

The background of the top half of the page is a landscape photograph showing rolling green hills and mountains under a clear blue sky. The hills are covered in dense green vegetation, and the mountains in the distance are hazy.

**Jouko Lönnqvist • Hannu Alho • Hillevi Aro • Peter Eriksson
Erkki Isometsä • Jaakko Kaprio • Kalervo Kiihanmaa
Kimmo Kuoppasalmi • Pirjo Lillsunde • Mauri Marttunen
Timo Partonen • Maria Portman • Timo Seppälä • Jaana Suvisaari**

National Public Health Institute Department of Mental Health and Alcohol Research

Background material
for the international evaluation

Kansanterveyslaitoksen julkaisu **B** 21/2007

Publications of the National Public Health Institute



Kansanterveyslaitos
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NATIONAL PUBLIC HEALTH INSTITUTE

**DEPARTMENT OF MENTAL HEALTH AND ALCOHOL
RESEARCH**

Background material for the international evaluation

KANSANTERVEYSLAITOS

MIELENTERVEYDEN JA ALKOHOLITUTKIMUKSEN

OSASTO

Kansainvälisen arvioinnin taustamateriaali

Kansanterveyslaitos

Mielenterveyden ja alkoholitutkimuksen osasto

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Kansanterveyslaitos (KTL)

Mannerheimintie 166

00300 Helsinki

Puh. vaihde (09) 474 41, telefax (09) 4744 8408

Folkhälsoinstitutet

Mannerheimvägen 166

00300 Helsingfors

Tel. växel (09) 474 41, telefax (09) 4744 8408

National Public Health Institute

Mannerheimintie 166

FIN-00300 Helsinki, Finland

Telephone +358 9 474 41, telefax +358 9 4744 8408

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1. EARLIER EVALUATION

In the early 1990s the Science and Technology Policy Council in Finland encouraged the Ministries to evaluate research institutions in their jurisdiction. In accordance to this policy, the Medical Research Council of the Academy of Finland carried out an evaluation of the research activities of the Finnish National Public Health Institute (KTL) in 1994-1995, in response to a proposal put forward by KTL and the Ministry of Social Affairs and Health (STM). The objective of this evaluation was to provide information on the public health functions, strategic importance, scientific merit and value for money of the scientific work undertaken and to make proposals for future work.

The international Evaluation Panel, chaired by Dr David Evered of the UK Medical Research Council, prepared an Evaluation Report to the Academy in October 1995. For the evaluation, KTL prepared a report describing the work in the Institute. The Evaluation Panel worked via internal meetings, discussions with important stakeholders of KTL, and through site visits to the three divisions of KTL. On the basis of their evaluation, the Panel made 35 major recommendations for further development of the organization, management and work of the Institute.

Over the past 10 years, most of the recommendations made by the Panel have been implemented: the organization of KTL has been changed, several areas of research and public health work have been directed towards new priorities, and more emphasis has been put on the public health impact of the work of KTL. In addition, a renewed strategy was prepared for the Institute in 2001 during a thorough process involving the whole organization. At the end of 2003, a new Director General was appointed to KTL.

Based on these developments, and on changes in the environment, the time is ripe for a new evaluation of KTL. The purpose of such a task would be to evaluate the effectiveness of the work and assess the scientific and public health impact of the Institute.

2. KTL IN BRIEF

2.1. Strategy and functions

The mission of KTL is to protect and promote the health of the Finnish people. As a research and expert institute belonging to the Ministry of Social Affairs and Health, KTL is responsible for providing decision-makers, professionals and citizens with the

best possible health-related information for their choices. A general strategy for the Institute was prepared in 2001, while detailed objectives for the work are agreed upon annually with the Ministry.

The three main areas of work in KTL have traditionally been: 1) infectious diseases and immunizations, 2) chronic diseases and health promotion, and 3) environmental health. In all these areas, both research and public health functions are carried out. Activities of the Institute include basic research, ranging from the detailed analysis of the molecular mechanisms of pathogenesis to large-scale epidemiological and preventive studies and research into factors influencing health.

KTL monitors public health, diseases and their determinants through surveys and registers. Research and expert information is transferred into action by developing health-promoting and preventive measures and by advising and collaborating with various stakeholders. National vaccine service, many centralized laboratory functions and forensic medicine investigations are some of KTL's service functions.

Several of KTL's functions are based on laws, such as surveillance of infectious diseases and protection from communicable diseases by vaccinations. In the prevention of chronic diseases KTL works in close collaboration with various non-governmental organizations. In promoting healthy environment and preventing diseases KTL collaborates with environmental authorities and municipalities. A strong presence in the media is a way to reach the people. The ultimate goal is to reduce the human suffering and economic cost caused by illness and to help people enhance their quality of life.

2.2. Organization, personnel and budget

KTL's main facilities are located in Helsinki and three other facilities in Kuopio, Oulu and Turku. The Institute has 11 departments, each of which is built of various laboratories and units.

Ultimate responsibility for leading and managing the whole Institute rests on the Director General of KTL. He is assisted by the Deputy Director General, the Administrative Director and the Steering Group, consisting of the Directors of Departments. The Director General is also advised by a Scientific Council of KTL, where representatives of the most important stakeholders are present.

At the end of 2005, KTL had a staff of 887 persons, of whom 367 were scientists or experts. Women make up 73% of the staff. In addition to the permanent or temporary staff, KTL is also a working place for non-paid students or scientists who pursue their

studies and research together with the staff of KTL. Altogether, there were 158 PhD students working at KTL in 2005.

The total expenditure of KTL was 63 million euros in 2005, and the operating expenses were 54 million euros when the acquisition of vaccines is excluded. The majority (65%) of the operational funding comes from the national budget, 25% from external sources like the Academy of Finland, the European Union, the US National Institutes of Health, or various foundations supporting scientific research. The remaining 10% of KTL's budget is covered by income from chargeable services and from miscellaneous other funding.

3. EVALUATION PROCESS

3.1. Scope and purpose of evaluation

The objective of the review is to provide an evaluation of the work of KTL for the Ministry of Social Affairs and Health. The evaluation should examine the functions, strategic importance, scientific merits and value for money of the scientific and expert work undertaken, and to make proposals for future work. A special emphasis will be placed on the evaluation of the relevance and effectiveness of the work and of its impact on the health of the Finnish people.

The evaluation and the Evaluation Report should address the following main issues:

- a.** National relevance and effectiveness of the activities
- b.** Appropriateness and adequacy of the research, expert functions and services
- c.** Output and quality of research activities
- d.** National and international co-operation
- e.** Resource allocation
- f.** Research fundraising
- g.** Development needs, especially regarding processes and organization

The main purpose of the evaluation is to guide the Ministry of Social Affairs and Health so that they can use it for the strategic management of KTL. The practical implementation of the results, based on the decisions made at the Ministry, is the responsibility of the Director General of KTL.

3.2.Entities to be evaluated

The first round of detailed evaluations consists of four separate, partly parallel evaluations covering the main functional areas of KTL:

1. Environmental health
2. Chronic disease prevention and health promotion
3. Infectious diseases
4. Molecular medicine - the evaluation of this area will depend on whether the results of the planned evaluation conducted by the Ministry of Education will provide sufficient information for the purposes of the Ministry of Social Affairs and Health.

After the first round has been completed, the entire Institute will be evaluated. This evaluation will focus merely on the general strategy, function and management of the Institute, with less emphasis on the evaluation of individual research and expert functions.

3.3.Information sources for the evaluation

KTL will provide the Panels the following information:

Published documents concerning the whole Institute

1. Annual Report 2006
2. Kansanterveyslaitoksen toimintakertomus ja tilinpäätöslaskelmat 2006 (available only in Finnish)
3. Evaluation of the National Public Health Institute of Finland. Report of the Evaluation Panel 1995

A document prepared by the Director of each relevant Department involved in the evaluation will be provided for the evaluation. These documents describe 1) a report on progress in research over the 1996-2007 period and research plans for the 2007-2011 period, 2) the arrangement for governance and management, and 3) allocation of staff and resources, and 4) his/her plans for the future development of the Department.

Each Department involved in the evaluation will also provide the Panel a self-evaluation of 1) the appropriateness of its work to the national public health needs, 2) its role in the dissemination of research results and knowledge and technology transfer, 3) a description of the interfaces between the Department and the key players in Finland and abroad.

3.4. Evaluation of the Department of Mental Health and Alcohol Research

Previous evaluation of the department was conducted in 1995 by the international panel reviewing the KTL. The panel recommended that:

- a. the programme should be focused further and directed primarily at developing the programmes in a) the genetics of mental disorders, b) the long term studies of the determinants of mental illness in adults and in childhood and adolescence, and c) on the psycho-social aspects of genetic screening;
- b. studies in health psychology should be more directly focused and form an integral component of the principal research themes of the Division and that other projects should be allowed to lapse in due course;
- c. the work on the possible viral origin of schizophrenia should not be undertaken.

Since 1996 the genetics of mental disorders has been one of the key research areas of the department. The long-term cohort studies from childhood and adolescence to adulthood and studies concerning development during adulthood have been strongly represented on our research agenda. Research on genetic screening was continued by the same team responsible for health psychology, but due to an organizational change, in the Department of Epidemiology. The laboratory-based studies on infectious etiology of schizophrenia were never started. However, register-based epidemiological studies on the association between schizophrenia and viral epidemics in Finland were successfully conducted in our research program as part of a more general approach to the etiol-

ogy of schizophrenia. Finland and our Institute have internationally exceptionally good health statistics to conduct such studies.

The Academy of Finland evaluated the psychiatric research in Finland in 1995 by using an international peer review (Marie Åsberg, John Cooper, Eugene Paykel and Per Vaglum: Psychiatric Research in Finland 1995. Publications of the Academy of Finland 8/96). The psychiatric research conducted at the KTL was evaluated very positively.

Department of Alcohol, Drugs and Traffic was also evaluated as a part of general evaluation of the KTL in 1995. The Panel recommended that:

(1) a detailed and radical appraisal of opportunities for the future should be undertaken in the light of impending changes and transfer of research staff from the State Alcohol Monopoly to the KTL;

(2) those small scale research activities which do not relate directly to the main research themes of the Department (ie the studies on mechanisms of addiction and those on the pharmacokinetics and safe use of drugs) should be accorded a low priority and discontinued.

The functions and laboratories of the department joined the Department of Mental Health on May 1, 1996. The structure, functions and research program of the current Drug Research Unit has been totally renewed in the course of years.

Research staff of the former State Alcohol Monopoly moved to the KTL on May 1, 1996 as a separate department, but was merged with the Department of Mental Health from January 1997 on. Alcohol Research Unit has not been evaluated. However, two internationally famous alcohol researchers (professors Henri Begleiter and Harold Kalant) reviewed the research based on genetic animal models (mainly so-called AA- and ANA-rats) used by the unit, and supported the continuation of this activity and underlined the scientific opportunities it would offer to basic alcohol research at the KTL. The raising of rat lines was moved away from the department and it is nowadays a special supportive function run by a separate animal unit.

4. DEPARTMENT OF MENTAL HEALTH AND ALCOHOL RESEARCH

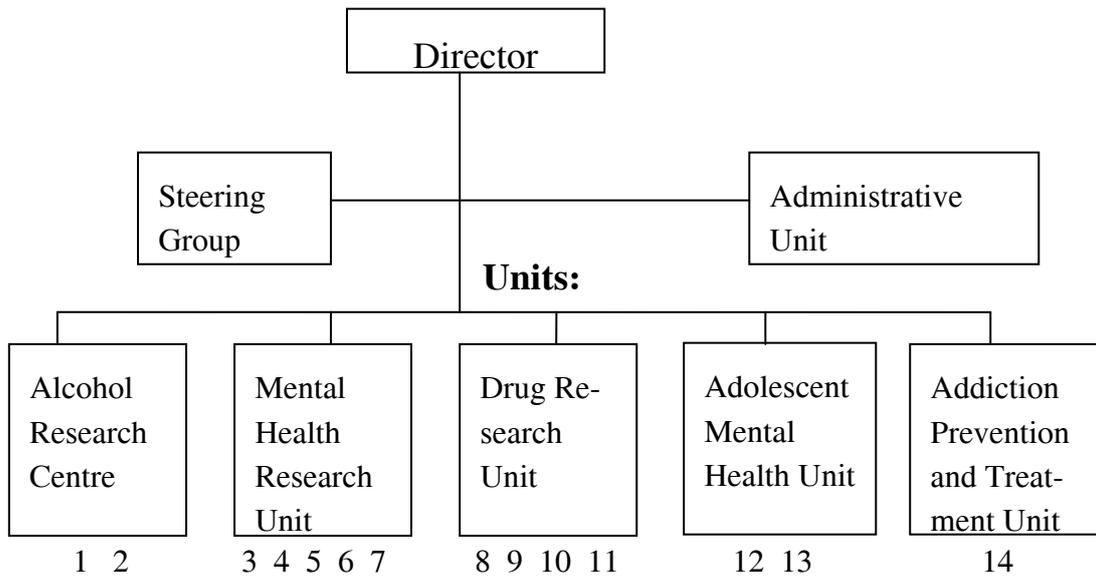
4.1. Background

The department of Mental Health and Alcohol Research started as Mental Health Research Unit, responsible only for the National Suicide Prevention Project, in May 1986. The functions extended in the course of the first five years. The Department of Mental Health was established as a part of the reorganization on the whole KTL in 1992. The functions of the Drug Research Unit were merged with the department in May 1996. The Department of Mental Health and Alcohol Research started in its current form in 1997 when biomedical alcohol research joined the department after being excluded from the state monopoly ALKO as a part of the national reorganization of the Finnish alcohol policy. The department has functioned in three separate locations relatively apart from each other. In October 2007 two units on mental health and administrative functions will move to the main building area (Mannerheimintie 166, building C) close to drug research unit (Mannerheimintie 166, building F). Alcohol research will remain apart in its current location (Tukholmankatu 2).

4.2. Objectives and organization

The primary task of the department is to study, monitor, promote and protect the mental health of the population. We aim to prevent and reduce problems caused by mental disorders and substance use. In order to achieve these goals our department (1) conducts high quality scientific research, (2) collaborates with both national and international organizations and experts, (3) provides expertise to decision makers, health professionals and the public, and (3) produces high quality laboratory services for screening and assessment of alcohol and drugs.

In 2006 there were five research units and a small administrative unit in the department. The scientific and expert work was mainly conducted in 13 different projects (research programs, Figure 1). Project teams consisted of KTL's researchers, assisting personnel and external experts participating in the project. Every researcher could be a member in one or several projects.

Figure 1. **Organization of the Department****Research projects:**

- | | |
|----|---|
| 1 | Alcohol and health |
| 2 | Neurobiology of drug dependence |
| 3 | Self-destructive behavior and suicide prevention |
| 4 | Mental health development |
| 5 | Mood disorder research |
| 6 | Mood and behavior |
| 7 | Severe Mental Disorders |
| 8 | Drug research |
| 9 | Drug dependence |
| 10 | Drugs and Driving |
| 11 | Paid Service Activity |
| 12 | Mental health and psychiatric disorders in adolescence |
| 13 | Finnish Twin Studies on Mental Health and Substance Use |
| 14 | Addiction Prevention and Treatment |

Alcohol Research Unit (ATY)

Currently and in the near future, substance abuse is the most serious threat to Finnish public health. Presumably, the consumption of alcohol will increase, and illnesses and deaths related to alcohol will become more common.

The objective of alcohol research is to provide Finnish society with scientific information about alcohol.

The Alcohol Research Centre (ATY) studies the relationship between heavy alcohol use and general health, functional capacity and quality of life.

Mental Health Research Unit (MTY)

Mental health is influenced by a wide variety of factors. In order to understand them, we need information about the way mental health manifests itself in people's lives and about the factors that protect from disorders or predispose to them.

One in every five Finns has some mental disorder. According to the WHO, depression, schizophrenia, bipolar disorder and alcoholism all figure among the ten most injurious disorders. In order to improve the well-being of Finns, information about, among others, the background, progress and treatment of these disorders is of crucial importance.

The Mental Health Research Unit (MTY) works to study and promote mental health and the factors determining it. Additionally, the unit focuses on studying the occurrence, causes, prevention and treatment of mental disorders and symptoms.

Drug Research Unit (HTY)

With the increase of drug abuse, Finnish authorities have started to pay more attention to drug users and to preventing the development of addictions and developing drug addiction treatment units and methods. A cornerstone of a successful therapy is a thorough understanding of the basic mechanisms of addiction.

The objective of these studies is to produce information to promote particularly the health and functional capacity of adolescents. Also, it is our goal to contribute to the prevention and treatment of marginalisation and to keep substance abuse under control.

Drug research also develops alcohol and drug analysis and screening methods for the needs of health care, police, occupational and other authorities.

Drug Research Unit works to provide its customers with services related to drug analytics, such as alcohol, drug and medicine determination, to conduct drug research and to act as an expert in the field.

Adolescent Mental Health Unit (NMY)

Adolescence is a developmental phase during which several of the mental health disorders of adulthood appear. The monitoring studies conducted during this phase offer a good opportunity to gain a thorough understanding of the development of mental health and various mental disorders. The department uses additionally twin studies to study the mental health, drug and alcohol use and smoking of adolescents. The Adolescent Mental Health Unit was founded in its present form in January 2005.

Addiction Prevention and Treatment Unit (RHY)

Addiction Prevention and Treatment Unit (RHY) was established in 2006 and is a continuation of the clinical team of Alcohol Research Center. Our mandate is to protect, maintain and improve the health of the Finnish people and also to prevent addiction related health problems and to evaluate and implement new treatments on substance abuse. As a clinical research unit, RHY plays an important role in this process in the areas of alcoholism, drug dependence and mental health. The strength of RHY comes largely from the unique ability to take a new treatments all the way from its beginnings in theory, through animal testing, to world-class double-blind placebo-controlled clinical trials, and then on to practical application.

4.3. Staff and resources

The Department has been functioning in its current form since 1997. The current functions and partially also the staff and basic resources of the Mental Health and Adolescent Mental Health Units are based on the functions launched as new functions 5-10 years earlier. The basic functions of the Substance Use Unit are from the 1970s and

early 1980s, from the period when the KTL produced mainly laboratory services. The basic staff and resources of the Alcohol Research Unit and the RHY come from the period before 1996, when the unit was a part of the state alcohol monopoly, ALKO. In 1996 staff with permanent service contract was 25. 3 of the total staff (n=48) had professor positions, 4 were assistant professors or lecturers (docents), 16 had some other academic degree, and the rest were technical staff. At the end of 2006 altogether 102 persons were employed by KTL. 8 had professor positions, 13 were assistant professors, 50 had some other academic degree, and 31 were technical staff.

About 40 % of the budget is direct funding by KTL, 20 % is based on income from laboratory services, and 40 % on external funding from outside the institute.

Table 1. Personnel employed by KTL 31.12.1996 and 31.12.2006

Year	Staff	Man-year	Researchers	Technical staff
1996	48	–	22	26
2006	102	85,66	50	52

Table 2. KTL Research Budget for the year 2007 by units and projects

UNIT	PROJECT	
	Alcohol an Health	243 236
	Neurobiology of Drug Dependence	353 536
ATY		676 554
	Self-destructive Behavior and Suicide Prevention	37 725
	Mental Health Development	76 603
	Mood Disorder Research	42 605
	Mood and Behavior	14 137
	Severe Mental Disorders	139 556
MTY		444 498
	Drug Research	83 385
	Drug Dependence	231 738
	Drugs and Driving	45 299
HTY		360 422
	Mental Health and Psychiatric Disorders in Adolescence	45 104
	Finnish Twin Studies on Mental Health and Substance Use	67 024
NMY		122 188
RHY	Addiction Prevention and Treatment	300 105
MAO		2 160 00

4.4. Research areas

The two main research areas of the department are mental health and substance use research.

Mental health research has been focused on depression and suicide, severe mental disorders (psychoses), determinants and development of mental health, and mental health of adolescents.

Within mental health our knowledge and competence has mainly been in epidemiological population, cohort and intervention studies using Finnish health registers, clinical assessments, questionnaire studies, brain imaging, neuropsychological testing, twin studies, molecular genetics and genetic epidemiology.

Substance use studies has been focusing on mechanism of alcohol drinking and its pathological effects, alcohol's effect on steroid hormones, neurobiology of alcohol dependence, pharmacological and clinical studies on drug dependence, drugs and driving.

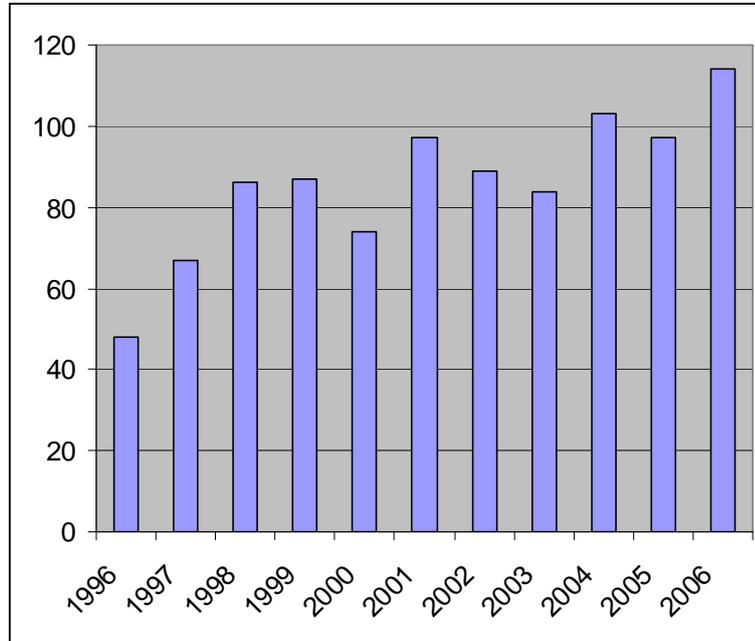
The special advantages in substance use studies have been the opportunity to use special genetic AA and ANA rat lines which have been developing in Finland since the 50ies for alcohol studies. Similarly we have had good opportunities to conduct drug dependence studies in mice. We also have nationwide prospective data on alcohol and drugs in the traffic and persons driving under the influence of alcohol and psychoactive drugs.

