Bernd Lenz

Narrative Academic Profile:

I have a broad scientific background in the field of psychiatric disorders and mental health with a special focus on addictive behaviors. In the research group, we investigate the role of bio-psycho-social mechanisms, neurodevelopmental factors over the lifespan, and clinical aspects in the pathogenesis of addictive disorders and mental health-related behaviors. We study humoral factors including neuropeptides, sex hormones, and neurosteroids. We are also interested in neural correlates. The results are used to develop novel preventive and therapeutic strategies. We follow a strong translational approach and wish to implement these strategies into daily use. We employ various research methods including virtual reality technologies, neuroimaging techniques, pharmaco-challenge experiments, deep longitudinal behavioral and clinical real-life phenotyping, and saliva as well as blood biomarkers. The research group conducts in-depth mechanistic studies, large-scale longitudinal cohort studies, and clinical trials with a strong translational emphasis.

Gender differences in addictive behaviors are well-established and include alcohol dependence, alcohol binge drinking, tobacco smoking, cannabis dependence, pathological gambling, and the novel research diagnosis internet gaming disorder. Against that background, my major research focuses are gender- and sex-related factors in addiction medicine to provide mechanistic insight and establish gender- and sex-sensitive interventions and outcome prediction.

We have extensively studied the role of lifetime sex hormone activity in addiction and other psychiatric conditions (Lenz B et al. 2012 *Prog Neurobiol*; Lenz B et al. 2019 *Prog Neurobiol*; Lenz B et al. 2021 *SUCHT*). According to our results, higher intrauterine androgen load associates with a higher risk and worse outcome of addictive behaviors in later life. For example, we established in biomarker-based work that higher prenatal androgenization relates to alcohol use disorder, binge drinking, and online sexual compulsivity (Buchholz VN, …, Lenz B 2021 *Front Psychiatry*; Lenz B et al. 2017 *Acta Psychiatr Scand*; Lenz B et al. 2018 *Prog Neuropsychopharmacol Biol Psychiatry*). We also provided meta-analytical support for this model (Siegmann EM, …, Lenz B, Kornhuber J 2019 *J Neural Transm (Vienna)*) and causal evidence from animal experiments (Huber SE, …, Lenz B, Kornhuber J, Müller CP 2018 *Addict Biol*). Our recent work also demonstrates associations between biomarker of prenatal androgenization and frontal brain volumes (Lenz B et al. 2022 *Eur Arch Psychiatry Clin Neurosci*). The data may have important implications for future prevention strategies. In a project funded by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung [BMBF]), we are currently conducting a prospective, controlled, and investigator-blinded study. The trial investigates the effects of a mindfulness-oriented ecological momentary intervention, which intends to reduce stress and substance use in pregnant women, on the prenatal androgen exposure of the unborn child (Lenz B et al. 2018 *Geburtshilfe Frauenheilkd*; DRKS00014920). This study is a subproject within the **IMAC-Mind Consortium** (Improving Mental Health and Reducing Addiction in Childhood and Adolescence through Mindfulness: Mechanisms, Prevention and Treatment; 2017 – ongoing; imac-mind.de; study co-leader in project TP3). In addition to prenatal sex hormone effects, we have also provided evidence that various sex hormone activities are dysregulated in alcohol use disorder and associate with alcohol use phenotypes, such as craving. This includes testosterone and dihydrotestosterone (Lenz B et al. 2017 *Acta Psychiatr Scand*), estradiol (Mühle C, …, Lenz B

2019 *Prog Neuropsychopharmacol Biol Psychiatry*), progesterone (Weinland C, …, Lenz B 2021 *Prog Neuropsychopharmacol Biol Psychiatry*), the progesterone/estradiol ratio (*medrxiv* 10.1101/2022.12.21.22282762), and dehydroepiandrosterone (Weinland C, …, Lenz B 2022 *Addict Biol*). For parts of that work, we have received the Wilhelm-Feuerlein Research Award of the Oberberg Stiftung Matthias Gottschaldt and Deutsche Suchtstiftung in 2016.

