Du weißt, dass der Leib ein Kerker ist;
Die Seele hat man hinein betrogen;
Da hat sie nicht freie Ellebogen.

The body is a prison-house, you know;
Within it was the free soul lured to come;
There where it cannot get bare elbow-room.

Goethe, West-östlicher Divan
(The West-Eastern Divan; transl. Edward Dowden)

Dear colleagues,

Was Goethe right? Are we prisoners of our somatic or, for that matter, neuroendocrine preconditions and processes? Does our biological sex determine our thoughts and emotions? If so, what happens when body and mind do not match and we want to break free of our bodily constraints?

We warmly welcome you in Tübingen where we will discuss these and many more topics in our Winter School on “Sex Hormones and the Brain”. Tübingen may be small, but it is an ancient and proud university town. As one of the first and most renowned universities in Europe, the University of Tübingen was founded in 1477 and has continued to promote lively and excellent research and teaching ever since. We hope that our Winter School, which is organized by the Departments of Psychiatry and Medical Psychology within the Matariki Network of Universities, will continue the tradition of bringing together aspiring and advanced researchers. We are looking forward to scientific exchange and lively discussions about the links between sex hormones and brain functions, viewed both from a basic and a clinical perspective.

Goethe himself spent some days in Tübingen in the autumn of 1797, but fortunately this welcome note is too short to discuss his mixed impressions any further… So, we do hope that you will very much enjoy your visit to Tübingen and our Winter School. We wish you an exciting and stimulating meeting!

Birgit Derntl and Manfred Hallschmid
Schedule

WEDNESDAY, JANUARY 31ST

13:30  Registration and Welcome Reception
Psychiatry Department (Calwerstraße 14, Tübingen)

14:00  Welcome word

SYMPOSIUM “SEX HORMONES AND MOOD”
Chaired by Birgit Derntl and Manfred Hallschmid

14:30  Julia Sacher (Leipzig),
“Sex-hormone fluctuations as a risk model for postpartum mood disorders“

15:00  Inger Sundström Poromaa (Uppsala),
“Mental health effects of hormonal contraceptives – a small problem affecting many”

15:30  Coffee break

KEYNOTE LECTURE

16:00  Ute Habel (Aachen),
“Putting gender into question: from sex differences to gender dysphoria”

17:00  POSTER SESSION 1

THURSDAY, FEBRUARY 1ST

9:00  POSTER SESSION 2

10:30  Coffee break

SYMPOSIUM “SEX HORMONES AND COGNITION”
Chaired by Inger Sundström Poromaa and Vibe G. Frokjaer

10:45  Belinda Pletzer (Salzburg),
“Menstrual cycle dependent changes in cognitive functions – the role of the hippocampus and basal ganglia”

11:15  Lydia Kogler (Tübingen),
“Impact of sex and sex hormones on stress reactions”

11:45  Janine Bayer (Hamburg),
“The effects of estrogen on emotional memory and its neuronal correlates”
12:15  Lunch break

HONORARY LECTURE
13:00  Niels Birbaumer (Tübingen), “From musical talent and hormones to brain computer interfaces”

POSTER TALKS
14:00  Esmeralda Hidalgo-Lopez (Salzburg), “Interactive effect of cycle phase and dopamine baseline levels on brain activation and functional connectivity during N-back task”

14:20  Anouk E. de Wit (Groningen), “Associations of oral contraceptive use and depressive symptoms in adolescents and young women”

14:40  Tess Beking (Groningen), “Two studies on testosterone and brain lateralization: from amniotic fluid to testosterone treatment”

15:00  Coffee break

SYMPOSIUM “SEX HORMONES AND CLINICAL”
Chaired by Ute Habel and Alkistis Skalkidou
15:15  Fotis Papadopoulus (Uppsala), “Gender dysphoria from a psychiatrist’s perspective”

15:45  Bastian Amend (Tübingen), “Gender reassignment surgery in gender dysphoria”

16:15  Martin Walter (Tübingen), “Sex differences and psychopathology”

19:00 – 23:00  Social dinner party and Poster Awards
Museum Restaurant (Wilhelmstraße 3, Tübingen)
FRIDAY, FEBRUARY 2ND

9:00  MEET AN EXPERT (3 parallel sessions):
“Women in Academia: path to a successful career and work-life balance”
Julia Sacher (Leipzig), Alkistis Skalkidou (Uppsala), Veronika Müller (Jülich)
Moderated by Gizem Altan

“Sex Hormones: planning a study, hormone application and beyond”
Anna-Karin Wikström (Uppsala), Inger Sundström Poromaa (Uppsala), Janine Bayer (Hamburg)
Moderated by Carolin Maier

“Sex and Gender: theoretical considerations and practical applications”
Ute Habel (Aachen), Fotis Papadopoulos (Uppsala), Pia Schober (Tübingen):
Moderated by Aiste Seibokaite

10:15  Coffee break

KEYNOTE LECTURE
10:30  Vibe G. Frokjaer (Copenhagen), “Sex hormone fluctuations as a risk model for depressive episodes; implications for stratification”

SYMPOSIUM “SEX HORMONES AND THE BRAIN”
Chaired by Julia Sacher and Martin Walter

11:30  Anna-Karin Wikström (Uppsala): “MR studies of cerebral physiology and metabolism in normal pregnancy and preeclampsia”

12:00  Veronika Müller (Jülich): “Functional connectivity and its implications in gender research”

12:30  Judy Kipping (Singapore): “Sex differences in brain development: A focus on cerebello-cortical functional connectivity and cognitive functions in boys”

13:00  Farewell word
13:15  Lunch break
14:00  The end
POSTER TALKS
Interactive effect of cycle phase and dopamine baseline levels on brain activation and functional connectivity during an N-back task

Esmeralda Hidalgo-Lopez¹,² & Belinda Pletzer¹,²
¹Department of Psychology, University of Salzburg, Salzburg, Austria; ²Centre for Cognitive Neuroscience, University of Salzburg, Salzburg, Austria

Female sex hormones interact with dopamine (DA), which relates to executive control functions in an ‘inverted u-shaped’ manner. Given the different optimum levels for different functions; cognitive performance, brain activation and connectivity are expected to change along the menstrual cycle, related to individual DA baseline levels. Accordingly, it has been demonstrated that inhibitory functions of working memory and related activation in the middle frontal gyrus (MFG) are enhanced or impaired during the pre-ovulatory phase of the menstrual cycle depending on DA baseline levels. In the present study we seek to extend these findings to changes in brain connectivity patterns.

38 naturally cycling women completed three fMRI sessions time locked to their menstrual cycle (menses: low estradiol and progesterone; preovulatory: high estradiol; and luteal: high estradiol and progesterone). During each session women performed a verbal N-back task as measure of working memory. Target trials were included to assess working memory and lure trials to assess inhibitory control. Spontaneous eye blink rate (EBR) was recorded during menses as an indirect measure of striatal DA levels. Saliva samples were collected before and after the session in order to analyse hormonal levels.

Behaviourally, women with higher EBR during menses showed impaired performance with lure trials during the luteal phase compared to menses, while women with lower EBR showed improved performance during the luteal phase. Brain activation in the IMFG during lure trials was lower during the luteal phase compared to the pre-ovulatory phase. Menstrual cycle dependent changes in activation of the MFG during targets was modulated by EBR. From the preovulatory phase to the luteal phase MFG activation during target trials increased significantly, but only for those women with higher EBR during menses. Accordingly, not only activation, but also connectivity patterns of MFG changed along the menstrual cycle depending on women’s baseline dopamine levels.
Associations of oral contraceptive use and depressive symptoms in adolescents and young women

Anouk E. de Wit¹, Sanne H. Booij¹, Erik J. Giltay², Hadine Joffe³, Robert A. Schoevers¹, Tineke A.J. Oldehinkel¹
¹University of Groningen, University Medical Center Groningen, Department of Psychiatry, PO Box 30.001, 9700 RB, Groningen, the Netherlands; ²Leiden University Medical Center, Department of Psychiatry, PO 9600 2300 RC, Leiden, the Netherlands; ³Harvard Medical School, Department of Psychiatry, Brigham and Women's Hospital, Boston, United States of America

Introduction: Findings regarding oral contraceptive pill (OCP) related mood changes are inconsistent. We aimed to determine the association between OCP use and depressive symptoms and to test whether these associations are influenced by age or long-term use, and whether the effects are symptom-specific.

Methods: In total, 1010 sixteen-year-old girls from a large longitudinal Dutch population survey TRAILS (TRacking Adolescents' Individual Lives Survey) were followed over 9 years (average 3.3 observations per girl). Associations between self-reported OCP use and concurrent sum score of and individual depressive symptoms (as measured) were determined with multilevel analyses. Depressive symptoms were measured with the depression scale of the Adult Self-Report. Effects of age and duration of OCP use were tested as well.

