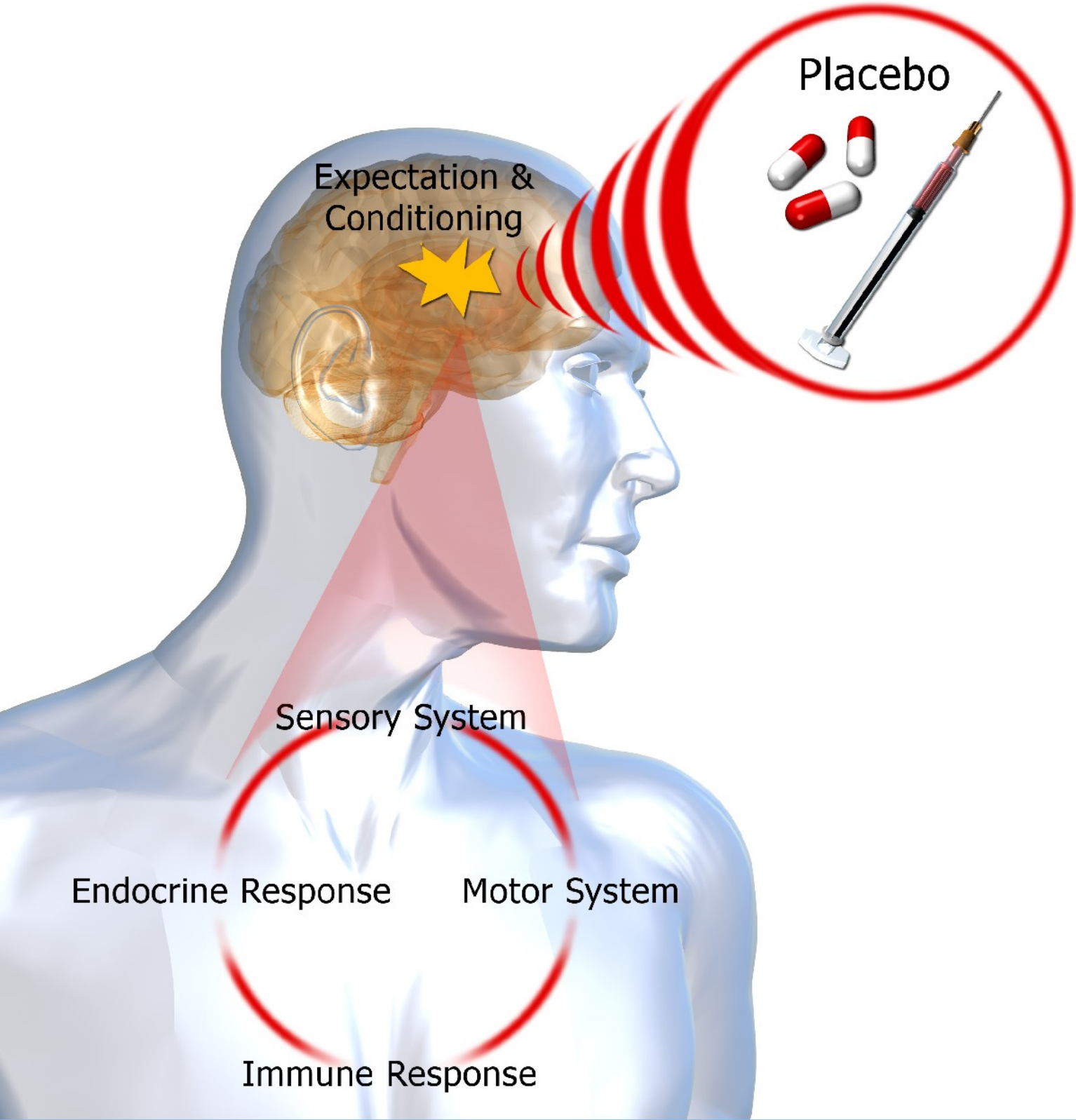
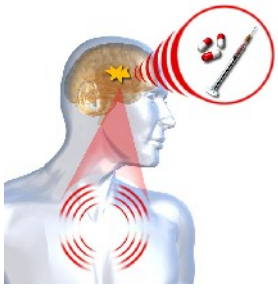
Mechanisms of Placebo/Nocebo Responses



28 - 30 November 2007 Tutzing, Germany

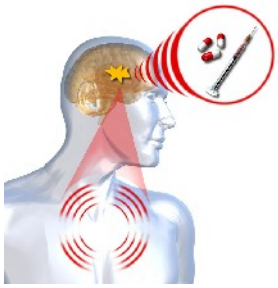
Funded by Volkswagen Foundation VolkswagenStiftung

Symposium on
Mechanisms of Placebo/Nocebo Responses



The widespread use of the term "placebo" in the medical literature as well as the frequent implementation of "placebo controls" in experimental protocols illustrate the importance of this phenomenon in biomedical sciences. If one considers that the modern clinical approach of evidence-based medicine basically relies on the superiority of a treatment over a placebo effect, the central role of the placebo response becomes even more evident. Thus, a refined understanding and knowledge regarding the placebo is obviously essential in modern medicine. The crucial questions which remains to be fully answered pertain to the "where", "when" and "how" of placebo responses. This symposium aims to address these questions from a truly interdisciplinary and international perspective. It is nothing but amazing that so many experts from all over the world come together to discuss the underlying mechanisms of placebo effects and their role in different diseases and different therapeutic interventions. In fact, until some years ago, the understanding of the mechanisms of the placebo effect could be explained in one, perhaps two lectures only, in which a few hypotheses rather than facts could be discussed. Today, we believe that the growing interest in and the recognition of placebo research resides in its multifaceted relevance, which involves key issues in modern science, from neurobiology to philosophy, from ethics to social psychology, and from clinical trial design to medical practice. Therefore, we hope that this symposium presents the starting point for a beginning decade of exciting discoveries on how the brain and placebo affects the aetiology, course, and treatment of diseases.

Fabrizio Benedetti, *Turin* Manfred Schedlowski, *Essen* Paul Enck, *Tübingen*



Organizers	Manfred Schedlowski, Essen Paul Enck, Tübingen Fabrizio Benedetti, Turin
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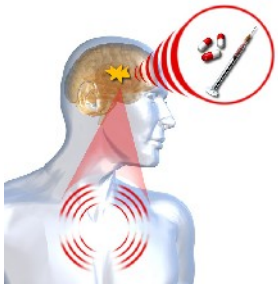
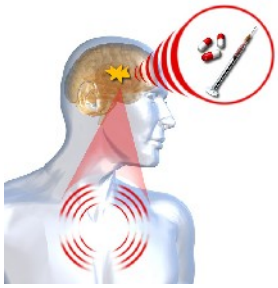
Symposium on
Mechanisms of Placebo/Nocebo Responses



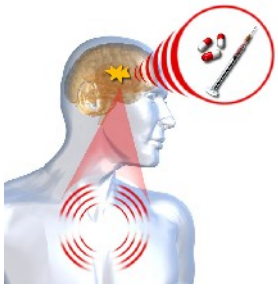
Wednesday, 28th November 2007

4:00 pm - 4:15 pm	**Welcome address** *Manfred Schedlowski, Christoph Meier, Paul Enck*
4:15 pm - 6:45 pm	**General Concepts of Placebo/Nocebo Effects** ***Chair:*** *A. Jon Stoessl*
4:15 pm - 5:00 pm	Placebo and placebo-related effects across diseases and treatments *Fabrizio Benedetti*
5:00 pm - 5:30 pm	Abolish the placebo concept or: Can scientific nonsense be highly effective? *Klaus Linde*
5:30 pm – 5:45 pm	**Coffee / Tea-Break**
5:45 pm - 6:15 pm	Predictors of the placebo/nocebo response in clinical trials *Paul Enck, Sibylle Klosterhalfen*
6:15 pm – 6:45 pm	Can the placebo be administered in a dose-dependent manner? *Ted J. Kaptchuk*
6:45 pm – 8:00 pm	**Dinner**
8:00 pm – 9:00 pm	**Short communication I** ***Chair:*** *Manfred Schedlowski*
8:00 pm – 8:15 pm	Operant conditioning as a putative mechanism of peripheral placebo effects *Karin Meissner*
8:15 – 8:30 pm	The placebo effect in the context of working memory performance: A naloxone study with healthy volunteers *Jair Stern, Victor Candia, Roseline Porchet, Dominik Ettlin, Gerd Folkers, Georg Schönbächler*
8:30 pm – 8:45 pm	Mirror, mirror on the wall: Placebo effects that exist *only* in the eye of the beholder *John M. Kelley, Ted J. Kaptchuk, Patrick R. Boulos, Peter A.D. Rubin*
8:45 pm – 9:00 pm	The role of learning in placebo and nocebo responses *Luana Colloca*



