NEW FINDINGS IN CLINICAL PAIN RESEARCH:
Results of the EFIC-Grünenthal Grants 2012
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Co-Chairs:  
Dr Luis Villanueva, DDS, PhD (Paris, France)  
Prof Esther Pogatzki-Zahn, MD (Muenster, Germany)

Speakers:  
Prof Samar M Hatem, MD, PhD (Brussels, Belgium)  
Upper limb pain after stroke: should we act on pain or neglect?

Dr Lannie Ligthart, PhD (Amsterdam, The Netherlands)  
The development of pain, anxiety and depressive symptoms over time.

Dr Ann Meulders, PhD (Leuven, Belgium)  
Fear generalization processes in chronic pain: an associative learning approach.

Prof Katharina Zimmermann, MD (Erlangen, Germany)  
Ciguatera fish poisoning: novel insight into an old disease.

Guest-Speaker:  
Prof Esther Pogatzki-Zahn, MD (Muenster, Germany)  
Postoperative pain: From bench to bedside.
Esther Pogatzki-Zahn is a professor of anaesthesiology and critical-care medicine at the Department of Anaesthesiology in the University of Münster. After completing her medical studies in 1995, she started her residency in the Department of Anaesthesiology in Münster. Between 1998 and 2002, she spent five years in the USA in two well-established pain research laboratories specializing in neurophysiological and pharmacological science. On returning to Münster in 2002, she completed her postdoctoral Habilitation degree in 2003 and has been a board-certified anaesthesiologist since 2004.

Prof. Pogatzki-Zahn’s clinical specialty is pain management. In addition, she runs a well-funded basic-science laboratory focusing on research into the neurobiology of acute and chronic pain. Currently, her laboratory is expanding its research to explore the mechanisms of acute and chronic inflammatory pain and chronic neuropathic pain. In addition, Prof. Pogatzki-Zahn’s laboratory is working with human surrogate models of postoperative and neuropathic pain. In collaboration with other researchers, she is using well-defined test methods such as the quantitative sensory testing (QST). These experiments will bridge the gap between basic animal research and clinical practice.

She collaborates with a number of well-known basic scientists throughout the world.

ABSTRACT:

POSTOPERATIVE PAIN: FROM BENCH TO BEDSIDE

Acute postoperative pain is still an unresolved question; as indicated by recent outcome-related reports more than 50 percent of patients are insufficiently treated the first days after surgery and still more than 20 percent suffer from severe postoperative pain. Problematic are not even patients after major surgical procedures; especially pain of patients after more minor procedures are not managed well in clinical practice. Besides organizational problems there still a need for new treatment options. The effectiveness of current analgesic therapies is inadequate and side-effects of analgesics (like opioids) and a high risk of otherwise effective procedures (like epidural analgesia techniques) limit their use. Thus, novel analgesics without side-effects and risks are needed for acute postoperative pain treatment. To guide the development of new and specifically effective therapeutic approaches for acute postoperative pain there is a need to understand and investigate the pathophysiology of pain caused by surgery. Several rodent animal pain models have been developed for studying the pathophysiology of postoperative pain. Among them, the plantar incision model is one of the most widely used animal pain models; a small skin and muscle incision in rat plantar hindpaw exhibits nonevoked guarding behavior that last for 2-3 days and correlates to pain at rest in patients after surgery. Furthermore, the incision also induces hyperalgesia to mechanical (and heat) hyperalgesia that last longer and correlates to evoked pain after incision. In addition, a human pain model developed to mimic incisional pain was developed. Basic research using these animal and human incision models increasingly addressed specific aspects of acute postoperative pain. They have provided translational approaches that are applied around the world for studying neurobiological mechanisms of postoperative pain. At the same time, interdisciplinary cooperation in research projects leads to a better understanding of complex correlations regarding predictors and mechanisms (including psychosocial aspects) of acute and – in recent times – also chronic pain after surgery. Acute pain registries and pain certification projects initiated in Germany are particularly interesting by generating large “real live” databases for further research. In parallel, evidence based medicine has found its way into acute pain medicine. In the future, questions concerning mechanism-based therapy of acute pain need to be equally in the center of attention of research as prevention of persisting pain after surgery and acute pain of different origin.
ABSTRACT:

UPPER LIMB PAIN AFTER STROKE: SHOULD WE ACT ON PAIN OR NEGLECT?

After cerebral stroke, about 50% of patients suffer from upper limb pain. Several types of pain are described: post-stroke shoulder pain, shoulder-hand syndrome (complex regional pain syndrome, CRPS), central post-stroke pain (central neuropathic pain) and musculoskeletal pain. Often, it is difficult to discriminate between these different pain syndromes as they share common features combining nociceptive and neuropathic pain symptoms, hemineglect signs, dysautonomic, sensory and motor disturbances. The mechanisms of upper limb pain after stroke fuel a dynamic field of research. It has been suggested that shoulder joint subluxation due to motor paresis may be a trigger of upper limb pain. However, several studies have failed to show a relationship between the distance of glenohumeral subluxation and upper limb pain.