Another aim of my research activities is to identify outcome predictors and establish novel treatments. In many preclinical and clinical studies on alcohol use disorder and heavy alcohol use, female individuals are widely underrepresented. Thus, the knowledge on mechanisms relevant to the disease onset, progression, and recovery in women is significantly weaker than for men. This hampers the development of efficient prevention and treatment strategies, especially for affected women. Thus, guidelines are based largely on data from men. Therefore, my research has spent extraordinary diligence to balance the cohorts for sex as well as gender and to test hypotheses separately for women and men. In a line of studies, we have identified that in in-patients with alcohol use disorder a worse outcome during 1- to 2-year follow-ups after detoxification is sex-separately predicted by the following parameters: (i) Increasing androgen levels during early withdrawal and higher prenatal androgen activity in men and women (Lenz B et al. 2017 *Acta Psychiatr Scand*). (ii) Increasing estradiol activity during early withdrawal in men (Mühle C, …, Lenz B et al. 2019 *Prog Neuropsychopharmacol Biol Psychiatry*). (iii) The AA vs. AG/GG *OPRM1* A118G genotype in men (Gegenhuber B, …, Lenz B 2018 *Eur Neuropsychopharmacol*). (iv) Higher oxytocin and oxytocin receptor serum concentrations in men (Lenz B et al. 2021 *Eur Neuropsychopharmacol*; Mühle C, …, Lenz B 2022 *Int J Mol Sci*). (v) Higher body mass index and thigh circumference in men (Lenz B et al. 2019 *J Clin Med*; Weinland C, …, Lenz B 2019 *Prog Neuropsychopharmacol Biol Psychiatry*). (vi) Alcohol instrumentalization goals in women (Müller CP, …, Lenz B 2021 *Alcohol Clin Exp Res*). (vii) Cloninger type 2 in men and women (Weinland C, …, Lenz B 2017 *Alcohol Clin Exp Res*). (viii) Higher scores on religious private practice in women and religious affiliation in men (Braun B, …, Lenz B 2018 *Alcohol Alcohol*). (ix) Non-crossed eye / hand laterality in men (Weinland C, …, Lenz B 2019 *Alcohol Clin Exp Res*).

In addition to the BMBF and the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG]), the STAEDTLER Foundation, the Forschungsstiftung Medizin at the Universitätsklinikum Erlangen, and the Interdisciplinary Center for Clinical Research Erlangen at the Friedrich-Alexander University Erlangen-Nürnberg (FAU) have funded my previous projects. I also contributed to drug studies: ON-ICE Trial, EudraCT 2021-003610-40, alcohol dependence; HOSAN-Studie, EudraCT 2015-004184-36, anorexia nervosa; ApaAD01-Studie, EudraCT 2007-005352-17, Alzheimer's dementia.

For the previous work, I have received the following awards: GebFra Award (2020), Wilhelm-Feuerlein Research Award of the Oberberg Stiftung Matthias Gottschaldt and Deutsche Suchtstiftung (2016), Research Award of the Norddeutscher Suchtforschungsverbund e.V. (2012), Fritz-Lickint Award of the Deutsche Gesellschaft für Nikotin- und Tabakforschung e.V. (2012), and the Young Scientist Award of the 8th World Congress of Biological Psychiatry (2005).

Key output of the years 2020 – now:

1. *Sex hormone activities over the life span, gender, and related drinking motives influence risk and course of addiction.*

In our most recent studies, we established that dehydroepiandrosterone and progesterone levels as well as progesterone/estradiol ratios and the menstrual cycle are related to alcohol use disorder phenotypes in men and women. This builds the basis for future mechanistic and interventional research within the scope of the DFG-funded **Collaborative Research Center / Transregio 265** (**CRC / TRR 265**; 2019 – ongoing; trr265.org; PI in projects A08 and S01). For example, we are currently testing in a randomized, placebo-controlled, double-blind, crossover finasteride challenge experiment whether the reduction of dihydrotestosterone by the 5-alpha reductase 2 inhibitor finasteride is able to modulate neuroimaging, neuropsychological, behavioral, and alcohol drinking phenotypes in heavy alcohol drinking men (DRKS00020569).