4.5. Scientific impact of research

The scientific level of research has increased steadily if measured by the impact factors of the publications. Annually we are publishing more than 100 international scientific reports, mostly in good international journals. Number of the publications cited more than 100 times is over 20. We are a leading scientific research center in Finland. We have a good international reputation and position in the field of mental health if measured by publications, international contacts, collaboration and funding. The impact of psychiatric and psychological research at our institute has been evaluated above that in the Karolinska Institut in Sweden and closes that at the University of Harvard (see Web of Science).

Table 3. **Original articles and reviews of the department 1996-2006**

1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
48	67	86	87	74	97	89	84	103	97	114



4.6. Public health impact

The expertise of the KTL concerning mental health and substance use issues is widely used by the the ministries (mainly by the Ministry of Social Affairs and Health, but also by Interior Affairs, Transportation, and Justice) in planning and law-drafting, occasionally directly also by the Government and the Parliament. In Finland the ministries are relatively small and expert institutes and agencies under the ministries are relatively large. This requires that The Department of Mental Health and Alcohol Research has to have expertise of the field quite broadly. We have participated in a number of committees and expert groups in various roles in developing national policies, programmes and guidelines. For example, we have had chairperson roles in national consensus meetings of depression, panic disorder, drug dependence and psychotherapy. Similarly, we have chairpersons and leading experts in task groups delivering the national guidelines both for the treatment of alcohol problems, drug dependence and depression. We have also participated as experts at the ministry of social affairs and health

in the planning and conducting the national alcohol and drug programs, working group for tsunami victims, treatment of drug dependence, national program for mental health and substance use problems. We have supported our ministry as experts of mental health and substance use issues in several international meetings as delegates of Finland, and participated in international collaboration as experts and consultants within WHO, European Union, Council of Europe and United Nations, and collaborated with Nordic and Baltic countries and with Russia.

We have continuously and largely used the internet, KTL's publications, domestic professional newspapers and the mass media to inform professionals, decision makers and the citizens about mental health and substance use, and to affect their health behaviour and healthy choices. We have had for several years close collaboration with municipalities of Helsinki, Vantaa and Espoo and with Helsinki University Central Hospital and with some other regions for the development of mental health care system and services and delivering modern and updated treatments in the field of mental health. We have been editing the leading Finnish textbooks of psychiatry and substance use disorders. Our senior members have several leading positions in professional associations, foundations, and associations representing "the third sector" of society.

4.7. Proposal for future directions

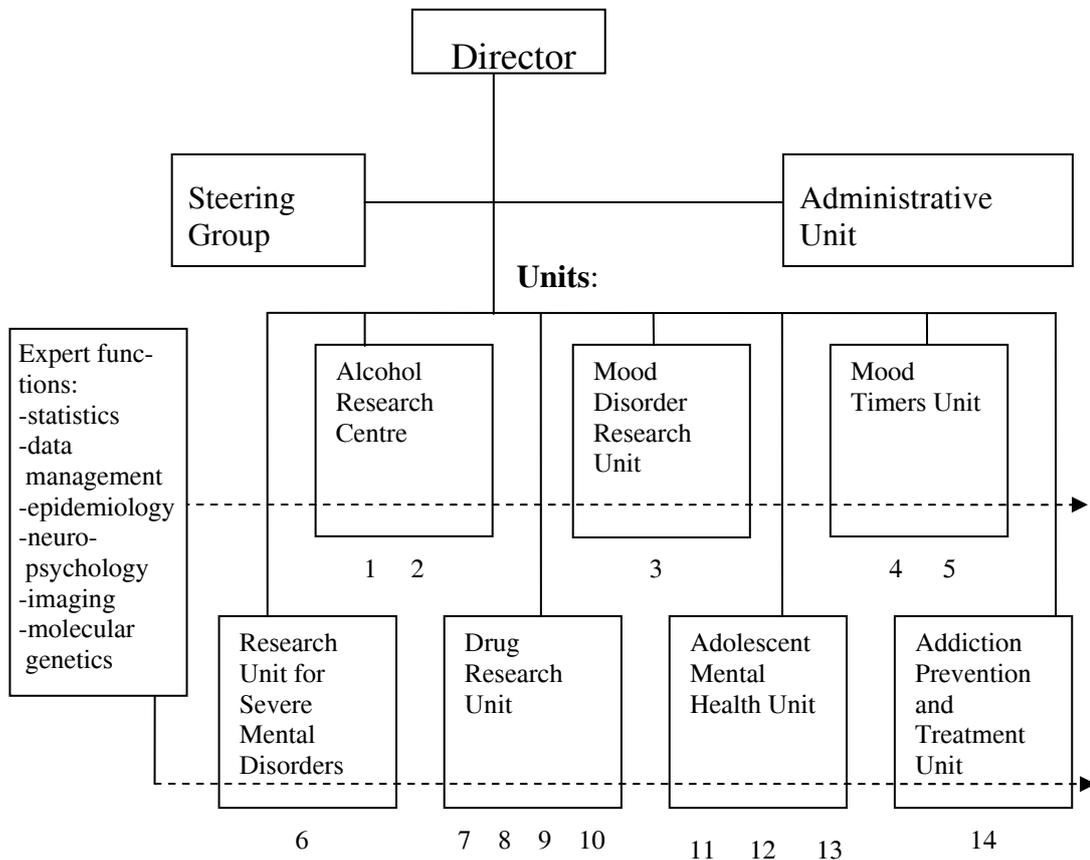
Our aim is to continue all the main research and public health areas we currently have. Our vision is to be a continuously changing leading expert and research center of mental health and substance use in Finland also in the future, providing all those services and support functions expected by our owners and based on the KTL law, the program of the government, the strategies of the Ministry of Social Affairs and Health and KTL, and annual action plans. The balance between public health work and scientific research is moving and will probably move in a direction which emphasizes even more the domestic needs of public health within mental health and substance use problems in Finland. To guarantee the knowledge base of our expertise and validity of public health work, our scientific work must stay at the high international level and be based on our national needs and special national opportunities. We have to develop our research programs more focused in every area to keep and enhance our current positions. We will need more external funding and yet keep stronger and more independent position as a partner in international collaboration. We need to strengthen the human resources directed especially to mental health work and critically plan possible reallocation of the resources now connected with substance use area. The new research area we are possibly launching in the future is widening the task of adolescent mental health to also in-

clude the whole childhood from pregnancy through all phases of childhood to adolescence and further to adulthood. In addition, we have plans to start to study pharmacoepidemiology of the use of psychotropic drugs. We sincerely believe that our current staff is qualified enough to adapt to continual changes and attain these goals.

The major challenges ahead are connected with very probable changes in the structure of current institutions under the Ministry of Social Affairs and Health. These changes expected to start from the year 2009 on will very probably concern also the area of mental health and substance use. So, we are prepared to integrate with the function from our sister organizations, even receive them as a part of our own functions. Our plan is that also in the future the mental health and alcohol and drug issues would be functioning well-integrated within the same department as they do in the WHO (Geneve) and in most public services in Finland.

In the near future, within next 3-10 years, we will have several changes in the senior staff of department due to the age-structure of the personnel.

We will change the structure and functions of the department from January 2008 by increasing the autonomy of some research projects by stabilizing their functions by forming three new units. We will also allocate projects in a little bit new way and strengthen the roles of several expert teams (statistics and data management, epidemiology, neuropsychology, imaging, and molecular genetics) in the matrix on the department.

Figure 2. **The Organization of the Department 2008-****Research projects:**

- 1 Alcohol and health
- 2 Neurobiology of drug dependence
- 3 Mood disorder research
- 4 Mood and behavior
- 5 Self-destructive behavior and suicide prevention
- 6 Severe Mental Disorders
- 7 Drug research
- 8 Drug dependence
- 9 Drugs and Driving
- 10 Paid Service Activity
- 11 Mental health and psychiatric disorders in adolescence
- 12 Finnish Twin Studies on Mental Health and Substance Use
- 13 Mental health development
- 14 Addiction Prevention and Treatment

5. ALCOHOL RESEARCH CENTRE

5.1. Alcohol and health

5.1.1. Research and public health significance of the area

Our research has been divided into three main areas: mechanisms of alcohol drinking and its pathological effects; alcohol, steroid hormones and behavior; and epidemiology of alcohol and health. Mechanisms of alcohol drinking and its pathological effects have traditionally been subdivided into two aspects: the role of acetaldehyde in the actions of alcohol and animal models of alcoholic liver disease. The acetaldehyde aspect has involved the development of the appropriate analytical methods, establishing the *in vivo* acetaldehyde levels, characterizing the regulation of its metabolism, and settling its role in the etiology of alcohol addiction and related diseases. In conclusion, our research shows that acetaldehyde plays a crucial role in the biological regulation of alcohol drinking and in most types of tissue damage and in the development of alcohol-related cancers.

The basic research on the alcohol-related liver disease in rats has involved the separation and characterization of the different hepatic cell types, assessing the differential vulnerability regarding pathological development, determining the impact of the P450 2E1 enzyme, settling the interrelations between the roles of endotoxin, CD14 receptors, complement, inflammation and cytokine factors. In conclusion, the perivenous cells in connection with active 2E1 are specifically vulnerable to the pathological developments. The interplay between endotoxin, CD14 receptors, complement, inflammation and cytokine factors is important in the development of alcoholic liver disease.

The area of alcohol, steroid hormones and behavior has been subdivided into three aspects: effect of alcohol on steroid hormones; alcohol, steroid hormones, sexual and aggressive behavior; and steroid hormones and alcohol drinking. The effects of alcohol on testosterone have been investigated in rats, *in vivo* and *in vitro* experiments, as well as in human intervention studies. In conclusion, the overall result of the effects by alcohol is depending on the subtle balance between inhibition of testosterone biosynthesis and breakdown. Especially in situations involving acute stress, testosterone elevation seems to be the prominent response to alcohol.

The effect of testosterone on sexual and aggressive behaviors has been studied in both men and women. In conclusion, testosterone associates with physical and violent

behavior. Estradiol reduces the physical but promotes the psychological aggression. High testosterone does not seem to initiate sexual or aggressive actions, but rather provides the force by which these actions are exerted.

Alcohol-derived testosterone elevation as a potential reinforcer, which could be an important factor in the etiology of alcohol addiction, has become a prime research target in our group. In conclusion, we propose the theory that alcohol-induced testosterone elevations could, through an increasing effect on the feedback regulation of testosterone biosynthesis, elevate the concentrations of hypothalamic β -endorphin and thus promote alcohol drinking. In addition, we suggest that stress could be a further promoting factor for the testosterone-mediated reinforcement of alcohol drinking.

Our epidemiological research is focused on hypothesis-derived approaches, in which we have tested in population studies some of our hypotheses derived from basic research. So far, we have been able to verify the role of the CD14 receptor in the etiology of alcoholic cirrhosis, the role of acetaldehyde metabolism in alcohol addiction and the role of testosterone in adolescent alcohol drinking.

The aim, purpose and significance of our basic research is to generate and pass out relevant knowledge, the larger information and evaluation of which would be helpful and beneficial for our society in reducing alcohol consumption, its harmful health effects and the amount of alcohol-related violence, as well as in developing new treatments for alcoholism.

In addition, our group members within the limit of their expertise and ability are encouraged to personally take active part in the alcohol-policy decision making at all relevant levels.

5.1.2. The main scientific achievements

Mechanisms of alcohol drinking and its pathological effects

Role of acetaldehyde in the actions of alcohol

The development of methods for the determination of acetaldehyde in blood and tissues of rats and mice by headspace gas chromatography. The discovery and elimination of ethanol-derived artifact acetaldehyde formation during the analytical procedures.

Thiourea blocks artifact acetaldehyde formation from tissue extracts but correction procedures should be used for minimal artifact acetaldehyde formation in blood extracts.

The assessment of acetaldehyde levels in blood, liver and brain during alcohol intoxication in rats and mice. In the brain, no detectable acetaldehyde levels can be found during normal alcohol intoxication. Most of the acetaldehyde in rat blood is bound to the hemoglobin.

The characterization of the hepatic acetaldehyde metabolism in rats. Novel data displayed that ethanol-derived acetaldehyde is mainly oxidized in the mitochondria and that this reaction is regulated by the aldehyde dehydrogenase activity and the reoxidation of NADH.

The development of the novel perchloric acid/saline method for the human blood acetaldehyde determination by headspace gas chromatography. The discovery and elimination of ethanol-derived artifact acetaldehyde formation during the analytical procedures. Correction procedures should be used for minimal artifact acetaldehyde formation in blood extracts. In spite of a number of early reports of human blood acetaldehyde levels our conclusion still holds, according to which no detectable ($<0.5 \mu\text{M}$), adequately determined "free and/or loosely bound" acetaldehyde has not yet been found in venous blood during normal alcohol oxidation in men. However, we have detected low acetaldehyde levels ($1\text{-}3 \mu\text{M}$ on average) in women at high estradiol conditions.

The assessment of breath and salivary acetaldehyde in humans. Breath acetaldehyde seems to reflect more accurately systemic concentrations compared with the saliva, the acetaldehyde of which almost exclusively is of microbial origin.

The role of acetaldehyde metabolism in the regulation of alcohol drinking. Elevated acetaldehyde levels as the consequence of decreased aldehyde dehydrogenase activity and or increase rate of alcohol metabolism was found to decrease voluntary alcohol consumption in rats (an animal model for Asian populations with elevated acetaldehyde levels during alcohol drinking).

Recognition of the dual effect of acetaldehyde on alcohol drinking in experimental animals as well as in humans. Peripherally elevated acetaldehyde levels protects against alcohol drinking, but centrally produced acetaldehyde promotes drinking.

The development of animal model for genetic manipulation to reduce alcohol drinking: demonstrated by transplanting aldehyde dehydrogenase deficient liver to rats selected for high alcohol preference and by a transgenic mouse model.

Animal models of alcoholic liver disease

Digitonin-collagenase perfusion method for the separation and characterization of periportal and perivenous rat hepatocytes. The perivenous region is specifically susceptible for the development of alcoholic liver disease (ALD). This seem to be explained by the ethanol-inducible cytochrome P450 2E1, which has potentially pro-oxidative and toxicological properties, and the expression of which is pronounced in the perivenous region of liver. The important events in the early development of ALD probably involve increased P450 2E1 expression, which subsequently leads to increased oxidative stress and the release of proinflammatory cytokines.

Gut-derived endotoxins (lipopolysaccharide, LPS), which activate liver Kupffer cells via their CD14 receptor, promote alcohol-induced liver injury.

Complement-mediated inflammation may promote the development of alcoholic liver disease. Ethanol-induced steatosis seen in normal (C3(/)) mice was absent in livers of C3-deficient (C3(/)) mice. Thus, these ethanol-induced alterations observed exclusively in complement factor C3(/) mice contribute to protection against fatty infiltration and subsequent inflammatory processes in the liver of these mice.

Alcohol, steroid hormones and behavior

Effect of alcohol on steroid hormones

Effect of alcohol on testosterone and corticosteroid metabolisms and levels in males. A high dose of alcohol generally elevates corticosteroid and lowers testosterone levels. The testosterone reduction was explained by inhibited testosterone synthesis in the testes. Recently we observed that a low dose of alcohol may, in fact, elevate testosterone levels in men. A landmark finding was that alcohol generally, regardless of dose, elevates testosterone levels in women. The testosterone elevation was due to inhibited breakdown of testosterone in the liver. The testosterone elevation explains the androgenization in women chronically drinking alcohol.

Alcohol, steroid hormones, sexual and aggressive behavior

Alcohol-derived testosterone elevations explain sustained activation of sexual behavior in women. Sex steroids play a role as cue factors in human pair mating.

Stress- and alcohol-mediated cortisol elevation is associated with increased aggressive behavior. Alcohol-related male physical aggression is promoted by elevated testosterone levels and inhibited by elevated estradiol levels. On the other hand, elevated estradiol levels enhance alcohol-related psychological aggression in men.

Steroid hormones and alcohol drinking

Stress and corticosterone promotes alcohol drinking in rats. High endogenous testosterone levels and alcohol-mediated testosterone elevation may promote alcohol drinking in rats and in humans. The alcohol-mediated testosterone elevation is pronounced during stress, which may be channeled via endorphin-opiate mechanisms to reinforcement and to the etiology of alcohol addiction.

Epidemiology of alcohol and health

Promoter polymorphism of the CD14 endotoxin receptor gene displayed a risk factor for alcoholic liver disease. The results suggest that the T allele confers increased risk of alcoholic liver damage. In particular, TT homozygotes are at a high risk to develop cirrhosis. Thus, the importance of the endotoxin-CD14 receptor pathway in the development of alcoholic liver disease is supported.

In analyses of twins as individuals, higher testosterone levels characterized boys reporting ever drinking, more frequent intoxication, high density drinking, more alcohol symptoms, and diagnosed alcohol dependency on interview. Adjusting for pubertal development, only associations with symptom count and diagnosis remained significant.

CYP 2E1 and ALDH1 A1 polymorphisms demonstrate risk factors for the disposition to develop alcoholism. These findings support the importance of the brain alcohol and acetaldehyde metabolism in the etiology of alcoholism.

5.1.3. The main public health achievements

Updating the carcinogenic effects of alcohol and its metabolic product acetaldehyde at the WHO associated International Agency for Research on Cancer (IARC) in Lyon 5-14.2007 (published in *Lancet Oncology* 8: 293-293, 2007), represents the main international health achievement of our group so far. The chairmanship of the mechanistic section, which was appointed to us based on our expertise on the role of acetalde-

hyde in the actions of alcohol, made it possible for us together with other leading scientist in the area to bring for the plenary sessions convincing new evidence for the carcinogenic effect of acetaldehyde. The inclusion of new WHO health directives regarding the alcohol-derived acetaldehyde will be beneficial for about 40 % of the Asian population having an inherited disposition for ineffective acetaldehyde metabolism. Currently, every third individual of such a genotype will create cancer in the upper digestive tract if they heavily consume alcohol.

National public health achievements include expertise from our group, which has contributed correct and improve the law enforcement procedures regarding drunken driving. Another example is the active part in the alcohol policy decision-making about the tax regulation of our alcoholic beverages. Here we have had an impact in enforcing actions to reduce the overall alcohol consumption in Finland. In general, our annual participation in the national alcohol policy discussion is including up to 100 public advisory tasks, statements, interviews, etc.

5.1.4. Funding for research and public health programs

The project has been funded to the main part by The National Public Health Institute and to some extent by grants from Signe och Ane Gyllenberg, Ella och Georg Ehrnrooth and Yrjö Jahnsson foundations, Finska Läkaresällskapet, the Finnish Foundation for Alcohol Studies, and from the Academy of Finland.

5.1.5. Personnel

Peter Eriksson, PhD, Docent, Group leader

Kai Lindros, PhD, Docent, Senior scientist (retirement 1.6.2007)

Sirkku Saarikoski, PhD, Senior scientist

Igor Bykov, MD, Scientist

Tiina Etelälähti, MSc, Graduate student

Sebastian Forsblom, Graduate student

Tuomas Saarenmaa, Graduate student

Katri Pakarinen, Graduate student

Maria Palmen, MSc, Research assistant

Hilkka Salohalla, Research assistant

Tuula Mäkelä, Research assistant

5.1.6. Collaboration

Carr, Lucinda, PhD, Professor, Department of Medicine, Indiana University

Fahlke, Claudia, PhD, Professor, Department of Psychology, Göteborg university

Henk Hendriks, PhD, Department of Nutritional Physiology, TNO Food and Nutrition Research, The Netherlands

Kaprio, Jaakko, MD, PhD, Professor, Department of Public Health, University of Helsinki, Helsinki

Kauhanen, Jussi, MD, PhD, Professor, Department of Public Health and Clinical Nutrition, University of Kuopio

Mäkisalo, Heikki, MD, PhD, Docent, Department of Transplantation and Liver Surgery, Helsinki University Hospital

von der Pahlen, Bettina, PhD, Professor, Department of Psychology, University of Åbo Akademi

Rose, Richard, PhD, Professor, Department of Psychological & Brain Sciences, Indiana university

Sarkola, Taisto, MD, PhD, Hospital for Children and Adolescents, University of Helsinki

Seppä, Kaija, MD, PhD, Professor, Department of General Practice, University of Tampere

Wilhelmsen, Kirk, MD, PhD, Professor, Department of Genetics, University of North Carolina

5.1.7. Proposal for future work and expected benefits

Mechanisms of alcohol drinking and its pathological effects

The investigation on the role of acetaldehyde in the actions of alcohol goes on. We will test our hypothesis on the dual effect of acetaldehyde on alcohol drinking, as well as the mechanisms of the toxic and pathological effects of acetaldehyde. The data and knowledge obtained from the basic research on alcoholic liver disease will be considered in our future epidemiological studies. Our research aim is to develop biochemical methods to reduce the levels of alcohol-derived acetaldehyde. The expected benefits of our planned research would be to establish new biomarkers for alcohol drinking and its pathological effects, to develop methods of reducing the harmful health effects by alcohol, and finding new approaches for the treatment of alcoholism.

