

4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER ABSTRACT BOOKLET

4th International Conference

of the Society for Interdisciplinary Placebo Studies (SIPS)

10 – 13 May, 2023 – Meet us in Duisburg, Germany

sips-conference.com





POSTER SESSION I

001	Investigating the role of multisensory sensitivity in chronic back pain Alina Panzel	p. 12
002	Agency in Placebo/Nocebo Pain Treatment and the Bayesian Pain Model Andreas Strube	p. 13
003	Implicitly or explicitly induced placebo effects – that is the question Annelie Claudia Meis	р. 14
004	Reduced activity in the left putamen preceding painful stimulation is associated with behavioural placebo analgesia: results from an individual participant data meta-analysis Balint Kincses	p. 15
005	The role of dopaminergic neurotransmission for positive treatment expectations and placebo analgesia Clara Erfurt	p. 16
006	A cream which makes the "boo boo" better: An experimental investigating of placebo hypoalgesia in kindergarten children Elisa Kamper-Fuhrmann	p. 17
007	Does Negative Expectancy Learning Influence Pain-Related Avoidance Behavior? An Experimental Investigation Gita Nadinda	p. 18
008	Does conditioned pain-related fear relate to nocebo hyperalgesia in patients with chronic pain? Hanna Öhlmann	p. 19
009	Positive and negative treatment expectations and their effects on pain: magnitude and stability over time Jens-Lennart Sperzel	p. 20
010	Neural mechanisms underlying the effects of positive and negative expectation on pain Maren-Isabel Wolf	p. 21
011	Merely Possessing a Placebo Analgesic With High (vs. Low) Perceived Self-connection Enhances Pain Resilience Rose Sze-Ki Ng	p. 22
012	Therapy expectations in interdisciplinary multimodal pain therapy for chronic pain patients Claudia G Levenig	p. 23
013	Active Placebos increase Treatment Expectation and Placebo Analgesia Lieven Schenk	p. 24
014	The role of anxiety in nocebo hyperalgesia Elif Buse Caliskan	p. 25





015	The association between personality or genetics and responsiveness to placebo effects – A RCT. Hans van Lennep	p. 26
016	Baseline heart rate variability as predictor for placebo hypoalgesia Marian van der Meulen	p. 27
017	Pain reduction as a reward. Development of a new experimental paradigm to study operant conditioning as a mechanism of placebo hypoalgesia Helena Bieniek	p. 28
018	Development of an objective measure of pain perception accuracy to predict differences in susceptibility to placebo analgesia Christopher Milde	p. 29
019	Fear and anxiety as traits and states in placebo effects in pain: A model summarizing the state-of-the-art Daryna Rubanets	p. 30
020	Performance and confidence in pain perception accuracy predict less placebo hypoalgesia Laura Sophie Brinskelle	p. 31
021	Applying placebo-induced expectancies to emotion regulation Roni Shafir	p. 32
022	A Bayesian account for the placebo and nocebo phenomena: The role of pain expectancy and its confidence. Eleonora Maria Camerone	p. 33
023	The placebo effect facilitates cortical excitability before movement onset Miriam Braga	p. 34
024	Can functional neurological disorder be explained by nocebo-like mechanisms? Evidence for a theoretical proposal Mirta Fiorio	p. 35
025	Testing a novel procedure to induce placebo anxiolysis in healthy volunteers Nathan Huneke	p. 36
026	Placebo and nocebo responses to dietary challenge in irritable bowel syndrome: Protocol for a double-blind, placebo-controlled, crossover trial Heidi Staudacher	p. 37
027	Placebolomics; Breath Metabolomics of Placebo Effects Melina Richard	p. 38
028	Placebo and Nocebo Effects as Bayesian- Brain Phenomena: The Overlooked Role of Likelihood and Attention Francesco Pagnini	p. 39





029	Placebo induced expectations of mood enhancement generate a positivity effect in emotional processing Jonas Rauh	p. 40
030	Placebo analgesia is primarily related to brain systems involved in motivation and value, not nociceptive pain Rotem Botvinik-Nezer	p. 41
031	Context re-exposure fails to elicit conditioned sickness responses in a contextual learning paradigm in rats Lisa Trautmann	p. 42
032	Taste-Immune Conditioning with Fingolimod (FTY720) as an Unconditioned Stimulus Marie Jakobs	p. 43
033	Taste-associative learning to induce behaviorally conditioned analgesia in an animal model of inflammatory pain Stephan Leisengang	p. 44
034	Conditioned Placebo Responses in Allergic Contact Dermatitis Yasmin Salem	p. 45
035	Optimizing expectations leads to enhanced efficacy of a mindfulness- based intervention in persons with low-baseline expectations: A randomized control trial Stefan Salzmann	p. 46
036	Ambulatory assessment of expectations and pain disability in women with endometriosis Ann-Katrin Meyrose	p. 47
037	Preoperative Expectations in Women with Endometriosis. Baseline results of a clinical mixed-method cohort study Nina Hirsing	p. 48
038	The Influence of Preoperative Mood and Treatment Expectations on Early Postsurgical Acute Pain After a Total Knee Replacement Julia Stuhlreyer	p. 49
039	What do US orthopaedic surgeons think about placebo-controlled surgical trials? Michael H. Bernstein	p. 50
040	Treating students suffering from procrastination with imaginary pills Nadja Heimgartner	p. 51
041	What our failure to define placebos tells us about the nature of medicine Dien Ho	p. 52
042	Is light touch an effective sham for randomized controlled trials on osteopathic manipulative treatment? Mahima Mangla	p. 53





043	Placebo and nocebo effects on experimental and clinical pain in neurodegenerative disorders Johanne Marie Berg Thøgersen	p. 54
044	My pain is your pain? The effects of (psycho)pharmacological pain manipulations on social emotions and behavior - a systematic literature review Helena Hartmann, Philipp Dammann	p. 55
045	Treatment expectation and observational learning: Systematic review of observationally induced placebo and nocebo responses Helena Klauß	p. 56
046	Can heightenedstate empathy amplify placebo and nocebo effects elicited through the observation of others? Stefanie Meeuwis	p. 57
047	EEG responses in socially-acquired pain modulation Nicolas McNair	p. 58
048	Exploring the effect of interpersonal synchrony on socially-transmitted nocebo hyperalgesia Kirsten Barnes	p. 59
049	Religiosity is related to expectation but not placebo effects Rachel L. Cundiff-O'Sullivan	p. 60
050	Placebo effects in Cannabidiol (CBD) treatment of psychological distress in stressed students at risk for depression: The role of treatment expectation. Alexander Winkler	p. 61
051	Placebo Response and media attention in randomized clinical trials assessing cannabis-based therapies for pain: A systematic review and meta-analysis Filip Gedin	p. 62
052	Can placebo and nocebo effects influence a weight loss in adults? A systematic review and meta-analysis, Julia Badzińska	p. 63
053	I may get sick: Impact of negative treatment context on pain-related fear extinction in placebo-treated participants in RCT Robert Jan Pawlik	p. 64
054	Placebo Effects in war, weather, pest control and olympic sport. Colin Brewer	p. 65
055	Want to be fit? Start with your mind! The role of the placebo effect in physical fitness in children: a systematic review and meta-analysis Magdalena Żegleń	p. 66





- 056 **Perception and use of contextual factors in eliciting placebo and nocebo effects: an online survey of health professionals from French-speaking countries in Europe** David Newell
- 057 An International Consensus Definition for Contextual Factors: Findings p. 67 from a Nominal Group Technique David Newell





POSTER SESSION II

057	The good doctor? Greater negative treatment expectations and anxiety correlate with lower perceived physician warmth and empathy Jana L. Aulenkamp	p. 69
058	A systematic review and meta-analysis of the placebo response in randomized, double-blind, placebocontrolled trials of ketamine and esketamin in the treatment of major depressive disorder. Alexandros Matsingos	p. 70
059	Can antidepressant treatment effects be predicted by patients' responsiveness to expectation manipulation? Eun Jin Shim	p. 71
060	What helps and what hinders antidepressant discontinuation? Qualitative analysis of patients' experiences and expectations Carina Meißner, Ann Katrin Meyrose, Yvonne Nestoriuc	p. 72
061	Nocebo side effects in open-heart surgery: A randomized clinical trial Mette Sieg	p. 73
062	What Factors Shape Expectations Towards Antidepressant Discontinuation?: A Cross-Sectional Study Claire Warren	p. 74
063	Harnessing healthcare providers' behavior to improve health outcomes: protocol of an experimental, controlled, and randomized study Julie Lasselin	p. 75
064	Persistence and enhancement of an active placebo protection spray preventing sadness Marcel Wilhelm	p. 76
065	"Special Needs by Placebo": Programme to Advise, Normalize And Control its European Administration (PANACEA) Katia Mattarozzi	p. 77
066	Placebo prescriptions among GPs in 21 countries: the PURE study Fabian Wolters	p. 78
067	Discontinuation of Fumaric Acid Esters is Influenced by Depressive Symptomatology – A Retrospective Analysis of Patient Records Frederik Krefting	p. 79
068	Capacity to consent and treatment expectations: reliability of a newly adapted interview for psychotherapy Sönke Ladwig	p. 80
069	Exploring how patients with Parkinson´s disease experience and understand their pain: a qualitative study Andrea Sondergaard Poulsen, Sophie RosenkJaer	p. 81

7





070	Perceived and objective measures of stress and their associations with pain and placebo analgesia: preliminary results from chronic back pain patients Adi Shani	p. 82
071	Nocebo effects and placebo response in patients with MDD receiving OLP-Treatment Alexandros Matsingos	p. 83
072	Virtual Reality communication training for optimizing placebo and minimizing nocebo effects Janine Westendorp	p. 84
073	Can antidepressant treatment effects be predicted by patients' responsiveness to expectation manipulation? Eun Jin Shim	p. 85
074	Worth a try – Attitudes towards open-label placebos among laypeople and healthcare professionals Diana Müßgens	p. 86
075	Not a magic pill – Evidence of absence for cognitive enhancement aftera three-week open-label placebo treatment in healthy young adults Helena Hartmann	p. 87
076	Open-label-placebo effects in adolescents: An experimental investigation of placebo effects on sadness Alannah Hahn	p. 88
077	Can expectation management and open label placebos improve treatment outcome after gluten exposition in patients with pain? Lena Paschke	p. 89
078	Effects of open-label placebos and pilates on primary dysmenorrhea – a randomized controlled pilot study Sandra Ort	p. 90
079	Open-label placebos and paced breathing in patients with functional post-COVID syndrome Katja Weimer	p. 91
080	Open-label placebos - A systematic review and meta-analysis of experimental studies with non-clinical samples Stefan Schmidt	p. 92
081	Patients' beliefs and expectations regarding the efficacy of open label placebo and hypnosis for chronic neuropathic pain Fernandez Aurore	p. 93
082	Patients' Attitudes Towards Open-Label Placebo Implementation into Clinical Practice (PATOLP) Berfin Bakis	p. 94
083	Placebo effects after disclosure: the role of self-efficacy Diletta Barbiani	p. 95





084	lt's All in Your Mind: A qualitative study on open-label placebo and imaginary pills in test anxiety Berfin Bakis	p. 96
085	Observational learning in open label placebos and the role of expecation in chronic pain patients Marie Schwartz	p. 97
086	Impact of a 12-week open-label placebo treatment on headache days in episodic and chronic migraine Katharina Schmidt	p. 98
087	The case for Open Label Placebo Claudia Carvalho	p. 99
088	Implicit and explicit expectations of side effects caused by COVID-19 and flu vaccinations Anna E. Borgmann	p. 100
089	Emergency presentations due to headache after media coverage of SARS-CoV2- vaccination-associated cerebral venous or sinus thromboses in a tertiary emergency department in Essen, Germany Livia Asan	p. 101
090	Is the electrogastrogram (EGG) a suitable psychophysiological measure of nocebo effects in the gut-brain axis? Rossitza Draganova	p. 102
091	(Open label) placebo effects on sleep quality, sleep duration, appetite and food cue reactivity Jonas Potthoff	p. 103
092	Interindividual differences in anhedonia moderate antidepressant placebo effects on heart rate in healthy individuals. Li-Ching Chuang	p. 104
093	Generalization of placebo and nocebo effects: a narrative review Lingling Weng	p. 105
094	Difference in responsiveness to experimentally-induced nocebo hyperalgesia in fibromyalgia patients versus healthy controls Merve Karacaoglu	p. 106
095	Magnitudes and predictors of placebo analgesia responses in pharmacological and non-pharmacological trials: A meta-analysis of individual patient data Sigrid Juhl Lunde	p. 107
096	Amplified gut feelings under inflammation and negative mood: A randomized fMRI trial on nocebo effects in a model of interoceptive pain Sven Benson	p. 108

9





097	Cognitive control of pain in Aging – comparison of different pain modulation strategies Angelika Dierolf	p. 109
098	Neuroticism and low Extraversion show small associations with side- effect Expectations Anton Fischer	p. 110
099	Predicting Placebo: Brain Structural Signatures in Placebo Responders with Temporomandibular Disorder Jewel White	p. 111
100	Potential nocebo effects in primary dysmenorrhea - a mixed-methods approach Verena Thomann	p. 112
101	Influencing insulin system by placebo effect in patients with diabetes type-2 and healthy controls Aleksandrina Skvortsova	p. 113
102	Placebo Analgesia in Aging – the Impact of age-related cognitive decline Angelika Dierolf	p. 114
103	What to do about nocebo effects: can we reduce them via (open-label) counterconditioning or extinction? Simone Meijer	p. 115
104	Mindset interventions to facilitate taking cold showers: A randomized controlled study Emil Nissen	p. 116
105	Feasibility of using counterconditioning for reducing nocebo effects in chronic pain patients Simone Meijer	p. 117
106	Placebo/Nocebo research in the post-GWAS era: A narrative review Takeshi Watanabe	p. 118
107	Open-Label Placebo Treatment for Experimental Pain: A Randomized- Controlled Trial with Placebo Acupuncture and Placebo Pills Seoyoung Lee	p. 119

Poster Session I

Thursday, 11 May 13:00 – 14:30 Machine Foyer





Investigating the role of multisensory sensitivity in chronic back pain

Alina Panzel

Centralized chronic pain conditions commonly display multisensory sensitivity (MSS); the heightened sensitivity to non-painful stimuli. Which processing streams underly MSS, and if neural underpinnings are shared across centralized pain conditions, remains unknown. We designed a neuroimaging study investigating 142 patients with chronic back pain (CBP) during an aversive sound and mechanical pressure pain paradigm. To identify the neural substrates of MSS in CBP, we conducted a Region of Interest (ROI) analysis in primary sensory, sensory-integrative, and self-referential areas, and applied multivariate patterns of stimulus-specific (sound, pressure) and generalized negative affect. To test if MSS is shared across centralized pain conditions, we applied a multivariate classifier trained on multisensory stimulation in fibromyalgia to CPB patient data. ROI responses to aversive auditory stimuli for CBP vs. controls revealed hyperactivity in the primary auditory and insular cortex and hypoactivation of the medial prefrontal cortex. Multivariate pattern analysis revealed increased stimulus-specific and generalized negative affect processing and increased fibromyalgia MSS classifier values for CBP vs. controls. Together, these findings suggest that MSS-related evoked brain responses in CBP are shared with other centralized pain conditions, like fibromyalgia, and reflect both increased stimulusspecific and generalized negative affect processing.





Agency in Placebo/Nocebo Pain Treatment and the Bayesian Pain Model

Andreas Strube

The Bayesian pain model has been successful in explaining treatment effects of placebo hypoalgesia and nocebo hyperalgesia, but it is unclear how other contextual factors like agency interact with placebo/nocebo expectations and how this can be represented in this model. In the Bayesian pain model, somatosensation (likelihood) and expectations (prior) are weighted by their precision and integrated to form a pain percept (posterior). In this study, heat pain was sham-treated either externally or by the subject, while a predictive cue was used to create placebo or nocebo treatment expectations. The results showed additive effects of agency and placebo expectations, i.e. a greater pain relief was achieved under self-treatment, and under placebo treatment expectations. Formal model comparisons favored models that allowed for a shift in the likelihood or prior mean by agency, rather than differences in likelihood or prior precision. Electroencephalography revealed an effect associated with an interaction of expectations and agency, which was also correlated with trialby-trial pain ratings. This effect was found to be temporally associated with expectations, indicating that a shift in expectations rather than somatosensation is the mechanism through which agency can be implemented in the Bayesian pain model.







