ADHD/SUD:
A Great Opportunity

AADPA Conference 2018

Dr Dianne Grocott MBBS, FRANZCP

Two shoe salesmen on a business trip to a Pacific island in 1950's sent telegrams home

- No-one here wears shoes!
- Total Disaster! I'm coming home!

- No-one here wears shoes!

Great Opportunity! Send hundreds of pairs!

ICASA - INCAS Study

International Naturalistic Cohort Study of ADHD and Substance Use Disorders

- ICASA - International Collaboration on ADHD & Subst Abuse
  - Karolinska Institute, Sweden
  - 12 sites in 9 Countries Overseas

- First Step Addiction/Mental Health, St Kilda
- University of Melbourne, School of Pop & Global Health
- AADPA - Australian ADHD Professionals Association
  Cairns, Brisbane, Gold Coast, Coastal NSW, Sydney, Melbourne, Rural SA, Perth, Northam, North West WA
- State Addiction Services to Partner

Summary

- A strange set of circumstances leading to INCAS
- ADHD/SUD is well-known to be common
- Why no Treatment Programs?
- ICASA
- Prevalence Research
- ICASA Guidelines and Textbook
- New Treatment Study - INCAS
- Australian Guidelines
- Genes, Microbiota, Gut, Inflammation, Micronutrients

It’s not a secret

ADHD with SUD and SUD with ADHD

Waid, et al. 2004
In: Kranzler and Tinsley:
Dual Diagnosis and Psychiatric Treatment

Prevalence childhood ADHD in general population: 6-9%
Prevalence adult ADHD in general population: 2-4%

About 33% of adults with ADHD have history of AUD
About 20% of adults with ADHD have history DUD

Treatment seeking alcoholics have *childhood* ADHD in 17-50%
Treatment seeking drug addicts have *childhood* ADHD in 17-45%

Treatment seeking SUD patients have *adult* ADHD in about 23% →

A strange set of circumstances leading to INCAS

- 1988 RANZCP thesis: Alcohol Hx in Psych Outpatients
- 2006-2010: Dual Diagnosis Consultant, 2 ADHD/SUD Pts
- 2012: “Will you take a patient on Ritalin?”
- 2015: VAADHDIG “No Guidelines for ADHD/SUD”
- 2017: IMiA Wim vd Brink ICASA “high doses w
- 2017: AADPA Conference ADHD/SUD lecture
- I suggested to AADPA:
  - “Intercollege Working Party on guidelines for ADHD/SUD??”
  - Good idea, Di, would you?
  - No way!

- Jan 2018: APHRA notification from anonymous health professional co-managing complex PTSD/pain/SUD patient "Danger to public - Diagnosed ADHD & prescribed Dex"
- Rang Amsterdam ICASA Director Guert van de Glint
  - "Help, I'm in trouble, do you have any Guidelines for ADHD/SUD?"
  - Yes, about to be published, I'll send you the draft.
  - And Textbook will be published soon.
  - Researchers don't use Dex, but I'll connect you to USA Prof
  - By the way, we don't have Australians for the next phase of our research. Are you interested?"

- Yes, if I'm still registered. Send info on INCAS & Contacts.
  - Jesse Young (Perth) & Sharlene Kay (ICASA Sec, Sydney)
- Jesse Young:
  - I'm now at Uni Melb. I'll join INCAS; I could get you "a pot of money for a Research Assistant and Medical Ethics approval"

- Feb 2018 Submitted APHDRA defence – Over 3 weeks, angst, loss of productivity, loss of income, reviewed literature & 100 pages of case notes, $5,000 legal expenses.
  - Complaint Form: “Did you talk to the doctor?” No.

- Patient struggling, phoned Fresh Start, Perth
  - Did you know we set up The First Step Program in St Kilda?

- First Step:
  - Our GP is keen on ADHD but can’t get patients assessed.
  - Oh by the way, we’ve just got a grant for a psychiatrist to assess complex cases – would you be interested?
  - OK, I’ll see your complex cases on my day off if you’ll do INCAS

- AusPAN: Anyone interested in International Research Study?
  - Yes, I’m in! 14 Psychiatrists from 5 States

- April 2018 – Vindicated by AHPRA

- Sharlene Kay - Do you want the Australian Guidelines for SUD+ADHD. They mention Dex!!!

- Working at First Step
  - Guess how many “complex” patients have undiagnosed ADHD?
  - Benevolent Foundation gave $42K grant for Research Assistant
  - ASRS imbedded into Intake Form
  - Comprehensive Psychiatrist Assessment Form online
  - Educate Staff,
  - Feeling our way forward - Psychostimulant Stimulant Protocols
  - Treatment options

- Aug 2018 Research Assistant starts
  - Planning meetings
  - Contact Collaborators
  - Obtain Ethics
  - Pitch to Potential Partners

Integrated Motivational Assessment Tool (IMAT)* for Motivation to Treat ADHD/SUD

Motivation regarding SUD Treatment

Motivation regarding ADHD Treatment

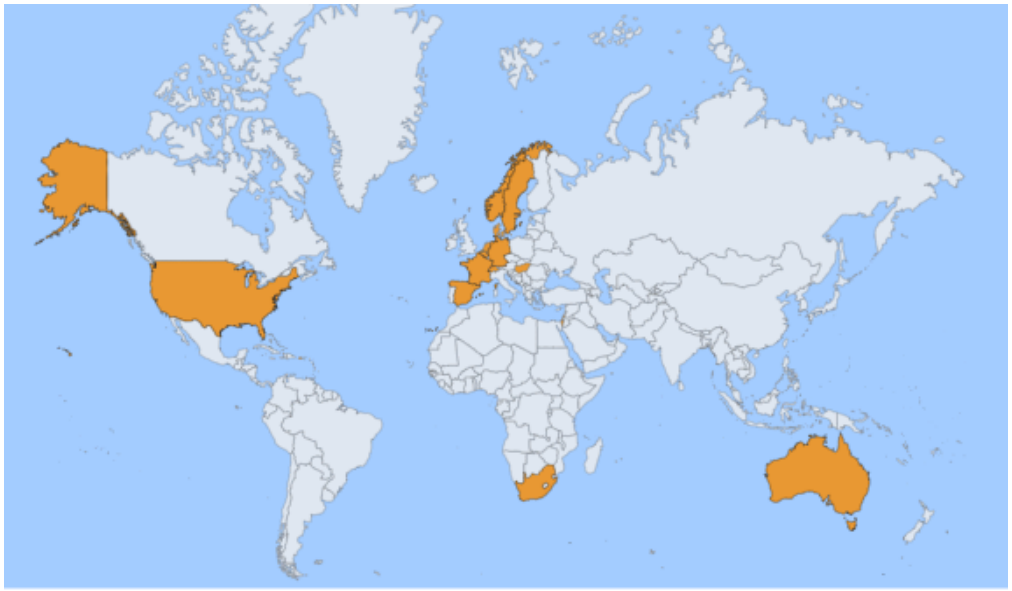
	Pre-contemplation	Contemplation	Preparation / Determination	Action	Maintenance
Pre-contemplation				Public Psychiatry	
Contemplation					Addiction Psychiatry
Preparation / Determination					
Action					
Maintenance		AAPDA			ICASA

*Source: NSW Department of Health (2007). Mental health reference resource for drug and alcohol workers.

ICASA
INTERNATIONAL COLLABORATION ON ADHD AND SUBSTANCE ABUSE

www.adhdandsubstanceabuse.org

ICASA aims to contribute to a substantial decrease in the proportion of ADHD patients developing an addiction/substance use disorder (SUD) and to substantially improve the detection, diagnosis and treatment of patients having both ADHD & SUD.



50 members in 15 countries

High Quality Research
Database
Network
Publications
Information Sharing
Guidelines
Textbook
Training

Detailed overview of the field by Wim van den Brink, Chair of ICASA. Available on request

ADHD and Substance Use Disorder Epidemiology, Genetics, Neurobiology, and Treatment

Wim van den Brink
Academic Medical Centre, University of Amsterdam,
Amsterdam, The Netherlands

International Medicine in Addiction (IMiA) Conference 2017
Sydney, 26 March 2017

ICASA - IASP Study 2010-11

International ADHD in Substance use disorders Prevalence study

Previous research showed:

- **Strong association** between adult ADHD and SUDs
- **Adult ADHD over-represented** among people with SUD (20-40% prevalence).
- **ADHD complicates the course of SUD**
  - earlier onset
  - and greater severity among those with ADHD, and
  - be more difficult to treat,
  - with higher rates of relapse.
- **Increased harms in ADHD/SUD vs Non-ADHD/SUD populations**
  - inattention, carelessness, and impulsive risk-taking associated with ADHD.
  - high frequency substance use,
  - harmful routes of drug administration,
  - blood-borne virus risk behaviours
  - high-risk driving behaviours.

https://ndarc.med.unsw.edu.au/project/examining-prevalence-adhd-among-those-sud

ICASA - IASP Study 2010-11

International ADHD in Substance use disorders Prevalence study

Description:

- 11 Countries - Australia, Belgium, Finland, France, Hungary, Norway, Spain, Sweden, Switzerland, The Netherlands and the US.
- Largest Australian study of adult ADHD/SUD
- First Australian study to examine risk behaviours in ADHD/SUD
- 47 Inpatient and Outpatient Treatment Centres (16 Australian)
- Total 3588 ADHD/SUD patients
- Australians = 489 (Sydney 302, Perth 187)
- Cross-sectional survey design.
- Method - A structured interview screened for adult ADHD and examined SUD, psychiatric history, and drug-related, sexual and driving risk

https://ndarc.med.unsw.edu.au/project/examining-prevalence-adhd-among-those-sud

ICASA - IASP Study 2010-11

International ADHD in Substance use disorders Prevalence study

Publications about the International Cohort:

- **Psychiatric comorbidity in treatment-seeking substance use disorder patients with and without attention deficit hyperactivity disorder: results of the IASP study.** **van Emmerik-van Oortmerssen, K. et al.** *Addiction, 2013, 109(2): 262-272.*

- **The International ADHD in Substance Use Disorders Prevalence (IASP) study: background, methods and study population.** **van de Glind, G., et al.** *International Journal of Methods in Psychiatric Research*, 2013, 22: 232–244.

- **Validity of the Adult ADHD Self-Report Scale (ASRS) as a screener for adult ADHD in treatment seeking substance use disorder patients,** **van de Glind, G. et al.** *Drug and Alcohol Dependence*, 2013, 132 (3): 587-596,

- **Variability in the prevalence of adult ADHD in treatment seeking substance use disorder patients: Results from an international multi-center study exploring DSM-IV and DSM-5 criteria,** **van de Glind, G. et al.** *Drug and Alcohol Dependence*, 2013, 134: 158-166.

