

Neurobiologie und Pharmakotherapie der Alkoholabhängigkeit

DGPPN
Berlin 2011

Prof. Dr. med. Falk Kiefer

Universität Heidelberg
Klinik für Abhängiges Verhalten
und Suchtmedizin
Zentralinstitut für Seelische Gesundheit (ZI),
Mannheim



**American Psychiatric Association
DSM-5 Development**

Home About DSM-5 Meet Us Research Background Progress Reports Proposed Revisions Newsroom

DSM-5: The Future of Psychiatric Diagnosis

Publication of the 99th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in May 2013 will mark one of the most anticipated events in the mental health field. As part of the development process, the preliminary draft revisions to the current diagnostic criteria for psychiatric diagnoses are now available for public review. We thank you for your interest in DSM-5 and hope that you use this opportunity not only to learn more about the proposed changes in DSM-5, but also about its history, its impact, and its development. Please continue to check this site for updates to criteria and for more information about the development process.

Participate

User Name:
Password:

How User? Register New
Forgot Password?

**A Message from the
DSM-5 Task Force
Chairs**

Dear Reader:

Welcome to the DSM-5 Development web site. This site provides information culminated from over 10 years of revision activities, made possible thanks to the generous dedication of more than 500 global experts in the field of mental health.

The DSM-5 Task Force and Work Group members are working to develop criteria for diagnoses that not only reflect new advances in the science and conceptualization of mental disorders, but also reflect the needs of our patients. We encourage you to share with us the wealth of information contained

Important Notice to Applicants for DSM-5 Field Trials in Large, Academic Settings

The deadline for receipt of proposals for DSM-5 Field Trials has now passed. All applications are currently under review. The full Request for Proposals can still be viewed by clicking here.

Proposed Draft Revisions to DSM Disorders and Criteria

DSM-5 Field Trials in Large, Academic Settings

The draft disorders and criteria that have been proposed by the DSM-5 Work Groups can be found on these pages. Use the links below to read about proposed changes to the disorders that interest you. Please note that the proposed criteria listed here are not final. These are initial drafts of the recommendations that have been made to date by the DSM-5 Work Groups. At this time, visitors are no longer able to submit comments on this web site. The work group members are currently reviewing all submitted comments, and we will be providing updates to this site to reflect any changes in proposed criteria as a result of these reviews.

What's New

A Consumer-Friendly Version of Frequently Asked Questions about DSM-5 Field Trials is Now Available

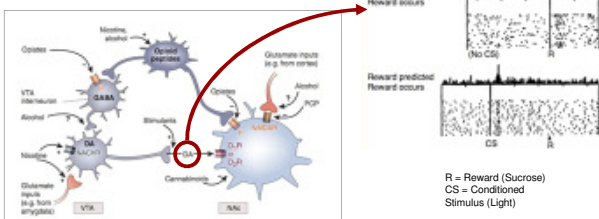
A Description of DSM-5 Field Trials is Now Available

Revised DSM-5 Field Trial Protocol for Large, Academic Settings

DSM-5 Field Trial Protocol for Routine Clinical Practice Settings

Sign Up to Participate in DSM-5 Field Trials for Routine Clinical Practice

Mesolimbisches DA System und Belohnungserwartung

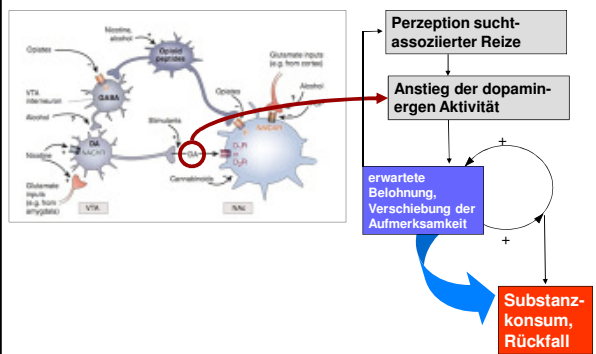


"Dopamine transforms the brain's representation of conditioned stimuli from a neutral representation into an attractive and wanted incentive that grabs attention"