Implicitly or explicitly induced placebo effects – that is the question

Annelie Claudia Meis

Background: Both explicit and implicit expectations, e.g. acquired by conditioning combined with suggestions, are known to induce placebo hypoalgesia. Interestingly, it is unclear whether implicit conditioning without verbal suggestion yields placebo hypoalgesia, especially when a clinically convincing (yet sham) TENS apparatus is used. Since subjective measures are prone to many biases like the Hawthorne effect, it seems promising to also obtain physiological measures (e.g., facial EMG, SCL, heart rate). Healthy participants were either explicity instructed about the analgesic effect of the TENS apparatus turned on or were told the device might influence body perception. During conditioning, stimulus intensity was reduced when the TENS device was activated (LED on). Subjective pain intensity was rated, heart rate, EMG and SCL were recorded continuously. We obtained a conditioned placebo effect for pain self-report in the implicit (d = 0.47) and explicit (d = 0.61) condition. Analysis of the physiological responses is ongoing. Placebo hypoalgesia can be induced implicitly using a sham medical device, yet it is less robust. It will be crucial to demonstrate whether the physiological measures show a corresponding pattern. Clinically, implicit conditioning may either boost or counteract treatment expectation based on verbal suggestion.





Reduced activity in the left putamen preceding painful stimulation is associated with behavioural placebo analgesia: results from an individual participant data meta-analysis

Balint Kincses

Uncovering the underlying mechanisms of placebo effects is key to systematically targeting and harnessing them in clinical scenarios. While neural correlates of the placebo analgesia during painful stimulation have been widely investigated, relatively little is known regarding anticipatory responses during the expectancy of analgesia before stimulation is applied.

Here we capitalize on the data trove of the Placebo Imaging Consortium, which has collected individual participant level neuroimaging data from over eight hundred participants. We used individual activation maps during pain anticipation in placebo and control conditions. Using a voxel level generic inverse variance approach, correlations between placebo related brain activity changes and individual's behavioural placebo analgesic response were calculated.

We found a significant behavioural analgesic effect of placebo intervention with a medium effect size (Hedge's g: -0.63). This effect was correlated with decreased activity in the left putamen in the phase preceding painful stimulation (p < 0.05, FWER corrected). We also observed a subthreshold positive correlation between bilateral DLPFC (p<0.05, uncorrected) and behavioural analgesia. The striatum has been previously associated with pain-related expectation and placebo analgesia, but further investigation is needed to explore its role in placebo analgesia.





The role of dopaminergic neurotransmission for treatment expectations and placebo analgesia

Clara Erfurt

Dopaminergic neurotransmission has been previously linked to placebo analgesia. However, the distinct role of dopamine in the acquisition of positive treatment expectations and their analgesic effects on pain is not fully understood. This study aims to shed light on the role of dopamine in the acquisition of positive treatment expectations and its influence on pain perception by manipulating dopaminergic signaling during the conditioning phase of an established placebo analgesia heat pain paradigm. To this end, 165 healthy volunteers will be randomized to either receive a single oral dose of sulpiride, levodopa or an inactive control pill in a double-blind, randomized, controlled trial using a between-subject design.

The expectation of analgesia and its effect on experimental pain perception is assessed in two test sessions, with the second test session being conducted six days later to check the persistence of the analgesic response. We expect that the dopaminergic manipulation during the conditioning phase modulates treatment expectation as well as the magnitude and persistence of the analgesic response. A better understanding of the neurochemical mechanisms of placebo responses promises to systematically target the placebo component of active analgesic treatments and thereby improve treatment outcomes.





A cream which makes the "boo boo" better: An experimental investigation of placebo hypoalgesia in kindergarten children

Elisa Kamper-Fuhrmann

Little is known about expectations in treatment effects of young children. Kindergarten children might be especially prone to expectancy-based placebo effects, as they are particularly susceptible to suggestions. We aimed at investigating verbally-induced placebo hypoalgesia in children aged 3-6.

In one group (N=58) a placebo vs. active control, in the other group (N=59) a placebo vs. natural history condition were compared. Heat pain tolerance (using a simplified method-of-limits) and pain self-report (Simplified-FPS) were assessed. Child characteristics (e.g. temperament) as potential determinants were assessed by the mother.

We found a significant placebo effect for pain tolerance (placebo vs. natural history: d=.31, vs. active control: d=.72), but not for pain self-report. Optimism, shyness and negative affect were identified as significant predictors.

Our findings suggest that in young children behavioral pain measures and selfreport do not necessarily match, possibly due to the limited validity of self-report measures in this age. The difference in magnitude of placebo effect depending on the control condition underlines the role of contextual effects potentially being crucial in this age. Interestingly and in line with contextual effects, shyness emerged as predictor of placebo hypoalgesia.





Does negative expectancy learning influence pain-related avoidance behavior? An experimental investigation

Gita Nadinda

Dopaminergic neurotransmission has been previously linked to placebo analgesia. However, the distinct role of dopamine in the acquisition of positive treatment expectations and their analgesic effects on pain is not fully understood. This study aims to shed light on the role of dopamine in the acquisition of positive treatment expectations and its influence on pain perception by manipulating dopaminergic signaling during the conditioning phase of an established placebo analgesia heat pain paradigm. To this end, 165 healthy volunteers will be randomized to either receive a single oral dose of sulpiride, levodopa or an inactive control pill in a double-blind, randomized, controlled trial using a between-subject design.

The expectation of analgesia and its effect on experimental pain perception is assessed in two test sessions, with the second test session being conducted six days later to check the persistence of the analgesic response. We expect that the dopaminergic manipulation during the conditioning phase modulates treatment expectation as well as the magnitude and persistence of the analgesic response. A better understanding of the neurochemical mechanisms of placebo responses promises to systematically target the placebo component of active analgesic treatments and thereby improve treatment outcomes.





Does conditioned pain-related fear relate to nocebo hyperalgesia in patients with chronic pain?

Hanna Öhlmann

Background: Although the induction of negative expectations by learning is particularly relevant in patients experiencing recurring pain, classically conditioned fear was never studied in the context of nocebo responses in patients with chronic pain. Using a 2-day fear conditioning paradigm, acquisition and extinction of fear responses to visual cues predicting pain (acute thermal pain on abdominal wall) or an equally aversive tone were assessed in patients with inflammatory bowel disease (IBD; N=22) and healthy controls (HC; N=22). On day 2, responses to re-exposure to pain were tested. Groups did not differ in conditioned fear or pain perception during acquisition. During re-exposure, IBD reported greater perceived pain intensity (PPI; t(42)=-2.13, p=.039, d=.64) and fear of pain (FOP; t(42)=-2.05, p=.046, d=.62) than HC, and the magnitude of learning correlated with PPI (R=.45, p=.035) and FOP (R=.52, p=.013) in IBD.

Results were partially specific for pain-related conditioning. Pain-related fear acquired by associative learning relates to enhanced pain perception during reexposure to pain in patients with chronic pain, and might therefore contribute to nocebo effects, with implications for treatment.





Positive and negative treatment expectations and their effects on pain: magnitude and stability over time

Jens-Lennart Sperzel

Previous studies hardly allow a direct comparison between the mechanisms underlying placebo and nocebo effects on pain. In particular, very little is known regarding common and distinct mechanisms and potentially different temporal dynamics of the effects of positive and negative treatment expectations on pain, also referred to as placebo analgesia and nocebo hyperalgesia. Here we investigated the magnitude and persistence of placebo analgesia and nocebo hyperalgesia using a within-subject design in healthy volunteers. Analgesic or hyperalgesic expectations towards a sham treatment were induced by a conditioning procedure in combination with verbal instructions. The effects of positive and negative treatment expectation on experimental heat pain stimuli were tested immediately following conditioning and after seven days. Based on the preliminary results we show that placebo and nocebo effects can be induced using a within subject design and that these responses persist over time. Data acquisition and analyses are ongoing. At the SIPS meeting we will present potential differences in the magnitude and persistence of placebo analgesia and nocebo hyperalgesia, as well as the association with person-related state and trait factors.







Neural mechanisms underlying the effects of positive and negative expectation on pain

Maren-Isabel Wolf

Pain perception can be influenced by expectations. Studies showed that neural activity reflects pain-related expectations in the anticipation phase prior to the application of painful stimuli, but the exact timing and localization of these effects remain unclear. To test the neural mechanisms underlying the effects of expectation generation, we examined 47 participants in a combined EEG-fMRIstudy. Positive, negative, or no expectations were induced by verbal instructions and a conditioning procedure of differently colored visual stimuli on a trial-by-trial basis using a sham-BCI. In each trial, participants were presented with heat pain stimuli at an individually calibrated fixed target intensity. EEG and fMRI data as well as expectation and pain ratings were collected for each trial. The expectation manipulation procedure proved to be effective, as participants reported higher expected and actual pain in the negative compared to the positive expectation condition. Over all participants, there was a strong correlation of single-trial expectations with subsequent pain ratings. Neural correlates of expectations in the anticipation phase were found e.g. in the right amygdala and the posterior insula. These results show that it is possible to modulate expectations and pain perception using a sham-BCI.







Merely possessing a placebo analgesic with high (vs. low) perceived self-connection enhances pain resilience

Rose Ng

Previous study found merely possessing a placebo analgesic cream has similar pain outcomes with using a placebo analgesic cream, but the underlying mechanism is unclear (Yeung et al., 2020). We demonstrated a possessionbased placebo effect existed and observed how self-object association affects pain outcome. The 126 healthy adults were randomly assigned to either the experimental (EXP) conditions (EXP1: possessed a placebo analgesic cream with high self-object connection; EXP2: possessed a placebo analgesic cream with low self-object connection) or control (CO) conditions (CO1: possessed a pain-irrelevant cream; CO2: no-possession). In EXP1, participants received a placebo analgesic cream which was labelled their own name and they were asked to write about the importance of this cream to them. In EXP2, participants received a placebo analgesic cream which was labelled the other participant's name, and they were required to write how the given analgesic cream is useless to them. All participants completed a cold pressor test. Participants in EXP1 showed significantly better pain outcomes (longer pain tolerance and higher pain threshold) than the other three conditions.









Therapy expectations in interdisciplinary multimodal pain therapy for chronic pain patients

Claudia G Levenig

The role of treatment expectations (TE) in treatment outcomes of interdisciplinary multimodal pain (IMPT) therapy for chronic low back pain (CLBP) remains incompletely understood. 200 patients (68.5% female, 60.23+12.99 years) with CLBP undergoing an IMPT filled in questionnaires at three measuring points. To investigate the influence of TE on pain and disability, we conducted analyses of (co-)variance with repeated measures. The predictive value of TE for changes within pain outcomes was investigated by regression analyses. Analyses revealed a significant "group x time" interaction (F(3.78,258.88)=2.86,p<.05). Patients with high TE showed significantly less pain after therapy compared to patients with moderate (SMD 6.07, p<.05;SMD 8.33, p<.05) and low (SMD 9.73, p<.01; SMD 11.99, p<.01) TE, and further, significantly less disability (adjusted for depression and pain), indicating that patients with high TE were less disabled than patients with low TE at follow-up. We found an explained variation of 15% for TE adjusted for depression regarding pain intensity and 20% regarding disability. Treatment expectations contribute to interindividual variability in outcomes, paving the way for optimized therapy approaches.







24

POSTER SESSION I

Active placebos increase treatment expectations and placebo analgesia

Lieven Schenk

Treatment expectation effects can be augmented by vividly perceiving the treatment. Here we ask the question whether negative side effects during a sham treatment (i.e. active placebos) can improve treatment expectation effects. A 2x2 design with the factor expectancy and side effect (nasal spray with capsaicin/ without capsaicin) was employed. During the experiment, participants received nasal sprays with the belief that 50% contain pain relief medication before receiving thermal pain stimuli that were rated on a VAS scale. During the initial reinforcement phase when all participants expected the possibility of a real pain relief treatment, we observed a significant main effect of capsaicin, indicating that participants report less pain when the nasal sprays had a noticeable side effect. During the subsequent test phase, when only half of the participants expected a real pain relief treatment, we observed a significant interaction. Only the pain relief expectancy group showed less pain when a side effect was experienced as compared to the no-expectancy group. Together, this shows that even negative side effects (e.g. burning feeling) can increase treatment expectation effects, which is highly relevant for randomized clinical trials. Future analyses will focus on acquired fMRI data.







The role of anxiety in nocebo hyperalgesia

Elif Buse Caliskan

Nocebo hyperalgesia is defined by increased pain perception in response to negative treatment expectations. Pain related anxiety, induced by negative treatment expectations, has been shown to facilitate pain transmission and thereby contribute to nocebo hyperalgesia. Midazolam, a commonly used anxiolytic in clinical practice, can reduce anxiety levels of patients and may therefore mitigate nocebo hyperalgesia and nocebo-related effects. This study aims to investigate impact of a single dose of midazolam on pain related and general state anxiety, their effects on treatment expectation and pain perception in healthy volunteers undergoing Cold Pressor Task.

Negative treatment expectations are induced by a sham infusion introduced as "the opioid antagonist naloxone that can increase an individual's pain sensitivity". Further aims of the study comprise potential psychometric predictors of nocebo hyperalgesia and neuroendocrine markers of stress. Our findings suggest that our nocebo treatment has successfully induced negative treatment expectations, but without increasing anxiety levels of participants. Also, no significant nocebo hyperalgesic effect was observed. We will discuss methodological peculiarities that may have contributed to these unexpected results and implications for future developments of the experimental design that will hopefully allow to further elucidate anxiety's role in clinical effects of negative treatment expectations.





The association between personality or genetics and responsiveness to placebo effects - A randomized controlled trial.

Hans van Lennep

This study investigated placebo responsiveness and its association with personality traits (optimism, neuroticism, worrying, empathy, and somatosensory amplification) or three single nucleotide polymorphisms (SNPs) on genes involved in pain and expectations (OPRM-1, COMT, and FAAH).

208 healthy participants were randomized across 1 of 8 conditions in which placebo analgesia in heat pain was induced with different manipulation combinations (verbal suggestions, classical conditioning, social learning) or none (control). Personality traits were studied with the Life Orientation Test–Revised (LOT-R), Eysenck Personality Questionnaire (EPQ), Penn-State Worry Questionnaire (PSWQ), Interpersonal Reactivity Index (IRI), and the Somatosensory Amplification Scale (SSAS). The three different SNPs were examined by collecting saliva cells and analyzing DNA with next generation sequencing.

None of the personality traits were significant moderators of the association between learning and placebo analgesia, all p > 0.05. The DNA analysis is currently finalized and the results regarding the association of the three SNPs with placebo responsiveness is available by January 2023. Placebo responsiveness does not seem to be predicted by optimism, neuroticism, worrying, empathy or somatosensory amplification.





Baseline heart rate variability as a predictor for placebo hypoalgesia

Marian van der Meulen

Placebo hypoalgesic effects vary greatly across individuals, making them challenging to control for in clinical trials and difficult to use in treatment. There is an urgent need for the identification of reliable predictors of placebo responsiveness. We investigated resting vagally-mediated heart rate variability (vmHRV) as a potential predictor of placebo hypoalgesia, and explored whether sex would moderate the association. 77 participants took part in two independent studies (Study I: n=36; Study II: n=41). In both studies, we first measured resting HRV and then administered a placebo paradigm. In Study I, we delivered heat pain stimuli to the forearm, on skin treated with 'real' analgesic and 'control' cream (identical inactive creams). In Study II, electrical pulses to the forearm were modulated by sham transcutaneous electrical nerve stimulation. In both studies, we found a significant overall placebo effect. Importantly, both studies also revealed a significant positive association between vmHRV and the placebo effect size. However, this effect was driven mainly by men. These results support the potential of developing vmHRV as a non-invasive, easily obtained predictor for placebo hypoalgesia. Further studies are necessary to extend these first results and explain the sex differences found.







Pain reduction as a reward. Development of a new experimental paradigm to study operant conditioning as a mechanism of placebo hypoalgesia

Helena Bieniek

Placebo hypoalgesia (PH) is considered a learning phenomenon. Many studies have shown that it can be induced by classical conditioning, observational learning and verbal suggestions. However, recently another learning process, operant conditioning, has gained some attention as a few studies attempted to use an operant conditioning paradigm to induce PH. The aim of the presentation is to compare the existing methodologies examining operant conditioning in PH as well as proposing a new paradigm to study PH induced by operant conditioning. To achieve this aim, we compared the methodology of existing studies which aimed at implementing any kind of operant paradigm to induce PH. We analyzed and compared those studies regarding whether their methodologies 1) implemented operant conditioning and included all three necessary elements of the process (antecedent, behavior, consequence), 2) contained any type of a placebo intervention, 3) were relevant to placebo use in clinical practice. Next, based on those conclusions, we underwent a process of developing a new operant conditioning paradigm in inducing PH. During the presentation, every step of that process will be discussed.

To conclude, the proposed new paradigm seems to induce PH in pain in accordance with operant conditioning principles with good clinical relevance.





