

THE FINNISH FOUNDATION  
FOR ALCOHOL STUDIES

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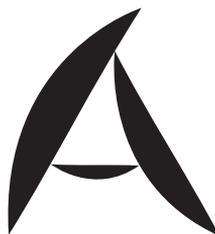
REPORT ON ACTIVITIES

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2014

# THE FINNISH FOUNDATION FOR ALCOHOL STUDIES

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## REPORT ON ACTIVITIES

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2014

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## **THE FINNISH FOUNDATION FOR ALCOHOL STUDIES**

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## GENERAL OVERVIEW

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In 2014, the projects funded by the Finnish Foundation for Alcohol Studies resulted in the publication of six academic doctoral dissertations, 17 original peer-reviewed articles in international and four original peer-reviewed articles in national scientific journals. Five other papers were published.

Alcohol and drug research received 311.073 euro in support for projects. In addition, 251.626 euro was granted to projects on gambling. Ongoing contract projects will be described below under the title *Research activities*.

The Foundation kept its office at the National Institute for Health and Welfare (THL) in Helsinki.

## ADMINISTRATION

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The Board of the Foundation was composed of following members: four appointed by the Ministry of Social Affairs and Health, four appointed by the Federation of Finnish Scientific Societies, and one appointed by the Finnish Alcohol Retail Monopoly. The majority of the Board must consist of academically established scientists with special expertise in alcohol research. The Executive Committee was composed of four members of the Board and three external experts. The Gambling Research Committee was appointed by the Board and consisted of one Board member, the Research Director and seven external experts.

The Foundation's Research Director *Tomi Lintonen* is the only full-time staff member. A contract between the Foundation and the National Institute for Health and Welfare (THL) provided administrative and technical support for the Foundation.

## RESEARCH ACTIVITIES

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### PHD DISSERTATIONS SUPPORTED BY THE FOUNDATION

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*Michael Egerer: Institutional footprints in the addiction image: A focus-group study with Finnish and French general practitioners and social workers.*

The concept of addiction is increasingly applied in order to understand various problematic behaviours. However, this inclusion remains disputed. The study examines the conceptualisation of addictions by analysing stimulated group discussions of general practitioners and social workers in Finland and France on the topics of alcoholism, pathological gambling and eating disorders. The dissertation consists of one methodological working-paper (I), three empirical sub-studies (II, III, and IV) and a summary article. Sub-study III was written together with Matilda Hellman and Pekka Sulkunen. The study builds on the assumption that social reality is constructed and taken-for-granted. Concepts develop in a certain cultural context. Culture in its different occurrences is the framework for thinking and acting. This study is particularly concerned with institutions as one occurrence of culture. The empirical bases of the enquiry are 27 Reception Analytical Group Interviews, which challenged the participants to question their taken-for-granted understanding of addiction by presenting them with short film clips. Finnish informants focus on the harm done towards the family and society and therefore follow the traditional Finnish non-medical model. French participants by contrast laid emphasis on the suffering of the individual addict and consequently express characteristics of the medical model (II, III, and IV). Secondly, Finnish social workers understand all three problem behaviours similarly as social problems, whereas their French colleagues understand alcohol and eating problems as individual issues. A common denominator in both countries is a functional explanation of all three problem behaviours as a form of poor coping with life's hardships (except for gambling in France) (III and IV). Finally the study shows that in the context of the modern Finnish welfare state the importance of citizens autonomy allows individual excess to some extent, as long as innocent others are not harmed (III). This study traced the influence of institutions on images of addiction. It suggests considering addiction as culture-level bound. Beside the traditional concept of addiction other institutional settings also have an impact on the images of addiction. Due to the complexity of the contexts involved, this dissertation recommends cautiousness when including behavioural excesses under the umbrella of addiction. Treatment research should take into account institutionally embedded understandings of addictions when implementing new treatment strategies and policy approaches from other cultural contexts. This dissertation asks for

a layered concept of culture, which can account for the multifarious influences of the social context on the concept of addiction. <http://urn.fi/URN:ISBN:978-952-10-9122-3>

*Tanja Hirschovits-Gerz: Images of addictions in Finland.*

This doctoral thesis examines common images of eight different addictions in the light of a Finnish population survey (n = 740) conducted in 2007. Addictions to alcohol, illicit drugs, prescription drugs, nicotine, gambling and internet were selected as the targets of the study. The variation of these images is analysed at the individual level by exploring the effects of such back ground variables as age, sex, and the respondents' personal experience of addictions on these images. The variation at the institutional level is analysed by comparing general population views with those of professionals in substance abuse treatment (n = 520), and at the cultural level by comparing the Finnish views on alcohol addiction with those of Canadian (n = 864), Swedish (n = 1098) and Russian (n = 1023) lay people. Theoretically this study is based on the ideas of Serge Moscovici on social representations and Kenneth Boulding on the role of images in the regulation of human behaviour. The images are built in human interaction. They are based on media information, private and shared experiences, the general attitude "climate" of a society, as well as scientific knowledge. The motivation to study the images of addictions stems from their decisive influence on the political decision-making and on the attitudes toward addicts and addiction problems in the society. In this summary, the societal background for this study is provided by first describing the position of addictive substances and behaviours in the Finnish society in the light of previous research. The aims, methods and the main results of the four articles included in the doctoral thesis are then described. The methods used in the data analysis include descriptive statistical methods, analysis of covariance, logistic and ordinal regression analysis. The results are here scrutinized by relating them to the existing societal reality, previous studies and theory. The results show that illicit drugs were considered the most difficult forms of addictions for the individuals and the functional or so called non-substance addictions were perceived as the lightest forms. Alcohol addiction was assessed as the most difficult problem for society. Finnish images were mostly shared or hegemonic. However, the back ground variables also produced some group variation in these images. For example, women believed more in the recovery with treatment compared with men and men believed more in the spontaneous recovery. Substance abuse professionals assessed prescription drug and functional addictions less and cannabis addiction more easy to overcome without treatment compared with lay people. Group differences in the images were connected with more recently found forms of addiction. Finns believed more than the citizens of the comparison countries in spontaneous recovery from alcohol addiction. The results show that the images vary between the different addictions

as well as between different groups. The aim of the thesis is thus to increase the understanding about addictions as socially and culturally constructed phenomena. <http://urn.fi/URN:ISBN:978-951-44-9539-7>