ICASA - IASP Study 2010-11

International ADHD in Substance use disorders Prevalence study

Publications about the Australian cohort:

Comorbid attention deficit hyperactivity disorder and substance use disorder complexity and chronicity in treatment-seeking adults

Drug and Alcohol Review, 2015, 34(6): 683–693

Risk behaviours among substance use disorder treatment seekers with and without adult ADHD symptoms

Drug and Alcohol Dependence, 2014, 144: 70-77

Jesse Tyler Young, Susan Carruthers, Steve Allsop
National Drug Research Institute, Curtin University, Perth
Sharlene Kaye (Goodhew), Joanne Gilsenan,
National Drug & Alcohol Research Centre, University NSW, Sydney
Louisa Degenhardt, Melbourne School of Population and Global Health, University Melb
Geurt van de Glind, Wim van den Brink
ICASA Foundation, Amsterdam Institute for Addiction Research, Uni of Amsterdam, The Neth
David Preen School of Population Health, Uni of Western Australia, Perth

ICASA - IASP Study 2010-11

International ADHD in Substance use disorders Prevalence study

Findings:

- **International Prevalence 5-30%.** Varies by Country, Treatment Setting, Substance
- **Australian Prevalence 44%:** 215 ADHD of 489 SUD patients in 16 Settings

- **Significant positive association with ADHD**

Current amphetamine use: (odds ratio (OR) = 1.85; 95% CI: 1.19–2.36).
History of heavy alcohol use: ADHD (OR = 2.05; 95% CI: 1.21–3.45)
History amphetamine use: ADHD (OR = 1.96; 95% CI: 1.26–3.06)

- **Significantly increased risk**

Early onset (<15yo) nicotine use
Moderate duration (3–4 years) of benzodiazepine or amphetamine SUDs
Long duration (≥5 years) of alcohol, opiates other than heroin or methadone, and amphetamine SUDs.
Comorbid depression, anxiety or personality disorder
Driving offences, licence suspensions, at-risk MVA's

Adult ADHD Among NSW Prisoners: Prevalence and Psychiatric Comorbidity

Moore, E et al (Sharlene Kaye) *Journal of Attention Disorders* 2016, Vol. 20(11) 958-967

- Overall prevalence ADHD 200 NSW Prisoners = 17%

Males: 15%, Females: 24%, Indigenous:31%, Non: 10%

- ADHD had higher rates of nicotine, alcohol, stimulant, opioid, ecstasy, cannabis, BZDZ, but not cocaine
- ADHD had higher rates of BPD, ASPD, MDD, social phobia, PTSD, suicidal thoughts than non-ADHD

Table 1. Prevalence of ADHD.

	Total % [95% CI]	Male % [95% CI]	Female % [95% CI]	Aboriginal % [95% CI]	Non-Aboriginal % [95% CI]
Screening assessment	(*N* = 200)	(*n* = 150)	(*n* = 50)	(*n* = 53)	(*n* = 147)
ADHD positive (using ASRS 6-item)	35.0 ([28.5, 42.1])	36.7 ([29.1, 45.0])	30.0 ([18.3, 44.8])	45.3 ([31.8, 58.5])	31.3 ([24.0, 39.5])
Full assessment only	(*N* = 88)	(*n* = 67)	(*n* = 21)	(*n* = 29)	(*n* = 59)
ADHD diagnosis (M.I.N.I. Plus)	17.0 ([10.2, 26.9])	14.9 ([7.8, 26.2])	23.8 ([9.1, 47.6])	31.0* ([16.0, 51.0])	10.2 ([4.2, 21.5])

*$p < .05$. **$p < .001$.

ICASA – Guidelines 2018

International Consensus Statement on Screening, Diagnosis and Treatment of SUD Patients with Comorbid ADHD

Crunelle, C and ICASA Consensus Group *Eur Addict Res 2018;24:43–51*

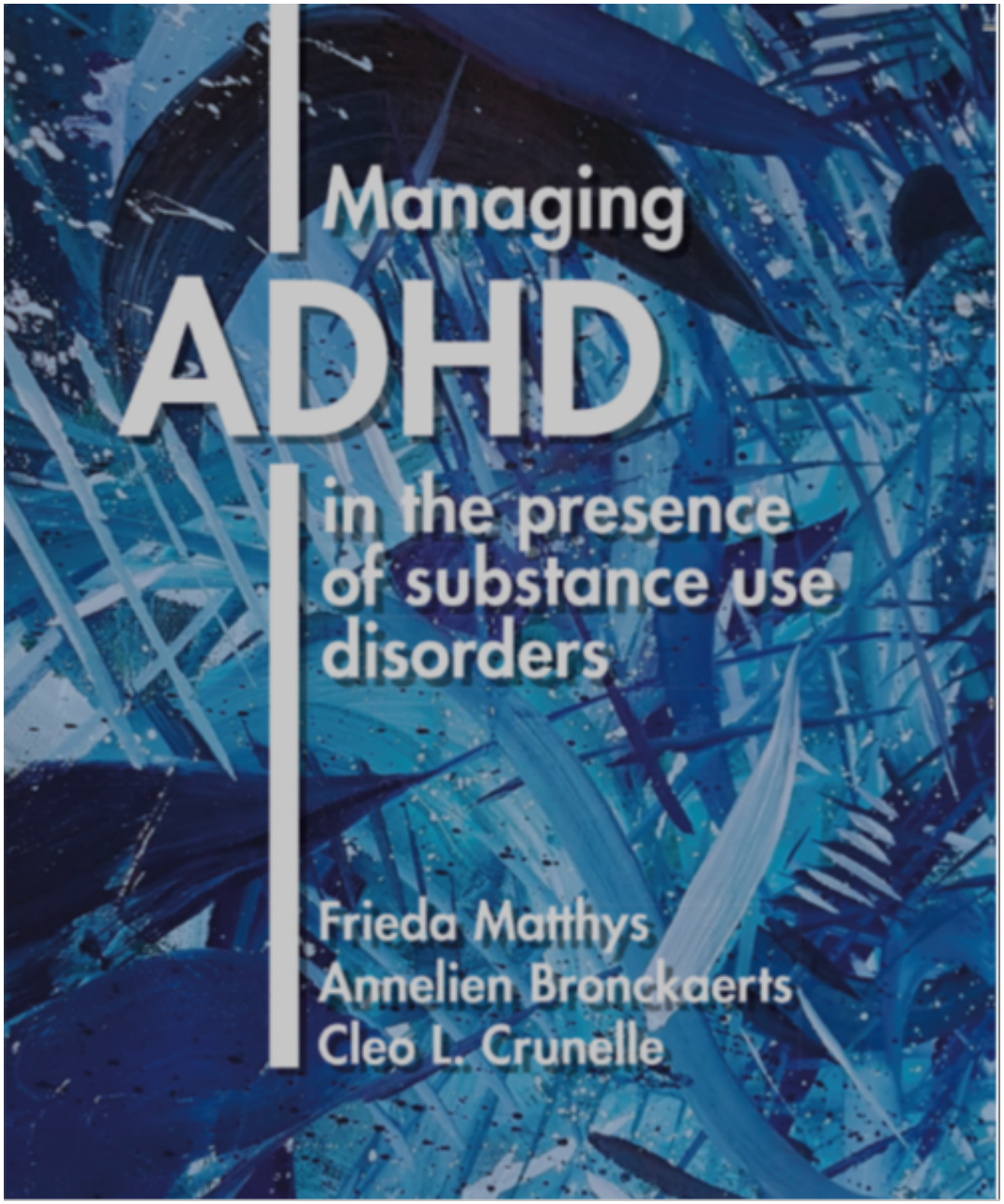
- Screen all SUD patients for ADHD
- ASRS, Wender Utah Rating Scale and Conners' Adult ADHD Rating Scale have been sufficiently validated as screeners.
- Diagnosis by a physician or psychologist trained in ADHD/SUD - questionnaires, semi-structured interviews, collateral history from family and school reports, longitudinal observation by staff to reduce the risk of over- or under-diagnosis.
- Anticipate other psychiatric comorbidities

ICASA - Guidelines

International Consensus Statement on Screening, Diagnosis and Treatment of SUD Patients with Comorbid ADHD

Crunelle, C and ICASA Consensus Group *Eur Addict Res 2018;24:43–51*

- Integrated multimodal therapies for ADHD and SUD
- Medication
  - Psychostimulants - long acting, +/- high doses, limited supply
    - Methylphenidate, Lisdexamfetamine
    - Atomoxetine - alcohol, delayed onset
  - Treat SUD - anticraving, ORT etc
  - Treat other comorbidities – eg antidepressants
- Psychotherapy
  - Integrated CBT



ICASA Textbook 2018

Table of Contents

- Guidelines ADHD/SUD
- Principles of treatment
- Modules
  - Psychoeducation
  - Planning/Organisation
  - Better Sense of Time
  - Reducing distractions
  - Managing SUD
  - Emotional Regulation
  - Negative Thoughts
  - Reducing Impulsivity
  - Social skills
  - Relapse Prevention
- Worksheets

ICASA - INCAS Study 2018-20

International Naturalistic Cohort Study of ADHD and Substance Use Disorders

- **First Step Addiction/Mental Health, St Kilda**
- **University of Melbourne, School of Population and Global Health**
- **AADPA - Australian ADHD Professionals Association**
- **ICASA - International Consortium on ADHD & Substance Abuse**
- **Karolinska Institute, Sweden**
- **12 sites in 9 Countries**

INCAS - Aims

To describe the treatments provided and the outcomes regarding ADHD symptoms and substance use in adult treatment seeking SUD patients with ADHD:

- to describe the treatment modalities provided to treatment seeking adult SUD patients with comorbid ADHD
- to describe differences in outcome for different treatment modalities (pharmacological psychological/psychosocial treatment)
- to identify predictors (such as gender, SUD and ADHD severity, comorbidity) for retention in treatment, ADHD symptoms, and substance use
- to investigate the safety profile of pharmacological treatment of ADHD in a naturalistic cohort of treatment seeking substance users with regard to adverse events (e.g. cardiovascular, psychiatric, misuse and diversion of medication)
- to derive hypotheses for future randomized trials

INCAS - Design

- This is a naturalistic multicentre observational cohort study in 600 treatment seeking adult DSM-5 SUD patients with DSM-5 adult ADHD.

- Information is collected at baseline (treatment initiation), at four weeks, at three months, and at nine months after inclusion.

- Participants will be enrolled until December 2019. Final data will be collected by September 2020

- Ethical approval will be obtained

- Participant consent will be obtained

INCAS - Research Subjects

- Patients will be consecutively recruited from the caseload of the participating addiction/psychiatric treatment centres.
- All patients with ADHD diagnosis starting a new treatment period at that particular treatment centre are asked to participate.
- A patient who is assessed for ADHD at the start of the treatment period will be invited to join the study after the diagnostic procedure.
- For all patients included in the study ADHD diagnosis is confirmed using a checklist for DSM-5 symptoms

Inclusion Criteria

- Men and women ≥18 years of age seeking treatment for SUD at any of the participating sites
- ADHD diagnosis according to DSM-5
- SUD diagnosis (DSM-5 moderate to severe, ICD-10 dependence)
- Informed consent

Exclusion Criteria

- There are no formal exclusion criteria except
- incapability to complete the assessment