Results: An age-specific but not duration-specific pattern for mood complaints with OCP use was found. Although overall OCP users did not show a higher sum score on depressive symptoms compared to non-users, younger girls using OCP did report higher sum scores compared to younger non-OCP users (B for interaction-term Age*OCP use -0.023 95% Confidence Interval [CI]: -0.039 – -0.07, p = .005). Also, OCP use was associated with more crying (OR 1.40 95%CI: 1.22 – 1.61, p < .001) and hypersomnia (OR 1.38 95%CI: 1.18 – 1.62, p < .001), but in contrast also with fewer feelings of guilt (OR 0.75 95%CI: 0.64 – 0.90, p < .01) and non-succeeding (OR 0.70 95%CI: 0.59 – 0.84, p < .001).

Conclusions: The finding that younger girls are more prone to develop OCP use associated mood complaints, and that OCP use relates to depression in a symptom-specific manner might explain the overall non-significant effect with depression found in previous studies.
Two studies on testosterone and brain lateralization: from amniotic fluid to testosterone treatment

Beking, T.1,2,3, Kreukels, B.P.C.3, Geuze, R.H.1 & Groothuis, A.G.G2.
1Clinical & Developmental Neuropsychology, University of Groningen; 2Behavioural Biology, GELIFES Institute, University of Groningen; 3Center for Expertise on Gender Dysphoria, VU medical center Amsterdam.

Brain lateralization is the functional specialization of the brain, with some functions performed primarily by the left hemisphere, and other functions by the right hemisphere. Prenatal testosterone has been put forward as a major causal factor in the development of brain lateralization, but after decades of research its role is still elusive. More recently it has become evident that puberty is also an important developmental phase in which testosterone can have organizational effects on brain and behavior, but this aspect has been neglected in studies on brain lateralization. In my PhD I investigate the influence of prenatal and pubertal testosterone on brain lateralization, both in healthy adolescents whose prenatal hormone levels are known, and in persons diagnosed with Gender Dysphoria who receive cross-sex hormone treatment. I am now at the end of my PhD and I will present the main outcomes of two studies. In the first longitudinal study we investigated the influence of prenatal testosterone (measured in amniotic fluid) and pubertal testosterone (in saliva) on brain lateralization (measured with functional Transcranial Doppler sonography) of the Mental Rotation, Word Generation and Chimeric Faces tasks at the age of 15 years (30 boys; 30 girls). Both prenatal and pubertal testosterone relate to brain lateralization, and the influence of testosterone differs between right- and left-lateralized tasks. In the second study we investigated the influence of testosterone on functional amygdala lateralization in 21 transboys (girls assigned at birth diagnosed with Gender Dysphoria) before and during testosterone treatment, and in 19 control boys and 17 girls (mean age session 1 = 16 years; mean age session 2 = 17 years). Preliminary analyses show that testosterone is related to lateralization of the amygdala, but the direction seems to differ between control boys and transboys. Final analyses will be discussed at the presentation.
The endocrinology of empathy: oxytocin and testosterone response to an emotional video

Tanya Procyshyn, Bernard Crespi
Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, UK

The hormones oxytocin and testosterone are evolutionarily ancient regulators of sociality, serving to coordinate adaptive social behaviour with stimuli in the environment. Administration of oxytocin and testosterone has been shown to increase and reduce empathy, respectively; yet if and how levels of both hormones change in response to naturalistic empathy-inducing stimuli has seldom been tested. In our study, healthy adults watched an emotional, empathetic video, with salivary oxytocin and testosterone measured before and after. Overall, on average, there were significant increases in oxytocin (p<0.01) and decreases in testosterone (p<0.001). Moreover, these changes in hormone levels tended to occur together. Research participants also completed the short-form Empathizing Quotient and Systemizing Quotient questionnaires. Individuals with higher Systemizing relative to Empathizing showed higher baseline testosterone relative to oxytocin, when questionnaire scores and hormone levels were normalized to adjust for sex differences (correlation = 0.16, p < 0.05). These findings indicate that testosterone relative to oxytocin represents an important correlate of cognitive style related to empathizing and systemizing cognition.
The role of provocation sequence in a monetary modified Taylor Aggression Paradigm (mTAP)

Konzok, J1, Kreuzpointner, L1, Henze, G I1, Kärgel, C2, Weidacker, K3, Schiffer, B2, Wüst, S1, Kudielka, B M1
1Department of Medical Psychology, Psychological Diagnostics and Research Methodology, University of Regensburg, Germany; 2Division of Forensic Psychiatry, Department of Psychiatry, Psychotherapy and Preventive Medicine, LWL- University Hospital Bochum, Germany; 3School of Human and Health Sciences, Department of Psychology, University of Swansea, Swansea, UK

The Taylor Aggression Paradigm (TAP) is widely used to measure reactive aggression in laboratory settings. While most research on this task so far has focused on different stimuli modifications to determine reactive aggression (e.g., shocks, noise, pressure, money) and the order of these stimuli (random vs. block design), less attention has been paid to compare directly different stimulus sequences.

In this experimental study, 118 subjects (58 males, 61 females) participated in a mock competitive reaction time task against a fictional opponent with 40% preprogrammed win- and 60% lose-trials. In the lose-trials, participants were provoked by subtracting a low (0-20 cents), medium (30-60 cents) or high (70-90 cents) amount of money either presented randomly or in a fixed sequence. In contrast to a random sequence, the fixed sequence was generated by repeating trials from the same provocation category in triplicates to simulate a more “naturalistic” strategic response of the mock opponent based on former data analysis. Because of the more homogeneous provocation in the fixed condition, we expected higher aggression after higher provocation and lower aggression after lower provocation in this condition.

Results indicated that, in general, the aggression rate increased in accordance with stages of provocation (low, medium, high). Further, in terms of convergent validity, the reactive aggression rate during the mTAP was positively correlated with trait aggression psychometrically measured by the K-FAF. Surprisingly, aggression rates were not mediated by gender. Finally, we found no significant difference in reactive aggression between the two experimentally manipulated stimulus sequences (random vs. fixed).

The findings provide new evidence for the monetary mTAP as a valid paradigm to induce and measure reactive aggression. Additionally, there was no indication that a fixed sequence order would be advantageously since the current level of reactive aggression appeared to be most affected by the last provocation trial.
Task of Mental Rotation: Estrogen versus Testosterone

Sandra Stojić
Doctoral School of Psychology, Department of Cognitive Psychology, ELTE PPK, Budapest, Hungary

Aim of the study was to evaluate the results of the mental rotation tasks (MRT) among men and women, including different phases of menstrual cycle among the female participants. Since the sexual dimorphism is predominantly influenced by hormonal levels, it was expected that the overall performance of the participants would depend on gender or different phases of menstrual cycle. Examination was conducted on a sample of students (N=90; 60 females and 30 males, aged from 19 to 24 (M=22.6; SD=2.1)), divided into three groups. Statistical analysis of data showed a significant difference in time of performance in MRT, regarding to the degree of figure rotation (0°, 45°, 90°, 135° and 180°) and the type of figure representation (rotated and mirror-rotated), but the effects of gender and/or phase were not demonstrated. Further studies should include relevant physiological measures, and assess phases more precisely, what was considered as the biggest restriction of the current one.
Sex differences and menstrual cycle dependent changes in cognitive strategies during spatial navigation and verbal fluency

Andrea Scheuringer, Belinda Pletzer
Centre for Cognitive Neuroscience, University of Salzburg, Salzburg, Austria

Background: Sex differences in cognitive performance have been consistently observed in spatial navigation tasks, indicating a robust male advantage. A female advantage in verbal fluency tasks is more controversial, suggesting stronger sex differences in phonemic compared to semantic fluency. Differences in cognitive performance have been suggested to arise from sex-specific cognitive strategies on the one hand and sex hormone influences on the other hand. Specifically, holistic strategies (e.g. the use of an allocentric perspective during navigation) and testosterone levels have been related to improved performance during spatial tasks. Detail-oriented strategies (e.g. switching between categories during verbal fluency) and estradiol or progesterone levels, which are high in women’s luteal cycle phase, have been related to improved performance in verbal tasks. However, a link between sex hormones and cognitive strategies has not been previously established.

Method: To investigate the influence of sex hormones and menstrual cycle on cognitive strategies, 51 men and 49 women completed a 2D-matrix navigation task and a phonemic and semantic verbal fluency task. All participants were tested twice, with test sessions in women time-locked to the early follicular (low estradiol and progesterone) and mid-luteal cycle phase (high estradiol and progesterone). Cognitive strategy was modulated using different task instructions.