*Antti Maunu: Together in the Night. Nightclubs, Partying and Finnish Sociability.*

Social and cultural studies have drawn a picture of Finland as an urbanizing and globalizing society since the 1980s. A main thread in this discussion has dealt with a shift from a collectivist and relatively conformist way of life towards a more individualist one - much like in other Western countries. This is well embodied in Finnish bar and partying studies. According to them, 1980's suburban pubs were crowded by the descendants of the traditionalist, conformist culture, whereas the partygoers of the 2000s stroll in the night searching for unique, individual experiences to construct their unique, personal identity. However, this story probably pertains only to some small elite groups. It does not depict the so-called average partygoers who actually fill the Finnish nightclubs and keep them going. In addition, social and cultural studies in the 2000s claim that individualist hedonism and other sensation seeking has made room for neo-traditionalist neo-collectivism that prefers traditional, down-to-earth values. Recent studies also suggest that social and cultural one-sidedness - whether it was traditional collectivism or late modern individualism - has vanished in contemporary way of life which is rather characterized by social and cultural omnivorousness. In this study I examine the types or forms of sociability that the so-called average partygoers of the 2000s pursue and express in their nightclub partying. Average partygoers are represented by 23-35-year-old young white adults who live in Helsinki metropolitan area, work in socioeconomic middle positions and identify themselves as culturally ordinary, average Joes and Janes. I ask if they search for individual enjoyment or other individual experiences in their partying, or if they rather follow the ideals of neo-traditional neo-collectivity. On the other hand, I ask if social omnivorousness is important for them, and if it is, what elements it contains and what motivates it. The main data of the study is ethnographic observation in 13 nightclubs in Helsinki city center. I spent 100 hours during five years in different party spots in order to find out what kind of sociability they embody and offer. To understand average partygoers' own perspectives and experiences, I analyze their interviews on partying and nightclubs (117 thematic interviews and 7 focus group interviews) as well as their diary narratives (altogether 316 diary accounts) in which they describe their real nights out in their own words. The methodological framework of the study is analytic ethnography, and as analytic tools I apply perspectives offered by ritual analysis. The study shows that average young adult Finns' partying or their way of life more generally cannot be characterized by a clear-cut shift from collectivism to individualism. Instead, both moralities are well represented. On the one hand, their world is strongly collectivistic: they do not want to be self-sufficient individual atoms but prefer strong and

binding communities. On the other hand, the world of average partygoers is individualistic. They are independent and autonomous actors, and they want to choose the course of their life by themselves. However, they use their personal freedom and competence to pursue strong and binding social experiences. The reason for this is that without active pursuing their life-world does not offer such strong feelings of togetherness. In other words, the partying of young, average Finns satisfies social needs their everyday life does not otherwise satisfy. The study also shows that the communities of average young urban Finns are relatively loose and changing. They allow and also require that their members belong also to other communities because no single community can fulfil its members' all social needs. It follows that the sociability of young, average Finns is versatile and omnivorous, and that omnivorousness is motivated by a wish to become attached to social reality through rich and versatile bonds. Social versatility, by turn, requires active individual contribution and good social skills from these young average Finns so that they are able to maintain their communities and group memberships in the first place. The study then describes and interprets their partying as a true ritual, a technique of togetherness that turns these abstract moral principles into concrete actions. <http://urn.fi/URN:ISBN:978-952-10-9099-8>

*Erkki Nieminen: Spiritus contra spiritum. The Birth and Development of AA Activity in Lahti, Finland, in 1950-1995.*

The study focusing on history of education examines the initial stages and development of AA activities in the City of Lahti, Finland, during the period of 1950-1995. Alcoholics Anonymous (AA) is a mutual help movement, founded in the USA by alcoholic for alcoholics. Form of action is transaction that takes place in AA groups, founded on a spiritual recovery program consisting of 12 steps. However, AA is not a religious community. Questions of research are: how AA activities originated in 1950s; how these activities developed qualitatively and quantitatively; how AA groups and AA members effectuated their goals, and, what kind of relationship AA had had with institutions outside. The source material contains literature of the AA movement and magazines for its members, minutes of the meetings of boards and service committees, group catalogues and guest books of groups. Material from outside AA consists of earlier studies, archive sources, newspapers and magazines. On top of this historical method, interview and observation have been used. The research shows that AA activity begun in Lahti by non-alcoholics in 1950 to have endured for four years. It restarted in 1958, this time by alcoholics, and on a permanent basis. During the research period, a total of 15 AA groups have worked in Lahti, and at most seven of them at any one time. In addition some were groups in surrounding communities founded and supported by Lahti denizens. AA groups are autonomous but mutual interaction has been lively. At the end of 1995, the number of AA members with sobriety of one year or more was 184 in Lahti and 248 in the Lahti area. The proportion of female members was one-sixth. <http://urn.fi/URN:ISBN:978-952-61-1337-1>

*Tapio Paljärvi: Subjective measures of binge drinking and adverse health outcomes: Self-reported intoxications, hangovers, and alcohol-induced pass-outs as indicators of at-risk drinking patterns in the Finnish adult population.*