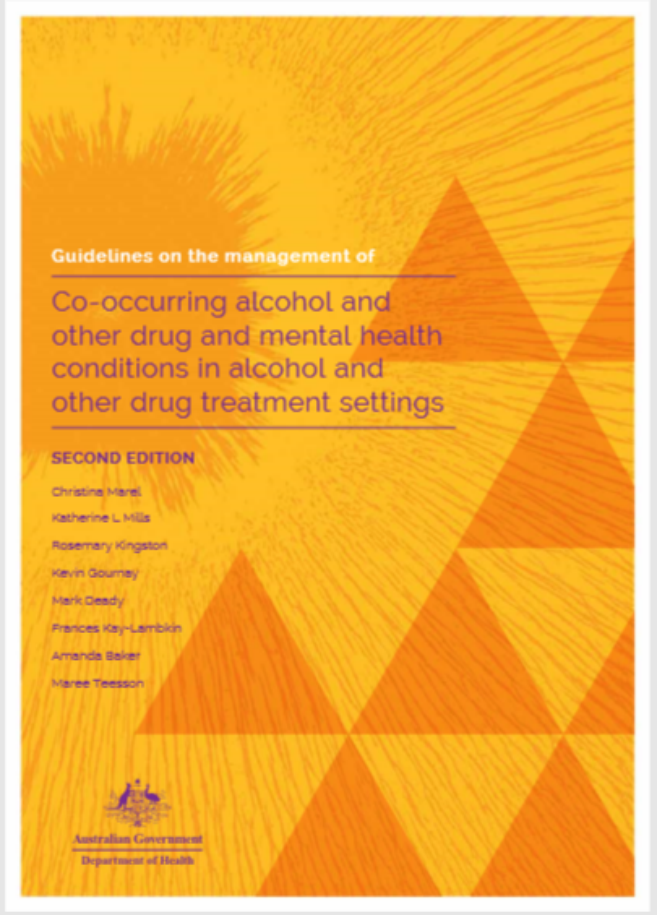
INCAS - Outcome Measures

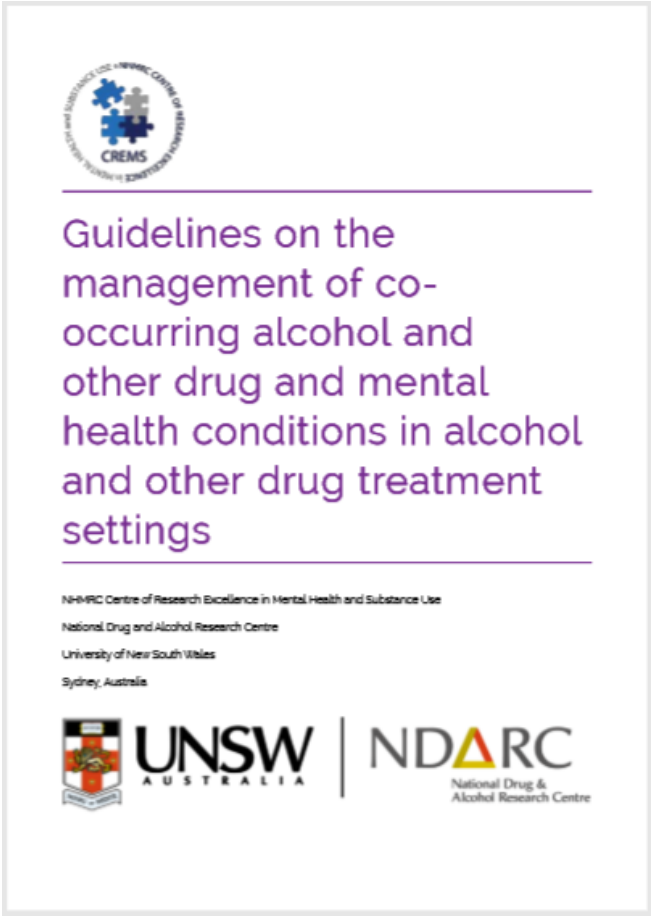
- ADHD symptoms measured with adult the Adult ADHD Self-Report Scale (ASRS) at 3 months follow-up.
- Substance use measured with Time Line Follow-Back (TLFB) (14) defined as number of days with heavy alcohol use or days of illicit drug use in the last 30 days at 3 months follow-up.

- ADHD symptoms measured with adult ASRS at 9 months follow-up
- Substance use measured with TLFB defined as number of days with heavy alcohol use or days of illicit drug use in the last 30 days at 9 months follow-up

- Retention to treatment- number of days to drop-out (last contact with service) after inclusion.
- ADHD symptoms according to the Adult ADHD Self-Report Scale extended version
- Employment
- Use of emergency services: data collected through public records reported by the participant
- Number of accidents as reported by the participant
- Days with any alcohol use during the last 30 days
- Australian Cohort – Linked Administrative Data

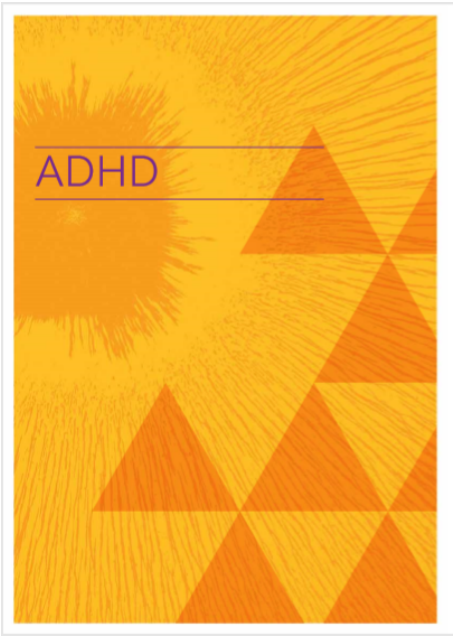
Australian Guidelines





https://comorbidity.edu.au/sites/default/files/National%20Comorbidity%20Guidelines%202nd%20edition.pdf

Integrated multimodal approach



- Psychoeducation
- Psychotherapy – individual, group
- Peer & Family Support
- Pharmacotherapy
  - Methylphenidate, Dexamphetamine, Lisdexamfetamine, Atomoxetine,
- e-health interventions, smartphone Apps
- physical activity
- complementary and alternative therapies (e.g., dietary supplements).

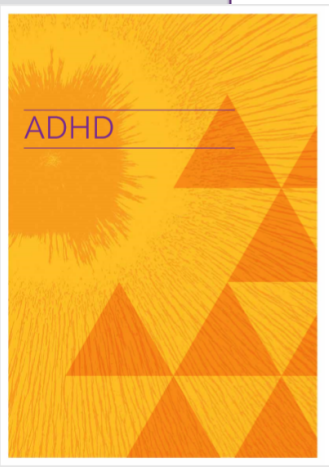
Table 30: Dos and don'ts of managing a client with symptoms of ADHD

Do:

- ✓ Assist the client plan activities and organise prompts or reminders (e.g., using a smartphone).
- ✓ Encourage stress-reduction methods, such as progressive muscle relaxation.
- ✓ Encourage physical exercise.
- ✓ Monitor closely during times of stress – these may lead to fluctuations in symptoms and may necessitate the adjustment of medication.
- ✓ Involve family members and friends – educating them about the condition and treatment will provide long-term benefits.
- ✓ Offer to help the client engage with education courses or training, which can assist with attention training.

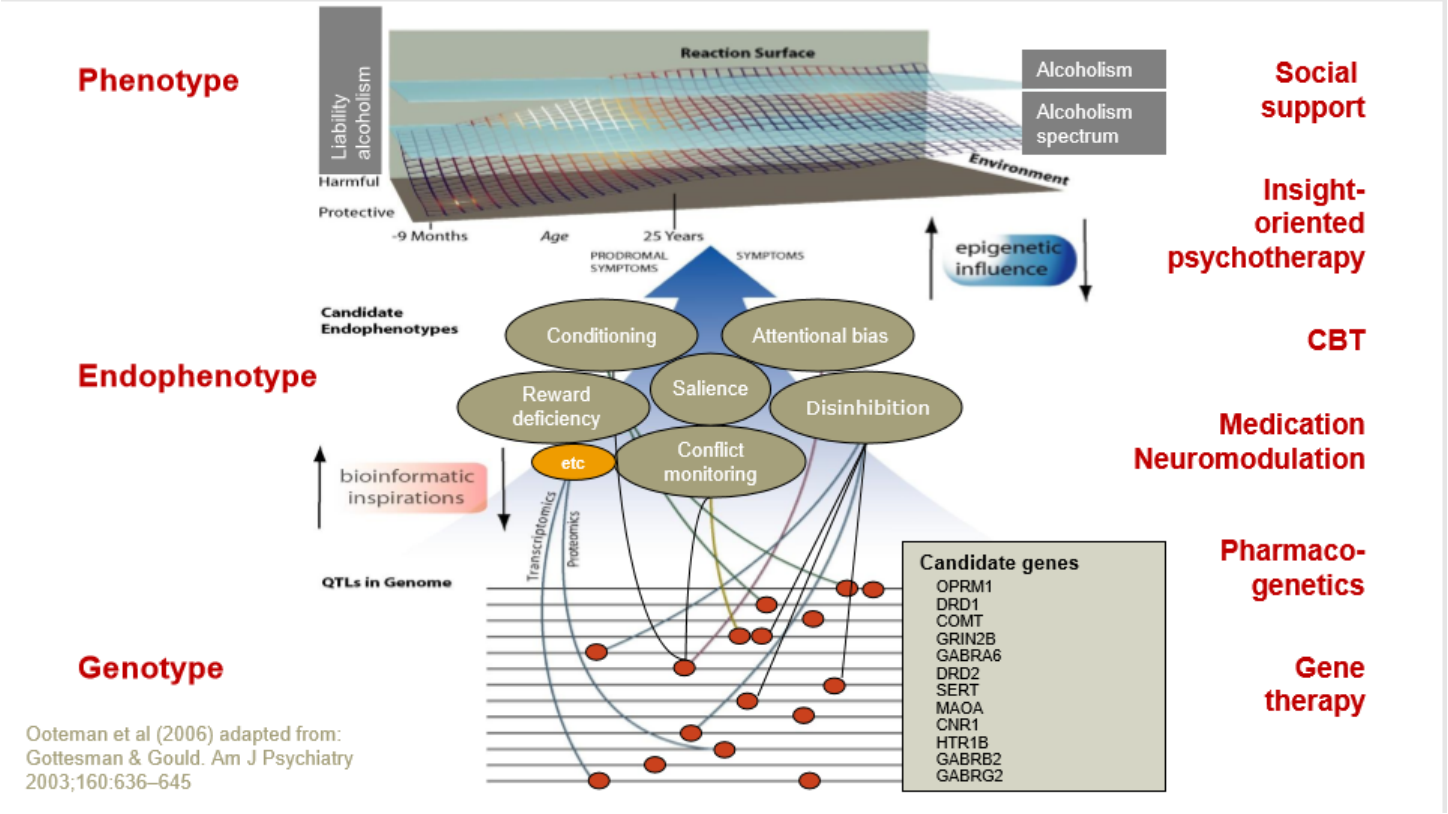
Don't:

- x Get visibly upset or angry with the client.
- x Confuse the client by conducting unstructured, unfocused sessions.



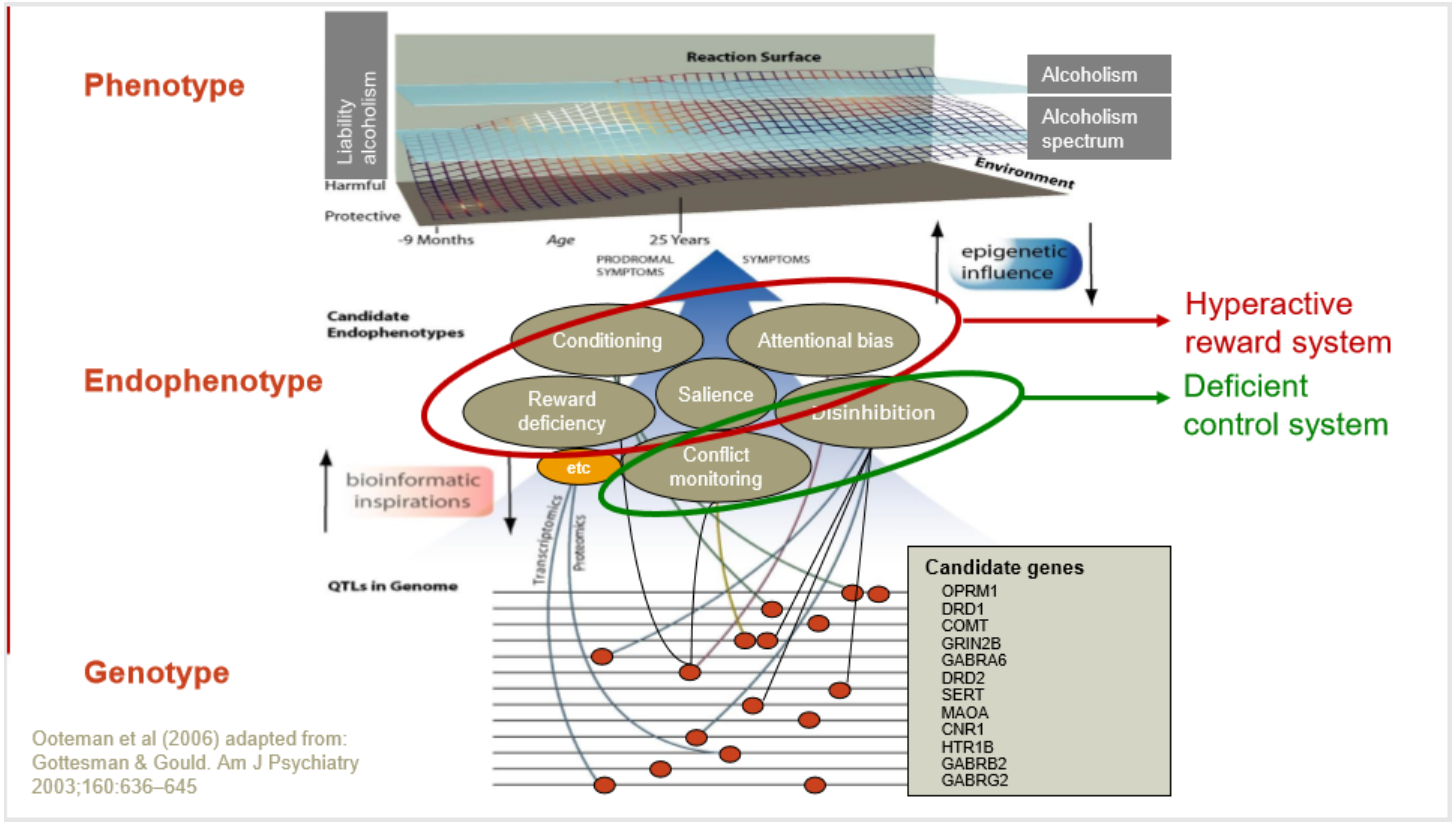
Adapted from Gournay [488] and Zulauf [477].