Development of an objective measure of pain perception accuracy to predict differences in susceptibility to placebo analgesia

Christopher Milde

Background: Recent computational models emphasize the predictive role of pain perception accuracy (PPA) in placebo analgesia. The Focused Analgesia Selection Test (FAST) was developed to assess PPA by estimating reliability in pain intensity ratings to repeated heat pain stimuli. However, the FAST comprises temperatures frequently perceived as nonpainful (e.g., 43 °C) or maximum tolerable (e.g., 51 °C), leading to floor and ceiling effects in pain ratings. We tested an optimized FAST paradigm using stimulation temperatures adjusted to the individuals' pain range to derive a valid measure of PPA.The optimized FAST was conducted with 7 temperatures evenly located between the individuals' pain and tolerance threshold. Reliability in pain perception (PPA) was assessed by presenting these temperatures in 7 randomized sequences.

Variance was constant between the highest and lowest and the central stimulation intensities. Furthermore, pain and tolerance thresholds were not related to PPA. Constant variance in pain ratings across stimulation temperatures and absence of correlations between psychophysical thresholds and PPA indicate that our PPA measure was not affected by floor or ceiling effects. An individually tailored FAST thus offers more objective PPA measures, which can be used as predictors of placebo analgesia.





Fear and anxiety as traits and states in placebo effects in pain: A model summarizing the state-of-the-art

Daryna Rubanets

Background:

Pain-related expectancy is proven to be the mechanism underlying the placebo hypoalgesia and nocebo hyperalgesia, much less is known about the role of affective traits and states. Even though the involvement of fear and anxiety in the formation of placebo effects was confirmed in several studies, they provided mixed results. We aimed to summarize the current state-of-the-art in the field of studies and theoretical models on the role of fear and anxiety in placebo effects in pain. A narrative review.

Concepts of fear and anxiety overlapped in some research works. Most previous studies intended to assess fear and anxiety as additional measures. Little research was focused on the experimental manipulation of fear and anxiety and their influence on the magnitude of placebo effects in pain.More attention should be drawn to the definitions of fear and anxiety in future works. We propose a theoretical model summarizing the research findings and theoretical advances with the differentiation of fear and anxiety as states and traits. The model's implications for clinical practice and experimental studies are discussed.

Study was funded by National Science Centre in Poland (grant no.2020/39/B/ HS6/03551)





Performance and confidence in pain perception accuracy predict less placebo hypoalgesia

Laura Sophie Brinskelle

Individuals largely vary in their susceptibility to placebo manipulations. Recent computational models emphasize that perceiving and interpreting bodily processes predicts placebo effects. We propose that placebo hypoalgesia results from a perceptual weighting of the confidence in an analgesic effect and the confidence and objective performance in judging nociceptive signals accurately. Therefore, we investigated whether high confidence and performance in pain perception accuracy mitigates placebo hypoalgesia in a verbal suggestion paradigm, since it is assumed that higher precision is assigned to the corrective nociceptive data than to suggestions of pain relief. Placebo hypoalgesia was operationalized by contrasting pain intensity ratings of individually adjusted thermal noxious stimuli before and after receiving a placebo. Pain relief expectations were manipulated in two placebo groups that were suggested to receive a lidocaine cream with either 100% or 50% confidence. Performance and confidence in pain perception accuracy were measured using individualized version of the Focused Analgesia Selection Test. We found that performance and confidence in pain perception accuracy predicted less placebo hypoalgesia with partially independent effects. We conclude that the assessment of interindividual differences in the ability to perceive and interpret nociceptive signals would facilitate prediction of placebo hypoalgesia in pain treatments.





Applying placebo-induced expectancies to emotion regulation

Roni Shafir

Placebo treatments are typically external interventions, such as creams, pills, etc. Thus, the use of the placebo treatment, rather than an internal action of individuals, is the trigger for their improvement in conditions. I will present results from a novel study showing that robust placebo-induced expectancies can be harnessed to improve individuals' internal emotion regulation (ER) attempts. Participants implemented two similar types of distraction, an attentional disengagement ER strategy, to attenuate fear of pain. The placebo-distraction was introduced as an effective strategy (verbal suggestion) and was surreptitiously paired with reduced pain (conditioning), whereas the control-distraction was introduced as noneffective and was surreptitiously paired with increased pain. Findings showed that during a later test phase, where pain intensity was identical, the placebo-distraction resulted in reduced fear of pain, relative to the controldistraction. Moreover, we utilized a behavioral choice measure, demonstrating increased preferences for the placebo-distraction over the control-distraction. Testing whether these effects generalize to a different emotional context of fear of unpleasant pictures, we found that the placebo-distraction was as effective as the control-distraction, yet was substantially preferred. I will discuss these results in light of the relations between placebos and ER.







A Bayesian account for the placebo and nocebo phenomena: The role of pain expectancy and its confidence.

Eleonora Maria Camerone

The Bayesian framework is giving promising insights into the modulatory role of expectations on pain. Here, we investigated whether this framework is a good model to describe both placebo analgesia and nocebo hyperalgesia.Participants' were administered a (sham-)treatment and their expectations were modulated by combining a conditioning procedure with verbal suggestions (Exp1;N=80) and by verbal suggestions alone (Exp2;N=60). Participants received noxious electrical stimulations and were told that the treatment would either decrease, increase, or have no effect on their pain, depending on group allocation. We measured participants' expected pain, expectations certainty and experienced pain. To date, data collection has been completed for both experiments, while data analyses only for Exp 1. In Exp1, by using Linear Mixed Models, we found that expectations magnitude is a better predictor of perceived pain than the specific placebo or nocebo condition, while expectations precision was shown to be a significant predictor of the magnitude of pain judgment shifts. Similar results are expected for Exp2 because we hypothesise that the underlying mechanism is independent from how expectations are generated. We demonstrated that expectations magnitude and precision are the key determinants of pain modulation, also when measured at the metacognitive level.





The placebo effect facilitates cortical excitability before movement onset

Miriam Braga

The placebo effect can change the excitability of the motor cortex during a motor task. It is still unknown whether neurophysiological signs of this effect could be present during action preparation. We aimed at evaluating the placebo effect on the premovement facilitation (PMF), a cortical wave that precedes voluntary movement execution. We applied transcranial magnetic stimulation (TMS) on the primary motor cortex and recorded motor evoked potentials (MEP) during a motor task of thumb contraction. Thirty healthy participants were randomly assigned to a placebo group or to one of two control groups (N = 10 each). In the placebo group, we administered 10Hz transcutaneous electrical nerve stimulation (TENS) as placebo intervention, along with verbal information about its positive effect. In the control-TENS group, we administered TENS together with overt information about its inert nature, while the control-noTENS group served as natural history.

Results showed that reaction times (RT) were faster in the placebo group after the manipulation compared to baseline and to the control groups. MEP amplitude was increased in the placebo group 100ms and 50ms before the movement onset. These findings suggest that the placebo effect can modulate cortical excitability during the preparation phase of a motor act.





Can functional neurological disorder be explained by nocebo-like mechanisms? Evidence for a theoretical proposal

Mirta Fiorio

Functional Neurological Disorder (FND) is characterized by symptoms that are clinically incompatible with those caused by neurological diseases. Among the etiological models of FND, of note is the Bayesian account based on hierarchical models of brain functioning. The overweighting of prior beliefs over sensory data is a common phenomenon in predictive coding networks and can concern non-pathological experiences like placebo and nocebo effects. Indeed, placebo/ nocebo effects may be considered an example of how sensory information may be molded by prior expectations and learning. To date, the relationship between placebo/nocebo effects and FND has primarily been explored from a diagnostic and therapeutic standpoint. We propose a new perspective by which the link between FND and placebo/nocebo effects could be deeper than previously thought. We develop this hypothesis by leveraging some sources of similarities between FND and placebo/nocebo effects, namely the interplay between attention, prior beliefs and expectation (according to a Bayesian framework) and the role of personality traits. In this extended model of FND, we hypothesize that nocebo-like mechanisms stemming from maladaptive prior expectations that are reinforced via heightened attentional focus, stress and anxiety could be involved in the maintenance of functional symptoms.





Testing a novel procedure to induce placebo anxiolysis in healthy volunteers

Nathan Huneke

Placebos exerts large effects in randomised-controlled trials for anxiety disorders (d = 0.65-1.29). Despite this, placebo anxiolysis is largely unexplored, possibly due to low availability of convenient experimental paradigms. We aimed to develop and test a novel protocol for inducing placebo anxiolysis. We used inhalation of 7.5% CO2 for 20 minutes (CO2 challenge) as the anxiogenic stimulus. Following a baseline CO2 challenge, 32 healthy volunteers were administered a placebo intranasal spray labelled either as the anxiolytic 'lorazepam' or 'saline'. Following this, participants surreptitiously underwent a 20-minute inhalation of normal air. Post-conditioning, a second dose of the placebo was administered, after which participants completed another CO2 challenge. Participants administered 'lorazepam' reported significant positive expectations (F = 12.72, p = 0.001) but there was no effect of group on anxiety following CO2 challenge (F's < 1.10, p's > 0.350). Surprisingly, we found many participants exhibited unexpected nocebo effects, despite positive expectations. Our novel paradigm did not induce a placebo response, on average. Instead, several participants experienced nocebo effects, despite undergoing placebo conditioning. This could have resulted from unregulated autonomic arousal or could be consistent with a predictive coding framework of placebo/nocebo effects.




Placebo and nocebo responses to dietary challenge in irritable bowel syndrome: Protocol for a double-blind, placebo-controlled, crossover trial

Heidi Staudacher

The pathophysiology of irritable bowel syndrome (IBS) involves psychological factors. Some carbohydrates cause gastrointestinal symptoms in IBS; restriction can be beneficial in some but not all patients. Placebo and nocebo responses may contribute to these observations. In a randomised double-blind crossover trial we will examine the 1) proportion of people with IBS who experience nocebo response to diet, 2)characteristics predicting placebo and nocebo responses.

Individuals aged 18-65 years with Rome IV IBS (n=30) without severe mental illness will be randomised to four 3-day challenges, labelled correctly (A: fructans labelled 'fructans', B: maltodextrin labelled 'fructan-free') and incorrectly (C: maltodextrin labelled 'fructans', D: fructan labelled 'fructan-free'). Gastrointestinal symptoms will be measured and symptom responders identified. Psychological questionnaires will be completed at baseline. The primary endpoint is the proportion of participants with difference in symptom severity between Drinks B and D that is \geq 2 SD of symptom severity for Drink D. Modifiers of response will be examined using multivariable regression.

This study will evaluate the contribution of cognitive-affective processes to dietinduced IBS symptoms. If nocebo response is prevalent in a subgroup, they may be prime candidates for brain-gut psychotherapy.





Placebolomics; Breath Metabolomics of Placebo Effects

Melina Richard

This pilot study is addressing the question of whether placebo effects induce measurable changes at the metabolic level. Our hypothesis is that placebo effects exist, and that they modulate certain metabolic pathways. We tested this hypothesis by harnessing the breath metabolome using real-time mass spectrometry while using an objective method of measurement for placebo effects in pain (Cold Pressor Test; CPT) before and after the administration of a placebo (i.e. crossover design, n=20). Univariate and multivariate methods are currently being applied to analyze the data.CPT pain threshold time showed no significant difference (p=0.1) between placebo and no placebo experiments. At the breath metabolomic level, we found ~240 features with a FDR < 0.05 for the pain vs. no-pain group. For the placebo effects, we found ~200 features that differ significantly (FDR < 0.5) from the placebo vs. no-placebo group. Ongoing work aims to unveil the main metabolic pathways governed by the pain and by the placebo effects.

Metabolomics is pioneering a new understanding and possible quantification of placebo effects. A validation study is currently underway. Expanding the clinical trial with more subjects involved is in planning. (Sponsors: SNSF. ClinicalTrials.gov: NCT04956718)





Placebo and Nocebo Effects as Bayesian- Brain Phenomena: The Overlooked Role of Likelihood and Attention

Francesco Pagnini

Bayesian-brain framework applied to placebo responses suggests that the effects on the body result from the interaction between priors, such as expectations and learning, and likelihood, such as somatosensorial information. Significant research in this area focuses on the role of the priors, but the relevance of the likelihood has been surprisingly overlooked. One way of manipulating the relevance of the likelihood is by paying attention to sensorial information. We suggest that attention can influence both precision and position (i.e., the relative distance from the priors) of the likelihood by focusing on specific components of the somatosensorial information. Two forms of attention seem particularly relevant in this framework: mindful attention and selective attention. Attention has the potential to be considered a "major player" in placebo/nocebo research, together with expectations and learning. In terms of application, relying on attentional strategies as "amplifiers" or "silencers" of sensorial information could lead to an active involvement of individuals in shaping their care process and health. In this contribution, we discuss the theoretical implications of these intuitions with the aim to provide a comprehensive framework that includes Bayesian brain, placebo/nocebo effects, and the role of attention in mind-body interactions.

39





Placebo induced expectations of mood enhancement generate a positivity effect in emotional processing

Jonas Rauh

A perceptual bias towards negative emotions is a consistent finding in mood disorders. Placebo responses in antidepressant treatment are substantial, but it is unclear whether and how underlying expectancy effects can modulate response biases to emotional inputs. We conducted a controlled cross-over study with 44 healthy subjects in which we induced positive treatment expectations by an alleged oxytocin nasal spray and a hidden training manipulation. Following the induction, participants performed an emotion classification paradigm, in which they had to discriminate subtle emotional facial expressions with varying intensity. A positive expectation specifically lowered the threshold for identifying happy emotions in general, and in particular for subtle expressions. Direct correlation of these effects was found with subjective treatment expectations as well as their experiences, and were accompanied with a significant mood enhancement. Expectations can induce a perceptual positivity effect in healthy individuals probably modulated by top-down emotion regulation and which may be able to improve mood state. Clinical implications of these promising results need to be explored in studies of expectation manipulation in patients with mood disorders.







Placebo analgesia is primarily related to brain systems involved in motivation and value, not nociceptive pain

Rotem Botvinik-Nezer

How strongly, and in which cases, placebo treatments modulate 'bottom up' nociceptive processes is still an open question. Some studies find modulation of processes that seem consistent with early nociceptive effects, including spinal cord activity, endogenous opioids, and activity in dorsal posterior insula and ventrolateral thalamus. However, effects on the latter regions in meta- and mega-analyses are modest. Here, we conducted pre-registered analyses of 391 participants who experienced painful heat and pressure during fMRI with placebo compared to a control treatment. Placebo effects transferred from conditioned heat to unconditioned pressure pain. The Neurologic Pain Signature (NPS), a neuromarker related to nociceptive pain, showed no effects of placebo treatment. A second neuromarker, the Stimulus Intensity Independent Pain Signature (SIIPS)-related to higher-level pain processing and systems for motivation and value (including ventromedial prefrontal cortex and nucleus accumbens)-showed reduced responses to both heat and pressure pain with placebo treatment. Reductions in both NPS and SIIPS predicted individual differences in behavioral analgesia, in both heat and pressure pain. Our results indicate that higher-level processes, not early nociception, primarily drive placebo analgesia. Reductions in nociceptive pain processing may be present in strong placebo responders.





Context re-exposure fails to elicit conditioned sickness responses in a contextual learning paradigm in rats

Lisa Trautmann

Nonspecific sickness symptoms are common negative side effects of immunoand chemotherapy. During the course of such therapies, which typically involve repeated treatments, many patients develop sickness symptoms after mere reexposure to the treatment context. The mechanisms underlying this anticipatory nocebo response remain elusive and can only partially be addressed in patients. This project aims at establishing a contextual learning paradigm in rats as translational model of conditioned sickness. During learning phase, animals receive an injection of endotoxin as sickness-inducing agent and are subsequently placed into an unfamiliar context consisting of visual, tactile, and olfactory cues. This protocol is performed up to three times to vary the amount of prior learning experience. During test phase, animals are reexposed to the treatment context alone to test for conditioned behavioral and physiological sickness responses. During acquisition, animals mounted strong behavioral and physiological sickness responses including immune activation and decreased explorative behavior. However, independent of the number of association trials, context reexposure during test phase failed to elicit conditioned sickness responses.

The difficulties to obtain a successful association between context and sickness symptoms might be due to the complexity of the context or a lack of contingency awareness.





Taste-Immune Conditioning with Fingolimod (FTY720) as an Unconditioned Stimulus

Marie Jakobs

During taste-immune conditioning, a novel taste (CS) is presented together with an immunomodulating drug (US). After CS and US have been associated successfully, conditioned effects similar to the pharmacological effects of the US can be retrieved by CS re-exposure. Applying such paradigm in rats with CsA or Rapamycin as US, a diminished T cell activity upon CS re-exposure has already been shown. The present report investigated whether this phenomenon generalizes across immunosuppressive drugs.