The purpose of this study is to validate three subjective measures of binge drinking, i.e. subjectively defined intoxications/drunkenness, hangovers, and alcohol-induced pass-outs as indicators of at-risk drinking patterns. There are no previous prospective studies which would have assessed the relative performance of these three separate indicators. This study used data from the Health and Social Support Study (HeSSup), which consists of a baseline measurement in 1998 (n=25 901), and a repeated measurement after five years in 2003 (n=19 629). The baseline sample was stratified by gender and four age groups (aged 20–24, 30–34, 40–44, 50–54 years at baseline). Measures of alcohol use included beverage-specific average total intake, frequency of intoxications/drunkenness, frequency of hangovers, and frequency of alcohol-induced pass-outs. The baseline postal survey data was linked with follow-up information from national registers on hospitalizations and deaths. The results showed that subjects at higher frequency levels of a given binge drinking measure drank on average more than subjects at lower frequency levels. Hangover frequency levels were associated with slightly higher average intake than the corresponding frequency levels of intoxication, suggesting that hangovers, on average, reflected somewhat heavier drinking than intoxications. All three binge drinking measures were markedly more frequently reported by persons who were diagnosed with an alcohol-specific diagnosis than by persons who were not. The relative differences were largest in high-frequency binge drinking, and in binge drinking measures potentially capturing higher intensity binge drinking, i.e. in hangovers and pass-outs. The results on the ability of each binge drinking measure to predict adverse health outcomes showed positive graded relations (dose response relation). The results of this study, thus, support the feasibility and utility of using these three measures as indicators of at-risk drinking patterns in epidemiological research. The results demonstrated that in terms of methodological performance, the three indicators were complementary to each other, meaning that each measure contained additional information of the risk of adverse health outcomes that was not captured by the other two indicators, or by total intake. Self-reported intoxications, alcohol-induced hangovers, and alcohol-induced pass-outs had both diagnostic and prognostic utility in identifying harmful alcohol drinking patterns at the population level. Because asking about the number of drinking occasions leading to intoxication, experiencing a hangover, or passing out as a consequence of drinking is much simpler and quicker than asking about quantities of intake of various different beverage types and beverage ethanol strengths, these results have important implications to clinical and public health practice as well. Public health messages aimed to reduce alcohol-related harm should be formulated to encourage avoiding/cutting-down drinking until intoxication in general, but highlighting the prognostic

role of experiencing alcohol-induced hangovers and alcohol-induced pass-outs could potentially enhance that message further as these indicators could serve as face valid self-screening instruments.

<http://urn.fi/URN:ISBN:978-952-10-9300-5>

*Sari Tuomisto: Intestinal Bacteria - Post-mortem changes, migration and association with alcoholic liver cirrhosis.*

The intestinal microbiota, that has been estimated to consist of around  $10^{14}$  bacteria, is known to affect the well-being of the host, and has been linked to various diseases such as alcoholic liver cirrhosis. Alcohol has been hypothesised to alter intestinal bacterial populations and enhance bacterial migration from the intestine into the liver. These bacteria and their residuals could then promote chronic inflammation that could eventually lead to fibrosis and cirrhosis. After death, bacteria start to migrate into the organs as a part of normal putrefaction. Bacterial migration, i.e., translocation from the intestinal lumen into the blood and visceral organs, occurs also normally during life. The time sequence of post-mortem changes in intestinal bacterial populations and their migration into organs has not been extensively studied. Therefore, it is not known whether results obtained from post-mortem samples reflect conditions during life. The aim of this doctoral thesis was to examine time-dependent changes in the intestinal microbiota after death and the translocation of these bacteria into tissues. Finally, we used these results to evaluate the role of intestinal bacteria in alcoholic liver cirrhosis. Post-mortem changes in major intestinal bacterial groups (*Bacteroides* spp., *Bifidobacterium* spp., *Clostridium coccoides*, *Clostridium leptum* group, *Enterobacteriaceae*, *Lactobacillus* spp.) and *Streptococcus* spp. were evaluated in 61 rectal and ceecal samples obtained at autopsy and in 7 healthy volunteers using quantitative real-time PCR (RT-qPCR, Study I). Bacterial migration after death into the liver, mesenteric lymph nodes, pericardium, portal vein and peripheral blood was examined in a time-dependent manner with RT-qPCR and conventional bacterial culturing in 33 post-mortem samples. RT-qPCR was used to study the following bacterial groups: *Bacteroides* spp., *Bifidobacterium* spp., *Clostridium leptum* group, *Clostridium coccoides* group, *Enterobacter* spp., *Staphylococcus* spp. and *Streptococcus* spp. (Study II). The composition of selected intestinal bacteria (*Bacteroides* spp., *Bifidobacterium* spp., *Clostridium leptum* group, *Enterobacteriaceae* and *Lactobacillus* spp.) was investigated in 42 rectal samples obtained at autopsy (13 cirrhotics, 15 alcoholics, and 14 controls) and in faecal samples from 7 healthy volunteers (Study III). Intestinal bacterial translocation into the liver (n=42) and its association with cirrhosis and ascites (n=12) was also studied with RT-qPCR and CD14 immunohistochemistry. Our results show that the relative amounts of *Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., *Streptococcus* spp., *Enterobacteriaceae* and *Lactobacillus* spp. remained stable in the rectum for up to 5 days after death (Study I). The proportions of the major intestinal bacteria populations in rectal