Model of where to intervene in AUD and overlap with ADHD - 1 (Wim van der Brink)



Ooteman et al (2006) adapted from: Gottesman & Gould. Am J Psychiatry 2003;160:636–645

Model of where to intervene in AUD and overlap with ADHD -2 (Wim van der Brink)



Ooteman et al (2006) adapted from:
Gottesman & Gould. Am J Psychiatry 2003;160:636–645

And there's more

- Diet
- Microbiota
- Gut defences
- Oxidative stress/inflammation
- Micronutrients
- Gliopathy/Neuroimmunopharmacology

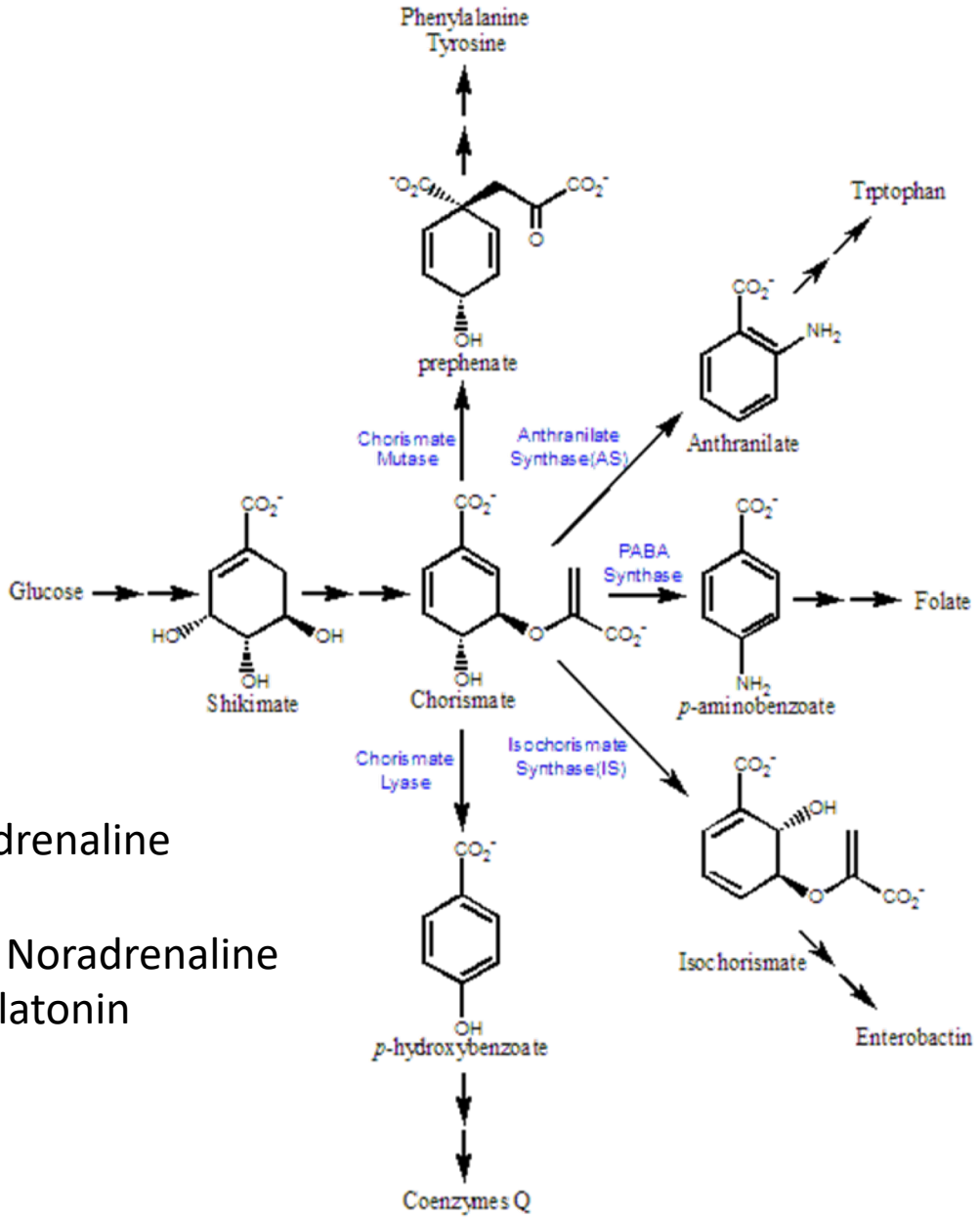
Gut Bacteria
Microbiota = live critters
Microbiome = DNA

E coli

(80% of gut aerobes)

Produces:

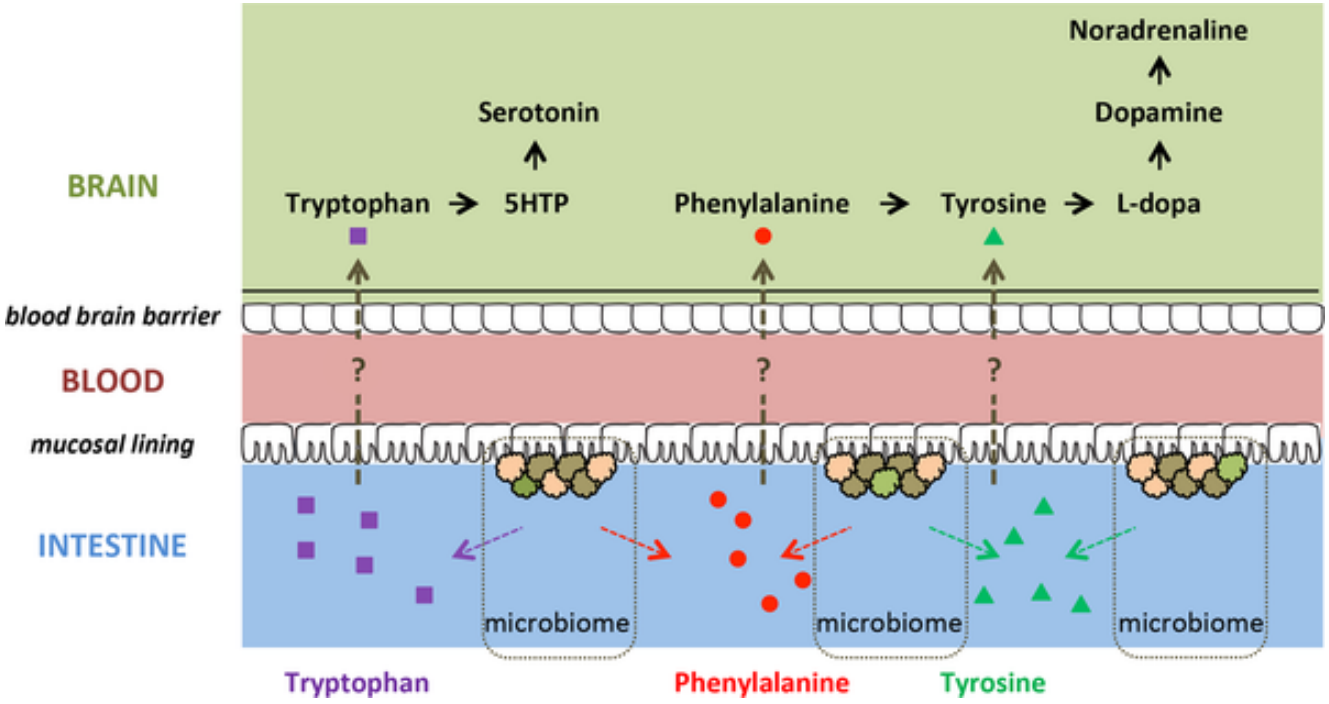
- GABA
- CHORISMATE
  - Tyrosine => Dopamine => Noradrenaline
  - Tyrosine =>Thyroxine
  - Phenylalanine => Dopamine => Noradrenaline
  - Tryptophan => Serotonin=> Melatonin
  - Folate => methyl
  - Vit K2 (menaquinone)
  - CoQ10 (ubiquinone) for ATP



Gut microbiome in ADHD and its relation to neural reward anticipation

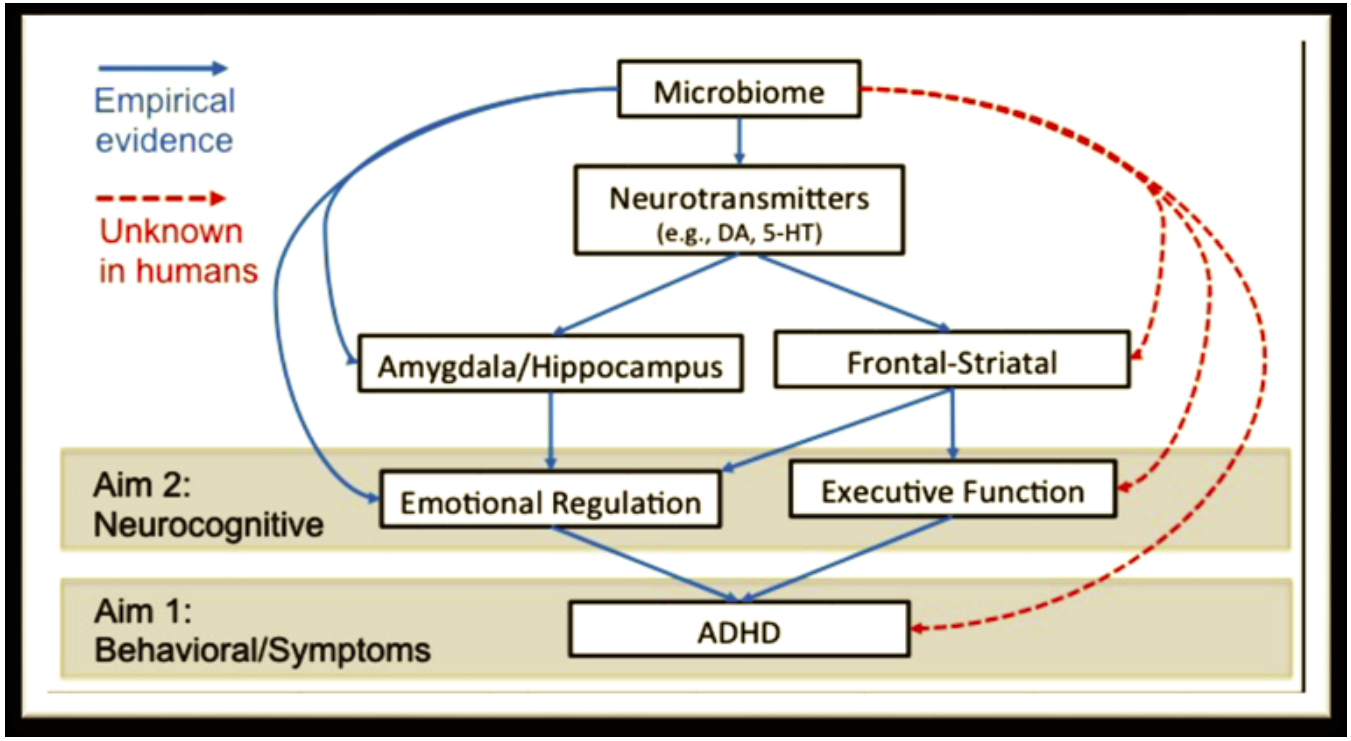
1. ADHD patients => more *Bifidobacterium* => more Phenylalanine producing enzymes => => more Dopamine
2. AND decreased ventral striatal fMRI responses during reward anticipation

