a shared environment, and genetics.
In summary, placebo effects could be induced through direct observation of an effective treatment and verbal suggestions in children (except on cognitive performance), and trough conditioning in twins. However, there were no relationships in placebo analgesia between family members, neither between children and parents nor between twins. Placebo effects seem to be mainly affected by individual learning experiences.

Parallel Session 2.1

Nocebo effects

Tuesday, April 4 11:30 AM - 01:00 PM
Grote Zaal
Chair: David Yarnitsky

Parallel Session 2.1: Nocebo effects

1. **Neural mechanisms of the nocebo effect and its modulation through price information in cortical, subcortical and spinal regions using cortico-spinal imaging**

Alexandra Tinnermann[1], Stephan Geuter[2], Christian Sprenger[1], Jürgen Finsterbusch[1], Christian Büchel[1]
1) Institute of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2) Institute of Cognitive Science, University of Colorado Boulder, Boulder, Colorado, United States

Background and Aims: Placebo research shows that value (e.g. price information) can modulate the placebo response. In this study, we investigated the influence of a medication's price (cheap vs. expensive) on the magnitude of the nocebo response and the underlying modulation of the cortico-spinal pain network.
Methods: 52 subjects underwent a heat pain stimulation protocol while BOLD responses in the brain and spinal cord were recorded using functional MRI. The nocebo treatment was introduced as a medical cream that increases pain sensitivity as a negative side effect and was compared to a control cream. Subjects were randomly assigned to one of two groups, one receiving the cheap cream whereas the other group was tested with the expensive cream.
Results: The nocebo effect was significantly stronger in the expensive group compared to the cheap group ($t = -2.6$, $p<0.05$). BOLD responses in the expensive group were increased in prefrontal brain regions, amygdala, brainstem and the spinal cord. The anterior cingulate cortex (ACC) showed a strong correlation with the behavioral nocebo effect and a mediation analysis confirmed that the ACC mediated the behavioral outcome, leading to differences in the nocebo response between the cheap and expensive group. Furthermore, coupling between spinal cord and brainstem also correlated with the behavioral nocebo effect.
Conclusion: Behavioral results indicate that an expensive medication elicits stronger side effects than a cheap medication. The fMRI results suggest that complex cognitive constructs such as value can influence subcortical and spinal activity through top-down modulation of the descending pain pathway.

2. **Dizzy but positive - an experimental manipulation of side effect expectancy**

Bettina Doering[1], Winfried Rief[1], Marcel Wilhelm[1]
1) Philipps-University Marburg, Marburg, Germany

Introduction: Expectations influence the effectiveness of clinical treatment. Negative expectations may even produce side effects that occur due to an inert substance or treatment. This "nocebo effect" is associated with content of information and the context it is delivered in. The informed consent process in clinical trials has been found to induce nocebo effects. We investigated whether framing information about a side effect (dizziness) could positively change perceptions of all side effects associated with beta-blocker medication.
Methods: Our sample consisted of 80 healthy participants who were randomly assigned into two groups that both received a beta-blocker. In the positive framing group, participants were informed that dizziness is an indication that the drug is taking effect. The neutral framing group received usual information about dizziness as a side effect. Before and after medication intake participants had to complete an exercise test and then rate their symptoms in intensity and perceived threat.
Results: Participants who received positive framing rated their symptoms as less threatening compared to the neutral framing group. They were also more likely to attribute their symptoms to a drug effect than an adverse side effect. The groups did not vary in intensity of symptoms.
Conclusions: Participants must be told about side effects to ensure a process of informed consent. However, nocebo research suggests that information about side effects may decrease positive expectations of treatment. Our results show that the way in which information is presented can reduce perceptions of threat related to side-effects.

3. **Tying side effects to pain relief, an experimental model of a clinical interaction modulation**

Chantal Berna[1], Aurore Fernandez[1], Louis Noël[2], Isabelle Décosterd[1], Marc Suter[1], Ted Kaptchuk[3], Irving Kirsch[3]
1) Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
2) Université de Lausanne, Lausanne, Switzerland
3) Program in Placebo Studies, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

Background: We recently identified that induced side effects can act as unblinding agents in a model of an analgesic RCT, leading to increased expectancy and effects. Given the frequency of medication adverse effects in pain management, there is a need to better understand links between side effects and expectations in the clinical context. We tested if framing side effects positively during informed consent could favor noticing them and lead to enhanced analgesia.
Methods: A study "validating pupillometry as a measure of analgesia" recruited 66 healthy males(mean age: 24.3), who were randomized double-blind to two different information sets regarding side-effects: neutral or enhanced. The information was provided through a video, in which a physician described the effects/side effects of the medications. Participants underwent pre-treatment heat pain testing, took a combination of 100 mg diclofenac (non-steroidal anti-inflammatory drug) and 1.2mg atropine (given to induce side effects). After an hour of wait for the medication to become active, participants reported side-effects and underwent a second session of heat pain.
Results: The enhanced information group reported more side effects than the neutral one ($p=.012$). Analgesia was observed (Treatment effect: $F(1,64)=35.7$, $p<0.0001$), however, there was no significant difference in analgesia

between groups (Information effect: F(1,64)=0.39, p>0.5), nor a significant interaction.
Conclusions: The differences in design between an RCT model where the presence of induced side effects associated to diclofenac led to increased analgesia and this study will be presented, leading to a discussion of possible limitations in the clinical context, and suggestions for future research.

4. **Emotion-specific nocebo effects: an fMRI study**

Carina Höfler[1], Albert Wabnegger[1], Sonja Übel[1], Anne Schienle[1]
1) Clinical Psychology, Graz, Austria

The neurobiological mechanisms of nocebos are still poorly understood. We invited 38 female participants to a 'smell study' using functional magnetic resonance imaging. They were presented with an odorless stimulus (distilled water) together with the verbal suggestion that this fluid has an aversive odor which enhances disgust feelings. The nocebo was presented while the participants viewed disgusting, fear-inducing, and neutral images. Participants' affective and neuronal responses during nocebo administration were compared with those in a control condition without nocebo. Twenty-nine participants (76%) reported perceiving a slightly unpleasant and arousing odor. These 'nocebo responders' experienced increased disgust during the presentation of disgusting images in combination with the nocebo and showed enhanced left orbitofrontal cortex (OFC) activation. It has been suggested that the OFC is involved in the generation of placebo/nocebo-related expectations and appraisals. This region showed increased functional connectivity with areas involved in interoception (insula), autobiographical memories (hippocampus), and odor imagery (piriform cortex) during nocebo administration. The nocebo-induced change in brain activation was restricted to the disgust condition. Implications for psychotherapy are discussed.

5. **'The Powerful Nocebo': the need to avoid invalidating people with chronic pain.**

Paul Dieppe[1], Maddy Greville-Harris[2]
1) University of Exeter Medical School, Exeter, United Kingdom
2) University of Exeter, Exeter, United Kingdom

Background: Research in the social sciences, education and medicine all suggest that 'Bad is More Powerful than Good'. Our work with chronic pain patients supports this notion, and indicates that we should strive to avoid activating a nocebo response.
Methods: 5 female patients with chronic widespread pain provided signed informed consent to take part in a study in which their first consultation with a pain specialist was video-recorded. After the consultation the patients were interviewed, and shown selected video clips and asked to rate how these clips made them feel. The doctors were also interviewed.
Results: It was clear that the patients with chronic pain struggled to find meaning for their pain, to deal with the disbelief of others (including some doctors), to accept the absence of any 'magic cure' and to find agency and control. Listening and validation by their health care professionals was helpful. However, it was apparent that the negative effect of remarks that could be interpreted as invalidating their experience were particularly powerful and damaging. Simple remarks, aimed at providing reassurance, were often interpreted as lack of belief in the patient's suffering, leading to a worsening of the condition, and a tendency to stop looking for further help from health care professionals.
Conclusions: Nocebo effects are more powerful than placebo effects. Invalidation is a powerful agent for activation of a nocebo response. Medical education should concentrate on helping professionals avoid invalidation and activation of a nocebo response.

6. **Harnessing nocebo withdrawal in tapered dose redcutions**

Llewellyn Mills[1], Ben Colagiuri[1]
1) School of Psychology, Sydney, NSW, Australia

Background: The search for a way to ethically harness expectancies in a clinical setting has proven elusive. Tapered dose reduction - where dose of an addictive drug is steadily reduced in small increments - is an addiction treatment that is widely used and could easily be tailored to take account of patients' expectancies. By asking patients to voluntarily blind themselves to the timing and magnitude of impending dose reductions, it may be possible to remove the nocebo component of withdrawal and improve treatment outcomes.
Method: Three groups of coffee drinkers had their dose of caffeine reduced at the same rate over five days (Mon-300mg; Tues-200mg; Wed-100mg; Thurs-0mg; Friday-end) under differing instructional sets. The Informed group were told the truth about their dose reduction schedule, the MisInformed group were told their schedule was Mon-300mg; Tues-300mg; Wed-300mg; Thurs-0mg; Friday-end, and the NonInformed group were given no information. Caffeine withdrawal was measured twice each day.
Results: Caffeine withdrawal increased across the five days both in the morning and the afternoon. There were no significant between-group differences in rate of increase in the morning. In the afternoon the Informed group showed a significantly greater rate of increase in withdrawal symptoms than the MisInformed and NonInformed groups. Conclusion: Awareness of dose reductions led to a nocebo withdrawal effect. Removing this awareness, by misinformation or lack of information, removed this nocebo effect and led to lower withdrawal symptoms. Blinding patients in tapered dose reductions may reduce withdrawal symptoms and improve prospects of successful transition to a drug-free state.

Parallel Session 2.2

Biological predictors of placebo effects

Tuesday, April 4 11:30 AM - 01:00 PM
Breezaal
Chair: Kathryn Hall

Parallel Session 2.2: Biological predictors of placebo effects

1. **Experimenter characteristics and the participants' gender impact placebo hypoalgesia**

Philipp Reicherts[1], Yannik Stegmann[1], Eva Nees[1], Paul Pauli[1], Matthias J. Wieser[2]
1) Department of Psychology, University of Wuerzburg, Wuerzburg, Germany
2) Institute of Psychology, Erasmus University Rotterdam, Rotterdam, Netherlands

Psychosocial factors, for instance the appearance and status of the caregiver or the patient´s gender are supposed to have a strong influence on the placebo effect. However, so far only few studies systematically manipulated these phenomena. In the present experiment, two groups of participants (52 men vs. 50 women) were investigated by an experimenter, who introduced himself being either a doctoral student in psychology (PSY) or medicine (MED). To establish the two different professional roles, the MED experimenter wore a white coat and took the participants´ blood pressure, the PSY experimenter instead did a clinical psychological interview. Afterwards participants received a placebo-instruction ("observing visual black and white stripe pattern decreases pain") which was reinforced during a placebo-conditioning phase. During the subsequent test phase, identical heat pain stimuli were applied, while participants watched placebo patterns and control cues again. In addition to VAS pain intensity and unpleasantness ratings, skin conductance responses (SCR) were recorded. Pain was rated significantly lower during placebo trials. However, male participants showed no placebo effect when treated by a PSY experimenter. Female participants showed significantly stronger placebo effects than male participants. In general, pain ratings were lower for MED compared to PSY experimenter. SCR and behavioral placebo effects were significantly correlated in the beginning of the test phase. The present results demonstrate a general pain modulating effect by the MED experimenter, which might be suggestive for a "white coat hypoalgesia" and suggest the consideration of social context variables when harnessing placebo effects.

2. **The genetic influence on fear of pain and placebo analgesia**

June Forsberg[1], Johannes Gjerstad[2], Magne Arve Flaten[3], Per M. Aslaksen[1]
1) The Arctic University of Norway, Tromsø, Norway
2) Statens Arbeidsmiljøinstitutt, Oslo, Norway
3) Norwegian University of Science and Technology, Trondheim, Norway

The purpose of this experimental study was to investigate the influence of COMT val158met and OPRM1 A118G polymorphism on fear of pain and placebo analgesia. A two Group (placebo and natural history) by five Trial (pre 1, pre 2, post 1, post 1 and post 3) between subjects design was employed. A contact heat-evoked stimulator was used to induce pain. The participants rated pain intensity using a Computerized Visual Analog Scale. The Fear of Pain Questionnaire-III quantified fear of pain and saliva was obtained for genotyping. Data from 223 healthy participants were included in the analysis. OPRM1 AA-carriers reported lower mean pain level compared to OPRM1 */G carriers ($p < .01$), and the interaction Trial by Group ($p < .01$) displayed a significant placebo analgesic effect. The AA-carriers experienced significantly better pain reduction in the post-tests compared to the */G-carriers in both the placebo group ($p = .001$) and the natural history group ($p = .044$). The COMT val/val-carriers reported significantly higher fear of medical pain compared to the met/met-carriers ($p = .048$). COMT was not found to be associated with pain reports or placebo analgesia. We conclude that OPRM1 predicts placebo analgesia and that COMT is associated with fear of pain.

3. **Gender differences in pain and conditioned placebo analgesia**

Jeanette Weigama Svendsen[1], Sara Magelssen Vambheim[1], Magne Arve Flaten[2]
1) University of Tromsø - The Arctic University of Norway, Tromsø, Norway
2) Norwegian University of Science and Technology, Trondheim, Norway

Background: Studies have shown that males respond with larger pain reduction than females after verbally induced placebo treatment. No studies have reported gender differences in conditioned placebo analgesia. This study examined gender differences in conditioned placebo analgesic responses, and if gender differences are influenced by stress and fear of pain.
Method: A 2 Gender x 3 Group (placebo, cream control, pain control) x 2 Test (pre-test, post-test) mixed design with 96 participants was conducted. In the conditioning procedure, electrically induced experimental pain was surreptitiously reduced in the placebo condition, in order to create an association between the placebo treatment and reduced pain. Pain, fear of pain and stress was measured verbally, and blood pressure was used as a physiological measure of stress
Results: Preliminary analyses showed no placebo effect. However, several other gender differences emerged from the results. Females reported higher fear of pain ($p = .006$) and responded with higher pain intensity ($p = .003$) than males. Regression analyses revealed that fear of pain predicted pain intensity ($R^2 = .22$, $p = .001$), pain unpleasantness ($R^2 = .25$, $p < .001$) and anticipatory stress ($R^2 = .14$, $p = .008$) in females, but not in males.
Conclusions: The findings suggest that fear of pain may negatively impact pain experience in females and contribute to gender differences in pain. The present work provides further support for the mediating effect pain-related fear has on pain.

4. **Enhancing the effects of positive verbal suggestions on pain and itch through oxytocin**

Aleksandrina Skvortsova[1], Judy Veldhuijzen[1], Henriët van Middendorp[1], Andrea Evers[1]
1) Health, Medical and Neuropsychology Unit, Leiden University, Leiden, Netherlands

Somatosensory symptoms such as pain and itch can be reduced by means of positive suggestions through placebo-inducing mechanisms. It is of high clinical relevance to find ways to maximize these placebo effects in order to obtain the best therapeutic results. Oxytocin administration may potentially enhance the effect of positive suggestions. Oxytocin is a well-studied hormone that has many behavioural effects in humans: among others it increases trust, has an anxiolytic effect and mediates empathy and social learning. These parameters may play an important role in positive treatment expectations and therefore contribute to a placebo effect. The primary objective of this study is to investigate whether exogenous oxytocin administration enhances the placebo effect of positive suggestions as measured by subjective pain intensity and itch ratings in response to validated pain (Cold Pressor Test) and itch-inducing (histamine iontophoresis) tasks. A randomized, placebo-controlled study design is used. Participants are randomly allocated to one of four groups: 1) oxytocin group with positive suggestions, 2) oxytocin group without positive suggestions, 3) placebo group with positive suggestions, 4) placebo group without positive suggestions. We hypothesize that oxytocin will increase the placebo effect induced by positive suggestions by demonstrating that participants in the oxytocin group with positive suggestions will demonstrate the lowest ratings of pain and itch compared to other groups. The results will be presented at the conference.

Parallel Session 2.3

Placebo effects in psychology and psychiatry

Tuesday, April 4 11:30 AM - 01:00 PM
Jan Willem Schaap zaal
Chair: Miranda Olff

Parallel Session 2.3: Placebo effects in psychology and psychiatry

1. **Efficacy and safety of SSRIs, SNRIs, and placebo in common psychiatric disorders: A comprehensive meta-analysis in children and adolescents**

Helen Koechlin[1,2], Cosima Locher[1], Sean Zion[2], Christoph Werner[1], Daniel S. Pine[4], Irving Kirsch[5], Ronald C. Kessler[6], Joe Kossowsky[1,2]
1) Department of Clinical Psychology & Psychotherapy, University of Basel, Basel, Switzerland
2) Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States
3) Department of Psychology, Stanford University, Stanford, CA, United States
4) National Institute of Mental Health, Intramural Research Program, Bethesda, Maryland, United States
5) Program in Placebo Studies, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States
6) Department of Health Care Policy, Harvard Medical School, Boston, MA, United States

Background: To examine the relative efficacy and safety of SSRIs, SNRIs, and placebo for the treatment of depressive disorders (DD), anxiety disorders (AD), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) in children and adolescents.
Method: PubMed, Embase, PsycINFO, Web of Science, and Cochrane were searched for studies published through August 2016. Randomized, double-blind, placebo controlled studies of SSRIs or SNRIs in youth diagnosed with DD, AD, OCD, or PTSD were included. Primary outcomes as defined by authors were extracted. Effect sizes (ES) were summarized as standardized mean differences (Hedges'g) in a random-effects model.
Results: We deemed 36 studies eligible, including 6778 participants. No overall differences were found between effect sizes of SSRIs and SNRIs. AD (g=0.557, p<0.001) showed significantly larger between group ES than DD (g=0.201, p<0.001). This difference was driven primarily by the placebo response: patients with DD exhibited significantly larger placebo responses (g=1.569, p<0.001) compared to those with AD (g=1.023, p<0.001). No moderator was significant in the multivariate meta-regression. Compared to placebo, patients taking either SSRIs or SNRIs reported significantly more serious adverse events (SSRI: 6.80% and SNRI: 7.59% vs. placebo: 3.32%; ps≤0.05), but showed no significant difference in treatment emergent adverse events (p=0.73).
Conclusions: The magnitude of drug versus placebo differences varies significantly by disorder, with a larger placebo effect in DD than AD in between group analyses. One explanation might be that children and adolescents with DD may be more demoralized than patients with anxiety disorders and are therefore more sensitive to changes in hope and favorable meanings.

2. **The mechanisms of placebo response in antidepressant trials: an experimental investigation**

Julia Glombiewski[1], Julia Rheker[1], Winfried Rief[1]
1) University of Marburg, Mabrurg, Germany

The mechanisms of placebo response in antidepressant treatments have not been experimentally investigated. Therefore we aimed at examining whether expectations have an impact on experiencing sadness as one major symptom of depression.
We hypothesized that participants who receive an active placebo nasal spray (but are told that it is a fast operating antidepressant that protects them from experiencing negative emotions) would become less sad than the control groups.
To induce sadness, 128 healthy female participants saw a film sequence from "The Champ" (Gross & Levenson, 1995). Participants were randomly allocated to one of four groups: The experimental group receiving an active placebo and the expectancy-modulating instruction and three different control groups. Sadness was assessed three times (T0: Baseline, T1: After randomization, and T2: After film) with the subscale for sadness of the Positive and Negative Affect Schedule-Expanded Form (PANAS-X) (Watson & Clark, 1999).
In line with our hypotheses, the experimental group experienced significantly less sadness after having watched the film sequence as compared to the three control groups (effect size Hedges's g between 0.59 and 1.04) (group effect F (1, 124) = 1.26; p = .292, time effect F (3, 124) = 43.52; p ≤ .001, group*time interaction effect F (3, 124) = 6.99; p ≤ .001).
According to our results at least one symptom of depression (sadness) can significantly be influenced by placebos. The effect sizes were surprisingly large. Further studies are needed.

3. **Placebo effects in children and adults: same mechanisms, but different moderators?**

Katja Weimer[1]
1) Medical University Hospital Tübingen, Department of Psychosomatic Medicine and Psychotherapy, Tübingen, Germany

Reviews revealed higher placebo effects in children compared to adults when similar clinical trials on pain, ADHD and other diseases were compared (Weimer et al., 2013). However, only few experimental studies investigated this finding in children and adults with the same paradigm. Probably the same placebo mechanisms are effective in children and adults, but they could be affected by different mediators and moderators. Therefore, we investigated placebo effects on cognitive performance and mood as well as on pain in children and their parents.
The study about cognitive performance and mood revealed no significant placebo effects in both children (14 ± 2 years, 54% female) and parents, and only few relationships between them. We speculate that this might be due to

the paradigm used which aimed to enhance a normal and healthy functioning which is difficult to improve. In the control group of a study about observational learning of placebo effects, placebo analgesia was induced through verbal suggestions only, and children (11 ± 3 years, 44% female) and their mothers both showed significant placebo analgesia which did not differ in their magnitude. However, their responses were not related to each other. In both, placebo analgesia was not related to their expectations about the treatment.
In summary, children and adults both showed placebo effects on pain, but not on cognitive performance what could be due to the paradigm used. Effects of psychological variables will be further explored.

4. **Placebo Research in Children: Achievements, Obstacles and Untapped Potential**

Joe Kossowsky[1]
1) Harvard Medical School, Boston, United States

At current, most research investigating the mechanisms and implications of the placebo response are based on studies in adults. To a large extent, this is due to ethical and feasibility issues in conducting research in children, such as language, compliance and informed consent.
This presentation aims to summarize the findings of past research, offer an overview of current research projects and to provide directions for future studies in pediatric placebo research. Based on an ongoing open-label placebo study for children with Irritable Bowel Syndrome at Harvard Medical School, potential roadblocks in conducting placebo-controlled RCTs in children will be addressed. Strategies for data collection and data sharing will be discussed, as well as the important task of linking pediatric placebo research to the fields of Pediatrics and Child Development.

5. **Placebo can enhance creativity**

Liron Rozenkrantz[1-3], Lior Noy[2,3], Avi Mayo[2,3], Tomer Ilan[2], Yuval Hart[2,3], Uri Alon[2,3]
1) Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel
2) Theater Lab, Weizmann Institute of Science, Rehovot, Israel
3) Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

Background: Placebo is usually studied for reduction of negative symptoms; there is also interest in exploring its effect on enhancing positive aspects of performance or cognition. Several studies indicate that placebo can enhance cognitive abilities including memory, implicit learning and general knowledge. Placebo in these contexts is thought to weaken inhibitory mechanisms that normally impair performance. Here, we ask whether placebo can enhance creativity, which is also thought to depend on inhibiting self-incapacitating inner criticism.
Methods: Ninety subjects completed two manual creativity tests (Torrance, alternate uses) and a novel automated creative foraging test (CFT) in which participants create interesting and beautiful shapes in a well-defined geometric space. Subjects were randomly assigned to a control group who smelled an odorant (n=45), and a placebo group who were also told that the odorant increases creativity and reduces inhibitions (n=45).
Results: The placebo group created shapes that were more unique than the control group ($p<0.05$), reached higher number of meaning themes (also called flexibility) ($p<0.001$) and explored the space of shapes more extensively ($p<0.001$) in the CFT. The placebo group showed higher creativity and flexibility scores in the alternate uses test ($p<0.05$), but not in the Torrance test.
Conclusions: Our results demonstrate that placebo can enhance creativity. This finding, together with the automated CFT creativity assay which can quantitate multiple aspects of the creative search without need for manual coding, opens the way to explore the behavioral and physiological mechanisms by which placebo might amplify creativity.

Parallel Session 2.4

Concepts in placebo research

Tuesday, April 4 11:30 AM - 01:00 PM
Cornelis Schuytzaal
Chair: Per Aslaksen

Parallel Session 2.4: Concepts in placebo research

1. **Placebo is a bitter pill - why many German physicians prefer complementary or alternative treatments to placebos**

Klaus Linde[1], Agnes Ostermaier[1], Niklas Barth[1]
1) Institute of General Practice, Technical University Munich, Munich, Germany

Background: Survey data suggests that many physicians working in outpatient care in Germany use controversial complementary and alternative (CAM) treatments and placebos. We aim to understand the characteristics of and reasons for this behavior better.
Methods: We re-analyzed data from a quantitative survey among general practitioners (n=319), internists (n=305) and orthopedists (n=311), linking the parts on CAM and placebo use which had been so far analyzed separately. Based on the findings of this survey and theoretical considerations we started an ongoing qualitative project. The pilot study - narrative interviews with 19 experienced general practitioners - is currently under analysis using an approach based in grounded theory and systems hermeneutics.
Results: The quantitative survey clearly showed that CAM treatments are used much more frequently (77% used at least one CAM treatment more often than once a week in the previous year) than impure or pure placebos (28% and 4%, respectively, >10 times in the previous year). The frequency of the use of each single CAM treatment was strongly associated with the belief in its specific effects. The qualitative pilot study suggests that even the (minor) possibility of a specific effect makes CAM treatments (and, in particular, homeopathy) clearly preferable to placebos for the majority of physicians.
Conclusion: Giving a placebo seems to be experienced as a therapeutic defeat and a morally dubious act by many physicians. Using CAM treatments is a much easier option. While an empathic therapeutic encounter is considered relevant providing something “material” remains important to physicians.

2. **'Human beings in trouble': Wittgensteinian investigations of sustainable placebic empathy**

Ryan van Nood[1]
1) Purdue University, West Lafayette, Indiana, United States

Revelations regarding the challenges of manifesting empathy in healthcare and its role in eliciting placebo responses have generated a wealth of literature. These discussions frequently present clinical empathy as navigating between two extremes, i.e., between self-protective, self-isolating cognitive empathy and self-identification or fusion with a patient’s affect. Concerns about the sustainability and effectiveness of one’s approach follow from this picture in various ways, depending upon one’s background theories of mind and ethics. This paper proposes that philosopher Ludwig Wittgenstein’s reminders about how we learn sensation language (in his example of an elder responding to a child crying out in pain) can dissolve this impasse. In particular, his tale helps us to see (1) that bare cognition of another’s pain without affect is a deficient mode of knowing another’s pain in ordinary practice, (2) that affective identification with the sufferer is not satisfying by itself, because, (3) the criterion of a successful case of empathy (especially as relevant in the clinic) is not merely identity with the sufferer’s pain, but rather the sufferer’s achievement of non-identity with her own pain. In Wittgenstein’s vignette, the gift of language to a crying child enables her to articulate and thus find some distance to her pain; in the clinical context, rigorous empathy may stave off the overwhelm that threatens to swallow patient and clinician alike. This vision of empathy provides a best case that may prove salubrious for patients and clinicians, and useful in experimental design, discussions of clinical ethics, and clinician education.

3. **Growing evidence for neurophysiological mechanisms of placebo effects does not legitimise the use of complimentary and alternative medicines by athletes.**

Chris Beedie[1]
1) Canterbury Christ Church University, Canterbury, Kent, United Kingdom

Complimentary and alternative medicines (CAM) are treatments proposed to prevent, manage or cure symptoms of ill health, but which lack scientific evidence for efficacy and/or mechanisms. It has been suggested that many forms of CAM are effective, albeit via the placebo effect. Furthermore, it has been argued that the fast developing neurological, biochemical and physiological evidence base for the placebo effect provides a mechanism for, and therefore legitimises, the use of CAM. CAM treatments are widely used to enhance performance in sport, and range from the relatively harmless such as magnetic bracelets, the potentially harmful such as natural and synthetic ergogenic aids, to high-risk such as medicines and/or procedures developed for clinical applications (arguably CAM also includes treatments proven in one context but applied without evidence to another). Research has demonstrated significant placebo effects associated with several such forms of CAM in sport. In this paper it is argued that a range of factors, for example professional ethics relating to deliberate deception, pragmatic factors such as the variability and instability of placebo responding between and even within individuals, and humanistic factors such as the potential limits to human performance associated with the reliance on unstable external as opposed to stable internal cues, determine that placebo mechanisms do not legitimise CAM. Practitioners should seek treatments on the basis of valid and reliable evidence of mechanisms as well as potential efficacy, and accept that placebo effects, whilst often augmenting treatment effects, should not constitute the entire effect of a treatment.