Berridge & Robinson (1998)

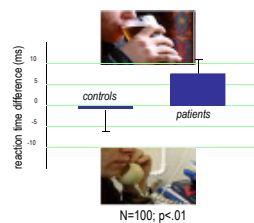
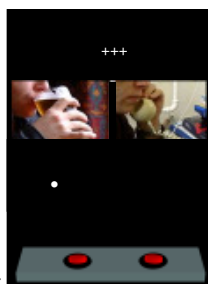
Schultz et al., Science 1997
Hyman, 2006

Mesolimbisches DA System und Belohnungserwartung



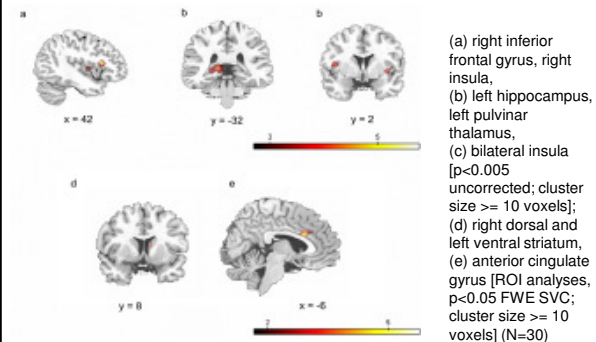
Franken, 2007
Hyman, 2006

Messung der selektiven Aufmerksamkeit (attentional bias) mit dem dot-probe task



Löber, ..., Kiefer (2008)
Addiction Biology

Association between attentional bias and cue-induced fMRI brain activation



Vollstädt-Klein, ..., Kiefer 2011, Addiction Biology

Extinktion: Expositionstraining

„Cue exposure therapy is efficacious in the treatment of alcoholism“

Study	Effect size
Drummond und Glastier (1994)	0,17-0,3
Monti et al. (1993)	0,7354
Rohsenow et al. (2001)	0,5420
Sitharthan, Sitharthan & Hough (1997)	0,6070

Conklin & Tiffany, 2002

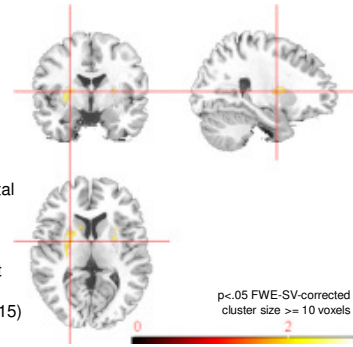


Extinktion: Expositionstraining

SFB 636



larger decrease of striatal cue-induced activation (alc. vs. neutral) after three weeks of cue-exposure treatment (N=15) compared to standard treatment (N=15)

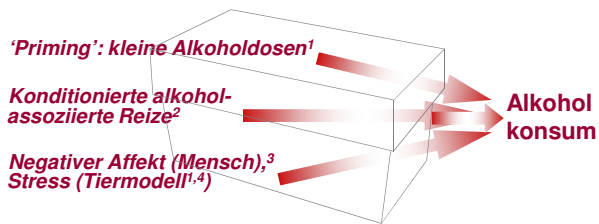


p<.05 FWE-SV-corrected cluster size >= 10 voxels

Vollstädt-Klein, ... , Kiefer (2011) Biological Psychiatry

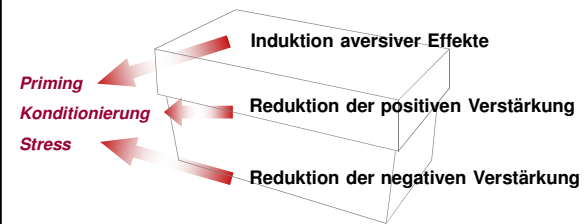


Individuelle Risikokonstellation und Intervention



1. Le AD, Quan B, Juzych et al. *Psychopharmacology (Berl)* 1998; 135: 169–174.
2. Katner SN, Weiss F. *Alcohol Clin Exp Res* 1999; 23: 1751–1760.
3. Brownell KD, Marlatt GA, Lichtenstein E, Wilson GT. *Am Psychol* 1986; 41: 765–782.
4. Vengeliene V, Siegmund, Singer MV et al. *Alcohol Clin Exp Res* 2003; 27: 1048–1054.

