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Narrative academic profile

Dr. Kiefer's primary interest in **neuroscientific experimental research** has been on the neurobiological aspects of relapse-associated cognition and behavior in alcoholism. Based on the study of two molecules (acamprosate and naltrexone) he focused primarily on **glutamateric neurotransmission** in addiction disorders. His group provided first data on the significance of the **glycine binding-site of NMDA receptors** for alcohol-associated behavior and the modulation of affect related behavior during alcohol withdrawal. Dr. Kiefer extended these findings through a RCT using **D-Cycloserin**, an agonist at the glycine binding-site, resulting in a facilitation of the effects of cue-exposure treatment on neural cue-reactivity. In 2003 he presented the first "COMBINE study", a placebo-controlled, randomized IIT, that compared **and** combined acamprosate and naltrexone in relapse-prevention in alcoholism. Apart from showing superiority of the combination of both drugs and naltrexone alone over placebo, the results also point to the existence of differentiable patient subgroups thus representing a first step towards personalized medicine in alcoholism treatment. More recent studies of Dr. Kiefer focused on the pharmacodynamics of both drugs (and a potential pathway of action associated with an altered calcium concentration) and structurally related molecules (nalmefene).

Related major contributions:

- **Kiefer F**, Jahn H, Koester A, Montkowski A, Reinscheid R, Wiedemann K (2003) Involvement of NMDA receptors in alcohol-mediated behavior: mice with reduced affinity of the NMDA R1 glycine binding site display attenuated effects of ethanol. **Biological Psychiatry** 53(4): 345-351
- **Kiefer F**, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R, Kämpf P, Stracke R, Baehr M, Naber D, Wiedemann K (2003) Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. **Archives of General Psychiatry** 60: 92-99
- **Kiefer F**, Witt SH, Frank J, Richter A, Treutlein J, Lemenager T, Nöthen MM, Cichon S, Batra A, Berner M, Wodarz N, Zimmermann US, Spanagel R, Wiedemann K, Smolka MN, Heinz A, Rietschel M, Mann K. (2010) Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk and treatment response to acamprosate. **Pharmacogenomics J**. 11(5):368-74.
- **Kiefer F**, Kirsch M, Bach P, Hoffmann S, Reinhard I, Jorde A, von der Goltz C, Spanagel R, Mann K, Loeber S, Vollstädt-Klein S (2015) Effects of D-cycloserine on extinction of mesolimbic cue reactivity in alcoholism: a randomized placebo-controlled trial. **Psychopharmacology** (Berl). 232(13):2353-62.
- Vollstädt-Klein S, Bumb JM, Otto A, Dinter C, Karl D, Koopmann A, Hermann D, Mann K, **Kiefer F** (2019) The effects of nalmefene on emotion processing in alcohol use

disorder - A randomized, controlled fMRI study. **Eur Neuropsychopharmacol** 29(12):1442-1452.

- Bach P, Vollstadt-Klein S, Kirsch M, Hoffmann S, Jorde A, Frank J, Charlet K, Beck A, Heinz A, Walter H, Sommer WH, Spanagel R, Rietschel M, **Kiefer F** (2015) Increased mesolimbic cue-reactivity in carriers of the mu-opioid-receptor gene OPRM1 A118G polymorphism predicts drinking outcome: a functional imaging study in alcohol dependent subjects. **Eur Neuropsychopharmacol**. 25(8):1128-35.
- Bach P, Schuster R, Koopmann A, Vollstaedt-Klein S, Spanagel R, **Kiefer F** (2022) Plasma calcium concentration during detoxification predicts neural cue-reactivity and craving during early abstinence in alcohol-dependent patients. **Eur Arch Psychiatry Clin Neurosci**. 272(2):341-348.

Apart from psychopharmalogical studies, Dr. Kiefer's work concentrated on the **neuroendocrine regulation of addiction-associated symptomatology**. He provided early evidence showing the **lowered stress-response** of the **hypothalamic-pituitary-adrenocortical (HPA) axis** to be associated with relapse behavior, identifying the HPA-axis as a potential pharmacotherapeutic target.

Related major contributions:

- **Kiefer F**, Jahn H, Schick M, Wiedemann K (2002) Alcohol self-administration, craving and HPA-axis activity: an intriguing relationship. **Psychopharmacology** 164: 239-240
- **Kiefer F**, Wiedemann K (2004) Neuroendocrine pathways of addictive behavior. **Addiction Biology** 9(3-4): 205-212
- **Kiefer F**, Jahn H, Otte C, Naber D, Wiedemann K (2006) Hypothalamic-pituitary-adrenocortical axis activity: a target of pharmacological anti-craving treatment? **Biological Psychiatry** 60(1): 74-76
- Koopmann A, Bez J, Lemenager T, Hermann D, Dinter C, Reinhard I, Schuster R, Wiedemann K, Winterer G, **Kiefer F** (2016) The effect of nicotine on HPA axis activity in females is modulated by the FKBP5 genotype. **Ann Hum Genet**. 80(3):154-61.