Sensory and autonomic disturbances after the central nervous system lesion may play a role. Though neglect and ‘neglect-like’ phenomena have been suggested to exist in non-stroke complex regional pain syndrome, in stroke the relationship between neglect and pain remains unclear. Recent studies in non-stroke CRPS suggest that modulation of visuospatial references concerning the body and near-space may influence pain levels. Preliminary results of an ongoing clinical study will be presented, describing the relationship between post-stroke upper limb pain and possibly aggravating phenomena such as shoulder joint abnormalities and neglect. Treatment of visuospatial disturbances with prism adaptation will be described briefly as a means to act on neglect and post-stroke upper limb pain.
Dr. Lannie Ligthart completed her BSc in Biological Psychology at VU University Amsterdam, followed by an MSc in Neuroscience. After a successful internship at the Queensland Institute of Medical Research in Brisbane, Australia, on the genetics of migraine, she started a PhD on the same topic at the Biological Psychology Department in Amsterdam, under joint supervision of Prof. D.I. Boomsma (VU University Amsterdam) and dr. D.R. Nyholt (Queensland Institute of Medical Research). Her PhD thesis focused on the genetic architecture of migraine, and the question why migraine often co-occurs with major depressive disorder. After her PhD, Lannie continued this work, supported by an EMGO+ fellowship, which allowed her to conduct a large-scale questionnaire study at the Netherlands Twin Registry with a focus on anxiety, depression, migraine and general pain symptoms. Her current research focus is the relationship between depression and broader pain symptomatology, and specifically, the hypothesis that pain occur as a symptom of depression.

**Abstract:**

**THE DEVELOPMENT OF PAIN, ANXIETY AND DEPRESSIVE SYMPTOMS OVER TIME**

**Background:** Many studies have attempted to determine the possible causal relationship between pain symptoms and depression by studying the order of onset of the two conditions, assuming that what occurs first must cause what follows. The moment of onset is typically defined as the moment of diagnosis. However, subclinical symptoms may be present long before a diagnosis is made. The aim of this study was to study order of onset while taking subclinical symptoms into account.

**Methods:** We used survey data on pain and anxious depression symptoms collected in Dutch twin families over a period of 20 years, with a maximum of 7 measurements per individual. Individuals were subdivided in groups whose symptoms increased, decreased, remained stable, or varied over time. We identified subsets of individuals who developed pain first, followed by anxious depression, and vice versa, to test whether pain predicted anxious depression and vice versa, at the symptom level.

**Results:** The majority of individuals showed varying symptom severity over time, indicating that neither pain nor anxious depression is a stable trait with a clear moment of onset. Only small subgroups of patients showed a pattern where the condition arose and persisted over time.

**Conclusion:** Zooming in on symptoms rather than endpoint diagnosis revealed that the moment of onset is hard to determine in most patients, which may explain the inconsistent results of studies focusing on order of onset. Based on these observations, a clear-cut causal relationship between pain and anxious depression seems highly unlikely. Alternative methods, including genetic studies, should be considered to investigate the relationship between these conditions.
In 2008, Dr. Ann Meulders obtained her doctoral degree in Psychology at the Centre for the Psychology of Learning and Experimental Psychopathology of the University of Leuven (Belgium). Her doctoral dissertation entitled “Unpredictability induces context conditioning and interferes with subsequent learning” focused on associative learning processes in anxiety disorders. In 2009, she became a postdoctoral fellow at the Research Group Health Psychology, also at the University of Leuven and started collaborating with Prof. Johan Vlaeyen on his Psychology of Pain and Disability Research Program. During her postdoctoral research her aim was to incorporate and translate her fear conditioning expertise to the field of pain-related fear which resulted in the development of an innovative pain-relevant human fear conditioning paradigm, that has received ample international attention and resulted in several high-impact publications.

In 2012, she travelled Down Under for a 7-month stay at the Body in Mind Research Group directed by Prof. Lorimer Moseley (UniSA, Australia), a collaboration that continues to yield novel research opportunities. Also in 2012, with her project “Fear generalization as a pathway to chronic widespread pain”, she won the prestigious EFIC-Grünenthal Grant supporting young scientists early in their career to carry out innovative pain research. In October 2013, she started working as a postdoctoral fellow of the Research Foundation Flanders (FWO-Vlaanderen). She hopes that her work will contribute to enhance the experimental research on basic learning mechanisms in chronic pain.