Results: As expected, men outperformed women in the navigation task and women outperformed men in the verbal fluency task. The superior performance of women during both verbal fluency tasks was explained by them switching more often between categories. Sex differences in navigation strategies however did not conform to the outcomes of previous studies. Nevertheless, menstrual cycle phase did modulate strategy use during navigation, with a preference for more holistic strategies in the follicular compared to the luteal cycle phase. Menstrual cycle did not affect switching or clustering during verbal fluency. This suggests a modulation of cognitive strategy use during spatial navigation, but not during verbal fluency, by relative hormone increases during the luteal phase of the menstrual cycle. However, absolute sex hormone levels as assessed from saliva samples were only weakly associated with cognitive strategies.
Sex differences in navigation strategies

Tianni Harris
Department of Psychology, University of Salzburg, Salzburg, Austria

The influence of sex, and in particular a difference in strategy, on spatial navigation was investigated. Men tend to perform better with allocentric instructions (“go North/East/South/West…”) with a Euclidian strategy (“… for 3 Blocks”), while women benefit from egocentrical instructions (“turn right at…”) with a landmark-based strategy (“…at the Bridge”). To test these claims a new computer-based 3D navigation task was developed, with different types of instructions (allocentric Euclidian, allocentric landmark, egocentrical Euclidian, egocentrical landmark).

All 68 participants had a first-person view of the environment and followed the instructions on the screen, leading them to their destination. Lastly, the participants had to estimate where North was by clicking one of four arrows on the screen.

It was found that that sex had a significant influence on the perspective for reaction times. Further, a significant interaction was found between sex and interaction. The allocentric instruction was beneficial for men and the egocentrical instruction was more beneficial for women.

The newly created navigation task could replicate earlier findings of sex differences in spatial navigation and showed promising results in demonstrating the different strategies used by men and women.
Sex modulates the interaction between neuropeptide S gene variants and endocrine and central stress responses

Sandra Zänkert¹, Fabian Streit¹,², Leila Haddad¹, Ceren Akdeniz¹, Heike Tost¹, Robert Kumsta⁴, Sonja Entringer⁵, Ilona S. Yim⁶, Stephanie Witt¹, Peter Kirsch¹, Marcella Rietschel¹, Stefan Wüst¹

¹Central Institute of Mental Health, University of Heidelberg/Medical Faculty Mannheim, Germany; ²Institute of Psychobiology, University of Trier, Germany; ³Institute of Experimental Psychology, University of Regensburg, Germany; ⁴Department of Genetic Psychology, Ruhr University Bochum; ⁵Institute of Medical Psychology, Charité Universitätsmedizin, Berlin; ⁶Department of Psychology and Social Behavior, University of California, Irvine (SSD, ISY), United States

The brain neuropeptide S (NPS) system could be of major relevance for central stress regulation and has recently generated substantial interest. The NPS receptor (NPSR1) is highly expressed in the limbic system and exogenous NPS exerts pronounced anxiolytic and fear-attenuating effects in rodents. In humans, associations between NPSR1 variants and anxiety and panic disorder, amygdala responsiveness to fear-relevant faces and prefrontal cortex activity in a fear conditioning paradigm have been reported. Moreover, a NPSR1 sequence variant was found to be associated with cortisol stress responses in males. Here we performed a NPSR1 haplotype analysis covering rs2530547, rs324981 and rs727162 in 277 healthy subjects who have been exposed to the Trier Social Stress Test. For “haplotype 2” (frequency of about 20%) a significant sex-specific association with salivary cortisol response to acute psychosocial stress was detected. In an additional investigation using an imaging genetics approach, 65 healthy subjects were exposed to a social stress paradigm for scanner environments (“ScanSTRESS”). We found a significant and, again, sex-specific interaction between rs324981 (whose minor allele is harbored by haplotype 2) and the neural stress response in a cluster close to the parahippocampal gyrus (whole brain corrected). Moreover, salivary cortisol responses showed (on a trend level) the same sex-specific pattern as in our TSST-study. Our findings suggest that the NPS system significantly influences stress responsivity and that sequence variation in NPSR1 may contribute to sex differences in stress regulation.
ScanSTRESS and its application in a prospective-longitudinal study

Gina-Isabelle Henze, Julian Konzok, Brigitte M. Kudielka & Stefan Wüst
Institute of Experimental Psychology University of Regensburg, Regensburg, Germany

With the advent of accessible and affordable neuroimaging techniques, it was a logical next step in human stress research to scrutinize the interaction between CNS activity and HPA axis regulation. This research requires paradigms that are suitable for scanner environments and that induce significant HPA axis responses. After the successful establishment of the Montreal Imaging Stress Task, we recently developed the ScanSTRESS paradigm. Consistent with the Trier Social Stress Test this paradigm particularly aims at inducing (moderately) the psychological factors uncontrollability and social-evaluative threat. ScanSTRESS prompts the subject to perform mental arithmetic and mental rotation tasks under time pressure, while being monitored by an investigator panel.

In a current prospective-longitudinal study, we implemented a protocol that includes a repeated collection of saliva samples and psychological stress ratings during the ScanSTRESS paradigm. Furthermore, we assess two resting state sequences, one directly after the stress induction and the other one on a separate weekday at rest to investigate differences in functional connectivity of stress-related structures in the brain. While a first cohort will compromise young, healthy, non-smoking males and females (using oral contraceptives), a second cohort will consist of students facing a long-lasting and significant stress phase in a determined future period. In this context, we want to explore neural predictors of biopsychological responses to chronic stress in real life by applying the ScanSTRESS paradigm.
Cortisol affects fear memory reconsolidation differently in men and women

Shira Meir Drexler, Christian J. Merz, Tanja Hamacher-Dang, Oliver T. Wolf
Department of Cognitive Psychology, Ruhr-University Bochum, Germany

Reactivation of an already consolidated memory item via its retrieval can make it once again fragile and susceptible to interruption until it reconsolidates. During this period, reactivated memories can be altered (enhanced, impaired or otherwise updated) by behavioural or pharmacological manipulations. Cortisol is a stress hormone and a potent modulator of learning and memory, yet its effects on human fear memory reconsolidation are largely unknown, and were therefore the aim of our work. Forty-two men and seventy-two women (oral contraceptive users and free cycling) were assigned to one of three groups (Reactivation+Cortisol, Reactivation+Placebo, Cortisol+No-reactivation) and were tested on a three-day reconsolidation design. For fear acquisition, three geometrical shapes were used as conditioned stimuli (CS): two stimuli (CS1+, CS2+) were paired with an electrical shock; one stimulus (CS-) was never paired with a shock. On the second day, cortisol/placebo was administered prior to a single unreinforced presentation (i.e. memory reactivation) of CS1+, one of the previously reinforced stimuli. On the third day, the return of fear to all stimuli was tested. Our results revealed a different pattern of response in men and women. In men, cortisol led to an enhancing effect on the reactivated fear memory, suggesting a role for cortisol in the persistence of aversive memories. In women, however, no effect of cortisol was found. We will suggest a significant role of cortisol in fear memory reconsolidation in anxiety-and stress-related disorders, e.g. phobias and post-traumatic stress disorder, and discuss its possible modulation by alternating concentrations of sex hormones.
The effect of progesterone on functional resting state connectivity in ECN and eSAD

Gizem Altan, Birgit Derntl, Veronika I. Müller, Simon B. Eickhoff, Lydia Kogler
1Vision and Cognition Lab, Department of Psychology, University of Tübingen; 2Centre for Integrative Neuroscience, Tübingen; 3Max Planck Institute for Biological Cybernetics, Physiology of Cognitive Processes, International Max Planck Research School for Cognitive and Systems Neuroscience, Tübingen; 4Department of Psychiatry and Psychotherapy, Medical School, University of Tübingen; 5LEAD Graduate School and Network, University of Tübingen; 6Institute of Neuroscience und Medicine, INM-7, Research Centre Jülich, 7Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf

Progesterone (PROG), a sex hormone that is present in both women and men, has shown to be involved in social bonding and been linked to well-being and motivation of individuals (Brown et al., 2009). Besides being synthesized in the brain, it is also involved in regulation of cognitive and affective processes both on neuronal and behavioral levels (Poromaa and Gingnell, 2014). In a recent study PROG levels were shown to modulate resting-state functional connectivity (rsFC) in default mode network (DMN) regions in women (Syan et al., 2017). In addition to the DMN we would expect specific networks to be modulated by PROG. For affective processes we think that the extended social-affective default network (eSAD) is the right network to look for correlation with PROG as it is established by mapping regions involved in social, affective and introspective processes (Amft et al., 2015). Moreover, for the cognitive processes we think the executive-control network (ECN) may reveal correlation with PROG.

In this study (N=85, women and men) we looked at rsFC within the eSAD and the ECN in association with PROG. Within the eSAD, PROG correlated negatively with rsFC of left temporo-parietal junction (TPJ) and precuneus (PrC) across the whole group, thus a higher rsFC between these regions was going along with less endogenous PROG. Interestingly, within ECN there was no significant correlation with PROG. For both networks, no sex differences appeared.