autopsy samples were comparable to faecal samples from living persons. In contrast, post-mortem caecal samples proved to be microbiologically unreliable, as significant time-dependent post-mortem differences were observed in bacterial populations of *Bacteroides* spp. ( $p=0.014$ ) and *Lactobacillus* spp. ( $p=0.024$ , Study I). Bacterial culturing and RT-qPCR analyses revealed the presence of bacteria in peripheral blood soon after death as a result of post-mortem bacterial migration. Outside the intestinal tract, the most reliable post-mortem microbiological sampling sites at up to 5 days after death were the pericardial fluid and the liver (Study II). Based on the results of Studies I and II, cases over 5 days post-mortem were excluded from Study III, and RT-qPCR measurements of *Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* leptum group, Enterobacteriaceae and *Lactobacillus* spp. were selected for the samples. Alcoholic liver cirrhotics harboured 27 times more DNA of Enterobacteriaceae in their faeces than living controls ( $p=0.011$ ). Genomes of this bacterial species were also found in the liver and ascites samples from cirrhotics (Study III). The total amount of bacterial DNA was associated with the level of CD14 expression ( $p=0.045$ ). Furthermore, the CD14 expression percentage was statistically significantly higher in cirrhotic livers than in autopsy controls ( $p=0.004$ , Study III). In conclusion, post-mortem samples from the rectum and liver can be used in basic research if taken within 5 days after death. Alcoholic cirrhotics harboured more gramnegative Enterobacteriaceae in their faeces and had higher amounts of Enterobacteriaceae in the liver. This suggests the possible involvement of intestinal bacteria in the development of alcoholic liver cirrhosis. <http://urn.fi/URN:ISBN:978-951-44-9580-9>

#### RESEARCH CONTRACTS AND COLLABORATIVE PROJECTS

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##### 213 *The role of brain-derived neurotrophic factor in the regulation of alcohol drinking.*

BDNF is a member of the nerve growth factor family of neurotrophins and has multiple tasks in central nervous system, such as neuronal survival and plasticity, learning, regulation of locomotor activity and appetite and also in addiction. BDNF signals through TrkB- receptor and alcohol and other drugs are known to acutely induce them both. The aim of this study is to clarify the role of BDNF in the rewarding effects of alcohol and in the regulation of alcohol drinking. In the studies performed in the Institute of Health and Welfare we have seen dose-dependent and temporal region-specific changes in the levels of BDNF mRNA after acute alcohol exposure in the brains of wistar rats. The results were published in the European Journal of Pharmacology journal (Raivio et al. Eur J Pharmacol. 2012, 687(1-3):9-13). Also, we have found that acute alcohol exposure alters the BDNF mRNA levels in AA and ANA rats in a similar manner as in wistar rats. Furthermore, we found a line-difference between AA and ANA rats in the basal levels of BDNF in the ventral tegmental area, amygdala and hippocampus, as

well as in the response to alcohol in the frontal cortex. This suggests that BDNF in different brain regions may have a role in the different drinking preference of these rat lines. The results were published in the Brain Research journal (Raivio et al. Brain Res. 2014 Sep 4;1579:74-83). We have repeated the same measurements of the BDNF mRNA levels of AA and ANA rats after acute morphine administration, and a manuscript of these results is on the works. On the year 2014 the researcher has been (mainly) on a maternity leave. Researcher: Noora Raivio, Department of Alcohol, Drugs and Addiction, National Institute for Health and Welfare. (noora.raivio@helsinki.fi)

217 *The Division of Labor between Social Care health care, the Prison and the Police in the Handling of Intoxicant Related Harm.*

My PhD study, for the Department of Social Research at the University of Helsinki analyses developments in societal approaches toward intoxicant abusers with focus on the new developments within the Finnish prison sector. Colleagues and I have found that substance abuse problems became more common among prisoners from the year 1985 to 2006 and that the nature of the abuse problems shifted from alcohol to drugs. The developments mirror the developments in “overall society” to some extent. (Lintonen & Obstbaum et al 2012). I have related this development to the overall development in other intoxicant related institutionalisations, using register data from the health authorities, social care authorities and the police. The mean number of institutionalised persons per day had increased between 1985-2006. Before the economic recession in the 1990s the growth was due to an increasing share of rehabilitative substance abuse treatment within social care, and after the, due to an increasing share of new admissions of substance abusers to prison. The study parallels criticism directed at the adequacy of non-residential care particularly for troubled substance abuser; both in quantity and sufficiency (Obstbaum et al 2011). The second part of the study deals with strategies for countering substance abuse in Finnish prisons, which in accordance to international trends prisoner rehabilitation relies on assessing and targeting so-called criminogenic needs. I have scrutinized how often prisoner’s abuse problems are recognized in prisons’ risk and needs assessments and/or sentence plans by analyzing data from the prisoner information database in connection to the prisoner health investigation of 2006 the same persons. (Obstbaum et al 2014 in review). I have additionally analysed to what degree support is given to those prisoners whose sentence plans or risk and needs assessments indeed states that they have problems with intoxicant abuse, using prisoner database information of all prisoners release during the year 2011 and what factors (of the prison and of the prisoner himself) contributes to the support (Obstbaum & Tyni 2015, accepted for publication). The broader cultural perspective of the study is the changing locus of troubled substance abusers in connection to the increasing risk management particularly within the prison. During 2014

I have presented my findings at the Control and Rehabilitation Ph.D. course at Aarhus University; for the Criminal Sanctions agency and at other national seminars. A working space and collegial environment is provided by Institute for Criminology and Legal Policy (KRIMO) at the University of Helsinki (former Optula). I am currently finalising my thesis supported by the Foundation for Alcohol Studies and the University of Helsinki. Researcher: Yaira Obstbaum, University of Helsinki. (yaira.obstbaum@om.fi)

221 *Polydrug use related deaths: trends, prescription drug abuse and regulation of risks.*

