Consensus Statement or Guidelines? 
In any case a big step forward in Baltimore.

A short report on the meeting of the SIG “Sex, Gender and Pain” in Baltimore from the 27th to 29th of September.

Day one of the SIG meeting was reserved to set the stage for the discussion on guidelines by a scientific symposium at the Dental School of the University of Maryland. Introductory remarks were given by Richard J. Traub (co-chair, host), Christian S. Stohler (Dean) and Vivian Pinn (director of Office of Research on Women’s Health at the National Institutes of Health). The session was chaired by the co-host Joel Greenspan. Nobody could have been better apt than Margaret M. McCarthy (University of Maryland) and our distinct SIG member Karen J. Berkley (Florida State University) to share their insights into the recent developments on sex differences in endocrinology, brain structure/function and pain with the auditorium and to put a variety of critical items on the list of agenda for the SIG meeting. This burden of responsibility was best overcome by the scientific reception with posters and the wonderful dinner following this evening.

Next day the SIG members started to discuss in plenaries and subgroups, which conditions should be given when sex matters in pain research. The three groups were (i) a basic research group, (ii) a translational research group and (iii) a clinical research group the leaders and recorders of which were (i) Jeff Mogil and Rebecca Craft, (ii) Roger Fillingim and Joel Greenspan, and (iii) Anita Holdcroft and Linda LeResche. Furthermore, some distinct endocrinologists (e.g. M.M. McCarty, M. Steiner, E. Young) provided feedback from an especially relevant perspective outside of the field of pain.

Since the most knowledgeable colleagues of the field joined the discussion, there were numerous individual insights and inspirations for all those SIG members who were present in Baltimore. However, there was clearly more than that. The basic research group returned from their discussions with the clear conclusion that sex has been strongly neglected so far in animal research. Therefore, the most urgent mission was to create awareness for the relevance of sex as critical factor. In contrast, the translational and clinical research groups were, as far as human research was concerned, more positive. Sex has been considered already for a while allowing for proposing a taxonomy of components of pain processing, which might be critically affected by the sex of the subject and which should be considered in future research on pain. These factors can be grouped into those relating to the noxious stimulus, those relating to the state of the subject, those relating to the situation of and those relating to the type of response measures used. The many valuable suggestions have now to be screened by the recorders, who are not to be envied because of the mass of material and the need of a systematic storage, which should finally lead to a proposal for a consensus statement or for guidelines.

There was ample evidence that the meeting was of critical importance for the future development of the SIG’s policy. However, it did not become clear whether all the observations, ideas, opinions and speculations will lead the SIG towards a consensus statement or towards guidelines. The latter should preserve the best scientific practice available at present. Whereas in some domains of pain research such a practice appears to exist already and could be written down, it is not even to be seen at the horizon in others. Furthermore, some members argued against prescriptions for colleagues, which might still lack empirical authority. Therefore, it seems more likely that the SIG meeting will

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lead to a consensus statement on the status quo of the study of sex differences in pain and, more important, on the necessary developments and likely challenges of our research. Such a consensus statement might also be suitable to attract new interest and convert some nonbelievers.

However, the next step is to gain an overview over all the spoken and written material. This will be an immense effort for our recorders, who will try to deliver a first proposal of such a statement under the supervision of Joel (Greenspan). Good luck!

On behalf of our SIG I would like to cordially thank especially Richard and Joel, but also Anne Murphy, Emeran Mayer, Michael S. Gold, Jeff Mogil, Rebecca Craft, Karen J. Berkely as committee members as well as those behind the scenes for making this meeting possible and for attracting so much support for our endeavour. Many thanks also for the experiment we all ran at the end of the second day, which informed us why it is that important
to get a hammer when eating crabs.
Stefan Lautenbacher (SIG co-chair)

**Other interesting articles:**
Larry Cahill has recently written an interesting overview (Cahill L: Why sex matters for neuroscience. Nature reviews neuroscience 2006, 7: 477-484). His conclusion is (beyond others): Active investigation of sex influences is mandatory to full understand and treat a host of brain disorders with sex differences in the incidence and/or nature. Highly worth reading. He has published earlier his view in Scientific American (May 2005). If anyone is interested, I can send a PDF.
Gernot Ernst