The ECN includes regions involved in attention, working memory, response selection and suppression (Seeley et al., 2007). Thus we hypothesized that the cognitive processes of memory formation (Horst et al., 2011) might be modulated by PROG, but to our surprise we did not find any correlation within the regions of this network. Both TPJ and PrC were previously shown to be involved in social cognition, emotion and theory of mind and are included in the eSAD. Specifically the TPJ is associated with evaluating others’ mental states in social context (Saxe and Kanwisher, 2003), and the PrC is associated with experience of agency (Farrer and Frith, 2002) and emotional state attribution (Ochsner et al., 2004). Our results show that the rsFC between TPJ and PrC is modulated by level of PROG, not only for women but also for men.
Sex influences genetic and metabolic interaction in anxiety endophenotype

Lejla Colic1,2, Meng Li1,3, Liliana Ramona Demenescu1, Shija Li4, Iris Müller5, Anni Richter2, Constanze I. Seidenbecher2,6, Oliver Speck2,6–8, Björn H. Schott2,6,9, Oliver Stork6,10, Martin Walter1–3,6,11–12 *

1CANLAB, Magdeburg, Germany; 2Leibniz Institute for Neurobiology, Magdeburg, Germany; 3Department of Psychiatry and Psychotherapy, Otto von Guericke University of Magdeburg, Magdeburg, Germany; 4School of Psychology and Cognitive Science, East China Normal University, Shanghai, China; 5Department of Psychological Sciences, College of Health and Human Sciences, Purdue University, West Lafayette, Indiana, USA; 6Center for Behavioral Brain Sciences, Magdeburg, Germany; 7Department of Biomedical Magnetic Resonance, Otto von Guericke University, Magdeburg, Germany; 8German Centre for Neurodegenerative Diseases (DZNE), Site Magdeburg, Germany; 9Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin; 10Department of Genetics and Molecular Neurobiology, Institute of Biology, Otto von Guericke University of Magdeburg, Magdeburg, Germany; 11Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany; 12Max Planck Institute for Biological Cybernetics Tübingen, Germany

Background

Anxiety disorders are more prevalent in women, but factors contributing to it are unknown. GABAergic dysregulation was reported both in pre-clinical models and patient studies of anxiety. Interestingly, steroid hormones modulate GABAergic system, indicating one possible substrate for these sex differences. Imaging markers furthermore emphasized the role of cortico–limbic circuit, including pregenual anterior cingulate cortex (pgACC), an affect regulating region, in anxiety endophenotypes. Therefore, we investigated whether a SNP in GABA synthesizing enzyme – GAD65 and sex are associated with the inhibitory/ excitatory balance in ACC regions (pgACC and aMCC). Moreover, we explored the relationship between GAD65 polymorphism, sex, metabolites and harm avoidance (HA).

Methods

105 healthy subjects (44 females, age= 27.09± 6.72) underwent a magnetic resonance spectroscopy in 7T. GABA and Glu levels were measured in aMCC and pgACC. Subjects completed TCI questionnaire and were genotyped for the GAD65 promoter polymorphism (65 AA and 40 G-carriers). Region by genotype by sex ANOVA was calculated including age as confound for GABA/Glu levels. Next, we tested differences for HA, and its association to the pgACC metabolism. Lastly, we performed an analysis of mediating effects of GABA/Glu on GAD65 to HA, moderated by sex.

Results

We found an interaction effect on GABA/Glu levels (F(1,63)= 8.66, p= 0.005). Post-hoc analysis revealed that this interaction was driven by the genotype difference in females in the pgACC (t(36)= –2.19, p= 0.035). There was an effect of sex on HA (U= 327.5, p= 0.039), and HA correlated to the pgACC GABA/Glu levels only in women (p(24)= –0.593, p= 0.001; men: p(32)= 0.068, p= 0.70). We furthermore observed an effect for the moderated mediation (index= –3.147, bootstrapped 95%
CI= [-9.479, -0.519]), where for women pgACC GABA/Glu mediated the relationship of GAD65 polymorphism and HA.

**Conclusion** Our results show that GABAergic gene polymorphisms and sex are factors contributing to anxiety endophenotypes in women via metabolic correlates in the pgACC. This interaction could be relevant for the observed sex bias in frequency of anxiety disorders and possible sex specific treatment strategies.
Somatic awareness is person’s ability to sense signals emerging from one’s own body. The prevalence of disorders with somatic disturbances differs in manifestation between genders – females suffer more frequently from depression and anxiety disorders. These observations raise questions whether females differ from males in their ability to be more focused and sensitive to their own body sensations. Based on the set experimental data of both – subjective evaluation (questionnaires) and objective evaluation (by measuring the brain activity with electroencephalography (EEG)) – collected by our group, we try to answer this question.

Three different methods were applied in groups of young adults: 1) a self-rated Multidimensional Assessment of Interoceptive Awareness (MAIA) questionnaire (376 subjects; 51% males); 2) a self-reported Amsterdam Resting State Questionnaire (ARSQ) with parallel evaluation of resting state EEG markers (94; 45% males); 3) Proprioceptive evoked potential paradigm (PEP) to measure the brain activity to passive proprioceptive stimulation (20; 50% males).

Results revealed gender differences in all groups. First, with the self-assessment of one’s general interoceptive abilities (MAIA) females scored higher on the ability to notice interoceptive stimuli (Noticing) and Emotional Awareness, and lower on the tendency not to undergo emotional distress with physical discomfort (Non-Worrying) and the experience of own body as safe and trustworthy (Trusting). Then, during the resting state evaluation (ARSQ) females had more thoughts about themselves, their feeling and behavior (Self-dimension). Moreover, the EEG microstate D (representing one’s interoceptive-automatic processing) correlated to Somatic Awareness scores in females only. Lastly, PEP results showed that females possess stronger brain activity in response of unexpected applied weight to arm resulting in a better evaluation in sensation of one’s body position in space.

As a conclusion, we suggested that females are better to recognize their somatic state. Acknowledgement: we thank all our colleagues who contributed to abovementioned studies.
**Interference processing and visuospatial cueing are influenced in a sex-specific manner during an fMRI-study investigating men, oral contraceptive users and luteal women**

Jonas Hornung¹, Lydia Kogler¹, Hannes Noack¹, Michael Erb¹, Jessica Freiherr², Birgit Derntl¹
¹Klinik für Psychiatrie und Psychotherapie Tübingen; ²RWTH Aachen

**Introduction**

Previous studies suggest sex differences with respect to the relevance of different emotional information. Men report anger more often (Biaggio, 1989), show stronger emotional experience with angry stimuli than women (Deng et al., 2016). Furthermore, within women hormonal levels as induced by the natural menstrual cycle or by use of oral contraceptives (OCs) have an impact on cognitive and emotional processing. In this regard it has e.g. been shown that women during their follicular cycle phase show better general emotion recognition than women during their luteal cycle phase (Derntl et al., 2008a; Derntl et al., 2013b). Regarding the intake of oral contraceptives (OCs), even less is known about the effects on behavioural and neural outcome. In the present experiment we therefore aimed at addressing task-dependent behavioural and neural differences depending on sex and menstrual cycle phase / use of OCs.

**Methods**

In a functional magnetic resonance imaging (fMRI), a total of 80 participants were tested (including 29 men, 30 OC-users, 21 luteal women). We used an emotional Stroop task (eSTROOP) to measure interference processing and an emotional dot-probe taks (eDOT) to measure visuospatial cueing of attention. A resting state scan preceded task-dependent functional brain imaging.

**Results**

Behavioral data eSTROOP. Intake of oral contraceptives led to faster reactions (p = .014) and fewer errors (p = .025) compared to men but not compared to luteal women (ps > .14). Also, luteal women and men did not differ regarding reaction times and error rates (ps = 1). Also, no interactions in connection with the factor Group were significant (ps > .12).

Behavioral data eDOT. Attentional bias indices (reaction times) as measured by the dot-probe task did not reveal group differences (ps > .082) nor were any interactions in connection with the factor Group significant (ps > .26).

fMRI analyses eSTROOP. Men and women mainly differed in activation of visual areas with men activating clusters in the right lingual, bilateral fusiform and left middle temporal gyrus and bilateral superior parietal lobule more strongly than women. Women activated clusters in the left middle...
occipital and left calcarine gyrus more strongly than men. Comparing luteal women to OC-users revealed no significant clusters.

fMRI analyses eDOT. Women activated clusters in the left calcarine gyrus, right cerebellum, left supramarginal gyrus, left middle occipital gyrus and right lingual gyrus more strongly than men. Men did not activate any cluster more strongly than women. Comparing luteal women to OC-users, revealed that OC-users activated clusters in the bilateral middle temporal gyrus, right postcentral gyrus, left posterior-medial frontal cortex, right precentral gyrus, left superior frontal gyrus, and left calcarine gyrus more strongly than luteal women. Luteal women did not activate any cluster more strongly than OC-users.