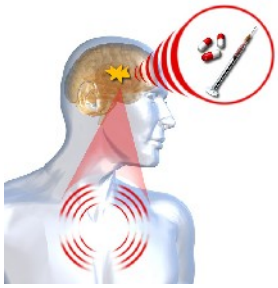
Thursday, 29th of November 2007

7:30 am	**Breakfast**
8:30 am - 9:30 am	**Learning and Memory** ***Chair:*** *Jon-Kar Zubieta*
8:30 am - 9:00 am	Modulating placebo effects: Insights from memory research *Yadin Dudai*
9:00 am - 9:30 am	Conditioned analgesia in mice selected magnitude of stress-induced analgesia *Artur H. Swiergiel*
9:30 am - 10:30 am	**CNS-Immune Interaction** ***Chair:*** *Predrag Petrovic*
9:30 am – 10:00 am	Behaviorally conditioned immune responses *Manfred Schedlowski*
10:00 am – 10:30 am	Receptor sensitivity and regulation: A target for the placebo response? *Cobi J. Heijnen*
10:30 am – 11:00 am	**Coffee / Tea-Break**
11:00 am – 12:00 am	**Parkinson`s Disease and Reward Mechanisms** ***Chair:*** *Serge Marchand*
11:00 am – 11:30 am	Parkinson's as a model to study the placebo effect *A. Jon Stoessl, Sarah C. Lidstone, Raul de la Fuente-Fernandez*
11:30 am – 12:00 am	The placebo-reward hypothesis: Biochemical bases and predictions *Raul de la Fuente-Fernandez*
12:00 am – 1:00 pm	**Short communication II** ***Chair:*** *Fabrizio Benedetti*
12:00 am – 12:15 am	Opioids and fear conditioning: Effects of the opioid antagonist naloxone on pain processing *Falk Eippert*



Thursday, 29th of November 2007

12:15 am – 12:30 am	The effect of subject and experimentor gender on pain and placebo analgesia *Per Aslaksen, Magne Arve Flaten*
12:30 am – 12:45 am	Fibromyalgia: Changes in the neurobiology of expectancy-mediated analgesia *Philippe Goffaux, Juliana Barcellos de Souza, Serge Marchand*
12:45 am – 1:00 pm	The contribution of left and right prefrontal cortex to the placebo and nocebo process by means of a pain paradigm and transcranial magnetic stimulation (TMS) in healthy volunteers *Peter Krummenacher, Victor Candia, Gerd Folkers, Manfred Schedlowski, Jair Stern, Georg Schönbächler*
1:00 pm – 2:00 pm	**Lunch break**
2:00 pm – 5:30 pm	**Pain** ***Chair:*** *Ted J. Kaptchuk*
2:00 pm – 2:30 pm	Cognitive processes inducing placebo analgesia *Predrag Petrovic*
2:30 pm – 3.00 pm	Expectancy modulation of pain affect: Electrophysiological evidence and opioid mechanisms *Tor Wager*
3:00 pm – 3:30 pm	Neuroimaging of dopaminergic and opioid mechanisms in placebo and nocebo effects *Jon-Kar Zubieta*
3:30 pm – 4:00 pm	**Coffee / Tea-Break**
4:00 pm – 4:30 pm	Psychophysical and electrophysiological studies of the placebo responses in healthy subjects and patients suffering from chronic pain syndromes *Serge Marchand*
4:30 pm – 5:00 pm	Placebo analgesia, classical conditioning and endogenous opioids *Christian Büchel*
5:00 pm – 5:30 pm	Emotional factors in placebo analgesia *Magne Arve Flaten, Per Aslaksen*
5:30 pm – 5:45 pm	**Break**

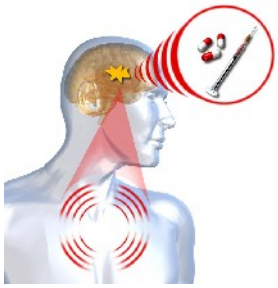


Thursday, 29th of November 2007

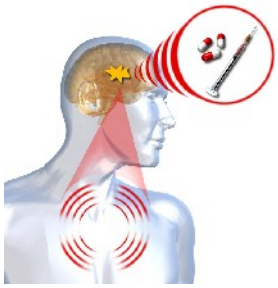
5:45 pm – 7:00 pm	**Short communication III** ***Chair:*** *Paul Enck*
5:45 pm – 6:00 pm	Behavioral conditioning of anti-histamine effects in patients with allergic rhinitis *Marion U. Goebel, Ulrich R. Hengge, Manfred Schedlowski*
6:00 pm – 6:15 pm	Brain substrates of suppression in posthypnotic amnesia *Avi Mendelsohn, Yossi Chalamish, Yadin Dudai*
6:15 pm – 6:30 pm	Investigation of expectation and the placebo effect in Parkinson's disease using high-resolution positron emission tomography (PET) with [^{11}C] raclopride *Sarah C. Lidstone, E. Bogusz, K. Dinelle, S. Blinder, T.J. Ruth, A.G. Phillips, V. Sossi, A.J. Stoessl*
6:30 pm – 6:45 pm	Why aren't we all placebo responders? – Possible genetic underpinnings of the placebo effect *Karin Jensen, Predrag Petrovic, Eva Kosek, Martin Ingvar*
6:45 pm – 7:00 pm	Influencing pain behaviors through placebo effect in patients with chronic low back pain (CLBP) *Regine Klinger, Jens Tretrop*
7:00 pm – open end	**Dinner**

Friday, 30th of November 2007

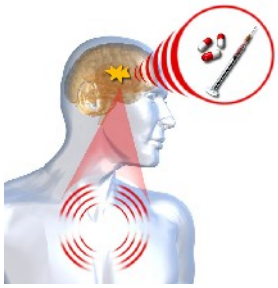
7:30 am	**Breakfast**
9:00 am – 12:00 am	**Clinical implications of the placebo/nocebo response** ***Chair:*** *Cobi J. Heijnen*
9:00 am – 9:30 am	Ethical aspects of placebo/nocebo *Urban Wiesing*
9:30 am – 10:00 am	Is the antianalgesic effect of acupuncture a "placebo"-response? *Gustav Dobos, Iven Tao, Andreas Michalsen, Frauke Musial*
10:00 am – 10:30 am	Physician-patient relationship and the placebo response *Hans-Christian Deter*



10:30 am – 11:00 am	Oxytocin enhances the experience of attachment security *Anna Buchheim, Markus Heinrichs, Eva Koops, Harald Gündel*
11:00 am – 11:30 am	Metaanalysis of placebo groups in antidepressant trials *Winfried Rief*
11:30 am – 12:00 am	**Closing remarks** *Fabrizio Benedetti* *Manfred Schedlowski* *Paul Enck*
12:00 am – 1:00 pm	**Lunch / farewell**
1:00 pm – 2:30 pm	**Meet the press**



Abstracts



Wednesday, 28th November 2007, 4:15 pm - 6:45 pm

General Concepts of Placebo/Nocebo-Effects

Chair: A. Jon Stoessl

Placebo and placebo-related effects across diseases and treatments

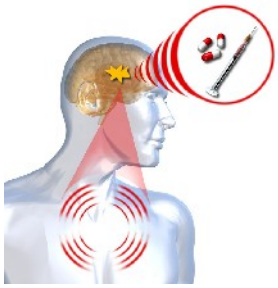
Fabrizio Benedetti
Department of Neuroscience, University of Turin Medical School, and National Institute of Neuroscience, Turin, Italy

The placebo effect has passed in recent times from a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation in its own right. It is now clear that the term placebo effect is too restrictive and, in fact, many placebo-related effects have recently been investigated. A placebo effect differs from a placebo-like effect in that the former follows the administration of a placebo whereas in the latter no placebo is administered. However, in both cases, the psychosocial context around the treatment plays a key role. In recent years, placebo and placebo-related effects have been analyzed with sophisticated biological tools that have uncovered specific mechanisms at both the biochemical and cellular level. Many diseases and treatments have been found to be affected by placebos, like pain, movement disorders, some mental disorders, the immune and endocrine systems, the cardiovascular and respiratory systems. What has emerged from recent research is that these psychosocial-induced biochemical changes in the patient's brain and body in turn may affect the course of a disease and the response to a therapy. The many implications and applications of these findings will be discussed.

Abolish the placebo concept or: can scientific nonsense be highly effective?

Klaus Linde
Centre for Complementary Medicine Research, Department of Internal Medicine II, Technical University Munich, Germany

Available research suggests that the size of placebo effects can vary with the type, context and meaning of the placebo intervention. This contribution will focus on potential methodological consequences of these findings for clinical research and health care decision making. There is widespread agreement that any discipline whose practitioners make specific claims for being able to treat specific conditions should have evidence of being able to do this above and beyond the placebo effect. Therefore, placebo-controlled trials are fundamental in the evaluation of effectiveness. Interventions for which "specific" effects over placebo cannot be shown are considered ineffective and should not be reimbursed. A number of recent studies of acupuncture from health care research programs in Germany did not find convincing evidence for "specific" effects over sham interventions in several chronic pain conditions. At the same time, these studies showed that acupuncture and sham acupuncture were (in the German setting) as effective, or even significantly more effective, than guideline-based standard treatments which had been shown to have effects over (their respective) placebo in the past. These results put health authorities into a dilemma: Including acupuncture into reimbursement means reimbursing a placebo treatment, not including it means – according to findings of clinical trials – withholding patients the most effective treatment option. While the findings of the German studies might be wrong or while sham acupuncture might not be a "true placebo" the author beliefs that they are a good examples of the consequences of the misleading, non-logical concept of placebo. The "placebo research community" should seriously work on an alternative concept which reflects the current knowledge on mechanisms and takes into account the consequences for decision-making. Some preliminary proposals from the perspective of clinical research will be presented which could be part of a new concept.