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**BASIC SCIENCE RESEARCH CORNER**

**The McCarthy Top 10 List of Things We Are Not Thinking Enough About**

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Because the vast majority (~80%) of pain research is performed on male subjects, and even a smaller fraction of studies are designed to identify differences between males and females (Mogil and Chanda 2005), one might expect to have to look long and hard to find signs of progress in the study of sex and gender issues related to pain. Such has not been the case over the last several months. Two notable examples were the special issue of the American Journal of Physiology: Regulatory, Integrative and Comparative Physiology and a conference held in Baltimore under the auspices of the IASP SIG on Sex and Gender Differences in Pain. The special issue of AJP contains the results of a call for papers on Sex and Gender Differences in Pain and Inflammation. The issue was edited by Berkley and Zalcman and is full of a dizzying array of intriguing observations and analyses spanning the distance from molecules to human perception and back again. However, because the contents of this issue may be accessed via the web, I will simply urge you all to find the time to take a look at it.

The conference held in Baltimore was originally organized with the goal to develop comprehensive guidelines for the conduct of basic, translational and clinical pain research with regard to sex and gender. It evolved into a two-tier event consisting of a public session featuring keynote lectures by Drs. Karen Berkley and Margaret McCarthy and a closed door session in which guidelines were discussed by experts in the fields of neuroendocrinology and pain. The result of the closed door session will ultimately be published and therefore readily accessible. While both keynote lectures were excellent and touched on a number of critical points worthy of further discussion, I have chosen to focus on the points raised by Dr. McCarthy for two reasons: first, as a neuroendocrinologist, Dr. McCarthy comes to the table with a different perspective than those of us originally trained as pain researchers; second, Dr. McCarthy was able to eloquently distill a wide range of issues into 10 principles we all should consider as we study sex and gender differences in pain. These 10 principles were as follows:

1) The organizational/activational principal may not always apply. The basic tenets of the organizational/activational principle are that hormone exposure, within some critical period during development, permanently organizes the brain. Once organized, the neural structure(s) may later become activated by circulating hormones; these organizational and activational effects of gonadal steroids serve as the basis for specific patterns of behavior. This principle has been further refined with the notion of the bi-potential brain whereby “masculinization” involves an active process induced by testicular release of testosterone; while “feminization” is the default pattern that develops in the absence of testosterone. Further refinement of this principle came with the observation that both male and female patterns of behavior can be generated in the same animal. This led to the appreciation that an active process of “defeminization” must also occur to remove female behavioral capacity from males. While organizational/activational principle clearly holds for reproductive behavior (McCarthy and Konkle 2005), what remains to be determined is whether these concepts of masculinization, feminization, defeminization or even demasculinization apply to nociceptive circuitry. It is certainly possible that rather than a bi- or even tri-potential “brain” the underlying nociceptive circuitry in males and females develops and/or is modified by hormones over a continuum. Minimally, the observation that the neural circuitry underlying swim stress-induced analgesia in the male appears to be the default phenotype (Mogil et al. 1993) suggests that impact of sex and/or hormones on nociceptive circuitry endogenous antinoceception may in fact be unique.

2) The brain is really a gonad. Researchers have historically focused the gonads as THE source of gonadal hormones (i.e., testosterone and estriadiol). Consequently, experimental manipulations designed to assess the influence of testosterone and
estradiol typically involve gonadectomy and hormone replacement. However, it is clear that steriodogenesis occurs in the brain (Azcoitia et al. 2005). All of the synthetic enzymes necessary for the conversion of cholesterol to testosterone and estradiol have been localized in neural tissue and these enzymes have been shown to be functionally active. Thus, the potential for local hormone synthesis must be considered when interpreting results from experiments involving hormonal manipulations. One of the important implications of local synthesis is that it may be necessary to reassess what is considered to be “physiologically relevant” concentrations of hormones that have historically been defined on the basis of plasma levels.