4. **Communicated beliefs about action-outcomes: The role of initial confirmation in the adoption and maintenance of unsupported beliefs**

Toby Pilditch[1], Ruud Custers[2]
1) University College London, London, United Kingdom
2) Utrecht University, Utrecht, Netherlands

As agents seeking to learn how to successfully navigate their environments, humans can both obtain knowledge through direct experience, and second-hand through communicated beliefs. Questions remain concerning how communicated belief (or instruction) interacts with first-hand evidence integration, and how the former can bias the latter. Previous research has revealed that people are more inclined to seek out confirming evidence when they are motivated to uphold the belief, resulting in confirmation bias. The current research, explores whether merely communicated beliefs affect evidence integration over time when it is not of interest to uphold the belief, and all evidence is readily available. In a novel series of on-line experiments, participants chose on each trial which of two options to play for money, being exposed to outcomes of both. Prior to this, they were exposed to favourable communicated beliefs regarding one of two options. Beliefs were either initially supported or undermined by subsequent probabilistic evidence (probabilities reversed halfway through the task, rendering the options equally profitable overall). Results showed that while communicated beliefs predicted initial choices, they only biased subsequent choices when supported by initial evidence in the first phase of the experiment. Findings were replicated across contexts, evidence sequence lengths, and probabilistic distributions. This suggests that merely communicated beliefs can prevail even when not supported by long run evidence, and in the absence of a motivation to uphold them. The implications of the interaction between communicated beliefs and initial evidence for areas including superstition, impression formation, and placebo effects are discussed.

5. **Medical students' understanding of placebo and nocebo effects (PNEs). Implications for future practice.**

Mark Arnold[1], Finniss Damien[2], Georgina Luscombe[1], Ian Kerridge[2]
1) School of Rural Health/University of Sydney, Dubbo/Camperdown, NSW, Australia
2) Northern Clinical School Pain Management and Research Institute, St Leonards, NSW, Australia

Introduction: It is essential that students are aware of PNEs and their effect on patient-doctor interactions.
The Sydney Graduate Medical Program (SMP) accepts approximately 300 students yearly with appropriate undergraduate (UG) or postgraduate (PG) humanities or science entry qualifications from diverse ethnic and cultural backgrounds (typically 20% International (IS), 80% Domestic (DS)).
Methods: A web-based questionnaire assessed knowledge and attitudes of students to PNEs at commencement of their two (clinically immersive) years of the SMP. Associations between responses and student demographics (age, gender, UG versus PG qualifications, cultural background and IS versus DS) were explored.
Null hypotheses: There would be no differences in knowledge and values regarding PNEs based on age, gender, IS/DS, Caucasian (C)/Non-Caucasian (NC) ethnicity or entry qualification (UG/PG). HREC/IRB approval was granted.
Results: There were 35 respondents (year cohort: 288). The following demographic associations were statistically significant ($p \leq 0.05$): males and DS felt that placebo responses could differentiate organic from non-organic disease; UG recognised placebo administration in practice; IS designated placebo administration as deceptive; NCs felt that if a doctor told them a medication was a placebo they would think it "useless"; IS felt that placebos work better in patients who are anxious or complain, prescribing a placebo is unscientific and did not identify anticipation responses.
Conclusions: Students displayed highly normative and generally unsophisticated beliefs regarding PNEs potentially associated with their demographics. Students' identification of and reflection upon these beliefs may be necessary to optimise their appreciation of their effect as actors when beginning clinical interactions.

6. **Patients' Expectations regarding medical treatment: A comprehensive Review of Concepts and their Assessment**

Johannes Laferton[1], Tobias Kube[2], Stefan Salzmann[3], Charlotte Auer[4], Meike Shedden-Mora[5]
1) Psychologische Hochschule Berlin, Berlin, Germany
2) Phillips University of Marburg, Marburg, Germany
3) Philipps University of Marburg, Marburg, Germany
4) University Hospital Lübeck, Lübeck, Germany
5) University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Patients' expectations predict health outcomes across a variety of medical conditions. However, the aggregation of evidence is complicated due to inconsistent and disintegrated application of expectation constructs and a heterogeneity of assessment strategies. Therefore, based on current expectation concepts, this comprehensive review provides an integrated model of patients' expectations in medical treatment. Moreover, we review existing assessment tools in the context of the integrative model of expectations and provide recommendations for future assessment.
The most relevant expectation concepts we identified include social cognitive theories, the response expectancy theory, and the common sense model of illness representation. The integrative model includes expectations regarding treatment and the patient's treatment related behavior. Treatment and behavior outcome expectations

can relate to aspects of benefit and side-effect expectations and can be referring to internal and external outcomes. Further, timeline, structural and process expectations are important aspects with regards to medical treatment. Moreover, generalized expectations such as generalized self-efficacy or optimism have to be considered.
Several instruments exist in the literature assessing different aspects of expectations in medical treatment. However, many have been developed without conceptual standardization and psychometrical evaluation. Mostly, only single aspects of expectations are assessed, which hinders more differential evidence among the various aspects of expectations. Moreover, many instruments assess treatment specific expectations that are not comparable between conditions.
In order to generate a more comprehensive understanding of expectation effects in medical treatments future research should apply standardized, psychometrically evaluated measures, assessing multidimensional aspects of patients' expectations that are applicable across various medical treatments.

Plenary Session 5

The neurobiology of placebo and nocebo effects

Tuesday, April 4 02:00 PM - 03:45 PM
Grote Zaal
Chair: Younbyoung Chae

Plenary Session 5: The neurobiology of placebo and nocebo effects

1. 

The effects of instructions, expectations, and conditioning on pain

Lauren Atlas[1]
1) NCCIH Investigator & Affective Neuroscience and Pain, National Institutes of Health, Bethesda, Maryland, United States

About Lauren Atlas

Dr. Atlas received her B.A. in psychology from The University of Chicago in 2003, and her Ph.D. in psychology in 2011 from Columbia University, where she studied under the mentorship of Dr. Tor D. Wager. Her doctoral work combined functional magnetic resonance imaging, experimental psychology, and psychopharmacology to examine the mechanisms by which beliefs and expectations influence pain and its modulation. Her dissertation, "Brain mechanisms of expectancy effects on pain experience," was awarded with distinction. Dr. Atlas's postdoctoral research was conducted in Dr. Elizabeth A. Phelps's laboratory at New York University, where she extended computational models of decision-making to isolate components of expectancy, and to understand how these components influence physiological and neural markers of aversive learning. In July 2014, Dr. Atlas joined NIH as an NCCIH investigator and chief of the Section on Affective Neuroscience and Pain. She also holds a joint appointment with the National Institute on Drug Abuse (NIDA). Her laboratory uses a multi-modal approach to investigate how expectations and learning influence pain and emotion, and how these factors influence clinical outcomes.

Plenary abstract

Placebo effects are thought to depend on two main psychological processes: conscious expectations and conditioning, or associative learning. In this talk I will present a series of mechanistic studies designed to isolate each of these processes and measure effects on pain, autonomic responses, and brain activation. Using computational models, we are able to dissociate the joint contributions of instructions and learning. We show that these two factors have dissociable effects on neural systems involved in aversive learning, and that they have separable influences on pain reports and autonomic responses. This approach indicates that rather than arguing over whether placebo effects depend on conditioning or conscious expectancy, we should recognize that outcomes will be beneficial when we combine these two approaches, which are largely independent.

2. 

Avoiding nocebo effects to optimize treatment outcomes

Ulrike Bingel[1]
1) Department of Neurology, University Hospital Essen, University Duisburg-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

There is converging evidence that the occurrence of unwanted adverse events during drug treatment is highly determined by non-pharmacological effects. For instance, the majority of UAEs and symptoms reported by patients in clinical trials are not caused by the drug itself, as suggested by the fact that UAEs can also occur to a comparable degree in the placebo arm of the study. Negative expectations and negative prior treatment experiences not only determine the occurrence of side effects, but can critically impair the therapeutic efficacy of the drug itself. These negative effects on treatment efficacy and tolerability induced/driven by psychological factors are referred to as nocebo effects. Although mechanisms steering nocebo effects are much less well understood than those of placebo effects, it is evident that these effects are not the result of a report bias but have neurobiological and peripheral physiological substrates. Nocebo effects can be triggered by a variety of psychosocial and contextual factors. The mechanisms that are best supported by empirical evidence are expectancy (i.e. patients' expectations regarding the effect of a treatment) and learning processes induced by pre-treatment experiences such as the prior occurrence of UAEs or prior treatment failure. Importantly, learning processes mediating nocebo effects do not necessarily have to be based on first-hand experience but can also be the result of social observational learning.
In my presentation I will outline the negative impact of nocebo effects on treatment outcomes and highlight potential mechanisms-based strategies to prevent or minimize nocebo effects in the clinical context.

Plenary Session 5: The neurobiology of placebo and nocebo effects

3.

Neural underpinning of nocebo hyperalgesia in visceral pain

Sigrid Elsenbruch[1]
1) Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

About Sigrid Elsenbruch

Sigrid Elsenbruch is a Professor of Experimental Psychobiology & Gender Research at the University Hospital of Essen, University of Duisburg-Essen, Germany. Her interdisciplinary research focusses on biological and psychological aspects of the brain-gut axis in human visceral pain, especially in irritable bowel syndrome. She has accomplished several research studies on placebo and nocebo effects in visceral pain, including brain imaging studies to elucidate the neural mechanisms mediating effects of expectations and conditioning in a clinically-relevant model of experimental visceral pain. This research is closely connected to her work on stress and anxiety, providing evidence on the role of emotions and cognitions in the pathophysiology of IBS and other medically-unexplained symptoms involving disturbed interoception.

Plenary abstract

Knowledge from placebo and nocebo research aimed at elucidating the role of treatment expectations and learning experiences in shaping the response to visceral pain fills an important research gap. First, chronic abdominal pain, such as in irritable bowel syndrome (IBS), is highly prevalent, with detrimental individual and socioeconomic impact and limited effective treatment options. At the same time, IBS patients show high placebo response rates in clinical trials and benefit from placebo interventions. Second, psychological factors including negative emotions (e.g., anxiety) and cognitions (e.g., pain-related fear) in the context of visceral pain have been implicated in the pathophysiology of IBS and other conditions characterized by medically-unexplained somatic symptoms. Hence, the study of nocebo effects and underlying neural mechanisms in visceral pain constitutes a model to assess the contribution of psychological factors. Herein, the clinical relevance of visceral pain is introduced with a focus on IBS as a bio-psycho-social disorder, followed by a review of existing clinical and experimental work on nocebo effects in IBS and in clinically-relevant visceral pain models in healthy volunteers. Finally, emerging research trends are highlighted along with an outlook regarding goals for ongoing and future research.

4.

Alternative placebos: From magic to neurofeedback

Amir Raz[1]
1) Cognitive Neuroscience of Attention, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

About Amir Raz

Professor Amir Raz is the Canada Research Chair in the Cognitive Neuroscience of Attention in the Faculty of Medicine at McGill University and a member of the departments of psychiatry, neurology and neurosurgery, and psychology. He teaches many courses at McGill, including a popular elective course on placebos for medical students. He has authored more than 120 peer-reviewed publications, including in top journals such as Nature, Nature Reviews Neuroscience, The Lancet Psychiatry, Archives of General Psychiatry (JAMA Psychiatry), Proceedings of the National Academy of Sciences, Brain, and Journal of Cognitive Neuroscience (with over a thousand citations). In addition, he has published his programmatic research efforts in leading niche journals including Psychological Science, PLoS Medicine, Cortex, and NeuroImage. By way of books, Dr. Raz published three peer-reviewed volumes, commissioned by reputable academic publishing houses (i.e., Open University of Israel and Oxford University Press) and is currently completing two more volumes. His contributions are multi-factorial and apply both outside and within the University. He is a former member of the McGill Board of Governors and an active communicator in the media and community outreach programs.

Plenary abstract

Not all placebos are straightforward; some are rather subtle. Blurred and tenuous rubrics such as magic, hypnosis, and psychotherapy have long raised some interesting operative questions about placebos. More recently, neurofeedback, an ostensibly “scientific” tool available for moulding brain function and bolstering mental processes, gained visibility. A careful look at the available findings suggests that the benefits of neurofeedback, and many other twilight appellations, may derive largely from placebo-like effects.

Plenary Session 5: The neurobiology of placebo and nocebo effects

5.

Placebos, expectations, and self-fulfilling prophecies

Tor D. Wager[1]
1) Department of Psychology and Neuroscience and the Institute for Cognitive Science,The University of Colorado, Boulder, United States

About Tor Wager

Dr. Wager is a Professor of Psychology and Neuroscience and a faculty member in the Institute for Cognitive Science at the University of Colorado, Boulder. 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 2010, he has directed Boulder's Cognitive and Affective Neuroscience laboratory. He has a deep interest in how thinking influences affective experiences, affective learning, and brain-body communication. His laboratory also focuses on the development and deployment of analytic methods, and has developed several publically available software toolboxes for fMRI analysis.

Plenary abstract

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 expectations and other future-oriented cognition. An underappreciated consequence of placebo effects is their capacity to induce 'self-fulfilling prophecies' — positive feedback loops between expectations and experience that can cause resistance to new information and persistent effects of prior beliefs, for good or ill. In this talk, I present a pair of behavioral and fMRI experiments that demonstrate reciprocal positive influences of expectations on pain experience and neurophysiology, and vice versa. This feedback system creates placebo effects that, once established, do not extinguish in spite of a complete absence of primary reinforcement. This empirical study helps provide a foundation for understanding why seemingly innocuous placebo interventions can end up having large and durable clinical effects in some cases.

Parallel Session 3.1

Towards applications of placebo effects in clinical practice

Tuesday, April 4 04:15 PM - 05:45 PM
Grote Zaal
Chair: Irving Kirsch

Parallel Session 3.1: Towards applications of placebo effects in clinical practice

1. **Increasing patients' knowledge about placebo effects: developing and testing a person-based digital intervention**

Felicity Bishop[1], Maddy Greville-Harris[1], Jennifer Bostock[2], Amy Din[1], Cynthia Graham[1], George Lewith[1], Christina Liossi[1], Tim O'Riordan[1], Peter White[1], Lucy Yardley[1]
1) University of Southampton, Southampton, Hampshire, United Kingdom
2) Institute of Psychiatry, Psychology & Neuroscience, London, United Kingdom

Placebo-controlled trials remain the gold standard for establishing the efficacy of new pharmacological interventions. When taking part in trials, patients should be informed of the potential benefits and risks of participating in order to give fully informed consent. However, existing information leaflets often fail to describe potential benefits and/or adverse effects associated with placebo allocation. This project developed and then tested the effects of a new person-based, evidence-based, and theory-based digital intervention (website) about placebo effects on patients' knowledge about and informed choice to try placebos. A web-based randomized evaluation compared the new person-based website to a control website based on existing UK patient information leaflets. 350 adults with back pain (Mean age 47.88, 56.3% female) were recruited from 26 GP practices in England. The two primary outcome measures were change in knowledge (pre-post viewing the website) and informed choice (composite measure based on knowledge, attitudes, and informed choice, assessed after viewing the website). Participants who viewed the person-based website had a significantly greater increase in their knowledge about placebos (M=2.11, SD=2.29) than participants who viewed the standard website (M=-0.11, SD=1.61), $F(1, 330)=105.397$, $p<.001$, $\eta 2 = .242$. Participants who viewed the person-based website were 3.16 times more likely than those who viewed the standard website to make an informed choice about placebos $\chi 2$ (1) = 36.524, $p<.001$. The person-based website could be used to improve knowledge about placebo effects among the public. After further testing in clinical trial settings it could be used to support informed consent in placebo-controlled trials.

2. **Effects of open-label verbal suggestions on itch**

Stefanie Meeuwis[1], Henriët Van Middendorp[1], Judy Veldhuijzen[1], Antoinette van Laarhoven[1], Jan de Houwer[2], Andrea Evers[1]
1) Health, Medical, and Neuropsychology unit, Leiden University, Leiden, Netherlands
2) Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

Negative and positive outcome expectancies, induced by verbal suggestions, have been shown to influence subjective symptoms such as itch. Although most studies on placebo and nocebo effects have only informed participants after participation that they received an inert substance (closed-label placebo/nocebo), there is a growing body of literature that suggests that placebo effects can occur even when it is known that a given substance is inert (open-label placebo).
An experimental study was conducted to investigate the effects of open-label positive verbal suggestions on itch. Healthy volunteers (n = 92) were randomized to either an experimental or a control group. Itch was evoked experimentally during a single laboratory session by histamine iontophoresis. In the experimental group, participants were told that the test would elicit little itch and received information on how expectations could influence itch (i.e. open-label positive verbal suggestions).
Open-label verbal suggestions were found to affect itch expectations in this study, but not itch symptoms. Additionally, within the experimental group only, pre-suggestion expected itch was significantly associated with self-reported itch.
A second study was set up in order to investigate whether effects on itch can be found, when open-label verbal suggestions are strengthened by application of an inert substance (i.e. tonic). This study investigates whether negative and positive outcome expectations, induced by verbal suggestions under both open-label and closed-label conditions, can influence itch evoked by histamine iontophoresis. The data of the second study are currently being collected and the results will also be presented at the conference.

3. **Open-label placebos in healthy participants: an experimental pain investigation**

Cosima Locher[1], Joe Kossowsky[2], Jens Gaab[1]
1) University of Basel, Basel, Switzerland
2) Harvard Medical School, Boston, United States

Recent literature shows the efficacy of open-label placebo treatment in various disorders. In an open-label placebo condition, patients receive a detailed scientific rationale about how placebos work. Open-label placebos were never evaluated in healthy participants and, methodologically, various control conditions are lacking. We tested the efficacy of open-label placebos in a standardized experimental heat pain paradigm. We hypothesized that the open-label group would show (1) smaller placebo analgesic responses compared to a deceptive placebo group and (2) higher placebo responses than control groups.
One hundred sixty healthy volunteers were randomly assigned to four condition groups (i.e., open-label placebo, deceptive placebo, passive control group, and no treatment group). Besides the no treatment group, all trial arms received an inert placebo cream. Participants in the passive control group were only informed that they will receive

a placebo cream, without any additional information. Pain thresholds and tolerances as well as subjective pain judgments (i.e., pain intensity and pain unpleasantness) were assessed before and after the placebo cream application. Primary outcomes were the within-subject difference scores of subjective pain intensity and pain unpleasantness. Primary outcomes were subjected to two separate repeated-measures ANCOVAs with treatment group as between-subject factor and pain thresholds and tolerances as covariates.
The potential and novel treatment with open-label placebos would provide an ethically acceptable way to harness placebo effects, without violating key principles of openness and transparency in clinical practice. We belief that basic research can make an important contribution in order to understand the underlying mechanisms of open-label placebos.

4. **Effect of a three-session expectation optimization training to prevent side effects and enhance quality of life in breast cancer patients undergoing adjuvant endocrine treatment: a multi-center randomized clinical trial**

Yvonne Nestoriuc[1], Yiqi Pan[1], Sarah Heisig[1], Pia von Blanckenburg[2], Meike Shedden-Mora[1], Peyman Hadji[3], Ute-Susann Albert[3], Isabel Witzel[1], Arthur Barsky[4], Winfried Rief[2]
1) Medical Center Hamburg-Eppendorf, Hamburg, Germany
2) Philipps-University Marburg, Marburg, Germany
3) Krankenhaus Nordwest, Frankfurt, Germany
4) Harvard Medical School, Boston, United States

Background. Although patients' treatment expectations substantially modulate the efficacy and tolerability of medical treatments, expectation-based interventions have not been clinically investigated. This clinical trial aims to evaluate the efficacy of an expectation optimization training to improve side-effect load and health-related quality of life in patients undergoing endocrine treatment for breast cancer.
Methods. This three-group randomized clinical trial was conducted in four certified breast centers in Germany between November, 2012, and December, 2015. Participants included 191 women with hormone-receptor positive breast cancer scheduled to start adjuvant endocrine treatment, randomized to either a three-session expectation optimization training (n=65), treatment-as-usual (n=61) or a manualized supportive therapy (n=65). The primary outcome was patient-reported side-effects three and six months after the start of endocrine treatment. Secondary outcomes included health-related quality of life (EORTC-QLQC30 and BR23) and coping.
Results. Among 191 randomized patients (mean age: 58.0 years, 71.2% postmenopausal), 161 (84.3%) and 157 (82.2%) completed the follow-ups at 3 and 6 months. Intention-to-treat mixed model analysis with adjustments for baseline values, medical, and psychological variables showed statistically significant differences in outcome among the three groups for number of side-effects, coping with side-effects, and health-related quality of life. Effect estimates for expectation optimization training included fewer side-effects (-3.3 symptoms, CI95%: -0.98 to -5.6) and higher quality of life (7.8 EORTC-scores, CI95%: 3.1 to 12.4) compared to supportive therapy. No significant effect was seen for intensity of side-effects.
Conclusions. A psychological expectation optimization training was effective at reducing side-effects and improving quality of life during adjuvant endocrine treatment.

5. **Mechanisms of open-label placebo effects**

Kari Leibowitz[1], Alia Crum[1]
1) Stanford University, Palo Alto, California, United States

Recent studies suggest that open-label placebos, or placebos given to patients who are aware they're receiving inert treatment, can be effective treatments in conditions including irritable-bowel syndrome, lower back pain, ADHD, and depression (Kaptchuk et al., 2010; Kelley, Kaptchuk, Cusin, Lipkin, & Fava, 2012; Sandler & Bodfish, 2008; Carvalho et al., 2016). However, there are still many roadblocks to physicians actively prescribing and using placebos in medical care, even without deception. How can we feasibly harness the power of open-label placebos in routine medical care? An important first step is to understand the mechanisms driving open-label placebo effects. The present study attempts to tease apart several potential mechanisms by examining them in a carefully-manipulated laboratory study. In this study of 150 participants, we used a histamine skin-prick test to examine participant allergic reactions and discomfort across five conditions that emphasize and leverage combinations of three possible mechanisms of open-label placebos: (1) patient expectations, (2) medical rituals and conditioning, and (3) explanations about the power of the placebo effect or "meta-mindsets." By understanding which mechanisms drive open-label placebo effects, we can begin to harness these mechanisms in conjunction with active medications and treatments, thereby creating an additive effect that boosts the efficacy of medications and treatments. This talk will explore results from the current study and its implications for clinical practice.

Parallel Session 3.1: Towards applications of placebo effects in clinical practice

6. **Placebos without deception improve symptoms in allergic rhinitis**

Michael Schaefer[1], Rebecca Harke[1], Claudia Denke[2]
1) Medical School Berlin, Berlin, Germany
2) Department of Anesthesiology and Intensive Care Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany

Numerous studies have demonstrated that placebo treatment may have a significant impact on allergic symptoms. Whereas in the classic understanding deception of the patient is necessary for beneficial responses due to placebo treatment, recent research demonstrated that placebos may work even without concealment. Given that there are known ethical problems linked to the use of placebos (e.g., trust and patient-physician relationship), the possibility of using open-label placebos is fascinating. Here we report first results that placebos without deception reduce symptoms in allergic rhinitis. We conducted a two-group randomized controlled trial including 25 participants with allergic rhinitis. One group received placebos without deception (open-placebo group), the other group received no pills (control group). Patient-provider relationship and amount of contact time was held similar for both groups. After two weeks allergic symptoms of the open placebo group significantly decreased, in contrast to the control group. These improvements of the symptoms were significantly related to the subjective well-being. A second study could replicate these findings in a different set of participants. We conclude that open label placebos seem to improve symptoms of allergic rhinitis better than a control group with comparable patient-adviser contact. Future studies are needed to further examine these results, in particular with respect to biological markers.

Parallel Session 3.2

Neurobiological & pharmacological placebo effects

Tuesday, April 4 04:15 PM - 05:45 PM
Breezaal
Chair: Pedrag Petrovic

Parallel Session 3.2: Neurobiological & pharmacological placebo effects

1. Expectation of L-dopa intake in Parkinson's disease: an EEG study

Elisa Carlino[1], Alessandro Piedimonte[1], Giulia Guerra[1], Elisa Frisaldi[1], Alberto Romagnolo[1], Leonardo Lopiano[1]
1) University of Turin, Turin, Italy

Background: Placebos have been found to affect the patient's brain in different conditions, such as pain and Parkinson's disease (PD). The aim of the present study is to investigate the role of expectations in PD patients. EEG has been used to measure the Readiness Potential (RP), an event-related potential involved in motor preparation and influenced by fatigue.
In particular, we aimed at analyzing: (1) whether L-Dopa intake induces a clinical improvement, an increase of motor performance, a subjective reduction of fatigue and a decrease of RP amplitude (2) whether these changes are influenced by the expectation of drug intake and occur also with a surreptitious reduction of L-Dopa intake.
Methods: Patients were asked to lift a load and to repeat the movement until exhaustion. This task was repeated in an OFF condition (without L-Dopa) and in an ON condition (with L-Dopa). Patients were randomly assigned to two different groups: 100% group or 50% group, based on the percentage of L-Dopa received. Both groups were informed they would receive their standard daily dose of L-Dopa, in order to induce the expectation of clinical and motor improvement.
Results: We found that the 100% group improved in both clinical and motor parameters (decrease in fatigue, increase of motor repetitions and reduction of RP amplitude). The same results were obtained in the 50% group.
Conclusions: These data confirm the pivotal role of expectations in PD. This study has important clinical implications, such as the possibility to reduce L-dopa intake, maintaining a good clinical condition.

2. Conditioning of amitriptyline-induced rem-sleep suppression

Alexander Winkler[1], Julia Rheker[1], Bettina K. Doering[1], Winfried Rief[1]
1) Philipps-Universität Marburg, Marburg, Germany

Introduction: Clinical trials in sleep disorders report substantial improvement in symptoms in their placebo groups. Conditioning processes contribute to the placebo response in addition to patients' expectations and doctor-patient communication. However, we do not know whether and if so, the extent to which sleep architecture is influenced by behavioral conditioning, similarly to other physiological responses, i.e., those in the immune system.
Methods: We applied a conditioning paradigm to 39 healthy adults pairing a novel-tasting drink (CS) with the REM-sleep suppressing tricyclic antidepressant amitriptyline (US) during the acquisition phase. Participants in the control group received placebo pills instead. We hypothesized that, after having undergone the acquisition phase and a three to four day washout phase with no pill intake, re-exposure to the CS together with a placebo pill in the evocation night would lead to less REM-sleep in the amitriptyline group. Sleep was measured via ambulatory polysomnographic recordings. To test for differences in the proportion of REM-sleep between groups, we conducted an analysis of variance (ANOVA) for repeated measures.
Results: Instead of the expected REM-sleep suppression, sole presentation of the CS (together with a placebo pill) in an evocation night led to significantly more REM-sleep in the amitriptyline group ($p = .033$).
Conclusions: In our first proof of principle study, we were unable to demonstrate that REM-sleep suppression triggered by amitriptyline is simply accessible to conditioning. More complex influences like conditioning of the drug-antagonistic response or rebound could be involved.

3. The effects of intranasal oxytocin on cardiovascular and psychological stress response: a double blind placebo-controlled RCT

Zelda Di Blasi[1], Mike Murphy[1], Sinead Forde[1], Janelle Logan Lane[1]
1) School of Applied Psychology, University College Cork, Cork, Ireland

Overview: The stress-attenuating effects of oxytocin are well documented and there is some evidence that intranasal oxytocin can attenuate cortisol response in laboratory tasks, especially in clinical populations. Recently, a number of commercial intranasal Oxytocin products have appeared on the market (e.g. Oxytrust, Oxyluv), but there is little empirical research on the efficacy of these products.
Method: We conducted a double-blind randomized control trial with 37 healthy volunteer college students who received either 20 IUs of Oxytocin spray (n=19, 11 females) or placebo spray (n=18, 9 females). Stress was induced via the Trier Social Stress Test (TSST). Cardiovascular reactivity and recovery were monitored using Blood Pressure and Heart Rate. Anxiety and affectivity were assessed using the Positive and Negative Affect Scale (PANAS) and the State Trait Anxiety Inventory (STAI) pre- and post-stress exposure.
Results: There was no significant difference between Oxytocin and placebo spray and cardiovascular reactivity and recovery. Females who received Oxytocin had a decrease in negative affect, while males had a significant increase in negative affect.
Conclusions: Intranasal oxytocin failed to reduce reactivity during a stress task, compared to placebo among our group of healthy participants. We found sex differences in the emotional response to stress tests as identified previously in the literature.