Alcohol, steroid hormones and behavior

Our future research on the steroid area will concern the mechanisms of the alcohol-mediated testosterone elevations, and how these changes relate to the alcohol reinforcement and development of alcohol addiction. Emphasis will be put on the role of stress factors in these developments. Also other addictive drugs than alcohol will be investigated with a view to the steroid aspect. Our research aim is to evaluate our new hypothesis on the role of steroids in addiction. The eventual benefit would be to establish new markers for the disposition to addiction and to find new approaches for the treatment of addiction.

The genetics and epidemiology of alcohol and health

The future basic research on the genetics of alcohol drinking will concern our alcohol-preferring AA and alcohol-nonpreferring ANA rat lines. Here we continue from earlier results on candidate gene regions for the regulation of alcohol preference obtained in studies using whole-genome scan and which have been verified in F2 intercrosses of the AA and ANA lines. The aim is to further narrow down the relevant genomic areas by using more dense sets of microsatellite markers. The eventual benefit would be to find the relevant genes, and subsequently the mechanisms, of alcohol addiction.

Our planned collaborative epidemiological research program represents a multidisciplinary investigation of the socio-biological etiology of alcoholism in Finnish populations. The basic design is molecular-epidemiological population study (both case-

control and cross-sectional) involving both male and female control and alcoholic populations. The molecular aspect includes candidate genes and genome scanning, especially in the vicinity of known candidate polymorphisms. Other epidemiological parameters include the determination of blood steroids and state markers for excessive alcohol consumption, and a number of other more exogenous phenotypes of psycho-social nature.

An important feature of the present investigation is the hypothesis-derived approach. Thus we will put emphasis on our previously derived new hypotheses about the etiology of alcohol addiction and its harmful health consequences. These new mechanisms involve, on one hand, the metabolism of alcohol and acetaldehyde in the brain. On the other hand, we also propose that a stress-related testosterone elevation, which subsequently causes increased hypothalamic beta-endorphin affecting opiate receptors, will also increase the reinforcement and the probability to develop addiction. Thus, the primary biological trait markers to be determined in the present study will be the basal sex-steroid levels and gene polymorphisms involved in the regulation of brain alcohol and acetaldehyde metabolism and sex-steroid homeostasis.

In addition to the pathways for reinforcement we also will focus attention on the protective mechanisms against alcohol drinking. Such mechanisms relate to the alcohol and acetaldehyde metabolism outside the brain.

The overall aim of our future research program is to realize the first comprehensive multidisciplinary investigation of the socio-biological etiology of alcoholism and its harmful health effects in the Finnish population.

5.1.8. Main publications

Mechanisms of alcohol drinking and its pathological effects

Eriksson CJP, Koivisto T, Srivatanawongsa V, Martelius T, Mäkisalo H, Höckerstedt K: Manipulation of alcohol drinking by liver transplantation. *Alcohol Clin Exp Res* 21: 763-765, 1997

Alcohol-preferring AA and alcohol-avoiding ANA rat lines differ in their acetaldehyde metabolism and this has been suggested to be one reason for their different ethanol drinking behavior. To study whether acetaldehyde accumulation is indeed associated with alcohol drinking behavior and to evaluate which enzymatic differences previously observed in these rat lines are of importance in this regard, we produced an F2 generation from them. ADH and ALDH activities, and ALDH patterns were then assessed from these hybrids and correlated with their voluntary ethanol drinking and blood acetaldehyde concentrations measured during ethanol metabolism. A significant negative correlation between voluntary ethanol intake and blood acetaldehyde concentration was observed in F2 females drinking less than 17% of the total fluid as ethanol. In F2 males, hepatic microsomal high Km ALDH activities correlated negatively with blood acetaldehyde concentrations, indicating that low activity of this isoenzyme in ANA rats

could be at least in part responsible for the accumulation of acetaldehyde in their blood. Finally, F2 rats that possessed the cytosolic ALDH isoenzyme pattern most frequently found in the AA rat line drank significantly more ethanol than the animals with typical ANA pattern, suggesting that this polymorphism might also be relevant in the regulation of voluntary ethanol drinking although it is probably not associated with acetaldehyde metabolism.

Järveläinen HA, Fang C, Ingelman-Sundberg M, Lindros KO: Effect of chronic coadministration of endotoxin and ethanol on rat liver pathology and proinflammatory and anti-inflammatory cytokines. *Hepatology* 29: 1503-1510, 1999

To better understand how gut-derived endotoxins influence alcohol-induced liver injury and the expression of inflammatory cytokines a new animal model was developed. After 2 weeks on a modified ethanol-containing liquid diet, some rats also were infused with endotoxin via osmotic minipumps for 4 additional weeks. Ethanol diet alone increased plasma endotoxin threefold to 9.3 pg/mL. Endotoxin infusion increased the levels to 388 and 513 pg/mL in controls and ethanol-fed animals, respectively. Panlobular macrovesicular and microvesicular steatosis and inflammatory foci were observed in livers from both ethanol- and ethanol-endotoxin-treated animals, but there was no significant potentiation by endotoxin. Only minor changes, mainly polymorphonuclear infiltration, were seen in animals treated with endotoxin alone although the messenger RNA (mRNA) expression of both proinflammatory cytokines tumor necrosis factor alpha (TNF-alpha), interleukin 1beta (IL-1beta) and anti-inflammatory cytokines IL-4 and IL-10 were markedly increased, as shown by competitive polymerase chain reaction (PCR) analysis using cyclophilin as standard. The effect of endotoxin infusion on cytokine mRNA expression in ethanol-fed animals was not significantly different. Expression of transforming growth factor beta1 (TGF-beta1) mRNA was increased twofold by ethanol, eightfold by endotoxin, but only threefold by ethanol-endotoxin treatment. The mRNA expression of lipopolysaccharide binding protein (LBP) and CD14 endotoxin receptor was not significantly increased by chronic endotoxin treatment, contrasting with the marked elevation observed after acute endotoxin challenge. These results suggest that the tolerance observed despite sustained hepatic expression of proinflammatory cytokines is counteracted by the anti-inflammatory cytokines and by down-regulation of CD14 and LBP. Furthermore, a similar adaptation may occur in alcoholics with continuous endotoxemia.

Eriksson CJP: The role of acetaldehyde in the actions of alcohol (Update 2000). *Alcohol Clin Exp Res* 25: 15S-32S, 2001

BACKGROUND: Recent advances in the field of acetaldehyde (AcH) research have raised the need for a comprehensive review on the role of AcH in the actions of alcohol. This update is an attempt to summarize the available AcH research. **METHODS:** The descriptive part of this article covers not only recent research but also the development of the field. Special emphasis is placed on mechanistic analyses, new hypotheses, and conclusions. **RESULTS:** Elevated AcH during alcohol intoxication causes alcohol sensitivity, which involves vasodilation associated with increased skin temperature, subjective feelings of hotness and facial flushing, increased heart and respiration rate, lowered blood pressure, sensation of dry mouth or throat associated with bronchoconstriction and allergy reactions, nausea and headache, and also reinforcing reactions like euphoria. These effects seem to involve catecholamine, opiate peptide, prostaglandin, histamine, and/or kinin mechanisms. The contribution of AcH to the pathological consequences of chronic alcohol intake is well established for different forms of cancer in the digestive tract and the upper airways. AcH seems to play a role in the etiology of liver cirrhosis. AcH may have a role in other

pathological developments, which include brain damage, cardiomyopathy, pancreatitis, and fetal alcohol syndrome. AcH creates both unpleasant aversive reactions that protect against excessive alcohol drinking and euphoric sensations that may reinforce alcohol drinking. The protective effect of AcH may be used in future treatments that involve gene therapy with or without liver transplantation. CONCLUSIONS: AcH plays a role in most of the actions of alcohol. The individual variability in these AcH-mediated actions will depend on the genetic polymorphism, not only for the alcohol and AcH-metabolizing enzymes but also for the target sites for AcH actions. The subtle balance between aversive and reinforcing, protecting and promoting factors will determine the overall behavioral and pathological developments.

Bykov IL, Väkevä A, Järveläinen HA, Meri S, Lindros KO: Protective function of complement against alcohol-induced rat liver damage. *Int Immunopharmacol* 4: 1445-1454, 2004

The complement system can promote tissue damage or play a homeostatic role in the clearance and disposal of damaged tissue. We assessed the role of the terminal complement pathway in alcohol-induced liver damage in complement C6 (C6^{-/-}) genetically deficient rats. C6^{-/-} and corresponding C6^{+/+} rats were continuously exposed to ethanol by feeding ethanol-supplemented liquid diet for six weeks. Liver samples were analyzed for histopathology and complement component deposition by immunofluorescence microscopy. Prostaglandin E receptors and cytokine mRNA levels were analyzed by RT-PCR and plasma cytokines by ELISA. Deposition of complement components C1, C3, C8 and C9 was observed in C6^{+/+} rats, but not in C6^{-/-} animals. The histopathological changes, the liver weight increase and the elevation of the plasma pro-/anti-inflammatory TNF- α /IL-10 ratio were, on the other hand, more marked in C6^{-/-} rats. Furthermore, ethanol enhanced the hepatic mRNA expression of the prostaglandin E receptors EP2R and EP4R exclusively in the C6^{-/-} rats. Our results indicate that a deficient terminal complement pathway predisposes to tissue injury and promotes a pro-inflammatory cytokine response. This suggests that an intact complement system has a protective function in the development of alcoholic liver damage.

Bykov I, Jauhiainen M, Olkkonen VM, Saarikoski ST, Ehnholm C, Junnikkala S, Väkevä A, Lindros KO, Meri S: Hepatic gene expression and lipid parameters in complement C3(*l*) mice that do not develop ethanol-induced steatosis. *J Hepatol* 46: 907-914, 2007

The complement system can provoke but also participate in the repair of liver injury. Here we investigated by microarray analysis the effect of chronic ethanol consumption on hepatic mRNA expression of complement components and acute-phase proteins in complement C3-deficient (C3(*l*)) and wild-type (C3(*/*)) mice. Up-regulation by ethanol of factor B, C1qA-chain and clusterin but down-regulation of factor H, Masp-2, factor D and the terminal components C6, C8 α and C9 was seen in both strains. Ethanol up-regulated C2 and down-regulated C4bp only in C3(*l*) mice, while in C3(*/*) mice up-regulation of C1qB-chain and vitronectin was observed. The expression of factor B, C6, C1qB and factor I was lower but that of factor D higher in C3(*l*) than in C3(*/*) mice. Ethanol induced mRNA synthesis of many acute-phase proteins including SPARC and lipocalin-2, but reduced the expression of SAP. The induction of early classical and alternative pathway components and suppression of terminal pathway components and soluble regulators may thus contribute to alcohol-induced liver injury. Lipocalin-2 and SPARC emerge as new candidate markers for early detection of liver damage.

Eriksson CJP, Saarenmaa TP, Bykov IL, Heino PU: Acceleration of ethanol and acetaldehyde oxidation by d-glycerate in rats. *Metabolism* 56: 895-898, 2007

The aim of the present study was to investigate whether d-glycerate (glycerate) could accelerate ethanol and acetaldehyde (AcH) oxidation in vivo in rats by circumventing the rate-limiting step, that is, the reoxidation of the reduced form of nicotinamide adenine dinucleotide. Male rats belonging to the ANA (Alko, nonalcohol) and AA (Alko, alcohol) rat lines were challenged with 1.2 g ethanol per kilogram with or without glycerate administration (0.1-1.0 g/kg). Blood ethanol, blood AcH, and liver free glycerol concentrations were determined during ethanol intoxication. Glycerate treatment, regardless of the dose, accelerated ethanol elimination by approximately 25% ($P < .001$) in the ANA animals. Glycerate also accelerated the AcH oxidation, but perhaps not as much as the ethanol oxidation, as indicated by a trend toward elevated AcH levels. In the experiments with the AA rats, glycerate treatment elevated hepatic free glycerol levels by about 50% ($P < .05$) during alcohol intoxication. The acceleration of ethanol and AcH oxidation in conjunction with elevated glycerol levels by the treatment with glycerate supports the hypothesis that the aldehyde dehydrogenase-mediated AcH oxidation can be coupled with the reduction of glycerate to d-glyceraldehyde catalyzed by the same enzyme. Such a coupling should increase the availability of the oxidized form of nicotinamide adenine dinucleotide and thus accelerate both ethanol and AcH oxidation. Further studies are needed to investigate how the AcH could be even more efficiently oxidized to reduce the harmful effects of ethanol-derived AcH.

Alcohol, steroid hormones and behaviour

Sarkola T, Adlercreutz H, Heinonen S, von der Pahlen B, Eriksson CJP: The role of the liver in the acute effect of alcohol on androgens in women. *J Clin Endocrinol Metab* 86: 1981-1985, 2001

The hypothalamic-pituitary-gonadal and -adrenal axes are regarded as the main sites of the actions of alcohol on steroids. In the present study the effect of alcohol (0.4-0.5 g/kg, orally) on venous plasma and urinary androgens was investigated in 21 premenopausal women using oral contraceptives as well as in 10 premenopausal nonusers. After intake of alcohol, an acute elevation in plasma testosterone, a decline in androstenedione levels, and an elevation in the ratio of testosterone to androstenedione were observed in both groups. The effects lasted throughout the period of ethanol elimination and were abolished during pre-treatment with 4-methylpyrazole (10-15 mg/kg, orally). The acute effects were higher in the group using oral contraceptives than in the nonusers. The testosterone effect in plasma was reflected in the free testosterone fraction. A decline in urinary androsterone and etiocholanolone levels, the principal catabolic products of androgens, was observed during alcohol intoxication. In conclusion, the present acute effects on plasma and urinary steroid hormones seem to be explained by an inhibited catabolism mediated by the alcohol-induced change in the redox state in the liver. Our results suggests that the liver should be included as a major site in the acute endocrinological effects of alcohol on steroid hormones in women.

von der Pahlen B, Sarkola T, Seppä K, Eriksson CJP: Testosterone, 5 α -dihydrotestosterone and cortisol in men with and without alcohol-related aggression. *J Stud Alcohol* 63: 518-526, 2002

OBJECTIVE: The present investigation was designed to study steroid hormones, alcohol and aggression interactions in men with a history of alcohol-related aggression (AGG+) and in a cross-sectional control population (AGG-). **METHOD:** AGG+ (n = 40) and AGG- (n = 44) male volunteers completed the Buss-Perry Aggression Questionnaire and the revised Michigan Alcoholism Screening Test (MAST), after which plasma-free and total testosterone, 5 α -dihydrotestosterone (DHT) and cortisol were determined. **RESULTS:** The AGG+ men displayed significantly ($p < .05$) higher aggression and MAST measures compared with the AGG- men; however, no significant group differences were observed re-

garding the hormone values. Independently of the steroid hormones, MAST correlated positively with the hostility subscale in both AGG- and AGG+ groups. Free and total testosterone correlated positively with anger and DHT correlated positively with verbal aggression and anger, whereas cortisol correlated negatively with physical aggression and anger in the AGG- group. No significant correlations between steroid hormones and aggression parameters were observed in the AGG+ group. The age factor explained part of the MAST and steroid hormone correlations with aggression. A hormone and MAST independent moderation effect of age upon aggression was also found. **CONCLUSIONS:** The present study demonstrates an association between alcohol drinking and self-reported sober-state aggression, which implies that the etiology of alcohol misuse and aggressive behavior may involve common biological and/or social factors. These mechanisms, as well as age, androgens and cortisol, all represent factors that, in combination, regulate human aggression.

Apter SJ, Eriksson CJP: The effect of alcohol on testosterone concentrations in alcohol preferring and non preferring rat lines. *Alcohol Clin Exp Res* 27:1190-1193, 2003

BACKGROUND: Previous studies have reported associations between human alcohol drinking and testosterone levels. **METHODS:** In this study we investigated serum testosterone concentrations without and under the influence of alcohol in alcohol-preferring (AA) and nonpreferring (ANA) rat lines. Animals were tested in both mornings and afternoons and the alcohol doses were 0.75 and 1.50 g/kg. **RESULTS:** Higher basal serum testosterone levels were detected in the AA rats compared with the ANA rats in both mornings (152%, $p = 0.028$) and afternoons (75%, $p = 0.035$). The high alcohol dose decreased the testosterone concentrations of both the AA and the ANA rats ($p = 0.001-0.01$). The low dose, however, decreased testosterone concentrations only in the ANA line (line difference in the morning: $p = 0.027$; in the afternoon $p = 0.000$). **CONCLUSION:** The present results support previous indications of a positive association between testosterone and alcohol drinking. Furthermore, the present results, together with earlier reports on the AA and ANA rats, introduce the possibility of a connection between this association and the hypothalamic opiate system, which is also involved in the feedback regulation of testosterone synthesis.

Sarkola T, Eriksson CJP: Testosterone increases in men after a low dose of alcohol. *Alcohol Clin Exp Res* 27: 682-685, 2003

BACKGROUND: Heavy acute alcohol drinking decreases blood testosterone in men due to an effect on the testicular level. An acute increase in blood testosterone levels after a low alcohol dose has, however, recently been reported in women. The objective of this investigation was to study the effect of a low alcohol dose on testosterone in men and further elucidate the mechanism behind the effect by using 4-methylpyrazole, an inhibitor of alcohol metabolism. **METHODS:** A double-blind placebo-controlled interventional crossover trial in random order ($n = 13$). **RESULTS:** After intake of alcohol (0.5 g/kg, 10% w/v), an acute increase in plasma testosterone (from 13.5 \pm 1.2 nmol/liter to 16.0 \pm 1.6 nmol/liter, mean \pm SEM; $p < 0.05$), a decrease in androstenedione (from 5.1 \pm 0.4 nmol/liter to 4.0 \pm 0.3 nmol/liter; $p < 0.05$), and an increase in the testosterone:androstenedione ratio (from 2.8 \pm 0.3 to 4.2 \pm 0.4; $p < 0.01$) were observed. The effects were not observed during pretreatment with 4-methylpyrazole (10-15 mg/kg orally), which inhibited the ethanol elimination rate by 37 \pm 3%. **CONCLUSIONS:** Alcohol intake affects the androgen balance in men through an effect mediated by the alcohol-induced change in the redox state in the liver.

Eriksson CJP, von der Pahlen B, Sarkola T, Seppä K: Oestradiol and human male alcohol- related aggression. *Alcohol Alcohol* 38: 589-596, 2003

AIMS: In comparison to androgens, almost nothing is known about the role of endogenous oestrogens in human aggressive behaviour. This new aspect was studied in the present investigation involving men with a history of alcohol-related aggression (AGG+) and in an age-matched male control population (AGG-). **METHODS:** Male AGG+ volunteers were recruited through advertisements and the controls were drawn from the Finnish Population Register. Alcohol misuse and interpersonal partner violence were estimated by questionnaires. Endogenous hormone levels were measured from morning plasma samples. **RESULTS:** A positive association emerged between plasma oestradiol and emotional negotiation during interpersonal conflict situations. Furthermore, a negative association was observed between oestradiol and testosterone-related physical, violent, aggression in the AGG+ men. In addition, oestradiol, rather than testosterone, was positively associated with psychological aggression in both groups of men. **CONCLUSION:** It is suggested that endogenous female sex hormones may be related to empathic behaviour and could, thus, represent a counter-balancing factor in alcohol-related male aggressive behaviour. Altogether, oestrogen may represent a multifactor ingredient in the complex interactions of partner conflicts.

Apter S, Eriksson CJP: The role of social isolation in the effects of alcohol on corticosterone and testosterone levels in alcohol-preferring and non-preferring rats. *Alcohol Alcohol* 41: 33-38, 2006

AIMS: Alcohol has been reported to affect the hypothalamic-pituitary-gonadal axis (HPG-axis) and hypothalamic-pituitary-adrenal axis (HPA-axis) as expressed by increased or decreased corticosterone and testosterone levels. Both hormones have also been related to the aetiology of alcohol drinking and the development of alcoholism. Our aim has been to study these interrelations in animal models of alcohol drinking by using social isolation as a model of anxiety. **METHODS:** The effects of alcohol on serum testosterone and corticosterone concentrations were investigated in alcohol-preferring (AA) and alcohol non-preferring (ANA) rat lines. Animals were tested in mornings and afternoons with 0.75 and 1.5 g alcohol/kg. Half of the animals were kept in single cages, while the control animals were housed in groups of four individuals. **RESULTS:** The group-caged ANA rats displayed higher control corticosterone levels than the corresponding AA rats during morning sessions ($P = 0.007$). The AA rats displayed elevated corticosterone levels (AM: $P = 0.047$) and the ANA rats displayed reduced control corticosterone levels (PM: $P = 0.016$) in the single cage situation compared with the group-cage situation. Corticosterone concentrations were not affected by low doses and increased ($P < 0.05$) by high doses of alcohol in all test groups except for isolated AA rats during afternoon sessions. In general, more significant reductions in testosterone levels following alcohol administration were found in the ANA line. In group-caged AA rats, alcohol reduced testosterone levels, while no such effect was observed in isolated AA rats. **CONCLUSIONS:** We suggest that social isolation, representing stress, may constitute a situation in which the HPA and HPG axes are connected together in promoting alcohol drinking.