3) Sometimes the sexes are trying to be the same. There are two general ideas at play in this principle that have far reaching implications. One is that there may be biological processes/responses that are optimal, if not necessary for survival. For example, it is necessary to be able to detect and appropriately withdraw from a noxious stimulus. The second idea is that there may be and often are multiple ways of achieving the same endpoint. Thus, even though withdrawal latencies may be similar between males and females, the underlying circuitry establishing the threshold for the withdrawal may be different. Dr. McCarthy used data from the Morris water maze to illustrate this point. It has been reported repeatedly in the literature that the latency to locate a submerged platform is shorter in male versus female rats; this result has historically been interpreted as indicating that males have enhanced spatial memory. However, studies employing a more complete behavioral analysis revealed that the longer latencies observed in female rats is not due to decreased ability to locate the platform but rather, due to the employment of a more cautious approach to the platform (Beiko et al. 2004).

4) Steroids no longer behave themselves. In the traditional view, hormones produce an action on remote targets by binding to their cognate nuclear receptors, thereby inducing changes in gene transcription. This traditional view has been challenged on virtually every front. There is now strong evidence for (1) the local synthesis and release of hormones; (2) rapid and signal mediated changes in the activity of metabolic enzymes (i.e., Ca\(^{2+}\) dependent changes in aromatase activity); and (3) local and rapid signaling cascades initiated following hormone-receptor binding. In addition, there is increasing evidence that at least some rapid signaling involves membrane bound receptor activation. The weight of these data has led some to question whether estradiol in the brain functions as a hormone, or a neurotransmitter, or both (Balthazart and Ball 2006).

5) One has to consider mechanism and mechanism is a local phenomenon. As suggested by the organizational/activational principal, it is widely accepted that hormones produce a multiplicity of effects. The mechanisms underlying these effects may be just as diverse, however, as the effects themselves. This point was illustrated with an example of the organizational influence of testicular release of testosterone on 3 sexually dimorphic regions of the brain: the medial preoptic area (MPOA), the ventral medial nucleus (VMN) of the hypothalamus, and the arcuate nucleus. The ‘masculinization’ and ‘defeminization’ of all three regions depends on the actions of testosterone aromatization to estradiol. However, the mechanisms underlying the effect of estradiol are unique for each brain region, involving estradiol-induced changes in COX-2 expression in the MPOA (Amateau and McCarthy 2004), glutamate release in the VMN (McCarthy and Konkle 2005), and GABA release in the arcuate (McCarthy and Konkle 2005). Identification and/or recognition of distinct and site-specific mechanisms involved in the regulation of nociception will facilitate the development of therapeutic interventions for the treatment of pain sensitive to changes in hormone levels.

6) One has to consider all players. As suggested above, hormones produce a multiplicity of effects, but they do so through a multiplicity of cell types. Importantly, this concept holds for the central nervous system as well as for peripheral tissues. Thus, while investigators have long appreciated hormonal influences on peripheral targets such as smooth muscle cells, immune cells and specific tissues such as the adrenal medulla, it is clear hormones influence virtually all cells types within the CNS as well (McCarthy et al. 2003). For example, an estradiol-induced increase in the excitability of dorsal horn neurons may reflect both an estradiol-induced increase in glutamate release from the presynaptic neuron as well as an estradiol-induced decrease in glial cell mediated glutamate re-uptake.

7) Genes matter. With all of the focus on the organizational and/or activational actions of hormones, it is easy to forget that genes are also important. That it may be possible to distinguish influences of genetic sex from gonadal sex arose from the observation that the SRY gene is necessary for the development of the testes: in the absence of SRY, a genetic male will fail to develop testes and therefore have a female phenotype, even though his genotype is XY (Arnold et al. 2004). Thus, with a combination of XY or XX, with or without SRY (i.e., XX+/-SRY; XY +/-SRY), it is possible to distinguish genetic from gonadal sex (De Vries et al. 2002). This type of genetic manipulation indicates that ~14% of the genes in the brain show a genetic sex difference (Rinn and Snyder 2005). The implication of this principle is that it may no longer be sufficient to make the distinction between sex (i.e., biology) and gender (i.e., a social construct), given that sex may be either gonadal or genetic.