Presentation of FTY720 (US) was paired with the presentation of a sweet tastant (CS). Subsequently, the development of a conditioned taste avoidance (CTA) was assessed and blood immune cell subsets and splenic cytokine secretion were analyzed by flow cytometry, ELISA and MSD.Conditioned animals developed a weak CTA upon CS re-exposure. Moreover, cytokine analyses revealed a slight conditioned reduction in splenic IL-4, IL-5 and IL-13 production. However, our data did not show a conditioned reduction of blood leukocytes via flow cytometry. Overall, these results indicate that taste-immune conditioning does not generalize across all immunosuppressive drugs. Moreover, these results underline the need to further investigate the mechanisms underlying taste-immune conditioning to assess its clinical relevance as a supplementary therapy.



4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION I

Taste-associative learning to induce behaviorally conditioned analgesia in an animal model of inflammatory pain

Stephan Leisengang

While the phenomenon of placebo analgesia is well-documented in humans, the translation into a reliable animal model is still challenging. In this study, we aim to apply an established protocol of taste-associative learning to induce behaviorally conditioned analgesia. We use a rat model of Complete Freund's Adjuvant (CFA)-induced paw edema to induce inflammatory pain. From day 2 after injection, rats are repeatedly treated with ibuprofen or morphine. We assess spontaneous and induced pain-related behaviors and examine inflammation-associated changes in structures of the nociceptive system. Intraplantar injection of CFA induces a robust paw edema for eight days, accompanied by a consistently enhanced mechanical and thermal sensitivity compared to saline injected controls. Activity, water consumption and weight gain are reduced for 24h but return to baseline from day 2. Repeated intraperitoneal injection of ibuprofen (100 mg/kg) on every other day results in a drug-induced analgesia.

After having established a reliable model of inflammatory pain with druginduced short-term analgesia, we will be able to apply a taste-associative learning paradigm in rodents in order to analyze mechanisms of learned analgesic effects, which might form the basis for developing conditioned analgesic responses in humans.





Conditioned Placebo Responses in Allergic Contact Dermatitis

Yasmin Salem

Allergic contact dermatitis is an inflammatory skin disease, which requires therapy with immunosuppressive drugs. The amount of detrimental drug side effects urges the need for developing supportive treatment strategies. Experimental studies document that protocols of associative learning may be applicable to reduce drug doses while simultaneously maintaining treatment efficacy.

Paradigms of taste-immune conditioning in rats most commonly pair the presentation of a novel taste -saccharin- as conditioned stimulus (CS) with an injection of an immunomodulatory drug, such as cyclosporine A, as unconditioned stimulus (US). Sole presentation of the CS at later time leads to immunopharmacological responses similar to the US. Since cyclosporine A reduces inflammation and swelling at allergen contact site, in the present report, animals with experimentally induced contact hypersensitivity via DNFB are subjected to a taste-immune conditioning paradigm with this drug. Even though rarely analyzed under the perspective of associative learning, reframing continuous drug intake as a learning process may open a new path for treatment optimization in diseases such as allergic contact dermatitis. Therefore, supportive treatment by means of learned placebo effects may be used to reduce drug dosages, unwanted adverse drug effects, as well as treatment costs.



4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION I

Optimizing expectations leads to enhanced efficacy of a mindfulness-based intervention in persons with lowbaseline expectations: A randomized control trial

Stefan Salzmann

Placebo mechanisms may help optimize the efficacy of psychological interventions. This study examined whether i) optimizing treatment expectations would augment the efficacy of a mindfulness intervention and ii) whether participants' characteristics would moderate these effects. Sixty-six healthy subjects were randomized to one of 3 experimental groups: i) body scan and an instruction aiming to optimize treatment expectations, ii) body scan and a neutral instruction, or iii) listening to an audiobook and neutral instruction (active control condition). Outcomes were changes in participants' mood, treatment expectations, perceived stress, and mindfulness. Baseline expectations were assessed as a moderator. Participants with low baseline expectations reported increased treatment expectations and mindfulness and decreased perceived stress when provided with positive instruction and the body scan compared to both other groups from baseline- to post-assessment. In contrast, individuals with high baseline expectations indicated less stress reduction when undergoing the body scan and receiving the instruction with positive expectation induction compared to the group with body scan and neutral instruction. Inducing positive outcome expectations seems beneficial for individuals with low baseline expectations but may be counterproductive for individuals with high baseline outcome expectations.







Ambulatory assessment of expectations and pain disability in women with endometriosis

Ann-Katrin Meyrose

Endometriosis is a burdensome chronic disease in women of procreative age. Satisfactory long-term treatments are lacking; optimizing expectations seems promising. This study investigates expectations and pain disability in women with endometriosis after laparoscopy in everyday life as a basis for interventions and to assess usefulness of ambulatory assessments.

A subsample of 30 women with endometriosis in a large clinical cohort-study rated their endometriosis-related complaints, disability, pain medication, and expectations every evening for 30 consecutive days after laparoscopy via smartphone (m-Path).

For most patients, higher symptom expectations for the next day were directly related to higher experienced disability for that day (r=.50 to .98) and for the next day (r=.39 to .78). Trajectories of expectations and disability ranged from no expected and experienced disability to a complex course. Some patients seem to adjust expectations according to their experiences. Technical issues were rated as very good (M=9.2, potential range: 0-10), burden (M=0.4), positive (M=1.4) and negative (M=0.3) influence of study participation as low.

Applied smartphone-based ambulatory assessment seems feasible and promising to provide insights into individual patient data in treatment expectations in future studies including RCTs.





Preoperative Expectations in Women with Endometriosis. Baseline results of a clinical mixed-method cohort study

Nina Hirsing

20-30% of women with endometriosis report persistent pain disability despite successful laparoscopy. Expectations might be important for these partially negative treatment outcomes . This study aims to describe preoperative expectations in women with endometriosis.N=261 women (M=29.2 years; SD=6.57) with endometriosis were assessed regarding clinical characteristics and preoperative expectations (TEX-Q, GEEE improvement/worsening/adverse events).Women were more disabled, depressive, and anxious than women of the general population (t(1625)=30.75, p<.001; t(3256)=21.63, p<.001; t(3256)=19.50, p<.001). The average for expected improvement, worsening, and adverse effects were M=7.25 (SD=2.02), M=1.10 (SD=1.71), M=3.84 (SD=2.38), and for overall positive treatment effects (TEX-Q) M=6.74 (SD=1.26). Expected improvement was negatively correlated with expected worsening to a small degree (r=.124, p=.05) but not with expected adverse effects (r=-.097, p=.12). Expected improvement was correlated with overall treatment effects (TEX-Q) to a substantial degree (r=.68, p<.001).

Women with endometriosis are disabled and have primarily positive expectations concerning laparoscopy. Expectations have a multidimensional nature, which should be considered separately.





The Influence of Preoperative Mood and Treatment Expectations on Early Postsurgical Acute Pain After a Total Knee Replacement

Julia Stuhlreyer

Preoperative emotional states and treatment expectations are significant predictors of postoperative pain. However, the interaction between emotional states and preoperative treatment expectations and their effect on postoperative pain have not yet been studied. Patients who received a TKR rated preoperatively their pain on a numeric rating scale (NRS) 0–10, emotional states on the Pain and State of Health Inventory (PHI), treatment expectations on the Stanford Expectation of Treatment Scale (SETS), and postoperatively their level of pain on a NRS 0–10.

The questionnaires were completed by 122 patients. Negative emotional states predict negative treatment expectation F(6, 108)= 8.32, p<0.001, with an excellent goodness-of-fit. A mediator-analysis revealed that the indirect effects and therefore relationship between the emotional states sad, anxious, and irritable, and postoperative pain is fully mediated by negative treatment expectations. Whereas the emotional, but more somatic states tired, dizzy, weak are partially mediated by negative treatment expectations. The relationship between emotional states and postoperative pain is mediated by negative treatment expectations. Therefore, innovative treatment strategies to reduce postoperative pain should focus on modifying negative treatment expectation through establishing a preoperative pain management that focuses on expectation and emotional states.





What do US orthopaedic surgeons think about placebocontrolled surgical trials?

Michael H Bernstein

Randomized placebo-controlled trials (RPCTs) are the gold standard for evaluating novel treatments. However, this design is rarely used to test the efficacy of orthopaedic interventions. The present study examines the attitudes of US orthopedic surgeons towards RPCTs (N=687). When presented with a vignette describing an RPCT for orthopaedic surgery, 52.3% of surgeons viewed it as 'completely' or 'mostly' unethical. Participants were also asked to rank-order the value of five different types of evidence supporting the efficacy of a surgery, ranging from RPCT to an anecdotal report. The perceived value of RPCTs were polarized; 26.4% viewed it as the least valuable (even less valuable than an anecdote) and 35.7% viewed it as the most valuable. If orthopaedic surgeries are to be supported by evidence from RPCTs before they are implemented in clinical practice, it is necessary to educate surgeons on the value and the ethical aspects of placebo surgery control conditions. Otherwise, invasive procedures may be performed without any benefits beyond possible placebo effects.







Treating students suffering from procrastination with imaginary pills

Nadja Heimgartner

Academic procrastination is a wide-spread phenomenon among students with 20-30% of university students being impacted in their academic achievements and quality of life by procrastination. Therefore, there is a need to develop cost-effective, low-threshold treatments. One promising approach is the administration of imaginary pills: Extending the idea of openly administered placebos, the patient experiences the idea of taking a pill through the suggestions of a therapist and experiences its effects in a similar way to a pharmacologically active pill. Any desired effect can be attributed to an imaginary pill, making it a perfect treatment for procrastination which is associated with different symptoms like, e.g., fear of failure, perfectionism, and distractibility. A first trial showed promising results of an imaginary pill treatment in students with test anxiety.We plan a RCT to compare the imaginary pill to cognitive-behavioral treatment and no-treatment in 120 students suffering from procrastination. Before and after the treatment, subjective levels of procrastination, depressive symptoms, anxiety, well-being, and stress will be assessed. Preliminary results will be presented.

Conclusion: This trial will provide valuable insights into the effectiveness and applicability of imaginary pills in the context of procrastination.





What our failure to define placebos tells us about the nature of medicine

Dien Ho

Identifying precise placebo-related concepts has proved challenging. The reliance on secondary concepts like "specific/non-specific actions" merely pushes the problem back. By identifying better definitions, we ensure that placebo research in fact investigates placebo phenomena. For the therapeutic use of placebos, definitions that avoids obvious incoherence will contribute to the success of their clinical deployment.

Following Grünbaum, I identify the conceptual connections between background theories of medicine and micro-ontology (i.e., the delineation of treatments). Clinical examples provide additional evidence for the analysis.Placebo-related concepts rely on a distinction between a treatment's characteristic and incidental features. Since the latter are determined by background theories of medicine and these often contain arbitrary distinctions and internal inconsistencies, the boundary between characteristic and incidental features inherits the same messiness. Thus, defining "placebo" and "placebo effect" in a rigorous manner becomes impossible.My analysis has two consequences. Firstly, it suggests that there is no fundamental difference between placebogenic and non-placebogenic effects. Secondly, if placebogenic effects involve factors that are typically relegated to non-clinical contextual domains (e.g., a pill's color), then it behooves us to examine how we delineate treatments in general.





Is light touch an effective sham for randomized controlled trials on osteopathic manipulative treatment?

Mahima Mangla

Osteopathic manipulative treatment (OMT) is a hands-on modality. Studies comparing OMT to sham are limited. We evaluated light touch as an acceptable sham for randomized controlled trials (RCT) on OMT. This is a sub-study of an RCT examining OMT vs. sham light touch for cardiac arrhythmias. Participants who never received OMT (N=21) were randomized to OMT (N=11) or sham (N=10). Surveys collected pain, tension, and anxiety levels before/after treatment and post-treatment satisfaction. Patients also assessed on ability to accurately guess their randomization.

5/11 (45.5%) in OMT arm and 5/10 (50.0%) in sham arm correctly perceived their randomization. Both arms reported post-treatment reduction in pain, tension, and anxiety. 9/11 (81.9%) in OMT arm and 8/10 (80.0%) in sham arm were somewhat or very satisfied with treatment.Light touch was an effective sham as patients guessed their randomization correctly half the time. Considering both arms had similar post-treatment results, light touch may have had a therapeutic placebo effect. Larger studies discerning impact of light touch warranted to understand its effects and further validate its use as a sham in OMT RCTs.







Placebo and nocebo effects on experimental and clinical pain in neurodegenerative disorders

Johanne Marie Berg Thøgersen

Placebo and nocebo effects in pain in healthy participants are well-established. Progressing neurobiological deterioration may be associated with differential placebo and nocebo effects, e.g., presence of placebo and nocebo effects on motor symptoms in Parkinson's Disease (PD) and diminished placebo analgesia effects in Alzheimer's Disease (AD). Knowledge is lacking about these effects in pharmacological and non-pharmacological treatments in PD and AD. Three within-subjects studies examining placebo and nocebo effects on experimental and clinical pain: 1=PD receiving deep brain stimulation and hypertonic saline induced pain; 2=PD receiving levodopa and hypertonic saline induced pain; 3=AD receiving lidocaine and thermally induced pain. In PD, effects of deep brain stimulation and levodopa on experimental pain may be modulated by placebo and nocebo suggestions, although these effects are not necessarily related to motor symptoms. For analgesic treatment placebo and nocebo effects may be absent in AD patients experiencing experimental pain. Neurodegenerative processes may differentially affect placebo analgesia effects. Our results contribute to the knowledge about altered placebo and nocebo effects in clinical populations of neurogenerative disorders and, in this line, investigating how pharmacological and non-pharmacological treatments may interplay with these effects.



4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION I

My pain is your pain? The effects of (psycho) pharmacological pain manipulations on social emotions and behavior - a systematic literature review

Helena Hartmann, Philipp Dammann

To date only a handful of studies have investigated effects of pain-modulating substances on social capabilities. However, a systematic and comprehensive overview and summary of these studies is still missing. This review therefore aims to identify how interfering with the perception of pain in oneself affects our abilities to perceive, process and react to positive and negative emotions in other individuals. We will include studies 1) where one's own pain system was modulated via sham treatments and positive or negative expectations (placebo analgesia and nocebo hyperalgesia), but also via opioidergic and non-opioidergic pharmacological substances 2) where the effects of these manipulations on social emotions and behavior (e.g., empathy, prosocial behaviour) were measured. Our preregistered protocol will be published on OSF prior to the start of the search. Databases such as Pubmed, Scopus, Google Scholar, and preprint servers will be used for data collection and extraction. These studies will then be subjected to different bias assessments and their results will be synthesized in form of a literature review.





Treatment expectation and observational learning: Systematic review of observationally induced placebo and nocebo responses

Helena Klauß

Observational Learning (OL) refers to learning through the observation of others' behavior. OL has been suggested as an effective and simple tool to evoke treatment expectations in patients, leading to placebo and nocebo effects. However, the exact mechanisms by which OL induces expectations and the possible areas of application remain unclear. We conducted two independent systematic literature reviews to answer the following questions: How does OL induce positive and negative treatment expectations? In which medical fields has OL been used to influence treatment expectations and outcomes? The two systematic searches took place on September 20, 2022. Concerning the first research question, we identified 21 studies, which investigated OL effects in relation to pain, itch, treatment effectiveness, or side effects. The studies showed that OL can efficiently induce placebo and nocebo

responses across different presentation modes, with effect sizes ranging from small to large. In the second search, we found 12 studies. They showed that OL was applied in preventive, diagnostic, therapeutic, and rehabilitative interventions. Together, OL can have both positive and negative effects on treatment outcomes. Future research is needed to investigate how OL can be most effectively implemented in everyday clinical settings.





Can heightenedstate empathy amplify placebo and nocebo effects elicited through the observation of others?

Stefanie Meeuwis

Observing someone experience pain relief or exacerbation following a treatment (observational learning; OBL) could trigger placebo hypoalgesia or nocebo hyperalgesia. As trait empathy was related to these effects, we hypothesize that heightened empathy for the observed person may amplify them. Healthy volunteers are randomized to one of 6 groups: 1) placebo-OBL; 2) high-empathy placebo-OBL; 3) nocebo-OBL; 4) high-empathy nocebo-OBL; 5) random-ratings OBL; 6) no-observation control. Pain is evoked with heat stimuli at baseline and post-OBL. An ointment is applied to the participants' arm, and they observe a model rate pain as lower or higher after this ointment compared with the other arm, or rate pain randomly (depending on group allocation). State empathy is modulated in two groups via an imagination exercise, in which participants are asked to identify with the model. Pain ratings are collected as a primary outcome. State empathy, pain expectations and physiological parameters (heart rate, skin conductance) are assessed as secondary outcomes. The data is currently being collected and will be presented at the conference. Investigating how OBL lead to pain modulation could be relevant, for instance, given that stories about pain treatment can readily be found online.