Epidemiology of alcohol drinking and related diseases

Järveläinen HA, Orpana A, Perola M, Savolainen VT, Karhunen PJ, Lindros KO: Promoter polymorphism of the CD14 endotoxin receptor gene as a risk factor for alcoholic liver disease. *Hepatology* 33: 1148-1153, 2001

Twin concordance studies indicate that genetic factors influence the individual susceptibility for alcoholic liver disease (ALD). Both clinical and experimental data suggest that Kupffer cell activation by gut-derived endotoxins and other bacterial products is an important pathogenic factor. Activated Kupffer cells release proinflammatory cytokines, a process that is regulated by the CD14 endotoxin receptor (CD14). Recently, a C→T (-159) polymorphism in the promoter region of the CD14 gene was detected and found to confer increased CD14 expression. In the present study, the association of CD14 promoter polymorphism with different forms of ALD was examined in 3 separate autopsy series. Among 442 men with valid alcohol-consumption data, 381 men had been moderate or heavy alcohol consumers. The allele frequency of the CD14 promoter genotype, determined by a modified cycle minisequencing technique, was 0.34 (CC), 0.51 (CT), and 0.16 (TT). The T allele was found to be associated with advanced ALD, i.e., with alcoholic hepatitis (odds ratio OR: 2.48; P = .018), and especially with cirrhosis (OR: 3.45; P = .004), but not with fatty liver, periportal fibrosis, or bridging fibrosis. The overall age-adjusted risk for cirrhosis was 3.08 (P = .01) for the carriers of the CT genotype, and 4.17 (P = .005) for the homozygous TT genotype. These results suggest that in the relatively isolated Finnish population, the T allele confers increased risk of alcoholic liver damage. In particular, TT homozygotes are at a high risk to develop cirrhosis.

Spence JP, Liang T, Eriksson CJP, Taylor RE, Wall TL, Ehlers CL, Carr LG: Evaluation of aldehyde dehydrogenase 1 promoter polymorphisms identified in human populations. *Alcohol Clin Exp Res* 27: 1389-1394, 2003

BACKGROUND: Cytosolic aldehyde dehydrogenase, or ALDH1A1, functions in ethanol detoxification, metabolism of neurotransmitters, and synthesis of retinoic acid. Because the promoter region of a gene can influence gene expression, the ALDH1A1 promoter regions were studied to identify polymorphism, to assess their functional significance, and to determine whether they were associated with a risk for developing alcoholism. **METHODS:** Sequence analysis was performed in the promoter region by using Asian, Caucasian, and African American subjects. The resulting polymorphisms were assessed for frequency in Asian, Caucasian, Jewish, and African American populations and tested for associations with alcohol dependence in Asian and African American populations of alcoholics and controls. The functional significance of each polymorphism was determined through in vitro expression analysis by using HeLa and HepG2 cells. **RESULTS:** Two polymorphisms, a 17 base pair (bp) deletion (-416/-432) and a 3 bp insertion (-524), were discovered in the ALDH1A1 promoter region: ALDH1A1*2 and ALDH1A1*3, respectively. ALDH1A1*2 was observed at frequencies of 0.035, 0.023, 0.023, and 0.012 in the Asian, Caucasian, Jewish, and African American populations, respectively. ALDH1A1*3 was observed only in the African American population, at a frequency of 0.029. By using HeLa and HepG2 cells for in vitro expression, the activity of the luciferase reporter gene was significantly decreased after transient transfection of ALDH1A1*3-luciferase compared with the wild-type construct ALDH1A1*1-luciferase. In an African American population, a trend for higher frequencies of the ALDH1A1*2 and ALDH1A1*3 alleles was observed in a population of alcoholics (p = 0.03 and f = 0.12, respectively) compared with the control population. **CONCLUSIONS:** ALDH1A1*2 and ALDH1A1*3 may influence ALDH1A1 gene expression. Both ALDH1A1*2 and ALDH1A1*3 produce a trend in an African American population that may be indicative of an association with alcoholism; however, more samples are required to validate this observation. The underlying mechanisms contributing to these trends are still unknown.

Saarikoski ST, Suihiala T, Holmila R, Impivaara O, Järvisalo J, Hirvonen A, Husgafvel-Pursiainen K: Identification of genetic polymorphisms of CYP2S1 in a Finnish Caucasian population. *Mutat Res* 554: 267-277, 2004

CYP2S1 is a recently discovered member of the cytochrome P450 (CYP) gene superfamily. Interestingly, even though the DNA sequence identifies it as the sole member of the new CYP2S family, CYP2S1 exhibits many features typical to CYP1 family members, e.g. dioxin-inducibility mediated by the aryl hydrocarbon receptor (AHR) and the aryl hydrocarbon receptor nuclear translocator (ARNT). In addition, CYP2S1 metabolises some aromatic hydrocarbons as well as cellular substances. These characteristics, together with a wide extrahepatic tissue distribution, suggest that CYP2S1 may have an important role in both exogenous and endogenous metabolism. This is the first study characterising CYP2S1 alleles and naming them with the recommended CYP allele nomenclature. We used denaturing gradient gel electrophoresis (DGGE) and direct sequencing to investigate genetic variation of CYP2S1 in 100 male Finnish Caucasians. Those exons in which variation was found were examined in subsequent 100 subjects. The coding region of all of the nine exons, as well as a 449 bp fragment of the proximal promoter region, was analysed. This systematic investigation revealed eight single nucleotide polymorphisms (SNPs), which comprise nine different variant alleles (haplotypes), in addition to the wild-type allele. Seven of the SNPs occurred in the protein-coding areas and one in the proximal 3' untranslated region (3'UTR). Two of these sequence variations (10347C > T and 13106C > T) result in non-conservative amino acid substitutions, i.e. Arg380Cys and Pro466Leu, respectively. The respective allelic variants, CYP2S1*2 ([10347C > T]) and CYP2S1*3 (13106C > T; 13255A > G), occurred in our study population at frequencies of 0.50 and 3.75%, respectively. The most common of the variant alleles was CYP2S1*1H (23.8%), harbouring a 13255A > G substitution located in the 3'UTR.

Eriksson CJP, Kaprio J, Pulkkinen L, Rose RJ: Testosterone and alcohol use among adolescent male twins: Testing between family associations in within family comparisons. *Behav Genet* 35: 359-368, 2005

We examined associations of testosterone (T) and alcohol use in adolescent twin brothers, conducting both between- and within-family analyses. The twins completed semi-structured interviews, provided two saliva samples to assay T, and reported their drinking patterns and pubertal development. We adjusted T levels for diurnal/seasonal effects and association with pubertal maturation. In analyses of twins as individuals, higher T levels characterized boys reporting ever drinking, more frequent intoxication, high density drinking, more alcohol symptoms, and diagnosed alcohol dependency on interview. Adjusting for pubertal development, only associations with symptom count and diagnosis remained significant. The association with frequent intoxication replicated among drinking-discordant twin brothers, effectively ruling out between-family confounds, but that association was not significant after adjustment for pubertal development. The phenotypic correlation between T and pubertal maturation is largely genetic, inviting study of the magnitude and meaning of linkages between testosterone and symptoms of alcoholism on follow-up in early adulthood.

5.2. Neurobiology of drug dependence

5.2.1. Research and public health significance of the area

The burden of disease attributable to alcohol-related health consequences in Finland is remarkable. Although intoxication is often an important mediator of harm, dependence can significantly exacerbate the hazards. Majority of the burden comes from heavy drinking and alcohol dependence, because heavy drinkers consume a significant proportion of total alcohol consumption. It is also evident that alcohol dependence predisposes to use of other drugs including nicotine. Treatments and other interventions for problem drinkers and alcoholics are potentially beneficial in the management of alcohol-related problems.

Alcohol addiction is characterized by compulsive, chronic and relapsing consumption of alcohol. Moreover, the vulnerability to develop an addiction to alcohol is influenced by a combination of environmental and genetic factors. The transition from recreational alcohol use to alcohol abuse and addiction is not well understood. It probably involves a number of neural mechanisms, such as acute sensitivity of various neuronal systems to alcohol and neuroadaptations resulting from repeated and chronic exposure to alcohol. Understanding these mechanisms is of great importance in translating basic findings on the neural actions of alcohol into potential clinical applications.

Development of effective pharmacotherapies, however, relies on our understanding of the mechanisms underlying addiction to alcohol. Animal models have proved useful particularly in exploring the neural basis of addiction to alcohol and other drugs of abuse. The purpose of the present project is to clarify the role of various neurochemical systems as well as the contribution of neurobehavioral sensitization to the development of addiction to alcohol using the animal model of alcohol-preferring AA and alcohol-avoiding ANA lines of rats.

Role of central opioidergic systems and neurobehavioral sensitization in addiction to alcohol

Several strain-specific differences have been previously found in opioidergic mechanisms both on behavioral and neurochemical level between the AA and ANA rats. These differences may contribute to the higher sensitivity of AA rats to the effects of acute and repeated administration of opioids, and higher preference for oral etoni-

tazene than ANA rats. The project addresses on neurochemical, behavioral and molecular levels the role of specific neuronal and neuroadaptive mechanisms in intake of ethanol, and development of addiction to it. Neurochemical aspects include neurobehavioral characterization of the rat lines by measuring opioid peptides in the nucleus accumbens, ventral tegmental area, and central amygdala, as well as GABA in the ventral pallidum of AA and ANA rats administered ethanol or morphine. Behavioral analyses include investigation of the role of ventral pallidum in ethanol intake, and testing AA and ANA rats for possible differences in the rewarding effects of morphine and nicotine, using conditioned place preference. Molecular studies will address the role of the expression of μ and δ opioid-receptors in ethanol self-administration using viral transfer of opioid receptor gene into the brain. Differences in deltaFosB and BDNF expression, as well as in the chromatin structure or DNA methylation pattern of BDNF and trkB genes between drug naïve and drug-treated AA and ANA rats will be studied.

Long-term neurochemical and behavioral effects of exposure to drugs of abuse in an adolescent, genetic animal model

Human adolescent studies suggest that during adolescence drugs of abuse may have distinctive effects making adolescents more vulnerable than adults to the long-term effects of exposure to alcohol or other drugs of abuse, and contributing to increased risk to develop drug dependence not only on the particular drug but also on other drugs, and that genetic factors may further increase vulnerability.

The neurobehavioral and genetic mechanisms underlying increased risk for alcohol and drug dependence during adolescence are not well understood. The developing brain undergoes extensive maturation processes during adolescence. On the other hand, drugs of abuse induce adaptive changes in the brain that are hypothesized to contribute to development of addiction and are manifested for instance as behavioural sensitisation.

The overall goal of the study is to provide information for better understanding of the association between early onset substance abuse and the risk for alcohol or drug dependence later in life. The study will characterize the neurobehavioral and genetic mechanisms of enhanced vulnerability to substance abuse during adolescence by studying the long-term neurobehavioral effects of drugs of abuse using selectively bred alcohol-preferring AA (Alko Alcohol) and alcohol non-preferring ANA (Alko Non-Alcohol) rats, developed in this laboratory, which offer a model to study neurobehavioral and genetic factors of enhanced vulnerability to drugs of abuse. Consequently, behavioral sensitization induced by repeated administration of four major drugs of abuse - alcohol, nicotine, morphine, or a cannabinoid drug - during adolescence or during adulthood will be studied. The role of neuroadaptive changes (sensitization) in vul-

nerability to drugs of abuse self-administration of alcohol will be assed by comparing adult AA- and ANA-rats that have been exposed to drug treatment during adolescence to those receiving the same regime of drug treatment during adulthood.

Drug-induced release of monoamines and amino acids in the nucleus accumbens and ventral tegmental area, two structures of the reward pathway, using in vivo microdialysis will also be compared between differentially treated, adult AA- and ANA-rats. The molecular studies will examine the putative differences in the expression of the key genes known to be involved in plasticity-related phenomena in the brain, as well as the genes for the primary molecular targets for each specific drug.

Neural pathways and transmitter systems in relapse

Drug and alcohol dependence are chronic relapsing disorders characterized by impaired ability to control drug taking, continued use at the expense of other behaviors and despite negative consequences, and craving. Converging human and animal literature point to three important categories for initiating relapse: negative affect or stress, priming doses of drugs, and conditioned drug-associated stimuli. Insight into the neurobiological mechanisms by which these factors induce relapse will contribute to development of pharmacotherapies that could diminish the likelihood of relapse and improve other clinically relevant outcomes in dependent patients.

Many aspects of drug and alcohol addiction, including relapse, can be successfully modeled and studied in laboratory animals. In this study, we have developed animal models for examining the neural pathways modulating cue-induced relapse and for testing potential candidates for pharmacological relapse prevention. Because glutamate transmission has a central role in mediating associative learning, including the impact of environmental cues on likelihood of relapse, our studies have investigated the involvement of various glutamate receptor subtypes in relapse. In addition, we have initiated studies on the pharmacological manipulation of the brain endocannabinoid system for controlling excessive alcohol drinking and relapse propensity. Future molecular studies will evaluate plastic synaptic processes involved in relapse, including participation of both down- and upstream components of the mitogen-activated protein kinase (MAPK) family.

Gene expression profiling of rat lines selected for differential alcohol drinking

Until recently, by far the most common strategy for probing the mechanisms behind regulation of alcohol drinking has been the comparison of various central neurotransmitter systems in the selected lines. The multiplicity of the neurotransmitter sys-

tems participating in mediation of alcohol reward and the complex interactions between them set limitations to this approach. However, advancement of functional genomic approaches based on microarrays has offered a novel approach for studying the neurobiology of the lines that is not limited by pre-existing hypotheses on the role of particular neuronal systems in alcohol drinking. Specifically, high-throughput functional genomics allows analysis of gene expression simultaneously and in a non-biased manner on a genomic scale, may yield new candidate targets for further verification, and shift research of neural basis of alcohol drinking to a more system-oriented view of neurobiology. In this study, we compared the expression of several hundred genes in four brain regions of AA and ANA rats using the Affymetrix oligonucleotide microarray platform.

5.2.2. The main scientific achievements

Selectively bred as well as inbred rodent lines differing in ethanol-related phenotypes have been widely used to identify the neuronal mechanisms underlying drug and ethanol abuse. The alcohol-preferring AA (Alko Alcohol) and non-preferring ANA (Alko Non-Alcohol) rat lines were among the earliest rodent lines produced by selection. This breeding program based on bi-directional selection was initiated in Finland in the sixties, and the lines have been maintained beyond the 90th generation at the National Public Health Institute of Finland. AA and ANA rats represent two non-overlapping phenotypic distributions of voluntary alcohol consumption, with an approximately ten-fold difference in the mean voluntary alcohol consumption between the lines.

The utility of selected animals for unraveling the biological factors underlying predisposition for high (or low) alcohol consumption, is based on the assumption that the animals produced by selectively breeding from a heterogeneous base population for a specific ethanol-related trait differ from each other only in the trait upon which selection has been applied, and in traits that are related to the selected trait either causally or through genetic linkage. Consequently, much effort has been put by us on the characterization of these rat lines in search for the neurochemical correlates of differential alcohol drinking between AA and ANA rat lines.

Dopaminergic neurons are probably not critically involved in the differential ethanol self-administration behavior of the AA and ANA rat lines. Measurements of the effect of ethanol on the levels of the metabolites of dopamine as well as data from microdialysis studies suggest that there are no consistent differences in ethanol- or drug-induced changes in functioning of dopaminergic neurons between the lines have been

found. Moreover, injections of 6-hydroxydopamine into the nucleus accumbens of AA rats do not impair acquisition or maintenance of ethanol self-administration behavior.

Neurochemical studies have revealed strain-specific differences in the opioidergic systems between the AA and ANA rat lines. AA rats showed lower spontaneous release of hypothalamic beta-endorphin release compared to ANA rats, although there is no difference in the ethanol stimulated release between the lines. AA rats also present a greater content of proopiomelanocortin mRNA in the arcuate nucleus of the hypothalamus compared to ANA animals. The content of proenkephalin mRNA in the prefrontal cortex and that of prodynorphin mRNA in the mediodorsal nucleus of the thalamus were also higher in the AA rats than in the ANA rats. Lower levels of pro-enkephalin-derived peptides in the nucleus accumbens and pro-dynorphin peptides in the VTA of AA rats relative to those of ANA rats have also been reported, and that pro-enkephalin-derived peptides were elevated to a greater extent in the NAC of AA than of ANA rats following exposure to ethanol.

Studies comparing the distribution and density of the various classes of opioid receptors between the lines indicate greater density of μ -opioid receptors in numerous brain parts, particularly in the shell of NAC and in the prefrontal cortex in AA rats compared to ANA rats, while a higher density of σ binding sites is found in the ventromedial hypothalamus of ANA rats. Such differences were not seen in receptor density.

Behavioral studies present more evidence for the endogenous opioid system playing a role in determining the differences in ethanol consumption between the AA and ANA rats. The AA rats have been found to consume more etonitazene (a potent agonist of opiate receptors) solution than the ANA rats, and AA rats also learn to lever press for intravenous heroin more rapidly than ANA rats. The lines also differ in their sensitivity to the locomotor stimulatory effect of morphine AA rats showing higher sensitivity. In parallel with these findings, increased metabolism of dopamine in the caudate-putamen has been found. No differences between the lines in the effects of morphine on accumbal dopamine levels have been found either in postmortem or microdialysis studies.

AA and ANA rats have also been shown to differ in their susceptibility to morphine-induced behavioral and neurochemical sensitization. AA rats treated repeatedly with morphine were more susceptible than ANA rats to morphine-induced locomotor activity, rotational behavior and mesolimbic dopaminergic neurotransmission. Sensitization to the neurochemical effects of morphine was, however, transient. Consequently, increased susceptibility to morphine-induced sensitization in AA rats compared to ANA rats may be a reflection of functional differences in their opioidergic systems and may contribute to their differential ethanol self-administration behavior. The findings may also suggest that the behavioral sensitization to morphine may not involve sensitized dopaminergic mechanisms, or that the role of dopamine is transient.

Increased susceptibility to morphine-induced sensitization in AA rats compared to ANA rats might predict enhanced ethanol reinforcement in AA rats sensitized to morphine. Sensitization of AA rats to the behavioral effects of morphine alone does not, however, seem to enhance the reinforcing properties of voluntarily consumed ethanol in AA rats. AA rats sensitized to the behavioral effects of morphine did not, show enhanced acquisition of ethanol intake when given continuous access to ethanol solution after discontinuation of repeated treatment with morphine. Neuroadaptations induced by repeated treatment with morphine, however, further enhance the reinforcement from ethanol when challenged with morphine.

Glutamatergic neurotransmission plays an important role in the pathogenesis of alcohol and drug addiction. Prolonged drug use has been suggested to lead to alterations in glutamatergic neurotransmission that could predispose subjects to development of addiction and increase the propensity to relapse. In agreement with this framework, we demonstrated that systemic administration of AMPA/kainate antagonists, an NMDA/glycine antagonist, or an mGlu5 receptor antagonist attenuates cue-induced alcohol and cocaine seeking in rats. Particularly metabotropic glutamate receptors may offer interesting targets for pharmacological manipulation in humans with a good safety profile.

In the first study comparing gene expression profiles between the AA and ANA rats using the Affymetrix oligonucleotide platform, we detected 48 differentially expressed genes between AA and ANA rats. The nucleus accumbens, a key component of brain reward systems, appeared to be the most divergent region and showed increased expression of a cluster of signal transduction genes in the AA line. These differences in mRNA levels seem to be associated with altered mitogen-activated protein kinases (MAPK) signaling. A robust downregulation of β -arrestin was found in several brain regions of the AA rat. This finding provides a possible mechanism underlying the increased responsiveness in opiate systems observed in this line.

5.2.3. The main public health achievements

The overall goal of the project is to provide information for better understanding of the association between early onset substance abuse and the risk for alcohol or drug dependence later in life, as well as better knowledge of these mechanisms will also help to understand genetically determined predisposition to develop alcohol dependence and liability co-use drugs of abuse. The information will be valuable for planning of preventive measures, policies and treatments for related problems.

Conducting research on drug dependence will also provide the National Public Health Institute with the scientific expertise needed for health education in the prevention of drug dependence and other drug-related health problems.

5.2.4. Funding for research and public health programs

The project is funded by the National Public Health Institute (KTL) as well by grants from the Academy of Finland, the Finnish Foundation for Alcohol Studies, Yrjö Jahansson Foundation, and Ella and Georg Ehrnrooth Foundation.

