Curriculum vitae

Prof. Falk Kiefer, MD

Place of birth: Hannover, Germany
Date of birth: February 7, 1969

Summary

Chair in Addiction Research, Professor of Psychiatry and Psychotherapy,
University of Heidelberg, Germany

Director, Dept. of Addictive Behavior and Addiction Medicine
Central Institute of Mental Health (CIMH), Mannheim, Germany

Board certified for Psychiatry and Psychotherapy
Board certified for Addiction Medicine
Diploma in Health Economics (Dipl. oec. med.)

Fellowship award 1999, World Psychiatric Association (WPA)
Fellowship award 2001, German Society of Biological Psychiatry (DGBP)
Fellowship award 2002, European College of Neuropsychopharmacology (ECNP)

Wilhelm-Feuerlein Research Award 2002/2003, German Addiction Foundation, Berlin
EPA-Research Prize 2004, European Psychiatric Association, Geneva

Funded by the German Federal Ministry of Education and Research (BMBF), German National Genome Research Network (NGFN), German Research Foundation (DFG), Collaborative Research Center SFB 636 and Priority Program SPP1226, European Union, Horizon 2020

Chairman of the German Addiction Foundation (Deutsche Suchtstiftung)
Vice-Chair of the section "Addictive Behaviors" of the European Psychiatric Association (EPA),
Treasurer of the German Society for Addiction Research and Treatment (Deutsche Gesellschaft für Suchtforschung und Suchttherapie; DG-Sucht)

Editor-in-Chief of *European Addiction Research*, member of the Editorial Boards of *Alcohol and Alcoholism*, *Addiction Biology* and *Sucht*; member of the Advisory Board of *Pharmacopsychiatry*

Medical qualification

1990 - 1996	**Medical Studies** at the Friedrich Alexander University, Erlangen–Nuremberg, Germany. Graduated in May 1996
7/1996 - 9/1996	**Resident** (*Arzt im Praktikum*), **General Psychiatry**, Dept. of Psychiatry, Friedrich Alexander University, University of Erlangen–Nuremberg (Director: Prof A. Barocka)
11/1996 - 2/2002	**Resident** (*Arzt im Praktikum* and *Assistenzarzt*), **addiction treatment unit**, **intensive care unit**, and closed ward, Dept. of Psychiatry, University of Hamburg (Director: Prof. D. Naber). Medical License, Federal State of Bavaria, Germany
3/2002 – 2/2003	**Resident in Neurology**: Dept. of Neurology, University of Hamburg (Director: Prof. C. Weiller)
6/2002	**Board certification in Addiction Medicine** (*Fachkunde Suchtmedizinische Grundversorgung*), Medical Association Hamburg
5/2003	**Board certification in Psychiatry and Psychotherapy** (*Facharzt*), Medical Association Hamburg
5/2003	**Senior Attending Physician of the outpatient and addiction-treatment units**, Dept. of Psychiatry, University of Hamburg (Director: Prof. D. Naber).
2/2004	**Associate Professor of Psychiatry**, University of Hamburg
1/2005	**Diploma in Health Economics** (Dipl. oec. med.), Chur, Switzerland
4/2005 – 04/2014	**Assistant Medical Director**, Central Institute of Mental Health (CIMH), Mannheim
4/2014 – ongoing	**Director, Dept. of Addictive Behavior and Addiction Medicine**, Central Institute of Mental Health (CIMH), Mannheim
1/2016 – ongoing	**Chair in Addiction Research,** University of Heidelberg, Medical Faculty Mannheim

Scientific qualification

6/1996	MD, Dept. of Psychiatry, Friedrich Alexander University of Erlangen–Nuremberg, Dissertation: *Occurrence, treatment and outcome of depressive disorders during inpatient alcohol detoxification treatment*
8/1998 – 03/2005	Head of the Addiction Research Group, Dept. of Psychiatry, University of Hamburg
10/1998	Established a pre-clinical research lab for addiction research (including transgenic animal models, S1) within the Neurobiology Lab, University of Hamburg
2/2004	Habilitation (postdoctoral thesis), *Craving in alcohol dependence: neuroendocrine und pharmacological targets*; Venia legendi in Psychiatry, University of Hamburg
4/2004	Neuroscience Excellence Program, Massachusetts General Hospital and

	Harvard Medical School
4/2005	Full Professor of Addiction Research, Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health (CIMH), University of Heidelberg (reframed in 2010: Full Professor of Psychiatry and Psychotherapy)
10/2012 - ongoing	Head of the Research Group on Neuroenhancement, Central Institute of Mental Health (CIMH), Mannheim, Germany
6/2013 - ongoing	Co-chair the Research Group on Translational Addiction Research, jointly with Wolfgang Sommer, MD, Institute of Psychopharmacology, Central Institute of Mental Health (CIMH), Mannheim, Germany
1/2016 - ongoing	Chair in Addiction Research, University of Heidelberg, Medical Faculty Mannheim