Parallel Session 3.2: Neurobiological & pharmacological placebo effects

4. Conditioning immune and endocrine parameters in humans: A systematic review

Judith Tekampe[1,2], Henriët van Middendorp[1,2], Stefanie H. Meeuwis[1], Jelle W.R. van Leusden[1], Gustavo Pacheco-López[3], Ad R.M.M. Hermus[4], Andrea W.M. Evers[1,2]
1) Health, Medical and Neuropsychology Unit, Leiden University, Leiden, Netherlands
2) Department of Medical Psychology, Radboud university medical center, Nijmegen, Netherlands
3) Health Sciences Department, Campus Lerma, Metropolitan University (UAM), Lerma, Mexico
4) Division of Endocrinology, Department of Internal Medicine, Radboud university medical center, Nijmegen, Netherlands

Background: Conditioned pharmacological effects may provide relevant clinical opportunities to improve treatment for patients with a variety of conditions. The aim of this systematic review was to create a systematic overview of studies in this field of research and to investigate whether specific characteristics of the study design make successful conditioning.
Methods: The protocol of this review was registered in Prospero (PROSPERO 2015:CRD42015024148). A systematic literature search was conducted in the databases PubMed, Embase, and PsychInfo. Studies were included if they were placebo-controlled trials in humans in which the effects of a pharmacological agent on immune or endocrine outcomes (e.g., cortisol, interleukin-2) were conditioned, using a specific conditioned stimulus. Risk of bias of each study was assessed using the Cochrane risk of bias tool.
Results: The final selection included sixteen studies. Overall these studies indicate that conditioning immunosuppression, conditioning allergic responses, and conditioning insulin and glycemic responses is possible. Regarding immunostimulants, anti-allergic effects, and cortisol conditioning, preliminary results are promising, but additional studies are needed.
Conclusions: This systematic review shows classical conditioning of immune and endocrine responses for various pharmaceutical substances. The studies reviewed here indicate that the number of acquisition and evocation sessions, and characteristics of the unconditioned and conditioned stimulus, are important determinants of the effectiveness of pharmacological conditioning on immune and endocrine parameters. In the future, conditioned pharmacological effects may be used clinically, as adjunct therapy in various patient populations.

Parallel Session 3.3

Generalization of placebo effects

Tuesday, April 4 04:15 PM - 05:45 PM
Jan Willem Schaap zaal
Chair: Martina Amanzio

Parallel Session 3.3: Generalization of placebo effects

1. **Expectations shape the emotional response of experimentally-induced sickness**

Julie Lasselin[1], Predrag Petrovic[2], Mats Olsson[2], Sofie Paues-Göranson[3], Mats Lekander[2], John Axelsson[2], Karin Jensen[2]
1) Institute of Medical Psychology and Behavioral Immunobiology / University Hospital Essen, Essen, Germany
2) Department of Clinical Neuroscience / Karolinska Institutet, Stockholm, Sweden

Introduction: Experimentally-induced sickness (EIS) is a well-established model to assess the neuropsychiatric effects of inflammation. Although high inter-subject variability exists in EIS response, predictors are scarcely studied. The aim of this study was to assess the effect of expectations on EIS outcomes, using a Bayesian predictive coding perspective.
Methods: In a placebo-controlled crossover design, 22 healthy volunteers were injected with lipopolysaccharide (LPS), which activates the immune system. Expectancy of treatment effect was assessed using a numerical scale based on previous experience of sickness (e.g., “I think that today I will feel much worse than usually when I am sick”). Interleukin-6 (IL-6) plasma concentration was used as an index of the input (immune) signal magnitude. Treatment effect was assessed by measuring sickness symptoms. State anxiety and positive affect/arousal were measured to evaluate emotional responses.
Results: LPS resulted in increased IL-6 concentrations, sickness symptoms and state anxiety, while positive affect and arousal decreased. After LPS, the immune signal (IL-6 concentrations) predicted stronger sickness symptoms, higher state anxiety and more negative arousal. Negative expectations of LPS were associated with less adverse emotional outcomes. The “error signal”, defined as the discrepancy between the immune signal and expectation of the treatment effect, was a significant predictor of negative emotional outcomes after LPS.
Conclusions: These findings indicate that when low expectations of becoming sick are met with a strong immune activation, it results in a strong error signal and more negative emotional response. We propose than knowledge of expectations are important to understanding inflammation-induced neuropsychiatric symptoms.

2. **Is the intention to use sport supplements a predictor of placebo and nocebo responding among athletes?**

Philip Hurst[1], Chris Beedie[1], Damian Coleman[1], Abby Foad[1]
1) Canterbury Christ Church University, Canterbury, Kent, United Kingdom

Background: Placebo and nocebo effects have been observed in relation to many interventions in sport. Given variance in response, a key question is whether individual difference variables identify likely ‘responders.’ Hypothetically, such a variable might be the person’s intention to use the intervention. We aimed to explore relationships between athletes' intention to use sport supplements and their responses to a placebo/nocebo intervention. Methods: Participants completed a single-item measure of intention to use sport supplements (‘intending’, ‘undecided’ or ‘not intending’) prior to 5×20-m sprints. Participants were then randomised to Placebo (n=219), Nocebo (n=168) and Control (n = 134) conditions. Participants in Placebo and Nocebo conditions were administered a capsule deceptively presented as a sport supplement that would have a positive (Placebo) or negative (Nocebo) effect on performance. Controls were provided with no instructions and received no capsule. After 20 minutes, all participants completed another set of 5×20-m sprints. Results: Among ‘intending to use’ participants, the Placebo treatment was associated with faster times than the Nocebo treatment (P=0.023, Cohen’s d [d]=0.34). In the Placebo treatment, ‘intending to use’ participants were significantly faster than ‘not intending to use’ participants (P=0.004, d=0.49), as were ‘intending to use’ participants in relation to ‘undecided’ participants in the Nocebo treatment (P=0.044, d=0.44). No significant differences in performance by intention were observed in the Control condition. Conclusions: Placebo and nocebo responses appear to be mediated by the participant’s intention to use supplements. These findings have value in explaining placebo/nocebo responses, and should be tested in clinical medical settings.

3. **How motor-induced analgesia shapes placebo and nocebo effects in a heat model of human pain**

Nicole Corsi[1,2], Luana Colloca[1]
1) University of Maryland Baltimore, Baltimore, Maryland, United States
2) University of Verona, Verona, Italy

We distance our body from the painful stimulations to protect ourselves. These protective movements initiating defensive behaviors are precise and coordinated, and it is well-known that there is a profound influence of the motor cortex on pain processing. Pioneering studies suggest that the motor system per se produces analgesia via direct connections to descending modulatory pain pathways [1]. We aimed to investigate the interaction between pain modulation and the motor system in a behavioral laboratory setting in which carefully and individually calibrated noxious painful and motor tasks were given alone or in combination. We used a well-established stimulus-cue conditioning paradigm [2-3] to create expectancy of pain reduction and increase, respectively.
We recruited 46 healthy participants at University of Maryland Baltimore to perform extension-flexion movements while individually calibrated moderately painful stimulations were given to the volar forearm. We controlled for attention and fatigue, and pain reports were measured trial by trial. Interestingly, our findings demonstrated that identical painful stimulations were perceived significantly as less painful when movements were performed along with the delivery of control painful stimulations. Moreover, expectancy reinforced via conditioning produced robust

placebo and nocebo responses. Interestingly, the same cues resulted in larger placebo analgesic responses and smaller nocebo hyperalgesic effect when participants were performing a movement. This is the first study showing that motor tasks can be shaped to increase analgesia and minimize algesia shedding light on the interplay between pain and motor execution and indicating potential new applications for pain management in real-world settings.

4. **Differential effects of placebo oxygen on fatigue and pain in hypoxic conditions at high altitude**

Diletta Barbiani[1], Fabrizio Benedetti[1]
1) University of Turin Medical School, Department of Neuroscience, Turin, Italy

Background: Placebo responses have been studied in the clinical setting and across a variety of systems. What has emerged from these studies is that there is not a single placebo effect, but many, with different mechanisms across different conditions. The aim of the present study is to assess the placebo response at an altitude of 3500 m, where blood oxygen saturation (SO2) drops from the normal value of about 99% to about 85%, due to a drop of atmospheric oxygen pressure.
Methods: In a trial in which a double-blind administration of either 100% O2 or sham O2 was administered, we tested physical performance, fatigue, and post-exercise headache.
Results: Whereas real O2 breathing increased SO2 along with a decrease in fatigue and post-exercise headache and an increase in physical performance, sham (placebo) O2 only decreased fatigue and increased physical performance, with no changes in SO2 and post-exercise headache. However, in another group of subjects, when placebo O2 was delivered after two prior exposures to O2 (O2 pre-conditioning), it decreased both fatigue and post-exercise headache and increased physical performance, yet without any increase in SO2.
Conclusions: Two main findings emerge from these data. First, fatigue, physical performance and headache do not depend completely on SO2, psychological and learning factors playing a crucial role. Second, fatigue and physical performance are more susceptible to a placebo treatment than headache pain. Thus, not all sensory experiences are equally sensitive to placebos, some of them being affected by verbal suggestions alone whereas some others requiring learning.

5. **Specific expectations of therapeutic benefit produces generalized placebo improvement of pain and pleasure**

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Expectation of therapeutic benefit is often considered a cornerstone of placebo effects. However, as most studies have investigated expectations and placebo outcomes within the same modality (e.g. expectation of analgesia and pain reduction), it is not known whether expectations need to be outcome-specific to produce placebo effects, or whether positive expectations can generalize to produce placebo effects in other modalities (e.g. positive affect). To investigate this, we employed a crossover design, in which 47 healthy volunteers self-administered a saline nasal spray suggested to either (1) reduce pain (ANA) or (2) enhance touch pleasantness (HYP). To strengthen participants' expectations of treatment benefit, they were, immediately before treatment, shown a video documentary that summarized scientific findings supporting either treatment-induced improvement of pain (ANA) or touch pleasantness (HYP). Next, they rated (un)pleasantness and sensory intensity (Visual analogue scale) of moderate heat pain and gentle stroking touch. After placebo treatment, relative to a control condition without treatment, both groups reported statistically significantly reduced pain unpleasantness and increased touch pleasantness. This was mirrored by reduced pain intensity and increased touch intensity, in both groups. Furthermore, a mediation analysis showed that the relationship between expectations and placebo analgesia (but not hyperhedonia) was mediated by a placebo-induced positive shift in generalized affective state. The results indicate that placebo effects can be produced by non-specific expectations of therapeutic improvement. This is consistent with a view of placebo responses as a generalized mechanism of reward prediction, by which a placebo-induced 'affective state' shapes both positive and negative hedonic feelings.

6. **Genetics, shared, or non-shared environment? An experimental twin study on placebo analgesia**

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To investigate the impact of genetics, social learning as well as individual learning on placebo analgesia, an experimental pilot study with mono- and dizygotic twins was performed for the first time.
This study employed 48 healthy participants comprising 16 monozygotic (MZ) and 8 dizygotic (DZ) twin pairs (29±8 years). To induce an individual learning experience, participants were conditioned on the efficacy of an inert ointment by manipulation of heat pain temperatures on one forearm. Afterwards, the conditioned analgesic effect

was tested on the other forearm, and compared to a control ointment. Pain ratings and expectations about the efficacy of the ointments were rated on a visual analog scale, and psychological questionnaires were assessed. Twins reported significant placebo analgesia through lower pain ratings when the “potent” compared to the control ointment was applied (MZ: p=.003; DZ: p=.021). Pain ratings during conditioning and test were significantly related in MZ twins (r=.556, p=.001), but not in DZ twins. However, the extent of placebo analgesia was neither significantly related within MZ nor within DZ twin pairs. Assessed expectations and psychological variables partially influenced pain ratings, but not placebo analgesia.
Due to the missing relationship in placebo analgesia between MZ and DZ twins, neither genetics nor shared environmental influences seem to affect placebo responses. The partial relations found between conditioning and placebo response as well as between psychological variables and pain ratings point to an impact of individual learning experiences.

Parallel Session 3.4

Placebos in RCTs

Tuesday, April 4 04:15 PM - 05:45 PM
Cornelis Schuytzaal
Chair: Michel Ferrari

Parallel Session 3.4: Placebos in RCTs

1. The placebo effect of psychological interventions in the treatment of irritable bowel syndrome

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Background: In psychological treatment methods, the treatment effect is possibly the result of increased attention for and time investment in the patient rather than the effect of therapy itself. In randomized controlled trials, a placebo group should be used to control for this effect. The aim of this study was to determine the placebo response rate (PRR) for placebo interventions used in psychological intervention studies for irritable bowel syndrome.
Methods: Randomized controlled trials on psychological interventions for the treatment of irritable bowel syndrome, using an adequate placebo control treatment and published between 1966 and 2016, were selected. Placebo interventions with the same number of sessions and time spent with the therapist as in the active treatment were considered adequate. The PRR was computed for IBS symptom severity.
Findings: Six studies with a total of 555 patients, met the inclusion criteria. The pooled mean of the PRR for IBS symptom severity was 41.4%. Contrary to our expectations, this was comparable to the PRR in pharmacological treatments, treatment with dietary bran and with complementary medicine.
Discussion: The PR seems more determined by patient- than by doctor- related factors. The combination of the patient's expectation of and desire for symptom relief, which is influenced by the way the therapy is introduced and executed, is important. Future RCT's should therefore map the expectations of patients in both RCT arm before starting the intervention. It seems interesting to investigate the effect of the preference of patients for a certain treatment arm on treatment outcome.

2. Applicability and Justification of a Placebo Control in Surgery

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Objective: In surgery a placebo-control is challenging and therefore rarely used in randomised controlled trials (RCT). This systematic review was performed to investigate the ethical justification, validity and safety of placebo controls in surgical RCT.
Methods: CENTRAL, MEDLINE and EMBASE were systematically searched to identify RCT comparing a surgical procedure to a placebo. "Surgical procedure" was defined as a medical procedure involving an incision with instruments. Placebo was defined as a blinded sham operation involving no change to the structural anatomy and without an expectable physiological response in the target body compartment.
Results: A total of 1741 articles were screened and 10 surgical RCT were included, all of them published in high-ranking medical journals (mean impact factor: 20.1). Eight of ten failed to show statistical superiority of the experimental intervention. Serious adverse events did not differ between the groups (RR 1.38, 95% CI: 0.92-2.06, p=0.46). The ethical justification for the use of a placebo control remained unclear in two trials.
Conclusion: Placebo-controlled surgical RCT are feasible and provide high-quality data on efficacy of surgical treatments. The surgical placebo entails a considerable risk for study participants which is a critical difference to placebo-controls in drug development. Consequently, a placebo should be used only if justified by the clinical question and by methodological necessity. Based on the current evidence the Study Center of the German Surgical Society (SDGC) made a pragmatic proposal for the use of placebo controls in future surgical trials.

3. Sham surgery for SLAP-lesions of the shoulder: a randomized clinical trial

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Background: Labral repair and biceps tenodesis are routinely performed worldwide for superior labrum anterior posterior (SLAP) lesion of the shoulder, but evidence of their efficacy is lacking. This study evaluates the effect of labral repair, biceps tenodesis and sham surgery on SLAP lesions.
Methods: A double-blind, sham-controlled trial was conducted with 118 surgical candidates (mean age 40 years), with patient history, clinical symptoms and MRI arthrography indicating an isolated type II SLAP lesion. Patients were randomly assigned to labral repair, biceps tenodesis, or sham surgery if arthroscopy revealed an isolated SLAP II lesion. Primary outcomes at 6 and 24 months were clinical Rowe score ranging from 0 to100 (best possible) and Western Ontario Shoulder Instability Index (WOSI) ranging from 0 (best possible) to 2100. Secondary outcomes were Oxford Instability Shoulder Score, change in main symptoms, EuroQol (EQ-5D and EQ-VAS), patient satisfaction, and complications.
Results: There were no significant between-group differences at any follow-up in any outcome. Between-group differences in Rowe scores at two years were: biceps tenodesis versus labral repair: 1.0 (95% CI -5.4 to 7.4), p=0.76; biceps tenodesis versus sham surgery: 1.6 (95% CI -5.0 to 8.1), p=0.64; and labral repair versus sham surgery: 0.6 (95% CI -5.9 to 7.0), p=0.86. Similar results were found for WOSI scores. Postoperative stiffness occurred in five patients after labral repair and in four patients after tenodesis.
Conclusion: Labral repair and biceps tenodesis did not have significant clinical benefit over sham surgery for patients with SLAP II lesions in the population studied.

4. Aspects of interferences on the course of placebo in clinical trials with chronic pain conditions

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Psychosocial components like patient's perceptions and expectations as well as the natural history/course of the disease and methodological factors contribute to the placebo phenomenon. Research on these parameters with regard to placebo analgesia is prevalently done by investigating healthy volunteers. In order to better understand the behaviour in patients placebo data from RCT is needed. Herewith a detailed view on clinical trials is helpful to optimise study designs and to further explicitly investigate the placebo effect in patients with chronic pain conditions.
The course of disease is recognised as one of the main aspects that can influence outcome in pain reduction. However, continuous placebo data over time is sparse. Even supposed small differences of diseases may run distinctly different symptomatic courses of self-healing effect which have to be considered when the contribution to total placebo is investigated. In this context a three months course of placebo in knee and hip osteoarthritis patients has been evaluated resulting in a time dependent decrease in pain intensity only in knee OA patients [1]. Consequently it might be important to best determine the natural performance of symptoms in the particular disease before starting the investigation in this patient group.
In order to analyse RCT placebo groups the applied method (e.g. per protocol versus intention to treat analyses) is also of interest as it may generate constructive outcome or include data which don't lead ultimately to a meaningful results. In terms of adverse events documented under placebo treatment a critical review in detail helps to avoid misleading global conclusions.

5. The paradox of sham therapy and placebo effect in osteopathy: A systematic review

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Placebo, defined as "false treatment," is a common gold-standard method to assess the validity of a therapy both in pharmacological trials and manual medicine research where placebo is also referred to as "sham therapy." The aim of the present systematic review was to report how and what type of sham methods, dosage, operator characteristics, and patient types were used in osteopathic clinical trials and, eventually, assess sham clinical effectiveness.
A systematic Cochrane-based review was conducted by analyzing the osteopathic trials that used both manual and nonmanual placebo control. Pragmatic searches were conducted on 8 databases up to December 2015. Two independent reviewers conducted the study selection and data extraction for each study. The risk of bias was evaluated according to the Cochrane methods.
A total of 64 studies were eligible for analysis collecting a total of 5024 participants. More than half (43 studies) used a manual placebo; 9 studies used a nonmanual placebo; and 12 studies used both manual and nonmanual placebo. Data showed lack of reporting sham therapy information across studies. Risk of bias analysis demonstrated a high risk of bias. High heterogeneity regarding placebo used between studies, lack of reporting information on placebo methods and within-study variability between sham and real treatment procedures suggest prudence in reading and interpreting study findings in manual osteopathic randomized controlled trials (RCTs). Efforts must be made to promote guidelines to design the most reliable placebo for manual RCTs as a means of increasing the internal validity and improve external validity of findings.

6. Are surgery and invasive procedures effective beyond a placebo response in chronic pain?

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8) Ludwig-Maximilians-University Munich, Institute of Medical Psychology, Munich, Germany

Background: Surgery and invasive procedures are thought to produce large placebo effects. A systematic review/meta-analysis was conducted to estimate the effect of sham surgical and invasive procedures compared to active surgery for chronic pain.
Methods: Randomized, sham controlled studies were selected through January, 2016. Risk of bias was assessed. Data were pooled using random-effects meta-analysis. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was applied to determine the confidence in effect estimates.
Results: 25 studies were included; 15 provided data for inclusion in the main analysis (1600 patients). The overall standardized mean difference (SMD) for a reduction in pain closest to six months between treatment and sham surgery groups was.0.12 (95% CI,.-0.03 to 0.27; p=0.12; I2=51. The quality of the evidence was moderate. The pooled SMD for changes from baseline was 0.61 in sham (95% CI 0.30 to 0.92, p<0.0001, n=15, I2=79%) and 0.71 (95% CI 0.43 to 0.98, p<0.0001, n=159, I2=86%) in the verum groups. On average, changes in the sham groups accounted for 87% of the overall improvement. The contribution of placebo effects was largest in endometriosis (94%) followed by angina pectoris (75%), low back pain (73%), abdominal pain (71%) and migraine (57%). In arthritis, sham surgery is superior to active surgery.
Conclusions: The current evidence does not support the efficacy of surgery or invasive procedures for chronic pain as placebo effects of these procedures are large. Given the high cost and safety risks of invasive procedures more rigorous evidence is required before these treatments are used.

Monday April 3
Poster presentation abstracts

1.01 Conditioned nocebo allodynia: A prelude to chronic pain?

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Background: Classical conditioning is a hypothesized mechanism by which nocebo hyperalgesia is elucidated in humans and one of the pain modulation procedures. Research on conditioned nocebo allodynia is sparse although the majority of clinicians believe that it might account for pain persistence. The aim of the study was to investigate whether a neutral visual cue (conditioned stimulus) can transform a tactile non-nociceptive sensation into a pain experience (conditioned response) using a differential conditioning paradigm.
Material and Methods: Healthy participants were randomly assigned to either experimental or control group. In the experimental group, participants were exposed to the conditioning and subsequently to the testing phase. The conditioning phase consisted of three blocks of electrical painful and non-painful stimuli. Painful stimuli were paired with a visual cue (white circle on black background) displayed on the computer screen while non-painful tactile stimuli were presented without any cues. In the testing phase, non-painful electrical stimuli were applied in both conditions, i.e. with and without a visual cue. In the control group only non-painful stimuli were applied during both phases of the study to control for sensitization and habituation effects.
Results: In the testing phase, non-painful stimuli preceded by visual cues were rated as painful in the majority of participants in the experimental group indicating that nocebo allodynia can be induced by classical conditioning.
Conclusions: Classical conditioning might be a mechanism of nocebo allodynia. However, further research is needed to answer the question in whom and under which circumstances classical conditioning can induce nocebo allodynia.

1.02 More than placebo: A general strategy for pain perception

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Background: Why does placebo exist? We propose a general strategy of pain perception which can provide a unified explanation of placebo and other forms of pain modulation. In the framework of Bayesian decision theory we developed a theoretical model which, through past experience, integrates nociceptive signals with cues relevant for effective perception. Our model suggests that the analgesic placebo effect emerges from the logic followed to bring forth pain perception. It can also explain other pain related phenomena and make predictions which can drive experimental and clinical research. Here we present model driven findings of how expectation and experience participate in pain perception.
Methods: During a conditioning stage, 52 subjects experienced electrically induced pain of low (i.e. analgesia) and high intensity in different proportions (30-70 or 70-30). In a subsequent stage we induced milder analgesia, while the subjects expected the same pain and analgesia occurrence as in conditioning.
Results: Our model predicted that in the test stage the subjects would report not intermediate but high and low pain levels and, if experience shapes only expectation (prior probability, in Bayesian terms), with a proportion mirroring that experienced during conditioning. The results showed an inverse relationship with the frequency previously experienced.
Conclusions: This suggests that the more samples of a condition are experienced, the more the system is able to evaluate if subsequent events are similar or not, meaning that past experience not only affects expectation but also refines the accuracy in weighting incoming nociceptive information (in Bayesian terms, the likelihood).

1.03 Investigating the possible placebo effect of consuming pre-workout and the effect on powerlifting performance

Jessica Anderson[1]
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Background: Sport drinks and pre-work-out beverages are becoming increasingly popular among gym users. This study aims to examine the relationship between the use of a popular pre-workout drink compared with placebo on levels of performance in weightlifting.
Method: In this placebo-controlled double-blind randomized controlled experiment, weight-lifters will be randomly assigned to a common pre-workout drink or to a credible placebo control condition. The study will take place in one of two gyms, in the South of Ireland, with experienced weight-lifters.
Results: Each participant will perform two powerlifting compound movements -the squat and bench-press - at baseline and following either the pre-workout or the placebo solution. Beliefs about the pre-workout drink and placebo will be assessed pre and post-intervention. Debriefing will be conducted at a one week follow up, assessing the effects of placebo unmasking at trial closure.
Conclusion: This trial study has been approved by the Social Research Ethics Committee, in accordance with the Psychological Society of Ireland's code of ethics and will be completed in March 2017.

1.04 Effects of maxillary expansion and placebo effect of appliances on nocturnal enuresis - Preliminary results

Fatemeh Bahramnia[1]
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The purpose of this study was to evaluate the therapeutic and placebo effects of slow maxillary expansion on nocturnal enuresis. Four children with enuresis aged between 7-12 years were selected. Rigid acrylic expansion appliances were fabricated and delivered to them. The frequencies of enuresis were recorded by parents during three stages: 1) before appliance delivery; 2)

after appliance insertion without expansion; and 3) during expansion and retention. The frequency of wetting decreased significantly during the period of appliance use without expansion. During expansion and retention phase, two patients become completely dry, and two patients improved significantly.
Therefore, maxillary expansion can have positive effect on treatment of nocturnal enuresis. Also, the placebo effect of expansion appliance has significant effects on enuresis.

1.05 Does relaxation affect placebo and nocebo effects in a visceral pain model?

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2) University Hospital Tuebingen, Tuebingen, Germany

Background: This study aimed to test if visceral placebo analgesia and nocebo hyperalgesia are modulated by relaxation.
Methods: N=120 healthy volunteers (60 women, 60 men) first underwent a four-week training in a relaxation technique (i.e., progressive muscle relaxation; PMR). On the study day, visceral pain was induced by rectal distensions, and pain intensity and unpleasantness were measured using VAS during a baseline and a test phase. After baseline, participants were randomized to a relaxation (N=60) or a control condition (N=60), and instructed to practice PMR for 15 minutes or to complete an easy cognitive task, respectively. A second randomization was accomplished to groups receiving positive (placebo), negative (nocebo) or neutral (control) verbal instructions regarding an intravenous treatment with a substance that in reality was only saline. Next, during test phase, distensions were repeated, and changes in VAS were compared between groups using ANOVAs.
Results: Pain intensity and unpleasantness ratings were significantly influenced by the placebo and nocebo instructions across groups (condition effect: $p<.05$). Relaxation per se had no effect on pain ratings. Interestingly, an interaction between instruction and condition was observed for unpleasantness ($p<.05$), but not for pain intensity. Post-hoc testing revealed that relaxation increased the magnitude of placebo ($p<.001$), but not nocebo effects on pain unpleasantness.
Conclusion: Placebo effects on pain unpleasantness ratings were increased by relaxation in a visceral pain model. This finding suggests that relaxation may specifically increase placebo effects on affective-emotional, but not sensory-discriminative aspects of viscerosensation.

1.06 Baseline pain measurements as predictors of the placebo response in neuropathic patients

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In analgesia randomized clinical trials (RCTs), the magnitude of the placebo response has a negative influence when testing the statistically significant superiority of active compounds compared to placebo. In chronic pain, meta-analyses have already highlighted the baseline pain amongst the many parameters correlated with the placebo response.
One of the objectives of this study was to investigate the relationship between the placebo response and the baseline pain intensity collected by the average pain intensity (API), the brief pain inventory (BPI), etc. Eighty-eight patients with peripheral neuropathic pain were enrolled and blindly given a placebo in addition to their regular analgesic treatment during 4 weeks. The multiple endpoints (placebo responses) were estimated as the pain differences between baseline and the end of the treatment, computed with the API, BPI, etc.
As expected, the baseline pain measures were significantly correlated between each other and with their respective placebo response (API-baseline correlated with API improvement, etc). To go further in the prediction, we combined the baselines in a global pain intensity scale which turned not to be correlated with any placebo responses. However, this scale can be used to estimate if a patient has over-evaluated his baseline pain which then correlated with the multiple endpoints. Indeed, a patient with an over-estimated baseline pain has more chances to show a pain improvement.
Those results challenge the classical view of the baseline pain in the placebo response. An alternative use of the multiple baseline measurements could then help to predict the placebo response, a major confounding factor, in RTCs.

1.07 Cortical processes underlying the ergogenic placebo response in endurance athletes

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Background: The purpose of this study is to investigate the change in the motivational valence system, measured as frontal alpha asymmetry, of athletes in response to a highly salient placebo ergogenic aid during an isokinetic all out cycling time trial using electroencephalography (EEG).
Methods: Nineteen male competitive cyclists participated in two time trials spaced one week apart, consisting of five 9 min blocks at a fixed cadence of 95rpm and maximal possible power output. On the second visit, 11 athletes randomly received a placebo, which they were told could increase endurance performance, while the rest received no treatment (control). During cycling EEG was recorded from 32 active electrodes and frontal alpha asymmetry (FAA) was calculated by subtracting the natural log transformed alpha power in the left frontal region (F3, F7, Fp1) from the right frontal region (F4, F8, Fp2).
Results: We found a significant interaction of time and group for FAA. This indicates that athletes, who received a placebo ergogenic aid immediately prior to the time trial show significantly larger FAA than those athletes who received only water compared to baseline ($p<.05$) and this was not influenced by the time spent cycling.
Conclusions: This is the first study investigating the cortical mechanism underlying performance enhancement through placebo

administration in a maximal effort cycling time trial. According to our results, the administration of a placebo ergogenic aid leads to changes in cortical processing during maximum effort cycling, specifically increased FAA, indicating an approach motivated positive affective response.