EEG responses in socially-acquired pain modulation

Nicolas McNair

We investigated neurophysiological responses related to socially-acquired pain modulation.Participants (N=60) were assigned to a Direct Experience (DE), Social Observation (SO), or Control group. DE participants underwent a standard conditioning paradigm, experiencing high/low-temperature stimuli contingent on supposed 'activity' / 'inactivity' of sham-treatment. SO participants instead watched another 'participant' undergo this same procedure. Control participants experienced the thermal stimuli non-contingent on treatment 'activity'. All participants underwent a test phase where only low-temperature stimuli were applied with the treatment. Pain and Expectancy ratings, electrodermal activity (EDA) and electroencephalography (EEG) data were collected.DE and SO groups exhibited evidence of behavioural and physiological (EDA) pain modulation at test. Two time-windows (220-288ms, 588-752ms) of EEG activity related to hyperalgesia during conditioning in DE were used to analyse EEG responses at test for all three groups. We found differences associated with hyperalgesia at these times for both DE and SO groups, but not for the Control group.Watching another individual experience pain triggers measurable changes in brain activity associated with nocebo hyperalgesia that are similar to that observed when such pain is directly experienced.







Exploring the effect of interpersonal synchrony on sociallytransmitted nocebo hyperalgesia

Kirsten Barnes

Background: Research concerning socially-acquired nocebo hyperalgesia has focused on Observers' intrapersonal experience, with little known about interpersonal synchrony.

Methods: Socially-acquired pain modulation was explored via a multigenerational social transmission chain. Participants (N=101) were assigned to three Generations (G1-G3). G1(Demonstrators) – witnessed by G2(Observers) – experienced high/low-temperature stimuli contingent on supposed 'activity'/'inactivity' of a sham-treatment. G2(Demonstrators) subsequently underwent a test-phase with only low-temperature stimuli. This was witnessed by G3(Observers), who then underwent an identical test-phase, as G3(Demonstrators), observed by G4(Observers). Pain and expectancy ratings, electrodermal activity (EDA), and facial action units were measured.

Results: Pain experienced by G1(Demonstrators) propagated throughout the chain, with G2(Observers) and G3(Observers) exhibiting subjective and physiological pain modulation to sham-treatment (hyperalgesia in G2 triggered hyperalgesia in G3). Interpersonal physiological synchrony (EDA) predicted the magnitude of nocebo hyperalgesia. This was also found for psychological synchrony (Expectancy) but only in G3. G3(Demonstrators) with high synchrony, who observed greater hyperalgesia in G2(Demonstrators), also experienced greater hyperalgesia.

Conclusions: Findings have implications for the spread of maladaptive pain experiences, including situations where interpersonal connection is encouraged (support groups).

Abstract No.: 048





Religiosity is related to expectation but not placebo effects

Rachel L. Cundiff-O'Sullivan

Religious beliefs influence the understanding and interpretation of health and disease, but how religiosity influences placebo effects is unknown. This study examined the association between religiosity and placebo effects in healthy control and temporomandibular disorder (TMD) participants (374 Christian, 140 Non-Christian, 94 Atheist). Heat pain intensity applied to the forearm was assessed using a visual analogue scale (0-100) in a classical conditioning placebo paradigm. Participants were told green screens signaled pain relief via a sham electrode whereas red screens signaled full painful stimulation. Red and green screens were paired with high- and low-pain during conditioning and medium-pain during testing. Participants reported expectation and religion and completed the Chronic Pain Coping Inventory and Pain Catastrophizing Scale. The association between religiosity and TMD pain severity and interference was also examined. There was no effect of group or religion on placebo effects, although Christians reported greater expectation than Non-Christians and Atheists. Christians endorsed the highest use of guarding, resting, seeking help, relaxing, social support, catastrophizing, and soothing self-statements as coping strategies, yet Christians had greater pain severity than Atheists. This study is among the first to find an association between religiosity and expectation but not placebo effects.





4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION I

Placebo effects in Cannabidiol (CBD) treatment of psychological distress in stressed students at risk for depression: The role of treatment expectation.

Alexander Winkler

Cannabidiol (CBD) have been suggested to have a therapeutic role for certain mental health conditions in spite of a lack of empirical evidence. We investigated the effect of a 30 days CBD treatment and treatment expectation on psychological distress in an at risk sample of highly stressed college students. As part of an ongoing study, a preliminary sample of intended 180 students are assigned to an CBD-oil or Placebo-oil or no-treatment control group. All participants receive the same information about CBD. Participants took the respective oil on 30 consecutive days. Before, after intervention and at 4 weeks follow up, the Depression Anxiety Stress Scale was administered. Upon completion and unblinding, participants in the CBD-oil group are expected to report a greater reduction of depression, anxiety and stress symptoms than participants in the placebo-oil and no-treatment group. The role of treatment expectations in mediating these effects will be delineated. The findings will be helpful to better understand the efficacy of CBD treatments and its underlying (placebo) mechanisms. Implications for the understanding of the placebo effect of complementary medicine treatments will be discussed.



4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION I

Placebo Response and media attention in randomized clinical trials assessing cannabis-based therapies for pain: A systematic review and meta-analysis

Filip Gedin

To evaluate the size of placebo responses in randomized clinical trials where cannabinoids were compared to placebo in treatment for pain and correlate these responses to objective estimates of media attention. A systematic literature search was conducted within MEDLINE and Embase. Cannabinoid studies with a double-blind, placebo-controlled design with participants aged >18 years with clinical pain of any duration were included. Studies were excluded if they treated individuals with HIV/AIDS, or severe skin disorders. Data were extracted by independent reviewers. Attention metrics for each trial were extracted from Altmetric and Crossref. Data were analyzed using a random-effects statistical model. Change in pain intensity from pre to post treatment.

Results: 20 studies, including 1459 individuals. Pain intensity was significantly reduced in response to placebo, with a moderate to large effect-size (Hedges g, 0.635; P<.001). The amount of media attention linked to each trial was proportionally high, with a strong positive bias, yet unrelated to the clinical outcomes.

Placebo contributes significantly to pain reduction seen in cannabinoid clinical trials. The positive media attention, may uphold high expectations and shape placebo responses in future trials.





Can placebo and nocebo effects influence a weight loss in adults? A systematic review and meta-analysis

Julia Badzińska

Placebo and nocebo effects may influence the weight reduction interventions. However, these effects have not yet been well described, no systematic review or metaanalysis is available.

The review included studies indexed on PubMed, Cochrane, Embase, PsycINFO, PsycARTICLES, TripDatabase, involving adults participating in weight loss programs or examining the placebo effect in weight loss. The studies had to include a no-intervention group and report body weight or derived indices before and after the studied intervention.

Five studies were included in the review, and four in the metaanalysis. The difference between the placebo and control groups in the final BMI and Body Mass values was not statistically significant, but approached significance for Body Fat Percentage. The superiority of the placebo intervention was noted, while the nocebo effect was observed only in a study using medically connoted placebo. When designing an intervention aimed at weight reduction, not only physical and physiological but also psychological and behavioral aspects should be considered, as they can play a role in therapeutic success, like the placebo or nocebo effect. Interventions with a medical connotation can induce a nocebo effect, while others (ie. related to behavioral changes) are associated with the placebo effect.





I may get sick: Impact of negative treatment context on pain-related fear extinction in placebo-treated participants in RCT

Robert Jan Pawlik

Many RCTs assess pharmacological effects on conditioning processes, but possible nocebo effects generated by treatment context-induced expectations in placebo-treated participants remain unknown. We analyzed placebo arms of two complementary RCTs involving injection of lipopolysaccharide (LPS) as sickness-inducing agent or saline as placebo in healthy volunteers. A two-day fear conditioning paradigm involving visual conditioned stimuli (CS) paired with either interoceptive pain or aversive tone as unconditioned stimuli (US) was implemented. Studies differed in the timing of LPS-treatment, effectively creating different expectancy context. Group differences in CS and US valence ratings during learning, extinction, and US re-exposure were analyzed. Treatment context did not impact on acquisition of conditioned fear. However, acquisition in a negative context resulted in enhanced retrieval of fear responses to painpredictive CS, and a more pronounced extinction learning curve. Response to painful US was also shaped by treatment context. Placebo-treated participants expecting drug-induced sickness appear to generate negative treatment-context related expectations impacting on CS extinction and US responses. Further studies are needed given implications for interpretation of nocebo effects in RCTs.







Placebo Effects in war, weather, pest control and olympic sport.

Colin Brewer

Placebo effects can be seen in non-therapeutic settings and involve the same basic psychological mechanisms - including belief, faith, hope and expectation that mediate placebo effects in medicine. This paper discusses examples from two very different fields. 1. War. a) A supposed method of avoiding detection and anti-aircraft shells during mass bombing raids in world war 2 was actually increased detection and was therefore a nocebo. b) A device that was supposed to detect explosives but could not do so was bought in large numbers by the Iraqi military c 2005. 2. Sport. A permitted technique (cupping) was supposed to increase athletic performance although its physiological effects could only be to diminish it, albeit marginally.







Want to be fit? Start with your mind! The role of the placebo effect in physical fitness in children: a systematic review and meta-analysis

Magdalena Żegleń

Physical activity is crucial to prevent and reduce excess body mass. The placebo effect can influence the outcomes of fitness interventions; however, this topic has not yet been extensively investigated in children. Summarising the data on placebo effects in fitness-related interventions is essential to understand this problem better. A systematic review of PubMed, Cochrane, PsycINFO, PsycARTICLES, TripDatabase and Embase was carried out. A meta-analysis of the results of studies with comparable research plans was performed. There were significant differences, favouring the placebo intervention. At the final follow-up, the children in placebo groups had higher maximal heart rates, shorter recovery times, longer ergometry phases, running time and lower peak and average perceived exertion than the control.

The placebo effect is present in fitness-related parameters in children, regardless of the Body Mass Index status. It is crucial, as for youth with excess body mass, it is difficult to be active, especially to show appropriate levels of motivation and involvement. Importantly, the benefits of the placebo were the strongest in the motivation/ engagement-related parameters and self-assessed exertion. Notably, the nocebo effect was not observed, which is advantageous when considering placebo interventions in practice.





- 1) An International Consensus Definition for Contextual Factors: Findings from a Nominal Group Technique
- 2) Perception and use of contextual factors in eliciting placebo and nocebo effects: an online survey of health professionals from French-speaking countries in Europe

David Newell

Evidence suggests contextual factors are important components of therapeutic encounters and may influence the patients' clinical outcomes, triggering placebo and nocebo effects. Currently, a single consensus definition of contextual factors is lacking. This study aimed to create a consensus definition of contextual factors. The study used a multi-stage virtual Nominal Group Technique (vNGT) to harmonize a common contextual factor definition. The 10 international vNGT participants had a variety of clinical backgrounds and research specializations and were all specialists in contextual factors research. The initial stages of the vNGT resulted in 14 independent contextual factor definitions. After a prolonged discussion, the initial definitions were modified, and 12 final definitions (from fist to last) were ranked by the vNGT participants. A sixth-round was used to identify a final consensus, which reflected the complexity of contextual factors and included three primary domains: 1) an overall definition; 2) qualifiers that serve as examples of the key areas of the definition; and 3) how contextual factors may influence clinical outcomes. Our consensus definition of contextual factors seeks to improve the understanding and communication between clinicians/researchers. These are especially important in recognizing their role in moderating/mediating clinical outcomes.

Poster Session II

Friday, 12 May 12:30 – 14:00 Machine Foyer





The good doctor? Greater negative treatment expectations and anxiety correlate with lower perceived physician warmth and empathy

Jana L. Aulenkamp

The role of doctor-patient relationship in shaping treatment expectations is increasingly acknowl-edged, but remains incompletely understood especially in the context of nocebo effects. In a translational experimental study on nocebo effects in interoceptive pain, we assessed associations between negative treatment expectations and perceived study physician attributes.







4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION II

A systematic review and meta-analysis of the placebo response in randomized, double-blind, placebocontrolled trials of ketamine and esketamin in the treatment of major depressive disorder.

Alexandros Matsingos

Ketamine and esketamine offer a novel approach in the pharmacological treatment of major depressive disorder (MDD). This meta-analysis aimed to investigate the placebo response in double-blind, randomized controlled studies (RCTs) on patients with MDD receiving esketamine or ketamine. Multiple databases were searched systematically. Double-blinded RCTs using a pharmacologically inert substance as a comparator to the treatment group were selected. Pooled effect sizes (Cohen's d) were calculated using a restricted maximum likelihood model for pre to post within group effects of placebo groups and treatment groups, respectively. Possible moderators of the placebo response were investigated by performing meta-regressions. We identified 5017 abstracts. A total number of 10 studies and 1014 participants (546 receiving verum and 468 placebo) meeting the inclusion criteria were selected. We estimated the pooled effect sizes of the placebo (0,86 [0,20; 1,53]) and treatment (2,31 ([Cl:1,64; 2,98]) response. The placebo response accounts for 37% of the treatment response. No moderators of the placebo response were identified. Ketamine and esketamine show robust antidepressant treatment effects. However, our findings suggest that the placebo response also plays an important role and should be considered in clinical practice.





Can antidepressant treatment effects be predicted by patients' responsiveness to expectation manipulation?

Eun Jin Shim

Background: One consistently observed finding in the development and maintenance of depression is a strong focus on negative emotions. Recently, we established an experimental protocol that induces a positivity bias by expectation manipulation in healthy individuals. In this ongoing, longitudinal study we are now applying this protocol to inpatients with major depressive disorder (MDD) to investigate whether patients similarly benefit from such manipulation and whether expectation effects are predictive for clinical treatment outcomes.

Methods: In a controlled cross-over design, manipulation of positive treatment expectation is combined with an emotion classification task in MDD inpatients. Weekly follow-up assessments target ongoing pharmacological and nonpharmacological treatment expectation and current depressive symptoms.

Results: Preliminary data show positive expectation effects on mood state in the experimental setting and demonstrate associations between the course of treatment expectation and outcomes.

Conclusions: We are able to elicit positive expectation effects in patients with MDD, which now makes it possible to study the impact of individual expectation responsiveness on antidepressant treatment effects.

Funding: We gratefully acknowledge funding from the German Research Foundation (DFG) - Project-ID 422744262—TRR 289.





What helps and what hinders antidepressant discontinuation? Qualitative analysis of patients' experiences and expectations

Carina Meißner, Yvonne Nestoriuc, Ann-Katrin Meyrose

Background: Antidepressant prescriptions are rising, mainly due to increasing long-term use. Patients continue intake albeit lacking clinical indication, with high individual and societal costs. It is important to understand what helps or hinders discontinuation and consider patients' experiences and expectations.

Methods: We conducted semi-structured interviews with 32 patients with (partially) remitted Major Depressive Disorder taking antidepressants to derive thematic categories using qualitative content analysis.

Results: Experiences with intake included effectiveness, but also side effects; discontinuation experiences included recurrence and discontinuation symptoms. Patients' prior experiences contributed to their expectations towards future discontinuation. While patients frequently reported an inclination to discontinue, partly motivated by positive expectations such as getting rid of antidepressants' side effects, not all assessed this inclination as feasible. Patients also held negative expectations, such as recurrence or occurrence of discontinuation symptoms, and perceived these expectations as hindering discontinuation. Aside experiences and expectations, barriers and facilitators to discontinuation included availability of support, treatment information, time, stability, and structure.

Discussion: Primary health care needs to implement a structured framework helping patients discontinue their antidepressants safely and effectively. This framework should consider the utility of functional expectations and specify an individualized approach improving dysfunctional expectations, adapted to patients' previous experiences.




Nocebo side effects in open-heart surgery: A randomized clinical trial

Mette Sieg

Nocebo side effects are caused by context factors, such as patient expectations, rather than the treatment itself. Since evidence suggests that context factors may play a role in open-heart surgery, a proportion of side effects following open-heart surgery may be nocebo side effects. This study investigates whether expectations about side effects, formed by verbal suggestions, influences side effect occurrence following open-heart surgery. Included participants (N=120), undergoing open-heart surgery at Aarhus University Hospital, are randomized to receive verbal information about the surgery with a focus on 1) side effect information or 2) procedural information (i.e. high versus low focus on side effect information). The main outcome measure is the occurrence of side effects four days after the surgery, followed up by telephone interviews one month, three months, and 12 months after the surgery. Preliminary results are presented at the 4th International Conference of the Society for Interdisciplinary Placebo Studies in Duisberg, Germany, 2023. The fact that health care professionals may cause patients unnecessary harm by disclosing side effects is a critical issue, and well-conducted empirical studies carried out in clinical populations are needed to understand the impact of nocebo effects in clinical practice.