His findings on the HPA-axis and its physiological regulation led to more-detailed studies on the **appetite-regulating system and its interaction with motivational, reward-associated neural pathways**. In 2001, Dr. Kiefer published the first study that showed a classic "appetite-regulating" peptide (leptin) to have a direct influence on alcohol craving and replicated this finding in the corresponding animal model for addiction-associated behavior. Others have now confirmed it repeatedly. In the meantime, mesolimbic dopaminergenic neurons were shown to carry leptin receptors. This new finding increased the understanding of the **interaction of lateral hypothalamic (homeostatic) appetite-regulating functions with mesolimbic (motivational) reward-associated functions**, namely, showing that **motivational behavior depends on homeostatic requirements**. His group has also extended these findings to other addictive disorders (nicotine addiction) as well as other neuropeptides (orexin, ghrelin).

Related major contributions:

- **Kiefer F**, Jahn H, Keller M, Naber D, Wiedemann K (2001) Leptin as a possible modulator of craving for alcohol. **Archives of General Psychiatry** 58: 509-510

- von der Goltz C, Koopmann A., Dinter C, Richter A, Grosshans M, Rockenbach C, Wiedemann K, Mann K, Winterer G, **Kiefer F** (2010) Orexin and leptin are associated with nicotine craving: a potential link between smoking, appetite and reward. **Psychoneuroendocrinology** 35(4): 570-577
- Grosshans M, Vollmert C, Vollstädt-Klein S, Tost H, Leber S, Bach P, Bühler M, von der Goltz C, Mutschler J, Loeber S, Hermann D, Wiedemann K, Meyer-Lindenberg A, **Kiefer F** (2012) Association of leptin with food cue-induced activation in human reward pathways. **Arch Gen Psychiatry** 69(5):529-37.
- **Kiefer F** (2014) Ghrelin in addictive behaviors: plenus venter non studet libenter. **Biol Psychiatry** 1;76(9):676-7.
- Koopmann A, Bach P, Schuster R, Bumb JM, Vollstädt-Klein S, Reinhard I, Rietschel M, Witt SH, Wiedemann K, **Kiefer F** (2019) Ghrelin modulates mesolimbic reactivity to alcohol cues in alcohol-addicted subjects: a functional imaging study. **Addict Biol.** 24(5):1066-1076.
- Bach P, Koopmann A, Bumb JM, Vollstädt-Klein S, Reinhard I, Rietschel M, Witt SH, Wiedemann K, **Kiefer F** (2020) Leptin predicts cortical and subcortical gray matter volume recovery in alcohol dependent patients: A longitudinal structural magnetic resonance imaging study. **Horm Behav**. 124:104749.

These findings in alcohol and other addictive disorders were the basis for Dr. Kiefer's research where he extends his approach to study **motivational mechanisms regulating eating behavior in obese patients**. Again using functional MRI scans (fMRI cue-reactivity) he recently found an interaction between appetite-regulating factors and stimulus-induced, mesolimbic reactivity. This is currently developing into a very promising new field of research, not least with regard to the reassessment of **hyperalimentary obesity as a disorder within addiction psychiatry**.

Related major contributions:

- Grosshans M, Vollmert C, Vollstädt-Klein S, Leber S, Bach P, Bühler M, von der Goltz Ch, Mutschler J, Loeber S, Hermann D, Wiedemann K, Tost H, Meyer-Lindenberg A, **Kiefer F** (2012) Association of leptin with food cue-induced activation in human reward pathways. **Archives of General Psychiatry** 69(5):529-37
- Loeber S, Grosshans M, Korucuoglu O, Vollstädt-Klein S, Schneider S, Vollmert C, Wiers R, Mann K and **Kiefer F** (2012) Impairment of inhibitory control in response to food-associated cues and attentional bias of obese patients and normal-weight controls. **The International Journal of Obesity** 36(10):1334-9
- Bach P, Grosshans M, Koopmann A, Pfeifer AM, Vollstädt-Klein S, Otto M, Kienle P, Bumb JM, **Kiefer F** (2021) Predictors of weight loss in participants with obesity following bariatric surgery - A prospective longitudinal fMRI study. **Appetite** 1;163:105237.
- Bach P, Grosshans M, Koopmann A, Kienle P, Vassilev G, Otto M, Bumb JM, **Kiefer F** (2021) Reliability of neural food cue-reactivity in participants with obesity undergoing bariatric surgery: a 26-week longitudinal fMRI study. **Eur Arch Psychiatry Clin Neurosci** 271(5):951-962.