**ABSTRACT:**

**FEAR GENERALIZATION PROCESSES IN CHRONIC PAIN: AN ASSOCIATIVE LEARNING APPROACH**

Increasing evidence, mostly from studies with chronic musculoskeletal pain patients, indicates that pain-related fear plays a fundamental role in the transition from acute to chronic disabling pain. Fear generalization, however, has been largely neglected in the study of pain-related fear so far. Recent research using a Voluntary Joystick Movement (VJM) paradigm demonstrated that fear of movement-related pain can be acquired through associative learning, that is, after pairing a neutral joystick movement (conditioned stimulus, CS) with a painful stimulus (unconditioned stimulus, US), this movement starts to elicit protective responses (conditioned response, CR). In the clinic, however, spreading of fear and avoidance is observed beyond movements/activities that were associated with pain during the original pain episode. One mechanism accounting for this spreading of fear is stimulus generalization. In a first study, we tested the hypothesis that fear generalization occurs based on perceptual similarity and showed that pain-related fear spreads towards novel movements sharing proprioceptive features with the original pain-associated movement in healthy participants. In contrast, non-differential fear generalization was observed in fibromyalgia patients; fear provoked by novel movements did not depend on the similarity with the original pain-eliciting stimulus in these patients. In a second study, we wanted to address the intriguing question of whether fear can also spread based on conceptual knowledge. We adapted the VJM paradigm so that exemplars of 2 distinct superordinate action categories (opening/closing boxes) served as Cs. Different movements were performed to open/close boxes, and irrespective of these movement directions, one of the superordinate categories was followed by pain, and the other was not. Results showed that pain-related fear develops for different movements belonging the reinforced conceptual category and that this fear generalizes to novel exemplars of that category.
Prof. Dr. Katharina Zimmermann, born in Rothenburg ob der Tauber, Germany, earned her medical degree at the Friedrich-Alexander University Erlangen-Nuremberg in 2002 and completed her medical thesis in Neurophysiology in the laboratory of Prof. Peter Reeh earning the title “Dr. med.” in 2003. After a one year internship in Anesthesiology at the University Hospital in Erlangen she returned to the Reeh Lab as PostDoc where she started to learn electrophysiology and extracellular recordings from skin nociceptors. She revealed the role of the sensory neuron specific sodium channel NaV1.8 as a frost-proof ignition in nociceptors, a work she published in Nature. With the aim of widening her interests and practical skills, she joined Prof. David Clapham’s Lab at Harvard Medical School in Boston in 2006 to work on cold-sensitive transduction channels and identified TRPC5 as an additional, third cold transduction channel in nociceptors of mice and men. In 2009 she returned to the Department of Physiology and Pathophysiology in Erlangen to complete the Habilitation in Physiology in 2010. She continued to work on ion channels in cold temperature detection and developed a first model for studying the molecular pathomechanisms of cold allodynia using ciguatoxin together with Prof. Richard Lewis and Dr. Irina Vetter at the University of Queensland in Australia. Both has been extremely rewarding, earning her the award of an EFIC-Grünenthal-Grant in 2012 and culminating in a Heisenberg-Professorial appointment at the Department of Anesthesiology of the University Hospital Erlangen in 2014. She continues to study cold sensing pathways while developing broader interests in revealing the genetic factors underlying cold pain states.

ABSTRACT:

CIGUATERA FISH POISONING: NOVEL INSIGHT INTO AN OLD DISEASE

Cold pain states like cold allodynia (normally innocuous cool stimuli produce pain) are specific and frequent pain symptoms for which patients seek medical care and for which there is still lack of curative therapy. Cold allodynia occurs as a major symptom of neuropathic pain states or nerve injury. This includes also increased neuronal excitability at the primary afferent level caused by fish poisoning with ciguatoxins (CTXs) that act as sodium channel activator toxins in humans. Ciguatera has become a major human health problem of rising global incidence frequency, which is evidenced by a recent 2012 outbreak in Germany which will be reviewed. The disease is of particular scientific interest, because cold alloynia occurs in up to 94% of patients without presence of heat or mechanical allodynia. To investigate the peripheral and central pathophysiology of acute cold allodynia we established a human model of acute, reversible cold allodynia by intracutaneous injection of low nM concentrations of CTX that permitted us to identify the framework of cold allodynia activated central pain pathways by high resolution 3 tesla scanning. Our findings demonstrate that our previous discovery of a substantial peripheral sensitization of A-fibers to dynamic cooling stimuli is retrieved in all activated areas in the brain, including insula, cingulate cortex, frontal lobe and the secondary somatosensory cortex and may be the defining feature of this pain percept. Our findings further illustrate why Ciguatera sufferers often report of a perceptual temperature reversal and why warming is perceived as beneficial.
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