Individuelle Risikokonstellation und Intervention



Pharmakologische Entkopplung von Alkoholeinnahme und Dopaminfreisetzung

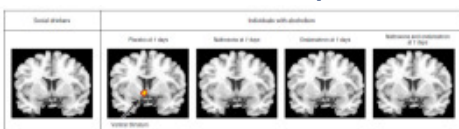


Figure 2. Striatal regions with significantly increased activation in one task (alcohol) compared with another (naltrexone) are depicted in color on coronal standard magnetic resonance images (P < .001). Naltrexone group vs. placebo-treated participants.

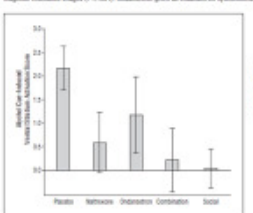
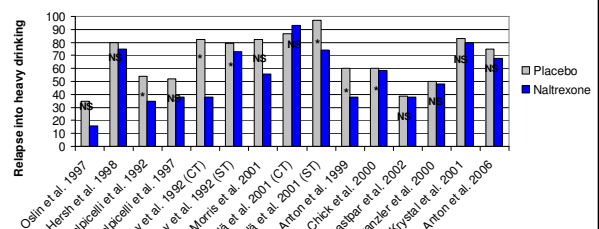


Figure 3. Ventral striatal activation (contrast of alcohol use activation minus naltrexone use activation) was significantly decreased in the combination naltrexone and ondansetron group (P < .001) compared with the placebo-treated participants. Bars indicate mean values; error bars, standard error of the mean.

Non-treatment-seeking alcoholics, 7 days intake of
 – 50 mg of naltrexone (anticraving drug), n=23
 – 0.50 mg of ondansetron (5HT₃ antagonist), n=23
 – combination of those 2 medications, n=20
 – Placebo, n=24

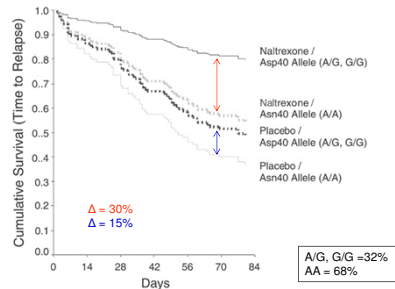
Myrick et al. *Arch Gen Psychiat* (2008)

Studienlage Naltrexon



Hermann, Mann (2010)

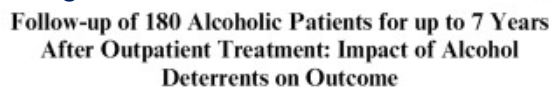
Oslin et al., 2003. Neuropsychopharmacology 28:1546-1552



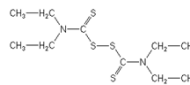
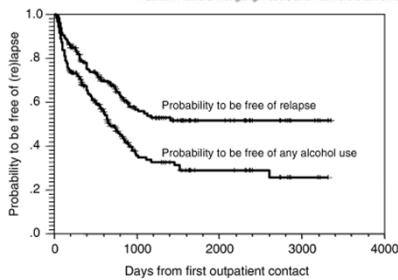
Gegenanzeigen:

- Schwere Leberschäden, akute Hepatitis
- Behandlung mit Opioidanalgetika, positiver Opioid-Nachweis im Urin, opioid-abhängigen Patienten ohne erfolgreichen Entzug oder Patienten, die Opiat-Agonisten erhalten (z.B. Methadon)

- Schlafstörungen, Nervosität, Antriebsschwäche, Kopfschmerzen, Bauchschmerzen und -krämpfe, Erbrechen, Übelkeit, Gelenk- und Muskelschmerzen, gesteigerte Energie, Niedergeschlagenheit, Appetitlosigkeit, Durchfall, Verstopfung, Durstgefühl, Potenzstörungen.