Predictors of the placebo/nocebo response in clinical trials

Paul Enck and Sibylle Klosterhalfen
Department of Internal Medicine VI/Psychosomatic Medicine and Psychotherapy, University Hospitals Tübingen, Germany

Despite the fact that different tools are available to identify potential predictors of the placebo and nocebo response (PNR), little insight has been gained from them:

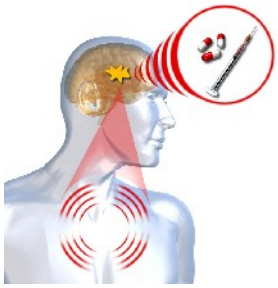
a) Systematic reviews of the published body of placebo literature (currently: approx. 110.000 citations in PUBMED) may identify relevant groups of factors that are associated with PNR, but usually carry little empirical evidence and often produce conflicting results.
b) Meta-analyses of published trials usually contain insufficient individualized data but may point towards structural and design-related factors that contribute to the PNR.
c) Re-analyses of the "raw data" of such trials may eventually identify individual characteristics that are associated with high PNR, such as symptom severity, gender, and habits and profiles, but in registered clinical trial the number of data is usually rather restricted.
d) Experiments that include volunteers and/or patients can then allow to test such predictors for their validity and efficacy in an experimental or clinical set-up. This may also include brain imaging techniques, but was is needed is sufficient individualization of data.

We will discuss examples of the respective research strategies at all levels, with a focus on intestinal symptoms and functions.

Deconstructing the placebo effect: A randomized controlled trial of three different placebo and patient-practitioner "doses" in irritable bowel syndrome (IBS) patients

Ted J. Kaptchuk[1,2], John M. Kelley [3,4,], Lisa Conboy [1], Roger B. Davis[1,2], Catherine E. Kerr[1], Eric E. Jacobson[5], Irving Kirsch[6], Rosa N. Schyner[1], Bong Hyun Nam[7,], Long T. Nguyen[1], Min Park[1], Andrea L. Rivers[1], Claire McManus[1], Efi Kokkoto[2], Douglas A. Drossman[8], Peter Goldman[1], Anthony J. Lembo[2]
[1]Osher Institute, Harvard Medical School, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]Massachusetts General Hospital, Boston, MA [4]Endicott College, Beverly, MA ; [5]Department of Social Medicine, Harvard Medical School, Boston, MA; [6]University of Hull, United Kingdom; [7]Korea Food and Drug Administration, Seoul, South Korea; and [8]UNC Center for Functional GI and Motility Disorders, University of North Carolina, Chapel Hill, NC

Background: Although recent experiments in human subjects demonstrate that placebo treatment causes short-term objective changes in brain neurobiology, the clinical significance and relationship to chronic disease of such physiological effects is unknown. Nevertheless, it has been suggested that placebo effects in randomized controlled trials (RCT) result from a combination of three components: patient responses to 1) observation and assessment (Hawthorne effect), 2) the administration of a dummy treatment, and 3) a positive patient-practitioner relationship.
Methods: We designed a 3 arm RCT that enrolled 262 patients with irritable bowel syndrome to investigate whether these three postulated components of the placebo could be added independently to effect incremental improvements of symptoms. In one arm, patients were simply wait-listed. In the other two arms, they were "treated" with sham acupuncture, one arm having also an enhanced relationship with a therapist. Videotapes of all interactions in the trial will be analyzed with the Psychotherapy Process Q-Set Measure (PQS) in order to study psychological variables that arise in the patient-practitioner encounter. Additionally, 27 patients were randomized to the three arms to perform a qualitative study of their experiences in the trial. Blood samples of all patients will be used to look for hormonal, neuropeptide and neurotransmitter predictors and modulators of placebo response. Hypothesis driven genetic analysis will look for genetic predictors of response.
Results: Data is currently being furiously analyzed. Hopefully some results will be available to share at the Tutzing meeting in this placebo "dose escalation" study.



Wednesday, 28th November 2007, 8:00 pm - 9:00 pm

Short communication I

Chair: Manfred Schedlowski

Operant conditioning as a putative mechanism of peripheral placebo effects

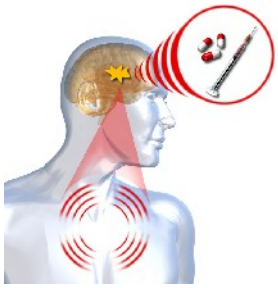
Karin Meissner
Institute for Medical Psychology, Ludwigs-Maximilians-Universität of Munich, Germany

The mechanisms of placebo effects on peripheral organ systems have scarcely been studied. In a systematic review on placebo effects in clinical trials we have recently demonstrated that parameters representing the physical state of an organ or tissue, e.g., cardiovascular and pulmonary parameters, are more susceptible to placebo treatment than parameters representing biochemical substrates, e.g., metabolic and endocrine parameters. This differential response suggests that a mechanism similar to operant conditioning may be involved in the mediation of peripheral placebo effects, since neural afferents, and thus a quick central-peripheral feedback loop as a prerequisite for visceral learning, are only provided for physical parameters. In this model, verbal suggestions about the effect to be expected from treatment may act as a directory sign for the patient to draw his attention to specific organ states, and to set into motion positive reinforcement of organ improvement. According to this model, physical organ functions may be affected quite selectively by placebo interventions. We tested this hypothesis in a series of experimental placebo studies, in which we measured not only the activity of the organ targeted by the placebo intervention but also that of other organ systems. First results indicate that there is not one global placebo response pattern. Instead, peripheral placebo effects appear to be mediated in an organ-specific manner. In conclusion, our results lend support to the hypothesis that operant conditioning is involved in the mediation of peripheral placebo effects.

The placebo effect in the context of working memory performance: A Naloxone study with healthy volunteers

Jair Stern[1], Victor Candia[1], Roseline Porchet[1], Dominik Ettlin[2], Gerd Folkers[1], Georg Schönbächler[1] *Collegium Helveticum, Zurich, Switzerland,* [2] *University Hospital Zurich, Switzerland*

The mu-opioid antagonist Naloxone has been historically of key importance for the demonstration of the opioid system's involvement in the placebo response: Naloxone was consistently shown to contribute to the reversal of placebo-induced analgesia, implying a role for endogenous opioids in the mediation of suggestive, „psychosomatic" alleviation of pain. Pain, however, persists to be notoriously difficult to evaluate objectively. Therefore, we ventured to investigate the effect of Naloxone/placebo on a suggestive intervention beyond the context of pain. We chose a series of working memory tasks in which the performance can be easily quantified.
In this ongoing, double-blind study, we aim to assess the following topics: (1) the placebo effect within the memory domain, (2) the correlation between objective and subjective measures of the placebo response, (3) the reversibility of the placebo response by Naloxone in cognitive functions, and (4) the effect of Naloxone on subjective appraisal of memory performance. Preliminary results will be presented.



Mirror, mirror on the wall: Placebo effects that exist only in the eye of the beholder

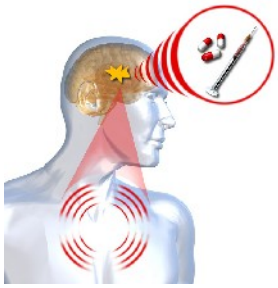
John M. Kelley[1], Ted J. Kaptchuk[2], Patrick R. Boulos[3], Peter A.D. Rubin[4]
[1]Endicott College and Harvard Medical School, [2]Osher Institute, Harvard Medical School, USA
[3]Sherbrooke University and University of Montreal, Canada, [4]Harvard Medical School, USA

Objective: The extent to which placebo effects can be driven exclusively by subjective impressions of improvement independent of any objective change is unclear.
Methods: In an open trial, 36 self-referred participants were treated with a new light therapy device intended to rejuvenate facial skin. At each of eight weekly treatments, participants' facial skin was exposed for 40 seconds to multi-spectral LED-generated light in the range of 590 nm wavelength at 0.1 J/cm2. Outcomes were assessed subjectively by participants as well as objectively by the treating physician and by independent blinded raters.
Results: Participants reported robust and statistically significant improvements in seven facial features at the conclusion of the 8-week treatment regimen as well as at 1-month follow-up (for all comparisons, $p < .003$, median $d = 1.14$). In sharp contrast, both the treating physician and independent, blinded raters were unable to detect any improvement whatsoever (for all comparisons, $p > .05$). Moreover, effect sizes were close to zero and in the opposite direction from improvement (median $d = -.06$ for the physician ratings; and for observer ratings, there was only a 46% success rate at identifying post-treatment as compared with pre-treatment photographs).
Conclusion: The robust placebo responses documented in this trial are clearly not objective in nature; rather, they are entirely a subjective impression of the participants. Thus, patients can perceive improvement in medical interventions even when there are absolutely no objective changes. This result is used as a heuristic to more clearly define the components of the placebo response.