Topic of this doctoral study is polydrug use related deaths. The prevalent paradigm in addiction research for the past decades has been a single substance driven orientation. Studies have concentrated on particular substances and harms they cause. However, empirically it is evident that polydrug use – concurrent or simultaneous use of licit or illicit substances - is very common. As research has concentrated on the use of single substances, polydrug use and its harms have remained little-studied. Recent studies and statistics show that drug situation in Finland has been rather stable past 10 years. Exception to this is drug-related deaths which have increased since 2003. This has been explained by the increase of poisonings due to prescription opioids, especially buprenorphine, often in combination with other drugs. Finland is not alone in this development as the non-medical use of prescription drugs has increased rapidly in Western countries in the past decades. This PhD study will address these themes a) by examining the trends of polydrug use deaths in Finland, b) by comparing polydrug related mortality across diverse population groups, c) by describing association between prescription drugs and polydrug deaths, and d) by exploring the users' perceptions of risks related to polydrug use. In 2014, results of the study have been presented in the Conference of the European Society for Health and Medical Society and various national seminars. One peer-reviewed article was published. The researcher was on maternity leave May-December 2014. Researcher: Sanna Rönkä, University of Helsinki.

222 *The role of opioidergic receptors in the development of alcohol addiction.*

A main characteristic of alcohol addiction is the compulsion to drink alcohol despite its adverse effects on health. Pharmacological treatments are available for alcohol addiction but unfortunately not all patients benefit from them. Development of new pharmacological treatments is hindered by the fact that not all biological mechanisms underlying alcohol addiction are understood. From the different neurotransmitter systems that mediate the effects of alcohol, the opioidergic system has shown to play a central role in controlling alcohol intake and in the development of alcohol addiction. Alcohol releases endogenous opioid peptides in e.g. the nucleus accumbens, which is a central brain area when studying alcohol addiction. Opioid receptors, e.g.  $\mu$ - and  $\kappa$ -opioid

receptors that mediate the effects of opioid peptides, are also found in the nucleus accumbens. In the field of alcohol addiction  $\kappa$ -opioid receptors have been less studied than  $\mu$ -opioid receptors. The aim of the current experiment is to clarify the role of  $\mu$ - and  $\kappa$ -opioid receptors in controlling alcohol intake. In these studies we used the alcohol preferring AA (Alko Alcohol) line of rats. In order to study the role of accumbal  $\mu$ -opioid receptors in controlling alcohol intake, we dosed  $\mu$ -opioid receptor agonists (DAMGO, morphine) or an antagonist (CTOP) directly into the nucleus accumbens. In these experiments, CTOP increased and DAMGO tended to decrease alcohol intake in AA-rats. In a currently ongoing experiment, we increased the amount of accumbal  $\mu$ -opioid receptors with the help of  $\mu$ -opioid receptor overexpressing AAV-viral vectors. According to the results accumbal  $\mu$ -opioid receptors have an important role in controlling alcohol intake. As when studying  $\mu$ -opioid receptors, in order to study the role of  $\kappa$ -opioid receptors in alcohol intake, we dosed a  $\kappa$ -opioid receptor agonist (U50488H) or antagonists (JDTic and nor-BNI) into the nucleus accumbens. JDTic was also administered subcutaneously. Accumbally dosed U50488H did not have an effect on alcohol intake. However, accumbally dosed JDTic tended to decrease alcohol intake long-term. Also subcutaneously dosed JDTic (10 mg/kg) decreased alcohol intake in a long-term fashion. The results suggest that  $\kappa$ -opioid receptors have an important role in controlling alcohol intake. Drugs targeted at  $\kappa$ -opioid receptors could also have clinical value in treating alcohol addiction. The results were presented at the Society for Neuroscience conference in Washington DC in November. These studies aim at a Doctoral Thesis. Researcher: Johanna Uhari-Väänänen, University of Helsinki & National Institute for Health and Welfare. (johanna.uhari@helsinki.fi)

### 223 *Interactions of dopamine and histamine in alcohol addiction.*

The study has been carried out by professor Pertti Panula, postdoctoral scientist Saara Nuutinen and MSc Jenni Vanhanen. The behavioral studies had already indicated that H3 receptor antagonists regulate functions which are considered dopaminergic. To reveal the mechanism of H3 receptor-mediated effects on alcohol behavior, we analyzed the roles of H3 receptor antagonist on dopamine-induced signaling systems. An important dopamine signaling pathway, ERK1/2 signalling, was blocked by these drugs, which suggests that the H3 receptor is necessary for some dopamine-mediated effects in the striatum. H3 receptor knock-out mice also displayed lower levels of dopamine D1 receptor mRNA in the striatum. Furthermore, H3 receptor antagonists modulated locomotor responses but not place conditioning induced by dopaminergic drugs. Importantly, amphetamine-induced place preference was not potentiated by H3 receptor antagonists. The research was presented at the European Histamine Research Society meeting in Lyon in May 2014. Jenni Vanhanen gave an oral presentation Histamine H3 receptor-dependent mediation of brain dopaminergic

regulation in mice and won the international Young Investigator Award with this. Pertti Panula presented a plenary lecture Interactions of the histaminergic and dopaminergic systems in the brain: Implications in alcohol-related behavior and Tourette syndrome in Lodz, Poland in October 2014 at the Biogenic Amines meeting. Two manuscripts are still in preparation. Researcher: Pertti Panula, University of Helsinki. (pertti.panula@helsinki.fi)

224 *Effects of gestational ethanol exposure on epigenome, gene regulation and the development of brain.*