What Factors Shape Expectations Towards Antidepressant Discontinuation?: A Cross-Sectional Study

Claire Warren

Background: Antidepressant (AD) discontinuation can be burdensome. German national S3 guidelines do not specify how to discontinue and many patients do not receive supporting information from prescribing physicians. Treatment expectations affect AD treatment through placebo/nocebo effects, indicating the possible relevance in the optimization of the AD discontinuation process.

Methods: N =104 patients with (partially) remitted major depressive disorder and currently taking an SSRI/SNRI completed a quantitative online questionnaire concerning past AD discontinuation experiences, expectations, and clinical factors. Bivariate associations and multiple linear regression analyses examined associated factors and potential predictors of expectations.

Results: Expectations correlated positively with intake duration, perceived benefit of AD, and supportive information from clinicians. Negative prior experience predicted more negative expectations overall, specifically towards the discontinuation process and occurrence of adverse events. AD-related side effects predicted more positive expectations overall, as well as increased perceived benefit and positive impact of AD intake.

Conclusions: Results show that expectations play a role in AD discontinuation and are predicted by prior negative experiences. Safe and effective discontinuation could include more support from prescribing practitioners in the form of AD sideeffect management, e.g., information and check-ups, as well as consideration of previous discontinuation experiences.





Harnessing healthcare providers' behavior to improve health outcomes: protocol of an experimental, controlled, and randomized study

Julie Lasselin

While the importance of the patient-provider relationship for health outcomes is well acknowledged, there is still a clear lack of basic science research investigating this notion. We will present the protocol of a study aiming at determining, in a fully experimental way, how healthcare providers' behavior contribute to health outcomes. To this aim, we will activate immunological processes experimentally in 120 healthy participants while manipulating the healthcare provider's behavior. The participants will be made sick experimentally and transiently using an intravenous injection of a bacterial endotoxin (lipopolysacharide), and healthcare providers will be trained to have augmented (e.g., warm, attentive, caring) versus limited interactions with sick participants. Healthcare providers' behavior will be rated by participants, as well as objectively from video recordings according to a validated checklist. Objective (fever, immune) and subjective (e.g. sickness symptoms, pain) responses of sick participants, as well as stress and neuroendocrine responses, will be assessed. Findings from this project will provide empirical evidence regarding the contribution of a healthcare provider's behavior to health outcomes, and may help for the development of clinical recommendations to promote effectiveness and quality of healthcare services.







Persistence and enhancement of an active placebo protection spray preventing sadness

Marcel Wilhelm

Background: A protective effect of active placebos on mood was demonstrated but its persistence remains unclear. Depicting side effects as onset sensations could boost this effect. This study examines if an active placebo nasal spray protects against sadness in a 6h follow-up and if framing enhances this effect.

Methods: Ninety-six healthy participants were randomized to one of three groups (framing group: framing+nasal spray; nasal spray group: nasal spray only; control group: no nasal spray or framing). Sadness was induced after application and after 6h using different methods.

Results: Sadness was significantly higher in the control group than in the framing group and the nasal spray group at post (p<.001) and at follow-up (p<.05). Withingroup analysis revealed that sadness increased from baseline to post in the control group (p=.002) but not in both nasal spray groups (p>.5). At follow-up, an increase in sadness was observed in the nasal spray group (p=.006) and the control group (p<.001) but not in the framing group (p>.05).

Discussion: Results show that the placebo effect persists at least six hours, possibly prolonged through the utilized framing strategy.





"Special Needs by Placebo": Programme to Advise, Normalize And Control its European Administration (PANACEA)

Katia Mattarozzi

Recent progress has been made in understanding the relevance of placebo/ nocebo mechanism for clinical outcomes. However, among health professionals, there is a lack of in-depth knowledge of the phenomenon and its implementation in clinical practice is not regulated by shared guidelines. PANACEA project aims to reducing the gap between evidence-based findings and their implementation in clinical practice, by defining an innovative Higher (HE) and Vocational (VET) Education programme, and practice guidelines on placebo/nocebo use among European countries.

To provide HE students and professionals in healthcare with knowledge and competences about placebo/nocebo mechanisms and assist health professionals' decisions about their appropriate use, PANACEA will produce learning materials and best practice guidelines grounded in evidence from a scientific literature systematic review, and practice-based information. To support HE/VET medical institutions in enriching students' curricula with a specific course on placebo/ nocebo, PANACEA will produce a course syllabus with recommendations and information about learning outcomes and teaching methods. To establish and enhance an effective student-centred active learning method on placebo/nocebo knowledge, PANACEA will produce an interactive webApp.

We expect short- and long-term impact on knowledge and clinical practice in European healthcare and education.





78

POSTER SESSION II

Placebo prescriptions among GPs in 21 countries: the PURE study

Fabian Wolters

Background: General practitioners (GPs) are known to sometimes initiate a treatment even when they believe it will not improve patients' symptoms by any known biological/physiological mechanism. The frequency, risks, and ethics of these essentially placebo treatments are a matter of discussion.

Methods: An online questionnaire was distributed to GPs in 21 mostly European countries. 952 currently practicing GPs responded to the questionnaire.

Results: Across countries, 84% of respondents indicated they had prescribed an essentially placebo treatment at least once. The median rate of essentially placebo prescriptions was once per 2 weeks or 0.67% of consultations. The rate varied per country, from 0.09% of consultations in the UK to 2.5% of consultations in France. Across countries, prescription rate was higher in male GPs (β = 0.11, p = 0.005), those who have more experience (β = 0.14, p < 0.001), and those who work fewer hours (β = -0.14, p = 0.001).

Conclusions: This study is the first to show differences in placebo prescription rates between countries within a single study. Gender, experience and work times predicted the rate of placebo prescriptions. Future research should specify the risks of placebo prescriptions to inform guidelines for ethical conduct.





Discontinuation of Fumaric Acid Esters is Influenced by Depressive Symptomatology – A Retrospective Analysis of Patient Records

Frederik Krefting

Background: Fumaric acid esters (FAEs) remain an often prescribed therapy option for psoriasis patients. However, premature discontinuation of therapy is common. Literature confirms a high degree of depressive disturbances in psoriasis patients, and it is hypothesized that depressive symptomatology is associated with more frequent adverse events (AEs) and therapy discontinuation. The aim of the study was to analyze whether psoriasis patients with a comorbid depressive symptomatology are more likely to discontinue treatment with FAEs.

Methods: Data was retrospectively extracted from patients' records starting therapy with FAEs between April 2017 and March 2022. Psoriasis severity, depressive symptomatology, the occurrence of AEs and the circumstances of a possible therapy discontinuation were analyzed.

Results: Psoriasis patients (N = 95, 47.4% female) with depressive symptomatology (42.1%) showed an increased probability of therapy discontinuation due to patient-reported AEs. However, the total number of reported AEs was not associated with depression.

Conclusions: The presented results give rise to the hypothesis that among psoriasis patients with depressive symptoms the associated increased introspection and somatization may result in AEs leading to quicker therapy discontinuation. In patients with evidence of depressive symptomatology, the occurrence of nocebo effects should be minimized, e.g. by using special communication techniques.





Capacity to consent and treatment expectations: reliability of a newly adapted interview for psychotherapy

Sönke Ladwig

Capacity to consent to treatment (CCT) is a prerequisite for informed consent. Since the MacArthur Competence Assessment Tool for Treatment is a reliable tool for assessing CCT, we adapted its German version to psychotherapy (MacCAT-PT) and investigated its reliability and connections with expectation-related and sociodemographic variables in a mixed clinical sample.

N = 108 patients with indication for psychotherapy participated. The MacCAT-PT was administered by trained psychologists, took 20 minutes, and was rated by two independent raters.

Sufficient interrater reliability and internal consistency were found for the total score of the MacCAT-PT (ICC=0.80; α =0.80) and the scale Understanding (ICC=0.79; α =0.77), scales Reasoning and Making a Choice provided moderate scores (ICC=0.57). Due to recruiting patients with predetermined wishes to partake in psychotherapy, the scale Appreciation showed an unacceptable interrater reliability (ICC=-0.01). No effects of age, education, and prior experience on CCT were found.

Our findings indicate that the MacCAT-PT is a reliable instrument to assess patients' CCT, especially when a sole clinical evaluation might be insufficient to identify potential incapacity. It provides insights into CCT as basis for shaping treatment expectations and support psychotherapeutic rapport.





Exploring how patients with Parkinson s disease experience and understand their pain: a qualitative study

Andrea Sondergaard Poulsen, Sophie RosenkJaer

Background: Pain is the most prevalent non-motor symptom in patients with Parkinson's Disease (PD). Yet, few empirical studies have examined pain in PD from a patient perspective.









Perceived and objective measures of stress and their associations with pain and placebo analgesia: preliminary results from chronic back pain patients

Adi Shani

Background: Current treatment for chronic backpain shows little advantage over the positive natural history. A better understanding of pain attenuation through nonspecific components of the therapeutic interaction such as change in stress levels, may improve outcomes. The aim of this study was to determine whether pain and placebo-analgesia are associated with perceived and objective measures of stress.







Nocebo effects and placebo response in patients with MDD receiving OLP-Treatment

Alexandros Matsingos

Informed consent (IC) can induce adverse effects through negative expectations (nocebo effects). Negative expectations can be modified by adding information about the nocebo effect in the IC. In this pilot-study, the impact of additional nocebo information over standard clinical information on the report of medication-related side effects after seven days of open-label placebo (OLP) administration in patients with major depressive disorder (MDD) is investigated. Participants (N=12) were randomized in one group receiving standard IC and one group receiving additional information about the nocebo effect to the standard IC. Depressive symptoms were evaluated during treatment using Montgomery-Åsberg Depression Rating Scale (MDRS). Regression analysis was performed to assess moderators of the nocebo effect. OLP side effects were evaluated using the General Assessment of Side Effects. Preliminary results show significant reduction of MDRS-scores 7 days after OLP-treatment (MT1 = 15.1, SD = 11.249) compared to baseline (MT0 = 19.1, SD = 11.04; t(9) = -2.344, p = .022, d = -.741). A total 30% of participants reported OLP-related adverse effects. Preliminary analyses show no significant effect of the different IC. No moderators of the nocebo effect were identified. Preliminary results show OLP-Treatment reduces MDD-symptoms.







Virtual Reality communication training for optimizing placebo and minimizing nocebo effects

Janine Westendorp

Virtual Reality communication training for optimizing placebo- and minimizing nocebo-effects







Can antidepressant treatment effects be predicted by patients' responsiveness to expectation manipulation?

Eun Jin Shim

Background: One consistently observed finding in the development and maintenance of depression is a strong focus on negative emotions. Recently, we established an experimental protocol that induces a positivity bias by expectation manipulation in healthy individuals. In this ongoing, longitudinal study we are now applying this protocol to inpatients with major depressive disorder (MDD) to investigate whether patients similarly benefit from such manipulation and whether expectation effects are predictive for clinical treatment outcomes.

Methods: In a controlled cross-over design, manipulation of positive treatment expectation is combined with an emotion classification task in MDD inpatients. Weekly follow-up assessments target ongoing pharmacological and nonpharmacological treatment expectation and current depressive symptoms.

Results: Preliminary data show positive expectation effects on mood state in the experimental setting and demonstrate associations between the course of treatment expectation and outcomes.

Conclusions: We are able to elicit positive expectation effects in patients with MDD, which now makes it possible to study the impact of individual expectation responsiveness on antidepressant treatment effects.

Funding: We gratefully acknowledge funding from the German Research Foundation (DFG) - Project-ID 422744262—TRR 289.





Worth a try – Attitudes towards open-label placebos among laypeople and healthcare professionals

Diana Müßgens

Open-label placebos (OLPs) can be effective in ameliorating various clinical symptoms and might thus circumvent the legal and ethical dilemmas posed by conventional (deceptive) placebos. Yet, for OLPs to be used in clinical practice, patients need to be willing to try such treatment. Therefore, we conducted an online survey (November 2019 to April 2021) to assess people's attitudes and preferences toward OLPs. Respondents first received a brief description of OLPs and were informed that initial studies had found positive effects of OLPs on various conditions. Then, attitudes about OLPs and dosage preferences were assessed. Respondents (N = 532) indicated being relatively open toward taking OLPs, especially when prescribed as an additional treatment by a physician. Research studies were listed as the most convincing argument for trying OLPs, with laypeople trusting recommendations by physicians about equally much as research results. Respondents thought OLPs could be most effective for mood and sleep disturbances and chronic pain. Interestingly, respondents preferred taking OLPs once per day but expected greater efficiency for taking them twice daily. Our results suggest that people are generally open to trying OLPs and that therefore, it is well worth exploring how to optimize their application in clinical practice.





4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION II

Not a magic pill – Evidence of absence for cognitive enhancement aftera three-week open-label placebo treatment in healthy young adults

Helena Hartmann

Cognitive functioning is positively associated with educational and occupational performance. Impaired cognitive functioning is a prevalent and burdening symptom of many illnesses. Previous work highlights evidence that openlabel placebos (OLP), treatments openly disclosed to individuals as inert, can improve symptoms such as pain, fatigue, or allergies. Next to promising effects in the clinical domain, preliminary evidence exists for OLPs enhancing cognitive functioning in healthy samples without a clinical burden. Prior work suggests that subjective complaints and symptoms may be more susceptible to placebo and expectation effects compared to objective measures. Here, we used a randomized-controlled design to systematically investigate the effect of a 21-day OLP treatment on cognitive functioning in 78 healthy volunteers. Participants completed subjective and objective measures of cognitive performance before (T0) and after the treatment period (T1). Using a hybrid approach of classic inferential and Bayesian statistics, we found no evidence for beneficial effects of the OLP treatment, neither on subjective nor objective parameters. Our study highlights limits of OLPs particularly with respect to cognitive enhancement in healthy volunteers. These findings are discussed in light of the possible role of motivational aspects and desire for symptom relief in healthy volunteers compared to patient groups.





88

POSTER SESSION II

Open-label-placebo effects in adolescents: An experimental investigation of placebo effects on sadness

Alannah Hahn

Background: Recent studies in adults demonstrate substantial deceptive and open-label placebos (OLP) effects on experimentally induced sadness. Adolescents are susceptible to depression and RCTs on antidepressants suggest a particularly large placebo effect in this age. Given promising OLP effects in adults on sadness, we investigate the effect of an OLP intervention on reported sadness and facial expression in adolescents.

Methods: In an ongoing study, 84 healthy adolescents (12-17y.) are randomized to an OLP or no-treatment control group differing in the intake of an OLP nasal spray. Before and after the OLP intervention, a sad mood induction (sad film scenes + rumination phase) is administered. Sadness is assessed by the Positive and Negative Affect Schedule for children, facial expression (EMG corrugator) is measured continuously.

Results: We expect that, after the OLP intake, the OLP group will report significantly less sadness and show an attenuated facial expression of negative affect than the controls. Compared to our findings in adults, the OLP effect is expected to be even larger.

Conclusions: Demonstrating a sadness protecting OLP effect is a first step towards a potential clinical use. Especially in adolescents, this might be helpful to reduce or even eliminate the need for antidepressants.





Can expectation management and open label placebos improve treatment outcome after gluten exposition in patients with pain?

Lena Paschke

Background:

Patients suffering from fibromyalgia syndrome (FMS), headache or chronic pelvic pain syndrome (CPPS) often complain about food intolerance. They expect specific food, especially wheat, for pain onset and increase. Our study investigates the influence of expectation on the perception of pain during gluten exposure by using open-label-placebos.

Methods:

In the 2x2 factorial clinical trial, 100 patients with FMS, headache or CPPS undergo a ten-day gluten-free diet, followed by a double-blinded gluten provocation along with OLP given with different instructions. This is followed by a three-week OLP therapy. We analyze the role of given information, inflammation-specific parameters and psychometric measurements.

Results:

The test phase of the study (N=10) shows that the trial is feasible and shows clinical changes. Expectation towards the placebos could be changed according to our instructions, which led to a reduction in pain in subjects with a high expectation. Expectation was already relevant during the dietary change, since subjects with a positive expectancy were able to benefit from the dietary change without gluten being identified as a pathophysiological symptom trigger.

Conclusions:

Placebo processes play a role in pain perception during gluten provocation. We expect further data until SIPS conference.





Effects of open-label placebos and pilates on primary dysmenorrhea – a randomized controlled pilot study

Sandra Ort

The aim of this 6-week study was to explore the effects of OLP and Pilates in women with primary dysmenorrhea. 34 participants (23.8±2.7SD years) were randomly assigned to OLP (n=11) or Pilates (n=13) or to a no-treatment control group (n=10). The participants kept an online diary to rate pain and expectations on 11-point NRS. Furthermore, they completed questionnaires (DASS-12, SF-12, TEX-Q) and collected saliva samples to determine prostaglandins (PGF2a, PGE2). The pre-post change in the composite score (minimum, maximum, average) of menstrual pain on days 1-3 of the menstrual cycles was non-significantly larger in the OLP group (-0.9±1.7SD) and the Pilates group (-1.1±1.3SD) compared with the control group (-0.1±1SD). Effect sizes were moderate-to-large (OLP vs. control, p=0.198, d=0.6; Pilates vs. control: p=0.087, d=0.83). Moderate effect sizes were also observed for improvements in physical QoL and PGF2a in the OLP group, and depression scores, stress ratings, PGF2a, and PGE2 in the Pilates group.