In the past few years, research on **the hereditary risk factors of mental disorders** has become more important. Since 2005, Dr. Kiefer has been the coordinator of the "DNA bank Addiction", that provided the data set for the **first genome-wide association study (GWAS)** to research genetic risk-factors in alcoholism. This study suggested several genetic

polymorphisms to affect disease risk. It was also the basis for his recently published **pharmacogenetic study.** A SNP that had been identified in the GWAS (rs13273672 in the ***GATA4*** gene) was associated with the response to acamprosate treatment. This finding could provide a new approach to optimize acamprosate treatment by subtyping patients according to their genotype. Since *GATA4* has a regulatory effect on the transcription of **ANP,** Kiefer's finding builds on earlier studies in which he found **affective symptoms and addiction-associated behavior** to be associated with ANP plasma concentration. Dr. Kiefer's also used **functional MRI** to study the influence of *GATA4*, as well as other (HPA-, glutamate- and dopamine-associated) alcoholism risk-genes, on neuronal function systems.

Related major contributions:

- **Kiefer F**, Andersohn F, Jahn H, Wolf K, Raedler TJ, Wiedemann K (2002) Involvement of plasma ANP in protracted alcohol withdrawal. **Acta Psychiatrica Scandinavica** 105(1): 65-70
- Treutlein J, Cichon S, Ridinger M, Wodarz N, Soyka M, Zill P, Maier W, Dahmen N, Scherbaum N, Wienker TF, Ludwig KU, Wichmann HE, Schreiber S, Sommer W, Gebicke-Haerter P, Steffens M , Sullivan PF, Nöthen MM, Frank J, **Kiefer** F, Spanagel R, Mann K, Rietschel M (2009) Genome-wide association study of alcohol
- **Kiefer F**, Witt S, Frank J, Richter A, Treutlein J, Lemenager T, Nöthen MM, Cichon S, Batra A, Berner M, Wodarz N, Zimmermann US, Spanagel R, Wiedemann K, Smolka MN, Heinz A, Rietschel M Mann K (2011) Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk, and treatment response to acamprosate. **The Pharmacogenomics Journal** 11(5):368-74.
- Jorde A, Bach P, Witt SH, Becker K, Reinhard I, Vollstädt-Klein S, Kirsch M, Hermann D, Charlet K, Beck A, Wimmer L, Frank J, Treutlein J, Spanagel R, Mann K, Walter H, Heinz A, Rietschel M, **Kiefer F** (2014) Genetic variation in the atrial natriuretic peptide transcription factor GATA4 modulates amygdala responsiveness in alcohol dependence. **Biol Psychiatry** 15;75(10):790-7.
- Zois E, Vollstädt-Klein S, Hoffmann S, Reinhard I, Bach P, Charlet K, Beck A, Treutlein J, Frank J, Jorde A, Kirsch M, Degenhardt F, Walter H, Heinz A, **Kiefer F** (2016) GATA4 variant interaction with brain limbic structure and relapse risk: A voxel-based morphometry study. **Eur Neuropsychopharmacol**.26(9):1431-1437.
- Koopmann A, Bach P, Schuster R, Bumb JM, Vollstädt-Klein S, Reinhard I, Rietschel M, Witt SH, Wiedemann K, **Kiefer F** (2019) Ghrelin modulates mesolimbic reactivity to alcohol cues in alcohol-addicted subjects: a functional imaging study. **Addict Biol**. 24(5):1066-1076.

One further focus of Dr. Kiefer's research currently is on reward-associated learning, reward conditioning, memory consolidation and extinction. Addiction disorders can be seen as models for understanding **pharmacologically enhanced learning** and **preference development.** Dr. Kiefer's group is currently researching **attentional bias** as well as its association with the severity of addiction, its prognostic value, and its manipulability, in addition to the reward-stimulus-induced activation of neuronal networks and the way this activation is emotionally and cognitively processed, the latter with the help of functional imaging (**fMRI**). In a recently published study his group added support for the **incentive sensitization theory** of addiction proposed by Robinson and Berridge by showing an association of alcohol cue-induced activation of mesolimbic pathways with a shift of attention towards these stimuli in alcohol-dependent subjects. Based on the impact of conditioned

response to alcohol-cues for relapse in addiction, his group recently concluded a **psychotherapy study** applying a manualized **cue-exposure therapy**, with which they were able to show stimulus-induced activation of mesolimbic areas to be significantly lowered.