We hypothesize that early ethanol exposure disrupts the epigenetic reprogramming of embryo, which leads to alterations in gene regulation and embryonic development. Our aims are 1) to reveal the molecular mechanisms, which lead to the phenotypic characteristics of fetal alcohol spectrum disorder (FASD) and 2) to find biomarkers for FASD diagnosis and to develop new diagnostic criteria. Because prevention of FASD is often impossible, early diagnosis and appropriate support for development have an important role in the therapy of FASD children. We are using mouse model of gestational ethanol exposure. The exposure period in this model is equivalent to the weeks 3-4 of human pregnancy, a time period when women are often not aware of their pregnancy. We are focusing on hippocampus, which is known to be particularly vulnerable to the effects of ethanol. We have observed alcohol induced changes in the hippocampal DNA methylation, gene expression and volume in the offspring. We also found altered volumes of olfactory bulbs and ventricles caused by gestational ethanol exposure. In addition to hippocampi, we observed similar trend of altered gene expression in two other tissues: bone marrow and main olfactory epithelium. This supports our hypothesis of early epigenetic origin of alcohol-induced disorders: changes in gene regulation may have already taken place in embryonic stem cells and therefore can be seen in different tissue types later in life. Those epigenetic changes could be considered to be biomarkers and would offer a new tool for the challenging diagnostics of alcohol-induced developmental disorders. We have proceeded to human studies and started the Epigenetics of Fetal Alcohol Spectrum Disorder project (epiFASD) in 2013. In collaboration with University Hospital and Finnish Red Cross Blood Service we are collecting samples from mothers that can be assessed to have increased risk based on their alcohol consumption, and from their offspring. Researcher: Nina Kaminen-Ahola, University of Helsinki. (nina.kaminen@helsinki.fi, <http://environmental-epigenetics.helsinki.fi>)

226 *Young people and a changing culture of crime control – policing alcohol drinking, delinquency and the use of public space.*

This sociological PhD research examines encounters between young people, police and private security guards. It studies underage youths' perspectives of social control, such as control of delinquency, alcohol use

and free time activities. The starting point for the study is an observation that social control of young people has intensified. For instance, police control has increased, although youth delinquency and alcohol use have not increased. Central criminological discussions for this study are citizens' trust on justice and social control biases. Prior research has focused mainly on adult perspectives and on police control. This study aims to offer new insights by focusing on young people and by including also private security. The main questions are twofold. First, are some groups disproportionately targeted for formal social control (social biases)? Second, how do young people constitute perceptions of trust and legitimacy toward control agents? How can trust be constituted between young people and control agents in 'adversarial' situations, for instance where control agents intervene in alcohol use? The study uses mixed methods. It consists of 4 articles and a summary article. Two sub-studies draw on a youth survey (N=5826) of youth aged 15 to 16. Multivariate regressions examine which factors increase the likelihood of police interventions (article 1, Saarikkomäki & Kivivuori 2013) and security guard interventions (article 2, Saarikkomäki & Kivivuori 2014). The findings show that police and security guard interventions disproportionately target lower class city youths. This finding holds when delinquency and alcohol use were controlled, which suggests biases in social control. As expected, delinquency, heavy drinking and living in a city increased the likelihood of intervention. Furthermore, the study indicates that it is highly common for youths to encounter control agents. Another two sub-studies draw on qualitative focus group data (9 interviews, 31 young people aged 14 to 17). The study analyses how trust is constructed between young people and control agents. The 3rd article analyses narratively young people's stories of fair and unfair encounters where police and security guards intervene in underage alcohol use. The plan for the 4th article is to analyse how trust and legitimacy are constituted by comparing youths' perceptions of police and security guards. The findings confirm that fair and respectful interactions were crucial for constituting trust between young people and control agents. However, there were differences between police and security guards. Trust between young people and adult society is important, because, if young people perceive treatment unfair it can increase conflicts and enhance feelings of not being a valued part of society. The project began in 2011 and from May 2012 it continued as a research contract project. During 2014, the second article of the PhD was published. The researcher has continued to analyse the focus group data and the 3rd article manuscript has been drafted. The findings were presented in several national and international conferences (e.g. University of York, PhD seminar in Aalborg University, security seminar for police officers in Helsinki). In addition, with the grant from the foundation, the researcher participated in the conference organized by Centre for Alcohol and Drug Research, Aarhus University. Researcher: Elsa Saarikkomäki. (elsa.saarikkomaki@helsinki.fi)

227 *Association between parental substance abuse problems and their children's cumulative risk factors for social deprivation at adolescence.*

This sociological dissertation study examines from different perspectives social deprivation which is related to parental substance abuse, and the inheritance of parental problems to the children. The study is based on the findings of an increase in alcohol consumption in Finland over the last forty years, especially among women who are at parenting age, and the more prevalent drug use and the stabilization of higher drug use level than before during the 1990s. Harmful parental substance use in the child's living environment can significantly affect the child's wellbeing, and it can also become entangled with other problems, such as parental mental health disorders and the family's livelihood difficulties. The aim of this study is to find out associations between parental substance abuse and child's risk factors for health, social and economic deprivation from birth to 20 years of age. The study is based on an extensive administrative register data of a total birth cohort of children born in 1991, and their biological parents. The data allows the follow-up of the cohort until year the 2011. The methods applied in analysis are statistical analysis suitable for longitudinal data. In 2014, the study was funded by the research contract. During this period, two article manuscripts were finalized and the results of the research project were presented at two international conferences. One of the article manuscripts describes how parental substance abuse is associated with other problems on a family level. The other manuscript focuses on the associations between parental substance abuse and adolescents' mental health disorders and harmful substance use. Results of the research project were presented at the conference of Kettil Bruun Society in Turin, Italy on June 9, 2014 with the title "Parental substance abuse and family separation". In addition, results were presented at the ESHMS (the European Society for Health and Medical Sociology) conference in Helsinki on August 29, 2014 with the title "Register-based research project on harms to children caused by parents' substance misuse". During the year 2015, the aim is to finalize two article manuscripts. Researcher: Marke Jääskeläinen, University of Helsinki. (marke.jaaskelainen@thl.fi)