1.08 Examining the assumption of additivity between placebo and active treatment effects - A meta-analysis of the balanced placebo design

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Introduction: In placebo-controlled trials, the difference between the treatment and placebo arms is often taken as the isolated treatment effect. This, however, assumes that the effects of active and placebo treatments are quantitatively additive. This meta-analysis examines this assumption using data from the balanced placebo design, a 2x2 factorial design which manipulates the receipt of an active treatment or placebo against the expectation of receiving an active treatment or placebo. In this design, the presence of an interaction between factors may be taken as evidence against additivity. To date, findings appear mixed, with this study representing a systematic attempt to integrate data across studies.
Methods: Four online databases were searched for the term 'balanced placebo design', finding a total of 218 potentially eligible studies. After further screening, data was extracted from a total of 11 studies and Hedges' g for the interaction effect calculated. Moderator effects of a number of characteristics were explored with meta-regression.
Results: Aggregated data indicated a small overall interaction effect, with meta-regression on moderator effects finding that the interaction between treatment and expectancy was greater in some modalities and with certain types of outcome measure.
Conclusions: The findings from the meta-analysis suggest that the assumption of additivity is invalidated in certain circumstances, with treatment and placebo effects often being quantitatively subadditive. This indicates that a portion of one, or both, is lost when measured together, potentially due to ceiling effects or mechanistic competition. This finding has particular implications for the interpretation of results from clinical trials.

1.09 The influence of the practitioner-patient relationship on pain perception: A placebo-controlled RCT

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Background: Pain is associated with high health care costs, work absenteeism and poor mental health. There is extant research on the influence of pain management interventions, however much less is known about the effects of different forms of health care interactions on pain perception. The aim of this study was to examine the effects of health care interactions on pain perception.
Methods: The effect of two styles of health care interaction was evaluated in a randomised, single-blind, placebo-controlled study of 100 pain free young adults (50 were male) in a single laboratory session. Fifty participants were randomised to receive an 'enhanced' interaction (e.g. friendly, reassuring) and 50 to receive a 'limited' interaction (e.g. formal, slightly rushed) on pain intensity, threshold and tolerance. Participants were told that the aim of this study was to examine the effects of intranasal oxytocin on pain perception, and that they would receive either oxytocin or placebo spray. All participants were randomised to placebo spray. Measures included the Consultation and Relational Empathy Scale (CARE), the Treatment Expectancy Questionnaire (TEQ), and pain tolerance, intensity and threshold were measured using the Cold Pressor Test (CPT).
Results: Participants who were randomised to the enhanced consultation had significantly lower pain threshold than those randomised to the limited consultation (p=.29). Those participants also had significantly higher CARE scores.
Conclusions: In a laboratory setting, when participants perceive the research clinician as empathetic, their pain perceptions change.

1.10 Best Possible Self: A Randomised Placebo-Controlled Trial

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Aim: Imagining and writing about a best possible self (BPS) has been shown to increase wellbeing, positive emotions and optimism, while alleviating depressive symptoms. The current study advances this research by testing context effects in the delivery of BPS on levels of stress and mood in a sample of Irish college students.
Method: 100 college students were randomised to the BPS interventions (n = 50), or to a placebo control condition, consisting of writing about their Typical Day (n= 50). In addition, each group was randomised to receive an enhanced (e.g. warm, caring) researcher-client interaction or a limited (e.g. formal, cold) interaction.
Stress was measured using the Perceived Stress Scale, Systolic and diastolic blood pressure were measured using a digital blood pressure monitor, and mood was assessed using the Positive and Negative Affect Scale (PANAS). Evaluation of the interaction was assessed using the Consultation and Emotional Empathy scale (CARE).
Results: Participants in both the intervention and the control group had significant increases in positive mood and decreases in perceived stress, systolic blood pressure and negative mood. However, there was no significant difference between the BPS and the control group. In addition, these effects were not maintained at the two week follow-up. The way in which these interventions are delivered can influence their effectiveness.**Conclusion:** Further research should include a no-treatment control group and include qualitative analysis to further understand the experience of these activities.

1.11 The nocebo effect in motor performance: A link between treatment perception and personality traits

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The aim of our study was to investigate whether individual differences in the magnitude of the nocebo effect in motor performance could be accounted for by the subject's perception of treatment effectiveness and by specific personality traits. Forty-one healthy volunteers executed a motor task in which a visual feedback signalled the amount of force. After a first training session, all the participants underwent the same nocebo procedure, in which a TENS device (actually inert) was applied to the hand together with verbal instructions about its negative effects on force. In the conditioning session, a surreptitious reduction of the visual feedback was applied. In the final test session, TENS was applied again and subjects performed the motor task without feedback reduction. Subjects' perception of TENS efficacy was measured after the conditioning and test sessions. In addition, personality traits were assessed with different questionnaires.
From the results, it turned out that 56.1% of participants perceived TENS as more effective in the test than in the conditioning session, whereas 43.9% of participants had the opposite pattern. Interestingly, the two groups had different perception and performance at the task, and different personality traits: The former perceived more sense of effort, showed a more pronounced reduction of force and presented with lower levels of optimism and higher anxiety traits than the latter group.
These findings highlight for the first time a link between changes in perception of treatment effectiveness, personality traits and the magnitude of the nocebo response in motor performance.

1.12 Placebo Responses and Health Disparities: An Unjust and Underexplored Connection

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This paper argues that by failing to acknowledge the substantial impact placebo and nocebo effects have on clinical outcomes, the medical community may inadvertently be contributing to an increase in health disparities. Placebo and nocebo responses can be initiated through many aspects of a healing encounter, including a clinician's empathy, trustworthiness, amount of attention, and confidence. Placebo responses are also variable in individuals depending on their beliefs and expectations related to the treatment and clinical encounter, and their unique histories of associations related to care. This paper connects this phenomenon to a large body of literature that suggests that minorities, poor English speakers, and people of low socioeconomic status elicit less empathy in physicians, receive less clinical tests, and have less trust in physicians than others. This suggests that nocebo effects are more likely to occur and placebo effects are less likely to occur in those who already have the worst health outcomes overall, and that neglecting this powerful phenomenon may be an injustice in itself. While the data relied upon is primarily drawn from the United States, there are reasons to think this argument could be extended to other parts of the world as well. The paper concludes with a brief discussion of how attending to the role of placebo and nocebo responses within the clinical encounter could work towards reducing inequality in health outcomes.

1.13 Increased Anxiety Interferes with Nocebo Hyperalgesia

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Background: Nocebo Hyperalgesia has been suggested to be mediated by anxiety. We tested the hypothesis that enhanced anxiety increases nocebo hyperalgesia in a series of behavioral experiments.
Methods: We tested 1) whether our manipulation successfully induced anxiety, 2) whether we could induce nocebo hyperalgesia, and 3) whether anxiety increases nocebo hyperalgesia. Anxiety was manipulated by the application of unpredictable electric shocks in one context and compared to a safe context without any shocks. A nocebo cream was combined with conditioning and expectation manipulations to increase the painfulness of heat stimuli. We recorded pain and fear ratings and in one experiment skin conductance and startle responses.
Results: In the first study (N=19), participants reported more fear of the anxiety context, showed enhanced skin conductance responses to the anxiety context onset, and had stronger startle responses during the anxiety context. When the nocebo treatment was applied without context manipulation, participants (N=17) rated the heat as more painful in the nocebo compared to the control condition. Combining the two manipulations into a 2x2 factorial design (N=32) eliminated the nocebo effect, while participants still reported more fear of the anxiety context.
Conclusions: While anxiety induction and nocebo treatment had the expected effects when manipulated in isolation, nocebo hyperalgesia was abolished by the anxiety manipulation. Although the underlying processes seem to interact, the relationship between anxiety and nocebo hyperalgesia is most likely not as linear as previously hypothesized. Other processes, including attention and stress induced analgesia, might be affecting pain processing in parallel.

1.14 Mind and Body - The placebo perspective

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The researches on the placebo effect seems to all have the same purpose: First, a better understanding of the process, thus being able to enhance its use in a clinical context. In order to help the patients to activate their healing factors, to reduce their pain, clinicians and researcher work together, looking for the ways to harvest the benefits of the placebo effect. However, for now the framework of research establish a complete split between the data's about the patient and the patient itself. In a patient centred care, shouldn't we focus all of our effort on the patient perspective? In this talk, I'd like to show how a change in our framework of understanding the brain can impact the way we do research about the placebo. Psychology and Neurology come from a long lasting tradition of exclusion of any data collected from a first person point of view. The main reasons for this epistemological choice are still accurate, nevertheless I'd like to show that new perspectives based on complementary framework have emerged in the recent years (e.g Neurophenomenology or similar qualitative approaches) and that they could be extremely valuable in our enquiry about the placebo effect. "Second person data" allows us to take in account simultaneously the data about the patient's brain and his emotions, feeling, or cultural background. It means that we can stop splitting the patients by investigate all the placebo's relevant factors together, and therefore focus on the solutions to harvest them in a clinical context.

1.15 An animal model of placebo analgesia in inflammatory pain rats

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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. We have previously evoked placebo responses in normal rodent (Guo et al. 2010, 2011). 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. 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. 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.

1.16 Phenomenological analysis of open-label placebo administration: A qualitative study

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Two randomized-controlled trials have shown that open-label administration has clinically significant effects (Kaptchuk et al., 2010; Carvalho et al., 2016). In these trials, the treatment rationale was based on and communicated to participants in four discussion points, which provided scientific findings regarding placebo effects. It may be reasoned that it is beneficial to include information that may be more relatable to subjective concepts of the average layperson and actual experiences with open-label placebo rather than scientific research.
To explore subjective experiences of placebo, a qualitative study nested in a quantitative study of open-label placebo analgesia was carried out. After having experienced a placebo phenomenon—albeit in different experimental groups—in the quantitative study part (N=160 healthy participants), 30 randomly selected participants (evenly distributed over three intervention groups) were asked to voluntarily participate in the qualitative follow-up. In qualitative semi-structured interviews, participants were asked a range of questions about their subjective conceptions and experiences—in their everyday lives as well as in the experiment—regarding placebos. The question framework was developed on the basis of Ashworth's (2003) seven lifeworld fragments, and transcribed interview data will be analyzed using a phenomenological approach.
If distinct core elements or general structures of these experiences should emerge, it might be possible to generate one or more new discussion points to be included in an open-label placebo rationale, and which could then be tested in future studies.

1.17 The use of an open-label placebo to treat cancer-related fatigue

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Background: While the open-labeled administration of placebo pills has been shown to improve patient-reported outcomes in patients with IBS, pain and depression, it is unknown whether it confers benefits for cancer-related fatigue.
Methods: To begin to evaluate the effects of open-labeled administration of placebo pills on fatigue among cancer survivors, we conducted a 21-day pilot study followed by a 21-day exploratory period. Seventy-four cancer survivors reporting at least moderate fatigue received a positive rationale about the possible effects of open-label placebos and were randomly assigned to either immediate or delayed administration of placebo pills. Participants in the "immediate" group were prescribed placebo pills during the first 21 days of the study while "delayed" participants served as controls. After a 7-day "washout" period, control group

participants were offered placebos and followed for 21 days.
Results: Preliminary results indicate that the use of open-label placebos is feasible and acceptable to participants. In addition, a preliminary, within-subjects analysis indicates that, participants taking the open-label placebo treatment experienced reduced fatigue-distressed quality of life and global fatigue symptom severity. **Conclusion:** Once completed, this pilot trial will provide preliminary information on the feasibility, acceptability and efficacy of using open-label placebos to treat cancer-related fatigue.

1.18 Generalization in placebo analgesia

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Placebo analgesia refers to a perceived pain relief due to cognitive modulation induced by mechanisms such as expectation or associative learning. The phenomenon is frequently studied using conditioning paradigms allowing to modulate both experiences and expectation. However, so far there is only little research on how experiences of pain relief are adaptively transferred to similar but novel situations in the future. This mechanism called generalization, well-studied in the fear domain, has so far not been linked to placebo analgesia as one form of appetitive learning. However, assuming generalization in this domain is highly intuitive: having experienced a substantial pain relief from one treatment in the past, one might expect similar outcomes, if the conditions of a novel treatment resemble the ones experienced before. Using a conditioning paradigm, we treated heat induced tonic pain on capsaicin pretreated skin. Pain relief was effectuated by furtively lowering temperatures after presenting face stimuli as cues. While we conditioned participants to expect better treatment for one face (CS+), another face (CS-) was paired with less pain relief. Following conditioning, participants were tested on a circular continuum of eight face cues ranging from CS+ to CS-. Pain relief ratings showed a significant placebo effect for the CS+ vs. CS-, with decaying (placebo) relief for increasing dissimilarity to the CS+. This gradient in the placebo effect was better explained by a Gaussian fit than a uniform null model. We thus conclude that generalization of learned analgesic associations occurs in novel situations that resemble previous experiences.

1.19 Effects of acute stress on the placebo response in nausea

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Background: Expectation of symptom relief is an important factor for placebo responses in nausea. In this randomized controlled study, we investigated whether acute stress can diminish the placebo response in nausea.
Methods: Eighty healthy women susceptible to motion sickness were included in the experiment. On two testing days, nausea was induced by a visual vection stimulus for 20 minutes. Participants were randomized in a two-factorial design to STRESS/NO STRESS and PLACEBO/NATURAL HISTORY. Stress was induced using the Maastricht Acute Stress Test, while the NO STRESS group completed a control version of the test. The placebo intervention consisted of a sham acupuncture-point-stimulation. Throughout the experiment, participants were asked to rate symptoms of nausea, and the electrogastrogram (EGG) was continuously assessed. Analyses of covariance (ANCOVA) were conducted to evaluate the effects of stress and placebo intervention on subjective and objective nausea outcomes.
Results: Participants developed significant nausea on the baseline day, with no difference between groups. On the testing day, participants in the placebo group experienced significantly less nausea than in the natural history group ($F=30.43$, $p<0.001$), while stress did not impact the behavioral placebo response ($F=0.30$, $p=0.59$). There was a significant interaction between `stress´ and `intervention´ for the normo-to-tachy ratio (NTT) in the EGG ($F=4.73$, $p<0.05$), which was due to a placebo response on gastric activity in the NO STRESS group ($F=4.83$, $p<0.05$) but not in the STRESS group ($F=0.92$, $p=0.34$).
Conclusions: Results suggest that acute stress inhibits placebo responses in nausea on a physiological, yet not on a behavioral level.

1.20 Bayesian prediction of placebo analgesia in an instrumental learning model

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Placebo analgesia can be primarily explained by the Pavlovian conditioning paradigm in which a passively applied cue becomes associated with less pain. In contrast, instrumental learning employs an active paradigm that is more similar to clinical settings. In the present study, an instrumental conditioning paradigm involving a modified trust game in a simulated clinical situation was used to induce placebo analgesia. Additionally, Bayesian modeling was applied to predict the placebo responses of individuals based on their choices. Twenty-four participants engaged in a medical trust game in which decisions to receive treatment from either a doctor or a pharmacy were made after receiving a reference pain stimulus. In the conditioning session, the participants received lower levels of pain following both choices, while high pain stimuli were administered in the test session even after making the decision. The choice-dependent pain in the conditioning session was modulated in terms of both intensity and uncertainty. Participants reported sigficantly less pain when they chose the doctor or the pharmacy for treatment compared to the control trials but the pain ratings between the doctor and pharmacy choices did not differ significantly. The predicted pain ratings based on Bayesian modeling showed significant correlations with the actual reports from participants for both of the choice categories. The instrumental learning paradigm allowed for the active choice of optional cues and could induce the placebo analgesia effect. A Bayesian modeling could successfully predict pain ratings in a simulated clinical situation that fit well with placebo analgesia induced by instrumental conditioning.

1.21 Effectiveness of radial Extracorporeal Shock Wave Therapy (rESWT) when combined with supervised exercises in patients with subacromial shoulder pain. A double-masked, randomized, sham-controlled trial

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Background: Subacromial shoulder pain is a common complaint and radial Extracorporeal Shock Wave Therapy (rESWT) is increasingly used to treat this condition. Although many therapists use rESWT in combination with supervised exercises, no studies have evaluated the additional effect of rESWT to supervised exercises for subacromial shoulder pain. The purpose of this study was therefore to assess whether radial Extracorporeal Shock Wave Therapy (rESWT) is more effective than sham rESWT when combined with supervised exercises for improving pain and function in patients with subacromial shoulder pain.
Methods: In this rancomized, sham-controlled tral, patients between 25 and 70 years, with subacromial shoulder pain with and without calcification in the rotator cuff, lasting at least three months were assessed for eligibility. 143 patients were recruited. Participants were allocated (1:1) by computer-generated randomization in blocks of 20 to receive either rESWT or sham rESWT in addition to supervised exercises. The rESWT/sham were performed once a week with additional supervised exercises once a week for the first four weeks. The following eight weeks, the patients received supervised exercises twice a week. The primary outcome was change in the Shoulder Pain and Disability Index (SPADI) after 24 weeks. Patients and outcome assessors were masked to group assignment.
Results: At 24 weeks, participants in both the sham group and the rESWT group had improved ($p < 0.001$) in SPADI score compared with baseline (-23.9 points (23.8) and -23.3 points (25.0), respectively), but there were no differences between the groups (mean difference 0.7, 95% CI -6.9 to 8.3, p=0.76). Pre-specified subgroup analysis of patients with calcification in rotator cuff showed that the rESWT group had a greater improvement in SPADI score after 24 weeks (mean difference -12.8, 95% CI -24.8 to -0.8, p=0.018).
Conclusions: Radial ESWT offered no additional benefit to supervised exercises in the treatment of subacromial shoulder pain after 24 weeks, except for the subgroup of patients with calcification in the rotator cuff.

1.22 The context of values in pain control : Understanding the price effect in placebo analgesia

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Background: The experience of pain relief arises from physiological as well as psychological factors, including expectation. Attributes such as commercial features have been shown to influence the placebo effect by affecting quality expectations. This study investigated whether valuation of pain treatment from price information influences placebo effect, and explored the neural mechanism of price effect.
Methods: A two-day experiment took place in this study. On day 1, participants (n=21) went through conditioning session of two placebo creams without any information on price. The pain on treatment site was given by mechanical stimulation, and was always lower than pain on the control site. On day 2, during the functional magnetic resonance imaging (fMRI) experiment, the same creams were applied with information on price ($8.00 and $120.00 each), and high pain was always delivered on both control site and treatment sites.
Results: The participants rated that the cream with higher price was more effective in pain relief (p=0.004). In the neuroimaging study, ventral striatum (Z=3.34, p=0.036), ventromedial prefrontal cortex (Z=3.19, p=0.027), and ventral tegmental area (Z=3.76, p=0.021) showed higher activation to higher price during placebo analgesia. Ventromedial prefrontal cortex was positively correlated with the difference of pain ratings during the testing session.
Conclusion: The behavior results shows the experience of pain is influenced the valuation of treatments. The brain response to price in our experience indicates an increase in expectation and reward circuitry. These results help understand the patient preference toward treatments implicated with higher effectiveness such as high-priced drugs.

1.23 Do placebo expectations toward acupuncture change over time? A survey comparing results from preoperative and postoperative self-reported questionnaires

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Background: Placebo expectancy may contribute to improved treatment outcome, which may in turn contribute to the production of placebo effects. Thus treatment outcome may mediate the connection between expectancies and placebo effects. Aims: To investigate whether parents' pre-treatment expectations towards acupuncture differ in relation to post-treatment expectations, and whether any change of expectations correlate with the actual treatment outcome (postoperative vomiting).
Methods: Parents of two hundred and eighty-two children admitted to surgery completed two closed-ended self-report questionnaires embedded in a double-blinded randomized controlled trial with two groups; acupuncture intervention and control. In order to promote equal placebo expectancy among the parents, all of them were told that their child would receive acupuncture treatment. The questionnaires were completed preoperatively and minimum 24 hours postoperatively by using a 10 point visual analogue scale; a higher rating indicated a higher expectancy. Occurrence of children's vomiting was collected along with the postoperative completion of the survey.
Results: Preliminary analysis using paired sample T-test shows changes of pre-treatment and post-treatment expectancy. An increase of expectancy scores from pre-treatment to post-treatment was significantly correlated with no vomiting, and,

conversely, a decrease of expectancy scores was significantly correlated with vomiting (p=0,014 and <0.001, respectively). Further, a regression analysis showed that the expectancy pre-treatment and the outcome vomiting significantly influenced the expectancy post-treatment scores (p<0.001).
Conclusions: One may speculate whether changes of expectancy scores caused placebo/nocebo effects, or if the changes are caused by the outcomes. Nevertheless, potential changes should be taken into consideration in future placebo studies.

1.24 The effect of sports drinks on sports performance: The placebo effect

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Background: Sports drinks are a growing and very lucrative industry, however the evidence for the benefits of sports drinks on exercise performance remains unclear. The aim of this study is to determine the effectiveness of a carbohydrate-electrolyte sports drink (Lucozade Sport) on performance enhancement and endurance.
Methods: This study is a double-blind, placebo-controlled, randomised controlled trial comparing the effect of a carbohydrate-electrolyte solution compared with a placebo solution. Performance will be assed using an individualised treadmill protocol structured to induce exhaustion in 7 to 10 mins. The primary endpoints will be the total number of steps taken and total distance covered. Assessments of blood pressure and heart rate will be recorded at baseline and at follow-up. Body Mass Index (BMI), fitness levels, health state, use of sports drinks will be assessed and an expectancy questionnaire will be administered to determine sports drink beliefs.
Conclusion: The protocol was approved by the University College Cork Social Research Ethics Committee. The trial will end in March 2017.

1.25 The analgesic effect of listening to music: Controlling for a placebo effect

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Background: The analgesic effect of listening to music, music analgesia, has been demonstrated in several studies. However, as these studies do not include a placebo control, it is uncertain if the observed analgesic effect is in fact a placebo effect.
Methods: Forty-eight healthy participants were exposed to thermal stimuli while listening to different auditory inputs: an active condition (unfamiliar musical pieces), a placebo condition (unfamiliar nature sounds) and a control condition (pink noise). Participants rated pain intensity and pain unpleasantness on 0-100 VAS scales after each thermal stimulus and rated each of the auditory inputs on valence, liking and arousal.
Results: The active (music) condition and the placebo (sound) condition reduced pain intensity and pain unpleasantness equally well when rated similarly on valence, liking and arousal. Furthermore, both the active (music) condition ($P < .014$) and the placebo (sound) condition ($P < .045$) significantly reduced pain intensity and pain unpleasantness in comparison to the control (noise) condition.
Conclusions: By providing an auditory input without any musical features the nature sounds can be seen as a placebo control for music. Consequently, to our knowledge, this is the first study to show a placebo effect in auditory inputs, i.e. significantly lower pain levels in the placebo (sound) condition as compared to the control (noise) condition. The study provides a model for further investigation of this placebo effect in auditory inputs as well as the mechanisms by which it acts to reduce pain.

1.26 Placebo effects on itch: Conditioning of antihistaminergic effects, a trial design

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The current evidence suggests that it might be possible to condition the effects of antihistamines, which may lead towards reduction of symptoms in allergic patients. Discovering the psychoneuroimmunological mechanisms involved in this process could provide a basis for new therapeutic possibilities and therapies. A randomized placebo-controlled conditioning paradigm consisting of 2 phases will be applied. In the acquisition phase-consisting of 3 sessions-an association between an unconditioned stimulus (UCS, levocetirizine diHCl) and a conditioned stimulus (CS, a distinctively tasting beverage) will be made. In the evocation phase-3 sessions in the following week -conditioning effects will be tested. Healthy participants will be randomly assigned to 1) an experimental condition (acquisition: CS + UCS, evocation: CS + placebo), 2) an open label condition (acquisition: CS + UCS, evocation: CS + placebo, with the conditioning procedure being explained to participants), 3) a placebo condition (acquisition and evocation: CS + placebo pill) or 4) a conditioned not evoked group (acquisition: CS + UCS; evocation: water + placebo pill). At baseline and during the final evocation session, participants will be exposed to histamine through iontophoresis, which induces itch and a short-term skin response. The primary study parameter is self-reported mean itch during iontophoresis. Secondary parameters (e.g. wheal and flare response to histamine) will be assessed as well. We hypothesize that conditioning will reduce itch in the experimental and open label conditions, compared to the placebo- and conditioned not evoked groups.

1.27 Can the use of placebos reduce the expected benefit of participants in randomized controlled trials? Development of a valid and reliable patient-reported measure of expectancy for placebo-controlled trials

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Placebo-controlled randomized clinical trials (placebo-RCTs) are the gold standard to assess novel treatments. Placebos are used to distinguish the clinical improvement due to the intrinsic action of an intervention and the placebo effect. One aspect that remains to be addressed systematically is how the use of placebos in RCTs (to control for the placebo effect) can negatively affect patient expectancy, as patients may have a preference toward being randomized to the active treatment rather than to an inert placebo. If using a placebo underestimates the measured efficacy of a treatment and placebo-RCTs are standard for therapeutic development, how could this dilemma be overcome? We propose that a standardized measure of patient expectancy in the form of a patient reported outcome (PRO)
should be used systematically in placebo-RCTs so to enable the quantification of baseline patient expectancy in placebo-RCTs and inform the interpretation of trial results. We present a standardized patient-reported outcome of baseline expectancy, the Expectancy Questionnaire, for which conceptual framework and pilot testing has been completed and discuss our vision for the future use of this new tool. IMPACT: The ability to more accurately interpret results of trials is expected to have a significant impact across all fields of Medicine, enhance knowledge translation to clinical practice, and thereby, save precious resources.

1.28 Classical conditioning of thermal perception in youth: The role of awareness, attention bias to threat, and executive function

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Little is known about the placebo effect in children and youth, or how it may be harnessed for therapeutic benefit. In this study, we explore classical conditioning - a key element underlying the placebo effect - of thermal perception in youth. We utilize a paradigm developed by Jensen and colleagues (2012) examining placebo and nocebo pain responses as a function of conscious awareness in adults. We are assessing differences in thermal ratings in response to conditioned supraliminal (consciously perceived) and subliminal (nonconsciously perceived) cues that indicate either attenuated or amplified thermal perception. Furthermore, we are testing whether attention bias to threat (an endophenotype of anxiety) moderates the effect, and whether executive function (EF) mediates the effect of classical conditioning on thermal perception.
The study is currently underway in Vancouver, BC and involves recruitment of 40 high-school students (14-18yrs). Participants will first complete a Dot-Probe task measuring attention bias to threat, an EF task (Reversed Flanker), and a questionnaire (State-Trait-Anxiety). Half of the participants (n=20) will then undertake Experiment 1 (conditioning with conscious awareness) and the other half Experiment 2 (conditioning without conscious awareness). For both experiments, a design is used where specific neutral faces are coupled to either lower or higher temperature thermal stimuli delivered by the Pathway system (Medoc). These results will contribute to our larger goal of identifying factors contributing to analgesic placebo responses in children and youth, determining reliable methods for optimizing benefits from placebo responses, and assessing their potential as novel approaches to managing complex chronic childhood pain.

1.29 The effects of oral Bach flower remedy versus a placebo, enhanced interaction, and cognitive reappraisal on physiological stress response

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Background: There are a number of psychological mechanisms whose impact on the placebo effect are well supported, such as expectancy and enhanced interaction. There are also cognitive factors, such as cognitive reappraisal, which have been shown to reduce effective impact and could potentially enhance a placebo response. The aim of this study is to examine whether context effects impact stress, more than commercially available treatments such as Bach flower remedies.
Method: This study will use a 2X2 double-blind placebo-controlled randomised trial design to evaluate the effects of Bach Flower solution versus placebo in stress reactivity and recovery and to examine the role of enhanced interaction and cognitive reappraisal (CRA). A group of 100 participants will be randomised to receive Bach flower remedy or Placebo. Within these treatment groups, participants will be further randomised to receive a) Enhanced interaction with placebo and stress CRA, or b) Neutral or limited interaction and CRA. Treatment is 4 drops of solution diluted in water. Participants will then be subjected the Sing-a-song stress test (SSST) post treatment. Heart rate reactivity and recovery will be measured to evaluate physiological stress. Baseline differences will be assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond, & Snaith, 1983), the interaction will be assessed using the Consultation and Relational Empathy Questionnaire (CARE, Mercer et al., 2004), and evaluation of treatment beliefs will be done using the Credibility / Expectancy Questionnaire (Devilly & Borkovec, 2000).
Conclusion: The study was approved by the University College Cork Social Research Ethics Committee.