5.2.5. Personnel

Kiianmaa, Kalervo, Ph.D., research professor

Hyytiä, Petri, Ph.D., senior scientist,

Saarikoski Sirkku, Ph.D., senior scientist,

Sarviharju, Maija, M.Sc., scientist,

Bäckström, Pia, Ph.D., scientist

Kemppainen, Heidi, graduate student

Malinen, Hanna, M.Sc., graduate student

5.2.6. Collaboration

Ahtee, Liisa, M.D., Professor, emerita, Division of Pharmacology and Toxicology, Faculty of Pharmacy, University of Helsinki, Helsinki

Baumann, Marc, BM, PhD, Associate Professor, Director, Protein Chemistry/Proteomics Unit and the Neuroscience Research Program, Biomedicum, University of Helsinki, Helsinki

Björk, Karl, M. Sc., graduate student, Laboratory of Clinical and Translational Studies, NIAAA, National Institutes of Health, Bethesda, USA

Castrén, Eero, M.D., Ph.D., Director, Professor, NeuroscienceCenter, Universityof Helsinki, Helsinki

Gianoulakis, Christina, Ph.D., Departments of Psychiatry and Physiology, Douglas Hospital Research Centre, McGill University, Montreal, Canada

Heilig, Markus, M.D., Ph.D., director, Laboratory of Clinical and Translational Studies, NIAAA, National Institutes of Health, Bethesda, USA

Marttila, Kristiina, M.Sc. (Pharm.), graduate student, Division of Pharmacology and Toxicology, Faculty of Pharmacy, Universityof Helsinki, Helsinki

Panula, Pertti, M.D., Ph.D. Professor, Department of Anatomy, University of Helsinki, Helsinki

Roman, Erika, Ph.D., Department of Pharmaceutical Biosciences, Division of Pharmacology, Uppsala University, Sweden

Ryabinin, Andrey, M.D., Ph.D., assistant professor, Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, USA

Seppä, Kaija, MD, Professor, Department of General Practice, University of Tampere, Tampere

Sommer, Wolfgang, M.D., Ph.D., Laboratory of Clinical and Translational Studies, NIAAA, National Institutes of Health, Bethesda, USA

Spanagel, Rainer, Ph.D., professor, Department of Psychopharmacology, University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany

5.2.8. Key publications

Koistinen, M., Tuomainen, P., Hyttiä, P., Kiianmaa, K. Naltrexone suppresses ethanol intake in 6-hydroxydopamine-treated rats. *Alcohol.: Clin. Exp. Res.* 25(11): 1605-1612, 2001

BACKGROUND: The suppressive effect of opioid antagonists, such as naltrexone, on ethanol intake has been suggested to be based on the interference with ethanol-induced stimulation of dopamine release in the nucleus accumbens. The aim of this study was to determine whether reduction of dopamine innervation to the nucleus accumbens with the neurotoxin 6-hydroxydopamine (6-OHDA) alters naltrexone-induced suppression of ethanol consumption. Because the mesolimbic dopaminergic neurons have also been implicated in ethanol reinforcement, the effects of 6-OHDA on the maintenance and acquisition of ethanol intake were also studied. **METHODS:** To damage accumbal terminals of the mesolimbic dopamine neurons, alco-

hol-preferring Alko Alcohol (AA) rats were given bilateral injections of 6-OHDA or vehicle into the nucleus accumbens after pretreatment with desipramine and pargyline. The effect of the lesion on the acquisition or maintenance of ethanol self-administration was studied in animals having continual access to ethanol solution (10% v/v) and water. Subsequently the effect of naltrexone on ethanol consumption was determined. RESULTS: Naltrexone (0.03-3.0 mg/kg subcutaneously) suppressed ethanol consumption in a dose-dependent manner both in 6-OHDA-treated and control animals given a daily 90-min access to ethanol solution. When the rats had continual access to ethanol, there was a clear day-to-day decline in ethanol intake during the first 5 days of the 7-day naltrexone treatment (10 mg/kg subcutaneously). 6-OHDA treatment had no effect on either the acquisition or maintenance of ethanol self-administration. Postmortem analysis of the brain dopamine content revealed approximately 92% depletion of dopamine in the nucleus accumbens of the 6-OHDA-treated rats. CONCLUSIONS: The suppressive effect of naltrexone does not depend on naltrexone's interaction with dopaminergic terminals in the nucleus accumbens. Furthermore, the role of the mesolimbic dopamine pathway is probably not central either in the acquisition or maintenance of ethanol self-administration in alcohol-preferring AA rats.

Ojanen S., Koistinen M., Bäckström P., Kankaanpää A., Tuomainen P., Hyttiä P., Kiiänmaa K. Differential behavioral sensitization to intermittent morphine treatment in alcohol-preferring AA and alcohol-avoiding ANA rats: role of mesolimbic dopamine. *Eur J Neurosci* 17: 1655-1663, 2003

Alcohol-preferring AA (Alko Alcohol) and alcohol-avoiding ANA (Alko Non-Alcohol) rats have well-documented differences in their voluntary ethanol consumption and brain opioidergic systems. The aim of the present study was to investigate whether these rat lines differ in their susceptibility to morphine-induced behavioural and neurochemical sensitization. The rats were given 15 injections of morphine (10 mg/kg, s.c.) or saline every other day. Locomotor activity and release of dopamine in the nucleus accumbens were monitored after a challenge with additional morphine injections (10 mg/kg) 1 and 5 weeks after withdrawal from the repeated treatment. Morphine increased locomotion more in the previously morphine-treated rats than in the saline-treated controls. Furthermore, AA rats were more sensitive to this effect of morphine than ANA rats. Accumbal morphine-induced dopamine release was significantly higher in the morphine-treated AA than ANA rats after the first challenge injection 1 week from withdrawal, but no differences were observed after the second challenge. The brain and plasma concentrations of morphine were similar among the lines suggesting that the differences in the effects of morphine cannot be explained in terms of differential pharmacokinetics of morphine in these lines. These data show that AA rats are more susceptible to morphine-induced behavioural sensitization than ANA rats. Furthermore, it suggests that mesolimbic dopamine has at best only a transient role in the expression of opioid-induced behavioural sensitization. The relationship between the mechanisms underlying the differential sensitivity of these rat lines to the effects of repeated morphine and voluntary ethanol drinking remains to be determined.

Arlinde C, Sommer W, Björk K, Reimers M, Hyttiä P, Kiiänmaa K, Heilig M. A cluster of differentially expressed signal transduction genes identified by microarray analysis in a rat genetic model of alcoholism. *Pharmacogenomics J.* 4(3):208-18, 2004

Analyzing gene expression patterns in genetic models of alcoholism may uncover previously unknown susceptibility genes, and point to novel targets for drug development. Here, we compared expression profiles in alcohol-preferring AA rats with the alcohol-avoiding counterpart ANA line, and unselected Wistar rats. Cingulate cortex, Nc. accumbens, amygdala and hippocampus of each line were ana-

lyzed using the Afymetrix RN U34 arrays and dChip 1.1 software. Analysis of line-specific expression revealed 48 differentially expressed genes between AA and ANA rats. Elevated hippocampal neuropeptide Y (NPY) was found in ANA rats in agreement with previous studies. A cluster of MAP-kinases indicating altered signal transduction was upregulated within the Nucleus Accumbens of the AA line, and is of particular functional interest. Within the amygdala, a more loosely inter-related cluster of cytoskeleton-associated genes may point to structural abnormalities. The observed dysregulations may contribute to the alcohol-preferring phenotype.

Bäckström P, Bachteler D, Koch S, Hyttiä P, Spanagel R. mGluR5 antagonist MPEP reduces ethanol-seeking and relapse behavior. *Neuropsychopharmacology* 29(5):921-8, 2004

The glutamatergic system plays an important role in mediating neurobehavioral effects of ethanol. Metabotropic glutamate receptors subtype 5 (mGluR5) are modulators of glutamatergic neurotransmission and are abundant in brain regions known to be involved in ethanol self-administration. Here, we studied the effects of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a highly potent, noncompetitive mGlu5 receptor antagonist, on voluntary ethanol consumption and relapse behavior. For this purpose, we used two models for the measurement of relapse behavior: (i) reinstatement of ethanol-seeking behavior by drug-associated cues and (ii) the alcohol deprivation effect in long-term ethanol-consuming rats. In the first set of experiments, rats were trained to lever press for ethanol in the presence of a distinct set of cues. After extinction, the animals were exposed to the respective cues that initiated reinstatement of responding. A response-contingent ethanol prime further enhanced responding compared to the conditioned cues alone. Under these conditions, MPEP (0, 1, 3, and 10 mg/kg) attenuated ethanol seeking significantly and in a dose-related manner. However, at the highest dose, MPEP also decreased the number of inactive lever responses. In the second set of experiments, rats with 1 year of ethanol experience and repeated deprivation phases were used. A subchronic treatment with MPEP (twice daily; 0, 3, and 10 mg/kg) resulted in a significant and dose-dependent reduction of the alcohol deprivation effect (ADE). Although the same MPEP treatment regimen decreased baseline drinking, this effect was not as pronounced as on the ADE. These results show in two commonly used models of relapse to ethanol that pharmacological targeting of mGlu5 receptors may be a promising approach for the treatment of alcoholism.

Ojanen, S.; Hyttiä, P.; Kiiänmaa, K. Behavioural sensitisation and voluntary ethanol drinking in alcohol-preferring AA rats exposed to different regimens of morphine treatment. *Pharmacol. Biochem. Behav.* 80: 221-228, 2005.

The purpose of the study was to investigate the effects of three different regimens of morphine treatment on subsequent voluntary ethanol drinking in alcohol-preferring AA (Alko Alcohol) rats. The rats were given morphine subcutaneously either intermittently on alternating days (15 x 10 mg/kg or 5 x 5-20 mg/kg in escalating doses) or subchronically on four consecutive days (3-20 mg/kg/d). Horizontal locomotor activity was monitored after challenges with additional morphine injections (3 mg/kg) ten days and six weeks after termination of the pretreatment to test if behavioral sensitization was induced by repeated morphine administration. Both intermittent pretreatments induced sensitized locomotor response after the first challenge, whereas subchronic injections did not. After the challenge the rats were given a free choice between tap water and 10% (v/v) ethanol solution for four weeks. The rats pretreated and challenged with morphine did not differ significantly in the acquisition of ethanol drinking from the saline-treated controls. In contrast, ethanol drinking was impaired during the first week of ethanol access in the saline-treated rats given a single morphine injection. The second morphine challenge given after the

ethanol-drinking phase did not reveal sensitization in any of the groups. The results suggest that pattern of morphine administration rather than the dose or number of exposures to the drug is the most important factor in induction of behavioral sensitization, and that exposure to ethanol may interfere with this process. They also support earlier findings showing that acute morphine may suppress voluntary ethanol drinking, but failed to provide clear evidence for behavioral sensitization to morphine contributing to predilection towards ethanol in AA rats.

Bäckström P, Hyytiä P. Iontropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* 31(4):778-86, 2006.

Neuroanatomical and pharmacological evidence implicates glutamate transmission in drug-environment conditioning that partly controls drug seeking and relapse. Glutamate receptors could be targets for pharmacological attenuation of the motivational properties of drug-paired cues and for relapse prevention. The purpose of the present study was therefore to investigate the involvement of ionotropic and metabotropic glutamate receptor subtypes in cue-induced reinstatement of cocaine-seeking behavior. Rats were trained to self-administer cocaine using a second-order schedule of reinforcement (FR4(FR5:S)) under which a compound stimulus (light and tone) associated with cocaine infusions was presented contingently. Following extinction, the effects of the competitive NMDA receptor antagonist CGP 39551 (0, 2.5, 5, 10 mg/kg intraperitoneally (i.p.)), two competitive AMPA/kainate antagonists, CNQX (0, 0.75, 1.5, 3 mg/kg i.p.) and NBQX (0, 1.25, 2.5, 5 mg/kg i.p.), the NMDA/glycine site antagonist L-701,324 (0, 0.63, 1.25, 2.5 mg/kg i.p.), and the mGluR5 antagonist MPEP (0, 1.25, 2.5, 5 mg/kg i.p.) on cue-induced reinstatement of cocaine seeking were examined. The AMPA/kainate receptor antagonists CNQX and NBQX, the NMDA/glycine site antagonist L-701,324, and the mGluR5 antagonist MPEP attenuated significantly cue-induced reinstatement. The NMDA antagonist CGP 39551 failed to affect reinstatement. Additional control experiments indicated that attenuation of cue-induced reinstatement by CNQX, NBQX, L-701,324, and MPEP was not accompanied by significant suppression of spontaneous locomotor activity. These results suggest that conditioned influences on cocaine seeking depend on glutamate transmission. Accordingly, drugs with antagonist properties at various glutamate receptor subtypes could be useful in prevention of relapse induced by conditioned stimuli.

Ojanen, S.; Hyytiä, P.; Kiianmaa, K. Enhanced morphine-induced ethanol drinking in alcohol-preferring aa rats sensitized to morphine. *Alcohol.: Clin. Exp. Res.* 30(4): 621-629, 2006.

BACKGROUND: Alcohol-preferring alko alcohol (AA) rats are more susceptible to morphine-induced behavioral and neurochemical sensitization than alcohol nonpreferring alko nonalcohol (ANA) rats. Alko alcohol rats sensitized to morphine, however, do not show enhanced acquisition of ethanol drinking. The purpose of the present study was to clarify further interactions between morphine-induced behavioral sensitization and voluntary ethanol drinking in the AA rats. **METHODS:** Alko alcohol rats drinking ethanol in a limited 6-hour access paradigm were sensitized to morphine with repeated injections of morphine (5-15 mg/kg). Injection days alternated with days of ethanol access. Controls had access only to water and/or were given injections of saline. After a 5-day washout period from ethanol and morphine, the rats were challenged with morphine or saline and subsequent ethanol drinking or locomotor activity was recorded. **RESULTS:** Ethanol intake was suppressed during the repeated treatment with morphine, and the morphine-treated rats did not differ in ethanol intake from the controls when given access to ethanol after the washout. Intake of ethanol was, however, increased when the rats were challenged with morphine [1 or 10 mg/kg, subcutaneously (s.c.)], while in the controls an increase in ethanol intake was seen only after 1 mg/kg morphine. Sensitization to the locomotor stimulating effects of morphine was revealed

in the morphine-treated rats after a challenge with morphine (3 or 10 mg/kg, s.c.). The controls that had been drinking ethanol also showed a sensitized response after morphine (3 mg/kg). **CONCLUSIONS:** Ethanol did not interfere with the development of sensitization to morphine. Furthermore, the neuroadaptations induced by repeated exposure to ethanol were sufficient to cause behavioral cross-sensitization to morphine. Sensitization to the behavioral effects of morphine alone, however, neither enhances the reinforcing properties of voluntarily consumed ethanol nor contributes to increase in its intake. The increase in ethanol intake found after an acute dose of morphine was augmented in rats withdrawn from repeated treatment with morphine. The data suggest that the neuronal mechanisms underlying behavioral sensitization to morphine probably are distinct from those mediating reinforcement from ethanol and that the morphine-induced neuroadaptations contribute to the enhancement of increase in ethanol intake by morphine.

Bäckström P, Hyytiä P. Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology* 192(4):571-80, 2007

RATIONALE: Nucleus accumbens glutamate transmission has been implicated in drug-seeking behavior, but the involvement of glutamate receptor subtypes in drug seeking maintained by drug-associated cues has not been fully investigated. **OBJECTIVE:** This study examined the effects of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate, N-methyl-D-aspartate (NMDA) and mGlu5 receptor blockade in the nucleus accumbens core on cue-induced reinstatement of cocaine seeking. **METHOD:** Wistar rats were trained to self-administer cocaine and associate a compound stimulus (light and tone) with the drug under an FR4(FR5:S) second-order schedule of reinforcement. After extinction, during which neither cocaine nor the compound stimulus was available, responding was reinstated by contingent presentations of the compound stimulus. The effects of the intra-accumbal AMPA/kainate receptor antagonist 6-cyano-7-nitro-quinoxaline-2, 3-dione (CNQX; 0, 0.01, and 0.03 microg/side), the NMDA antagonist D-2-amino-5-phosphonopentanoate (D-AP5; 0, 1, and 2 microg/side), and the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP; 0, 0.5, and 1 microg/side) on reinstatement were examined in a within-subjects design. **RESULTS:** CNQX and D-AP5 attenuated cue-induced reinstatement of cocaine seeking dose-dependently. MPEP, however, decreased cocaine seeking only relative to baseline because also the saline vehicle included in the within-subjects series of injections decreased responding, possibly reflecting conditioned anhedonic effects of MPEP. In additional experiments, none of the antagonists attenuated locomotor activity or responding for sucrose pellets. **CONCLUSIONS:** The results suggest that cue-induced reinstatement of cocaine seeking after a period of withdrawal from cocaine is sensitive to AMPA/kainate and NMDA receptor antagonism in the nucleus accumbens core and give further evidence for the role of the accumbal glutamate transmission in modulation of drug-seeking behavior.

Hansson AC, Bermúdez-Silva FJ, Malinen H, Hyytiä P, Sanchez-Vera I, Rimondini R, Rodriguez de Fonseca F, Kunos G, Sommer W, Heilig H. Genetic impairment of frontocortical endocannabinoid degradation and high alcohol preference. *Neuropsychopharmacology* 32(1):117-26, 2007.

Endocannabinoid signaling has recently been implicated in ethanol-seeking behavior. We analyzed the expression of endocannabinoid-related genes in key brain regions of reward and dependence, and compared them between the alcohol-preferring AA (Alko Alcohol) and nonpreferring ANA (Alko Non-Alcohol) rat lines. A decreased expression of fatty acid amidohydrolase (FAAH), the main endocannabinoid-degrading enzyme, was found in prefrontal cortex (PFC) of AA rats, and was accompanied by decreased enzyme activity in this region. Binding of the endocannabinoid-cannabinoid 1 (CB1) receptor ligand (3)[³H]SR141716A, and [³⁵S]GTPgammaS incorporation stimulated by the CB1 agonist WIN 55,212-2 were downregulated in the same area. Together, this suggests an overactive endocannabinoid

transmission in the PFC of AA animals, and a compensatory downregulation of CB1 signaling. The functional role of impaired FAAH function for alcohol self-administration was validated in two independent ways. The CB1 antagonist SR141716A potently and dose-dependently suppressed self-administration in AA rats when given systemically, or locally into the PFC, but not in the striatum. Conversely, intra-PFC injections of the competitive FAAH inhibitor URB597 increased ethanol self-administration in non-selected Wistar rats. These results show for the first time that impaired FAAH function may confer a phenotype of high voluntary alcohol intake, and point to a FAAH both as a potential susceptibility factor and a therapeutic target.

6. MENTAL HEALTH RESEARCH UNIT

6.1. Self-destructive behavior and suicide prevention

6.1.1. Research and public health significance of the area

There has been increasing awareness of the extent and burden of suicidal behaviour and suicide not only in Finland but also globally. WHO estimates that about 1 million people die by suicide. In Finland suicide mortality has increased steadily after the Second World War reaching the highest rate ever in 1990 (30/100.000), 1500 suicides in total. The increasing suicide rate was the main reason to start the National Suicide Prevention Project. The aim was to stop the increasing trend and decrease suicide mortality by 20% by the year 1995. This project, led by professor Jouko Lönnqvist, was the reason behind establishing a separate new unit for mental health in the National Public Health Institute in 1986. Suicide research was a starting point to the development of the Department of Mental Health in 1992. As the first country in the world, Finland published a national strategy of suicide prevention and an action plan for implementation in 1991. Suicide rate has decreased steadily during the last 15 years and was 18/100.000 in 2005. The annual amount of suicides has declined below 1000. Finland is not among the top ten countries in the world having a very high suicide rate any more. On the contrary, Finland is now internationally known as a model country for suicide prevention. However, Finland still has a relatively high suicide rate compared with other western EU countries. Suicide is a leading cause of death in Finland among those under the age of 35 years. Suicide also means a major loss of expected active life years and a huge stress and long-term burden to all survivors. Suicidal ideation, plans and suicide attempts are common symptoms associating tightly with psychological, social and physical problems in the general population. Attempted suicides are nowadays main causes for costly visits

into emergency rooms of general hospitals. During the last 15 years, National Public Health Institute has been one of the leading centers in the world in the field of suicidology. In 2004 Jouko Lönnqvist received the Annual Research Award of American Foundation for Suicide Research. We have already educated “the third generation” of internationally well-known experts in suicide research and prevention. Suicide is a global phenomenon of human society but it also has strong local, social, societal and cultural roots. We still need a strong research unit to study and prevent suicide in Finland, and to collaborate internationally.

6.1.2. The main scientific achievements

During the last ten years we have published about 100 scientific reports on suicidal behavior in international journals. Since 1996 twelve persons have published their doctoral thesis on suicidology based on our materials and supervised by our senior staff members. We have had the largest nation-wide psychological autopsy study conducted ever in the world. We have been successful in showing specifically how suicidal behavior and suicide especially is connected with mental disorders and comorbidity, and with several biological and circadian risk factors. We were among the first ones to show the lack of treatment among suicide victims before suicide as well as among suicide attempters, even after the suicide attempt. We also succeeded for first time ever in showing direct connection between the continuous use of antidepressants and decreased risk of suicide among depressive suicide attempters. We could also show that treatment adherence among schizophrenic patients prevents suicide. We were also able to show, against common beliefs, that dehospitalization has not increased suicide risk among schizophrenic patients in Finland.

6.1.3. The main public health achievements

Public awareness of the magnitude and character of suicide and suicidal behaviour and knowledge about this problem has been increasing. Suicide is not the taboo it used to be any more. The health care system is able to recognize and treat depression, attempted suicides, substance use disorders and psychoses in a more proper way than previously based on the models of good practice which we have been developing as core experts in Finland. We believe that many activities we have been promoting explain the decreasing trend of suicide mortality in Finland. We have assessed that during the last

15 years the expected loss of active life years saved from suicide has been about 100.000 person-years.

We have actively participated in international suicide prevention activities as experts within WHO and EU for years. We also have been a part of a global expert group which has published a meta-analysis on suicide prevention. We have arranged national and international meetings on suicide and suicide prevention, published textbooks and prevention material both internationally and in Finland. We also continuously receive international visitors, especially from Asia, to learn from our experience on suicide prevention.

6.1.4. Funding for research and public health programs

Since 1996, we have not received any extra funding from the state or KTL budget for suicide research. All resources have been allocated from our basic annual budget, or largely received from several private Finnish funds. However, during the last six years, we have received 30.000 euros from the health promotion budget of Ministry of Social Affairs and Health annually to develop guidelines for prevention activities among adolescents, mainly at schools. In addition, this year we received 20.000 euros from the KTL budget to arrange an international symposium on suicide prevention in Helsinki together with WHO (Geneva) and Suicide Prevention International Inc (USA).

6.1.5. Personnel

The project promotes and coordinates suicide research in the KTL. However, suicide research is also conducted in several other projects of the department. In 2006-2007 we published 15 articles and two doctoral theses on suicide and suicide related topics. In total, 10 of our researchers participated in these studies and total amount of work was about three person years.