Hypothesis: Gut Bacteria influence ADHD symptoms



Aarts E, Ederveen THA, Naaijen J, Zwiers MP, Boekhorst J, et al. (2017) Gut microbiome in ADHD and its relation to neural reward anticipation. PLOS ONE 12(9): e0183509. https://doi.org/10.1371/journal.pone.0183509
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0183509

Early days in research into Microbiota/Microbiome, ADHD and SUD



Akram, Hassan, "Characterizing A Link Between Gut Microbiome and Attention Deficit Hyperactive Disorder" (2017). *Honors College Research Collection*. 4. http://digitalcommons.fiu.edu/honors-research/4

Alterations of the Host Microbiome Affect Behavioral Responses to Cocaine.
Kiraly, D. D. *et al*. *Sci. Rep.* **6**, 35455; doi: 10.1038/srep35455 (2016).

Mice + Antibiotics => substantial reduction of gut bacteria and more addiction.

- enhanced sensitivity to cocaine reward
- Enhanced sensitivity to the locomotor-sensitizing effects of repeated cocaine administration.
- Changed synaptic proteins in the brain's reward circuitry
- Dysregulated brain-derived neurotrophic factor (BDNF)
- Changed monoamine metabolism

Targeting the ecology within: The role of the gut–brain axis and human microbiota in drug addiction Patrick D.Skosnik et al **Medical Hypotheses** Volume 93, August 2016, Pages 77-80

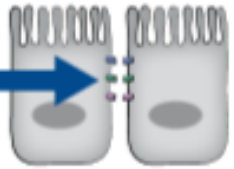
"No systematic programs of research have examined the role of microbiota in drug addiction

Leaky gut, leaky brain: the role of zonulin

Medicine

The discovery of **ZONULIN** began with a failed attempt to develop a cholera vaccine[1]

ZONULIN is a protein that can **OPEN TIGHT JUNCTION PROTEINS**[2]



GLIADIN & INTESTINAL BACTERIA are the main triggers for **ZONULIN RELEASE**[2]

ZONULIN has been identified as a biomarker for many conditions including:

COELIAC DISEASE, INFLAMMATORY BOWEL DISEASE, TYPE 1 DIABETES, ASTHMA, MULTIPLE SCLEROSIS, SCHIZOPHRENIA AND CANCER[2,3]

ZONULIN AND THE LEAKY BRAIN HYPOTHESIS[2-14]

1 ZONULIN RELEASE

- Release of zonulin triggered by endothelial cells exposure to gliadin and pathogenic bacteria.
- Zonulin stimulates opening of TJs.
- Increase in intestinal permeability.
- Increased passage of stressors into lamina propria.

L. RHAMNOSUS (LGG) increases TJ protein gene expression, inhibits zonulin release and restores intestinal permeability.[3]

L. PLANTARUM, L. ACIDOPHILUS and *B. LONGUM* increase TJ protein gene expression, inhibits zonulin release and restores intestinal permeability.[3]

ZINC enhances TJ barrier function.[15]

PROBIOTICS may competitively inhibit pathogenic bacteria from stimulating zonulin release.

2 IMMUNE RESPONSE DEVELOPMENT OF LEAKY GUT

- Increased exposure to stressors triggers immune response and inflammation.
- A vicious cycle develops where inflammation and tissue damage further increase intestinal permeability, leading to even greater passage of stressors therefore perpetuating the cycle.
- Altered immune responses and increased inflammation in the gut also interact with HPA axis and neurotransmitter metabolism.

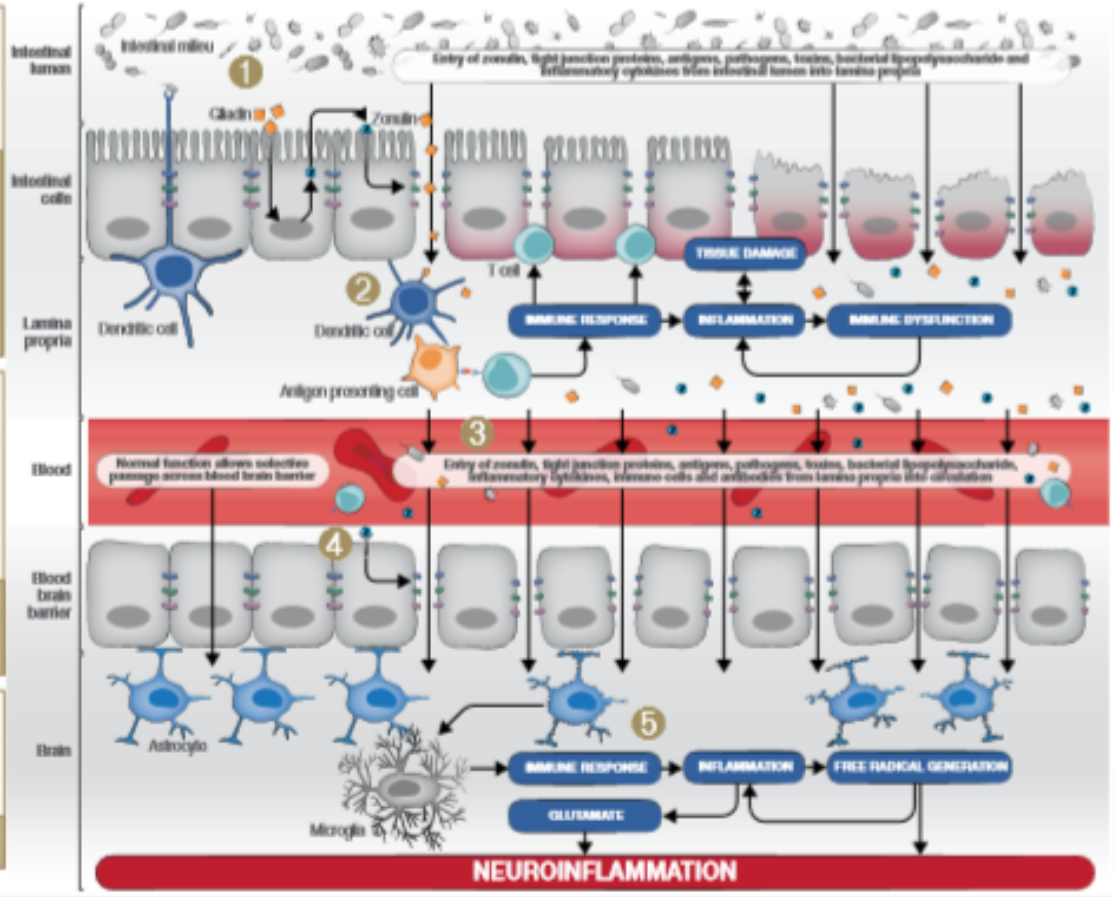
PROBIOTICS modulate immune response and down-regulate inflammation, thereby promoting healthy gut barrier function.[3]

ZINC supports healthy immune function and aids healing.[15]

3 STRESSORS ENTER CIRCULATION

- Stressors, including zonulin, TJ proteins, antigens, pathogens, toxins, bacterial lipopolysaccharide, inflammatory cytokines and antibodies enter into circulation.

PROBIOTICS reduce systemic inflammatory cytokines and lipopolysaccharide burden.[17]



4 BLOOD BRAIN BARRIER DYSFUNCTION — LEAKY BRAIN

- The BBB includes endothelial cells and TJs.
- Astrocytes located beneath endothelial cells prevent entry of unwanted molecules across the BBB.
- Zonulin from the blood binds to zonulin receptors on the BBB.
- Zonulin stimulates opening of TJs.
- Similar to what happens in leaky gut, stressors, including zonulin, TJ proteins, antigens, pathogens, toxins, bacterial lipopolysaccharide, inflammatory cytokines and antibodies are allowed passage into the brain.

Gut microbiota may regulate BBB via modulation of TJ protein expression and production of short chain fatty acids.[18] PROBIOTICS may be beneficial.

ZINC enhances TJ barrier function.[15]

5 IMMUNE RESPONSE NEUROINFLAMMATION

- Increased passage of unwanted molecules causes damage to astrocytes.
- Immune response is stimulated by microglia.
- A vicious cycle of increased passage of stressors and inflammation develops, leading to neuroinflammation.
- Neuroinflammation can also impact on brain communication with the gut and HPA axis.
- Chronic neuroinflammation has been associated with various conditions including mood disorders, Alzheimer's disease, autism spectrum disorders, dementia, schizophrenia, cognitive decline and mental fatigue.

Short chain fatty acids may reverse detrimental effects on brain cells.[18] PREBIOTICS may be beneficial.

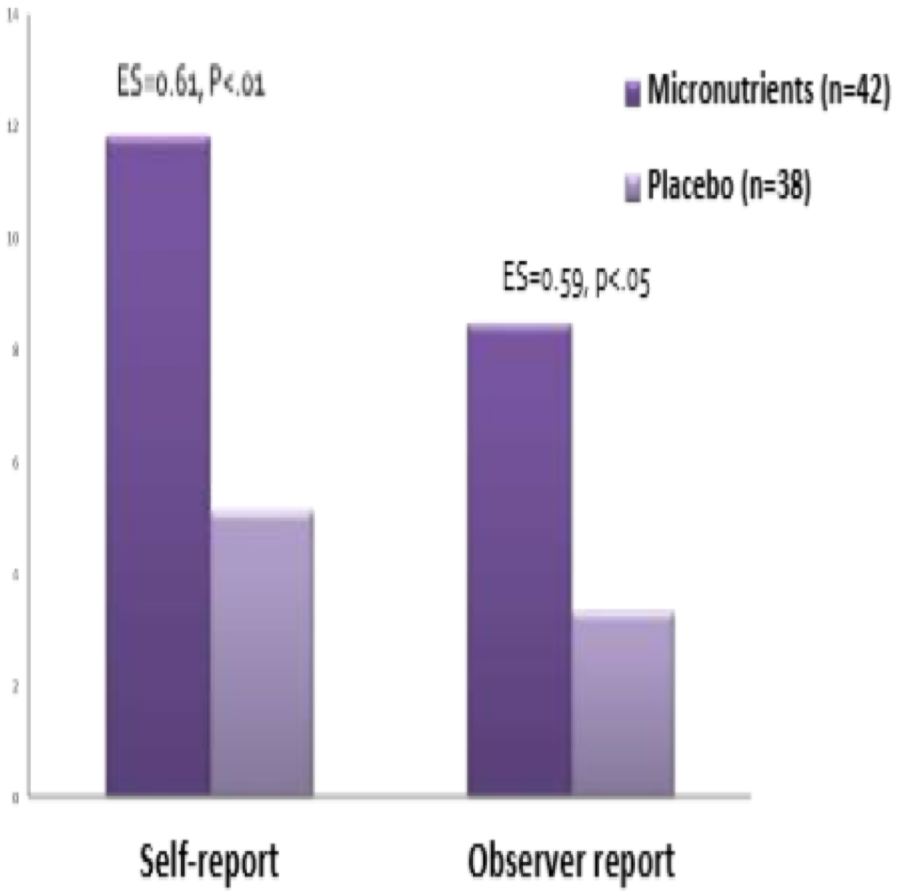
Micronutrients

Could some cases of psychiatric illness reflect inborn errors of metabolism?