Honours

- **GSP (Good Scientific Practice) Ombudsman** for the Central Institute of Mental Health.
- **Member of the PhD commission** of the Mannheim Medical Faculty of the Univ. of Heidelberg.
- **Chairman of the German Addiction Foundation** (Deutsche Suchtstiftung)
- **Vice-Chair of the Addictive Behaviors section of the European Psychiatric Association** (EPA).
- **Treasurer of the German Society for Addiction Research and Treatment** (*Deutsche Gesellschaft für Suchtforschung und Suchttherapie; DG-Sucht).*
- **Editor-in-Chief of *European Addiction Research***
- Member of the **Editorial Boards** of ***Alcohol and Alcoholism***, ***Addiction Biology*** and "***Sucht***"; Member of the Advisory Board of ***Pharmacopsychiatry***

Scientific Experience

My scientific career began in 1994, when I began my thesis and research assistantship at the Department of Psychiatry of the **University of Erlangen**, where I wrote my thesis on factors contributing to the development of depressive symptoms, as well as their neurobiological correlates in alcoholism. In 1996, I moved to the Psychiatric Department of the **University Hospital Hamburg–Eppendorf**, where I studied the neurobiological mechanisms underlying symptoms of addiction-related psychopathology both in animal models and in clinical studies, including pharmacological trials. In 2005, I moved again to the **Central Institute of Mental Health**, where my focus has evolved in a translational direction, including work with functional imaging (fMRI and MR spectroscopy), genetics (including pharmaco- and imaging genetics), experimental psychotherapy, and neuroendocrinology. Most of this work was sponsored by grants from the German Research Foundation (DFG), the Collaborative Research Center (*Sonderforschungsbereich* SFB 636); the German Research Foundation (DFG) Priority Program (*Schwerpunktprogramm* SPP 1226); as well as the National Genome Research Network (NGFN) of the German Federal Ministry of Education and Research (BMBF) and the European Union (Horizon 2020; Systems Biology of Alcoholism).

My primary interest within the field **neuroscientific experimental research** has been on the neurobiological aspects of relapse-associated cognition and behavior in addiction. Based on the study

of two molecules (acamprosate and naltrexone) I focused primarily on **glutamateric neurotransmission** in addiction disorders. My group provided early 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. Currently I am extending these findings through a investigator-initiated (IIT), randomized, placebo-controlled trial pharmacological intervention-study using **D-cycloserine**, a partial agonist at the glycine binding-site. Results support the hypothesis that DCS facilitates extinction of cue-reactivity in alcohol addiction. We also presented the first placebo-controlled, randomized **"COMBINE" study 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.

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**, Jiménez-Arriero MA, Klein O, Diehl A, Rubio G (2008) Cloningers typology and treatment outcome in alcohol dependent subjects during pharmacotherapy with naltrexone. **Addiction Biology** 13: 124-129
- Spanagel R, **Kiefer F** (2008) Drugs for relapse prevention of alcoholism: ten years of progress. **Trends in Pharmacological Sciences** 29(3):109-15
- Spanagel R, Vengeliene V, Jandeleit B, Fischer WN, Grindstaff K, Zhang X, Gallop MA, Krstew EV, Lawrence AJ, **Kiefer F** (2014) Acamprosate produces its anti-relapse effects via calcium. **Neuropsychopharmacology** 39(4):783-91
- **Kiefer F**, Kirsch M, Bach P, Hofmann S, Reinhard I, Jorde A, von der Goltz C, Mann K, Loeber S, Vollstädt-Klein S (2015) Effects of D-cyloserine on extinction of mesolimbic cue-reactivity: a randomized, placebo-controlled trial. **Psychopharmacology** (Berl.) 232: 2353-62

Apart from psychopharmalogical studies, my work concentrated on the **neuroendocrine regulation of addiction-associated symptomatology**. Our group 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

Our 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, we 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. It has now been confirmed repeatedly by others. 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**. My research 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
- **Kiefer F**, Jahn H, Wolf K, Kämpf P, Knaudt K, Wiedemann K (2001) Free-choice alcohol consumption in mice after application of the appetite regulating peptide leptin. **Alcoholism: Clinical and Experimental Research** 25: 787-789
- **Kiefer F**, Jahn H, Jaschinski M, Holzbach R, Wolf K, Naber D, Wiedemann K (2001) Leptin: a modulator of alcohol craving? **Biological Psychiatry** 49: 782-787
- **Kiefer F**, Jahn H, Otte C, Demiralay C, Wolf K, Wiedemann K (2005) Increasing leptin precedes craving and relapse during pharmacological abstinence maintenance treatment of alcoholism. **Journal of Psychiatric Research** 39(5): 545-551
- 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
- von der Goltz C, Koopmann A, Dinter C, Richter A, Grosshans M, Fink T, Wiedemann K, **Kiefer F** (2011) Involvement of orexin in the regulation of stress, depression and reward in alcohol dependence. **Hormones and Behavior** 60(5):644-50
- Koopmann A, von der Goltz C, Grosshans M, Dinter C, Vitale M, Wiedemann K, **Kiefer F** (2012) The association of the appetitive peptide acetylated ghrelin with alcohol craving in early abstinent alcohol dependent individuals. **Psychoneuroendocrinology** 37(7): 980-6
- **Kiefer F** (2014) Ghrelin in addictive behaviors: plenus venter non studet libenter. **Biological Psychiatry** 76(9):676-7