(Hoffmann S, …, Lenz B, the ReCoDe-Consortium *medrxiv* 10.1101/2022.12.21.22282762; Weinland C, …, Lenz B 2021 *Prog Neuropsychopharmacol Biol Psychiatry* 10.1016/j.pnpbp.2021.110278; Weinland C, …, Lenz B 2022 *Addict Biol* 10.1111/adb.13135)

We replicated and found novel evidence to indicate that prenatal androgenization (assessed via the biomarker second-to-fourth finger length ratio [2D:4D]) associates with addictive behavior in adulthood, including alcohol use disorder and online sexual compulsivity. Moreover, we identified that 2D:4D associates sex-specifically with frontal brain volumes in adolescents. These results and related work support our BMBF-funded **IMAC-Mind Consortium** TP3 project to investigate how the modulation of prenatal environmental factors affects the prenatal androgen load (imac-mind.de), for which we have received the GebFra Award in 2020.

(Buchholz VN, …, Lenz B 2021 *Front Psychiatry* 10.3389/fpsyt.2021.517411; Lenz B et al. 2020 *Addict Biol* 10.1111/adb.12815; Lenz B et al. 2021 *Sucht* 10.1024/0939-5911/a000736; Lenz B et al. 2022 *Eur Arch Psychiatry Clin Neurosci* 10.1007/s00406-022-01515-4)

Finally, we showed that women and men as well as different age groups vary in their use of alcohol for self-management. We also provided evidence that patients with masculine depression versus patients with non-masculine depression show more frequent and more severe use of alcohol, tobacco and illicit drugs as well as longer working times, but that patients with masculine depression also report fewer health services contacts due to mental complaints. Hence, we identified promising targets to establish specialized care offers

(Müller CP, …, Lenz B 2021 *Alcohol Clin Exp Res* 10.1111/acer.14550; Müller CP, …, Lenz B 2023 *Mol Psychiatry* 10.1038/s41380-023-02074-3; von Zimmermann C, …, Lenz B 2023 *Eur Arch Psychiatry Clin Neurosci* 10.1007/s00406-023-01567-0)

2. *Lipid and leptin levels, body mass index, and physical activity associate with alcohol use and depression.*

In several studies, we provided sex-separated evidence for dysregulated lipid and leptin levels in alcohol use disorder and depression. Moreover, we also showed a role of physical activity and related body measures such as the body mass index. We published a meta-analysis to show a gender-specific relationship between alcohol use and body mass index. We were also able to transfer our previous finding from a highly controlled pilot study that the body mass index predicts sex-specifically hospital readmissions in patients with alcohol use disorder (Weinland C, …, Lenz B 2019 *Prog Neuropsychopharmacol Biol Psychiatry*) in a clinical routine setting. These data are important as they provide a basis for the development of future behavioral-oriented interventions in patients with alcohol used disorder and/or depression.

(Bouna-Pyrrou P, …, Lenz B 2021 *Psychoneuroendocrinology* 10.1016/j.psyneuen.2021.105179; Hoffmann S, …, Lenz B 2023 *Addict Biol* 10.1111/adb.13239; Siegmann EM, …, Lenz B 2022 *Sci Rep* 10.1038/s41598-022-25653-w; von Zimmermann C, …, Lenz B 2020 *Front Psychiatry* 10.3389/fpsyt.2020.00494; von Zimmermann C, …, Lenz B 2022 *Front Psychiatry* 10.3389/fpsyt.2022.794351; Weinland C, …, Lenz B 2020 *Drug Alcohol Depend* 10.1016/j.drugalcdep.2020.107898)

3. *We optimized methods for diagnosis and care of patients with fetal alcohol spectrum disorder (FASD).*

Although FASD is highly prevalent, especially in the European region (WHO, 2018), FASD in adults is still underdiagnosed. Aiming to improve diagnostic procedures in FASD, we evaluated and optimized the German biographic interview for FASD as a screening instrument in adulthood. We found the interview to be resource-efficient, user-friendly, comprehensible, and easily applicable. It provides an overall good convergent and discriminant validity and can be used in daily clinical routine. Moreover, we showed that prenatal alcohol exposure measured via meconium ethyl glucuronide is related to the facial phenotype in adolescents. As representative of the German Society for Addiction Research and Addiction Therapy, I also contribute to the update of the S3 guideline 'Fetal Alcohol spectrum disorder in Children and Adolescents - Diagnosis and Intervention'.

(Maschke J, …, Lenz B, Kornhuber J, Eichler A, IMAC-Mind Consortium 2021 *Brain Sci* 10.3390/ brainsci11020154; Widder M, …, Lenz B 2021 *Sci Rep* 10.1038/s41598-021-83942-2)