- People inherit a *genetic defect* that results in decreased binding ability of an enzyme(s)
- results in slowed metabolic reactions
- Less efficiency in making chemicals for optimal functioning
  - resulting in psychiatric symptoms
- Can be corrected at endpoint by:
  - administration of high doses of the micronutrient component of corresponding coenzyme, restoring enzymatic activity

Reduction in ADHD symptoms using micronutrients

Rucklidge et al., 2014, *Br J Psychiatry*



Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial, Rucklidge et al, Br J Psychiatry, 2014

- **Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial,** *Rucklidge et al, Br J Psychiatry, 2014*
- ***"Specifically, participants taking the micronutrient formula reported greater improvement in both inattention and hyperactivity/impulsivity compared with those taking a placebo."***

- **Use of micronutrients attenuates cannabis and nicotine abuse as evidenced from a reversal design: A case study.** Harrison, R., Rucklidge, J. J., & Blampied, N. (2013). *Journal of Psychoactive Drugs, 45(2), 1-11.*

- ***Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial***
  The British Journal of Psychiatry, Published online ahead of print January 30, 2014, doi: 10.1192/bjp.bp.113.132126
  Full TextSummary***"Specifically, participants taking the micronutrient formula reported greater improvement in both inattention and hyperactivity/impulsivity compared with those taking a placebo."***

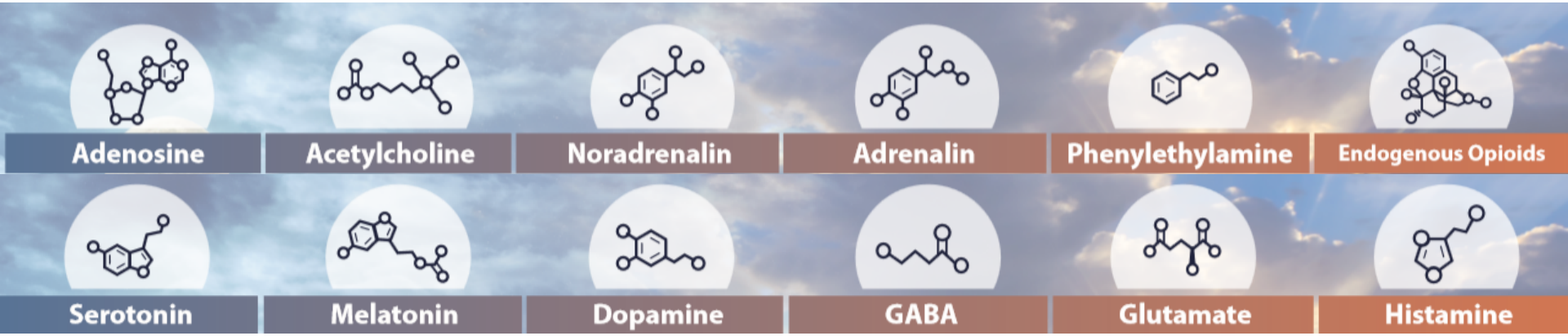
- **BACKGROUND**
  The role of nutrition in the treatment of attention-deficit hyperactivity disorder (ADHD) is gaining international attention; however, treatments have generally focused only on diet restriction or supplementing with one nutrient at a time.

- **AIMS**
  To investigate the efficacy and safety of a broad-based micronutrient formula consisting mainly of vitamins and minerals, without omega fatty acids, in the treatment of ADHD in adults.

- **METHODS**
  This double-blind randomised controlled trial assigned 80 adults with ADHD in a 1:1 ratio to either micronutrients (n = 42) or placebo (n = 38) for 8 weeks (trial registered with the Australian New Zealand Clinical Trials Registry: ACTRN12609000308291).

- **RESULTS**
  Intent-to-treat analyses showed significant between-group differences favouring active treatment on self- and observer- but not clinician-ADHD rating scales. However, clinicians rated those receiving micronutrients as more improved than those on placebo both globally and on ADHD symptoms. Post hoc analyses showed that for those with moderate/severe depression at baseline, there was a greater change in mood favouring active treatment over placebo. There were no group differences in adverse events.

- **CONCLUSIONS**
  This study provides preliminary evidence of efficacy for micronutrients in the treatment of ADHD symptoms in adults, with a reassuring safety profile.


Adenosine
Acetylcholine
Noradrenalin
Adrenalin
Phenylethylamine
Endogenous Opioids
Serotonin
Melatonin
Dopamine
GABA
Glutamate
Histamine

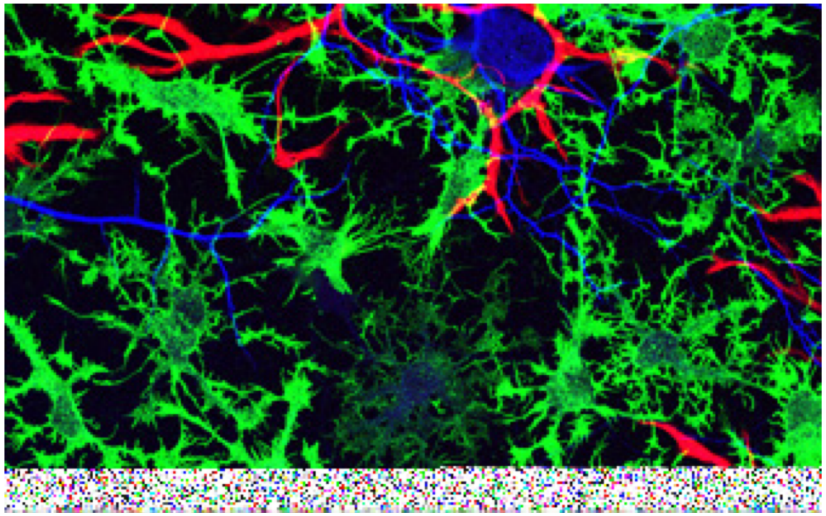
Prof Jon Currie's slides on

Neuroinflammation and Addiction

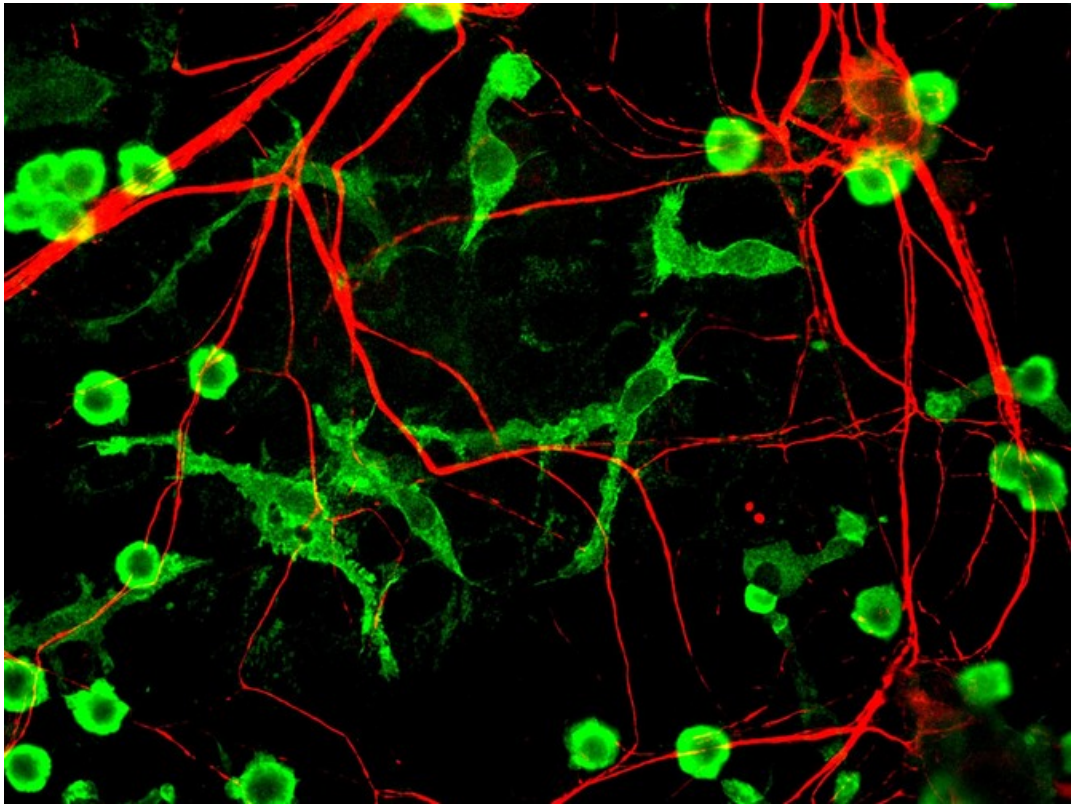
From

VAADHDIG meeting on ADHD/SUD Sept 2017

THE “OTHER” BRAIN



GLIAL CELLS



Review: The neuropathology of drug abuse

A. Büttner

Neuropathology and Applied Neurobiology (2011), **37**, 118–134

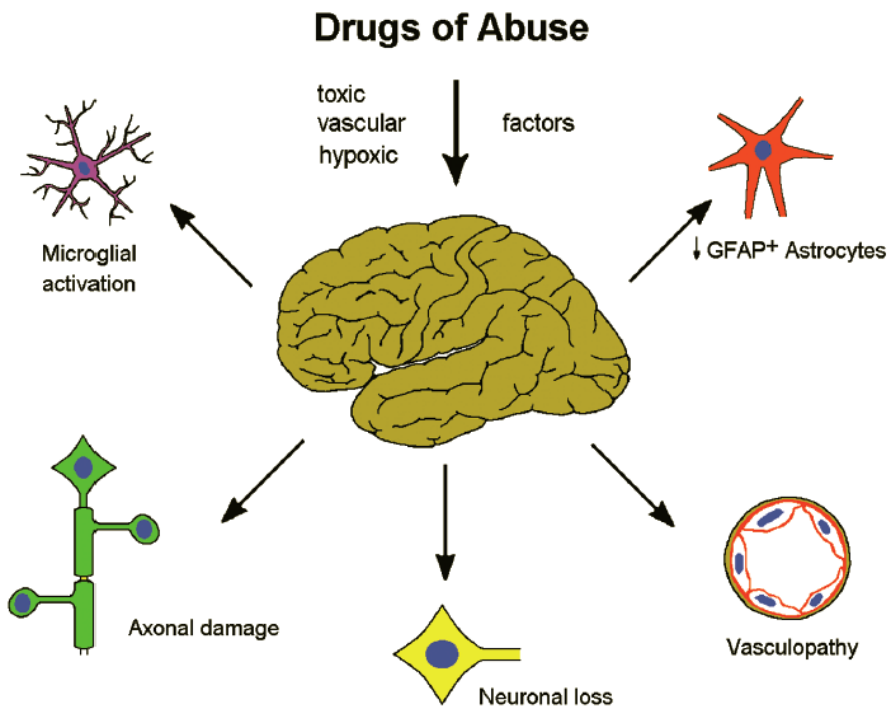


Figure 3. The consequences of drugs of abuse on the cellular elements of the CNS.