The role of learning in placebo and nocebo responses

Luana Colloca
Department of Neuroscience, University of Turin, Medical School Turin, Italy

We have previously demonstrated that placebo analgesia is finely tuned by prior experience and these effects can last, albeit reduced, several days, which indicates that the placebo effect is a learning phenomenon. Here, we extend these findings with two additional studies in healthy volunteers. The first addresses the question whether verbal suggestions and conditioning modulate differently Laser Evoked Potentials (LEPs), which represents an objective parameter for quantifying the placebo effect. The second is aimed at investigating the different role of verbal suggestions and learning (via conditioning) in the nocebo effect when tactile and low-painful stimuli are investigated. In the first work, we found that the conditioning procedure induced a reduction of N2-P2 amplitudes that was significantly larger than that induced by verbal suggestions alone. The second study shows that verbal suggestions turned both tactile stimuli into pain and low-intensity pain stimuli into high-intensity pain. Conditioned stimuli that were associated to pain were also capable of turning both tactile stimuli into pain and low-intensity pain stimuli into high-intensity pain. Therefore, in contrast to the learning effects in placebo analgesia, we did not find significant differences between conditioned and non-conditioned responses. These data indicate that the placebo responses are enhanced by conditioning procedures, suggesting that learning modulates both behavioral and neurophysiological placebo analgesic responses. Conversely, conditioning does not enhance the nocebo response, thus indicating that learning is likely to be less important in the nocebo effect. The next step is to gather information on neurophysiological responses in the nocebo hyperalgesic effect.



Thursday, 29th November 2007, 8:30 am - 9:30 am

Learning and Memory

Chair: Jon-Kar Zubieta

Modification of long-term conditioned responses: Relevance to the placebo effect

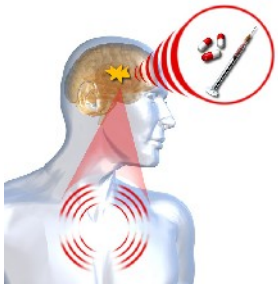
Yadin Dudai
The Weizmann Institute of Science, Department of Neurobiology, Revohot, Israel

Influential models of the placebo effect posit that it involves conditioning. Two main variants have been proposed within the aforementioned meta-hypothesis. The stimulus substitution models propose that the placebo response is itself the conditioned response, whereas expectancy models maintain that conditioning trials produce placebo response expectancies, rather than placebo responses, and that the expectancies elicit the response. In both cases much can be gained from understanding brain mechanisms of conditioning, and from the ability to modify conditioning once it has been established. I will present data, based on conditioned taste aversion in the rat, which will detail methods that can modify and even potentially erase conditioned behavior long after it has been established. The neural mechanisms that these methods target, and the light they cast on the persistence and modifiability of memory in brain, will be also addressed.

Conditioned analgesia in mice selected for high and low stress-induced analgesia

Artur H. Swiergiel
Polish Academy of Sciences, Institute of Genetics and Animal Breeding, Jastrzebiec, Poland

The placebo effect, whether stronger or weaker, plays an important role in the effective treatment of a number of ailments. However, a subpopulation of patients does not respond to placebo. The reasons for the non-responsiveness have not been well established. It may be postulated that this lack of placebo effect is due to impairment of either conditioning or neurophysiological mechanisms. The problems may be explored in lines of mice that have been selected for high (HA line) and low (LA line) stress-induced analgesia (SIA). Selection for the magnitude of SIA has altered the activity of the opioid system. HA mice, as compared with LA mice, are much more (100x) responsive to the analgesic effects of morphine and selective agonists of mu, delta and kappa opioid receptors, and display a significantly higher level of mu-opioid receptor mRNA in the nucleus raphe magnus. In the opioid-rich HA mice, the SIA is both opioid-and nonopioid-mediated and the animals develop tolerance to morphine. LA mice manifest low level of nonopioid-mediated SIA and morphine-induced analgesia. A tolerance to repeated stress and a two-way cross-tolerance of SIA with morphine-induced analgesia develops in the HA line, but not in the LA line. The lines also differ in a number of physiological responses, including anxiety- and depression-like behaviors, and responses to antidepressants. Experimental designs to study placebo effects in animal models will be presented and discussed.



Thursday, 29th November 2007, 9:30 am - 10:30 am

CNS-Immune-Interaction

Chair: Predrag Petrovic

Classical conditioning of immune responses: Pavlov and beyond

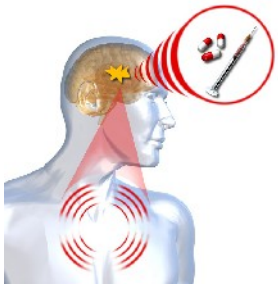
Manfred Schedlowski, Marion Goebel and Gustavo Pacheco-Lopez
Institute of Medical Psychology and Behavioral Immunobiology, University of Duisburg-Essen, Germany

Experimental data on the placebo response indicate that expectation and classical conditioning processes appear to be the major neuropsychological mechanisms driving the placebo response. In this context, by employing paradigms of classical conditioning, the brain's capability to modulate peripheral immune responses has been impressively demonstrated in animal experiments and human studies.
We have developed protocols of classical immunoconditioning in rodents in which a saccharin taste is employed as a conditioned stimulus (CS) and the immunosuppressive drug Cyclosporine A as an unconditioned stimulus (UCS). If paired during acquisition, re-exposure to the CS during evocation induces a significant inhibition of the proliferative capacity of splenic lymphocytes as well as interleukin-2 and interferon-gamma production and cytokine mRNA expression. These behavioral conditioned immunosuppressive effects are mediated on the efferent arm via the splenic nerve, noradrenaline and beta-adrenergic-dependent mechanisms. In addition, the insular cortex, the amygdala and the ventromedial nucleus of the hypothalamus have been identified as essential neuronal structures for these associative learning processes. The conditioned immunosuppression is of biological relevance, since behavioral conditioning significantly prolonged the survival of heart allografts and inhibited allergic reactions. Moreover, behaviorally conditioned immunosuppression has also been demonstrated in humans.
These data support the future use of classical conditioning paradigms as a systematically employed placebo response to support immunopharmacological regimens in clinical situations in order to maximize therapeutic efficacy, at the same time reducing unwanted drug side effects to the benefit of the patient and, last but not least, saving costs.

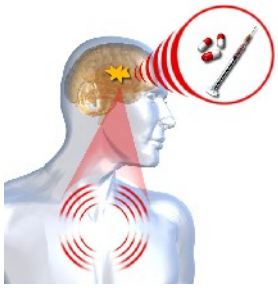
Cellular signalling and inflammatory pain

Annemieke Kavelaars[1], Niels Eijkelkamp[1], Wendy Kleibeuker[1], Sigrid Elsenbruch[2], Manfred Schedlowski[2], and Cobi J. Heijnen[1]
[1]Laboratory of Psychoneuroimmunology, University Medical Centre Utrecht, The Netherlands [2]Department of Medical Psychology and Behavioral Immunobiology, University Hospital of Essen, University of Duisburg-Essen, Germany

Inflammatory pain is a complex phenomenon, which represents a great burden for the patient and for society. We propose that inflammatory pain is the result of increased production of inflammatory mediators in combination with increased sensitivity of neuronal G protein coupled receptors (GPCRs).
Agonist-induced desensitization and internalization of GPCR comprise an important regulatory process to ensure adequate signaling and to prevent damage by overstimulation of GCPR. GPCR kinase (GRK)-dependent GPCR phosphorylation initiates this agonist-induced adaptive response that results in attenuation of signaling and removal of receptors from the cell surface. GRK2 is the most widely studied member of the GRK family. Low intracellular GRK levels result in increased receptor signaling. Moreover, GRKs may interact with a variety of key downstream signalling molecules. In chronic inflammatory diseases like rheumatoid arthritis and multiple sclerosis, we have already shown that the sensitivity of GPCRs is increased, a phenomenon which is due to decreased expression of GRK2. GRK2 regulates the sensitivity of many receptors including chemokine, adrenergic, opioid, serotonin, and metabotropic glutamate receptors.
Our recent research shows that changes in GRK not only have consequences for the inflammatory process but that regulation of GRK is also involved in the intensity and duration of inflammatory pain. Hyperalgesia caused by a local injection of CCL3 in the footpad of a mouse is not only significantly increased but also of much longer duration in



heterozygous knockout mice which express 50% of the protein compared to Wild type mice. To test possible effects of GRK2 on CCL3-induced effects in the central nervous system, we determined the level of p38 in the spinal cord. At 6 hours, p38 was increased in the lumbar region of GRK2+/- mice compared to WT mice, while there was no effect of genotype on p38 levels in the thoracic region.
In conclusion, these data suggest that GRK2 plays an important role in determining the extent of CCL3-induced inflammatory hyperalgesia, which is possibly mediated by increased GPCR-dependent activation of p38 in the spinal cord.