**Summary**

Our findings indicate that overall healthy men and women show hardly any behavioral differences in emotional processing as measured by the eSTROOP and eDOT. Only in connection with brain activation, stronger group differences emerged pointing to task-dependent differences in neural processing. In both the eSTROOP and the eDOT group differences mainly stem from activation differences in visual areas including bilateral calcarine and fusiform gyrus. More specifically, the use of oral contraceptives only led to more pronounced visual activation compared to luteal women during visuospatial cueing of attention (eDOT) but not during resolution of emotional conflicts (eSTROOP).
Humans can easily categorize images of human bodies and faces according to their sex/gender and weight. Objectively speaking this is a difficult task due to category-independent variability in image size, lighting, facial expression and body pose. We investigated which brain regions code for the sex and weight of faces and bodies, and whether the representations would be face- or body-selective. We used fMRI to record the brain activity of subjects viewing faces and bodies that varied in sex, weight, and image size (factor 2). Using multivoxel pattern analyses, we found that the extrastriate body area (EBA), fusiform body area (FBA) and occipital face area (OFA) consistently discriminated bodies of different sexes, including in a cross-classification analysis where training and test data were based on different stimulus sizes. Body weight could be decoded in OFA and FFA, size-invariantly in the latter. When voxels of body-regions were pooled, the sex and weight of bodies could be decoded invariant with respect to image size. No region consistently decoded the sex or weight of faces, nor did face-related decoding work when voxels were pooled across face- or body-selective regions. We hypothesize that this may be due to the fact that neither weight nor sex appeared very prominently in controlled face stimuli used here (e.g. excluding hair). We conclude that information relating to the body categories sex and weight is found in both body and face responsive brain regions, but that size-invariant information is mostly located in body responsive regions.
The interplay between sex hormone concentration, language abilities, and mood related behavior during infancy

Gesa Schaadt1,2, Claudia Männel1,2, Rachel Zsido3, Angela D. Friederici1, and Julia Sacher3
1Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1a, 04103 Leipzig, Germany; 2Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1a, 04103 Leipzig and Clinic for Cognitive Neurology, Medical Faculty, Leipzig University, Liebigstr. 16, 04103 Leipzig, Germany; 3Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1a, 04103 Leipzig

Gender differences in cognitive behavior as well as in mental disorders have been of great research interest in the past years. For example, boys and girls differ in their language development, with boys being delayed. In contrast, women are at greater risk to develop depressive symptoms compared to men, suggesting sex hormones to impact diversely on language abilities and mood related disorders. First studies could show that testosterone (i.e., the male sex hormone) impacts negatively on language development, whereas estradiol (i.e., the female sex hormone) impacts positively. Further, emotion regulation and affect also seems to be influenced by sex hormone concentration already during early childhood. Interestingly, children with language disorders are more likely to show emotional difficulties and internalizing problems, raising the question of how sex hormones, cognitive functions (i.e., language), and mental health problems interplay. To our knowledge there are no studies investigating the relationship between sex hormone concentration, language abilities, and mood related behavior during early development, when the brain undergoes massive changes. Thus, we aim to investigate the interplay between sex hormone concentration, language abilities, and mood related behavior during infancy and suggest that the relative concentration of testosterone and estradiol plays a role in boys’ and girls’ positive development of both, language abilities and mood related behavior.
Sex differences in targeting and the relation to prenatal testosterone in 70-month-old children

Judith Lawrenz, Martin Heil
Heinrich Heine University, Düsseldorf

Many studies reported sex differences in spatial ability tasks favoring males, but also in targeting or throwing accuracy. Targeting has been shown to be influenced by prenatal hormone levels. Individuals with congenital adrenal hyperplasia, who are exposed to higher prenatal testosterone levels in utero display enhanced targeting abilities (Hines et al., 2003). The present study is part of a longitudinal study. The reported results are based on a subsample of 111 healthy children (age: M = 70.87 months, SD = 0.93). In order to assess prenatal testosterone, the testosterone levels from an amniocentesis during pregnancy at the beginning of the study as well as the ratio between the second and fourth digit length for both of childrens’ hands were used. The 2D:4D digit ratio has proven to be sexually dimorphic and is often referred to as a marker for prenatal testosterone exposure. Subjects in our study were asked to throw velcro-covered balls from 2m and 3m distance to the middle of a velcro covered wall sized 1,40m x 1,40m, marked with a red cross. There were three practice trials and five test trials from each distance. The distance from the ball to the red cross in the middle was measured for each test trial. Boys threw significantly closer to the target than girls from the 2m distance. Sex differences in 2D:4D digit ratio were found, too. Concerning the relation to prenatal testosterone level we found correlations between 2D:4D digit ratio and targeting performances for the 2m distance throws. Better targeting performance was associated with lower 2D:4D digit ratio – in the girls sample with a stronger effect for the left hand, in the boys sample only in the right hand. This suggests that a higher exposure to testosterone is associated with better targeting performance. No relationship to prenatal testosterone levels from amniocentesis was observed, but the reason for this outcome may be the comparably early point of time during pregnancy at which the samples were taken.
Sex differences in self-control in 40-months-old children and the relationship with prenatal testosterone levels

Lisa M. Körner, Bettina M. Pause, Martin Heil
Heinrich Heine University, Düsseldorf

Over four decades ago, Walter Mischel (1970) introduced the “Marshmallow Test” which measures childrens’ ability to delay gratification by either choosing an immediate smaller or a later larger reward. Looking at sex differences in self-control, there is evidence for a female advantage. In this context, gonadal steroids influencing the neural structures essential for self-control could be a possible explanation for sex differences. Recent studies connected the ability to delay gratification to free testosterone (from saliva samples) in adults as well as to the second-to-fourth-digit-ratio, often interpreted as a marker for prenatal testosterone exposure, in children. This study is part of a longitudinal study, in which we used prenatal testosterone levels from amniocentesis samples as a more direct measure and conducted a modified version of the Marshmallow Test with 123 children (age: M = 40.17 months, SD = 0.42). By recording every child’s preferences for six different snacks, we were able to conduct the Marshmallow Test according to individual preferences. The children had to decide whether to wait for their preferred snack for a maximum of 8 minutes or to abandon the waiting period by ringing a bell signalizing the choice of the less preferred snack. Girls waited significantly longer for their preferred snacks than boys providing further evidence for sex differences in delay of gratification. Importantly, in the male sample waiting time as well as the parents’ ratings of their child’s self-control were negatively correlated with prenatal testosterone levels. This underlines the organizational effect of testosterone on the brain as an explanation for observed sex differences.
A Social Science Perspective on the Transgender Brain

Linda Weichselbraun
Department of Sociology and Work Science, University of Gothenburg, Box 720, 405 30 Gothenburg, Sweden

Since the mid-90s, neuroscience has produced a number of prominent studies concerned with the brains of transgender persons. For the social scientist, it is relevant to ask questions about the social implications of such research, and also to understand the knowledge production itself as a social process. To approach these questions, this ongoing doctoral dissertation project interrogates the “trans brain” from a perspective where other social worlds than the neuroscientific are taken into account. The aim is to understand what a trans brain is, and what it can mean and do in relation to various groups of actors who engage with it from different perspectives, and for different reasons. The poster will speak to an interdisciplinary audience, and introduce the research project, its theoretical/methodological approach and some preliminary results.
Hormone-mediated network changes driving depression susceptibility across the female lifespan

Rachel G. Zsido¹,² & Matthias Heinrich¹,², Frauke Beyer²,³, Christin Haucke¹,², Juergen Kratzsch⁴, Markus Löffler⁵,⁶, Michael Stumvoll³,⁷, Arno Villringer²,⁸, A Veronica Witte²,³, Julia Sacher¹,²,⁸

¹Emotion NeuroimaGinG(EGG)-Lab, Max Planck Institute for Cognitive and Brain Sciences, Stephanstrasse 1a, 04103 Leipzig; ²Department of Neurology, Max Planck Institute for Cognitive and Brain Sciences, Stephanstrasse 1a, 04103 Leipzig, Germany; ³Subproject A1, Collaborative Research Centre 1052 “Obesity Mechanisms”, University of Leipzig, Liebigstrasse 21, 04103 Leipzig, Germany; ⁴Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University of Leipzig, Paul-List-Strasse 13/15, 04103 Leipzig, Germany; ⁵LIFE – Leipzig Research Center for Civilization Diseases, University of Leipzig, Liebigstrasse 21, 04103 Leipzig, Germany; ⁶Institute for Medical Informatics, Statistics, and Epidemiology (IMISE), University of Leipzig, Haertelstrasse 16-18, 04107 Leipzig, Germany; ⁷IFB Adiposity Diseases Faculty of Medicine, University of Leipzig, Liebigstrasse 21, 04103 Leipzig, Germany; ⁸Clinic for Cognitive Neurology, University of Leipzig, Liebigstrasse 16, 04103 Leipzig, Germany