8) One should complement the use of gene arrays with other approaches. It is clear that hormones influence gene expression. As was noted above, this was part of the traditional view of hormone signaling. Techniques such as in situ hybridization and reverse transcriptase coupled polymerase chain reaction (RT-PCR) have enabled the localization and quantification of hormone-mediated changes in gene expression. More recently, use of gene microarrays have enabled pattern analysis of hormone-mediated changes in 10’s of thousands of genes. However, it is becoming increasingly clear that changes in gene expression are only a small part of the story. Rapid second messenger mediated signaling may have profound long lasting effects in the absence of a change in gene expression (McCarthy 2004). Furthermore, advances in our understanding of epigenetics have added further weight to the conclusion that the story neither begins nor ends with changes in gene expression. For example, recent evidence suggests that maternal behavior can influence methylation of genes in the infant which ultimately influences the response to stress in the adult (Weaver et al. 2004).

9) Sometimes the sexes start the same and diverge. This principle was illustrated with two striking examples. First, there is data to suggest that, on average, neuronal spine density in many brain regions are similar between males and females. However, if one assesses spine density across the estrous cycle, it becomes clear that there are times when spine density is high (i.e., proestrus) and others when spine density is low (i.e., diestrus) (Cooke and Woolley 2005). Second, data from a number of behavioral
endpoints suggest that learning is similar between male and female rats. However, there are significant sex differences in the effect of acute stress at the time of learning (increasing performance in males, decreasing performance in females) (Shors 2006). This divergence may contribute to the observation that differences between men and women with respect to nociceptive threshold and tolerance are small, if detectable in pre-clinical studies, yet the prevalence, severity and duration of pain syndromes is generally higher in females than in males.

10) What happens in development does not stay in development. While this final principal may sound a lot like a recapitulation of the organizational principal of hormone actions, it was made to underscore the point that there is not simply a critical period within which hormones will have a long lasting yet highly predictable impact of the brain. Rather, that the critical period within which hormones are able to produce long lasting effects corresponds to the critical periods in the development of a number of other neural circuits. Importantly, there may be an interaction between divergent developmental processes which ultimately impact on the phenotype of the adult. Evidence of such an interaction was recently obtained by Murphy and colleagues who observed that the long term consequences of noxious stimulation of the neonate are different in male and female rats (LaPrairie and Murphy 2006).

References:

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For some time now it has been acknowledged that patient expectations and experiences can have an impact on outcome from a range of different medical procedures e.g., postoperative analgesic requirements, time to discharge. There is also a much greater emphasis on the quality of care received by patients, with respect to medical services and procedures. Given that patient satisfaction is related to both expectations and experiences of the care they receive, it would seem that pain would be a fertile area to investigate such relationships, and perhaps also to consider the potential similarities and differences between the sexes.

A quick, non-systematic, search of a couple databases found an interesting study by Shabat et al. (2005). They report an investigation on 300 adult elderly patients who were followed up at least 1 year after receiving spinal surgery to assess a range of outcomes including function, pain and satisfaction. Although daily activity and pain were found to improve, the level of satisfaction experienced was different between men and women; women reported being less satisfied. Reasons for dissatisfaction included pain after the operation. Closer inspection revealed that pain intensity was not relieved in 9% of men and 17% of women, and reported to be aggravated in 6% and 17% respectively. This not only suggests that satisfaction with surgical outcome was related to pain experiences, but that there may be differences between the sexes in how this manifests.

If there are sex differences in outcomes such as pain and satisfaction, then it would be of interest to find out how best to manage such experiences. Amongst the many possible areas to target, one that caught my eye was that of information needs. Stewart et al. (2004) asked 906 patients who were followed up after an acute coronary event about what information they felt they required about their condition. The general outcome of the study was that both sexes would have preferred to have had more of a joint role with their doctor regarding decisions about their treatment. Furthermore, women reported a need for more information from healthcare professionals. Interestingly, there were also differences in the type of information that patients felt they required; women wanted more information on angina and hypertension, whereas men wanted information on sexual function.

Putting these two themes together, it would be interesting to discover what the similarities and differences are between male and female patients with respect to their information needs about pain, as well as consider whether addressing such needs can impact on patient satisfaction with medical services.

References