Related major contributions:

- Löber S, Vollstädt-Klein S, von der Goltz C, Flor H, Mann K, **Kiefer F** (2009) Attentional bias of alcohol dependent patients: Influences of duration of dependence and impairment of executive functioning – a pilot study. **Addiction Biology** 14(2):194-203
- Vollstädt-Klein S, Loeber S, Kirsch M, Bach P, Richter A, Bühler M, von der Goltz C, Hermann D, Mann K, **Kiefer F** (2011) Effects of Cue-Exposure Treatment on Neural Cue Reactivity in Alcohol Dependence: A Randomized Trial. **Biological Psychiatry** 69(11):1060-6.
- Vollstädt-Klein S, Loeber S, Richter A, Bach P, Kirsch M, Bühler A, von der Goltz C, Mann K, **Kiefer F** (2012) Validating incentive salience with fMRI: association between mesolimbic cue-reactivity and attentional bias in alcohol-dependent patients. **Addiction Biology** 17(4):807-16.
- Dinter C, Hermann D, Heckmann J, Hill H, Reinhard I, Vollstädt-Klein S, Kirsch P, Kiefer F (2020) Reconsolidation impairment of reward memory by stimulating stress response. Addict Biol. 25(1): e12712.
- Bach P, Reinhard I, Koopmann A, Bumb JM, Sommer WH, Vollstädt-Klein S, **Kiefer F** (2021) Test-retest reliability of neural alcohol cue-reactivity: Is there light at the end of the magnetic resonance imaging tube? **Addict Biol**. 15:e13069. Online ahead of print

<u>Key output of the years 2020-now</u>

Output relevant for Clinicians

- Scientific coordinator of the **S3-Guidelines of Alcohol-use-disorders**:
  -S3-Guideline Screening, Diagnosis and Treatment of Alcohol Use Disorders (Eds: **Kiefer F**, Hoffmann S, Petersen KU, Batra A) Springer (2022)
  -AWMF online: 076-001k_S3-Screening-Diagnose-Behandlung-alkoholbezogene-Stoerungen_2021-02.pdf (awmf.org)
  Co-coordinator on the **S-3 Guideline on Tobacco use disorder** (S3-Guideline on Smoking and Nicotine Dependence: Screening, Diagnosis and Treatment (Eds: Batra A, Petersen KU, Hoffmann S, **Kiefer F**) Springer (2022)
  -AWMF online: 076-006l_S3_Rauchen-_Tabakabhaengigkeit-Screening-Diagnostik-Behandlung_2021-03.pdf (awmf.org)
- Editor and author of several **Textbooks and Book Chapters** on (the treatment of) addictive disorders, including (Springer: Kompendium der Psychiatrischen Psychopharmakotherapie 2020; Oxford University Press: New Oxford Textbook on Psychiatry 2020; Thieme: Referenz Psychische Störungen 2021; Elsevier: Therapie Psychischer Erkrankungen (2022); etc.
- Extensive **further education and training** of MD's, psychologists and addiction therapists in workshops, meetings and at congresses.
  Treatment and Supervision as Medical Director of the Department of Addictive Behavior and Addiction Medicine

Output relevant for the Research Community

- **Editor-in-Chief** of “European Addiction Research” since 2010 (IF 2010: 1.78; IF 2022: 4.00)
- **Local Spokesperson** of the Collaborative Research Center, Transregio 265: Losing and Regaining Control over Drug Intake (2019/07-2023/06) and **PI** of additional funded research projects (BMBF, DFG and EU funding)
- Establishment of the **Feuerlein Centre for Translational Addiction Research** and establishment (and scientific management) of the annual “Feuerlein Symposium on Health Services Research in Addiction Therapy” 2020-2021-2022
- Extensive **publications** based on IIT’s of the department and continuous **third party funding** (incl. BMBF, DFG and EU)

Output relevant for the Public

- Extensive **press work** on addiction related topics (acc. to Landau Media analyses on behalf of KUM, CIMH) e.g. for *Falk Kiefer* in 2021: 518 reports (90% also print), 84.5 million reach, *2.2 million € advertising equivalent*
- Member of the **Expert Committee** of the Commissioner of the Federal Government for Drug an Addiction Policy (MP Blienert) on the regulation of controlled dispensing of cannabis to adults in Germany
- **President** of the German Society of Addiction Research and Treatment (DG-Sucht) and **Chairman** of the German Addiction Foundation (Deutsche Suchtstiftung)