Thursday, 29th November 2007, 11:00 am - 12:00 am

Parkinson's Disease and Reward Mechanims

Chair: Serge Marchand

Parkinson's as a model to study the placebo effect

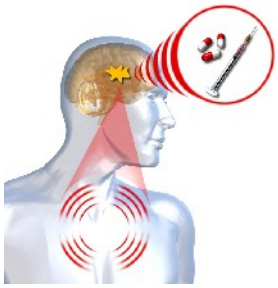
A. Jon Stoessl[1], Sarah C. Lidstone[1] and Raul de la Fuente-Fernandez[2]
[1] *Pacific Parkinson's Research Centre, University of British Columbia, Vancouver, Canada*
[2] *Section of Neurology, Hospital A Marcide, Ferrol, Spain*

Parkinson's disease (PD) is characterized by tremor, rigidity and poverty of movement, arising from loss of nigrostriatal dopamine (DA) neurons. Mesolimbic DA neurons are affected to a lesser degree. We previously demonstrated a remarkable degree of DA release in response to subcutaneous injection of placebo apomorphine in patients with moderately severe PD. In the dorsal striatum, there was a relationship between perceived therapeutic benefit and the magnitude of DA release, but in the ventral striatum, there was substantial release in all subjects, regardless of perceived benefit. We interpreted this as indicative of expectation-induced release of DA in reward circuitry and suggested that such expectation of therapeutic benefit as a form of reward may underlie the placebo effect in conditions other than PD. Our current work is attempting to address the effects of manipulating expectation on DA release by verbal suggestion and overt vs. covert therapy and to determine whether there are additional effects of conditioning, as well as the effects of treatment experience. An understanding of the relationship between expectation and the magnitude of the placebo response (both clinical and neurochemical) is of theoretical interest and will also be of major importance for the design of therapeutic trials in all conditions where a major placebo effect occurs. Although our original hypothesis appears to be supported by recent work on placebo analgesia (Scott et al., 2007), it remains an interesting question whether depressed patients, in whom anhedonia may be a cardinal feature, can generate expectation-mediated release of DA in limbic regions.

The placebo-reward hypothesis: Biochemical bases and predictions

Raul de la Fuente-Fernandez
Section of Neurology, Hospital A. Marcide, Ferrol, Spain

In 2002 we formally proposed the placebo-reward hypothesis according to which the activation of the ventral striatum could represent a common substrate for any placebo response, in any medical condition. In keeping with this hypothesis, converging evidence suggests that the placebo effect is indeed related to the activation of the reward circuitry. Specifically, PET studies on Parkinson's disease and pain conditions have shown that the clinical benefit induced by placebo administration is associated with the release of dopamine in the ventral striatum. Placebo investigations can therefore be used to examine different components of the ventral basal ganglia circuitry: anterior cingulate cortex – ventral striatum – ventral pallidum – mediodorsal nucleus of the thalamus – anterior cingulate cortex; other frontal and temporal regions also participate in this circuitry. In addition, pharmacological challenges may help disentangle the biochemical bases of placebo responses encountered in medical conditions not directly associated with the dopaminergic system (e.g., pain disorders). Thus, if our placebo-reward hypothesis is correct, treatment with dopamine antagonists should modify placebo analgesia. Similar pharmacological challenges can be used to explore whether the dopamine system may also play a significant role in mediating placebo-induced immune changes. Naturally, manipulations of the direct (D1-substance P) and indirect (D2-enkephalin) basal ganglia pathways may produce different effects on placebo responses.



Thursday, 29th November 2007, 12:00 am - 1:00 pm

Short communication II

Chair: Fabrizio Bendetti

Opioids and fear conditioning: Effects of the opioid antagonist naloxone on pain processing

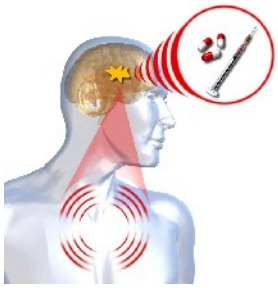
Falk Eippert
Institute of Systemic Neuroscience, University Clinic Hamburg-Eppendorf, Germany

The endogenous opioid system is strongly involved in pain modulation and pain-related learning such as fear conditioning. Studies in rodents have shown that opioid agonists attenuate and opioid antagonists facilitate acquisition of conditioned fear. We investigated whether blockade of endogenous opioid neurotransmission enhances acquisition of conditioned fear in human subjects, using functional magnetic resonance imaging (fMRI) in combination with behavioral recordings and a pharmacological intervention. In a classical fear conditioning paradigm, the opioid antagonist naloxone enhanced acquisition of fear on the behavioral level and led to more sustained conditioned responses in the amygdala over time. Naloxone also led to more sustained responses to the unconditioned stimulus over time, both on the behavioral level and in pain-sensitive regions such as the dorsal anterior cingulate cortex. This is likely mediated by naloxone blocking conditioned responses in a pain-inhibitory circuit involving opioid-rich areas such as the rostral anterior cingulate cortex, amygdala and periaqueductal gray. Thus the endogenous opioid system, the malfunction of which is evident in several anxiety disorders, has an inhibitory role in the acquisition of fear in humans.

The effect of subject and experimenter gender on pain and placebo analgesia

Per Aslaksen and Magne Arve Flaten
Department of Psychology, University of Tromsø, Norway

Pain report has in several reports been shown to be modulated by the interaction of subject gender with experimenter gender. Our studies showed that male subjects reported less pain to female experimenters compared with pain reported to male experimenters. The social context also modulated subjective reports of stress and arousal, with male subjects reporting less stress and arousal to female experimenters. These findings show the importance of objective measurement of pain and stress, alternatively that relevant controls for social context are used in the experiment.
As the pain report is a central element in placebo analgesia, gender could also play a role in placebo analgesia. Two experiments tested whether gender modulated placebo analgesia induced by verbal information or by classical conditioning.



Fibromyalgia: Changes in the neurobiology of expectancy-mediated analgesia

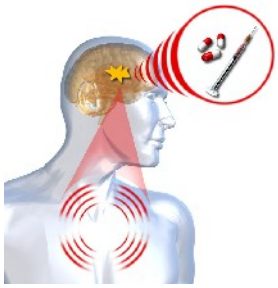
Philippe Goffaux, Juliana Barcellos de Souza and Serge Marchand
University of Sherbrooke, Centre of Clinical Research, Fleurimont, Quebec, Canada

In healthy adults, expectation effects partly depend on the activity of inhibitory bulbo-spinal projections, and can even block the analgesic properties of counter-irritation (a phenomenon that triggers descending inhibition). Since descending inhibition is known to be deficient in FM patients, we hypothesized that expectancy-mediated analgesia would depend only on supraspinal mechanisms. By measuring subjective pain ratings, spinal withdrawal reflexes (WR) and somatosensory evoked potentials (SEP) it was possible to test whether or not expectancy-mediated analgesia involves descending inhibition in FM patients.
Methods: 10 FM participated in this pilot project. Descending inhibition was triggered by immersion of the arm in cold water for 2 minutes. Electrical stimulation of the sural nerve was repeated every 7 seconds for 10 minutes while arm immersion started 4 minutes after testing began. Pain ratings relative to the electrical stimulations were recorded every minute. Prior to testing, expectations regarding the effects of the immersion procedure were measured by having participants rate the anticipated change in sural nerve pain.
Results: Analyses indicate that sural nerve pain ratings decrease when FMs expect the immersion procedure to be analgesic ($p>.05$). Concomitant changes in the SEP response further confirm this effect. However, the amplitude of spinal withdrawal reflexes increased ($p>.05$), despite expectations of analgesia. The spinal increase was comparable to the spinal increase observed when FMs expect the immersion procedure to be hyperalgesic ($p<.05$).
Conclusions: These results indicate that FMs are capable of expectancy-induced analgesia but that, unlike healthy subjects, this does not depend on the recruitment of descending inhibitory projections.

The contribution of left and right prefrontal cortex to the placebo and nocebo process by means of a pain paradigm and transcranial magnetic stimulation (TMS) in healthy volunteers

Peter Krummenacher[1], Victor Candia[1], Gerd Folkers[1], Manfred Schedlowski[2], Jair Stern[1], Georg Schönbächler[1]
[1] Collegium Helveticum, Zurich, Switzerland [2]Division of Medical Psychology and Behavioral Immunobiology, University of Duisburg-Essen, Germany

Several regions of the prefrontal cortex have been shown to be involved in anticipatory processes and in the placebo response (PR). The dorsolateral prefrontal cortex (DLPFC), more specifically, has been associated with appraisal mechanisms and the generation and maintenance of cognitive expectancies. However, the differential participation of the causal role of the two brain hemispheres in the PR and the nocebo response (NR) has been only partially assessed so far.
In a heat pain paradigm, single-blind study with healthy subjects, we used a parallel-matched group design, with expectation (placebo, nocebo, control) and repetitive transcranial magnetic stimulation (real rTMS, sham rTMS) as between-subject factors. Both hemispheres (rDLPFC, lDLPFC) were investigated in a within-subject design. Priming (induced by verbal suggestion, a manipulated visual feedback display, and the TMS device itself) served as placebo or nocebo condition. Thereafter, we disrupted supposed expectation-mediating prefrontal brain structures by applying non-invasive rTMS to the left and right DLPFC. Results on the relative contributions of both DLPFCs to the PR and NR, respectively, will be presented.