6.1.6. Collaboration

In suicide research we have collaborated with Jorvi, Peijas and Helsinki hospital districts and with Helsinki university Central Hospital to get clinical samples. In addition, in register studies we have had excellent co-operation with Kuopio University (Jari

Tiihonen), and with The Social Insurance Institution of Finland (KELA) and Research and Development Centre for Welfare and Health (Stakes). We have participated in the WHO (Euro) parasuicide study for years as well as in the EU multicenter study on attempted suicide in Europe (Armin Schmidtke, Wurzburg). We are actively planning, as one of eight European centers, a large EU evaluation study on suicide prevention (FP7, coordinated by Steven Platt, Edinburgh) starting possibly in 2008. Jouko Lönnqvist is the president of International Academy for Suicide Research, having about 100 most prominent suicide researchers in the world, in 2007-2009, and an expert member of the American Foundation for Suicide Prevention reviewing international applications (John Mann, Columbia University). We also have intensive co-operation with Karolinska Institute in research, prevention and education (Danuta Wasserman).

6.1.7. Proposal for future work and expected benefits

We will monitor the suicide trends in Finland, and analyze the main factors explaining the continuous decline of the suicide rate. The main focus has been and still is in effects of maintenance treatments (antidepressants and antipsychotics) on suicide and total mortality. We are starting to analyze the biological and genetic background of suicidal behaviour by using the Finnish twin cohort and our genetic cohorts of schizophrenia and bipolar disorder. In addition, we will participate in the EU- evaluation study on suicide prevention. Our aim is to also publish a total description and analysis of the national suicide prevention project since we now have a 20 years follow-up from the start of the project. We will also publish a 20 years follow-up study on survivors of suicide.

6.1.8. Main publications

Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort.

Department of Forensic Psychiatry, University of Kuopio and Niuvanniemi Hospital, Kuopio University Hospital, Kuopio, Finland. Jari.Tiihonen@niuva.fi

BACKGROUND: It is unknown if antidepressant treatment is associated with either increased or decreased risk of suicide. **OBJECTIVE:** To estimate the risk of suicide, attempted suicide, and overall mortality during antidepressant treatments in a real-life setting with high statistical power. **DESIGN AND SETTING:** A cohort study in which all subjects without psychosis, hospitalized because of a suicide attempt from January 1, 1997, to December 31, 2003, in Finland, were followed up through a nationwide computer-

ized database. **PARTICIPANTS:** A total of 15 390 patients with a mean follow-up of 3.4 years. **MAIN OUTCOME MEASURES:** The propensity score-adjusted relative risks (RRs) during monotherapy with the most frequently used antidepressants compared with no antidepressant treatment. **RESULTS:** In the entire cohort, fluoxetine use was associated with the lowest risk (RR, 0.52; 95% confidence interval [CI], 0.30-0.93), and venlafaxine hydrochloride use with the highest risk (RR, 1.61; 95% CI, 1.01-2.57), of suicide. A substantially lower mortality was observed during selective serotonin reuptake inhibitor use (RR, 0.59; 95% CI, 0.49-0.71; $P < .001$), and this was attributable to a decrease in cardiovascular- and cerebrovascular-related deaths (RR, 0.42; 95% CI, 0.24-0.71; $P = .001$). Among subjects who had ever used any antidepressant, the current use of medication was associated with a markedly increased risk of attempted suicide (39%, $P < .001$), but also with a markedly decreased risk of completed suicide (-32%, $P = .002$) and mortality (-49%, $P < .001$), when compared with no current use of medication. The results for subjects aged 10 to 19 years were basically the same as those in the total population, except for an increased risk of death with paroxetine hydrochloride use (RR, 5.44; 95% CI, 2.15-13.70; $P < .001$). **CONCLUSIONS:** Among suicidal subjects who had ever used antidepressants, the current use of any antidepressant was associated with a markedly increased risk of attempted suicide and, at the same time, with a markedly decreased risk of completed suicide and death. Lower mortality was attributable to a decrease in cardiovascular- and cerebrovascular-related deaths during selective serotonin reuptake inhibitor use.

Tiihonen J, Walhbeck K, Lonnqvist J, Klaukka T, Ioannidis JP, Volavka J, Haukka J. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study.

Department of Forensic Psychiatry, University of Kuopio, Niuvanniemi Hospital, FIN-70240 Kuopio, Finland. jari.tiihonen@niuva.fi

OBJECTIVE: To study the association between prescribed antipsychotic drugs and outcome in schizophrenia or schizoaffective disorder in the community. **DESIGN:** Prospective cohort study using national central registers. **SETTING:** Community care in Finland. **PARTICIPANTS:** Nationwide cohort of 2230 consecutive adults hospitalised in Finland for the first time because of schizophrenia or schizoaffective disorder, January 1995 to December 2001. **MAIN OUTCOME MEASURES:** Rates of discontinuation of drugs (all causes), rates of rehospitalisation, and mortality associated with monotherapy with the 10 most commonly used antipsychotic drugs. Multivariate models and propensity score methods were used to adjust estimates of effectiveness. **RESULTS:** Initial use of clozapine (adjusted relative risk 0.17, 95% confidence interval 0.10 to 0.29), perphenazine depot (0.24, 0.13 to 0.47), and olanzapine (0.35, 0.18 to 0.71) were associated with the lowest rates of discontinuation for any reason when compared with oral haloperidol. During an average follow-up of 3.6 years, 4640 cases of rehospitalisation were recorded. Current use of perphenazine depot (0.32, 0.22 to 0.49), olanzapine (0.54, 0.41 to 0.71), and clozapine (0.64, 0.48 to 0.85) were associated with the lowest risk of rehospitalisation. Use of haloperidol was associated with a poor outcome among women. Mortality was markedly raised in patients not taking antipsychotics (12.3, 6.0 to 24.1) and the risk of suicide was high (37.4, 5.1 to 276). **CONCLUSIONS:** The effectiveness of first and second generation antipsychotics varies greatly in the community. Patients treated with perphenazine depot, clozapine, or olanzapine have a substantially lower risk of rehospitalisation or discontinuation (for any reason) of their initial treatment than do patients treated with haloperidol. Excess mortality is seen mostly in patients not using antipsychotic drugs.

Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lonnqvist J, Malone K, Marusic A, Mehlum L, Patton G, Phillips M, Rutz W, Rihmer Z, Schmidtke A, Shaffer D, Silverman M, Takahashi Y, Varnik A, Wasserman D, Yip P, Hendin H. Suicide prevention strategies: a systematic review.

New York State Psychiatric Institute, Division of Neuroscience, New York, NY 10032, USA.
jjm@columbia.edu

CONTEXT: In 2002, an estimated 877,000 lives were lost worldwide through suicide. Some developed nations have implemented national suicide prevention plans. Although these plans generally propose multiple interventions, their effectiveness is rarely evaluated. **OBJECTIVES:** To examine evidence for the effectiveness of specific suicide-preventive interventions and to make recommendations for future prevention programs and research. **DATA SOURCES AND STUDY SELECTION:** Relevant publications were identified via electronic searches of MEDLINE, the Cochrane Library, and PsychINFO databases using multiple search terms related to suicide prevention. Studies, published between 1966 and June 2005, included those that evaluated preventative interventions in major domains; education and awareness for the general public and for professionals; screening tools for at-risk individuals; treatment of psychiatric disorders; restricting access to lethal means; and responsible media reporting of suicide. **DATA EXTRACTION:** Data were extracted on primary outcomes of interest: suicidal behavior (completion, attempt, ideation), intermediary or secondary outcomes (treatment seeking, identification of at-risk individuals, antidepressant prescription/use rates, referrals), or both. Experts from 15 countries reviewed all studies. Included articles were those that reported on completed and attempted suicide and suicidal ideation; or, where applicable, intermediate outcomes, including help-seeking behavior, identification of at-risk individuals, entry into treatment, and antidepressant prescription rates. We included 3 major types of studies for which the research question was clearly defined: systematic reviews and meta-analyses (n = 10); quantitative studies, either randomized controlled trials (n = 18) or cohort studies (n = 24); and ecological, or population-based studies (n = 41). Heterogeneity of study populations and methodology did not permit formal meta-analysis; thus, a narrative synthesis is presented. **DATA SYNTHESIS:** Education of physicians and restricting access to lethal means were found to prevent suicide. Other methods including public education, screening programs, and media education need more testing. **CONCLUSIONS:** Physician education in depression recognition and treatment and restricting access to lethal methods reduce suicide rates. Other interventions need more evidence of efficacy. Ascertaining which components of suicide prevention programs are effective in reducing rates of suicide and suicide attempt is essential in order to optimize use of limited resources.

Heila H, Haukka J, Suvisaari J, Lonnqvist J. Mortality among patients with schizophrenia and reduced psychiatric hospital care.

National Public Health Institute, Department of Mental Health and Alcohol Research, Mannerheimintie, Helsinki, Finland. hannele.heila@ktl.fi

BACKGROUND: There are suggestions that mortality, especially that due to suicide, increases among schizophrenia patients during a period of declining psychiatric beds. We investigated the mortality of schizophrenia patients in the general population of Finland during the reduction of psychiatric beds during 1980-1996. **METHOD:** Patients hospitalized for schizophrenia before 31 December 1996, and alive on 1 January 1980 (n = 58761) were identified via the National Hospital Discharge Register. General population data came from the National Population Register, and mortality data from the National Causes of Death Register. We calculated relative risks (RR) for total mortality, mortality due to natural causes (cancer, ischaemic heart disease, respiratory disease), unnatural causes (accident, homicide, sui-

cide), and suicide. RESULTS: Patients with schizophrenia had an increased mortality both from natural causes (RR 2.59, 95% CI 2.55-2.63) and from suicide (RR 9.9, 95% CI 9.43-10.30). The RR for both natural and unnatural deaths was highest among patients with < 5 years since onset of schizophrenia. Among them all-cause mortality rose in the 1990s, but decreased among patients with > 10 years from onset. Otherwise no major changes or linear trends were found in mortality during deinstitutionalization. CONCLUSIONS: Reduction of psychiatric beds did not generally increase the mortality of patients with schizophrenia. However, patients in their early years of illness experienced increased mortality after the steepest bed reduction. Improved recognition and treatment of somatic illness would benefit patients with schizophrenia.

Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression?

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. reeta.hakkarainen@ktl.fi

OBJECTIVE: This study examined the association between the dietary intake of omega-3 fatty acids and low mood, major depression, and suicide. METHOD: A total of 29,133 men ages 50 to 69 years participated in a population-based trial in Finland. The intake of fatty acids and fish consumption were calculated from a diet history questionnaire. Self-reported depressed mood was recorded three times annually, data on hospital treatments due to a major depressive disorder were derived from the National Hospital Discharge Register, and suicides were identified from death certificates. RESULTS: There were no associations between the dietary intake of omega-3 fatty acids or fish consumption and depressed mood, major depressive episodes, or suicide. CONCLUSIONS: Dietary intake of omega-3 fatty acids showed no association with low mood level.

Suominen K, Isometsa E, Suokas J, Haukka J, Achte K, Lonnqvist J. Completed suicide after a suicide attempt: a 37-year follow-up study.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. kirsi.suominen@ktl.fi

OBJECTIVE: Attempted suicide is the strongest known predictor of completed suicide. However, suicide risk declines over time after an attempt, and it is unclear how long the risk persists. Risk estimates are almost exclusively based on studies of less than 10 years of follow-up. METHOD: The authors followed a cohort of 100 consecutive self-poisoned patients in Helsinki in 1963, for whom forensically classified causes of death during the following 37 years were investigated. RESULTS: They found that suicides continued to accumulate almost four decades after the index suicide attempt. CONCLUSIONS: A history of a suicide attempt by self-poisoning indicates suicide risk over the entire adult lifetime.

Suominen KH, Isometsa ET, Lonnqvist JK. Comorbid substance use reduces the health care contacts of suicide attempters with schizophrenia spectrum or mood disorders.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. kirsi.suominen@ktl.fi

Utilization of health care services has been found to differ between psychiatric disorders. However, the pattern of health care contacts among suicide attempters with mental disorders is not known. This study systematically investigated the pattern of health care contacts among suicide attempters with schizophrenia spectrum versus mood disorders with or without comorbid substance use disorders both before and after attempted suicide. All consecutive medically treated suicide attempters in Helsinki from January 15, 1997, to January 14, 1998, were identified (n = 1,198). Data were gathered on all their health care contacts within the 12 months before and after the index attempt. Whereas the clear majority of all suicide attempters with schizophrenia spectrum or mood disorders had a treatment contact during the 30 days following the attempt, half of those with pure substance use disorders were without any contact with health care. Comorbid substance use made treatment less likely after attempted suicide among both psychiatric disorder groups; those with schizophrenia spectrum and comorbid substance use disorders were seven times more often left without aftercare recommendation than those without substance use comorbidity. Comorbid substance use disorders among suicide attempters with schizophrenia spectrum disorders decrease the likelihood of active aftercare, despite high suicide risk.

Suokas J, Suominen K, Isometsa E, Ostamo A, Lonnqvist J. Long-term risk factors for suicide mortality after attempted suicide--findings of a 14-year follow-up study.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

OBJECTIVE: To determine the risk of suicide over a 14-year follow-up period, and to investigate the long-term risk factors for suicide using survival analysis. **METHOD:** Data were collected on all unselected deliberate self-poisoning patients (n=1018) treated during 1983 in the emergency unit of Helsinki University Central Hospital. **RESULTS:** By the end of the 14 -year follow-up period 222 (21.7%) of these patients had died. Sixty-eight (6.7%) had committed suicide; 44 (9.2%) men and 24 (4.5%) women. The long-term risk factors for suicide were male sex, previous psychiatric treatment, previous suicide attempts, somatic disease and a self-reported 'wish to die' motive for the index suicide attempt. **CONCLUSION:** The essential risk factors for suicide were being male and having previous suicide attempts. In addition, history of earlier psychiatric treatment, presence of somatic disease and genuine intent to die in the index suicide attempt suggest that the long-term risk has remained high for over a decade. The findings emphasize the need for long-term planning and treatment of suicide attempters met in the emergency room of general hospitals.

Partonen T, Haukka J, Virtamo J, Taylor PR, Lonnqvist J. Association of low serum total cholesterol with major depression and suicide.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. timo.partonen@ktl.fi

BACKGROUND: It has been suggested that low serum total cholesterol is associated with an increased risk of suicide. **AIMS:** To study the association between serum total cholesterol, depression and suicide using versatile, prospective data. **METHOD:** A total of 29,133 men aged 50-69 years were followed up for 5-8 years. Baseline blood samples were analysed for serum total and high-density lipoprotein cholesterol concentrations. Self-reported depression was recorded, data on hospital treatments due to depressive disorders were derived from the National Hospital Discharge Register and deaths from suicide were identified from death certificates. **RESULTS:** Low serum total cholesterol was associated with low

mood and subsequently a heightened risk of hospital treatment due to major depressive disorder and of death from suicide. **CONCLUSIONS:** Our results suggest that low serum total cholesterol appears to be associated with low mood and thus to predict its serious consequences.

Heila H, Heikkinen ME, Isometsä ET, Henriksson MM, Marttunen MJ, Lonnqvist JK. Life events and completed suicide in schizophrenia: a comparison of suicide victims with and without schizophrenia.

National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland. hannele.heila@ktl.fi

Adverse life events are an established risk factor in completed suicide. However, few studies have examined life events and suicide in schizophrenia. We investigated and compared schizophrenia suicide victims and age- and sex-matched victims without schizophrenia as part of a psychological autopsy study of all suicides in Finland over a 12-month period. Recent life events were examined retrospectively by interviewing next of kin using a structured life event questionnaire. Overall, nearly half (46%) the schizophrenia subjects had had adverse life events before suicide, significantly less than the nonschizophrenia subjects (83%). In both groups, however, suicide was preceded by life events independent of the victims' own behavior, such as death of a close person or illness in the family. Life events overall were more common among schizophrenia outpatients (52%) than inpatients (22%), and the association of life events with suicide was clearest among a subgroup of outpatients in residual phase who had used neuroleptic medication regularly. Overall, the prevalence of recent adverse life events varied between clinical subgroups of victims with schizophrenia, which may have implications for suicide prevention.

Heilä H, Isometsä ET, Henriksson MM, Heikkinen ME, Marttunen MJ, Lönqvist JK. Suicide victims with schizophrenia in different treatment phases and adequacy of antipsychotic medication.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. Hannele.Heila@ktl.fi

BACKGROUND: To investigate clinical characteristics and adequacy of antipsychotic treatment in different phases of illness and treatment among suicide victims with schizophrenia. **METHOD:** As part of the National Suicide Prevention Project, a nationwide psychological autopsy study in Finland, all DSM-III-R schizophrenic suicide victims with a known treatment contact (N = 88) were classified according to the phase of illness (active/residual) and treatment (inpatient/recent discharge/other). Characteristics of victims in terms of known risk factors for suicide in schizophrenia, as well as adequacy of the neuroleptic treatment, were examined. **RESULTS:** Fifty-seven percent of suicide victims with active phase schizophrenia were prescribed inadequate neuroleptic treatment or were non-compliant, and 23% were estimated to be compliant nonresponders. Inpatient suicide victims had the highest proportion of negative or indifferent treatment attitudes (81%), whereas recently discharged suicide victims had the highest prevalence of comorbid alcoholism (36%), paranoid subtype (57%), and recent suicidal behavior or communication (74%), as well as the highest number of hospitalizations during their illness course and shortest last hospitalization. **CONCLUSION:** Suicide risk factors in different treatment phases of schizophrenia may differ. Substantial numbers of suicide victims with schizophrenia are receiving inadequate neuroleptic medication, are noncompliant, or do not respond to adequate typical antipsychotic medication. Adequacy

of psychopharmacologic treatment, particularly in the active illness phase, may be an important factor in suicide prevention among patients with schizophrenia.

Isometsa ET, Lonnqvist JK. Suicide attempts preceding completed suicide.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. erkki.isometsa@ktl.fi

BACKGROUND: This study investigated three questions with major implications for suicide prevention: the sensitivity of the history of previous suicide attempt(s) as an indicator of suicide risk, the time interval from a preceding suicide attempt to the fatal one, and switching of suicide methods by those eventually completing suicide. **METHOD:** The lifetime history of suicide attempts and the methods the victims (n = 1397) used were examined in a nationwide psychological autopsy study comprising all suicides in Finland within a 12-month research period in 1987-1988. **RESULTS:** Overall, 56% of suicide victims were found to have died at their first suicide attempt, more males (62%) than females (38%). In 19% of males and 39% of females the victim had made a non-fatal attempt during the final year. Of the victims with previous attempts, 82% had used at least two different methods in their suicide attempts (the fatal included). **CONCLUSIONS:** Most male and a substantial proportion of female suicides die in their first suicide attempt, a fact that necessitates early recognition of suicide risk, particularly among males. Recognition of periods of high suicide risk on the grounds of recent non-fatal suicide attempts is likely to be important for suicide prevention among females. Subjects completing suicide commonly switch from one suicide method to another, a finding that weakens but does not negate the credibility of restrictions on the availability of lethal methods as a preventive measure.

Heila H, Isometsa ET, Henriksson MM, Heikkinen ME, Marttunen MJ, Lonnqvist JK. Suicide and schizophrenia: a nationwide psychological autopsy study on age- and sex-specific clinical characteristics of 92 suicide victims with schizophrenia.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. Heila@ktl.fi

OBJECTIVE: The authors examined the clinical characteristics of suicide victims with schizophrenia in the general population of Finland. **METHOD:** As part of the nationwide National Suicide Prevention Project in Finland, all suicides over a 12-month period of persons with DSM-III-R schizophrenia were investigated by using the psychological autopsy method. Clinical characteristics and their variation with age, sex, and illness duration were examined. **RESULTS:** Among all suicide victims, 7% (N = 92) were identified as having suffered schizophrenia. Suicides occurred throughout the course of schizophrenia. Both active illness (78%) and depressive symptoms (64%) were highly prevalent immediately before suicide, and a history of suicide attempts (71%) was also common. Women were more likely than men to have committed suicide during an acute exacerbation of the illness. Marked variation in depressive symptoms, alcoholism, and suicide methods was found among sexes and age groups. Alcoholism was most common among middle-aged men (45%), whereas middle-aged women had a high rate of depressive symptoms (88%). Younger male subjects most often used violent suicide methods. **CONCLUSIONS:** Suicide may occur at any point during the course of schizophrenia. The results indicate clinically important variation in depression, alcoholism, and suicide methods among suicide victims with schizophrenia. This suggestion of age- and sex-specific risk factors for suicide in schizophrenia needs further investigation.

6.2. Mental health development

6.2.1. Research and public health significance of the area

1. The project provides information on mental health development from childhood through adolescence and adulthood. The focus of this research line is to study processes and mechanisms that risk or promote mental health during development.

2. The project contributes to epidemiological research on the occurrence and course of mental health problems and psychiatric disorders and their psychosocial etiology.

3. The project co-ordinates and carries out research done in the department on socioeconomic differences in mental health.

6.2.2. The main scientific achievements

National epidemiological studies

The Finnish Health Care Study (FINHCS) was a population-based nationwide study designed to monitor the health of the general population and evaluate the use and need for services. Based on a one-stage cluster sample of 15-75 year old persons (N=5993) who were interviewed in 1996. It was the first nationwide study in Finland to investigate depression using structured diagnostic interviews (e.g. Lindeman et al. 2000). A subsample of 15-24-olds was analyzed also separately to produce specific information on young adults (e.g. Haarasilta et al. 2001).