Estrogen and progesterone undergo major fluctuations across the female lifespan. While several studies have shown an association between changes in mood and ovarian hormone levels, we lack a detailed understanding of the specific neurobiological mechanisms underlying the relationship between mood and hormonal transitions. We aim to explore the interplay of ovarian hormones and brain structural and functional connectivity, and the subsequent effects on mood and cognition. Specifically, we use the Leipziger Research Center for Civilization Disease (LIFE) dataset to build a model of these interactions, and then use the Leipzig Study for Mind-Body-Emotion Interactions (LEMON) cohort to replicate and validate this model. Our preliminary findings already reflect a protective role of estrogen and progesterone on the preservation of grey matter network organization. We will use the insight gained from these analyses to build a longitudinal model to investigate causation in perimenopausal women. Perimenopause is defined by extreme fluctuations in estrogen, and this period is associated with an elevated risk of depression. Fluctuations in estrogen have also been linked to excessive weight gain, particularly in terms of visceral adipose tissue (VAT)—a decisive risk factor for inflammation, grey matter atrophy, and cognitive decline. If we understand the causal mechanisms behind hormone and brain changes in perimenopause, this will present a powerful opportunity to intervene before a vulnerable state develops into a diseased state in later life. This work will have fundamental implications on future intervention and prevention research, especially in how to design and individualize treatment during specific times of hormonal transitions.
Investigating the expression of genes associated with autism spectrum disorders to identify sex related differences

Simone Berkel, Ahmed Eltokhi, Gudrun Rappold
Department of Human Molecular Genetics, Heidelberg University Hospital, Heidelberg, Germany

Neurodevelopmental disorders such as autism, attention deficit and hyperactivity syndrome as well as language problems and learning difficulties have a higher prevalence in male individuals compared to females. Autism is characterized by impairments in social interaction, communication deficits and restricted and repetitive behaviors. Boys are more frequently affected than girls; the ratio of affected boys compared to girls is 4:1 for autism and 11:1 for Asperger syndrome.

In this study we aim to elucidate the reason for this gender difference by following up two hypotheses: (1) risk genes for autism spectrum disorders (ASD) might be expressed at different levels in males and females and (2) ASD risk genes might interact with sexually dimorphic pathways.

First, we investigated the expression of genes associated with autism spectrum disorders, including the Shank gene family, in the brain of male and female mice to identify sex-dependent differences. The RNA expression levels were analyzed in five different brain regions (cortex, hippocampus, striatum, cerebellum, thalamus) at different developmental stages (E15, E17, P1, P7, P12 and adult) in male and female mice. We identified a sex dimorphic expression of Shank1 and Shank3, but not of Shank2. Due to the fact that early brain development is strongly influenced by sex hormones (estrogen, testosterone), we further investigated the influence of these hormones on Shank expression in human neuroblastoma cells (SH-SY5Y) and primary mouse hippocampal neurons. A better understanding of the sex differences in the brain might help to explain the vulnerability for neuropsychiatric disorders like autism and paves the way to discover putative risk or protective factors for these disorders.
Sex hormones interact with oxytocin and predict fear of social interaction in high anxious individuals

Ekaterina Schneider¹, Laura E. Müller², Beate Ditzen¹, Sabine C. Herpertz², Katja Bertsch²
¹University Hospital Heidelberg, Institute of Medical Psychology, Bergheimer Str.20, D-69115 Heidelberg;
²University Hospital Heidelberg, Department of General Psychiatry, Voßstraße 2, D-69115 Heidelberg

Background
A growing number of studies investigate the association of the neuropeptide oxytocin with social anxiety. Studies focusing on the relationship between peripheral oxytocin levels and anxiety report inconclusive results and sex differences. We, thus, particularly focused on sex hormones as possible moderators of sex-specific oxytocin effects.

Methods
Within a larger project 181 individuals filled out the Liebowitz Social Anxiety Scale (LSAS) and provided a 5ml-blood sample and an additional saliva sample. Plasma concentrations of oxytocin, estradiol and progesterone as well as saliva concentrations of testosterone and cortisol, were analyzed in individuals with low (47 male, 44 female) and high (48 male, 42 female) social anxiety.

Results
In high anxious individuals, oxytocin x testosterone interactions (R² =.130; p=.014) in men and oxytocin x estradiol interactions (R² =.160; p=.026) in women predicted LSAS scores. These interaction effects were particularly pronounced with regard to “fear of social interaction” (oxytocin x testosterone interaction in men, R² =.181; p=.003; oxytocin x estradiol interaction in women, R² =.253; p=.004).

Conclusions
These findings suggest that the link between oxytocin and anxiety might be dependent on basal anxiety levels as well as on individual sex hormone levels. In high anxious women, lowest self-reported anxiety levels were associated with high concentrations of both estradiol and oxytocin. In highly anxious men, however, the lowest anxiety levels were associated with high hormone levels of oxytocin and low levels of testosterone.
Insulin and estrogen independently and differentially reduce macronutrient intake in healthy men

Rosemarie Krug¹, Linda Mohwinkel², Bernhard Drotleff³, Manfred Hallschmid¹,⁴,⁵
¹Department of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany; ²Department of Neuroendocrinology, University of Lübeck, Lübeck, Germany; ³Institute of Pharmaceutical Sciences, University of Tübingen, Tübingen, Germany; ⁴German Center for Diabetes Research (DZD), München-Neuherberg, Germany; ⁵Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen (IDM), Tübingen, Germany.

Context
Insulin administration to the central nervous system inhibits food intake, but this effect has been found to be less pronounced in female compared to male organisms. This sex-specific pattern has been suggested to arise from a modulating influence of estrogen signaling on the insulin effect.

Objective
We assessed in healthy young men whether pre-treatment with transdermal estradiol interacts with the hypophagic effect of central nervous insulin administration via the intranasal pathway.

Design, Setting, Participants and Intervention: According to a 2×2 design, two groups of men (each n=16) received a 3-day transdermal estradiol (100 µg/24 h) or placebo pre-treatment and on two separate mornings were intranasally administered 160 IU regular human insulin or placebo.

Main Outcome Measures: We assessed free-choice ad-libitum calorie intake from a rich breakfast buffet and relevant blood parameters in samples collected before and after breakfast.

Results
Estrogen treatment induced a 3.5-fold increase in serum estradiol concentrations and suppressed serum testosterone concentrations by 70%. Independent of estradiol administration, intranasal insulin reduced the intake of carbohydrates during breakfast, attenuating in particular the consumption of sweet, palatable foods. Estradiol treatment per se decreased protein consumption. We did not find indicators of eating-related interactions between both hormones.

Conclusions
Results indicate that in an acute setting, estrogen does not interact with central nervous insulin signaling in the control of eating behavior in healthy men. Insulin and estradiol rather exert independent inhibiting effects on macronutrient intake.
Influence of the ovarian cycle and estradiol on binge eating evoked in female rats by food restriction followed by frustration stress

de Ávila C1, Micioni Di Bonaventura MV2, Lutz TA3, Romano A4, Pucci M5, Geary N6, Asarian L3, Cifani C2
1CRIUCPQ, Faculty of Medicine, Department of Psychiatry and Neuroscience, Université Laval, Québec (Québec) G1V 0A6, Canada; 2School of Pharmacy, Pharmacology Unit, University of Camerino, Italy; 3Institute of Veterinary Physiology and Center for Integrated Human Physiology, University of Zurich, Switzerland; 4Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy; 5Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Italy; 6Department of Psychiatry (Retired), Weill Medical College of Cornell University, New York, 10065

Because binge eating and emotional eating vary through the menstrual cycle in human females, we investigated cyclic changes in binge-like eating in female rats and their control by estrogens. Binge-like eating was elicited by three cycles of 4 days of food restriction and 4 days of free feeding followed by a single frustrative nonreward-stress episode (15 min visual and olfactory exposure to a familiar palatable food) immediately before presentation of the palatable food. Intact rats showed binge-like eating during the diestrous and proestrous phases of the ovarian cycle, but not during the estrous (periovulatory) phase. Ovariectomized (OVX) rats not treated with estradiol (E2) displayed binge-like eating, whereas E2-treated OVX rats did not. The procedure did not increase signs of anxiety in an open-field test. OVX rats not treated with E2 that were subjected to food restriction and sacrificed immediately after frustrative nonreward had increased numbers of cells expressing phosphorylated extracellular signal-regulated kinases (ERK) in the central nucleus of the amygdala (CeA), paraventricular nucleus of hypothalamus (PVN), and dorsal and ventral bed nuclei of the stria terminalis (BNST) compared with nonrestricted or E2-treated rats. These data suggest that this female rat model is appropriate for mechanistic studies of some aspects of menstrual-cycle effects on emotional and binge eating in human females, that anxiety is not a sufficient cause of binge-like eating, and that the PVN, CeA, and BNST may contribute to information processing underlying binge-like eating.
Sex-specific effect of RLN3 on food intake and effect of estradiol levels on brain RLN3/RXFP3 system in rats

de Ávila Camila¹, Calvez Juliane¹, Lenglos Christophe¹, Timofeeva Elena¹, Cifani Carlo²
¹CRIUFCPQ, Faculty of Medicine, Department of Psychiatry and Neuroscience, Université Laval, Québec (Québec) G1V 0A6 - Canada; ²School of Pharmacy, Pharmacology Unit, University of Camerino, Italy