Thursday, 29th November 2007, 2:00 pm - 5:30 pm

Pain
Chair: Ted. J. Kaptchuk

Cognitive processes inducing placebo analgesia

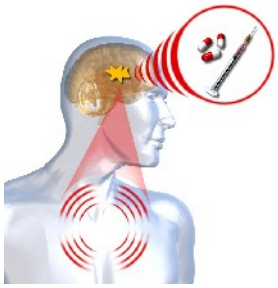
Predrag Petrovic
Department of Clinical Neuroscience, Karolinska Hospital, Stockholm, Sweden

Placebo analgesia is partly dependent on the endogenous opioid system as evidenced by the fact that the opioid receptor blocker naloxone suppresses the placebo response. We have previously suggested that an interaction takes place between the endogenous opioid system and attentional systems in anterior cingulate cortex since this region seems to contain a large concentration of opioid receptors, is highly activated during opioid treatment and placebo treatment and has a opioid system that shows lower opioid receptor binding potential during placebo. In this presentation I would like to emphasize another region in the opioid response, i.e. the orbitofrontal (Obfc) / ventrolateral prefrontal cortex (vlPFC), a region that is readily activated in placebo response. Unlike the ACC, the orbitofrontal/vlPFC does not appear to have as high a concentration of opioid receptors, and it does not increase in activity after treatment with opioids. However, it is highly involved in processing expectations about emotional and motivational goals. Since it has also been shown that the placebo response is dependent on expectation of treatment outcome, we suggest that expectation processing in Obfc / vlPFC is a cognitive mechanism preceding and inducing the more direct modulatory response in the ACC. We will show data suggesting that the processes in this region are unrelated to a pure opioid dependent response but interact with more opioid related mechanisms in ACC in placebo analgesia.

Expectancy modulation of pain affect: Electrophysiological evidence and opioid mechanisms

Tor D. Wager
Department of Psychology, Columbia University, New York, USA

Pain is an ideal model system for studying affect because the intensity of noxious input can be quantified, because pain pathways are well-characterized, and because pain is highly modifiable by attention and expectancy. Previously, we found that placebo expectancies engage a frontal cortex-periaqueductal gray (PAG) network and reduce pain-related brain activity in peri-limbic regions. (PAG is centrally involved in opioid production and brain regulation of pain.) In this presentation, I discuss two studies that examine the temporal and neurochemical bases of expectancy-induced pain control. First, I explore the relative contribution of fast, automatic processes to placebo analgesia using laser-evoked ERPs. The results suggest that there may be both fast anti-nociceptive and slower affect-based mechanisms for cognitive regulation of pain. A second study examines the role of opioid systems in expectancy-mediated analgesia using [11-C] carfentinil PET. Opioid activity in PAG, cingulate, and a network of interconnected frontal and limbic regions increased with placebo and was correlated with changes in reported pain. Multivariate analyses revealed that placebo expectancy increased functional integration of prefrontal and limbic opioid systems in general and connectivity between rostral cingulate and PAG specifically. These findings are related to an emerging model of brain systems involved in the cognitive regulation of affect.



Neuroimaging of dopaminergic and opioid mechanisms in placebo and nocebo effects

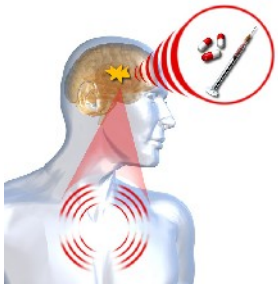
Jon-Kar Zubieta
Departments of Psychiatry, Radiology and Neurosciences Program, The University of Michigan, Ann Arbor, USA

Placebo effects are a substantial confound in clinical trials, but may also represent an example of cognitive-emotional assessments and expectations modulating biological processes. In this regard, a series of interconnected regions including the anterior cingulate, thalamus, nucleus accumbens, amygdala and periaqueductal gray have been shown to respond to the introduction of a placebo in healthy subjects undergoing pain or emotional challenges, as well as patients diagnosed with Major Depression and Parkinson's disease. This suggests that common pathways may, at least in part, contribute to various forms of placebo responses across challenges and disease processes. We examined two neurotransmitter systems known to be centrally involved in the regulation of this circuit with molecular imaging techniques and positron emission tomography in humans. The introduction of a placebo with expectation that it was an analgesic agent activated endogenous opioid neurotransmission and μ-opioid receptors throughout this circuit in a manner proportional to placebo-induced analgesia. Similar activation was obtained for nucleus accumbens dopamine and D2 receptors. The latter was related to individual expectations, but also correlated with the activity of endogenous opioid systems in the striatopallidal pathway and interconnected brain regions and predicted the formation of placebo effects. Moreover, hyperalgesic responses to placebo administration reduced the activity of both dopaminergic and opioid neurotransmission in some of these regions. These studies demonstrate that specific neurotransmitter systems become activated during the introduction of a placebo with expected therapeutic properties, and that this activation is related to the capacity of a placebo to modulate physiology.

Psychophysical and electrophysiological studies of the placebo response in healthy subjects and patients suffering of chronic pain syndromes

Serge Marchand
Faculty of Medicine and Science, University of Sherbrooke, Quebec, Canada

It is well supported that a patient's expectation toward a treatment influences perceived, but also functional outcomes. Recent research has clearly demonstrated that placebo is acting on objective physiological responses such as hormones levels and neurotransmitters expression. Different endogenous pain inhibitory mechanisms play a major role in pain perception in healthy subjects and patients suffering from chronic pain. The activation of diffuse noxious inhibitory control (DNIC) from brainstem structures is one of these mechanisms. In a recent study, we found that the expectation of hyperalgesia completely blocked the analgesic effect of DNIC, but also the related cortical (somatosensory evoked potentials : SEP) and spinal activity (nociceptive reflex : RIII). Considering our previous findings that fibromyalgia patient presents a deficit of DNIC, we tested the same manipulation of expectation to see if we could trigger a DNIC in fibromyalgia patients. Interestingly, we found that expectation of analgesia did improve the perceived and cortical analgesic effect of DNIC, but not the RIII response. These results suggest that even when they trigger expectation-related analgesia, fibromyalgia patients still present with a lack of spinal analgesia that may be due to a deficit of DNIC. During this talk, I will summarize some of our studies on the role of expectation and conditioning to placebo responses. The goal is to understand how clinical and experimental placebo studies allow to better characterize the mechanisms implicated in some chronic pain conditions and the variability in responses to pain treatments.



Placebo analgesia, classical conditioning and endogenous opioids

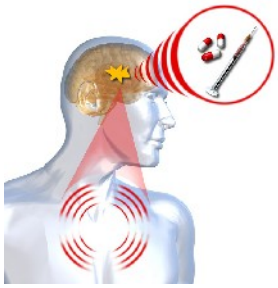
Christian Büchel
Institute of Systemic Neuroscience, University Clinic Hamburg-Eppendorf, Germany

This presentation will focus on the interplay between cognition and pain processing. Initial studies have concentrated on how attentional demanding tasks are able to change pain perception. We were interested in the reverse process, namely how pain processing, (and processing of negative emotional stimuli) can affect visual processing. The behavioral effects of decreased visual processing were paralleled by BOLD signal changes in the lateral occipital complex, irrespective of the nature of the distracting task (e.g. pain, negative emotions, working memory). However, using analyses of connectivity we could show that the source of modulation for each effect is distinct. We identified the rostral anterior cingulate as a potential modulator in the context of pain, the amygdala in the context of negative emotional stimuli and the inferior parietal cortex in case of working memory. These studies show that affective (pain and emotion) and cognitive (working memory) load seem to act on similar cortical regions, but that the origin of the modulatory signal is domain-specific.

Emotional factors in placebo analgesia

Magne Arve Flaten and Per Aslaksen
Department of Psychology, University of Tromsø, Norway

Treatment for pain induces an expectation that pain will be reduced after the treatment. Research has shown that the expectation alone can reduce pain, and this has been termed placebo analgesia. However, expectation of reduced pain may also have other consequences, one of them being a reduction in stress or negative emotion. Stress and negative emotions have been found to increase pain, and it could be hypothesized that placebo analgesia is mediated via a reduction in stress. Experiments that test the hypothesis will be presented. Subjects scoring high on the Fear of Pain questionnaire displayed high levels of stress before application of the pain stimuli, as expected, and data from these subjects are of special interest for the hypothesis.