Results provide preliminary evidence that OLP and Pilates may improve dysmenorrhea and accompanying inflammatory processes.





91

POSTER SESSION II

Open-label placebos and paced breathing in patients with functional post-COVID syndrome

Katja Weimer

Background: Patients with functional post-COVID syndrome (FPCS) often complain about symptoms that had been improved in other experimental studies with openly administered placebos or heart rate variability (HRV) biofeedback.

Methods: 80 patients with FPCS are randomised to: open-label placebo (OLP; 2 placebos/day), paced breathing training (PBT; 2 sessions/day), both (OLP+PBT), or waitlist (WL). At inclusion, after four and eight weeks, treatment expectations, somatoform complaints, depressiveness, anxiety, as well as cognitive performance are assessed by questionnaires and tests, and an ECG is recorded.

Results: 19 patients have been included (49±14 years, 47% female). Preliminary results show high expectations for symptom improvements (8.8±3.1 of 10), independent of group. There were no symptom changes yet, except for anxiety in the OLP+PBT group vs. WL (p=0.041). T-tests showed trends (p<0.1) toward symptom changes for somatoform complaints in OLP and PBT, and for symptoms in OLP. Cognitive tests and HRV data will be analyzed.

Conclusions: Preliminary data point towards benefits for patients with FPCS through open-label placebo and breathing interventions. However, this is an ongoing study and we are looking forward to present the completed study at the conference.





Open-label placebos - A systematic review and metaanalysis of experimental studies with non-clinical samples

Stefan Schmidt

In a systematic review and meta-analysis we examined whether open-label placebos (OLP) are effective in studies with non-clinical populations. We searched the literature and conducted analyses for self-reported and objective outcomes. We also examined whether the level of suggestiveness of the instructions influenced the effectiveness of OLPs. Twenty studies comprising 1,201 participants were included, of which 17 studies were eligible for meta-analysis. The studies investigated the effect of OLPs on well-being, pain, stress, arousal, wound healing, sadness, itchiness, test anxiety, and physiological recovery. We found a significant effect of OLPs for self-reported outcomes (SMD=0.43; p<.01) but not for objective outcomes (SMD=-0.02; n.s.). The level of suggestiveness of the instructions influenced the effectiveness of OLPs for objective outcomes (p=.02), but not for self-reported outcomes. The risk of bias was moderate for most studies. The overall quality of evidence was low to very low. In summary, OLPs appear to be effective for self-reported outcomes when examined in experimental studies with non-clinical populations. These results will be discussed in relation to a meta-analysis of OLPs in clinical trials.





Patients' beliefs and expectations regarding the efficacy of open label placebo and hypnosis for chronic neuropathic pain

Fernandez Aurore

Open Label Placebo (OLP) is promising for chronic pain. Here, we proposed to compare OLP to hypnosis with analgesic suggestions. This technique also involves expectations and mindset shifts, allowing for contrasts with OLP.

An ongoing RCT randomized patients with chronic pain to OLP, hypnosis or TAU. This work focuses on the description of beliefs, expectations, and preference between OLP and hypnosis prior to randomization. Each participant's beliefs (How much can hypnosis/OLP help patients with chronic pain?) and expectations (How much can hypnosis/OLP help YOU with YOUR pain?) were assessed for both hypnosis and OLP using VASs ("not at all=0"; "very Much=10"). Patients rated their treatment preference on a VAS ("OLP"=0; "hypnosis"=10).

The intermediate analysis (N=56) revealed high beliefs and expectations for both treatments, with significantly higher scores for hypnosis (beliefs: 7,30 ± 2.13 vs. 6.52 ± 2.25 , t(55)=2.5, p=0.02; expectations: 7.28 ± 2.10 vs. 6.15 ± 2.55 ; t(55)=3.8, p<0.001). Their mean preference was in favor of hypnosis (7.21±3.18).

This preliminary analysis shows interesting data on patient preferences when OLP is contrasted with a complementary medicine.





Patients' Attitudes Towards Open-Label Placebo Implementation into Clinical Practice (PATOLP)

Berfin Bakis

Background: Evidence supporting efficacy of open-label placebos (OLP) is promising a breadth of applicability that aligns with ethical principles. OLPs are defined by the transparent delivery of placebos along with a treatment rationale, and actively involving patients and their perspectives in clinical research is highly important as it potentially leads to higher treatment quality, compliance with ethical principles, and better intervention adherence. Therefore, understanding patient's acceptability of OLPs is crucial in order to harness placebo effects ethically in primary care.

Methods: We are conducting five online focus group discussions (FGD) with patients who share a specific condition to investigate attitudes, acceptance, and ideas towards the administration of OLPs in clinical practice. FGD with patients with chronic back pain, chronic migraine, and chemotherapy-induced emesis have already been conducted and two further FGDs with patients with Parkinson's disease and menopausal complaints are envisaged. A semi-structured topic guide with open-ended questions is used. Data is analyzed by the approach of thematic coding.

Results: Emerged themes and excerpts of the FGDs will be presented.

Conclusion: Our results provide insights into attitudes, acceptance, and concerns of patients suffering from different conditions regarding OLP implementation into clinical practice.





Placebo effects after disclosure: the role of self-efficacy

Diletta Barbiani

In open-label placebos, providing truthful information on the placebo upfront (i.e., before placebo administration) may put a break on the opportunity of fully exploiting its potential. This study seeks to investigate whether the disclosure of a placebo procedure during an experimental task, and alongside a particular disclosure style, could foster a different awareness and leverage individuals' self-efficacy. Healthy volunteers performed a motor fatiguing task in four sessions. Placebo groups, i.e., Placebo Pure and Placebo Reveal, received inert transcutaneous electrical nerve stimulation (TENS) in each session with the deceptive information of its force-enhancing properties. Before the final session, participants of the Placebo Reveal group were informed about the placebo procedure, along with a persuasive description of the placebo as a means to bring to light their inherent potential. Placebo groups preserved their force until the last session, and were stronger than two control groups. Self-efficacy was higher in both placebo groups, despite the disclosure. Computational analysis confirmed that self-efficacy acted as a "central hub" for the placebo response, especially for the Placebo Reveal group. This investigation provides a paradigm-shift in terms of exploiting honest disclosures as a tool to boost individuals' self-efficacy.







It's All in Your Mind: A qualitative study on open-label placebo and imaginary pills in test anxiety

Berfin Bakis

Background: Evidence supporting the efficacy of open-label placebos (OLP) is growing and promises applications compatible with basic ethical principles. Pushing this concept further, an imaginary pill (IP) intervention without the use of a physical placebo was developed. To investigate participants experiences and subjective views towards these two interventions a qualitative study was conducted.

Methods: A thematic analysis of semi-structured interviews with 20 randomly selected participants was nested within an RCT investigating OLP and IP in healthy students with test anxiety.

Results: Four key themes were identified: (1) attitude and expectation towards interventions, (2) effect of the pills, (3) applicability of the interventions, (4) characteristics of the imagination. High levels of satisfaction and openness towards reapplying the method in the future were expressed. Initial open attitude towards the intervention often coexisted with a certain level of skepticism. The effects of the pills were experienced on a physical, mental and emotional level and could be observed in both groups.

Conclusion: Both interventions demonstrate beneficial effects and are wellaccepted and -suited for students with test-anxiety. The gained insights may help improve future treatment designs, and the novel IP intervention promises to be as efficacious and acceptable as OLP.





Observational learning in open label placebos and the role of expecation in chronic pain patients

Marie Schwartz

Background: Observational learning as a learning mechanism for analgesic placebo effects was shown in laboratory studies using experimentally induced pain but not in chronic pain. Expectation mediates the learning effects resulting in the placebo effect. The effectiveness of open label placebo (OLP) in chronic pain has been demonstrated. This leads to the research questions: can observational learning enhance the effectiveness of OLP? Can observational learning influence treatment expectation? Can expectation predict treatment outcome?

Method: Sixty-nine chronic back pain patients were divided into three groups: the OLP-plus-observational learning group (OLP+) and the OLP-group (OLP) received the OLP for three weeks. The OLP group additionally saw a video of a patient benefitting from the OLP. The natural history group did not receive the OLP. The posttest was performed after 3 weeks and a follow up after three months. The primary outcome was the chronic pain rating. Secondary outcomes include videotaped everyday exercises.

Hypotheses: We hypothesize that both intervention groups (OLP+ and OLP) will significantly benefit in comparison to the NH group and that the Improvement of the OLP+ group will be significantly larger than the OLP group. Data collection (including follow-up) will be finished in 2 weeks.





Impact of a 12-week open-label placebo treatment on headache days in episodic and chronic migraine

Katharina Schmidt

Migraine is the most common neurological disorder and one of the major causes of years lived with disability. Its treatment (especially of chronic forms) is often challenging and accompanied with adverse effects. Although new therapeutic approaches have recently emerged (eg, calcitonin gene-related peptide antibodies), these are linked to strict prescribing guidelines and therefore limited to only a minority of patients. Recently, RCTs have demonstrated that open-label placebo treatments can lead to significant and clinically relevant improvements of chronic pain conditions.

This multicentre, randomised controlled clinical trial following a parallel group between-subject design aims to systematically investigate the impact of a 12week open-label placebo treatment on moderate to severe headache days (primary outcome) in patients with episodic and chronic migraine in addition to treatment as usual. Secondary outcomes comprise the number of migraine days, pain intensity, intake of acute medication, quality of life, disability, global impression of change, tolerability and a responder rate. Data acquisition is ongoing and results will be presented at the conference.





The case for Open Label Placebo

Claudia Carvalho

We argue that OLP occupies a unique niche among placebo research, describe key aspects of OLP that distinguish it from deceptive placebo, and present a review of the growing body of evidence that points to its usefulness across a range of medical conditions. We claim that OLP interventions must follow a specific procedure to be effective that share features with hypnotic techniques and psychotherapy interventions in the sense that they all target to alter subjective, behavioral, and physiological responses, access and bolster personal resources and facilitate self-regulation. We present a utility approach to OLP to guide its effective, responsible, and ethical usage in clinical and research contexts.







100

POSTER SESSION II

Implicit and explicit expectations of side effects caused by COVID-19 and flu vaccinations

Anna E. Borgmann

Background: Treatment expectations can alter the probability of experiencing unpleasant side effects from an intervention, including vaccinations. To date, expectations have mostly been assessed explicitly via self-report, which bears the risk of bias. This study aims to measure implicit expectations of side effects from COVID-19 and flu vaccinations and compare measures of implicit and explicit expectations.

Methods: N = 248 participants completed an online survey assessing explicit and implicit expectations, as well as vaccine-related topics and personal characteristics. A Single Category Implicit Association Test (SC-IAT) was developed to assess implicit side effect expectations. Explicit side effect expectations were measured with the Treatment Expectation Questionnaire (TEX-Q).

Results: Whereas explicit and implicit expectations regarding the COVID-19 vaccine were significantly correlated (r = -.33, p < .001), those correlations could not be found regarding the flu vaccine (r = -.07, n.s.). Only explicit measures predicted the intention to receive further vaccinations and the paricipant's current vaccination status in multivariate regression models.

Conclusion: Expectations to experience side effects from two vaccinations can be measured implicitly, in addition to explicit measures. Further investigation needs to determine the relative contribution and additive value of using implicit measures to assess treatment expectations.



4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



POSTER SESSION II

Emergency presentations due to headache after media coverage of SARS-CoV2- vaccination-associated cerebral venous or sinus thromboses in a tertiary emergency department in Essen, Germany

Livia Asan

Amidst the fight against the COVID pandemic, the warning about an increased risk of cerebral venous or sinus thrombosis (CVST) after vaccination against SARS-CoV2 seemingly lead to patients "flooding" ERs with complaints that could resemble symptoms of CVST, mainly headache. We suspect disproportionately high presentation rates with headache also in neurologic emergency wards. In this analysis, we retrospectively investigated weekly presentation numbers of patients complaining of headache before and after the first announcement of this potential health risk after vaccination (March 11, 2021) in a tertiary neurologic emergency department at Essen University Hospital, Germany. Using public data from the Robert-Koch-Institute, we relate them to vaccination rates in North Rhine-Westphalia and Essen. Mean weekly presentations rates due to headache were significantly higher in the 5 weeks after the first media report, amounting to 274% of presentation rates during the 5 weeks before. The increase in vaccination rates alone did not explain headache presentations. With these data, we want to spark discussions about the impact of media coverage and public communication on the utilization of medical services, potential harm to individuals and health care systems, and how to avoid such 'large scale' nocebo effects in the future.







102

POSTER SESSION II

Is the electrogastrogram (EGG) a suitable psychophysiological measure of nocebo effects in the gutbrain axis?

Rossitza Draganova

Background: Psychophysiological correlates underlying negative expectancy effect on the autonomic nervous system remain rarely studied, especially in the context of visceral pain. Electrogastrogram (EGG) recordings of gastric myoelectric activity, which is regulated by the autonomic nervous system, could represent a novel measure relevant to nocebo effects in the gut-brain axis.

Methods: Within an ongoing experimental study on visceral and somatic pain modulation by nocebo effects in healthy volunteers, we recorded EGG together with electrocardiogram (for heart rate variability, HRV) and behavioral measures relevant to expectations, stress, and pain perception. Based on 16min time segments, recordings were analyzed by running Fourier power spectra (EGG) and time- and spectral HRV analysis.

Results: In a nocebo group involving a negative learning experience regarding pain, a higher instability coefficient in frequency and amplitude of the dominant EGG activity was observed in the test phase.

Conclusions: EGG analyses may constitute an additional psychophysiological measure to elucidate nocebo mechanisms relevant to conditions involving the gut-brain axis. Further analyses are needed to elucidate the role of stress, and to compare the sensitivity and specificity with HRV measures reflecting cardiac sympathovagal balance.





(Open label) placebo effects on sleep quality, sleep duration, appetite and food cue reactivity

Jonas Potthoff

More than one-third of the population in German-speaking countries suffers from poor sleep quality. Short sleep duration and poor sleep quality are risk factors for weight gain and obesity. Observational studies suggest an increased craving for high-fat, high-carbohydrate foods and subsequent intake of these foods in sleep-deprived or sleep-disordered people. Open Label Placebos (OLPs) are promising tools to not only reduce stress and other negative affective states but also improve sleep quality. However, findings on sleep quality are preliminary, and evidence is still limited.

In the current study, we assess how a one-week OLP intervention (compared to a deceptive placebo intervention and a control group with no intervention, N = 50 per group) affects sleep quality, sleep duration, appetite, food choices during breakfast, and visual food cue reactivity. We will complete data collection for the present preregistered study in January 2023.





4th International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) 10 – 13 May, 2023 – Meet us in Duisburg, Germany



104

POSTER SESSION II

Interindividual differences in anhedonia moderate antidepressant placebo effects on heart rate in healthy individuals.

Li-Ching Chuang

Treatment expectations as induced by antidepressant placebos have been shown to reduce depressive symptoms in clinical applications. However, much of this work has heavily relied on self-report measures which are prone to demand effects in the context of explicit expectation manipulations. In addition, better knowledge about moderating personality variables is needed to further understand antidepressant placebo responses and to identify targeted approaches for individuals who may benefit from such interventions. Here, we administered placebo pills to n = 56 healthy participants and manipulated treatment expectations by labeling the pill as either inactive or antidepressant. Depressed mood was manipulated experimentally with a musical Velten induction and participants' current state was assessed via rating scales and heart rate. Trait anhedonia was measured as a depression-related personality variable which potentially moderates antidepressant placebo responses.

Results showed that the depressed mood induction led to a reduction of selfreported positive affect. Moreover, antidepressant treatment expectations reduced cardiac slowing to depressed mood in high vs. low anhedonic subjects. Taken together, the present findings suggest that individuals with high levels of trait anhedonia may be more susceptible to antidepressant placebo effects, and that placebo responses can be observed beyond self-reports on the cardiovascular level.