Relaxin-3 (RLN3) is a neuropeptide expressed in the nucleus incertus (NI) of the brainstem. RLN3 binds to its cognate receptor relaxin-like family peptide receptor 3 (RXFP3). Previously we demonstrated that, the intracerebroventricular injection of RLN3 increased chow intake in satiated rats and this effect was stronger in females. The present study was designed to investigate possible role of estrogen in higher sensitivity to RLN3 orexigenic effects in female rats. We first confirmed the well-known oscillation of food intake across the estrous cycle and the effects of ovariectomy (OVX) and estrogen replacement (OVX+E) on feeding. We used in-situ hybridization to assess the expression levels of RLN3 and RXFP3 mRNAs in the NI and parvocellular hypothalamic nucleus (PVN) of female rats across estrous cycle and in OVX and OVX+E as well as in the brain of male. Expression of RLN3 mRNA was significantly decreased in female during proestrus and estrus phases compared to diestrus suggesting the increased levels of estradiol suppress expression of RLN3 and thus may regulate food intake across estrous cycle. The subcutaneous injection of estradiol in OVX rats decreased expression of RLN3 in the NI. Detection of expression of RXFP3 in the parvocellular hypothalamic nucleus (PVN) revealed higher levels of expression of RXFP3 in female compared to male. Across estrous cycle, expression of RXFP3 decreased at diestrus and increased at proestrus, estrus, and metestrus. These results suggest RLN3 may mediate the effects of estradiol on food intake in female rats. Our results suggest that higher sensitivity of female to the orexigenic effects of RLN3 may depend on cyclic increase in expression of RXFP3 in the PVN.

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Effects of oestrogen receptor genotype on early-life trajectories to internalising symptoms in women

De Grauw, HHA¹,², Sundström Poromaa, I², Nilsson, K³ & Comasco, E¹,²
¹Department of Neuroscience, Uppsala University, Sweden; ²Department of Women’s and Children’s Health, Uppsala University, Sweden ³ Centre for Clinical Research, Västerås, Sweden

The aetiology of internalising symptoms in young adult women involves a complex interplay of biological and environmental factors. The risk of developing internalising symptoms increases, among others, with antenatal maternal anxiety, preterm birth and early life stress. Oestrogen is known to affect behaviours relating to anxiety and depression, and may contribute to the differences in prevalence for internalising disorders between females and males. Single-nucleotide polymorphisms in the oestrogen receptor gene, ESR1, have previously been implicated in geriatric depression.

In the present study we investigated the possible role of ESR1 genotype (rs2234693 and rs9340799) as a mediator in the aetiology of anxiety and depression in young adult women. Participants (n = 1036) were recruited at mean age 14.4 years (range 12.8–16.4); of these, n = 919 returned for follow-up at mean age 17.3 years (range 15.8–19.2). Questionnaire data were collected on anxiety and depression symptoms, early life events, parenting and personality. Additional information was collected from participants’ parents. Regression models and nonparametric tests were used to test for genotype–environment interactions as predictors for symptomatic outcomes. A path analysis model was fitted to study correlational and predictive relationships between environmental factors and outcomes.

Our preliminary findings are unsupportive of a role for ESR1 genotype in the aetiology of internalising disorders. The path analysis model showed distinct contributions of early life events and personality, particularly neuroticism, to symptomatic outcomes. Future genotype–environment interaction studies on depression and anxiety should be aware of the interplay of environment and personality effects.
Emotional hormones: the impact of endogenous and synthetic sex steroids on female's sexual responsiveness

**Ann-Christin S. Kimmig\(^1\,^2\), Carolin A. Maier\(^1\,^3\), Maria G. Mayer\(^1\), Sara Brucker\(^4\), Birgit Derntl\(^1\,^5\,^6\)**

\(^1\)Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany; \(^2\)International Max Planck Research School for Cognitive and Systems Neuroscience, Tübingen, Germany; \(^3\)International Max Planck Research School on Neuroscience of Communication: Function, Structure, and Plasticity, Leipzig, Germany; \(^4\)Department of Gynecology and Obstetrics, University of Tübingen, Tübingen, Germany; \(^5\)Werner Reichardt Centre for Integrative Neuroscience, University of Tübingen, Tübingen, Germany; \(^6\)Lead Graduate School, University of Tübingen, Tübingen, Germany

Oral contraceptives (OCs) are taken by millions of women worldwide every day. While evidence has accumulated that endogenous sex steroids affect a broad spectrum of human behaviour, little is known about the psychological and neurobiological effects of OC-intake. The few existing studies however point to significant changes in social behaviour, which may have far reaching individual and societal consequences: mating preferences shift across the menstrual cycle and are affected by OC-intake. Further, sex steroids affect sexual desire and arousal. Consequently, it may affect sexual appetence and thus the actual behavioural tendencies i.e. approach and avoidance behaviour, however, this has not been assessed up to now.

The main objective of this study is to investigate the impact of endogenous and synthetic sex steroids on sexual appetence. To do so, 3 groups of women are studied: 1) naturally cycling women in the early follicular phase, 2) naturally cycling women in the ovulation phase and 3) women with OC-intake longer than 12 months. All women undergo an approach-avoidance task targeting sexual appetence by presenting them with three different types of images (i.e. erotic, positive and aversive) depicting a man or a couple. Next to implicit measures (i.e. response times to erotic stimuli relative to other images) of sexual appetence also explicit ratings of attractiveness, sexual arousal and approach-avoidance tendency are recorded. The aim of this study is to validate and optimize this approach-avoidance task in order to provide the first measure of sexual appetence and its resulting behavioural tendencies in women with different hormonal states.
Seasonal variations in levels of inflammatory markers during pregnancy and the postpartum period

Hanna E. Henriksson¹, Richard A. White², Stavros I. Iliadis¹, Fotios C. Papadopoulos³, Inger Sundström Poromaa¹, Alkistis Skalkidou¹
¹Department of Women’s and Children’s Health, Uppsala University, Uppsala, Sweden; ²Norwegian Institute of Public Health, Oslo, Norway; ³Department of Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden

Background
Seasonality has been reported in bipolar disorder, major and peripartum depression, cardiovascular disease, and autoimmune conditions. In addition, a link between these diseases and inflammation has been suggested. Seasonal variations in gene expression and cellular composition linked to the immune system has previously been investigated, but so far no studies have been conducted in pregnant and postpartum women.

Methods
The study was conducted at Uppsala University Hospital, Sweden, between 2010–2014. Ninety-two inflammatory markers from 321 pregnant and 189 postpartum women were analyzed using proximity-extension assay technology and seasonality was investigated by using sine and cosine functions in a linear regression model.

Results
In pregnancy, 25 inflammatory markers, as well as an inflammation summary variable, expressed a seasonal pattern. The markers generally peaked in the spring and had a trough in the fall. In the postpartum period, only one inflammatory marker, MCP-4, expressed a seasonal pattern.

Conclusion
Seasonal variations in inflammatory markers were more common during pregnancy compared with postpartum. The results of this study could be valuable to professionals working within the field of psychoneuroimmunology and other immune-related areas.
Hypothalamic-Pituitary-Adrenal Axis Responsiveness and Startle Response in Pregnant Women

Julia Breedh¹, Erika Comasco¹², Charlotte Hellgren¹, Fotios C Papadopoulos², Alkistis Skalkidou¹, Inger Sundström-Poromaa¹
¹Department of Women’s and Children’s Health, Uppsala University, Uppsala, Sweden; ²Department of Neuroscience, Uppsala University, Uppsala, Sweden

Objectives
To investigate the relation of startle response with cortisol awakening response (CAR), as well as serum hormonal levels of cortisol and cortisone in pregnant women.

Purpose
To further understanding of correlates of sensorimotor response as a neurophysiological process related to endocrine and physiological alterations in women in their late pregnancy.

Methods
Totally, ninety eight women in gestational week 35-39 were recruited between January 2010 and May 2013. The startle response was measured as the blink response to an acoustic startle-eliciting stimuli delivered binaurally. All the participating women were screened for ongoing psychiatric disorders. Salivary cortisol levels were used to estimate the area under the curve with response to increase in cortisol following awakening, whereas the women where asked about sleep duration the night before the session. A venous blood sample was taken after the test session to measure cortisol and cortisone levels. To investigate the relation of startle magnitude with the CAR (measured as AUCi, AUCg and AUCab) and genes related to the HPA-axis, univariate ANOVA were performed.

Results
Our preliminary analyses show that startle magnitude was higher in pregnant women with greater AUCi (F(1,96) = 8.7; p = 0.004; η² = 0.083), AUCg (F(1,96) = 10.7; p = 0.002; η² = 0.1) and AUCab (F(1,96) = 9.9; p = 0.002; η² = 0.093). No association was found between startle magnitude and blood levels of cortisol (p = 0.81), cortisone (p = 0.57) or cortisol/cortisone ratio (p = 0.28). Analyses of the genetic data are ongoing.