Health 2000, carried out in 2000-2001, is a nationwide population-based comprehensive survey on health and functional capacity in Finland. Two-stage stratified cluster sampling was used to draw a representative sample of the adult population aged 30 years and over (N=8028) (<http://www.ktl.fi/terveys2000/julkaisut/baseline.pdf>) and a sample of young adults aged 18-29 years (N=1894) (http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_b/2005/2005b7.pdf). The survey consisted of a health interview, self-reported questionnaires, and a thorough health examination (which included the structured mental health interview CIDI) in age group 30 years and over. Our

department has been responsible for coordinating the planning and reporting the mental health part of this major study. The Health 2000 study has produced important information on the prevalences and risk factors of the most common DSM-IV mental disorders (Pirkola et al. 2005a, 2005b).

As a continuation of Health 2000, our department has launched two major psychiatric studies of the same study samples, PIF (Psychoses in Finland) and MEAF (Mental health in early adulthood). In MEAF, a study using a two-phase study design, extensive data collection including semistructured diagnostic interviews of the study sample of 18–29-year-olds was carried out to produce psychiatric diagnoses according to the DSM-IV-TR criteria. The questionnaire of the screening phase of the MEAF was also planned to generate a design of a short-term follow-up survey of the young adult sample of Health 2000. These studies build up unique data bases both for psychiatric epidemiological and other types of studies (e.g. those in molecular genetics and neuropsychology).

Developmental studies

The most important developmental study in the project is TAM (Stress, development and mental health. A 16-year follow-up study of adolescents). It is a long-term prospective follow-up survey on stress, development and mental health from adolescence to adulthood started in 1983. In the study one age cohort of adolescents in the town of Tampere (1967 birth cohort; N=2269) has been studied at ages 16, 22 and 32.

During recent years the main results concerning depression include some interesting gender differences and support the suggestion of different types of depression: In adolescent risk factors for depression in young adulthood externalizing factors were more typical for males and internalizing aspects for females. (Pelkonen et al. 2003). Midadolescent depressive symptoms predicted persistent but not episodic depression, and female sex increased the risk for episodic but not persistent depression (Pelkonen et al. 2007). At the age of 32 chronic illness associated with higher levels of depression among males only, and this marked gender difference was explained by the effects of psychosocial resource differences (Kiviruusu et al. 2007).

Other important foci of research include risk factors and course of psychosomatic symptoms and alcohol misuse, and the role of family and socioeconomic factors for development and mental health.

The main results on socioeconomic (SES) differences in mental health showed that these differences varied depending on the life stage, gender and health indicator (Huurre et al. 2003). Lower SES group subjects were also in adverse position with respect to social support and a greater effect of social support on depression was found among

subjects from lower social positions (Huurre et al .2007). The findings also highlighted the need of greater consideration of psychosomatic symptoms, particularly in adolescence, for later socioeconomic outcomes (Huurre et al. 2005).

SES differences in mental health (SES-project)

SES differences in health have been one of the foci of research in KTL during recent years. The project has been responsible for studying and coordinating research of socioeconomic differences in mental health in our department. In addition to research in TAM described earlier, this topic is studied in Health 2000 and other studies. There is a national register-based data set which is formed by linking hospital discharges and mortality registers with sociodemographic background variables from population census, to analyze SES differences in psychiatric inpatient care and mortality.

6.2.3. The main public health achievements

Health 2000 and its psychiatric substudies provide the current view of the mental health in the Finnish population forming the knowledge base for the strategic planning of Ministry of Social Affairs and Health. Our developmental studies have contributed to the understanding on child development, especially on the role of family stress, socioeconomic factors and psychosocial resources for future mental health. The project has produced information on socioeconomic differences in mental health and participated in the planning of actions to promote the attainment of the objective of the Health 2015 public health programme for reducing health inequalities. Joint report on inequalities in health in Finland including mental health will be published in 2007.

6.2.4. Funding for research and public health programs

The psychiatric studies of Health 2000 and SES-project have been mainly financed by KTL, supplemented by funding from Academy of Finland and foundations. The majority of the funding for TAM-project has come from external sources (Academy of Finland and Finnish foundations).

6.2.5. Personnel

The current personnel consists of Hillevi Aro (50%) and Taina Huurre. Much of the work is done also by researchers from other projects. In addition, several PhD students with external funding work in the project.

6.2.6. Collaboration

The collaborative networking in the Health 2000 mental health research is widespread in the Finnish research community.

The research team of TAM-project is multidisciplinary including researchers in epidemiology, public health, psychiatry, psychology, education, social policy, and statistics. The main collaborators outside KTL come from the universities of Helsinki, Tampere, Umeå and Birmingham.

The main collaborators in the SES-project come from National Research and Development Centre for Welfare and Health and University of Helsinki.

6.2.7. Proposal for future work and expected benefits

Monitoring and producing up-to-date information on the psychiatric morbidity and mental health development of Finnish people will be continued. The Health 2000 cohort will be followed up by registers, and the next large national health survey is planned to take place after 2010. In the TAM project the next follow-up survey will be carried out in 2009, when the persons will be 42 years old.

6.2.8. Main publications

1. Pelkonen M, Marttunen M, Kaprio J, Huurre T, Aro H. Adolescent risk factors for episodic and persistent depression in adulthood. A 16-year prospective follow-up study of adolescents. *J Affect Disord* 2007 (in press).

BACKGROUND: We examined mid-adolescent psychosocial problems as risk factors for subsequent depression up to adulthood proper, and differences in these for episodic and persistent depression. **METHODS:** In a 16-year follow-up of an urban Finnish community cohort (547 males and 714 females) from age 16 years risk factors for subsequent depression (S-BDI) were studied. Data were collected with a classroom questionnaire at 16 years and a postal questionnaire at 22 and 32 years. Differences in predictors for episodic depression (only at age of 22 or 32 y) and persistent depression (both at 22 and 32 y) were studied using logistic and multinomial regression analyses. **RESULTS:** Mid-adolescent depressive symptoms predicted persistent and female sex episodic depression. Low self-esteem, dissatisfaction with academic achievement, problems with the law, having no dating experiences, and parental divorce all predicted both episodic and persistent depression. **LIMITATIONS:** We had two assessment points in adulthood, but no information about depression between these. **CONCLUSIONS:** The associations between mid-adolescent psychosocial problems and subsequent depression extended up to adulthood proper, somewhat differently for episodic and persistent depression. Preventive efforts should be focused towards young people at risk.

2. Saarni SI, Suvisaari J, Sintonen H, Pirkola S, Koskinen S, Arpomaa A, Lönnqvist J. Impact of psychiatric disorders on health-related quality of life: general population survey. *Br J Psychiatry* 2007;190:326-332.

BACKGROUND: Measurement of health-related quality of life (HRQoL) with generic preference-based instruments enables comparisons of severity across different conditions and treatments. This is necessary for rational public health policy. **AIMS:** To measure HRQoL decrement and loss of quality-adjusted life-years (QALYs) associated with pure and comorbid forms of depressive and anxiety disorders and alcohol dependence. **METHOD:** A general population survey was conducted of Finns aged 30 years and over. Psychiatric disorders were diagnosed with the Composite International Diagnostic Interview and HRQoL was measured with the 15D and EQ-5D questionnaires. **RESULTS:** Dysthymia, generalised anxiety disorder and social phobia were associated with the largest loss of HRQoL on the individual level before and after adjusting for somatic and psychiatric comorbidity. On the population level, depressive disorders accounted for 55%, anxiety disorders 30%, and alcohol dependence for 15% of QALY loss identified in this study. **CONCLUSIONS:** Chronic anxiety disorders and dysthymia are associated with poorer HRQoL than previously thought.

3. Huurre T, Eerola M, Rahkonen O, Aro H. Does social support affect the relationship between socio-economic status and depression? A longitudinal study from adolescence to adulthood. *J Affect Disord*; 2007;100:55-64.

BACKGROUND: The aim of this prospective longitudinal study of adolescents was to investigate socioeconomic differences in adult depression and in the domain of social support from adolescence to adulthood. We also studied the modifying effect of social support on the relationship between socioeconomic status (SES) and depression. **METHODS:** All 16-year-old ninth-grade school pupils of one Finnish city completed questionnaires at school (n=2194). Subjects were followed up using postal questionnaires when aged 22 and 32 years. **RESULTS:** At 32 years of age there was a social gradient in depression, with a substantially higher prevalence among subjects with lower SES. Low parental SES during adolescence did not affect the risk of depression at 32 years of age, but the person's lower level of education at 22 years did. Lower level of support among subjects with lower SES was found particularly in females. Some evidence indicated that low level of social support had a greater impact on depression among lower SES group subjects. However, this relationship varied depending on the domain of social support, life stage and gender. On the other hand, the results did not support the hypothesis that social support would substantially account for the variation in depression across SES groups. **LIMITATIONS:** The assessments

and classifications of social support were rather brief and crude, particularly in adolescence and early adulthood. **CONCLUSIONS:** It is important to pay attention to social support resources in preventive programs and also in the treatment settings, with a special focus on lower SES group persons.

4. Kiviruusu O, Huurre T, Aro H. Psychosocial resources and depression among chronically ill young adults: Are males more vulnerable? *Soc Sci Med* 2007;65:173-186.

This population-based study examined the association between chronic illness and depression and the role of psychosocial resources (coping styles, locus of control (LOC) and social support) in this association, among young Finnish adults aged 32. Gender differences in these phenomena were also investigated. The study was based on questionnaire data from a Finnish cohort study. Participants with self-reported chronic illness (e.g. diabetes, asthma, migraine) were grouped together (n=257) and compared to healthy controls (n=664). The results showed that the chronically ill males were more depressed than healthy control males. They also used more emotion-focused coping, had a more external LOC and were less often married or cohabiting than healthy males. The association between chronic illness and depression among males attenuated when the effects of emotion-focused coping disposition and LOC were taken into account, indicating a possible mediating role for these resources. Among females no differences were found in depression or psychosocial resources between the chronically ill and healthy control groups. Psychosocial resources, especially LOC, explained the gender difference in the association between chronic illness and depression. Only a few buffering effects of psychosocial resources emerged: an active problem-solving coping disposition among the chronically ill males and perceived social support among the chronically ill females seemed to act as buffers against depression. The results indicated a significant gender disparity in the association between chronic illness and depression among young adults and emphasised the role of psychosocial resources in this context. With regard to prevention we suggest that, chronically ill young adult males should be recognised as a risk group for depression that would probably benefit from guidance in learning more active coping skills and maintaining a sense of personal control in facing chronic physical illness.

5. Huurre T, Junkkari H, Aro H. Long-term psychosocial effects of parental divorce. A follow-up study from adolescence to adulthood. *Eur Arch Psych Clin Neurosci* 2006;256:256-263.

OBJECTIVE: The purpose of this 16-year follow-up study was to investigate whether 32-year-old adults who had experienced parental divorce before 16 years of age (n = 317) differed in psychosocial well-being or life trajectories from those from non-divorced two-parent families (n = 1069). **METHOD:** The data were obtained from a follow-up survey of a Finnish urban age cohort from the age of 16 till 32 years (n = 1471). The long-term impact of parental divorce on a variety of outcomes in adulthood, including psychological well-being, life situation, health behaviour, social networks and support, negative life events and interpersonal problems, was assessed. **RESULTS:** Females from divorced compared to non-divorced families reported more psychological problems (higher scores in the Beck Depression Inventory, General Health Questionnaire and Psychosomatic Symptoms Score) and more problems in their interpersonal relationships. These differences were not found among males. Shorter education, unemployment, divorce, negative life events and more risky health behaviour were more common among subjects of both genders with a background of parental divorce. **CONCLUSIONS:** The study revealed that parental divorce is an indicator of sufficient stress in childhood for its influences to persist well into adulthood, possibly with wider scope among females. It is important to recognise specific needs of children in the divorce process in order to prevent or minimize negative consequences and chain reactions during their subsequent life.

6. Ahola K, Honkonen T, Isometsä E, Kalimo R, Nykyri E, Koskinen S, Aromaa A, Lönnqvist J. Burn-out in the general population. Results from the Finnish Health 2000 Study. *Soc Psychiatry Psychiatr Epidemiol* 2006;41:11-17.

BACKGROUND: Burnout is a chronic stress syndrome which develops gradually as a consequence of prolonged stress situation. Socio-demographic factors related to job-related burnout have not been studied in the whole population. We investigated the relative differences in the level of burnout between groups based on various socio-demographic factors in the population-based Finnish sample. **METHODS:** The nationally representative sample comprised 3,424 employees aged 30-64 years. Burnout was assessed with the Maslach Burnout Inventory-General Survey. The socio-demographic factors of interest were gender, age, education, type of employment, work experience, socio-economic status (SES), working time, and marital status. **RESULTS:** Only small differences in burnout were found between the different population groups. As a three-dimensional syndrome, burnout was associated with age. In contrast to what has been consistently reported so far, mostly among human service work and in non-representative studies, burnout seemed to increase somewhat with age. Among women, burnout was also related to education, SES, and work experience, and among men, to marital status. **CONCLUSIONS:** Burnout can evolve in all kinds of vocational groups. It seems that age does not generally protect against burnout. A low education level and low social status carry a possible risk of burnout for women, and being single, divorced, or widowed carry a possible risk of burnout for men.

7. Huurre T, Rahkonen O, Komulainen E, Aro H. Socioeconomic status as a cause and consequence of psychosomatic symptoms from adolescence to adulthood. *Soc Psychiatry Psychiatr Epidemiol* 2005;40:580-587.

BACKGROUND: Few follow-up studies have investigated psychosomatic health and socioeconomic status (SES) and associations between them at different life stages. The aim of this study was to investigate differences in psychosomatic symptoms by SES in adolescence, early adulthood and adulthood and to examine whether lower SES leads to higher levels of symptoms (social causation) or higher levels of symptoms to lower SES (health selection) or both. **METHODS:** All 16-year-old ninth-grade school pupils of one Finnish city completed questionnaires at school. Subjects were followed up using postal questionnaires when aged 22 and 32 years. **RESULTS:** Females reported significantly higher scores of psychosomatic symptoms than males at 16, 22 and 32 years of age. Higher rates of psychosomatic symptoms were found among females of manual class origin at 16 years. In addition, at 22 years, both females and males with only comprehensive school education and, at 32 years, those who worked in manual jobs had higher scores of symptoms. When low SES both as a cause and consequence of symptoms was investigated, the findings supported both these paths among females and more the health selection among males. In both genders, especially the path from psychosomatic symptoms in adolescence to lower education in early adulthood was strong. **CONCLUSIONS:** The results highlight the need of greater consideration of psychosomatic symptoms, particularly in adolescence, in later socioeconomic outcomes.

8. Pirkola S, Isometsä E, Aro H, Kestilä L, Härmäläinen J, Veijola J, Kiviruusu O, Lönnqvist J. Childhood adversities as risk factors for adult mental disorders. Results from the Health 2000 Study. *Soc Psychiatry Psychiatr Epidemiol* 2005a;40:769-777.

BACKGROUND: The sex-specific role of stressful or traumatic childhood experiences and adverse circumstances in developing adulthood mental disorders is complex and still in need of comprehensive research. **METHODS:** Within the Health 2000 project in Finland, a representative sample of 4,076 subjects aged 30-64 years were investigated to examine associations between a set of retrospectively self-reported adverse environmental factors during childhood (0-16 years) and mental disorders diagnosed in

the past 12 months by the Munich Composite International Diagnostic Interview. **RESULTS:** Of the 60% of adults reporting at least one childhood adversity, 17% had a current (past 12 months) mental disorder, compared to 10% of the non-reporters. A moderate dose-response relationship between the total number of adversities and current disorders was observed. Paternal mental health problems associated particularly strongly with male depressive disorders (OR 4.46), and maternal mental health problems with female depressive disorders (OR 3.20). Although seldom reported, maternal alcohol problems associated with alcohol use disorders in both sexes. Being bullied at school and childhood family discord predicted a variety of adulthood disorders in both sexes. All these four adversity items were more typical for depressive disorders with an earlier onset. Among females, more adversities were associated with mental disorders and their statistical significance was greater than among males. **CONCLUSIONS:** There are marked sex differences and several diagnosis-related patterns in the associations between reported childhood experiences and environmental circumstances and adulthood mental disorders. The impact of adversities is probably composed of a wide range of factors from direct causal associations to complex, interacting environmental effects. Variations in the reported associations reflect the differing genetic and environmental transmission mechanisms of mental disorders.

9. Pirkola S, Isometsä E, Suvisaari J, Aro H, Joukamaa M, Poikolainen K, Koskinen S, Aromaa A, Lönnqvist J. DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population. Results from the Health 2000 Study. *Soc Psychiatry Psychiatr Epidemiol* 2005b;40:1-10.

BACKGROUND: Information on prevalence, accumulation and variation of common mental disorders is essential for both etiological research and development of mental health service systems. **METHODS:** A representative sample (6005) of Finland's general adult (> or = 30 years) population was interviewed in the period 2000-2001 with the CIDI for presence of DSM-IV mental disorders during the last 12 months in the comprehensive, multidisciplinary Health 2000 project. **RESULTS:** Depressive-, alcohol use- and anxiety disorders were found in 6.5%, 4.5 % and 4.1% of the subjects, respectively. A comorbid disorder was present in 19% of those with any disorder. Males had more alcohol use disorders (7.3 % vs. 1.4 %) and females more depressive disorders (8.3 % vs. 4.6 %). Older age, marriage and employment predicted lower prevalence of mental disorders and their comorbidity. Prevalences of alcohol use- and comorbid disorders were higher in the Helsinki metropolitan area, and depressive disorders in northern Finland. **CONCLUSIONS:** Mental disorders and their comorbidities are distributed unevenly between sexes and age groups, are particularly associated with marital and employment status, and vary by region. There appears to be no single population subgroup at high risk for all mental disorders, but rather several different subgroups at risk for particular disorders or comorbidity patterns.

10. Hämmäläinen J, Isometsä E, Laukkala T, Kaprio J, Poikolainen K, Heikkinen M, Lindeman S, Aro H. Use of health services for Major Depressive Episode in Finland. *J Aff Disord* 2004;79:105-112.

BACKGROUND: A universal finding in psychiatric epidemiology is that only a minority of currently depressed people seek or receive treatment. **AIMS:** To investigate the predictors of use of health care services for depression. **METHODS:** A representative random sample of 5993 non-institutionalised Finnish individuals aged 15-75 years was interviewed in 1996. Major depressive episode during the last 12 months was assessed using the Short Form of the University of Michigan version of the Composite International Diagnostic Interview (the UM-CIDI Short Form). Characteristics and health service use of the 557 depressed individuals were assessed. **RESULTS:** The proportion of people classified as having a major depressive episode who used any health services for their depression during the past 12 months was only 31% for men and 25% for women. Use of services was not predicted by sociodemographic factors. Longer duration, and greater severity and perceived disability predicted overall health service use for

depression, but not significantly whether treatment was sought from primary or psychiatric care. **CONCLUSIONS:** The probability of use of health services for major depression increases with duration, severity and perceived disability related to depression. Only 59% of those suffering from even the most severe major depressive episodes use health services for depression. Use appears to be unrelated to socio-demographic factors in Finland.

11. Huurre T, Aro H, Rahkonen O. Well-being and health behaviour by parental socioeconomic status. A follow-up study of adolescents aged 16 until age 32 years. *Soc Psychiatry Psychiatr Epidemiol* 2003; 38: 249-255.

BACKGROUND: The aim of the study was to investigate the impact of parental socioeconomic status (SES) on subjects' well-being and health behaviour in adolescence, early adulthood and adulthood, and whether these impacts remained after controlling for the person's own SES. **METHODS:** All 16-year-old ninth-grade school pupils of one Finnish city completed questionnaires at school. Subjects were followed up using postal questionnaires when aged 22 and 32 years. **RESULTS:** Females of manual class origin had lower self-esteem and more distress symptoms from adolescence to adulthood than those from a non-manual background. Lower self-esteem was found among males from manual class families in adolescence and early adulthood. In both genders, no significant class differences were found in depression, health status or prevalence of chronic illness. Unhealthier behaviours regarding smoking and physical activity were more prevalent among both genders of manual class origin, and females of this group had higher rates of overweight and higher body mass index scores. After controlling for the person's own SES, the effect of parental SES diminished but remained significant for smoking in both genders and for physical activity in males up to 22 years, and for self-esteem and BMI in females up to 32. **CONCLUSIONS:** This follow-up study contributes to the health inequality debate investigating parental SES differences in health behaviour and somatic health, and particularly in psychological health, which is relatively rarely investigated. The results indicate that parental SES has effects on early adult and adult well-being and health behaviour other than those mediated by current SES.

12. Pelkonen M, Marttunen M, Aro H. Risk for depression: A six-year follow-up of Finnish adolescents. *J Aff Disord* 2003;77:41-51

BACKGROUND: Few longitudinal studies have attempted to identify risk factors in mid-adolescence for subsequent depression in young adulthood. Mid-adolescence is a critical developmental phase for studying vulnerability to depression due to high incidence and prevalence of depression. **METHODS:** In a longitudinal study, following an urban Finnish community cohort (761 males and 887 females) from age 16, mid-adolescent risk factors for depression at age 22 years were studied. Data were collected by a questionnaire at school at age 16, and by a postal questionnaire at age 22. **RESULTS:** Of the females 116 (13%) and of the males 69 (9%) had depression (S-BDI) in young adulthood. In multivariate analyses baseline depressive symptoms, low self-esteem, dissatisfaction with academic achievement, problems with the law, poor atmosphere at home and having no close friends predicted subsequent depression. Risk factors for males included more 'externalizing' aspects, for females more 'internalizing' factors. **CONCLUSIONS:** Mid-adolescence is an important age to study risk for depression, and self-reported perceptions of psychosocial well-being have predictive value. Preventive efforts can be selectively targeted at adolescents who have been exposed to identifiable risk factors.