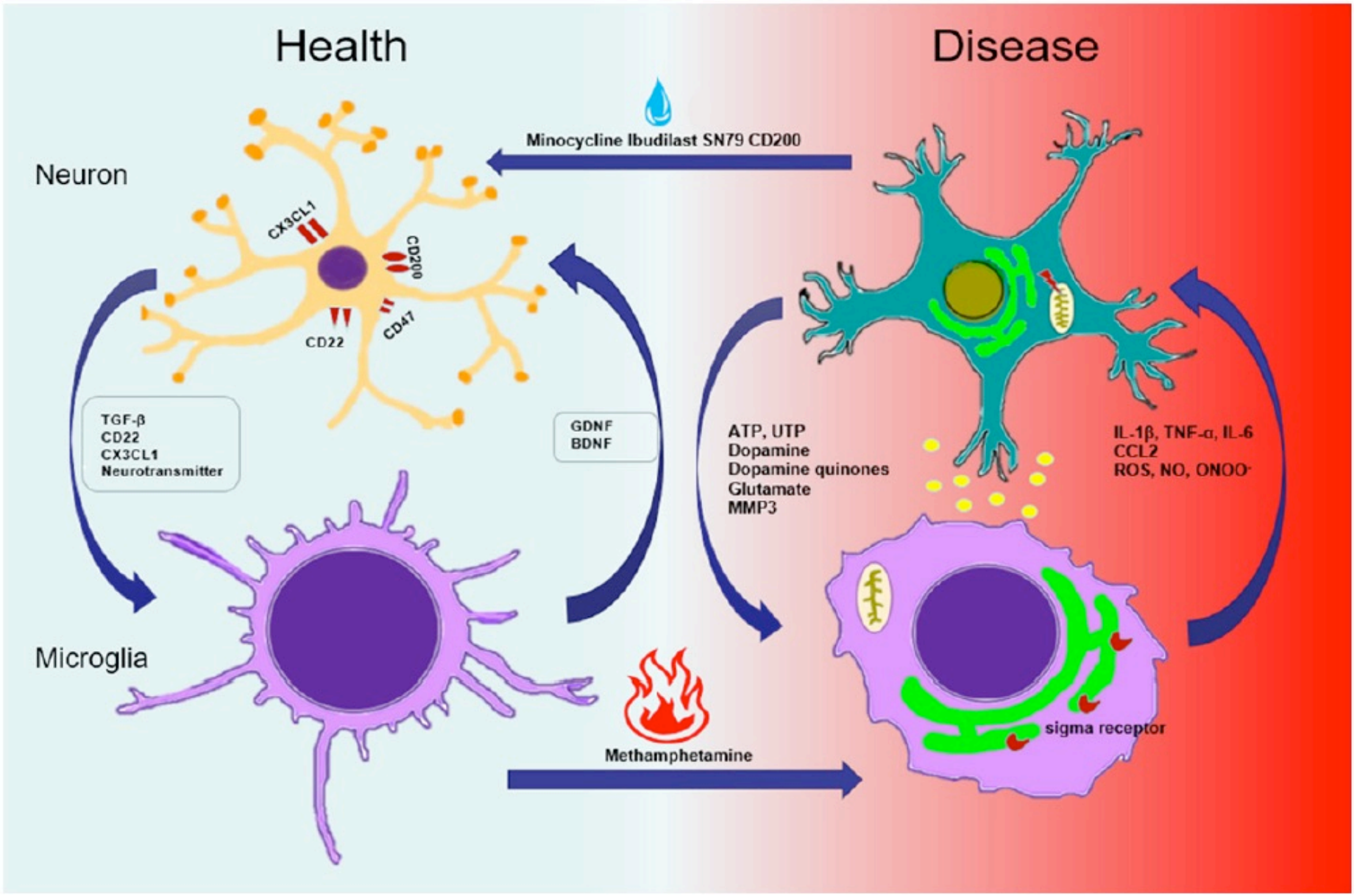
Why is Neuroimmunopharmacology crucial for the future of addiction research?

Dr Mark R Hutchinson and
Discipline of Physiology, School of Medic *Neuropharmacology*. 2014 January ; elaide, South Australia, Australia, 5005

Prof Linda R Watkins
Department of Psychology & Neuroscience, University of Colorado at Boulder, Boulder, Colorado, USA 80309

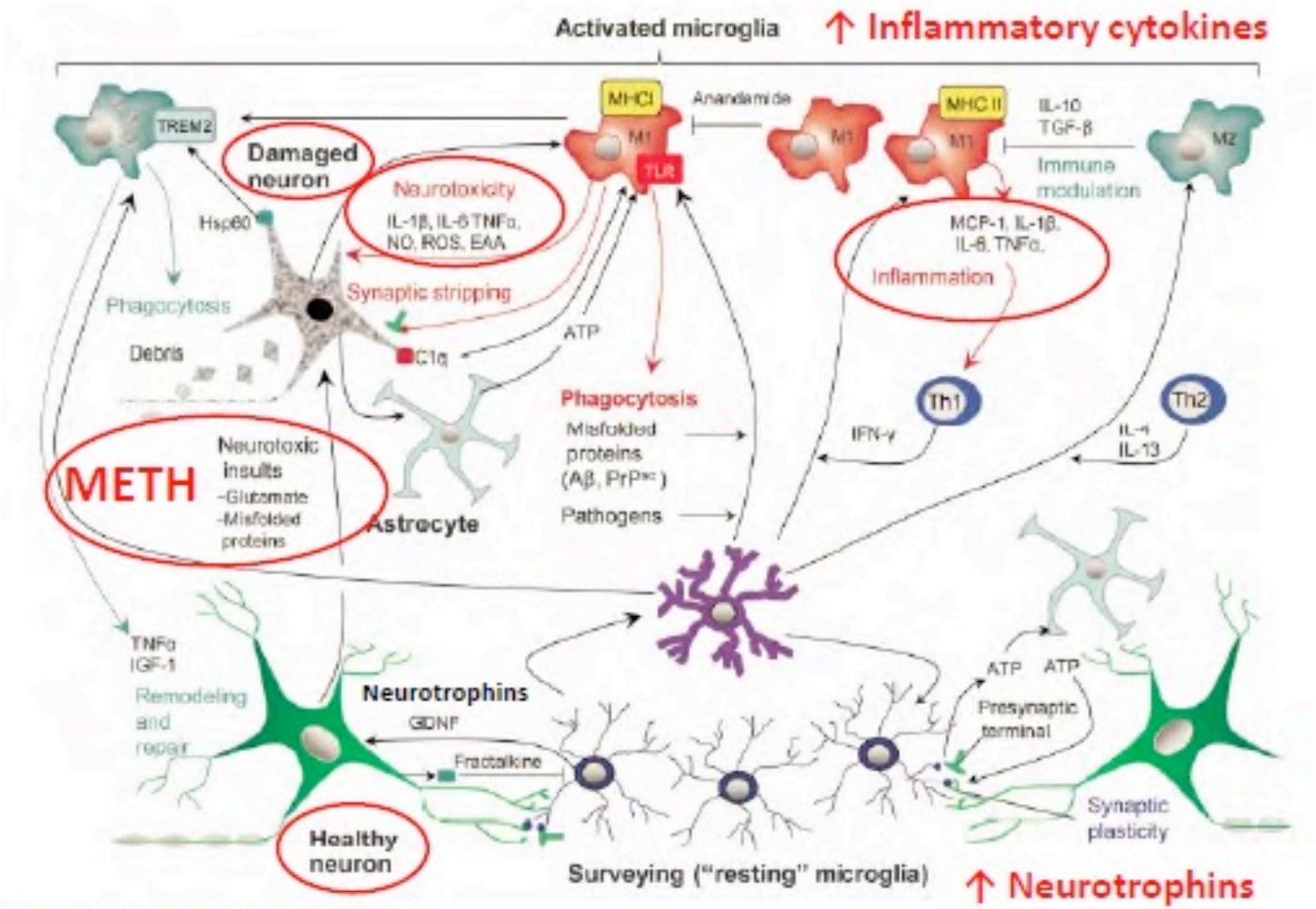
Highlights

- Central immune signaling contributes significantly to reward created by multiple drugs of abuse.
- Toll-like receptor 4 is capable of triggering proinflammatory reward facilitating signals that are necessary for reward behaviors.
- Pharmacological interventions targeting central immune signaling may prove to be crucial in future drug addiction interventions.



Int J Physiol Pathophysiol Pharmacol 2017;9(3):84-100

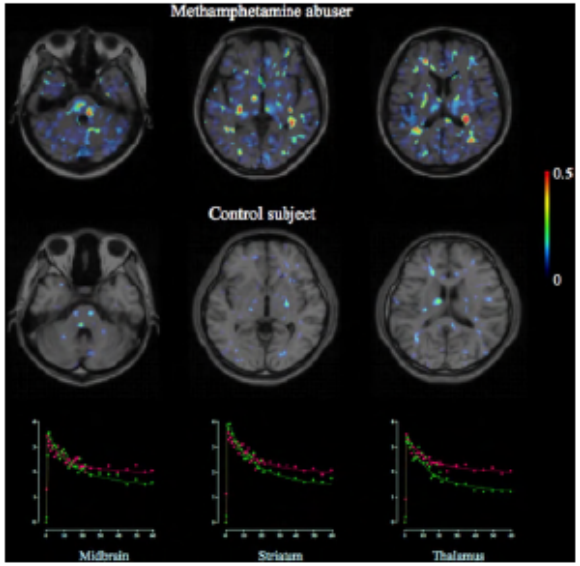
Resting Microglia = **Neuroprotective**
Activated Microglia = **Neurotoxic**



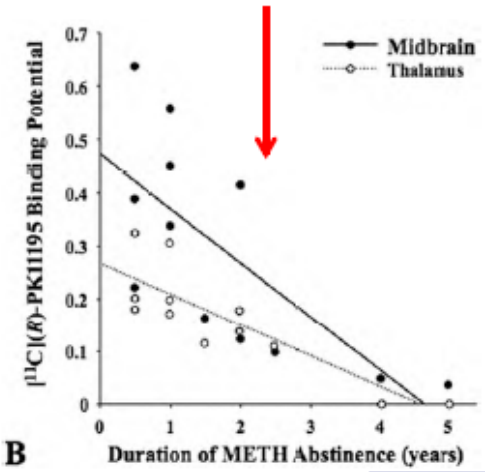
Benarroch EE. Neurology. 2013 Sep 17;81(12):1079-88.