These findings in alcohol and other addictive disorders were the basis for our current research where we extend this approach to study **motivational mechanisms regulating eating behavior in obese patients**. Again using functional MRI scans (fMRI cue-reactivity) we 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, Löber S, **Kiefer F** (2010) Towards a better understanding of obesity: Implications from addiction research. **Addiction Biology** 16(2):189-98
- 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):1334-39
- Grosshans M*, Schwarz E*, Bumb JM, Schaefer C, Rohleder C, Vollmert C, Vollstädt-Klein S, Tost H, Meyer-Lindenberg A, Leweke FM*, **Kiefer F*** (2014) Oleoylethanolamide and human neural responses to food stimuli in obesity. * equal contribution **JAMA Psychiatry** 71(11):1254-61

In the past few years, research on **the hereditary risk factors of mental disorders** has become more important. Since 2005, I was 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,** our finding builds on earlier studies in which he found **affective symptoms and addiction-associated behavior** to be associated with ANP plasma concentration. In the corresponding animal model (NPR-A receptor knockout), they were able to verify an increase in stress-induced alcohol consumption. Independent studies confirmed this significance of *GATA4*-associated SNP (Edenberg et al. 2010). In a very recent study using **functional MRI** to research the influence of *GATA4* on neuronal function systems in 81 alcohol dependent subjects an association of GATA4, amygdala activity and relapse was shown.

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 dependence. **Archives of General Psychiatry** 66(7):773-84
- Mutschler J, Bilbao A, von der Goltz C, Demiralay C, Jahn H, Wiedemann K, Spanagel R, **Kiefer F** (2009) Augmented stress-induced alcohol drinking and withdrawal in mice lacking functional natriuretic peptide A receptors. **Alcohol and Alcoholism** 45(1):13-16
- **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. **Biological Psychiatry** 15;75(10):790-7
- Buch S , Trépo E, Way M , Herrmann A, Nischalke H, Brosch M, Rosendahl J, Berg T, Ridinger M, Rietschel M, McQuillin A, Frank J, **Kiefer F**, Schreiber S, Lieb S, Soyka M, Semmo N, Datz C, Schmelz R, Brückner S, Wodarz N, Devière J, Clumeck N, Sarrazin C, Lammert F, Gustot T, Deltenre P , Völzke H, Lerch M, Mayerle J, Eyer F, Schafmayer C, Cichon S, Nöthen M, Nothnagel M, Franke A, Moreno C, Franchimont C, Morgan M, Hampe J (2014). A Two-stage genome-wide association study identifies SUGP1/TM6SF2 and TMC4/MBOAT7 as risk loci for alcoholic liver cirrhosis. **Nature Genetics**, 47:1443-1448
- Bach P, Vollstädt-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** (2014). 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 **Neuropsychopharmacology** 25:1128-35. [IF 4.369]
- Fauth-Bühler M, **Kiefer F** (2016). Alcohol and the human brain: a systematic review of recent functional neuroimaging and imaging genetics findings. **Curr Addict Reports**, *E-pub ahead of print*

One further focus of my 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.** Our 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, we recently concluded **psychotherapy studies** applying a manualized **cue-exposure therapy and neurofeedback**, 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
- von der Goltz C, Vengeliene V, Bilbao A, Perreau-Lenz S, Pawlak CR, **Kiefer F,** Spanagel R (2009) Cue-induced alcohol-seeking behavior is reduced by disrupting the reconsolidation of alcohol-related memories. **Psychopharmacology** 205(3):389-97
- 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
- **Kiefer F**, Kirsch M, Bach P, Hofmann S, Reinhard I, Jorde A, von der Goltz C, Mann K, Loeber S, Vollstädt-Klein S (2015) Effects of D-cyloserine on extinction of mesolimbic cue-reactivity: a randomized, placebo-controlled trial. **Psychopharmacology** (Berl.) 232: 2353-62
- Kirsch M, Gruber I, Ruf M, Kirsch P*, **Kiefer F*** (2015) Real-time fMRI neurofeedback can reduce striatal cue reactivity to alcohol stimuli – results from a pilot study. **Addiction Biology** * equal contribution; *E-pub ahead of print*