1.30 Effects of verbal suggestions on psychosocial parameter in female patients with stress-induced cardiomyopathy

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The etiology of stress-induced-cardiomyopathy (SCM) - a rare, reversible, and acquired form of primary myocardial disorders - is not yet fully explained. Stressful events are supposed to be triggers, and an exaggerated, inadequate activation of the sympathetic nervous system is discussed to be of key importance. Hence, we hypothesized that the autonomic response to stress of patients diagnosed with SCM differs from that of heart-healthy individuals. Within this randomized, single-blind experiment, 20 patients with a history of SCM and 20 catheter-confirmed heart-healthy individuals were examined in single sessions. After a baseline period, saline solution (NaCl) was successively administered three times in combination with either neutral, positive, or negative verbal suggestions that the given substance (NaCl) would either support or burden the heart, or would cause no changes. Numeric stress ratings and blood samples (copeptin, cortisol) were repeatedly obtained, and the electrocardiogram was continuously assessed. Results revealed nocebo effects on subjective stress levels and heart rate, with no differences between SCM patients and heart-healthy individuals. There was a significant increase in stress after the negative suggestion as compared to both other conditions ($p < .001$). Correspondingly, the mean heart rate showed no group difference, but a statistical trend for increase after negative suggestions as compared to positive ones ($p = .06$). Analysis of heartrate variability and hormonal correlates did not reveal any statistically significant results and positive verbal suggestions had no beneficial effect. In conclusion, we found no evidence that SCM-patients are generally more vulnerable to aversive stimuli than heart-healthy individuals.

1.31 Behavioral distinction between placebo and nocebo-effects

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Placebo and nocebo-like effects have traditionally been interpreted as reflecting two opposite effects: whereas the placebo-like effect reflects pain inhibitory effects, nocebo encompasses pain facilitation effects. To what extent these two phenomenon reflect truly independent effects, is poorly understood. One could argue, for example, that these effects are two aspects of the same behavioral (dis)inhibitory dimension, ranging from inhibition at one extreme to facilitation at the other extreme. I will present results from a behavioral study in which we tested 50 pain-free volunteers on various inhibition measures. These measures included two tests of cognitive inhibition performance, conditioned pain modulation, pain threshold and tolerance levels, as well as various pain cognition questionnaires (pain anxiety, pain catastrophizing, and pain coping). In addition, an experimental conditioning task was used to induce placebo and nocebo-like effects. The results showed that the placebo and nocebo effects were moderately correlated ($\rho=0.51$, $p<.001$). In addition, cognitive inhibition as measured with the Stroop task correlated with the nocebo ($\rho=0.36$, $p<.05$), but not the placebo ($\rho=-0.07$, $p=.66$) effect. Finally, a trend was found suggesting that a decreased conditioned pain modulation effect is associated with an increased nocebo response ($\rho=0.28$, $p=.07$); for the placebo effect, this association was not significant ($\rho=0.08$, $p=.61$). None of the pain cognition questionnaires correlated with the placebo or nocebo-like effect. Taken together, this study demonstrates that the placebo and nocebo-like effect represent clear distinct phenomenon at a behavioral level.

1.32 Measuring the efficacy of open label placebo with subjective and objectives measures: Preliminary results on concordance in a randomized controlled trial with menopausal women

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Background: Hot flushes (HF) are the most common symptoms related to menopause. Around 16-74% of women worldwide experience HF, yet duration, severity and interference with quality of life differ highly between individuals. Given the high symptom variance and a placebo response up to 58-63% in clinical trials, open label placebo (OLP) can be potentially efficacious in alleviating HF. We conduct a proof-of-concept study and furthermore expand on previous OLP research by using both subjective and objective outcome measures.
Methods: In a randomized-controlled study, women with menopausal HF are allocated to an OLP group or no treatment. Ambulatory measurements include a self-report diary for 14 days (x 3 times per day) and a sternal skin conductance monitor for 7 days. We applied a new criterion for scoring physiological HF data which combined a universal amplitude criterion and a more recently developed pattern criterion.
Results: Results as follow are based on a preliminary sample of n = 25 women. Rates of concordance were 45% with 31% over-reporting (more HF recorded in diary than by device) and 24% under-reporting, of which 44% occurred at night. Sensitivity and specificity was 0.65 and 0.97.
Conclusion: Using the new criterion, we found higher concordance rates when compared to other studies and an additional benefit of the objective measure (e.g. for HF at night). Yet, comparability was limited since less than half of all SSC-defined HF were detected in self-report. We advise considering subjective measures when interpreting objective measures of HF in placebo studies.

1.33 The impact of social modelling on the specificity of nocebo responses

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Background: Previous research has demonstrated that social modelling can trigger nocebo responses in healthy participants. The present study investigates how specific these responses are through secondary analyses of a social modelling experiment.
Methods: Eighty-two university students participated in an experiment investigating the impact of beta-blocker medications (actually placebos) on pre-examination anxiety. All participants were informed about eleven mild side effects of the medication. After taking the medication, participants were randomised to either witness a confederate report experiencing four of the earlier mentioned side effects, or no side effects at all. We compared differences in symptom severity and causal beliefs of the modelled side effects, non-modelled side effects, and unmentioned symptoms, across conditions.
Results: For symptom severity we did not find a significant interaction between changes in the severity of different types of symptoms and the modelling condition. In both conditions symptom severity increased to a larger extent for the modelled ($p = .045$) and non-modelled ($p < .001$) side effects when compared to changes in the unmentioned symptoms. We did find a significant interaction between condition and causal belief of the different types of symptoms ($p = .008$). After seeing a confederate report four side effects, the conviction became stronger that only these experienced symptoms were caused by the placebo medication.
Conclusions: Our results suggest that nocebo responses after social modelling are specific when causal beliefs of those exposed are concerned. Implications for the occurrence of mass sociogenic illness will be discussed.

1.34 How verbal suggestions affect loudness judgments: Roles of expectations and demand characteristics

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Expectations, induced by instructions or suggestions, can strongly influence our experience and evaluation of events, as is prominently illustrated in the placebo effect. Whereas most placebo studies report the 'assimilation' of experiences towards expectations, studies in other domains have reported the opposite: That experiences 'contrast' away from expectations. For example, a previous study found that participants evaluated identical tones as much louder when the experimenter had suggested that the tones would be soft—by saying "I hope these tones are not too soft"—compared to loud. Here, we examine whether these results were due to the phrasing of the suggestions in terms of the experimenter's hopes, which likely increased demand characteristics. To this end, we compared this phrasing with a more neutral phrasing of the same loudness suggestions, namely "These tones will be pretty soft" (versus loud). We varied the phrasing and direction (soft vs. loud) of the verbal suggestion across four groups of participants (N=20 per group). We hypothesize that these two ways of phrasing will have opposite effects on loudness judgments. Our results will help understand the mechanisms underlying expectancy effects on judgments, and may offer important recommendations regarding the phrasing of information in various domains of society.

1.36 Optimizing expectations and inducing positive emotions on stress response after an acute stressor

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Background: Expectations play a crucial role in placebo research, but positive emotions are also associated with positive outcomes in clinical trials. The purpose of this study was to determine whether short psychological interventions aiming at optimizing expectations or inducing positive emotions are able to improve expectations and emotions and whether both interventions would be effective in altering the stress response after an acute stressor compared to a control condition.
Methods: Randomized controlled trial with assessments at baseline, after a short psychological intervention (15 min writing task) and after stress induction. 70 healthy participants were randomized to one of three psychological interventions: either writing about ways how participants can influence stress to optimize personal control expectations, a gratitude-letter to foster positive emotions or a neutral writing task. After completing the writing task the Maastricht acute stress test was used to induce stress. Main outcomes were expectations, emotions, and stress parameters (subjective ratings, salivary cortisol and alpha-amylase). Personality traits (e.g. optimism) were considered as moderators.
Results: Specific effects for the expectation optimization intervention (higher personal control expectations after intervention compared to baseline; $p=.031$) and the gratitude intervention (higher gratitude after intervention compared to baseline; $p=.001$), were found. The intervention effects on stress parameters interacted with personality traits such as optimism.
Conclusions: Even short psychological interventions seem to have a positive impact on expectations, emotions and on stress parameters, while some individuals may profit to a greater extent due to certain personality traits.

1.37 The role of positive outcome expectancies in gaming your way to healthy food behaviors

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Background: Prior research demonstrated that serious gaming can be a promising tool in promoting health behaviors, such as a healthy food choice. To our knowledge it is not yet investigated whether health behaviors can also be optimized when participants do not perform health-related serious games, but are solely instructed about the effectiveness and working mechanisms of the games. Therefore, the aim of the present study is to investigate whether a positive outcome expectancy regarding serious gaming can optimize food preference and food choice.
Methods: One hundred and twenty participants were randomly allocated to one of four conditions, in which: (1) health-related serious games were performed, (2) health-related serious games were performed and a positive outcome expectancy considering the effectiveness and working mechanisms of health-related serious gaming was provided, (3) a positive outcome expectancy considering the effectiveness and working mechanisms of health-related serious gaming was provided, without performing health-related serious games, and (4) non-health-related games were performed. The primary study outcome was self-reported food preference and food choice, as measured by a food choice task. Secondary outcomes were actual food intake and implicit attitude towards food, as measured by a bogus taste test and an implicit association task. Analyses of (co)variance were performed to test the hypotheses.
Findings: Data collection was not completed before the abstract submission deadline. The findings will be presented during the conference.
Discussion: The present study will provide valuable information regarding the role of positive outcome expectancies in optimizing healthy food behaviors by playing health-related serious games.

1.38 The effects of a psychological intervention directed at optimizing immune function: A study protocol

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Background: In the placebo literature it has been shown that learned (conditioned) immune responses can improve treatment effects in somatic conditions. The link between psychological processes and immune function is further demonstrated by the promising effects of internet-based Cognitive Behavioral Therapy (e-CBT) in promoting immune function. In order to additionally target implicit learning strategies aimed to condition immune responses, serious gaming could be a promising add-on to e-CBT. Research on whether e-CBT combined with serious gaming elements is effective in modulating immune outcomes is however lacking. The aim of this study is to investigate the effects of a psychological intervention including implicit learning strategies in response to immune and psychophysiological challenges.
Methods: Sixty healthy males are randomly assigned to the experimental condition, receiving e-CBT combined with serious gaming elements for six weeks, or to the no intervention control condition. After the intervention, self-reported vitality is measured and participants are given an immune challenge through a M. Bovis Bacillus Calmette-Guérin (BCG) vaccination. One day after, participants undergo several psychophysiological stress tasks to explore the effects of the psychological intervention on participants' stress response following the immune challenge. To assess delayed effects of vaccination on self-reported and physiological health outcomes, a follow-up visit is planned four weeks later. The primary outcome measure is self-reported vitality measured directly after the intervention. **Discussion:** This study will offer further insights into underlying mechanisms of the link between psychological factors and immune function by combining e-CBT with implicit learning strategies.

1.39 Placebo responses - The influence of treatment history and expectations on itch relief

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Several studies in the analgesic field showed that the perception of the treatment and its meaning are relevant to placebo responses (Vase et al., 2011; Klinger et al., 2014), shaping expectancies towards the treatment. So, the treatment-specific expectation of patients arisen from the made treatment experiences play a key role for future therapy effects. This study aims to experimentally investigate the effects of made experiences with an antihistamine in a clinical setting with respect to treatment-specific expectations in patients with atopic dermatitis. It is assumed that positive treatment-specific experiences (itch relief) emphasize positive expectations towards itch relief and help to improve treatment benefits.
In this randomized-controlled study treatment-related information about the antihistamine is given to all included 48 patients, actual treatment and the treatment-specific experience realized via classical conditioning differed between three study groups. The effect of the treatment on the dependent variables itch sensation reduction and treatment-specific expectation was determined at 2 points via skin prick test (histamine dihydrochloride) and a numeric rating scale. The focus rested on the influence of the conditioning process and the treatment-specific experiences.
The results indicate the strong relationship between patient's treatment-specific experiences and the expectation towards future pharmacological treatments: patients who experienced a conditioning process while medicated reported stronger expectations towards the itch relief after intervention compared to patients who could not create a positive link between medication effects and itch intensity relief via classical conditioning, $t(32)=-2.33$, $p=.03$. The combination of conditioning with either the antihistamine or the placebo did not significantly differ from each other with respect to the expectation level, $t(30.89)=1.61$,

p=.118. Furthermore, treatment-specific expectations make a significant positive related contribution to itch relief (t=1.950, p=.05). Positively influencing experiences with medication which are observable by patients are benefits for establishing positive treatment expectations and furthermore improve placebo responses.

1.40 Placebo effects of information bias in context of a perceived energy drink on a 200 m running sprint performance

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Placebo and nocebo effects occur in response to cognitive beliefs and their subsequent neural actions. Studies show that information bias triggers beliefs that alter the behavioral outcome. In this work, we scrutinized the effects of an inert green-color energy drink provided to three groups (n=20/group) with different information. One group was told that the drink augments running performance, the second was told that the drink's effects are unknown, while the third was informed that the drink may decrease performance. At baseline, the groups did not differ in their mean running times (p>.05). One-week later, after ingesting the drink, all subjects run again 200m. The positive instruction (placebo) group increased its performance (p<.05) and also perceived its run-time shorter (p<.05) than the other groups. Better performance (p<.05) was also noticed in the neutral-, but not in the negative-information group (p>.05). However, the placebo group improved more than the neutral group (p<.05). These results reveal that drinking an inert liquid, primed with positive information, changes both the actual and self-perceived run-time on 200m. Possibly a self-generated belief has produced a similar effect in the neutral information group too. Thus, information triggers measurable performance effects.

1.41 Placebo Therapy - A randomized controlled trial

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In 1973, Jefferson M. Fish proposed Placebo Therapy. Fish's core assumption was that most of outcome in psychotherapy is due to social influence and a client's psychological processes and that processes are similar to those underlying placebo effects. With respect to psychotherapy, he assumed that it is not the intervention itself, but the client's beliefs that makes this intervention effective. However, no study so far has directly tested this concept. Therefore, we set out to develop a manualized version of Fish's Placebo Therapy and to assess its effects on well-being.
60 healthy subjects will be randomized to either the Placebo Therapy or a no-treatment control group. Placebo Therapy consists of 4 one-hour sessions conducted over a period of four weeks and is structured by the principles of Fish's Placebo Therapy. Primary outcome are symptoms of general well-being and discomfort, which will be assessed at baseline, post-treatment (4 weeks) and follow-up (8 weeks). According to previous evidence of beneficial effects of common factors, we expect large effects for pre-post and medium effect sizes for pre-follow up differences in favor of the Placebo Therapy. The study is currently in progress. First results will be shown at the conference.

1.42 Training the circadian rhythm by conditioning of the Cortisol Awakening Response

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Background: Sleep problems arising from a disruption of the circadian rhythm (e.g. circadian phase-delay) are common, as shown in delayed sleep-phase disorder or seasonal depression. Several therapies have adverse side-effects, or are difficult to endure. Therefore, new treatment options are timely and relevant. Evidence shows that Pavlovian conditioning - one of the main mechanisms inducing placebo effects - can modulate specific physiological responses of the endocrine and immune system in the awake state, both in animals and humans. It is not yet known whether physiological responses can be conditioned in humans using automatic learning processes during sleep. This project will study whether the automatically regulated circadian sleep-wake rhythm can be conditioned during sleep and whether this might be a new treatment for option for patients with disturbed circadian rhythms.
Design: To condition the circadian sleep-wake rhythm in healthy participants, we use a previously validated two-phase pharmacological conditioning paradigm. In the acquisition phase, all participants are woken up one hour before regular awakening during three consecutive nights at home. During the rising slope of cortisol towards the moment of awakening, they are exposed to a distinct odor to condition the odor to the circadian cortisol response. In the subsequent test phase, both the experimental and control group are exposed to an odor at random time points during sleep for one night at the lab.
Discussion: The study design will be presented. If this study shows the possibility to implicitly train the circadian rhythm, non-invasive placebo treatment possibilities for disorders with disturbed circadian rhythms could be developed.

1.43 Starting a Randomized Controlled Trial into the placebo-effects of clinical communication: Lessons learned from the ethical, practical and methodological challenges

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Background: Placebo-effects attributable to health care professionals' expectancy and empathy manipulation have primarily been shown in laboratory settings. We designed an RCT to determine the separate and combined effects of expectancy and empathy manipulation during routinely pre- and post-operative tonsillectomy analgesia care on patient outcomes. Doing so posed us with ethical, practical, and methodological challenges.
Methods: Using a 2x2 RCT design 128 adult tonsillectomy patients are randomly assigned to 1 out of 4 conditions differing in the level of expectancy manipulation (standard versus enhanced) and empathy manipulation (standard versus enhanced). Daycare ward nurses were trained to deliver the intervention, and patients are treated with standard analgesia and hospital routines. Primary outcome is patients' perceived pain.
Results: Ethical challenges included creating a standardized communication protocol, in which conditions differ as much as possible while remaining realistic and not including suboptimal communication.
Practical challenges included ensuring all providers not involved in the study used neutral communication and setting up electronic systems to identify patients and standardize practice.
Methodological challenges included the standardization of the pain protocol, in order to ensure found effects can be attributed to the manipulated communication.
These and other challenges and the chosen solutions will be discussed.
Conclusions: Studying the placebo-effects of communication in clinical care asks for intense collaboration between researchers, clinicians and the hospital logistic support system. A fine balance between experimental rigor and the sometimes uncontrollable clinical reality needs to be found. Future studies could benefit from taking the encountered challenges and solutions into account.

1.44 Misunderstood effect of medicinal drugs, also called the 'placebo effect'

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Background: The double-blind placebo-controlled research, in which neither the doctor nor the patient knows what they give/get, is the standard procedure for the registration of new drugs. The effect of the new drug is compared with an already used, recognized effective old drug and a placebo. For the past 30 years, almost every new registered drug has been compared with a placebo. The proportions of obtained beneficial effects for drugs to treat depression are usually: new drug 65%, old drug 60%, and placebo 40%. Placebo is not used to cure illnesses.
Status quo: The placebo is the most researched, yet least applied 'medicine'. It is widely used in effectiveness studies to compare with pharmaceutical drugs, but is not currently registered, and not used, as a drug itself in mainstream medicine. Despite beneficial effects of 20 of 30 or even 40%. **Results:** The use of EBM (Evidence Based Medicine) is the standard in mainstream medicine. The use of placebo's is by law prohibited (WGBO). The use placebo by alternative practitioners is allowed. Placebo effects are too important to leave the use of it to the alternative healers.**Conclusions:** Ensure that mainstream medical practice can use the placebo effect in a legal, systematic and scientific way. It should become an accepted method in main- stream medical treatment. The first step should be to register certain placebo's (in terms of name, content, size, color and shape) as a drug for a number of specific disorders.

1.45 In vino veritas? An experimental examination in a naturalistic setting.

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Placebo research shows that the effects of a given intervention is subject to contextual information, but does this also apply to one of the oldest interventions in mankind - red wine? Here, Plassmann and colleagues (2008) observed that both the subjective as well as the neuronal response to red wine is influenced by the manipulation of its price. However, since their results are based on a small sample in a laboratory environment, we set out to replicate their study in a naturalistic setting.
In a public university event, 140 participants (77 females) were randomly allocated to rate three different wines with either deceptive, real or no pricing for pleasantness and intensity. Each participant received a total of six small glasses (all three wines without pricing, the medium-priced wine with real pricing ("CHF 32"), the cheap wine with real ("CHF 10") or deceptive pricing ("CHF 40") and the expensive wine with real ("CHF 65") or deceptive pricing ("CHF 16").
First, the three wines differed marginally significant in intensity ($p = .002$), but not in pleasantness ($p = .230$) when administered without pricing ($p = .053$). These results were replicated when wines were administered with real pricing, with marginal significant differences for intensity ($p = .099$), but again not in pleasantness ($p = .631$). Second, deceptive pricing altered the pleasantness of wines ($p = .018$), with cheap wine tasting more pleasant when priced more expensive ($p = .02$), but expensive wine tasting not less pleasant if deceptively marked as cheaper ($p = .18$). Intensity ratings were not influenced by deceptive pricing ($ps > .15$).
We were able to partly replicate that deceptive pricing alters the perception of wine, as it is possible to make cheap wine taste better when priced higher. Rating of wines did not differ when given cheaper prices. However, when provided with no or correct information about their price, wines tasted more intensive in the order of their real price. Thus, these latter results partly confirming the term "In vino veritas".

1.46 Merely possessing a placebo analgesic reduced pain intensity: Preliminary findings from a randomized laboratory design

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An experiment was conducted to examine whether the mere possession of a placebo analgesic cream could reduce perceived pain intensity in a cold pressor test. Healthy participants were induced to have the motive to reduce physical pain and to believe that a placebo analgesic cream was an effective analgesic drug. Half of the participants were unexpectedly given the placebo analgesic cream as a gift, whereas the other half were not. Results showed that participants who merely possessed, but did not use, the placebo analgesic cream reported lower levels of pain intensity from the cold pressor test as compared to participants who did not possess the cream. The study provides preliminary evidence that simply possessing a placebo analgesic can reduce pain. Possible mechanisms and future directions are discussed.

1.47 Early symptom trajectories as predictors of treatment outcome for citalopram versus placebo

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Context: The high percentage of failed clinical trials for anti-depressant medications, especially in elderly populations, obscures the fact that some patients may benefit greatly from treatment. Early detection of patients who may benefit most from antidepressant medication may improve treatment decisions.
Objective: To examine whether depressed patients in a large clinical trial exhibit distinct trajectories of early symptom change that predict differential response to medication or placebo.
Design: We reanalyzed data of 174 patients aged 75 years and older with unipolar depression who were randomly assigned to citalopram or placebo. We used growth mixture modeling to identify distinct trajectories of early change (i.e., weeks 1-4 of the trial) on the Hamilton Rating Scale for Depression in the citalopram and placebo conditions.
Results: In the citalopram condition, two distinct trajectories of early change were detected that were associated with significantly different symptom reduction (p=.001). In contrast, only one trajectory was detected for the placebo condition. Whereas one of the early trajectories of patients receiving citalopram (N=33) showed significantly better symptomatic change than placebo (p=.0003), the other trajectory (N=51) did not differ significantly from placebo (p=.63). Poor baseline functional scores predicted trajectory membership, such that individuals with a score below 4.5 on baseline instrumental activities of daily living showed a higher tendency to be in the trajectory that outperformed placebo.
Conclusion: The sub-group of citalopram-treated patients exhibiting greater symptom improvement early in a trial are likely to have beneficial outcomes relative to placebo. Future research should focus on developing reliable pre-treatment clinical and biological measures to identify this subgroup.

1.48 Open-label placebo reduces fatigue in cancer survivors: A randomized trial

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Studies have shown a significant effect of placebo on cancer-related fatigue (CRF), but this has been limited to placebo administered in blinded trials. Extending this work, we investigated the effect of open-label placebo on CRF in 40 long-term cancer survivors (ages 22-74; ≥ 6 months off-treatment). Survivors were randomized to open-label placebo or usual care, with placebo group participants asked to take two placebo tablets twice daily. Both groups completed assessments at Baseline, Day 8 (reported here) and Day 22 (results pending). The primary end-point was change in fatigue on the FACIT-F analyzed using repeated-measures t-tests. Dispositional optimism (LOT-R), and single-item subjective ratings of change in fatigue, quality of life, and exercise tolerance were also assessed. At Baseline, the two groups did not differ on fatigue. At Day 8, however, the placebo group reported significantly improved fatigue on the FACIT-F (mean change = 5.4 points, $p<.01$, $d = .55$), while the control group did not (mean change = 1.7 points, $p = .19$, $d = .17$). Similarly, the placebo group reported significantly greater reduction in fatigue ($p<.05$) compared to controls, and their subjective quality of life and ability to exercise were marginally better than controls ($ps<.065$). Optimism was not associated with change in fatigue. Results demonstrate that when administered in an open trial, placebo improves self-reported fatigue in cancer survivors. This effect is similar in magnitude to that seen in blind placebo administration and appears to be independent of an optimistic outlook. Implications for clinical practice and future research are presented.

1.49 A taxonomy of techniques with potential to harness placebo effects in non-malignant pain

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Objectives: Placebo effects can be large and clinically meaningful but are seldom fully exploited in clinical practice. This review aimed to facilitate translational research by producing a taxonomy of applicable techniques that could augment placebo analgesia in clinical practice.
Design: Literature review and survey.

Methods: We systematically analysed methods that could be used to elicit placebo effects in 169 clinical and laboratory-based studies involving non-malignant pain, drawn from 7 systematic reviews. In a validation exercise we surveyed 33 leading placebo researchers (M=12 years' research experience, SD=9.8).
Results: The final taxonomy defines 30 procedures that may contribute to placebo effects in clinical and experimental research, proposes 60 possible clinical applications, and classifies procedures into 5 domains: the Patient's Characteristics and Belief (5 procedures and 11 clinical applications); the Practitioner's Characteristics and Beliefs (2 procedures and 4 clinical applications); the Healthcare Setting (8 procedures and 13 clinical applications); Treatment Characteristics (8 procedures and 14 clinical applications); and The Patient-Practitioner Interaction (7 procedures and 18 clinical applications).
Conclusions: The taxonomy provides a preliminary and novel tool with potential to guide translational research aiming to harness placebo effects for patient benefit in practice.

1.50 Specific and nonspecific factors in game-based intervention outcomes

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The use of e-health applications has grown rapidly, especially for mental health problems. Often times, e-health applications are developed to disrupt traditional intervention delivery models and to make treatment more effective. Recently, the videogame Mindlight has been developed to reduce anxiety symptoms in at-risk youth. The game incorporates evidence-based and empirically-validated techniques from cognitive behavioural therapy (CBT): relaxation, exposure, and attention bias modification. A recent randomized controlled trial (RCT) showed that Mindlight is as effective as CBT (Schoneveld et al., in prep.). Additionally, we found that changes in in-game play behaviours representing the relaxation and exposure principles predicted improvements in anxiety three month after termination of the intervention (Wols et al., in prep.). However, besides those specific factors in games a large amount of symptom improvement might be explained by nonspecific factors. This is supported by the fact that another RCT showed that anxiety symptoms equally decreased for children playing Mindlight and children playing a commercial (control) videogame (Schoneveld et al., 2016). Examples of those factors include expectations for improvement, implicit beliefs about the malleability of personal attributes, and motivation for change. In this poster, we present a theoretical framework to investigate those nonspecific factors in game-based interventions also in relation to specific factors. The ultimate goal is to utilize the potential of those factors to optimize the effects of videogames on mental health.

1.51 Will it work and has it worked? A priori expectations and perceived a posteriori efficacy estimates in children undergoing placebo hypoalgesia

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Background: Expectations play a significant role for the placebo response. Little is known about the relationship between a priori expectations and the actual placebo response, and how the latter contributes to recalled efficacy of the intervention. Moreover, the role of age and type of placebo induction in shaping a priori expectancy and recalled efficacy is unclear.
Methods: Participants were 172 children (52.33% female; age: 6-17yr, M=11.62 ± 3.21yr) and 32 adults (50% female; age: 19-29yr; M=21 ± 2.06yr,). Placebo hypoalgesia using heat pain was induced by verbal information and by classical conditioning, in counterbalanced sequence across subjects. Participants rated the efficacy of the "analgesic" cream prior to and after (a posteriori) placebo induction. Placebo response was determined based on pain intensity ratings.
Results: If placebo hypoalgesia was induced by verbal information there was a significant negative correlation between age and a priori expectations.
A posteriori effectiveness ratings were higher, when placebo hypoalgesia was induced by classical conditioning compared to verbal instructions, and decreased with age. Interestingly, a posteriori effectiveness ratings were most strongly associated with the actual placebo response in the last trial, regardless of the induction method. Age and the actual placebo hypoalgesia were the best predictors for a posteriori efficay.
Conclusion: Findings suggest that age influences a priori expectations. Moreover, estimated a posteriori efficacy depends on age, induction method, and immediacy of the placebo response. Such recalled efficacy may modulate future treatment responses given recent evidence that recalled rather than actual pain strongly influences future pain in children and adolescents.