Thursday, 29th November 2007, 5:45 pm - 7:00 pm

Short communication III

Chair: Paul Enck

Behavioral conditioning of anti-histamine effects in patients with allergic rhinitis

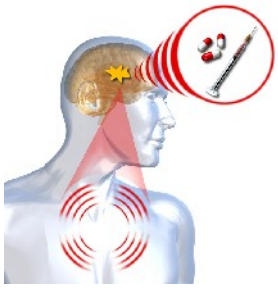
Marion U. Goebel[1], Nuschin Meykadeh[2], Manfred Schedlowski[1], Ulrich R. Hengge[2]
[1]Department of Medical Psychology and Behavioral Immunology, University of Duisburg-Essen, Germany [2]Department of Dermatology, Heinrich-Heine University of Duesseldorf, Germany

Allergic symptoms can be induced by behavioral conditioning. However, the conditionability of anti-allergic effects has not yet been studied. Thus, we investigated whether the effects of a Histamine1-receptor (H1) antagonist are inducible in patients suffering from house-dust mite allergy using a behavioral conditioning procedure. During the association phase, 30 patients with allergic house-dust mite rhinitis received a novel-tasting drink once daily, followed by a standard dose of the H1-receptor antagonist desloratadine, on five consecutive days. After 9 days of drug wash-out, the evocation trial commenced: 10 patients received water together with an identically looking placebo pill (wat group), 11 patients were re-exposed to the novel-tasting drink and received a placebo pill (CS group) and 9 patients received water and desloratadine (drug group). During the association phase, desloratadine treatment decreased the subjective total symptom scores, attenuated the effects of the skin prick test for histamine and reduced basophil activation ex vivo in all groups. During the evocation trial, the wat group, in which subjects were not re-exposed to the gustatory stimulus, showed a reduction in subjective total symptom scores and skin prick test results, but no inhibition of basophil activation. In contrast, re-exposure to the novel-tasting drink decreased basophil activation, the skin prick test and the subjective symptom score in the CS group to a degree that was similar to the desloratadine-induced effects observed in the drug group. These data show that behaviorally conditioned effects are not only able to relieve subjective rhinitis symptoms and allergic skin reactions, but also to induce changes in effector immune functions.

Brain substrates of suppression in posthypnotic amnesia

Avi Mendelsohn, Yossi Chalamish and Yadin Dudai
The Weizmann Institute of Science, Department of Neurobiology, Rehovot, Israel

Suggestions may potentially induce placebo effects. A special type of suggestion that is amenable to experimental analysis is the suggestion to disregard or forget information posthypnotically, i.e., posthypnotic amnesia (PHA). We will describe a study that identifies brain substrates of PHA of episodic memory. In the Study session, two groups of participants, one susceptible to PHA and the other not, viewed a 45 min documentary movie featuring a day in the life of a young woman. In the Test session, performed in the magnet a week later, all the participants were hypnotized and received a suggestion to forget the movie details upon exiting the hypnosis state, until they receive a cue to reverse that suggestion. On exiting the hypnotic state, the participants were presented with a memory test, including questions about the movie and about the context in which it was shown. Test 1 was conducted while under the "forget" suggestion, and Test 2 after its reversal. The brain was scanned in both tests. The PHA group showed a significant reduction in memory performance on movie questions during Test 1 compared to Test 2. In contrast, performance on context questions was unimpaired. The Non-PHA group did not show a difference in memory performance on neither movie nor context questions in both tests. fMRI analysis revealed higher activation in Non-PHA compared to PHA during movie questions in Test 1 in several brain regions, including left temporal pole and extrastriate cortex. In contrast, the left ventrolateral prefrontal cortex showed preferential activation in the PHA group. Correlation of performance in Test 1 with brain activation in all subjects revealed positive correlation in the left temporal pole and gyrus and in extrastriate cortex. We propose that some of these regions subserve the inhibition of retrieval already in a pre-retrieval monitoring stage. The same brain regions may also underlie other forms of executive suppression of brain processing and behavior.



Investigation of expectation and the placebo effect in Parkinson's disease using high-resolution positron emission tomography (PET) with [11C] raclopride

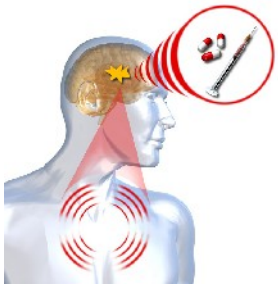
Sarah C. Lidstone, E. Bogusz, K Dinelle, S. Blinder, T.J. Ruth, A.G. Phillips, V. Sossi, A. Jon Stoessl
Pacific Parkinson's Research Centre, University of British Columbia, Vancouver, Canada

Expectation of therapeutic benefit plays a crucial role in the mechanism of the placebo effect in Parkinson`s disease (PD), and has been shown to stimulate striatal dopamine (DA) release. We used [11C] raclopride (RAC) PET to investigate DA release associated with expectation strength of levodopa delivery in PD patients. Eleven subjects with mild-moderate PD underwent 3 PET scans on a high resolution research tomograph (HRRT) over 2 days under the following conditions: baseline, following open oral administration of 250mg levodopa, and following placebo administration. For the final scan, subjects were divided into 4 groups based on their verbal instructions, and were told that they had a 25, 50, 75 or 100% chance of receiving levodopa, when in fact they all received placebo. Emission data were acquired for 60 minutes following bolus injection of 370 MBq [11C] RAC. Emission images were corrected for motion by inter-frame realignment. RAC binding potentials (BP) were estimated using a graphical tissue approach (Logan et al. 1996) with the cerebellum as a reference region. In response to placebo, preliminary results indicate a monotonic relationship between expectation level and DA release in the caudate nucleus and ventral striatum, exceeding the effect of levodopa in high expectation groups.
Placebo responders had increased DA release in all areas of the striatum as compared to non-responders. Interestingly, a nocebo negative response (decrease in DA release) was seen at the lowest expectation level. These results support striatal placebo-induced DA release in PD that is modulated by the strength of expectation. Ongoing work will attempt to extend these findings to a larger sample.

Why aren't we all placebo responders? –Possible genetic underpinnings of the placebo effect

Karin Jensen, Predrag Petrovic, Eva Kosek, and Martin Ingvar
Department of clinical neuroscience, Karolinska Hospital, Stockholm, Sweden

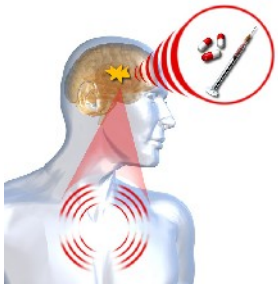
Background: There is growing evidence that there are functional polymorphisms related to specific psychological traits, pain perception and the ability to achieve analgesia. However, these genetic findings have not yet been applied to the investigations of the placebo effect, i.e. the ability to recruit endogenous analgesia by believing there is presence of an active anaesthetic. We wanted to use strong hypothesis-driven analyses in order to identify a possible relationship between variations of specific polymorphisms and variation in the ability to respond with placebo analgesia in an experimental setup.
Method: We use a straight forward placebo manipulation aiming at characterizing all subjects as "responder" or "non-responder" and correlate the result to genetic information from carefully chosen genetic polymorphisms. At least 100 healthy volunteers from 18 years old and up will be recruited by advertising. They are informed that they will go through a heat-pain experiment aiming at finding correlates between genetic variations and the response to 2 different anaesthetic compounds. In total five series of heat (48° Celsius) during 30 seconds are administered in the following order: one baseline, one with i.v. injection of Remifentanil (0.08µg/kg), (PAUSE), one control run, one with i.v. injection of saline and finally one more control run. Questionnaires including personality- and cognitive related inventories are completed by all subjects in order to assess the relationship between genetic variation, cognitive-/personality profile and placebo response (SSP, CSQ, GSES, STAI).
Results: This study is ongoing and the first analysis can be performed early 2008.
Concerning the genetic loci of interest, COMT and SERT polymorphisms have been characterized in all currently available subjects. Any additional polymorphisms of interest will be determined before the onset of group data analysis.



Influencing pain behaviors through placebo effect in patients with chronic low back pain (CLBP)

Regine Klinger and Jens Tretrop
Department of Clinical Psychology, University of Hamburg, Germany

Theory: The increasing interest in placebo research results from the proven analgetic effectiveness of placebos. However, only a few of those studies have included a component of objectively observing the influence of placebos on pain behavior. This pain behavior plays an important role in evaluating pain reduction. Patients with CLBP often exhibit extreme pain behaviors in particular avoidance behavior. An increase in their physical capacity and an improvement in their pain behavior are the main objectives of their treatment. Question: Is it possible to improve the physical capacity, pain behavior and pain intensity through placebo treatment (realized via manipulation of expectancy and/or classical conditioning)? Method: In a randomized clinical-experimental study 72 patients with CLBP were examined. They were asked to perform a number of defined standardized every day physical movements once before and once after the application of a placebo tincture. The patients were told they were being given an opioid tincture which reduced pain and improved motion. In fact the tincture was pharmacologically neutral. The additional influence of classical conditioning was achieved via manipulation of a pain experience (an electrical impulse) in correlation with the placebo application. The movements were observed by an independent agent who categorically rated the movements. Results: The application of the placebo („opioid" tincture) resulted in objectively observed improvements in the physical capacity and in pain reduction. The practical relevance of the placebo effect, its useful and targeted integration in clinical practice and its positive addition to the pharmacological effects of analgetics will be discussed.