229 *Neuroinflammation in mouse models of alcohol consumption; relevance of P2X7 receptor.*

Neuroinflammation appears to have an important role in alcohol addiction. Immune system has been shown to have relevance in regulation of acute and chronic effects of alcohol. For example, the inhibitor of microglial activation minocycline reduces alcohol consumption in mice. However the mechanisms of interaction between neuroimmune signaling and alcohol are not known. According to our hypothesis, immune system signaling molecule P2RX7 (P2X7 receptor), which has been connected to depression and alcoholism in genetic studies, could be important factor in this interaction. P2RX7 is activated by ATP and it regulates immune signaling also in microglial cells and influences

the production of proinflammatory cytokines. In recently described mouse model, acute lipopolysaccharide treatment (LPS) increased long term alcohol consumption in mice, supporting the hypothesis that neuroinflammation may promote alcohol consumption. We carried out drinking experiments according to this model, by monitoring 24-hour ethanol consumption in a two-bottle choice test with increasing ethanol concentrations. LPS treatment (1 mg/kg, i.p.) decreased alcohol consumption only in male mice, not in females, when compared to control group. This difference was significant only during consumption of 21% (v/v) alcohol. Interestingly, this finding was opposite to earlier reports of increased consumption after LPS treatment. After one week ethanol deprivation LPS-treated mice still tended to consume less alcohol than control mice. In the next experiment, mice treated with 1.5 mg/kg dose of LPS consumed less alcohol than other groups. As our results were inconsistent with the previously reported findings we also studied the effect of lower LPS doses (0.2, 0.5 and 1 mg/kg) for 2-4 hour ethanol (15%, v/v) consumption utilizing the drinking-in-the-dark (DID) method. As before, we did not see increase in alcohol consumption with the highest LPS dose, but 0.5 mg/kg treatment tended to increase ethanol consumption in some of the test days. Our results indicate that, the reported association between LPS-induced neuroinflammation and increased alcohol consumption depends on environmental factors and is not readily reproduced in other laboratories. We have also studied effects of acute and chronic treatment with P2RX7 antagonists, especially Brilliant Blue G (BBG), on alcohol effects on sedation, motor coordination and hypnosis (loss of righting reflex). In addition, we have studied the effect of subchronic BBG on alcohol consumption in the DID model. Our results indicate that BBG (50 mg/kg, i.p.) does not influence acute behavioral effects of alcohol nor the alcohol drinking in the DID model when dosed subchronically (75 mg/kg/daily, i.p.). This suggests that P2RX7 does not play a major role in mediating the acute effects of alcohol or in regulation of alcohol consumption when LPS treatment is given four weeks earlier. Next our plan is to analyze neuroinflammatory markers after LPS and alcohol treatments to find out how neuroinflammation interacts with the actions of alcohol in the brain. This PhD thesis aiming research began in April 2013. Researchers: Mira Lainiola and Anni-Maija Linden, University of Helsinki, Institute of Biomedicine, Pharmacology.

### 231 *Role of GDNF in incubation of alcohol craving.*

Withdrawal from alcohol leads often to relapse even after long periods of abstinence. It is known that there can be intensive craving for alcohol and that craving can last long periods. Drug and alcohol craving methods are well established with laboratory rats. In rats it has been observed that rat's response to cues increases over time after withdrawal from self-administration. The phenomenon is termed incubation of drug craving. The first aim in this study is to set up and validate a novel method to study

alcohol craving in mice by using IntelliCage. The use of fully automated IntelliCage is a new approach to study addiction related behavior in mice. Self-administration, following extinction and relapse paradigms in mice are still not well developed. Mice still pose enormous possibility for studies that cannot be conducted in rats. It is good to remember that gene modifications are much more diverse in mice as well as they are rather cost efficient. We have studied differences in alcohol, alcohol and sweetener, sweetener, and water on drinking related behavior in mice, as well as extinction responses on withdrawal days 1 and 10. We are currently analyzing the results and the new method will be used to study the role of glial cell line-derived neurotrophic factor (GDNF) in alcohol craving. GDNF is a protein that has survival promoting properties in dopamine neurons and effects on dopamine neurotransmission. It has been shown that GDNF has effects on behavioral responses of abused drugs and alcohol, but its role in alcohol craving is not fully clear. Researchers: FM Maryna Veremieva, FaT Mikko Airavaara, LT Vootele Voikar. Collaborators: FaT T. Petteri Piepponen, FT Jaan-Olle Andressoo.