1.52 Laboratory investigation of specific and non-specific (placebo) effects of a magnetic bracelet on a short bout of aerobic exercise performance

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The specific and non-specific (placebo) effects of a magnetic bracelet in aerobic exercise were studied in a double blind placebo controlled laboratory investigation. A total of 97 young athletes (49.5 % women, age: 22.02 years (SD=1.82)) were tested in three experimental conditions: 1) actual intervention (magnetic bracelet), 2)respective placebo intervention, 3) a no-intervention. Physical performance, expectation regarding the efficacy of the magnetic bracelet, perceived change in performance, and perceived fatigue were assessed. Data were analyzed with a mixed model multivariate repeated measures analysis of variance (group (3) x time (2) x dependent measures (6): distance, average speed, maximal speed, average heart rate, maximal heart rate, and perceived fatigue). There was a statistically significant multivariate main effect for time (Wilks' Lambda = .666, $F(6,80) = 6.69$, $p < .001$, partial $\eta 2 = .334$), but no group by time interaction. Two thirds of the participants did not believe that their performance would be altered by the magnetic bracelet. The results revealed that the magnetic bracelet did not have specific (actual) or non-specific (placebo) effect on objective and perceived performance. However, better performance over time that was independent of treatment, has emerged possibly due to learning. The virtual lack of expectancy could explain why placebo effects did not emerge in this laboratory inquiry.

The findings show, that the examined magnetic bracelet does not affect short aerobic exercise performance, and in low-challenge and low-subjective-importance situations, emerging in artificial research conditions, the placebo effects could not be observed.

1.53 Placebo analgesia and body representation

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Limb embodiment, and the restructuring of the body ownership and representation, has been examined in normal individuals exploiting the so-called rubber hand illusion (RHI). RHI refers to the experience -at different degrees- of a rubber hand (RH) as their own, if the RH is placed next to their covered real hand, and there is a coordinated touch (visually visible only on the RH) of the rubber and the real hand. In previous work we have shown that a placebo analgesic decreases perceived pain intensity if delivered on the rubber hand, while pain is delivered on the real hand (Coleshill, George & Mazzoni, under revision). This study represents a replication of that study, adding physiological measures of anxiety via EMG as well as measures of embodiment. In a within subjects design, thirty right-handed individuals, 19 females and 11 males, underwent the RHI procedure, and received heat-related pain delivered by a thermode on both the real hand and the RH. Their anxiety levels and degree of embodiment were measured before every delivery of painful stimulation, both at baseline, during conditioning and when a placebo cream and a control cream were applied to the site. The results replicate the placebo analgesic effect on the RH we already found, and indicate that the effect is strongest in those who have a higher level of reactive anxiety. The procedure also reveals that the strength of embodiment moderates the effect.

Tuesday April 4
Poster presentation abstracts

2.01 Placebo empathy analgesia: an indirect effect of trial design?

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Background: Empathy research often focuses on the shared representations mechanism. This mechanism postulates that processes underlying self-related experiences are used as proxy to understand the emotions of others. Several studies support this mechanism, including a recent placebo empathy analgesia study which indicates an association between reduced self-related pain and reduced empathy for pain (Rütgen et al. 2015). However, the question arose whether placebo empathy analgesia is just due to placebo analgesia, or whether it might also be due to an indirect effect of the used mixed trial design. Such a design has a continuous alteration of self- and other-related pain trials, and therefore participants also continuously switch between judging these events. Consequently, judging other's pain may be anchored in the preceding self-related pain responses and thus could lead to a potential judgment bias.
Methods: The previous placebo empathy analgesia study is replicated including an empathy for pain paradigm with subjective and neural measures of pain and empathy for pain (i.e. self-report and EEG). However, to exclude a possible anchoring effect, a blocked trial design is introduced with each block presenting either other- or self-related pain trials.
Results: Preliminary results suggest i) a replication of the previously reported placebo empathy analgesia; ii) that previous findings cannot solely be attributed to a confound in task design; iii) self-related pain experiences reduce effects of placebo empathy analgesia.
Conclusions: Data acquisition and analysis is still ongoing at the moment of abstract submission, however data will be presented during the conference.

2.02 Chronic pain: the twisted body stress syndrome (tbss) - asymmetrical activation of a central autonomic sympathetic network causes hemispheric motor cortex excitability imbalance

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Anticipation of a potential danger e.g. pain, a potentially aversive event or perceived threat activates central autonomous networks where left amygdala and Mid-Cingulate Cortices (MCC) are core areas. The amygdalae act as our threat radar and sounds the alarm for flight or fight. Cingulate pre-Motor Areas (CMA) in the MCC project mainly to the left Supplementary Motor Area (SMA-proper) where plans for appropriate motor actions are set up. A left-lateralized pre-movement EEG-pattern has been shown earlier. Through interhemispheric inhibition, left SMA and left M1 inhibits the contralateral right M1. This restricts left motor output. Clinically, a generalized non-conscious increase in pre-movement muscle tone on the right side of the body and a generalized decrease in left side muscle strength can be seen. If sustained, fascia and connective tissue changes will form, mostly on the right side of the body.
The aim of the described cognitive three-step treatment procedure is to reduce left-lateralized SMA/M1 pre-motor activity in order to release the inter-hemispheric inhibition of the right motor cortex M1.
As cortico-spinal excitability balance improves the pre-movement right-lateralized "muscle preparation" tone is reduced. Simultaneously left-side muscle strength instantly improves. The resulting improved muscle strength balance gives us better conditions for all other subsequent treatments. The cognitive treatment method is designed as follows:
Steps 1,2 reduce CMA/SMA activity by instead activating the pre-SMA, our centre for inhibitory control and visuospatial processing.
Steps 1,2 + 3 also reduce amygdala activity by activating the Anterior Cingulate Cortex (ACC) an emotion regulating and autonomic control area.

2.03 The effect of fear of pain on placebo analgesia induced by hidden and open classical conditioning

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Background: We aimed to investigate the influence of expectancy, fear of pain (trait), and fear (state) on the effectiveness of hidden and open conditioning to produce placebo analgesia.
Methods: Ninety healthy volunteers were randomly assigned to three groups (hidden conditioning, open conditioning, and control) who received electrical stimuli preceded by either orange or blue lights. One colour was paired with painful stimuli (control stimuli) and the other colour was paired with nonpainful stimuli (placebo stimuli) in both the hidden and open conditioning groups. Only participants in the open conditioning group were informed about this association. In the testing phase, both coloured lights were followed by identical control stimuli. In the control group, both colour lights were followed by control stimuli without any conditioning procedure. Participants were divided into two subgroups differing in fear of pain (measured by the Fear of Pain Questionnaire).
Results: A significant analgesic effect was found only in the hidden conditioning group, and it was limited to the participants with high fear of pain, even though participants with high and low fear of pain expected less pain in relation to placebo-associated stimuli. Only participants with high fear of pain experienced less fear in relation to placebo-associated stimuli, and only their difference in fear ratings, rather than their expectancy ratings, predicted placebo analgesia.
Conclusions: Hidden rather than open conditioning is effective in inducing the placebo effect. Fear of pain and fear seem to be more important factors than expectancy in producing the placebo analgesia induced by hidden conditioning.

2.04 Do autobiographical memories and expectations play a role in placebo responding?

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Purpose: Placebo effects are presumed to be based on one's expectations and previous experience with regard to a specific treatment. The purpose of this study was to investigate the role of the specificity and valence of memories and expectations with regard to itch, on experimentally induced placebo responses on itch. It was expected that cognitive schemas with more general and more negative memories and expectations with regard to itch contribute to less itch placebo responding. Methods: Validated memory (i.e. the Autobiographical Memory Test; AMT, and the Self-referential endorsement and recall task; SER) and expectation tasks (i.e. Future Event Task; FET, and the Self-referential endorsement and recall task; SER) were modified for physical symptoms, including itch. Specificity and valence of memories and expectations were assessed prior to a placebo experiment in which expectations for electrical itch stimuli were induced in healthy participants. Findings: Results showed that participants who are more specific in their memories regarding itch and who have less negative itch related expectations for the future were more likely to be a placebo responder. There were no significant effects for the nocebo responders versus non-responders. Implications: The adapted tasks to assess cognitive schemas with regard to memory and expectations for itch seem promising in explaining inter-individual differences in placebo responding on itch. Future research should investigate whether similar mechanisms apply for patients with chronic itch. This knowledge can be used to identify patients who will benefit most from the placebo component of a treatment.

2.05 Exploration of expectancy-induced analgesia in patients with Temporomandibular Disorder: a cohort study

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Background: Studies on expectancy-induced placebo analgesia have been mostly conducted in healthy volunteers, leading to substantial gaps in the understanding of how endogenous pain modulatory systems affect clinical pain phenotypes. Differences in endogenous pain modulation (EPM) may account for the high variability observed in the pain experience of chronic pain patients and could be related to different opioid-receptor binding availability. Here, we examine EPM in chronic orofacial pain patients, namely those with Temporomandibular Disorder (TMD).
Methods: Differences in expectancy-induced analgesia as a function of EPM were assessed through a behavioral pain modulation task in a cohort of twenty TMD patients (average age: 36.25/SD: 10.78) and twenty healthy matched-controls (35.60/10.68). Placebo analgesia was measured through a testing phase of 12 heat-pain consecutive stimuli after completion of a conditioning paradigm consisting of 24 heat-pain stimuli.
Results: Findings from this cohort demonstrate that there was no statistically significant difference in placebo-induced analgesia between patients and controls [$F(1, 434)=0.6$, $p=0.4$]. There was a main effect of condition [$F(1, 434)=99.0$, $p<0.001$] with no significant differences in extinction of placebo analgesia in either group [$F(1, 434)=1.3$, $p=0.3$].
Conclusions: To our knowledge, this is the first time that EPM between TMD patients and matched-controls is explored. Although no significant differences in placebo analgesia were observed between the populations in this cohort, further analyses with larger sample sizes need to be performed before drawing definitive conclusions. Knowledge from this research could help guide clinical practice towards more personalized and mechanism-oriented therapeutic strategies for effectively managing TMD.

2.06 Beware of electromagnetic fields! - Evidence for a nocebo effect in somatosensory perception by adverse television report and sham WiFi

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Background: People suffering from idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) experience numerous non-specific symptoms that they attribute to EMF. The cause of this condition remains vague and evidence shows that psychological rather than bioelectromagnetic mechanisms are at work. We hypothesized a role of media reports in the etiology of IEI-EMF and investigated how somatosensory perception is affected.
Methods: 65 healthy participants were instructed that "some people experience transient symptoms under exposure with EMF" and "some evidence exists showing enhancement of somatosensory perception by EMF". Participants were randomly assigned to watch either a television report on adverse health effects of EMF or a neutral report. During the following experiment, participants rated stimulus intensities of tactile electrical stimuli while being exposed to a sham WiFi signal in 50% of the trials.
Results: Sham WiFi exposure led to increased perception of electric stimuli in the WiFi film group, especially in participants with higher levels of somatosensory amplification. Participants of the WiFi group reported more anxiety concerning WiFi exposure than the control group and tended to perceive themselves as being more sensitive to EMF than before.
Conclusions: Sensational media reports can facilitate enhanced perception of tactile stimuli in healthy participants. People tending to perceive bodily symptoms as intense, disturbing, and noxious seem most vulnerable. Receiving catastrophizing media reports might sensitize people to develop a nocebo effect and thereby contribute to the development of IEI-EMF. By promoting catastrophizing thoughts and increasing symptom-focused attention, perception might more readily be enhanced and misattributed to EMF.

2.07 Investigating the evolved 'social placebo' in strenuous physical activity

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Recent studies have identified opioidergic and cannabinoid pathways in placebo analgesic effects. Both systems are also implicated in mammalian social bonding and reward, and may account for analgesic effects associated with social support in humans. These responses are likely elements of an evolved self-regulation system that flexibly deploys protective or healing mechanisms in response to environmental conditions, including implicit and explicit cues of threat and support. On this view, we suggest that support-based analgesia in highly socially interdependent species, especially humans, may be considered a kind of 'social placebo', in which known placebo analgesic pathways are activated specifically by perceived support. In a series of preliminary tests, we have developed this account with specific reference to the link between social cohesion and performance in strenuous physical activity. Three controlled experiments with non-elite athletes investigated the effects of perceived social support on pain, fatigue and/or performance in physical activity. Designs controlled for social facilitation effects. Analyses revealed greater pain threshold increases following group as compared with solo rowing; faster sprint-times in a solo running test following a subtle cue to social support (synchronous vs non-synchronous warm-up); and cycling performance profiles under conditions of support (vs. no support) that parallel profiles previously identified in a fentanyl intervention. Ongoing research is investigating overlap between neuropharmacological mechanisms mediating placebo analgesia via conditioning or explicit expectancy and support-based analgesia. The research will enable a fuller understanding of how both perceived social and biomedical support interact to influence top-down self-regulation of pain and fatigue.

2.08 Neurobiological mechanisms of the placebo effect: A comparative review

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While we are beginning to understand the neurobiological mechanisms of the placebo effect, how exactly expectancies can trigger specific and complex effects on physiology remains to be characterised. Furthermore, as most neurobiological studies have considered the placebo effect in isolation, it remains unclear whether the mechanisms underlying the placebo effect are similar to or unique from those underlying other cognitive-mediated techniques, such as meditation or cognitive behavioural therapy. A systems-level view of the neural, immune and pharmacological mechanisms that underlie different cognitive-derived biological effects is likely to expand our understanding of the placebo effect and other cognitive techniques, and their potential for therapeutic use. This poster describes a comparative review of the neural, immune and pharmacological mechanisms that underlie the known cognitive-derived biological effects of techniques including the placebo effect, meditation and cognitive behavioural therapy in order to identify the multiple systems and networks - and possible conserved mechanisms - responsible. It also reviews current methods and future directions for identifying these mechanisms and measuring effects. Based on these results, it will propose a methodology for integrating these mechanisms with cognitive theories to investigate the potential of neural, immune and pharmacological pathways to mediate physiological effects at a systems level.

2.09 Reconceptualising placebo as the 'Caring Response': qualitative data on the activation of the placebo response and healing

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Background: There is general dissatisfaction with the word 'placebo'. Other terms used include 'Context Effects' and the 'Meaning Response'. Our literature reviews and qualitative research suggest an alternative.
Methods: We have carried out 26 in-depth interviews with doctors (n=9) or CAM practitioners/healers (n=17) to explore their views on healing and placebos. In addition, we have obtained short written data on the nature of 'healing moments' from 69 healers/CAM practitioners. We have also observed healing events and rituals, had discussions with clients of healers, and reviewed relevant literature. The data have been analysed thematically.
Results: The interviews included a question about factors that facilitate a placebo response or healing of a client. Most respondents identified caring for the client as being critical. Phrases used included: 'unconditional love', 'good intention', 'wanting the best for the other person'. In the written data we found that the concept of 'connecting with another' was a key pathway to a healing moment: for example, one respondent commented - "when the connection leads to true understanding of the problem by both parties…there was a healing moment….". Discussions with the clients of healers also suggest that some form of connection between a professional and the client, based on the one caring for the other, is important. Nursing literature also puts emphasis on caring as the route to healing.
Conclusions: We suggest that the term placebo is replaced by 'The Caring Response' to emphasise the importance of caring in health care.

2.10 The brain basis of the patient-clinician relationship in placebo analgesia: A hyperscanning fMRI study

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A positive patient-clinician relationship can boost placebo effects for symptoms such as pain. However, unlike for the mechanisms of expectation and conditioning, the brain basis for socially driven 'placebo effects' is largely unknown. Here, we simultaneously record fMRI in patients and clinicians (hyperscanning), who interact via video transfer, during clinician-initiated treatment of the patient's pain. 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.
Ten healthy volunteers were matched into 5 'dyads', in which each participant assumed the role of 'patient' or 'clinician'. The patient received moderately painful cuff pressures to the left leg (15s), while the clinician used a button box to control (micro-current or placebo) electroacupuncture stimulation to the patient's leg to treat the cuff pain. MRI-compatible video cameras enabled the participants to communicate non-verbally throughout the scan. fMRI preprocessing included motion correction, skull stripping, and registration to MNI152. After single-subject GLM analysis, we conducted group GLM (whole-brain cluster-correction for multiple comparisons) followed by a group conjunction analysis, between patients and clinicians, of the pain+treatment>rest contrast.
Patients (receiving pain+treatment) showed activation of insula, somatosensory areas (S1/S2), vlPFC and dorsolateral prefrontal cortex (dlPFC). Clinicians (observing pain+treating) showed activation in anterior insula, S1, S2, vlPFC, and primary/secondary visual areas. A conjunction analysis indicated concordant activation of vlPFC and anterior insula for both patients and clinicians. Building on this pilot setup, we plan to enroll chronic pain patients and acupuncturists as participants.

2.11 The placebo analgesic effect in healthy individuals and patients: a meta analysis

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Objectives: The present meta-analysis investigates whether the magnitude of placebo analgesia is different in patients compared to healthy individuals, and whether placebo analgesia is different in experimentally induced pain compared to clinical pain in patients. Methods: A literature search in Web of Science (ISI) on the terms "placebo analgesia" and "placebo analgesic" was conducted. The search resulted in 71 studies, including 4239 participants. Fifty-five studies included healthy individuals and 16 studies included patients. Of the 16 studies with patients, five studies investigated clinical pain and 11 studies investigated experimentally induced pain. Results: The average effect size was $\bar{g}$= 1.24 for healthy individuals and $\bar{g}$= 1.49 for patients. In the studies with patients, the average effect sizes of placebo treatment was $\bar{g}$= 1.73 for experimentally induced pain and $\bar{g}$= 1.05 for clinical pain. A chi-square test revealed that there were relatively more studies with patients compared to healthy volunteers in which there was a clinically significant reduction in pain (p =.04). Conclusions: The findings suggest that patients benefited from placebo treatment to a greater degree than healthy individuals did and that studies on healthy individuals may underestimate the magnitude of the placebo analgesic effect in patients. Patient's clinical pain respond to placebo to the same degree as experimentally induced pain.

2.12 Do endogenous cortisol levels influence the placebo effect?

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It is assumed that placebo effects rely on learning processes such as conditioning, which in turn are strongly influenced and modulated by glucocorticoids. Accordingly, it has be reported that endogenous glucocorticoid fluctuations have a significant impact on the effects learning-dependent interventions (Lass-Hennemann & Michael, 2014). Therefore, we set out to examine the modulation of placebo effects through endogenous glucocorticoid fluctuations in 100 healthy male and female subjects. Participants were randomized to two conditions (see below) and then subjected to a two-phased placebo paradigm. First, all participants underwent placebo conditioning either in the morning (between 8.00 - 10.00, when endogenous cortisol is high) or in the evening (between 16.00 - 18.00, when cortisol is low). Two days after the conditioning, the recall of the conditioned placebo response was tested at midday (12.00 - 14.00) for all participants. Endogenous levels of salivary cortisol differ between the morning and afternoon conditioning group ($F(1,83)=25.45$, $p<.001$, $eta^2 =.24$), but not during the testing trials ($F(1,84)=0.41$, $p=.522$). Importantly, a significant placebo effect was observed ($t(86)=3.13$, $p=.002$, $d =0.34$), but morning and afternoon conditioning groups did not differ in their placebo effects ($F(1, 85)=0.25$, $p=.621$). The results indicate that although conditioning elicits a significant placebo effect, endogenous variations in cortisol do not influence the results placebo effect.

2.13 The differential effect of acute stress on pain modulation

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Introduction: Previous studies reveal that acute stress manipulations can induce either analgesia (SIA) or hyperalgesia (SIH). This differential effect of stress may be an artifact of the use of the highly variable measures; pain threshold and pain tolerance. Alternatively, it may genuinely occur, depending on the type of manipulation, populated tested or the pain test applied. The aim was to test whether stress has a differential effect on pain modulation by evaluating two different pain modulation paradigms under similar conditions of stress.
Methods: 31 healthy male subjects underwent the measurement of conditioned pain modulation (CPM) and pain adaptation. Testing was conducted before and immediately after exposure to the Montreal Imaging Stress Task (MIST), inducing acute psychosocial stress. Stress levels were evaluated using perceived stress and anxiety ratings, autonomic variables, and salivary cortisol.
Results: The subjects exhibited a significant elevation in perceived stress, salivary cortisol and autonomic variables validating the induction of stress. A differential effect of stress on pain modulation was found in that the magnitude of CPM was reduced while the magnitude of pain adaptation was increased following the stress manipulation. Moreover, the decrease in CPM and the increase in pain adaptation correlated with the level of perceived stress and the latter also correlated with cortisol level in the stress condition.
Conclusions: Stress may simultaneously decrease and increase pain modulation. This differential effect may be due to different connections between the hypothalamus and the brain structures mediating CPM/pain adaptation or from the specific characters of each of these tests.

2.14 Investigating expectation by means of contingent negative variation

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Background: Expectation has been studied with different approaches. The aim of the present study is to investigate pain expectation using contingent negative variation (CNV), an electrophysiological measure related to expectation.
Methods: Healthy volunteers participated in the study. Painful and non painful electrical stimuli were delivered to the hand and participants were asked to stop the stimuli as soon as possible. CNV amplitude, reaction time and pain rating were measured. Two participants were engaged simultaneously and CNV was recorded: when a participant was tested with electrical stimuli (T-session), the other observed (O-session). Thus, a group was first engaged in the T-session and then in the O-session and vice versa. In the T-session, subjects were presented a red or green cue, followed by a train of stimuli, and expected less pain after green and more pain after red cues. After 2 blocks of stimuli participants inverted their role.
Results: We found that: 1) the CNV is modulated by different visual cues, whereby pain expectation increases its amplitude; 2) the CNV is modulated by social observation, namely, not only participants who received the stimulation showed changes in CNV amplitude but also those who observed; 3) the CNV is sensitive to the sequence of stimuli presentation, viz, participants who first observed the stimulation showed higher CNV amplitudes.
Conclusions: CNV is an excellent model to investigate expectation of pain. Indeed, it is sensitive to social and temporal manipulation of stimuli as well as to associative learning.

2.15 Can mindfulness-based psychological treatment be placebo controlled?

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Background: The effect of mindfulness-based treatment for chronic pain has primarily been tested by comparing mindfulness-based psychological treatment to other psychological treatments, support groups or waiting lists. Hence, it is unknown whether mindfulness-based treatment has an effect beyond the placebo effect. We aimed at designing a carefully matched placebo control for mindfulness-based psychological treatment of chronic pelvic pain.
Methods: The mindfulness-based psychological treatment was scrutinized to determine exactly which aspects of the treatment that are specific for mindfulness-based treatment and which aspects that are common factors of psychological treatments. Based on this, an active mindfulness-based treatment and a placebo- treatment were manualized. Two licensed psychologist were trained to administer the two types of treatments. Until now 35 patients with endometriosis-related chronic pain have been randomized to receive the active treatment, the placebo treatment or waiting list for a period of 10 weeks. Patients reported pain intensity and pain unpleasantness daily on a 0-10 numeric rating scale.
Results: A meaningful placebo control for mindfulness-based psychological treatment was developed. Pilot testing showed interesting results for pain ratings in the two treatment groups, but the study is still ongoing, so preliminary results are expected to be presented later.
Conclusions: This study shows that it is possible to make meaningful placebo controls for psychological treatments and it suggests that inclusion of placebo control may influence the findings of efficacy studies.

2.16 Testing the effects of placebo analgesia on the multi-voxel representations of directly experienced pain and empathy for pain

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Background: Empathy for pain engages similar brain regions as directly experienced pain. This suggests common representations for the two experiences that appear anchored in mid-cingulate and anterior insular cortices (MCC, AI). Definitive evidence for such common representations is, however, missing (e.g., Krishnan et al., eLife, 2016). We recently demonstrated that placebo analgesia reduces both pain empathy and self-pain (Rütgen et al., PNAS, 2015). Here, we re-analyzed the functional magnetic resonance imaging (fMRI) data of this study. We used multi-voxel pattern analysis (MVPA) to investigate the neuronal representations of pain empathy and self-pain and how they were affected by placebo analgesia.
Methods:Participants (placebo/control groups, N=49/53) underwent fMRI while receiving painful and non-painful electrical stimulation, or when observing another person being exposed to such stimulation. MVPA in MCC and AI was used to test representations of self- and other-directed stimulation (painful vs. non-painful), as well as common or distinct representations for self- and other-directed stimulation (self, painful vs. non-painful ↔ other, painful vs. non-painful).
Results: We found that MCC and AI representations of self-directed stimulation generalized to other-directed stimulation and vice versa in both groups. Self- and other-directed painful and non-painful stimulation could be dissociated in the control group, but this was not possible for other-directed stimulation in the placebo group.
Conclusions: While analysis is currently being finalized, initial results suggest common representations for pain empathy and self-pain in MCC and AI. However, placebo analgesia may reduce the specificity of multi-voxel patterns representing the affect of others.

2.17 Modulation of appetite by placebo interventions - a randomized controlled study

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Background: Imbalance of satiety and appetite plays an important role in our society, in which obesity is an increasing problem. Little is known about the effects of expectation on appetite. Therefore, we investigated the hypotheses that placebo interventions together with verbal suggestions alter subjective levels of appetite and its neurobiological correlates.
Methods: After a 15-min baseline period, 90 healthy participants were randomized to one of three groups: ‘enhanced appetite’, ‘enhanced satiety’, or ‘control’. All participants received a placebo capsule together with an expectancy manipulation according to group allocation. Behavioral data (hunger ratings on visual analogue scales), blood samples (the ‘hunger hormone’ ghrelin) and autonomic parameters (ECG, electrogastrogram/EGG) were obtained during baseline and 60 minutes after the intervention. Changes from baseline were evaluated by using ANOVAs with the between-subject factors “group” and “sex”.
Results: Evaluation of the behavioral data showed that the expectancy manipulation was effective in modulating the perception of hunger ($p<0.001$). Post hoc tests indicated lower hunger ratings in the group ‘enhanced satiety’ as compared to the groups ‘enhanced appetite ($p<.001$) and ‘control’ ($p=.052$). Preliminary analyses of plasma ghrelin samples in 24 female participants showed a decrease of ghrelin in the group ‘enhanced satiety’ as compared to the group ‘enhanced appetite’ ($p<.05$).
Discussion: Especially the satiety-enhancing expectancy manipulation was effective in modulating the perception of hunger. Appetite modulation in women was accompanied by changes of plasma ghrelin levels according to group allocation, suggesting modulation of physiological hunger correlates by treatment expectations.

2.18 Is there a role for implicit and explicit information about placebo and nocebo effects in reducing the use of drugs in sport?

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Background: The gateway hypothesis posits that the use of sport supplements by athletes can lead to the use of banned and possibly harmful performance-enhancing drugs. Previous data suggest that athletes implicitly exposed to a placebo intervention and/or explicitly informed about the role of placebo effects in sport may be less likely to use sports supplements, and therefore - in line with the gateway hypothesis - less likely to progress to drugs. Methods: Participants (n=629) completed the Sports Supplements Beliefs Scale (SSBS), Performance Enhancement Attitude Scale (PEAS) and a Likert-type scale measuring intention to use sports supplements. They were then randomised to Placebo (n=263), Nocebo (n=209) and Control (n=157). All participants completed a performance trial (see Hurst et al., this conference). Placebo and Nocebo participants subsequently received the results of the trial as well as a brief educational session describing the role of placebo/nocebo effects in sports performance. Controls received no information. All participants re-completed the questionnaires. Results: Analyses indicated that following the intervention, beliefs ($P=0.009$, Cohens d [d]=0.43), attitudes ($P=0.047$, $d=0.29$) and intentions ($P=0.020$, $d=0.33$) relating to the use of drugs and sport supplements were significantly lower in the Placebo and Nocebo group compared to Controls. Conclusions: Implicit exposure to a placebo/nocebo intervention and explicit exposure to a brief educational intervention about placebo effects influenced athlete’s beliefs, attitudes and intentions about drugs and sport supplements. Given the gateway hypothesis, experience of, or education about the placebo and nocebo effect may prevent athletes transitioning towards doping.

2.19 How expectations affect experience: Assimilation or contrast?

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Expectations can influence experience in two opposing ways. First, experiences often assimilate toward one's expectation, which is a key principle underlying placebo effects. However, several other literatures have reported the opposite effect: That experience is biased away from one's initial expectation. This has been referred to as a contrast effect. One plausible factor determining whether expectations produce assimilation or contrast is the discrepancy between expectation and reality - if this is too large, people may revise their expectation. We tested the hypothesis that small expectancy violations result in assimilation whereas large expectancy violation result in contrast effects on people's experience of loud noise. In two experiments, participants were conditioned to associate specific visual cues with either low- or high-intensity white-noise stimuli. In the subsequent test phase, both cues were followed by identical (intermediate-intensity) white noise, and we tested the cueing effect on participants' aversiveness ratings and skin-conductance responses to the noise. Importantly, during conditioning, we varied the difference between the low and high noise intensities across three groups of participants, resulting in low, medium, or large mismatches between expected and actual noise in the test phase. Inconsistent with the contrast hypothesis, aversiveness ratings in all groups assimilated toward the conditioned value of the cues. This effect was most robust in the group with the medium expectancy violation. Thus, even extreme expectancy violations did not produce a contrast effect in the paradigm we used. These findings may help explain why placebo responses can be so persistent.