Conclusions
Increased startle magnitude in pregnant women with higher cortisol awakening response may be interpreted as heightened neurophysiological reactivity, likely associated with altered stress system functioning. Furthermore, the lack of association between startle response and serum hormonal levels of cortisol and cortisone, suggests that endocrine responsiveness rather than hormonal levels is relevant to the startle response.
Different patterns of attentional bias in antenatal and postpartum depression

Åsa Edvinsson¹, Alkistis Skalkidou¹, Charlotte Hellgren¹, Malin Gingnell², Lisa Ekselius³, Mimmie Willebrand³, Inger Sundström Poromaa¹

¹Department of Women’s and Children’s Health, Uppsala University, Sweden; ²Department of Psychology, Uppsala University, Sweden; ³Department of Neuroscience, Psychiatry, Uppsala University, Sweden

Background
Biased information processing in attention, memory, and interpretation is proposed to be central cognitive alterations in patients with major depressive disorder, but studies in women with peripartum depression are scarce. Because of the many similarities with depression in non-peripartum states as regards symptom profile and risk factors, we hypothesized that women with antenatal and postpartum depression would display attentional bias to negatively and positively valenced words.

Methods
One hundred and seventy-seven pregnant and 157 postpartum women were included. Among these, 40 suffered from antenatal depressive disorder and 33 from postpartum depressive disorder. An emotional Stroop task with neutral, positive, negative, and negatively valenced obstetric words was used.

Results
No significant difference in emotional interference scores was noted between women with antenatal depression and non-depressed pregnant women. In contrast, women with postpartum depression displayed shorter reaction times to both positive (p = 0.028) and negative (p = 0.022) stimuli, compared with neutral words. Pregnant women on antidepressant treatment displayed longer reaction times to negatively valenced obstetric words in comparison with untreated depressed women (p = 0.012), and a trend towards greater interference in comparison with controls (p = 0.061).

Conclusions
In contrast with the hypothesis, we found no evidence of attentional bias to emotionally valenced stimuli in women with untreated peripartum depression. However, the shorter reaction times to emotional stimuli in women with postpartum depression may indicate emotional numbing, which in turn, is a functional impairment that may have repercussions for child development and well-being. Our findings emphasize the need to identify and treat women with postpartum depression at the earliest possible time-point to ensure swift recovery and support for the family.
Oral contraceptives (OCs) are the most commonly used method to prevent pregnancy with 200 to 300 million users worldwide (United Nation, Department of Economic and Social Affairs, 2015). Given recent alarming reports suggesting an association of depression with hormonal contraception (Skovlund et al., 2016), a better understanding of the mechanisms underlying this substantial psychological impact of synthetic sex hormone administration in young women is of critical interest. Accumulating evidence suggests that depressive symptoms are associated with major alterations within the brain’s reward sensitivity circuitry (Macoveanu et al., 2016; Russo & Nestler, 2013), which normally serves to guide our attention towards consumption of rewards. Endogenous sex hormones, i.e. hormones naturally fluctuating across the menstrual cycle, have been shown to significantly influence reward sensitivity: in particular fluctuating levels of estrogen (e.g., Smith et al., 2014). However, the impact of synthetic sex hormones, i.e. OCs, on reward sensitivity remains unclear.

Because OCs introduce synthetic hormones and modulate the internal hormone production, an influence of OCs on women’s reward sensitivity is likely. Based on previous findings, we expect women taking combined OCs (n = 30) to show enhanced reward sensitivity compared to women not using OCs (n = 30). This hypothesis is tested on a behavioural level using a cross-sectional design: naturally cycling women are assessed during their periovulatory phase, i.e. when estrogen levels are high; in OC-taking women, estrogen levels will be down-regulated and thus, constantly low. To assess reward sensitivity, we use a delay discounting paradigm with an adaptive Bayesian approach (Pooseh et al., 2017). Additionally, participants complete self-report questionnaires on impulsivity, personality traits, and women’s health. First behavioural results of discounting rates will be presented together with a systematic overview of the status quo of research investigating the impact of sex hormones on reward sensitivity in women.
Transient structural changes in the female hippocampus across the menstrual cycle

Claudia Barth¹, Christopher J Steele¹,², Karsten Mueller¹, Vivien P. Rekkas³, Katrin Arélin¹,⁴,⁵, Andre Pampel¹, Inga Burmann¹, Jürgen Kratzsch⁶, Arno Villringer¹,⁴,⁵,⁷,⁸ & Julia Sacher¹,⁴

¹Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; ²Cerebral Imaging Centre, Douglas Mental Health Institute, Department of Psychiatry, McGill University, Montreal, Canada; ³CAMH Research Imaging Centre and Campbell Family Mental Health Research Institute at the Centre for Addiction and Mental Health and the Department of Psychiatry, University of Toronto, Toronto, Canada; ⁴Clinic of Cognitive Neurology, University of Leipzig, Leipzig, Germany; ⁵Leipzig Research Center for Civilization Diseases, University of Leipzig, Germany; ⁶Institute for Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital Leipzig, Leipzig, Germany; ⁷Integrated Research and Treatment Center Adiposity Diseases, University of Leipzig, Germany; ⁸Berlin School of Mind and Brain, Mind and Brain Institute, Berlin, Germany

Background: The levels of the ovarian hormones, estrogen and progesterone, fluctuate across the human menstrual cycle. Evidence from animal studies suggests similar subtle fluctuations in hippocampal microstructure. Abnormalities in hippocampal morphology have been reported in several sexually dimorphic neuropsychiatric pathologies, such as depression or Alzheimer’s disease. Yet, it is unclear how subtle ovarian hormone fluctuations impact the healthy human hippocampus. This lack of knowledge is a critical gap, as the understanding of physiological changes in the healthy hippocampus is an important prerequisite for any investigation of hippocampal pathology.

Material & Methods: Here, we utilized diffusion-weighted and T1-weighted neuroimaging methods to explore changes of hippocampal white and grey matter microstructure, respectively, associated with physiological changes in ovarian hormones across the menstrual cycle. In detail, we acquired a series of 30 non-invasive Magnetic Resonance Imaging (MRI) scans of a single, healthy, 32-year old Caucasian woman across four menstrual cycles. We calculated hippocampal fractional anisotropy (FA), a measure sensitive to changes in white matter structure, and hippocampal grey matter density to investigate their respective correlations with ovarian hormone levels.

Results: We found a significant positive correlation between hippocampal FA values and estrogen bilaterally; and grey matter density and estrogen in the left hippocampus. These results showed a transient peak in hippocampal FA and grey matter density that closely paralleled ovulation.

Conclusion: These findings indicate short-term changes in hippocampal white and grey microstructure to occur in response to peri-ovulatory estrogen levels on an acute time-scale, within days. Thus, the menstrual cycle phase should be considered as an important modulator when studying neuroplasticity in humans. Our study further introduces a novel approach of simultaneously mapping longitudinal characteristics of ovarian hormone fluctuations and brain dynamics. This approach can be applied to future MRI study-designs, most importantly when questions regarding sex differences are a main focus of the proposed research.
Digit Ratio (2D:4D) and Amniotic Testosterone

Gareth Richards1,2, Manuel C Gomes3, Teresa Ventura4,5
1Centre for Research on Play in Education, Development & Learning, Faculty of Education, University of Cambridge, UK; 2Autism Research Centre, Department of Psychiatry, University of Cambridge, UK; 3Faculty of Sciences, University of Lisbon, Campo Grande, 1749-016 Lisbon, Portugal; 4Centro Hospitalar de Lisboa Central; 5NOVA Medical School, New University of Lisbon

Foetal sex hormones can have powerful and far-reaching effects on later phenotype. However, obtaining accurate measurements is difficult for ethical reasons, and researchers often employ proxy variables to examine their effects. The relative length of the second and fourth fingers (digit ratio or 2D:4D) is frequently used for this purpose, and is hypothesised to reflect prenatal androgen and/or oestrogen exposure. Most studies that employ this method examine digit ratio for the right hand (R2D:4D) and/or left hand (L2D:4D), though some use the mean value (M2D:4D) (i.e. average of R2D:4D and L2D:4D) and/or asymmetry (D[R-L]) (i.e. R2D:4D minus L2D:4D). As no published studies have examined human M2D:4D or D[R-L] in relation to foetal testosterone (fT) measured from amniotic fluid, we conducted a secondary analysis of data published by Ventura et al. (2013). The sample was comprised of 101 neonates from Portugal (52 females, 49 males) whose mothers underwent amniocentesis during the second trimester. M2D:4D was negatively correlated with fT in females (p < 0.05) but not in males; fT and D[R-L] were not significantly correlated in either sex. The lack of consistent findings could reflect the idea that the ratio of testosterone to oestradiol (T:O) is more important in determining digit ratio than are the absolute concentrations of either hormone. Future research should therefore aim to examine amniotic T:O ratio and 2D:4D variables in larger samples of males and females.
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