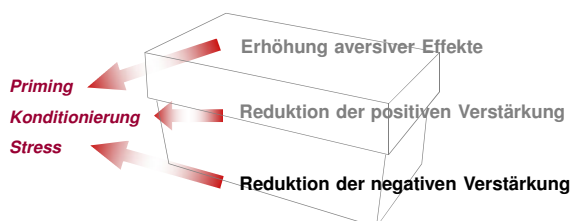
Hanning Krampa, Sabina Starwicz, Thilo Wagner, Claudia Bartels, Carlotta Aust, Eckart Rütger, Wolfgang Poser, and Hannelore Ehrenreich



Gegenanzeigen:

- Koronare Herzkrankheiten
- Schwerwiegende Herzrhythmusstörungen, klin. manifeste Kardiomyopathien, zerebrale Durchblutungsstörungen, fortgeschrittene Arteriosklerose, Ösophagusvarizen, Hyperthyreose

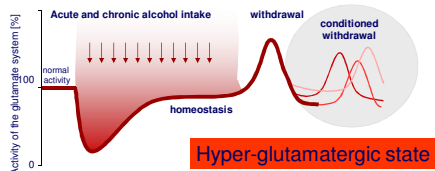
- Müdigkeit, Augenerkrankungen, unangenehmer Körper- und Mundgeruch, diffuse Oberbauchbeschwerden, Erkrankungen des Immunsystems, Schweregefühl im Kopf, Blutdruckabfall



- Im Rahmen der Entwicklung der Abhängigkeit wird Alkohol zu Abwehr/Bewältigung intrapsychischer und interpersoneller Konflikte eingesetzt
- Chronischer Alkoholkonsum initiiert neuroadaptive Veränderungen, die direkt mit Störungen der Affektregulation in Verbindung gebracht werden können

Alkoholinduzierte neuroadaptive Veränderungen

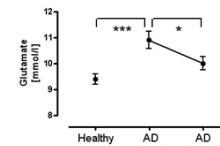
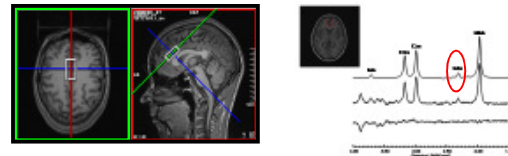
Glutamat assoziierte Hyperexzitabilität während Alkoholentzug und Reizexposition



"Acamprosate normalises progressive recruitment of elevated extracellular glutamate that occurs with repeated cycles of intoxication and withdrawal"

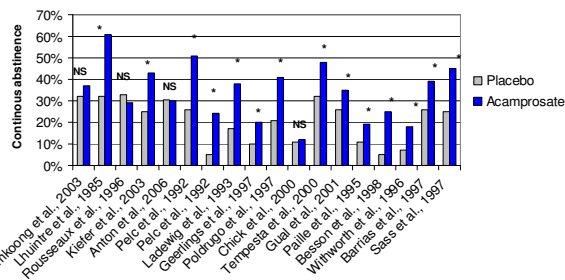
Spanagel and Kiefer, Trends Pharmacol Sci 2008

Glutamat Spektroskopie (MRS) mit 3T im humanen Hirn



Hermann et al., (Biol Psychiatry 2011)

Studienlage Acamprosat



Kiefer & Mann 2005

The Pharmacogenomics Journal
ORIGINAL ARTICLE

Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk and treatment response to acamprosate

F Kiefer^{1,13}, SH Witt^{2,13}, J Frank³, A Richter⁴, J Treutlein⁵, T Lemenager¹, MM Nöthen^{1,4}, S Cichon^{1,5}, A Batra⁶, M Beier⁶, N Wodarz⁷, US Zimmermann^{1,8}, R Spanagel⁹, K Wiedemann¹⁰, MN Smolke¹¹, A Heinz¹², M Rietschel^{2,13} and K Mann^{1,13}