2.20 To change or not to change? an experimental investigation on expectation change vs. expectation maintenance among individuals experiencing depressive symptoms

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Background: Recent research has suggested that psychological interventions aiming at modifying patients' dysfunctional expectations by confronting them with expectation-violating situations might lead to substantial symptom reduction (Craske et al., 2014). Clinical observations, however, suggest that patients tend to maintain their expectations despite expectation-violating experiences (Rief & Glombiewski, 2016). The present study aims to develop an experimental paradigm to investigate the hypothesized maintenance of expectations among individuals experiencing depressive symptoms.
Methods: We focus on expectations concerning personal achievement vs. failure, as these expectations are very common in major depression. In our paradigm, we initially induce negative expectations concerning personal achievement by confronting participants with an unknown test which is told to be very difficult. Then, participants perform the Test for the Measurement of Emotional Intelligence (TEMINT, Schmidt-Atzert & Bühner, 2002) and receive standardized performance feedback that can either confirm or disconfirm their prior expectation. It is examined in how far individuals change their generilzed expectation concerning personal achievement after receiving expectation-violating or expectation-confirming performance feedback. Participants are healthy controls and individuals diagnosed with major depression.
Results: Preliminary results indicate that healthy controls significantly change their expectations after expectation-violating performance feedback (F(40)=5,766; p=.021). The results concerning expectation change vs. expectation maintenance in individuals experiencing depressive symptoms can be provided until the conference.
Conclusion: The present study might provide an experimental paradigm to investigate the clinical observation that people suffering from major depression rather than healthy controls tend to maintain dysfunctional expectations despite contradictory experiences.

2.21 Attentional bias induced by expectancy manipulation of hunger and satiety

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Background: Due to limited capacity, our brain requires accelerated processing of pertinent stimuli to satisfy our actual needs as fast as possible. This bias of attention is important for physiological adjustments, but also plays a role for psychological diseases, such as eating disorders. The aim of this study was to investigate the effects of appetite modulating placebo interventions on the attentional bias (AB) for food-related stimuli.
Methods: This study was nested within a larger study investigating the effects of expectancy manipulation on hunger and satiety (Hoffmann et al., abstract submitted to SIPS). One hour after random allocation to either an appetite-enhancing or a satiety-enhancing placebo intervention, 41 healthy participants (20 female, 21 male) performed a visual-probe task (VPT) to assess AB for food-related stimuli. Task-specific reaction times (RT) for food-related and neutral stimuli at exposure durations of 100ms were compared between intervention groups. AB was defined as faster RT for food-related stimuli as compared to RT for neutral stimuli. The AB difference was evaluated using a two-factorial ANOVA with the between-subject factors "intervention" and "sex".
Results: Results revealed a significant interaction between "intervention" and "sex" (F=5.1, p=0.03). Post-hoc-tests confirmed an AB in the appetite-enhancing placebo group as compared to the satiety-enhancing group in females (F=5.5, p=0.03), but not in males (F=1.0, p=0.32).
Conclusion: Results indicate that selective attention to food-related stimuli can be modulated by treatment expectancies. This finding offers new approaches to the treatment of eating disorders.

2.22 A new animal model of placebo analgesia

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We suggest a new placebo analgesia animal model and investigated the role of the dopamine and opioid systems in placebo analgesia. Before and after the conditioning, we conducted a conditioned place preference (CPP) test to measure preferences for the cues (Rooms 1 and 2), and a hot plate test (HPT) to measure the pain responses to high level-pain after the cues. In addition, we quantified the expression of tyrosine hydroxylase (TH) in the ventral tegmental area (VTA) and c-Fos in the anterior cingulate cortex (ACC) as a response to reward learning and pain response. We found an enhanced preference for the low level-pain paired cue and enhanced TH expression in the VTA of the Placebo and Placebo + Naloxone groups. Haloperidol, a dopamine antagonist, blocked these effects in the Placebo + Haloperidol group. An increased pain threshold to high-heat pain and reduced c-Fos expression in the ACC were observed in the Placebo group only. Haloperidol blocked the place preference effect, and naloxone and haloperidol blocked the placebo analgesia. Cue preference is mediated by reward learning via the dopamine system, whereas the expression of placebo analgesia is mediated by the dopamine and opioid systems.

2.23 Psychiatric inpatients' perspectives on therapeutic moments - a qualitative study

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Psychiatric inpatients usually receive a multitude of psychopharmacological, psychotherapy as well as paramedical treatments, all of which have been subject to clinical trials and thus show effectiveness and efficacy. However, the mechanisms by which these therapies converge on patients and how these treatments are perceived by patients need to be explored, thus patients' idiosyncratic perspectives on healing moments are still lacking. Therefore, we performed qualitative assessments with patients in a specialist clinic.
Patients with depression, psychosomatic illnesses, obsessive and compulsive disorders, post-traumatic stress disorders, as well as addition and personality disorders were questioned before their exit from a specialist Swiss clinic. We used semistructured, open-ended questionnaires to explore patients' experiences. The questionnaire guide was designed to elicit patients' narratives of what was important and helpful for their treatment and which healing moments they remember. Statements regarding these aspects are currently qualitatively examined by computer-aided content analysis and results will be presented at the conference. Knowledge of healing moments in psychiatric and psychotherapy consultants can guide clinicians, health care providers, psychotherapists, and researches. Here, our findings highlight the importance of personalized healthcare and idiosyncratic perspectives on common factors.

2.24 What is wrong with the concept 'impure placebo'?

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The concept 'impure placebo' was introduced in the 1940s, but it has been used more widely in the context of placebo research in the past two decades. Traditional 'pure placebos' are clinically ineffective treatments, whereas 'impure placebos' form an ambiguous group of diverse treatments that are not always ineffective. According to several surveys, the use of 'impure placebos' is common for example in general practice.
The concept is, however, problematic, in three ways. First, 'impure placebo' is poorly defined. Second, the examples commonly given for 'impure placebos' are unsound and, in some cases, absurd from the point of view of clinical practice. To take just one example, positive suggestions in patient consultations is an example of 'impure placebo' in many surveys. Positive suggestions are, however, an important component of good doctoring and they should not be labelled as any kind of placebos. Third, there are methodological shortcomings in the surveys addressing the use of 'impure placebos'.
In my presentation I will examine these problems in detail and conclude that 'impure placebo' is a misleading concept and should not be used in scientific or medical literature. The issues behind the concept, however, deserve serious attention in future research.

2.25 Pharmacological conditioning in clinical populations: a comprehensive review

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Background: The (repeated) administration of a pharmacological agent can lead to the formation of cognitive associations between the agent and treatment effects. These associations, or conditioned effects, have been shown to either enhance pharmacological treatment strategies or to provide a way to achieve significant treatment effects on a lower dosage of active medication in various clinical populations. The aim of this review is to provide an overview of the current evidence on the effectiveness of pharmacological conditioning in clinical populations and to gain insight in the underlying psychophysiological mechanisms of pharmacological conditioning . This review will offer insight into the possibility to use conditioning paradigms as a way to optimize current treatment strategies in various clinical populations and into the optimal circumstances to establish conditioned treatment effects.
Methods: A literature search is conducted in the databases PubMed, Embase, and PsychInfo.

Findings: So far, 41 articles with pharmacological conditioning paradigms in various clinical populations have been identified. Of these articles, the majority found some form of a conditioned placebo effect. For instance, conditioned placebo responses were found in populations with Parkinson's disease, allergic rhinitis, atopic dermatitis, asthma, cancer, major depression, psoriasis, irritable bowel syndrome, and children with ADHD.
Discussion: This review provides insight in the possibilities and boundaries of pharmacological conditioning in clinical populations to either strengthen current pharmacological treatments or provide alternative treatment strategies for conditions that require long-term pharmacological treatment or require intensive treatments that come with considerable side effects in various clinical populations. Furthermore, this review provides determinants for optimal pharmacological conditioning application strategies.

2.26 Optimizing pharmacotherapeutic effects through pharmacological conditioning with or without an online health training: Study protocol

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Background: Implicit (conditioning) and explicit (health training) placebo learning mechanisms can enhance pharmacological treatment strategies in clinical conditions. Evidence indicates that these mechanisms are most effective when combined. Here, the effects of pharmacological conditioning and an online health training are investigated in a population of patients with rheumatoid arthritis (RA).
Methods: A multicenter randomized controlled trial is conducted in patients with recent-onset RA. Patients start on standardized pharmacological treatment. After four months, patients in clinical remission, are randomized to one of three groups: 1) the Control group continues with the standardized treatment, 2) the Pharmacological Conditioning group receives intermittent treatment (high doses of medication interchanged with low doses), and 3) the Pharmacological Conditioning & Health Training group receives intermittent treatment in combination with an online guided health training. When patients are still in clinical remission after eight months, treatment is tapered and discontinued linearly for group 1 and variably for groups 2 and 3. The primary outcome is the percentage of patients in clinical remission, 12 months after the start of the study. A follow-up takes place after 16 months.
Findings: Data collection started and is expected to be completed in the summer of 2019.
Discussion: For the first time, implicit and explicit learning mechanisms are investigated in RA. The ability to influence pharmacotherapeutic effects by means of psychological learning mechanisms could offer new therapeutic possibilities in the treatment of chronic diseases, and could provide insight in the underlying psychological and physiological mechanisms of these learning principles.

2.28 Suggestibility as a predictor of response to antidepressants: a preliminary prospective trial

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Background: The growing awareness that so many do not respond adequately to antidepressant (AD) pharmacotherapy has sparked research seeking to characterize those who do. While the pharmacological mechanisms of AD treatment have been extensively evaluated, much remains unknown about the placebo component of the response to medication. This study examined the association between suggestibility levels and response to ADs amongst depressed patients.
Methods: Twenty unipolar depression outpatients, recruited before starting AD monotherapy, received clear, standardized instructions that the therapeutic effects of AD, though not side effects, would require 2-4 weeks. At baseline (T1), 1 week (T2), and 1 month (T3), participants were evaluated for depressive symptoms, using the Hamilton Rating Scale for Depression 17-items (HAM-D); for anxiety by the Hamilton Rating Scale for Anxiety (HAM-A); for side effects by the Antidepressant Side Effect Checklist (ASEC); and for suggestibility, using the Multidimensional Iowa Suggestibility Scale (MISS).
Results: High levels of baseline suggestibility were associated with less improvement in depression level and more side-effects during the first week. In accordance with our hypothesis the more suggestible patients improved more between T2 and T3. No significant correlations were found between baseline suggestibility levels and change in anxiety. Small sample size and a self-report questionnaire assessing suggestibility were limitations.
Conclusion: This study offers a potentially new and clinically useful approach to understanding and predicting who will respond to AD treatment. Suggestibility seems to play a role, presumably by shaping expectation, in response to AD treatment. We hope that this avenue will be further explored.

2.29 Clinical assessment as therapy in medically unexplained symptoms

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Context: Although patients with medically unexplained symptoms (MUS) suffer from their symptoms and are functionally impaired, there seems to be a gap between what patients with MUS want and the care they actually receive. Effective and acceptable evidence-based treatment strategies in primary care are still lacking.

Objective: To develop an effective, acceptable and feasible treatment strategy for patients with MUS in primary care.
Design: Intervention Mapping (IM) approach: (1) innovative video consultation study in which patients and GPs observe and comment on their own video-recorded MUS consultation to identify relevant communication determinants, (2) focus group study with experts in the field of MUS and communication, GPs and patients to capture support needs, (3) developing MUS-specific communication intervention for GPs.
Intervention: Communication intervention for GPs in which the clinical assessment (i.e. history taking, physical examination, request of additional testing, explanation of what is wrong, and advice) of symptoms and non-specific therapeutic elements (such as expectations, positive communication, empathy and support) are captured.
Preliminary results: Qualitative research part: patients experience unpleasant feelings evoked by the GP, prejudgment of the GP, lack of empathy, limited understanding, lack of symptom management
Quantitative research part: although affect oriented communication reduces anxiety, affect oriented communication is limited in MUS
Linguistics research part: negatively loaded messages predict changes in patients' anxiety, GPs use more negatively loaded messages in MUS
Conclusion: The new intervention for MUS patients developed in close collaboration with MUS patients and GPs should focus of improvement with conscious use of non-specific elements as therapeutic agents.

2.31 Decreasing adverse information effects among MS patients: self-affirmation effects on cognitive performance

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The focus of the research is to find examine the role of information and patients expectations on their cognitive performance on a verbal learning task, and to test a self-affirmation intervention to reduce potential adverse information effects.
In total 341 MS patients were randomly assigned to three conditions; the information-only group (n=117); the information plus self-affirmation group (n=111); and the no-information control group (n=113). Patients in the information only group were informed about the relationship between MS and cognitive problems: patients in the information plus self-affirmation condition received the same information but filled out a kindness questionnaire before receiving this information, participants in the control group did not receive information about the relationship between MS and cognitive problems. Cognitive performance was measured with an adapted version of the Groningen Fifteen Word Test. Cognitive problem reporting was measured by six items of the MOS-scale (Medical Outcomes Study - scale, sub scale cognitive functioning (Stewart & Ware, 1992). Participants indicated on a 6-point Likert scale the frequency of experiencing cognitive problems. Patient expectations were assessed with items derived from the Perceived Sensitivity to Medicines Scale (Horner et al., 2013); the Revised Illness Perceptions Questionnaire (Moss-Morris et al., 2002); the Beliefs About Medicines Questionnaire (Horne, Weinman & Hankins, 1999); and the Modern Health Worries Scale (Petrie et al., 2001). Key patient and demographic characteristics were also assessed.
Findings showed that cognitive complaints and cognitive performance correlated moderately. Linear regression revealed that age, patients' lack of understanding of their illness, mood and self-affirmation predicted cognitive performance. Cognitive complaint reporting was predicted only by general complaints and mood.

2.32 Expected effectiveness of medication: The importance of route of administration and targeted symptom

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Background: Differential placebo effects and expectations have been found for different routes of medication administration (e.g., oral or topical). Comparisons of different routes are mostly indirect however, and research is generally limited to pain. In the current study, we directly compared the expected effectiveness of medication administered via three routes of administration for relieving pain and itch, and we additionally explored correlates of expected effectiveness.
Methods: We conducted an internet-based survey in a representative sample of the general Dutch population (n = 508). Respondents rated the expected effectiveness of medication administered via the oral, injection, and topical routes for relieving pain and itch. Additionally, expectations about other characteristics of the routes (e.g., side effects) and respondent characteristics (including demographic characteristics, health status, medication use and attitude, and personality characteristics) were measured.
Results: Respondents expected pain relieving medication to be most effective when administered via injection, while they expected itch relieving medication to be most effective when administered topically. Higher expectations of medication effectiveness were moderately associated with more positive expectations about onset and duration of effects, safety, and ease of use. Respondent characteristics were weakly or not significantly associated with expected medication effectiveness.
Conclusions: The expected effectiveness of pain and itch relieving medication depends not only on the route of administration, but also on the targeted symptom, and is associated most strongly with expectations about several other characteristics of the routes (onset, duration effects, safety, and ease of use).

2.33 Superstition predicts favorable weight change in an open-placebo trial: a prospective study

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Given the difficulty of losing weight via adhering to healthy lifestyle choices, this study sought to understand how a placebo may elicit favorable weight change. Specifically, we examined if superstition may be related to increased responsiveness to an open-placebo. In this pilot study of 25 undergraduate participants, it was hypothesized that individuals with higher levels of superstition may be more responsive to a 3-week open-placebo weight change trial. Participants were given once-daily saltine crackers to use as open-placebos for weight change in their preferred direction (gain or loss). The weight of each participant was measured before and after the 3-week open-placebo period. A Pearson's r correlation showed a significant positive relationship between superstition and placebo responsiveness, determined by weight gain or loss in the preferred direction, $r(25) = 0.493$, $p < 0.05$. We hope these preliminary results engender future research on open-placebo uses for weight management.

2.34 An argumentative review on the anthropological, social and proprioceptive benefits of thumb and dummy-sucking placebo habits, supporting children's right to do so

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Background: Although no one disputes fetal sucking as a natural human right, controversy remains on why children continue non-nutritive sucking, and whether the habit stimulates proprioceptive development. Available information on whether, how and when to stop children using non-nutritive sucking comes from popular misunderstandings, and weak evidence. Although Western countries deem non-nutritive sucking shameful in older children, parents usually permit it to soothe children, even if they feel guilty for allowing the habit to persist. Prompted by this conflicting evidence, we designed this review to seek additional information, including children's views, to extend current recommendations, and direct further research on the possible proprioceptive benefits of sucking.
Methods: In this argumentative review we synthesized the results obtained by multiple searching on empirical evidence and international guidelines, mapping quantitative and qualitative variables coded according to published results, including children's views, and physiological placebo benefits and risks.
Results: The review included about 40 papers and 4 guidelines. After non-nutritive sucking children's pain, crying-time, and sudden infant death syndrome incidence decreased, sleeping time lengthened, and proprioceptive development, including gait, improved. Risks included psychological shortfall, delayed language skills, and dental problems. Authoritative international guidelines worldwide recommend stopping sucking but reached no consensus on the appropriate age.
Conclusions Non-nutritive sucking placebo habits have clear benefits on life-threatening events and neuro-development. Even when children stop the habit at 5 years, no permanent dental problems ensue. Further studies using child-friendly methods to address children's emotional challenges will provide more reliable evidence on non-nutritive sucking habits and proprioceptive benefits.

2.35 Placebo, nocebo and contextual effect in nursing: do we need to rethink clinical care?

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Background: Placebo and nocebo represent complex and distinct psycho-neuro-biological phenomena in which behavioural and neurophysiological modifications occur with the application of a treatment. Despite a wide and an increasing number of evidence in the medical field, little is known about the impact of placebo and nocebo in nursing care. Aims of this review are to (a) describe the neurobiology and the psychological models underpinning placebo and nocebo mechanisms; (b) elucidate the role of the contextual factor in clinical nursing care and (c) debate the emerging research priorities.
Methods: In order to describe the state of the art, a narrative review was performed on articles extracted from three databases (Pubmed, Cinahl, Cochrane Library) in September 2016, without time limits. "Placebo effect", "Nocebo effect", "Contextual effect", "Expectation", "Conditioning", "Pain", "Nursing", "Nurses", "Nursing care", were combined by Booleans operators. Additional literature search was performed through the bibliography of the selected studies.
Results: Placebo and nocebo are sustained by specific neural networks mainly activated by mechanisms of conditioning and expectancy. Nurse's features and patient's features, patient-nurse relationship, characteristics of the treatment and overall healthcare setting are all contextual factors influencing nursing outcomes.
Conclusion: The efficacy of nursing care depends on the combined effect of specific and general contextual component of therapy. Nurses should manage the contextual factors as potentiation element of their intervention in order to improve placebo responses and avoid nocebo responses. More attention should be devoted to investigate the role of placebo, nocebo and contextual factors in nursing.

2.36 Placebo effect and focus of attention as a new strategy to modulate the motor performance

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Background: placebo effect and focus of attention represent strategies to influence motor performance. Despite interest in this field, literature is scant on the relationship between these two functions. The goal of this investigation was to analyse whether attentional focus and placebo procedure interact in modulating motor performance.
Methods: 60 healthy subjects were randomized in 4 groups: placebo internal focus of attention (PI), placebo external focus of attention (PE), control internal focus of attention (CI) and control external focus of attention (CE). Subjects performed a motor task by pressing a piston as strongly as possible with the right index finger. The PE and CE groups were instructed to "concentrate on the piston's movement"; the PI and CI groups were instructed to "concentrate on the finger's movement". The PE/PI groups were conditioned and verbally influenced that treatment with peripheral low-frequency transcutaneous electrical nerve stimulation (TENS) applied on the first dorsal interosseus would induce force enhancement. These groups were also conditioned after TENS application, with a surreptitious amplification of the visual feedback signalling the force level; the CE/CI groups instead, were told that TENS was not effective and they did not undergo the conditioning phase.
Results: The PE and PI groups reached higher levels of force, believed that TENS had been effective and expected to perform better compared with the CE and CI groups. The PI group presented higher force levels than the PE group.
Conclusion: These findings suggest that placebo effect in motor performance can be influenced by the subject's attentional focus.

2.37 Conditioning the neuroendocrine system: A systematic review.

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Substantial research has been done in the field of classical conditioning of physical responses such as immune responses and drug effects, but only a limited number of studies investigated classical conditioning of endocrine responses. The present paper is the first review that integrates evidence from both animal and human trials regarding the possibility to classically condition the endocrine system. The electronic bibliographic databases PsychINFO, PubMed, Embase and CINAHL were searched to identify the studies. Two main lines of classical conditioning designs were found: studies that used a two-phase conditioning design and studies that investigated anticipatory hormone release. The most well-researched hormonal systems are the insulin-glucose system and the hypothalamic-pituitary-adrenal axis, and evidence also exists for the reproductive and circadian systems. Animal and human studies show strikingly consistent results and demonstrate that it is possible to modify hormonal levels using the mechanisms of classical conditioning. Next to methodological recommendations for future studies, we suggest several ways to use classically conditioned endocrine responses in the clinical practice: in placebo-controlled dose reduction, enhancement of treatment favorable endocrine parameters and reduction of unfavorable conditioned endocrine responses.

2.38 Pain relief following placebo manipulations in neuropathic pain patients is related to expectancy and desire but possibly not to release of endogenous dopamine

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Background: Placebo effects can be obtained in neuropathic pain patients and expected pain levels and desire for pain relief, which are central elements of motivation, have been shown to contribute to the observed pain relief. As both motivation and placebo effects have been related to the dopaminergic system, it can be speculated whether placebo effects in neuropathic pain are mediated by the dopaminergic system. Method: Nineteen patients with neuropathic pain caused by thoracic surgery were exposed to a placebo manipulation where they received open and hidden administration of the pain relieving agent lidocaine (2 mL) as well as no treatment. The dopamine antagonist haloperidol (2 mg) and agonist levodopa/carbidopa (100/25 mg) were administered to test the involvement of the dopaminergic system. Expected pain levels and desire for pain relief as well as ongoing and stimulus-evoked pain were assessed on 0-10 Visual Analogue Scales. Results: Large and significant placebo effects were observed in ongoing ($p \leq .003$) and stimulus-evoked neuropathic pain ($p \leq .002$). Expected pain levels and desire for pain relief significantly predicted the pain reduction following open application of lidocaine ($p \leq .033$) but administration of haloperidol and levodopa/carbidopa did not affect the pain levels ($p > .05$). Conclusion: This study demonstrates that expectancy and desire contribute to the pain relief following placebo manipulations in neuropathic pain patients; yet, the dopaminergic system does not seem to be involved in this type of placebo effect. In future studies, it will be important to further test if other neurotransmitter systems are involved in placebo effects in neuropathic pain.

2.39 Verbal suggestions in voluntary joystick movement paradigm - factors influencing formation and magnitude of the placebo effect

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Background: The voluntary joystick movement paradigm (VMJP) is used to experimentally study the process of maintenance of chronic musculoskeletal pain. In this paradigm conditioned fear of movement-related pain and contextual pain-related anxiety are induced by using predictable and unpredictable painful stimuli respectively. The modification of the VMJP allowed us to investigate whether the placebo effect could be induced by verbal suggestions in those two conditions and how those two negative emotional states influence its magnitude.
Methods: A total of 56 female volunteers were asked to move the joystick in the direction pointed by an arrow and rate painful sensation on the Numerical Rating Scale. Two experimental and two control groups were tested (N=14 each). In predictable pain condition, the participants always received electric stimuli after completing one of the movements (right or left). In unpredictable condition, movements of the joystick were not related to the application of electric stimuli. In experimental groups the participants were informed that after one of the light colours (red or green) less painful stimuli would be delivered. In control groups such information was not provided. Either green or red colour acted as a placebo and as a control stimulus. The participants were not aware that they were receiving electric stimuli of the same intensity.
Results: It was found that placebo analgesia can be induced by verbal suggestions in predictable rather than unpredictable pain condition.
Conclusions: It is concluded that conditioned fear of movement-related pain rather then pain-related anxiety may influence induction of placebo effect.

2.40 Development of the General Attitude towards Medication Questionnaire (GAMQ)

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Background: Attitudes and beliefs about the effectiveness and side effects of medication can affect treatment adherence and outcomes. Measuring general attitudes towards medication is, therefore, important in understanding the factors that predict treatment adherence and outcomes and also has implications for research on placebo and nocebo effects. Patient's attitudes and beliefs towards medication are often assessed by self-report scales such as the Beliefs about Medication Questionnaire (BMQ), focusing on general beliefs about the harmfulness of medication and doctor's over-prescription of medication, and the Pain Medication Attitude Questionnaire (PMAQ) for attitudes towards pain medication. Methods: To assess both negative and positive attitudes and beliefs regardless of the targeted symptom, we developed the General Attitude towards Medication Questionnaire (GAMQ). This self-report questionnaire consists of 12 items rated on a 5-point Likert Scale. The GAMQ was validated in a representative sample of 508 Dutch volunteers as well as in a sample of patients with Rheumatoid Arthritis and a sample of patients with Atopic Dermatitis. Results: Preliminary factor analyses revealed three subscales that represent "trust in medication", "concerns about medication" and "reluctance to use medication". Furthermore, both total scores and the individual subscales showed good to acceptable internal consistency and good convergent validity, as reflected in moderate to high correlations with the BMQ. Discussion: These first results suggest that the GAMQ is suitable for assessing general medication attitudes in a wide variety of research and clinical settings.

2.41 Conditioning cortisol levels in humans: design and pilot study

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Background: Conditioning of physiological reactions can be achieved by repeatedly pairing a previously neutral conditioned stimulus (CS) with the administration of a pharmacologically salient unconditioned stimulus (UCS). This type of conditioning has been shown to be effective for immune and blood sugar responses, but results with regard to conditioning of cortisol levels are currently unclear. Method: A double-blind randomized controlled conditioning paradigm aimed at conditioning of cortisol levels was pilot-tested in ten healthy female participants. During the acquisition phase, the olfactory conditioned stimulus was paired with hydrocortisone (100 mg, capsulated, unconditioned stimulus) three times before being administered together with placebo during three evocation sessions in the subsequent week. During the third evocation session a validated short-term psychosocial stress task was applied to explore conditioning effects under stress. Results: Next to demonstrating feasibility of the design, indications of possible conditioning effects were found on salivary cortisol under basal conditions during the first and second evocation session, and on cortisol, and negative affect in response to a validated short-term psychosocial stress task during the third evocation session. Conclusion: These results provide further preliminary indications that cortisol levels can be conditioned and that conditioning of cortisol levels might affect the psychophysiological response to stress. Replications in larger studies are needed to enable more solid conclusions.

2.42 More Cartesian than Descartes: mind-body relations and the need for an ethical theory of patient agency

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In placebo studies, it is common to place some blame for our surprise at or overdue acceptance of the reality of placebo effects on the inheritance of Cartesian dualism. This is right and wrong in different respects. This is not a matter of mere historical interest, but is instructive for our thinking about placebo effects where those effects may be openly invoked. Descartes' study of the emotions and his ethico-medical regimen for cultivating some emotions but not others culminates in a prescription for neo-Stoicism. His metaphysics and the ethic they generate render that picture of healthy character untenable. However, the example is instructive if we see that failure as an urgent call for, if not that ethical theory, than some other. This paper is an invitation for philosophers and other researchers to collaborate in crafting a vision for the ethical agency of patients, and some criteria are offered for choosing between and among existing theories, with a view to devising one specialized for placebo studies.