232 *The role of  $\delta$ -containing GABAA receptors in ethanol intoxication.*

Synaptic GABAA receptors mediate fast inhibitory neurotransmission, but the extrasynaptic GABAA receptors maintain a constant low level inhibition.  $\alpha 6\beta\delta$  receptors are extrasynaptic receptors and they are only found in the cerebellum. The ongoing study investigates the differences in ethanol's effects in these receptors. Ethanol's binding site is not fully known and the results would help to model the putative binding site of ethanol and give new insight in the development of treatments for ethanol addiction and poisoning. Alcohol tolerant (AT) and alcohol non tolerant (ANT) rats that have been used in alcohol studies have a point mutation in  $\alpha 6$  codon 100 which has been shown to cause several of the differences between AT and ANT rats (Korpi et al. 1993). Analysing the data from our electrophysiological studies on  $\alpha 6$ -100Q $\beta 3\delta$  and  $\alpha 6$ -100R $\beta 3\delta$  recombinant receptors expressed in HEK 293 cells is still undergoing, but tentatively ethanol has been seen to potentiate GABA responses in  $\alpha 6$ -100Q $\beta 3\delta$  receptors and slightly inhibit GABA responses in  $\alpha 6$ -100R $\beta 3\delta$  receptors. I have done binding experiments with the cerebellar membranes of  $\alpha 6$ -100Q (QQ) and  $\alpha 6$ -100R (RR) rats,  $\delta$ KO and WT mice membranes and  $\alpha 6$ -100Q $\beta 3\delta$  and  $\alpha 6$ -100R $\beta 3\delta$  recombinant receptors expressed in HEK 293 cells to investigate the difference  $\alpha 6$ -100Q and  $\alpha 6$ -100R alleles make in the effect of ethanol. The concentrations of ethanol used in the experiments have mostly been 0.3 – 30 mM. In Finland the driving limit of blood ethanol is 11 mM. I have also studied the effect of ethanol in the association and dissociation of the GABAA-receptor agonist [3H]muscimol in  $\alpha 6$ -100Q- $\beta 3\delta$  and  $\alpha 6$ -100R- $\beta 3\delta$  recombinant receptors. In these experiments the only difference is that the maximal binding is around 10 % lower in  $\alpha 6$ -100R- $\beta 3\delta$  recombinant receptors with 30 mM ethanol. With the cerebellar membranes of a rat I did [3H] GABA dissociation experiments, but the results were not significant even

though by looking at the graph ethanol made the dissociation slightly faster. The differences have been small, but we need to keep in mind that there are  $\delta$  subunit containing receptors about 18 % of all GABAA receptors in the cerebellum of a rat and around 29 % in the cerebellum of a mouse (Sieghart et al. 2003), which means a smaller change in total binding measured in percents might mean greater effect in the  $\delta$  subunit containing GABAA receptors. Researchers: Asko Aalto ja Mikko Uusi-Oukari, University of Turku.

233 *Childhood predictors of life-span alcohol use trajectories and health related outcomes in adulthood.*

The purpose of this study is to examine the course of adult alcohol use trajectories and factors that influence those trajectories and their health-related outcomes. The study has been carried out in an on-going population-based Young Finns -Study including 3596 subjects who have been followed for 32 years since their early childhood. The study aims to determine developmental predictors of different alcohol use trajectories in adults and thereby identify early tools for prevention of alcohol use disorders. There is a dearth of previous longitudinal research on these associations. During 2014, we have examined the association between alcohol use and depressive symptoms in this study sample, taking into account the potential confounding effect of different potential environmental and socioeconomic variables. We have prepared a manuscript based on these findings and the manuscript is currently under peer review in an international alcohol journal. We have also performed preliminary analyses in which we have examined the associations between the subjects' temperamental and character dimensions and alcohol use trajectories and started preparing a manuscript on this subject. The funding has been used for researcher Salla Vuoristo-Myllys' salary based on 30% (12 hours a week) of worktime. Researchers: Salla Vuoristo-Myllys ja Marko Elovainio, University of Helsinki.

234 *Substance Abuse in the Family – Children's Experiences of Inequalities and Ambivalent Family Relations.*

In this post doc -study, interest lies in the experiences of family relations, inequalities and social class of children and young people in problem-drinking families. The qualitative part of the study is carried out by interviewing children and young people who have a problem-drinking parent. In addition, national 1987 -cohort data will be utilized in the study. During 2014, interview data collection of the study was completed. Children and young people have been interviewed as part of the "Growing up in the Finnish Drinking Culture"-project of the National Institute for Health and Welfare. Interviewees were recruited via organizations and treatment units working with problem-drinking clients. Interviews were collected evenly from different parts of Finland. The qualitative data consist of 30 interviews; most of the interviewees were aged 12-18 years. Some of these young people have also their own

problems with substance-abuse and some of them have been taken into foster care. However, most of the interviewees did not have their own substance abuse problems. Preliminary analysis of the interview data has started after the data collection was finalized. In 2015, analyses and writing up the results in the form of article and book chapter manuscripts will be continued. In addition to the qualitative data, the national 1987-cohort data, into which data from different sources has been combined, is now in the usage of the study. Different analyses related to inequalities and the parents' alcohol problems will be applied to the cohort data. Researcher: PhD Henna Pirskanen, National Institute for Health and Welfare / University of Jyväskylä. (henna.pirskanen@thl.fi)

235 *Immune response to alcohol metabolites.*

Alcohol consumption has been previously shown to associate with serum levels of antibodies recognizing protein adducts of various alcohol metabolites, such as acetaldehyde and malondialdehyde-acetaldehyde. Although lipids have been considered poorly immunogenic *in vivo*, we have demonstrated that alcohol-modified lipid, phosphatidylethanol (PEth) is immunogenic in mice. We have measured antibodies binding to PEth in the plasma samples of heavy and moderate drinkers. The objective of the present proposal is to investigate the immunological and cellular properties of alcohol metabolites. We seek to establish that alcohol-mediated alterations in cellular lipids and cell membrane proteins (adducts) alter the immune response in humoral and cell mediated immunity. Our aim is to investigate the mechanisms of antibody formation that we have observed in animals and in humans. We will investigate the specificity of antibody binding to alcohol metabolites and structurally related molecules. The genetic background of the antibodies binding to alcohol metabolites will be investigated using monoclonal cell lines that we have generated during the study. Researcher: Antti Nissinen, PhD, Institute of Clinical Medicine, Department of internal medicine and Institute of Diagnostics, Medical microbiology and immunology, University of Oulu. (antti.nissinen@oulu.fi)

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