Generalization of placebo and nocebo effects: a narrative review

Lingling Weng

Placebo- and nocebo(-like) effects are beneficial or adverse treatment outcomes due to expectancies. Importantly, these effects may generalize over stimuli and over symptoms, which can provide insight into carryover effects of treatment history in the clinic. However, it remains unclear to what extent generalization occurs in placebo- and nocebo(-like) effects. This review outlines the current literature on stimulus and response generalization of placebo- and nocebo(like) effects on somatic sensations that are commonly reported (i.e., pain, itch, dyspnea, nausea, and fatigue). A literature research was performed in the databases PubMed, Web of Science, and PsycINFO, resulting in 22 studies. These studies indicated that placebo- and nocebo(-like) effects can generalize over stimuli (at perceptual, categorical, and treatment levels) and over responses (i.e., within and across modalities). Evidence suggests that generalization of placebo and nocebo effects is more likely when the generalization stimuli and responses more closely resemble the initial stimulus or response. We conclude with recommendations for future experimental and clinical research on generalization of placebo- and nocebo(-like) effects. Understanding generalization of these effects ultimately helps healthcare providers to prevent carryover effects of treatment failure as well as harness carryover effects of treatment success.







Difference in responsiveness to experimentally-induced nocebo hyperalgesia in fibromyalgia patients versus healthy controls

Merve Karacaoglu

Chronic pain patients experience pain, and potential treatment failure, more frequently in daily-life than healthy individuals. Therefore, they might be more susceptible to nocebo effects than healthy individuals. The current study investigated group differences in the induction and extinction of nocebo effects on pressure pain at baseline (Patient=37;Control=32) and 1-month follow-up (Patient=29;Control=27) in female patients with fibromyalgia and matched healthy controls. Nocebo hyperalgesia was induced via conditioning and verbal suggestions and then decreased via extinction. The same experimental procedures were repeated one-month later to explore stability.

Results suggest that nocebo hyperalgesia was induced in the healthy control group during baseline and follow-up. In the patient group, nocebo effects were only induced during follow-up, without group differences. Extinction was only observed during baseline in the healthy control group. Comparisons across sessions suggest that the overall magnitudes of nocebo hyperalgesia and extinction were stable over time and across groups. Contrary to our hypothesis, patients with fibromyalgia did not have stronger nocebo hyperalgesia than healthy controls. The current direction of findings could be explained by the limitations surrounding the nocebo-conditioning paradigm as well as the potential learning differences in patients.





Magnitudes and predictors of placebo analgesia responses in pharmacological and non-pharmacological trials: A meta-analysis of individual patient data

Sigrid Juhl Lunde

Background: There is a great interest in estimating the magnitude of placebo responses across pharmacological and non-pharmacological trials. Yet, it is unclear whether more intense placebo procedures like sham acupuncture are associated with larger analgesic responses than less intense placebo pills, and little is known about factors predicting these responses.

Methods: This meta-analysis included individual patient data (N = 2768) from placebo arms of 11 randomized controlled trials (RCTs): Nine pharmacological RCTs and two acupuncture RCTs. All trials were conducted in patients with chronic pain (osteoarthritis or low back pain). The placebo response was calculated as the change in pain intensity (0-100) between baseline and week 12.

Results: A random effects model demonstrated that trials using pills or conducted in osteoarthritis had smaller placebo responses compared to acupuncture and low back pain (both p<0.001). A mixed effects model showed that treatment vehicle interacted significantly with baseline pain, premature termination, and the presence of adverse events in predicting the placebo responses. Predictors explained 20-25% of the individual variance in placebo responses.

Conclusions: Placebo sham acupuncture accounted for larger placebo responses than inactive placebo pills. Individual patient-level factors explained only a small amount of this variance.





108

POSTER SESSION II

Amplified gut feelings under inflammation and negative mood: A randomized fMRI trial on nocebo effects in a model of interoceptive pain

Sven Benson

Background: Nocebo effects can have detrimental effects on health outcomes, including interoceptive pain. It is unknown whether inflammation and negative mood as vulnerability factors interact in their impact on neural mechanisms engaged during the generation of conditioned negative expectations and the experience of interoceptive pain.

Methods: We performed a double-blind, placebo-controlled, crossover fMRI-trial in N=39 healthy volunteers, involving 2 study days with i.v. administration of lowdose lipopolysaccharide (inflammation condition) or saline (control). To test the interaction of inflammation and mood, scanning sessions were conducted in an experimentally-induced negative and in a neutral mood state on both study days. In all sessions, identical individually-calibrated cued painful rectal distensions were implemented.

Results: In response to conditioned predictors of interoceptive pain, we observed a significant inflammation X mood interaction for the activation of the caudate nucleus during anticipation. Perceived pain unpleasantness was enhanced in the condition combining stress and inflammation, and correlated significantly with caudate engagement.

Conclusions: Our finding may reflect a nocebo mechanism generated by the interaction of inflammation and negative mood, which contributes to amplified interoceptive pain experience. Patients with chronic inflammation and comorbid mood conditions may be more vulnerable to nocebo effects.




109

POSTER SESSION II

Cognitive control of pain in Aging – comparison of different pain modulation strategies

Angelika Dierolf

Background:

While older people report acute and chronic pain more often than younger people, and, therefore, would benefit significantly from non-pharmacological pain treatment, little is known about how age affects different psychological strategies of pain modulation. The few studies on cognitive distraction from pain suggest a reduced pain relief in older adults, whereas studies on placebo analgesia revealed inconsistent results. So far, verbal distraction and hypnotic analgesia have hardly been investigated in aging.

Methods:

Healthy young and older participants underwent either a cognitive pain distraction task, a placebo analgesia realized with a sham TENS intervention, a hypnotic analgesia intervention or a verbal pain distraction intervention, while receiving non-painful and moderate painful individually adjusted transdermal electrical pulse trains to the inner forearm. Pain ratings and pain-related evoked potentials via EEG were recorded.

Results:

First analyses on the currently small sample suggest a differential impact of age on pain modulation strategies. Since the current sample size is too small to draw reliable conclusions, results will be presented and discussed at the conference.

Conclusion:

Our results will contribute to a deeper understanding on the efficacy of cognitive pain modulation in aging, helping to optimize pain treatments in this population.





Neuroticism and low Extraversion show small associations with side-effect Expectations

Anton Fischer

Broad anxiety- and depression-related personality traits like neuroticism and low extraversion have previously been investigated in the context of nocebo effects. While mechanisms underlying potential personality-nocebo links are largely unknown, pre-treatment side effect expectations may play a crucial role. Here we tested if neuroticism and low extraversion are linked to higher side effect expectations in data from n = 748 participants from k = 7 studies involving assessments of expectations regarding a manipulation of pain or affective distress (DFG - ProjectNr.422744262). We measured extraversion and neuroticism by factorizing various scales (BFI 10, BIS/BAS, STADI) and correlated both factors with expectations regarding side effects across seven studies with medical manipulations. Our results show that a Neuroticism and an Extraversion factor show low but significant and unique correlations with side effects (r=.09 and r = -.10, p < .005 respectively). The results suggest, broad personality traits only show low direct associations with expectations of side effects. Future work should investigate more specific facets of these (and other) traits, neurobiological predictors and contextual factors that may moderate associations between personality and side effect expectations. Future studies should further test whether interindividual differences in pre-treatment side effect expectations indeed predict nocebo effects.







Predicting Placebo: Brain Structural Signatures in Placebo Responders with Temporomandibular Disorder

Jewel White

Placebo effects, as a form of descending pain modulation, have a definitive neurobiological basis involving distinct cortex activations. However, a major gap in our understanding is whether other neurobiological characteristics, such as brain structure, contribute to the variability of placebo effects among chronic pain patients. To address the gap, we assessed the placebo responses of participants diagnosed with Temporomandibular Disorders (TMD) and identified each participant as a placebo responder or non-responder. We then performed voxel-based morphometry (VBM) analysis of T1-weighted images to determine single-group correlations between local grey matter volume (GMV) and placebo responses in TMDs.

Data on 72 TMD participants in Phase 2 of our study identified 32 TMDs as responders, and 40 as non-responders. Behaviorally, responders exhibited significantly greater differences in visual analogue scale pain ratings than nonresponders (F1,69=60.41, p<0.001) controlling for age, sex and race. VBM analysis revealed a significantly positive correlation between placebo responses and GMV in TMDs (p<0.05, FWE-corrected) in the lingual gyrus, parahippocampal gyrus, temporal occipital fusiform cortex, supramarginal gyrus, superior parietal lobule. These results suggest a role for structural signatures as predictors of placebo responses in TMD patients.





Potential nocebo effects in primary dysmenorrhea - a mixed-methods approach

Verena Thomann

Negative expectations and emotions are known to trigger nocebo effects and may thus play a role in cyclic menstrual pain. We performed a case-control study in 20 women with primary dysmenorrhea and 20 matched controls. Participants completed the Depression Anxiety Stress Scale (DASS) and kept an online diary for 15 days before and during menstruation to rate expected and perceived menstrual pain as well as negative emotions when thinking about the next menstruation. Daily salivary samples served to evaluate the cortisol awakening response (CAR). Semi-standardized interviews were conducted to explore prior experiences of women with dysmenorrhea. Compared with controls, women with dysmenorrhea scored significantly higher in DASS-anxiety and pain expectation, and showed more negative emotions in the days before menstruation (p's<.05). The CAR did not differ between groups. Higher menstrual pain was associated with higher age and a blunted CAR (p's<.05) in women with dysmenorrhea. Content analysis of the interviews supported the notion that learning mechanisms could play a role in the development of dysmenorrhea.

Results confirmed increased negative expectations and emotions before menstruation in women with cyclic menstrual pain, which may contribute to learned nocebo effects in primary dysmenorrhea.





Influencing insulin system by placebo effect in patients with diabetes type-2 and healthy controls

Aleksandrina Skvortsova

Background: Placebo effect affects metabolism in healthy volunteers. It remains unknown if patients with metabolic disorders, such as diabetes type-2, can benefit from placebo interventions. This study investigated effects of pharmacological conditioning with intranasal insulin.







114

POSTER SESSION II

Placebo Analgesia in Aging – the Impact of age-related cognitive decline

Angelika Dierolf

Background:

Placebo analgesia is a cognitive pain modulation mechanism with high relevance in pain treatment. Older people would benefit especially form it, since they are disproportionately affected by pain, while pharmacological treatments are less appropriate. Although aging is known to affect physiological aspects of pain perception, the few studies on the effects on placebo analgesia revealed inconsistent results. Executive functions (EFs) have been considered a key factor in the age – pain relationship, indicating age-related decline in EFs being associated with reduced placebo analgesia in older adults.

Methods:

Placebo analgesia was assessed in 42 older and 39 younger adults via a sham trans-cutaneous electrical nerve stimulation (TENS) intervention, while participants received non-painful and moderately painful electrical stimuli to their arm. Beforehand, participants completed two EF tasks. A 64-channel EEG was recorded throughout all tasks.

Results:

Placebo analgesia was demonstrated in both age groups as evident in pain ratings and electrophysiological responses. However, the placebo effect magnitude in older adults was predicted by EFs showing age-related cognitive decline.

Conclusion:

Our results indicate that EFs play a key role in determining placebo analgesia efficacy in older adults, suggesting the use of EF trainings in optimizing pain treatments.





What to do about nocebo effects: can we reduce them via (open-label) counterconditioning or extinction?

Simone Meijer

Background:

Nocebo effects can adversely affect the experience of physical symptoms. It is therefore important to study how we can reduce nocebo effects, such as using counterconditioning. For clinical care, especially open-label procedures could be promising. However, only one study investigated open-label counterconditioning and it is unclear whether it is as effective as closed-label procedures and whether it can also effectively reduce nocebo effects induced by closed-label procedures.

Methods:

In a randomized controlled trial, we investigated in 66 healthy female participants: 1) whether conditioned nocebo effects on pain can be reduced via open-label counterconditioning, closed-label counterconditioning, or extinction and 2) whether these procedures differ in efficacy.

Results:

A significant reduction of nocebo effects was found after open-label counterconditioning (d = 1.13), closed-label counterconditioning (d = .69) and extinction (d = .66). No conclusive evidence on the absence or presence of a difference in efficacy between open- and closed-label counterconditioning was found.

Conclusions:

In addition to more deceptive nocebo-reduction procedures, open-label counterconditioning can modulate nocebo effects on pressure pain. This provides promise in designing non-deceptive learning-based treatments to reduce nocebo effects in patients with chronic pain disorders.





Mindset interventions to facilitate taking cold showers: A randomized controlled study

Emil Nissen

Background: Studies show that cold showers have several beneficial effects for physical and mental health. Also, cold showers have a significant impact on reducing CO2 emissions. However, taking cold showers typically is not an easy habit to sustain. Our research aims to find ways of facilitating taking cold showers using mindsets, which have a significant impact on human behavior.

Methods: A sample-size calculation showed that 200 participants are needed. Participants are randomized to either one of four mindset intervention groups or the control group. Each group receives a short information video about climate change and the impact of taking cold showers. The four mindset interventions additionally receive a short video providing a mindset, aimed at helping participants taking cold showers for the study's duration (12 weeks). Participants fill out weekly online surveys assessing their showering behavior.

Results: Preliminary results will be reported.

Conclusion: Taking cold showers has several positive effects on health and CO2 emissions. However, implementing the habit of taking cold showers comes with challenges. In this study, we want to investigate if providing mindsets is a possible approach to tackle these challenges.





Feasibility of using counterconditioning for reducing nocebo effects in chronic pain patients

Simone Meijer

Background:

Physical symptoms can sensitize due to negative learning experiences (e.g. by classical conditioning) leading to nocebo effects. As conditioned effects can be reduced by counterconditioning, this procedure could be a promising method for reducing conditioned nocebo effects, and thus sensitized physical symptoms in patients, such as in fibromyalgia.

Methods:

In the current study, we aimed to investigate the feasibility of an openlabel counterconditioning intervention on pain in 14 patients with fibromyalgia. A nocebo effect was induced in the lab and afterwards a 6-week counterconditioning intervention was used to reduce the nocebo effect.

Results:

Preliminary results indicate a drop-out rate of 26% (main intervention). Participants were satisfied with the procedure, both in terms of contact with the researcher as treatment duration and they graded the procedure as 7.6/10. A reduction of the nocebo effect does appear to be present in the intervention group, although no formal conclusions can be drawn, given the nature of the study.

Conclusions

These results show that using a counterconditioning protocol to reduce nocebo effects is feasible in patients with fibromyalgia. A large-scale trial could further investigate treatment efficacy as well as generalization of the effects to clinical practice.





Placebo/Nocebo research in the post-GWAS era: A narrative review

Takeshi Watanabe

Background:

Genome-wide association studies (GWASs) have unveiled the influence of various gene polymorphisms for human traits, lifestyle, and the risk of diseases. Moreover, the results of GWASs have been applied to various post-GWAS analyses. On the other hand, several studies have also shown the association between gene polymorphisms and placebo/nocebo, even though most of these studies are candidate-gene approach.

Methods:

A PubMed search was performed using keywords related to "placebo", "nocebo", "placebome", "post-GWAS". The search results were reviewed, and relevant references were selected. In addition, important references from the field of placebo/nocebo study, and epidemiology were added. Post-GWAS analytical methods, that might be useful to placebo researchers were selected.

Results:

Some studies of the association between gene polymorphisms and placebo/ nocebo have been reported. Several methods found in the present study may be applicable to placebo/nocebo research. Results will be presented at the 4th International conference of the Society for Interdisciplinary Placebo Studies (SIPS) conference, Duisburg, Germany, May 2023.

Conclusions (preliminary):

This narrative review is expected to provide an overview of genetic studies of placebo and nocebo, and future directions of post-GWAS analyses in the field of the placebo/nocebo research.





Open-Label Placebo Treatment for Experimental Pain: A Randomized-Controlled Trial with Placebo Acupuncture and Placebo Pills

Seoyoung Lee

An open-label placebo (OLP) is a placebo treatment in which the patient is aware that the treatment is a placebo. OLPs are considered effective for reducing pain, and previous studies have shown a stronger placebo effect for placebo acupuncture than for placebo pills. However, different types of OLPs have not yet been extensively compared yet, especially for the OLP effect of placebo acupuncture.

In this study, we compared the analgesic effects of OLP pills, OLP acupuncture, and a no treatment condition in healthy participants, then examined the factors contributing to the open-label placebo effect. Thirty-four healthy volunteers received three different treatments ("OLP-pill," "OLP-acupuncture," and "no treatment") on three separate days in random order. Before and after the treatment, heat pain stimuli were applied to the participants' hands, and pain tolerance, intensity, and unpleasantness were measured using a visual analogue scale (range, 0–10).

Data of thirty-one participants were included in the analysis. We found significant analgesic effects of the placebo pill and placebo acupuncture in the OLP condition. Regression analyses revealed that expectations regarding the treatment and practitioner identity influenced the analgesic effects of OLP acupuncture. There was no adverse event for both placebo interventions. Expectations regarding treatment and practitioner identity influenced the analgesic effect of placebo acupuncture without deception. These findings provide new information regarding the cognitive factors underlying pharmacological and non-pharmacological treatments.