2.43 The role of the dorsolateral prefrontal cortex in the motor placebo effect: a tDCS study.

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Knowledge on the brain regions involved in the motor placebo effect is still scant. Some evidence hints at the involvement of the primary motor cortex, but whether other brain areas are involved is unknown. One key area in the placebo effect is the dorsolateral prefrontal cortex (DLPFC), which is involved in higher-order cognitive functions, like expectation, and has been found to be activated in placebo-induced analgesia. The aim of our study is to investigate the role of this area in the motor placebo effect. To this purpose, we applied transcranial direct current stimulation (tDCS) over the left DLPFC during a placebo procedure.
Seventeen healthy volunteers received anodal, cathodal and sham stimulation over left DLPFC during the whole motor placebo procedure. Subjects performed a motor task by pressing as strongly as possible a piston with the right index finger. We applied an inert treatment to the first dorsal interosseous with peripheral low-frequency transcutaneous electrical nerve stimulation (TENS) and subjects were informed that this treatment would induce force enhancement. Moreover, subjects were conditioned about the effects of TENS with a surreptitious increase of the visual feedback signaling the level of force.
Subject showed stronger force levels at the end of the placebo procedure. This confirms that the paradigm was suitable to induce a placebo effect in motor performance. However, the type of tDCS stimulation (anodal, cathodal, sham) did not modify the level of force.
In conclusion, it appears that tDCS over the left DLPFC does not influence the motor placebo effect.

2.44 Facial pain expression induces nocebo hyperalgesia

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Nocebo hyperalgesia can be induced by social observation of a model who uses verbal pain ratings to report increased pain following an inert treatment. It is unknown whether such a nocebo hyperalgesia can also be induced by ecologically more realistic stimuli such as facial pain expressions and whether the model's pain coping competence influences the acquisition of nocebo hyperalgesia.
Eighty female participants (age: 22.4 ± 4.8) watched one of four videos. In a first part of the video, a conversation with a female model was shown, who reported either high (C+) or low pain coping competence (C-). In a second part, the model underwent a pressure-pain application and through her facial expression either demonstrated increased pain after the application of an ointment (N+) or remained neutral (N-). After the video, the participants were subjected to the same pressure-pain procedure. They received an ointment on one hand, but no explanation concerning it. Pain was rated on an 11-point numerical rating scale. A 2 x 2 x 2 ANOVA with the between-factors pain coping competence (C+/C-) and nocebo induction (N+/N-) and the within-factor ointment (with/without) revealed an interaction for nocebo induction x ointment, but no effect of model competence. Combining the N+ conditions, the pain ratings with ointment were higher than without the ointment.
Nocebo hyperalgesia was induced by watching a model demonstrating pain through facial expressions alone. This has implications for a number of settings in daily life, like in clinical settings or for the transmission of pain-related beliefs in families.

2.45 Colour as a placebo? The effect of colour on pain perception

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Background: Research shows that colours could have an effect on pain perception, however this area needs further investigation - especially since colours have been widely used in placebo studies, in colour light paradigm. The aim of two studies was to investigate whether colours have an impact on pain perception and what is the mechanism of the influence of colours on pain.
Methods: In both studies, participants received electric pain stimuli of the same intensity preceded by one of the six different colour lights (red, green, orange, blue, pink or yellow) or blank slide which served as a control condition. In the first study, the intensity of experienced pain was measured and in the second study, both experienced and expected pain were measured.

Results: The studies revealed that colours increased the intensity of experienced pain in comparison to non-colour condition (blank slide), regardless of the sex of the subject or the fact that a participant noticed a relationship between colour of the lights and pain intensity. Particularly, participants rated pain stimuli preceded by red lights as being more painful compared to other colours, especially green and blue lights. Expectations were found to predict the effect of colours on the experienced pain intensity.
Conclusions: It is concluded that colours have an impact on pain perception and that expectations play a significant role in the effect of colours on pain. Our results have important implication for colour light paradigm applied in the studies on the placebo effects.

2.46 Changing Expectation for Acupuncture Treatment (CHEAT)

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Background: Expectations about treatment effects can alter treatment outcomes and information about treatment benefits might change expectations about treatment efficacy. Methods: In this web-based study we randomly informed subjects in two different ways about the benefits of acupuncture: In the high expectation group (HEG) the subjects were told that acupuncture leads to a substantial decrease in symptoms in about 50% of cases. In the low expectation group (LEG) the participants were told, that about half of the patients get better but the specific effect of acupuncture is still unclear. Subjects were included if they remembered the message of the intervention adequately, provided information about their pain status and if the intervention time was sufficient long. The success of the intervention was assessed via manipulation check and the Expectation for Acupuncture Treatment (EAT) scale was the primary outcome. Results: Of 369 subjects 244 met the criteria and were included in the analysis (having pain n=78; HEG n=33, LEG n=45, having no pain n=166; HEG n=86, LEG n=80). For pain patients expectation did not differ between HEG and LEG (p>.60). For healthy subjects expectation differed between HEG and LEG (p=.02) with a robust effect even after controlling for sex, age, earlier acupuncture experience, and health status. Conclusion: Information about treatment effects might be a powerful tool for a broader audience, but patients with pain might not change their expectation after reading information about potential benefits of treatment. High dose interventions with boosters over the course of the treatment might have more effect.

2.47 How treatment history and route of administration shape treatment expectations and outcomes

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Experimental and clinical studies indicate that prior treatment failure can hamper the response to subsequent treatments. In principle, changing the Route of Administration (RoA) of a drug might reduce such psychological effects of treatment history, but evidence is lacking so far. Here we investigated the effect of treatment history on subsequent treatment outcome and whether these effects can be modulated by RoA changes in a between-group design. In six sub-studies with a total of 211 healthy volunteers, positive or negative treatment experiences with topical analgesic treatments were induced experimentally in a mock clinical trial setting. Over two days, the presence or absence of a treatment effect was simulated experimentally. On a third day, a novel inert drug was introduced in either topical or oral form and its analgesic efficacy was tested. The results corroborate that a negative treatment history significantly decreases the analgesic efficacy of a novel drug. Moreover, changing the RoA effectively modulated treatment expectations but not treatment outcomes, indicating that learned nocebo effects can generalize across RoAs — independent of conscious expectations. Thus, changing the RoA may be useful to influence patients' treatment expectations, but insufficient to modulate the impact of treatment history on analgesic treatment outcome. This study highlights the impact of individual treatment history on future outcomes and the need for systematic strategies to counteract the effects of prior treatment failure.

2.48 Can placebo be distinguished from active treatment - when the results at first sight look similar

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2) Department of Orthopaedic surgery, Elverum Hospital, Elverum, NA, Norway
3) Coordinating Research Unit, Frederiksberg Hospital, Frederiksberg, NA, Denmark

Background. Meta-analysis indicate a positive placebo responder rate of 50% in osteoarthritis, indicating that such patients can "benefit" from placebo. This study aimed to search for new methodologies to distinguish placebo from active treatment.
Methods: 120 patients were included in a 3 month randomized clinical trial in which 60 volunteers received active treatment (Rosa canina) subtype Lito 2.5 g daily and 60 patient received placebo. Pain and activity of daily living was estimated using the WOMAC score system and the initial scores were compared to the score after three month. In addition a correlation test: change in symptom score vs the weight of patient was made separately for the active as well as for the placebo treated group.
Results: A highly significant improvement, irrespective of treatment, was observed for pain (p<0.02) and for daily activity (p<0.01). The positive response rate was above 60% in each group with no significant difference comparing groups. Placebo was "proven" as effective as active treatment. However, correlation analysis, weight vs symptom score, revealed a significant negative correlation between weight and symptom score of pain (0.020) and of physical function (p<0.004). The less the patient`s weight the more pronounced the reduction in symptom score. No correlation was demonstrated during placebo.

Conclusion: The present data indicate that if active treatment and placebo at first sight looks similar, it may be possible to learn more and distinguish between two treatment groups by applying a correlation analysis weight vs symptom score. Placebo will not demonstrate any “dose-dependency”.

2.49 Study design using open-label placebo for food craving control

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Cravings are often conceptualized as intense urges or desires that thwart human will power to control drug or food consumption. Medications have been developed to curtail cravings and appetite, however the use of such medications is controversial. Open-label placebos (i.e., non-active pills taken without deception nor blind conditions) can produce symptom relief in randomized clinical trials (RCT). These findings raise the question if open-label placebo could present a safer alternative to food craving control medication. This study will attempt to replicate the finding that food satiation following a 12h fasting period reduces state food cravings, and compare this satiation-effect to two placebo conditions, deceptive-label and open-label instructions in a non-clinical sample of fasting college students.

2.50 Placebo and the Quantified Self

Uwe Heiss[1]
1) Healthcare Activist, South Burlington, Vermont, United States

Self-Tracking of mainly behavior, but also of outcomes and treatments has gained momentum in the general population and is finding its way into conventional care (Patient Reported Outcomes). Enabled by apps and wearable devices, the value of the Quantified Self (QS) is based on the promise to offer insight into personal trends, patterns, and correlations to identify “what works” for our health and well-being. Longitudinal QS graphs and analyses aim to support patient-provider communication and joint decision making. The QS phenomenon raises the question in how far the act of self-tracking solicits a placebo response, possibly mediated by providing patients with a more active role and sense of control. Self-tracking tools and methods further appear to be good candidates for the broad implementation of N-of-1 study designs in regular care delivery, allowing for the systematic, individual evaluation of placebo next to conventional treatments. This poster describes the journey of an early leader of the QS movement from pioneering self-tracking to supporting open-label placebo interventions.

2.51 Network analysis of the genomic basis of the placebo effect

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2) Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

The placebo effect is a phenomenon in which patients who are given an inactive treatment (e.g., inert pill) show a perceived or actual improvement in a medical condition. Placebo effects in clinical trials have been investigated for many years. Recent observations suggest that placebo effects may be modified by genetics. This observation gives rise to the term, “placebome,” which refers to a group of genome-related mediators that affect an individual’s response to placebo treatments. In this study, we conduct a network analysis of the placebome and identify a placebome module in the comprehensive human interactome using a seed-connector algorithm. The placebome module is significantly enriched with neurotransmitter signaling pathways and brain-specific proteins. We validate the placebome module using a large cohort of the Women’s Genome Health Study (WGHS) trial and demonstrate that the placebome module is significantly enriched with genes whose SNPs modify the outcome in the placebo arm of the trial. To gain insights into placebo effects in different diseases and drug treatments, we use a network proximity measure to examine the closeness of the placebome module to different disease modules and drug categories. The results demonstrate that the network proximity of the placebome module to disease modules in the interactome significantly correlates with the strength of the placebo effect in the corresponding diseases. The proximity of the placebome module to molecular pathways affected by certain drug classes indicates the existence of placebo-drug interactions. This study is helpful for understanding the molecular mechanisms mediating the placebo response, and sets the stage for minimizing its effects in clinical trials and for developing therapeutic strategies that intentionally engage it.

2.52 The placebo effect: an 'unconscious' model

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2) Cyclotron Research Center and Department of Neurology, Sart Tilman Liège University Hospital, Liege, Belgium
3) Program in Placebo Studies and Therapeutic Encounter Institution: Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, United States

Purpose: In a broad sense, placebo effects are improvements in patient’s symptoms that are attributable to their participation and interaction with the therapeutic environment; moreover, conscious expectations of treatment play a significant role in the occurrence of this phenomenon. The objective of this study is to expose a group of patients using a neuromodulation technique, to explore the presence of placebo effects on subjects with impaired conscious state. In this study, cerebral cortical areas will be stimulated via transcranial direct current stimulation (tDCS) in patients with disorders of consciousness (DOC) following severe brain injury. Methods: 35 patients in vegetative or minimally conscious state will be enrolled and evaluated using the following tools: (i) Coma Recovery Scale Revised (CRS-R); (ii) electroencephalography (EEG) at rest, as well as during active and passive tasks; and (iii) heart rate variability at rest and during passive task.

These measurements will be performed before and after tDCS (20 min; 2mA). Patients will receive 3 sessions, one for baseline measurements, one active tDCS and one sham tDCS, in a randomized order.
Conclusions: DOC represent a clinical valuable model to evaluate whether cortical functions are needed to present placebo effects or not. Expectation to treatment is considered to be an executive function organized at higher cortical level, by attempting to modulate the cortex via tDCS we expect to see some improvements in our measurements, conversely, if subjects exposed to sham stimulation present measurable improvements, an alternative explanation must be generated in order to explain the placebo effect.

2.53 EACH: International Association for Communication in Healthcare

Evelyn van Weel-Baumgarten[1], Evelyn van Weel-Baumgarten[2]
1) EACH: International Association for Communication in Healthcare, Salisbur, United Kingdom
2) Radboud University Medical Center, Department of Primary and Community Care 121, Nijmegen, the Netherlands

Background: EACH, founded in 2001 as a European Association with the overall aim to promote effective evidence-based patient-centred healthcare communication between patients, relatives and healthcare practitioners throughout the world has officially become International in 2016. Methods: To achieve its aims the association uses a variety of strategies and activities are overseen by three major subcommittees: tEACH, pEACH and rEACH, focusing on teaching, policy&practice, and research respectively. EACH: organises major international conferences on health care communication research, and teaching. The next one will be in Porto, Portugal 2-5 September 2018; provides workshops, courses and meetings every year on specific research and teaching components of healthcare communication, for example our unique workshop based Summer Event September 4-6 2017 London, UK; provides a website www.each.eu to raise awareness and share related resources on teaching and research with the wider community of healthcare practitioners, researchers, teachers and patients; is affiliated with a scientific journal, Patient Education and Counselling, to disseminate results of research on health care communication; carries out site visits to countries without established health care communication research and teaching programmes to help establish networks, and train teachers and researchers; promotes best practice in health care communication to other local and national organisations through a subcommittee dedicated to practice and policy issues: pEACH; collaborates with existing networks and associations, with similar purposes, for example with SIPS. Conclusion: To continue its development and increase its impact EACH hopes you will support us and become members too.

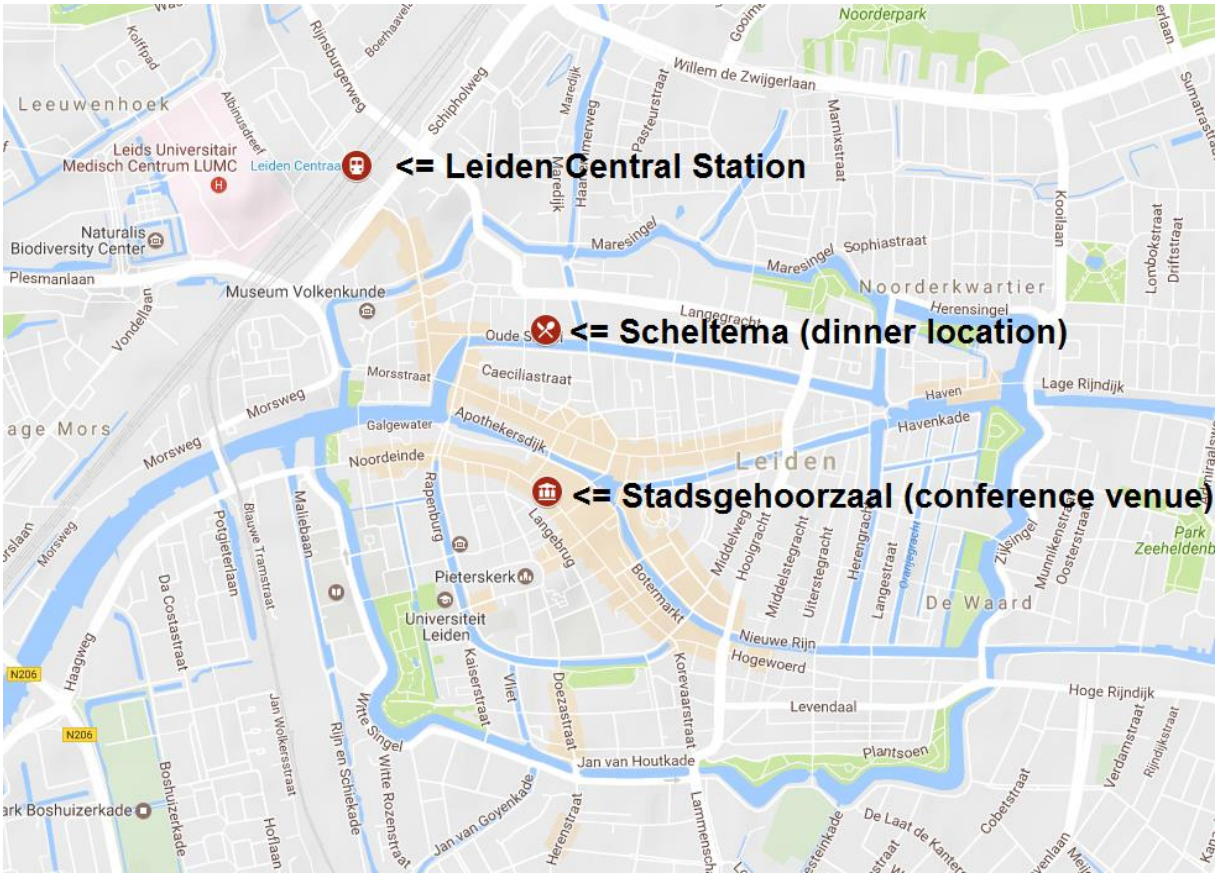
Practicalities

WiFi Passwords

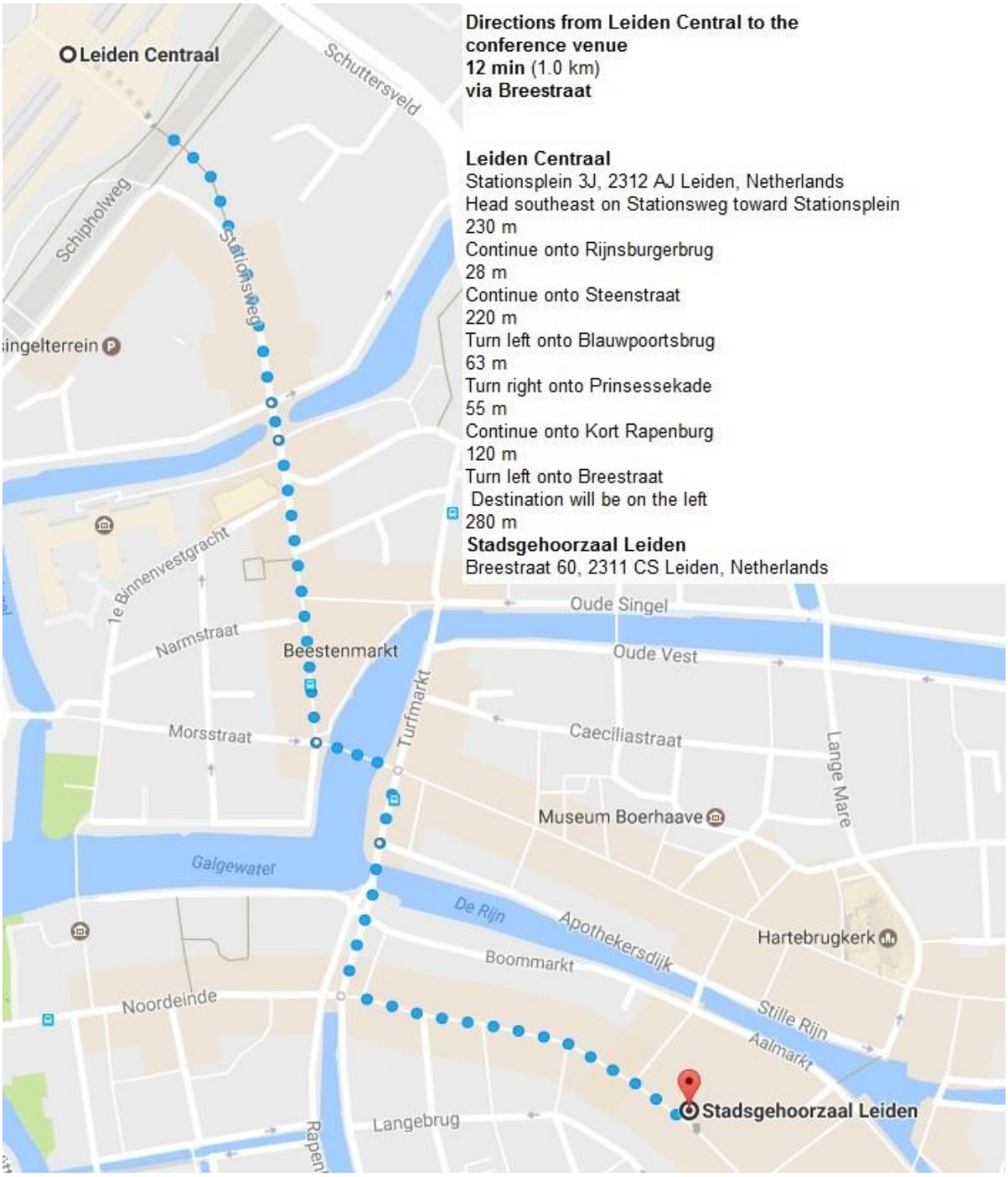
WiFi Password	Address
Stadsgehoorzaal (conference venue)	Network name: leidseschouwburg-stadsgehoorzaal Password: Applaus!

Address overview

Location	Address
Stadsgehoorzaal (conference venue)	Breestraat 60 2311 CS Leiden
Scheltema (dinner location)	Marktsteeg 1 2312 CS Leiden
Leiden Central Station	Stationsplein 3J 2312 AJ Leiden

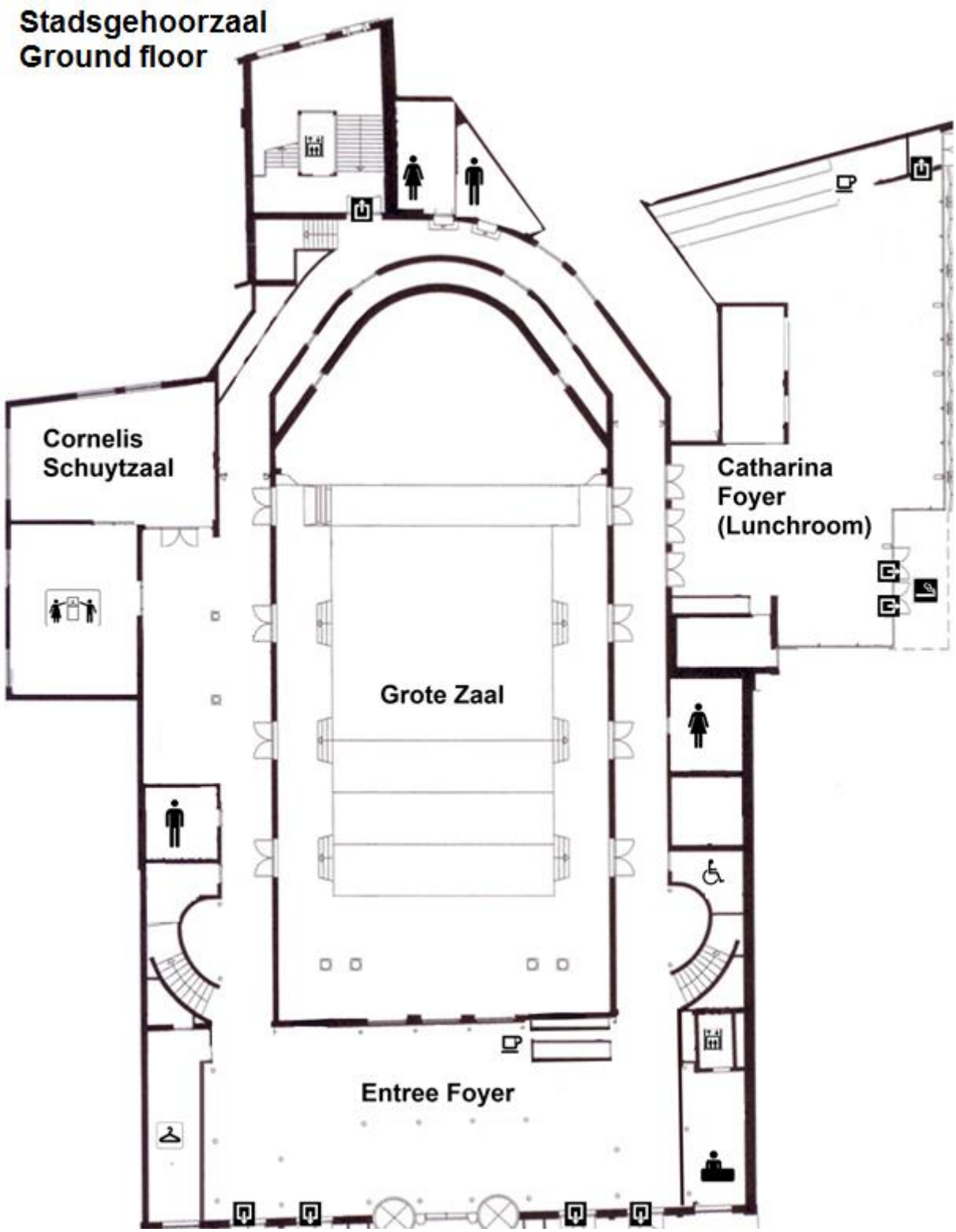


Leiden Central to Stadsgehoorzaal

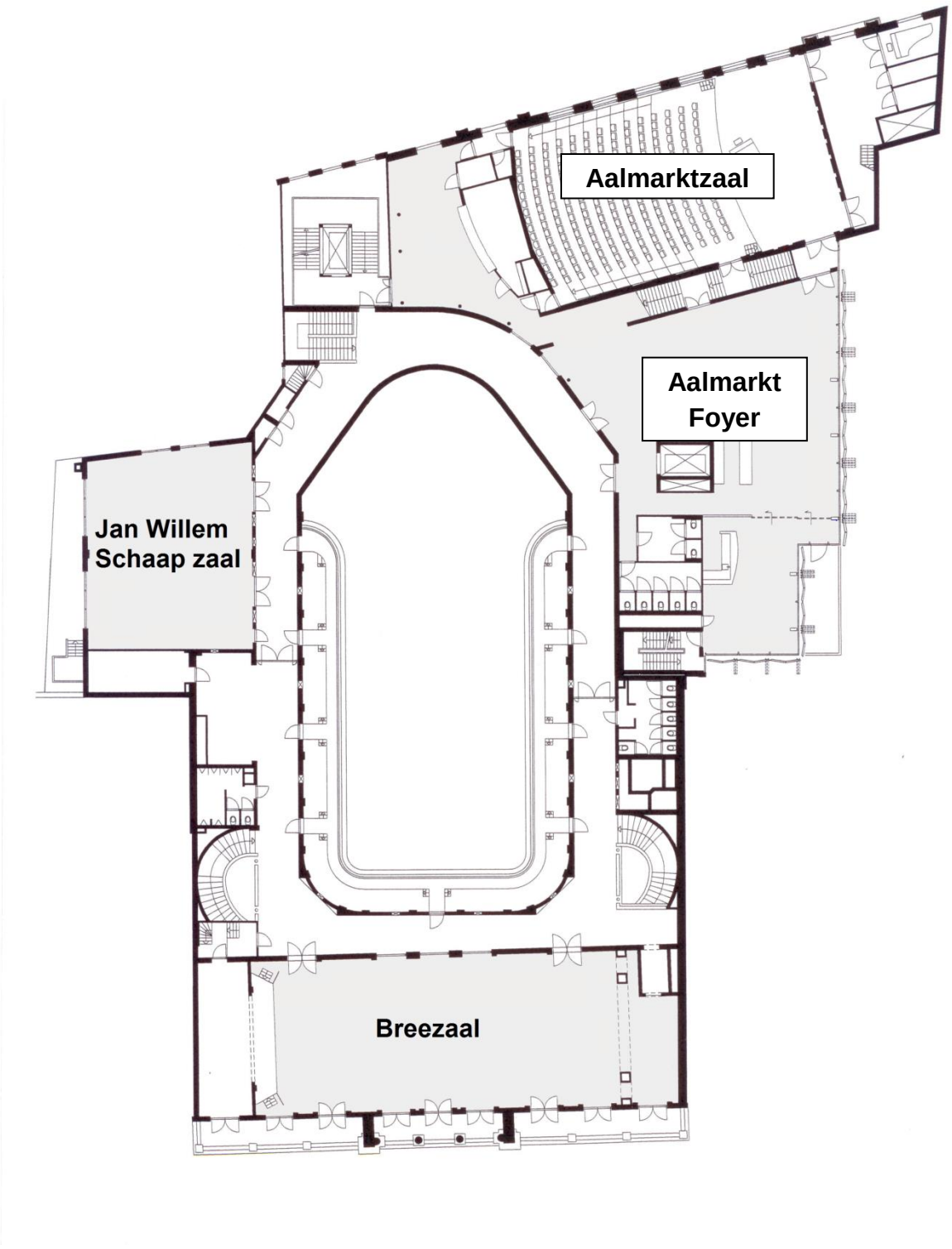


Directions from Leiden Central to the conference venue
12 min (1.0 km)
via Breestraat

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
First floor



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