Meth is toxic to the brain triggering glial activation and neuroinflammation

Activated microglia in meth users



Neuroinflammation persists despite years of abstinence and may trigger relapse

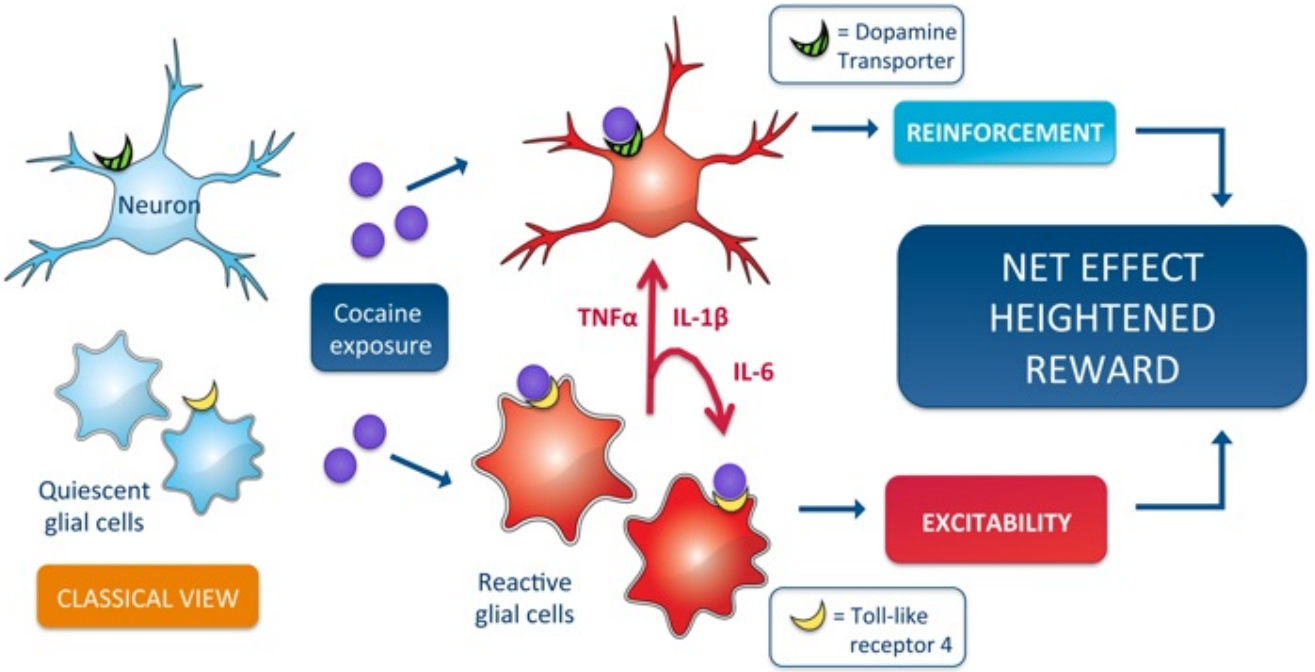


Sekine Y. J Neurosci. 2008 May 28;28(22):5756-61.

cbam
center for behavioral & addiction medicine

ROLE OF NEUROINFLAMMATORY MEDIATORS IN DRUG RELAPSE

Potential Contributions of Cocaine-induced Microglial Activation on the Dopamine System



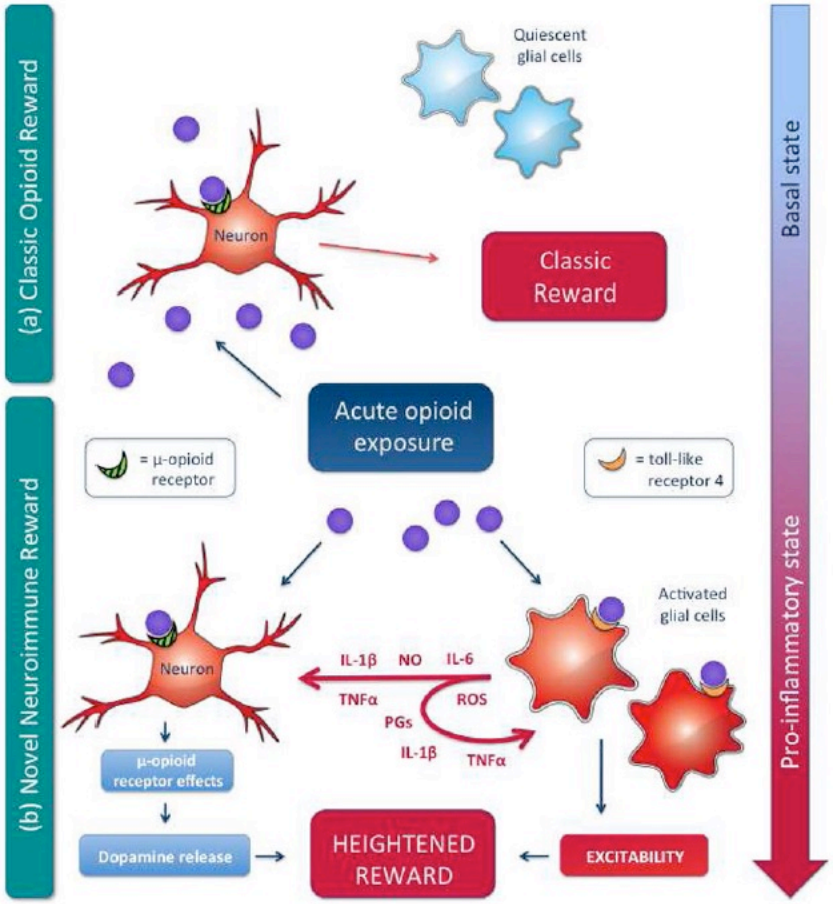


Figure 1. Hypothesized central immune signaling contributions to opioid reward

ADDICTION AS A GLIOPATHY

Adv Pharmacol. 2014 ; 69: 1–69. doi:10.1016/B978-0-12-420118-7.00001-9.

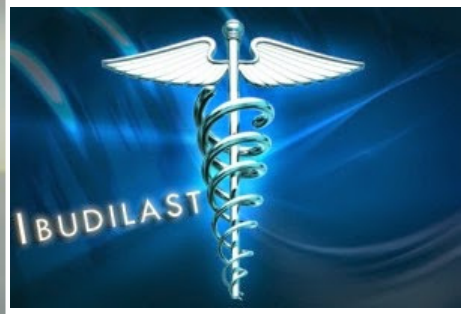
Glial Modulators as Potential Treatments of Psychostimulant Abuse

Patrick M. Beardsley[1] and **Kurt F. Hauser**


400 mg
PeaPure®
400 mg


PHARMACY MEDICINE
Robitussin®
DRY COUGH FORTE


56 Tablets
Ebixa® 10 mg
Tablets
Memantine hydrochloride


IBUDILAST


VIRTUS
NDC 76439-101-10
CEPHALEXIN
CAPSULES, USP
250 mg
Rx only
100 Capsules

Promise of rTMS in SUD and ADHD?

Neuroscience and Biobehavioral Reviews 37 (2013) 2472–2480

Contents lists available at ScienceDirect

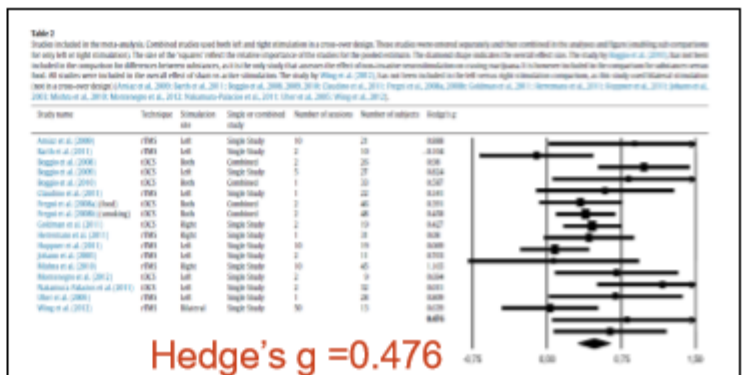
Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Effects of non-invasive neurostimulation on craving: A meta-analysis

Jochem M. Jansen[a,b,*], Joost G. Daams[c], Maarten W.J. Koeter[a], Dick J. Veltman[a,d], Wim van den Brink[a,b], Anna E. Goudriaan[a,b,e]



Psychiatria Danubina, 2013; Vol. 25, Suppl. 2, pp 366–367
© Medicinska naklada - Zagreb, Croatia

Conference paper

ADULT-ADHD AND POTENTIAL ROLE OF TRANSCRANIAL MAGNETIC STIMULATION (TMS & RTMS) INVESTIGATION AND TREATMENT

Rashid Zaman

South Essex Partnership University Foundation Trust, Department of Psychiatry University of Cambridge, Cambridge, UK

So far only 2 small studies have been reported where rTMS has been used for therapeutic purpose in ADHD.

Summary

- A strange set of circumstances leading to INCAS
- ADHD/SUD is well-known to be common
- Why no Treatment Programs?
- ICASA
- Prevalence Research
- ICASA Guidelines and Textbook
- New Treatment Study - INCAS
- Australian Guidelines
- Genes, Microbiota, Gut, Inflammation, Micronutrients


Do not go where the path may lead.
Go instead where there is no path
and leave a trail...
-Emerson

The human gut microbiome impacts human brain health in numerous ways: (1) Structural bacterial components such as lipopolysaccharides provide low-grade tonic stimulation of the innate immune system. Excessive stimulation due to bacterial dysbiosis, small intestinal bacterial overgrowth, or increased intestinal permeability may produce systemic and/or central nervous system inflammation. (2) Bacterial proteins may cross-react with human antigens to stimulate dysfunctional responses of the adaptive immune system. (3) Bacterial enzymes may produce neurotoxic metabolites such as D-lactic acid and ammonia. Even beneficial metabolites such as short-chain fatty acids may exert neurotoxicity. (4) Gut microbes can produce hormones and neurotransmitters that are identical to those produced by humans. Bacterial receptors for these hormones influence microbial growth and virulence. (5) Gut bacteria directly stimulate afferent neurons of the enteric nervous system to send signals to the brain via the vagus nerve. Through these varied mechanisms, gut microbes shape the architecture of sleep and stress reactivity of the hypothalamic-pituitary-adrenal axis. They influence memory, mood, and cognition and are clinically and therapeutically relevant to a range of disorders, including alcoholism, chronic fatigue syndrome, fibromyalgia, and restless legs syndrome. Their role in multiple sclerosis and the neurologic manifestations of celiac disease is being studied. Nutritional tools for altering the gut microbiome therapeutically include changes in diet, probiotics, and prebiotics.

Journal of Medicinal FoodVol. 17, No. 12 Review

The Gut Microbiome and the Brain

•Leo Galland
Leo Galland
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Published Online:5 Dec 2014https://doi.org/10.1089/jmf.2014.7000

The gut microbiota of rats voluntarily consuming a 20 percent ethanol solution, on alternate days, were compared with a non-exposed control group to identify differential taxonomic and functional profiles. Gut microbial diversity profiles were determined using culture-independent amplification, next-generation sequencing and bioinformatic analysis of bacterial 16S ribosomal RNA gene sequence libraries. Our results showed that, compared with controls, ethanol-consuming rats experienced a significant decline in the biodiversity of their gut microbiomes, a state generally associated with dysbiosis. We also observed significant shifts in the overall diversity of the gut microbial communities and a dramatic change in the relative abundance of particular microbes, such as the *Lactobacilli*. We also compared our results to human fecal microbiome data collected as part of the citizen science American Gut Project. In contrast to the rat data, human drinkers had significantly higher gut microbial biodiversity than non-drinkers. However, we also observed that microbes that differed among the human subjects displayed similar trends in the rat model, including bacteria implicated in metabolic disease.

Effects of moderate, voluntary ethanol consumption on the rat and human gut **microbiome**
KL Kosnicki, Addiction Biology , First published: 11 May 2018
https://doi.org/10.1111/adb.12626

The Emerging Field of Nutritional Mental Health Inflammation, the Microbiome, Oxidative Stress, and Mitochondrial Function

Clinical Psychological science We live in a transformational moment for understanding the etiology of mental disorders. The previous leap in understanding occurred 60 years ago, which led us to incorporate psychopharmacology into our curricula to address the chemical basis of neurotransmitter function, especially as explained through the then-popular catecholamine hypothesis. The current revolution is broader, consisting of the rapidly accumulating knowledge of how inflammation, microbiome imbalance (gut dysbiosis), oxidative stress, and impaired mitochondrial output affect brain function. Suitable interventions for fighting inflammation, restoring normal gut function, reducing oxidative stress, and improving mitochondrial metabolism incorporate lifestyle variables, including nutrients and probiotics. Volume: 3 issue: 6, page(s): 964-980
Article first published online: February 2, 2015; **Issue published:** November 1, 2015
https://doi.org/10.1177/2167702614555413