In alcoholism, both relapse to alcohol drinking and treatment response are suggested to be genetically modulated. This study set out to determine whether the top 15 single nucleotide polymorphisms (SNPs) of a recent genome-wide association (GWA) and follow-up study of alcohol dependence are associated with relapse behavior and pharmacological treatment response in 374 alcohol-dependent subjects who underwent a randomized, double-blind, placebo-controlled trial with acamprosate, naltrexone or placebo. The single nucleotide polymorphism, rs13273672, an intronic SNP in the gene for GATA-binding protein 4 (GATA4), was associated with relapse within the 90-day medical treatment period ($P < 0.01$). Subsequent

Kiefer et al. 2011, The Pharmacogenomics Journal

Acamprosat

Gegenanzeigen:

- Niereninsuffizienz
- Schwere Leberinsuffizienz

Nebenwirkungen:

- Verminderte Libido, Durchfall, Bauchschmerzen, Übelkeit, Erbrechen, Juckreiz, makulopapulöser Hautausschlag, Frigidität, Impotenz



Alkoholinduzierte neuroadaptive Veränderungen

Antiglutamaterge/GABAerge Substanzen

- Acamprosate:** how, where, and for whom does it work? (Kiefer&Mann Curr Pharm Des 2010)
- Topiramate** for treating alcohol dependence: a randomized controlled trial (Johnson et al., JAMA 2007);
- The effects of **lamotrigine** on alcohol seeking and relapse (Vengeliene et al., Neuropharmacology 2007)
- A pilot study of **oxcarbazepine** versus acamprosate in alcohol-dependent patients (Croissant ACER 2006)
- Effectiveness and safety of **baclofen** (GABA_B Agonist) for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study (Addolorato et al. Lancet 2007)

Baclofen

Gegenanzeigen:

- Spastizität bei Erkrankungen des rheumatischen Formenkreises, Parkinson, traumainduzierte zerebrale Erkrankung

Nebenwirkungen:

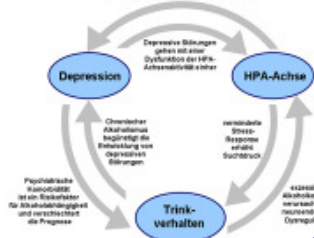
- Abnehmende Herzleistung, Ermüdung, Sehstörung, Übelkeit, Muskelschwäche, Albträume



Alkoholinduzierte neuroadaptive Veränderungen

- Corticotropin-Releasing Factor (CRF), insbesondere der CRF₁ Rezeptor, Schlüsselement neuroadaptiver Veränderungen: "major target for the treatment of relapse behaviour, especially under stressrelated conditions" (Heilig & Koob, *TINS* 2007)
- CRF Antagonisten reduzierten selektiv stress-induziertes, nicht aber reizinduziertes Trinkverhalten im Tiermodell (Liu & Weiss, *J Neurosci* 2002)

chronische Aktivierung des Stresssystems begünstigt die Entwicklung von depressiven Störungen



Kiefer & Wiedemann, *Addiction Biol* 2004

Zusammenfassung

- DSM-5: Addiction and Related Disorders: Dimensionalität
- Kernsymptome der Sucht: pathologische Präferenzbildung und Kontrollverlust
- Medikamentöse Behandlung Ziel auf differenzierbare Rückfallmechanismen, die gleichzeitig auch als Zielsyndrome dienen: "Priming", konditionierte Stimuli und Stressoren/negativer Affekt
- Ableitbare und aktuell verfügbare Interventionen:
 - Aversivtherapie
 - Opiatantagonisten (Ondansetron, Vareniclin: *off label*)
 - Acamprosat (Antikonvulsiva+Baclofen: *off label*)
- Identifikation individueller Profile von Therapierespondern lässt eine Effizienzsteigerung der Behandlung erhoffen
- Aufbau alternativer Verstärker und gestufte Adaptation der Therapieziele (risk reduction)