Friday, 30th November 2007, 8:00 am - 12:00 am

Clinical implications of the placebo/nocebo response

Chair: Cobi J. Heijnen

Ethical aspects of placebo/nocebo

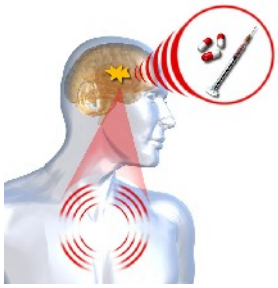
Urban Wiesing
Institute for Ethical Aspects and History of Medicine, University of Tübingen, Germany

The presentation examines the ethical aspects of placebo/nocebo and describes potential ethical research projects.
1. The use of placebo in clinical practise: The current medical codes demand that the patient has to give her or his informed consent before treated. If a physician informs the patient about a placebo treatment, it will probably lose its effectiveness or might even lead to nocebo-effects. How is the ethical conflict between respect of autonomy and beneficence to be solved? One highly controversial "solution" of this problem is the growing use of pseudoplacebos. Can they be justified?
2. The clinical research on placebo/nocebo-effects: The requirement of the informed consent makes it difficult but not impossible to do research on placebo/nocebo-effects. How can this problem be solved and where are the limits of this research?
3. The clinical research with placebo as a comparator: A decade ago in Third World countries drugs were tested to prohibit HIV-transmission from mothers to newborns. The patients in the control groups were given a placebo despite the fact that a proven and effective therapy was available which was very expensive. Thousands of newborns were infected with HIV in the placebo-group during these trials. After this scandal several ethical codes were changed, e.g. the revised Declaration of Helsinki by a "note of clarification" on placebo in 2002. Similar ethical problems are the use of placebo as a comparator in psychopharmacology and the inclusion of patients unable to give informed consent in placebo-controlled trails. How can placebo be justified in a control group when proven standard treatment is available?

Is the antianalgesic effect of acupuncture a "placebo"-response?

Gustav J. Dobos, Iven Tao, Andreas Michalsen and Frauke Musial
Chair of Integrative Medicine, Kliniken Essen Mitte, University of Duisburg-Essen, Germany

The expectation-mediated placebo response to experimental, ischemic pain is a well-investigated phenomenon. The expectation dependent process can be blocked by opiate-antagonist naloxone and enhanced by CCK-antagonist proglumide. However, on the cortical level, expectancy induced increase of pain threshold is indistinguishable from a real decrease of stimulus intensity in the areas of the motivational-affective pain processing system and the cortical structures involved are strongly associated with mu-opiate receptor activity.
The outcomes of two large German acupuncture trials, showing that sham-acupuncture was similarly effective compared to conventional treatment for migraine, tension type headache and chronic low back pain have raised the question, whether the antianalgesic properties of acupuncture are largely dependent on a possible expectancy effect. Similar to the expectation-induced analgesia, acupuncture induced analgesia can be blocked by naloxone and is thus mediated by the opiate system. Furthermore, it is well established from animal experiments, that the antinociceptive effect of acupuncture is also dependent on the brain CCK-system. Similarities to the expectancy dependent component of the placebo response are obvious and will be discussed.
However, the "diffuse noxious inhibitory controls" (DNIC) hypothesis would predict that "sham"-acupuncture at non-acupuncture points often used as "placebo-condition" to control for acupuncture can be neurophysiologically as effective as real acupuncture. Therefore, the analgesic properties of acupuncture may be a net-effect of cortical processes such as expectation, and antinociceptive effects at the level of the medulla and even the spinal cord.



Physician - patient relationship and the placebo response

Hans-Christian Deter
Clinic for Family and Natural Medicine, Psychosomatic and Psychotherapy, Charité, Berlin, Germany

There is evidence in the placebo literature that besides expectations of patients regarding therapeutic measures and drugs "unspecific factors" - like the kind of physician-patient interaction or situational factors - influence the placebo effect on individual subjective symptoms, autonomic behaviour, physical medical parameters , and possibly psycho-immunological factors. These therapeutic possibilities of a "helping alliance" (Luborsky) are in accordance with the knowledge of psychosomatic treatment strategies published in the literature (Balint 1957), especially in asthmatic patients (Deter, 1986). However only few data are published on specific factors influencing the present physician-patient relationship and the placebo response. Besides psychological and social factors of physician and patient, knowledge of the individual cognitive, emotional and psycho-physiological behaviour and their interaction between two persons seems necessary to understand the input of the physician-patient interaction on the placebo response. This analysis of "unspecific healing factors" in complementary and common medicine needs an evidence-based knowledge. A better understanding of this interplay could optimise the physicians' art of healing. Strategies to prove these important questions in scientific experiments will be discussed

Oxytocin enhances the experience of attachment security

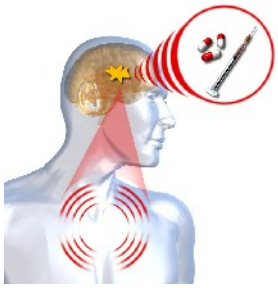
Anna Buchheim, Markus Heinrichs, Eva Koops and Harald Gündel
Department of Psychosomatic und Psychotherapy, Hannover Medical School, Germany

The attachment model suggests that repeated interactions between infant and caregiver result either in secure or in insecure lifelong stable relationship patterns, and that an insecure attachment style may negatively affect individual stress physiology, regulation of affect, and health. We show that a single dose of intranasally administered oxytocin is sufficient to induce a significant increase in the experience of attachment security in individuals classified as insecure. Oxytocin systematically induced a momentary state of mind change in which insecure subjects shifted to attachment security, i.e. identified themselves more with statements representing attachment security. What are the clinical implications of our results: Attachment regularly is activated during psychotherapy, and the stable shift from insecure to secure attachment representations usually occur after one or more years of psychotherapeutic work. Hence, future clinical studies should take into account that oxytocin might be a helpful tool integrated as an add-on treatment in the course of the psychotherapeutic process.

Metaanalysis of placebo groups in antidepressant trials

Winfried Rief
Department of Clinical Psychology and Psychotherapy, Phillips-Universität Marburg, Germany

The results of placebo groups do not only reflect methodological quality aspects of clinical trials (Rief et al., 2005), but may also reflect investigators' and participants' expectations. This was tested in a metaanalysis of 160 clinical trials using antidepressant. Results show that the (positive) placebo effect is substantially higher in expert-ratings than in self-ratings. Expert-ratings show a strong increase of effect sizes with publication year; this effect of publication year is not found for patients' self-ratings. The analysis of side effects in placebo groups confirms the influence of expectations of investigators and participants: in clinical trials with tricyclics as antidepressant drug, the placebo groups show substantially higher rates of side effects than placebo groups of clinical trials with SSRIs. This is especially true for side-effects that are more expected for tricyclics (such as mouth dryness), while side-effects that are more associated with SSRIs (e.g., sleeping problems) are more frequent in placebo groups of SSRI-trials. The more active drugs were used in clinical trials (e.g., 3-arm versus 2-arm trials), the more side-effects are reported in placebo groups. In the discussion, we will try to disentangle which effects are due to expectation and which effects are due to methodological flaws.



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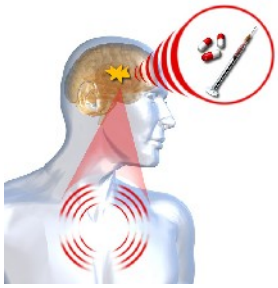

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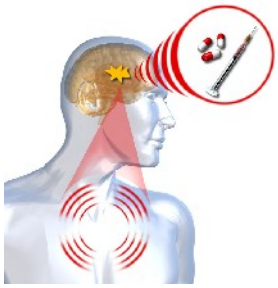

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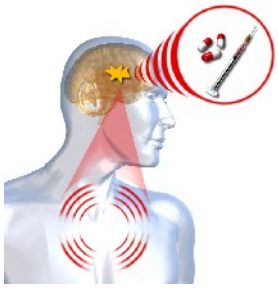

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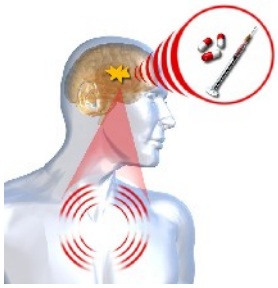

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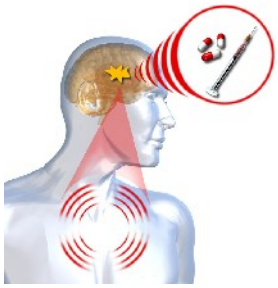

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