13. Haarasilta L, Marttunen M, Kaprio J, Aro H. The 12-month prevalence and characteristics of Major Depressive Episode in a representative nationwide sample of adolescents and young adults. *Psychol Med* 2001; 31:1169-1180.

BACKGROUND: This study set out to estimate the 12-month prevalence of DSM-III-R major depressive episode (MDE) and to analyse factors associating with psychosocial impairment, episode duration, phenomenology and symptom severity in a representative general population sample of adolescents (15-19-year-olds) and young adults (20-24-year-olds). **METHOD:** The Finnish Health Care Survey '96 (FINHCS '96) was a cross-sectional nationwide epidemiological study. A random sample of 509 adolescents and 433 young adults was interviewed in 1996. MDE was assessed by University of Michigan Composite Diagnostic Interview Short-Form. **RESULTS:** The 12-month prevalence of MDE was 5.3 % for adolescents (females 6.0%, males 4.4%) and 9.4% for young adults (females 10.7%, males 8.1%). When moderate psychosocial impairment was included in case definition, the prevalences were lowered by 20-25%. Increased impairment was associated with drunkenness at least twice a month, a higher mean number of depressive symptoms and impaired concentration. The median episode duration was 1 month. No factors associating with duration were found. With the exception of symptoms related to appetite being more common among females than males, the phenomenology of MDE was mainly independent of age and gender. **CONCLUSIONS:** Episodes of major depression among adolescents and young adults in the general population are short but often associated with psychosocial impairment, especially if frequent drunkenness coexists.

14. Laukkala T, Isometsä E, Härmäläinen J, Heikkinen M, Lindeman S, Aro H. Antidepressant treatment of depression in the Finnish general population. *Am J Psychiatry* 2001;158:2077-2079.

OBJECTIVE: Antidepressant use has increased in the last decade, but whether depression continues to be undertreated is unknown. The authors investigated the prevalence of antidepressant treatment and its predictors in a recent general population sample of depressed subjects. **METHOD:** As part of the Finnish Health Care Survey, in 1996 a representative sample of Finns (N=5,993) aged 15-75 years underwent a standardized face-to-face interview that used the DSM-III-R criteria for major depressive episode. **RESULTS:** Only 13% of subjects with a major depressive episode during the preceding 12 months (70 of 557) reported current use of an antidepressant. In logistic regression models, use of psychiatric services for depression, regular use of any other medication, more than 1 month of sick leave, and smoking were associated with antidepressant treatment. **CONCLUSIONS:** Most depressed subjects in 1996 in Finland were not receiving antidepressant treatment despite the several-fold increase in antidepressant use in the 1990s.

15. Lindeman S, Härmäläinen J, Isometsä E, Kaprio J, Poikolainen K, Heikkinen M, Aro H. The 12-month prevalence and risk factors for major depressive episode. Representative sample of 5993 adults. *Acta Psychiatr Scand* 2000;102:178-184.

OBJECTIVE: This study reports the 12-month prevalence of major depressive episode and its risk factors in a representative nationwide sample. **METHOD:** A random sample of non-institutionalized Finnish individuals aged 15-75 years (N = 5993) was interviewed in 1996. Major depressive episode during the last 12 months was assessed using the Short Form of the University of Michigan version of the Composite International Diagnostic Interview (the UM-CIDI Short Form). **RESULTS:** The population prevalence of major depressive episode was 9.3% [95% CI 8.5,10.0], and the age-adjusted prevalences for females and males were 10.9% [95% CI 9.7,12.0] and 7.2 [95% CI 6.2,8.2], respectively. In logistic regression analyses the factors associated with major depressive episode after adjustment for age were urban residency, smoking, alcohol intoxication and chronic medical conditions. In addition, being single and obese were found to be risk factors for males. **CONCLUSION:** The female to male risk ratio for major depressive episode was smaller than in many previous studies. The sex-specific risk factor associations warrant further investigation into sex differences in depression.

6.3. Mood disorder research

6.3.1. Research and public health significance of the area

Depressive and bipolar disorders are major public health problems. According to the estimates of WHO's Global Burden of Disease Study, unipolar depression is the fourth and bipolar disorder 22nd most important illness in terms of disability-adjusted life years (DALYs). Furthermore, mood disorders are the most important single risk factor for suicidal behavior, including completed suicide, attempted suicide and suicidal ideation. The overall mortality of patients with mood disorders is approximately two-fold as compared with the general population, due to not only suicides but also increased mortality to e.g. cardiovascular disorders. In addition, mood disorders are among the most frequent causes for disability pensions or sick leaves, causing remarkable costs to both the individual and the society.

Research presented here involves several major research projects focusing on various aspects of mood disorders, in particular their clinical epidemiology, focusing in particular to a) outcome in terms of chronicity, relapses and recurrences; b) suicidal behavior (completed and attempted suicide, suicidal ideation), c) disability (overall level of functioning, social adjustment, sick leaves and disability pensions), and d) quality and continuity of treatment provided in health care. Besides clinical studies, several projects are involved in investigating associated functional (magnetoencephalography) and structural (MRI, diffusion tensor imaging) brain abnormalities, neuropsychological dysfunctions and putative candidate genes for mood disorders.

The main projects include (but are not limited to) the Vantaa Depression Study (VDS), the Vantaa Primary Care Depression Study (PC-VDS), the Jorvi Bipolar Study, and the Molecular Genetics, Psychobiology and Neuropsychology of Mood Disorders (MMPN, acronym from the Finnish initials). The VDS (N=269), PC-VDS (N=137) and JoBS (N=191) are relatively large clinical, longitudinal cohort studies using life chart methodology, all based on screening for depression or bipolar I and II disorders; very careful and comprehensive diagnostic evaluation with structured interviews and excellent reliability (kappas 0.86-1.0), each effectively representing all psychiatric (VDS, JoBS) or primary care (PC-VDS) patients with mood disorders of city of Vantaa (VDS, PC-VDS) or the three neighbouring cities Espoo, Kirkkonummi and Kauniainen (JoBS). For most of the brain imaging, neuropsychological and molecular genetic studies, patients are recruited from these clinical cohorts. Besides these projects, other projects such as a magnetoencephalography (MEG) research project of depression, plus register-

based studies general population surveys of patients and subjects with mood disorders or symptoms have been conducted.

6.3.2. The main scientific achievements

The clinical studies have illuminated the clinical epidemiology of mood disorders in many ways:

- (a) The VDS has been the first major clinical cohort study that has comprehensively investigated psychiatric axis I and II comorbidity in patients with major depressive disorder (MDD), finding comorbidity the rule rather than an exception, and a factor that markedly influences the outcome and treatment of the patients. Nevertheless, the long-term (five-year) outcome of the VDS cohort is more variable, and not as consistently chronic as most of the current psychiatric literature suggests (typically based on unrepresentative, mostly inpatient, tertiary level patient samples).
- (b) The PC-VDS has documented presence of psychiatric comorbidity also in primary care settings, and suggested that the perceived mostly subthreshold nature of depression in primary care is largely an artefact caused by exclusively cross-sectional evaluation. In fact, most primary care patients with mild depressive symptoms suffer from MDD in lifetime perspective. The idea of mostly mild, self-limited and subthreshold disorders in primary care is not tenable.
- (c) The JoBS has documented poor rate of recognition of particularly bipolar II disorder even in psychiatric settings, high prevalence of depressive mixed states (mixed depression) in particular bipolar II but also bipolar I patients, and very high level of suicidal behaviour in both types of the illness, largely explicable in terms of time spent in high-risk illness states (depressive and mixed illness phases) during follow-up.

6.3.3. The main public health achievements

The clinical studies have illuminated the clinical epidemiology of mood disorders in ways that have major implications for developing health care services for patients with these disorders:

The PC-VDS documented major problems in recognition of depression in primary care,

raising the needs for education, screening and collaborative care models in primary care. The presence of psychiatric and somatopsychiatric comorbidity in both the VDS and the PC-VDS has major impact on planning treatments and services, as comorbidity usually complicates all treatment, and undermines generalizability of findings from clinical treatment trials into clinical practice. Finding that depressive patients in primary health care usually suffer from major depressive disorder suggest, that not only psychosocial interventions, but also antidepressant pharmacotherapy is usually warranted. As mood disorders are usually recurrent, continuity of acute and maintenance phase treatments is essential to prevent relapses and recurrences. However, the VDS has documented poor continuity of acute treatment for depression in psychiatric care. Moreover, maintenance antidepressant therapy is a cornerstone for prevention of recurrent depressive episodes, but the VDS found less than half (42%) of patients with a clear indication for maintenance antidepressant therapy to receive it all, and only for 18% of the months indicated, during the long-term follow-up. Thus, although treatments for depression are increasingly available, poor continuity of treatment remarkably compromises the public health benefits of these interventions.

The JoBS documented poor rate of recognition of particularly bipolar II disorder even in psychiatric settings, and largely as a consequence, major inadequacies in clinical treatment of patients with bipolar disorder. As these patients represent a highly suicidal group of patients in psychiatric care, measures to improve quality of care are urgently needed. They include screening for bipolar disorder, psychoeducation, and more systematic use of mood diaries and life charts in follow-up. The three clinical cohort studies have provided a necessary epidemiological background for developing national evidence-based clinical care guidelines for depression (professor Isometsä chaired the task force) and bipolar disorder (chaired by associate professor Kirsi Suominen, a member of the JoBS research group).

6.3.4. Funding for research and public health programs

The mood disorders research has received large EVO (state subsidiary) grants from the Helsinki and Uusimaa Health Care District (151.000 € for the years 1998-2000; total 180.000 € for 2005-2008), plus funding from the Academy of Finland (126.000 FIM for 2001-2003; 150.000 € for 2005-2007). In addition, the projects and individual researchers have received numerous smaller grants. The molecular genetic aspect of the MMPN have been separately funded by the Academy of Finland.

6.3.5. Personnel

At present, research professor Erkki Isometsä has a part-time (20%) position at the National Public Health Institute, his main affiliation being with the University of Helsinki. The research described above involves a large and complex multidisciplinary network of researchers (about 30) including clinical psychiatrists, psychologists, epidemiologists and statisticians, neuroradiologists and physicists, most affiliated with the Department of Mental Health and Alcohol Research or Department of Molecular Medicine of the National Public Health Institute in Helsinki, or the Departments of Psychiatry or Radiology at the Helsinki University Central Hospital. None of the researchers are in permanent research position, all work part-time or intermittently. However, the available funding has allowed sufficient time allocated for this research typically in periods of few months per year by the collaborators. Much of the clinical research has been undertaken as Ph.D. theses (six accomplished, twelve under preparation).

6.3.6. Collaboration

The nature of this research is multidisciplinary and involves mainly collaboration between the Department of Mental Health and Alcohol Research and Department of Molecular Medicine of the National Public Health Institute in Helsinki, and the Departments of Psychiatry and Department of Radiology at the Helsinki University Central Hospital. Although many of the researchers have close contact with the international networks of researchers of their own field, this research per se has been conducted as collaborative projects between these nationally leading institutions. Much of the clinical research has been undertaken as Ph.D. theses (six accomplished, twelve under preparation).

6.3.7. Proposal for future work and expected benefits

The clinical cohort studies VDS, PC-VDS and JoBS are all now focusing on medium (18 months) and long-term (five years) outcomes. These studies are based on life charts, and will illuminate the clinical course of illness in representative, unselected cohorts of patients. The studies will also be informative regarding the outcome of suicidal behaviour and level of functioning and work disability in the long-term.

A new cohort study of borderline personality disorder will be started during the fall 2007. The aim is to collect a regionally representative cohort of carefully diagnosed psychiatric patients with borderline personality disorder (BPD), to characterize their clinical picture and investigate their clinical outcome. As with the patients in the mood disorder cohorts, patient from this cohort will be recruited into molecular genetic, neuropsychological and structural brain imaging (MRI, including diffusion tensor imaging) studies as a part of the MMPN.

The ongoing diffusion tensor imaging (DTI) studies of the MMPN (now starting with a new 3T scanner at the HUCH) are beginning to provide detailed information on the abnormalities in brain white matter among patients with mood disorders. The ongoing MMPN molecular genetic association studies will provide information on genetic risk factors (candidate genes) for mood disorders, their possible influence on the phenotype and long-term outcome, and interactions with life events (G x E interactions) when influencing outcome. Furthermore, the possible impact of the putative candidate genes on brain structure will be investigated as a part of the MMPN project. This information can also be combined with data on neuropsychological abnormalities among these patients. Finally, a pilot study of actigraphy in mood disorders will be started during the fall 2007. The aim is to explore the potential usefulness of objective measurement of physical activity in measuring variations in mood state and sleep-wake-cycle. This kind of technology may prove to be a useful tool for differential diagnostic purposes in mood disorders, or indicator of escalating mood episodes. If the pilot study confirms the utility of actigraphy for these purposes, this line of research will proceed into more large-scale experiments.

6.3.8. Key publications in 2004-2007

1. Melartin T, Rytsälä H, Leskelä U, Lestelä-Mielonen, Sokero P, Isometsä E. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. *Journal of Clinical Psychiatry* 2004;65:810-819

2. Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). *Bipolar Disorders* 2004;6:395-405.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

OBJECTIVE: To obtain a comprehensive view of the clinical epidemiology of bipolar I and II disorder in secondary-level psychiatric settings. **METHODS:** In the Jorvi Bipolar Study (JoBS), 1630 non-schizophrenic psychiatric in- and outpatients in three Finnish cities were screened for bipolar I and II disorders with the Mood Disorder Questionnaire. Diagnoses were made using semistructured SCID-I and -II interviews. Information collected included clinical history, current episode, symptom status, and other characteristics. **RESULTS:** A total of 191 patients with bipolar disorder (90 bipolar I and 101 bipolar II) were

included in the JoBS. The majority of bipolar II (50.5%) and many bipolar I (25.6%) patients were previously undiagnosed; the remainder had a median 7.8 years delay from first episode to diagnosis. Despite several lifetime episodes, 26 and 58% of bipolar I and II patients, respectively, had never been hospitalized. A polyphasic episode was current in 51.3%, rapid cycling in 32.5%, and psychotic symptoms in 16.2% of patients. Mixed episodes occurred in 16.7% of bipolar I, and depressive mixed states in 25.7% of bipolar II patients. **CONCLUSION:** Even in psychiatric settings, bipolar disorders usually go undetected, or recognized only after a long delay. A significant proportion of not only bipolar II, but also bipolar I patients are never hospitalized. Polyphasic episodes and rapid cycling are prevalent in both types. Depressive mixed states are at least as common among bipolar II patients as mixed episodes among bipolar I.

3. Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET. Continuity is the main challenge in treating major depressive disorder in psychiatric care. *Journal of Clinical Psychiatry* 2005;66:220-227.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

OBJECTIVE: Several evidence-based treatment guidelines for major depressive disorder (MDD) have been published. However, little is known about how recommendations for treatment are adhered to by patients in current usual psychiatric practice. **METHOD:** The Vantaa Depression Study is a prospective, naturalistic cohort study of 269 psychiatric patients with a new episode of DSM-IV MDD who were interviewed with the Schedules for Clinical Assessment in Neuropsychiatry and Structured Clinical Interview for DSM-III-R Personality Disorders between February 1, 1997, and May 31, 1998, and again at 6 and 18 months. Treatments provided, as well as adherence to and attitudes toward both antidepressants and psychotherapeutic support/psychotherapy, were investigated among the 198 unipolar patients followed for 18 months. **RESULTS:** Most depression patients (88%) received antidepressants in the early acute phase, but about half (49%) terminated treatment prematurely. This premature termination was associated with worse outcome of major depressive episodes, and with negative attitudes, mainly explained by fear of dependence on or side effects of antidepressants. Nearly all patients (98%) received some psychosocial treatment in the acute phase; about one fifth (16%) had weekly psychotherapy during the follow-up. About a quarter of patients admitted nonadherence to ongoing treatments. **CONCLUSION:** Problems of psychiatric care seem most related to continuity of treatment. While adequate treatments are provided in the early acute phase, antidepressants are terminated too soon in about half of patients, often following their autonomous decisions. From a secondary and tertiary preventive point of view, improving continuity of treatment would appear a crucial task for improving the outcome of psychiatric patients with MDD.

4. Vuorilehto M, Melartin T, Isometsä E. Depressive disorders in primary care: Recurrent, chronic and comorbid. *Psychological Medicine* 2005; 35: 673-68.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

BACKGROUND: Preceding longitudinal course and current somatic and psychiatric co-morbidity of depression have been little investigated in primary care. **METHOD:** Consecutive patients (n = 1111) in primary care in the city of Vantaa, Finland, were screened for depression with the PRIME-MD, and positive cases interviewed by telephone. Cases with current depressive symptoms were diagnosed face-to-face with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P). A cohort of 137 patients with unipolar depressive disorders, comprising all patients with at least two depressive symptoms and clinically significant distress or disability, was recruited. The Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), medical records, rating scales, and a retrospective life-chart were used to obtain comprehensive cross-sectional and longitudinal information. **RESULTS:** Current major depressive disorder (MDD) was the most prevalent depressive disorder (66%); it was usually mild to moderate but

recurrent. A quarter of cases (23%) had MDD in partial remission or prodromal phase, and only 10% had true minor depression. Axis I co-morbidity was present in 59%, Axis II in 52%, and chronic Axis III disorders in 47%; only 12% had no co-morbidity. One third of patients presented with a psychological complaint, predicted by higher depression severity and younger age. **CONCLUSION:** From a lifetime perspective, the majority of primary-care patients with depressive disorders suffer from recurrent MDD, although they are currently often in prodromal or residual phase. Psychiatric and somatic co-morbidity are highly prevalent. Treatment of depression in primary care should not rely on an assumption of short-lived, uncomplicated mild disorders.

5. Sokero TP, Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Isometsä ET. A prospective study of risk factors for attempted suicide among psychiatric patients with DSM-IV major depressive disorder. *British Journal of Psychiatry* 2005;186:314-8.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

BACKGROUND: There are few prospective studies on risk factors for attempted suicide among psychiatric out- and in-patients with major depressive disorder. **AIMS:** To investigate risk factors for attempted suicide among psychiatric out- and in-patients with major depressive disorder in the city of Vantaa, Finland. **METHOD:** The Vantaa Depression Study included 269 patients with DSM-IV major depressive disorder diagnosed using semistructured interviews and followed up at 6- and 18-month interviews with a life chart. **RESULTS:** During the 18-month followup, 8% of the patients attempted suicide. The relative risk of an attempt was 2.50 during partial remission and 7.54 during a major depressive episode, compared with full remission (P 0.001). Numerous factors were associated with this risk, but lacking a partner, previous suicide attempts and total time spent in major depressive episodes were the most robust predictors. **CONCLUSIONS:** Suicide attempts among patients with major depressive disorder are strongly associated with the presence and severity of depressive symptoms and predicted by lack of partner, previous suicide attempts and time spent in depression. Reducing the time spent depressed is a credible preventive measure.

6. Valtonen H, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä ET. Suicidal Ideation and Attempts in Bipolar I and II Disorders. *Journal of Clinical Psychiatry* 2005;66:1456-1462.

Department of Mental Health and Alcohol Research, National Public Health Institute, 00300 Helsinki, Finland.

OBJECTIVE: Few studies have investigated the prevalence of and risk factors for suicidal ideation and attempts among representative samples of psychiatric patients with bipolar I and II disorders. **METHOD:** In the Jorvi Bipolar Study (JoBS), psychiatric inpatients and outpatients were screened for bipolar disorders with the Mood Disorder Questionnaire from January 1, 2002, to February 28, 2003. According to Structured Clinical Interviews for DSM-IV Axis I and II Disorders, 191 patients were diagnosed with bipolar disorders (bipolar I, N = 90; bipolar II, N = 101). Suicidal ideation was measured using the Scale for Suicidal Ideation. Prevalence of and risk factors for ideation and attempts were investigated. **RESULTS:** During the current episode, 39 (20%) of the patients had attempted suicide and 116 (61%) had suicidal ideation; all attempters also reported ideation. During their lifetime, 80% of patients (N = 152) had had suicidal behavior and 51% (N = 98) had attempted suicide. In nominal regression models, severity of depressive episode and hopelessness were independent risk factors for suicidal ideation, and hopelessness, comorbid personality disorder, and previous suicide attempt were independent risk factors for suicide attempts. There were no differences in prevalence of suicidal behavior between bipolar I and II disorder; the risk factors were overlapping but not identical. **CONCLUSION:** Over their lifetime, the vast majority (80%) of psychiatric patients with bipolar disorders have either suicidal ideation or ideation plus suicide attempts. Depression and hopelessness, comorbidity, and preceding suicidal behavior are key

indicators of risk. The prevalence of suicidal behavior in bipolar I and II disorders is similar, but the risk factors for it may differ somewhat between the two.

7. Linkenkaer-Hansen K, Monto S, Rytälä H, Suominen K, Isometsä E, Kähkönen S. Breakdown of long-range temporal correlations in theta oscillations in major depressive disorder. *Journal of Neuroscience* 2005;25:10131-10137.

BioMag Laboratory, Engineering Centre, Helsinki University Central Hospital, FIN-00029 HUS, Finland. klaus.linkenkaer@cncr.vu.nl

Neuroimaging has revealed robust large-scale patterns of high neuronal activity in the human brain in the classical eyes-closed wakeful rest condition, pointing to the presence of a baseline of sustained endogenous processing in the absence of stimulus-driven neuronal activity. This baseline state has been shown to differ in major depressive disorder. More recently, several studies have documented that despite having a complex temporal structure, baseline oscillatory activity is characterized by persistent autocorrelations for tens of seconds that are highly replicable within and across subjects. The functional significance of these long-range temporal correlations has remained unknown. We recorded neuromagnetic activity in patients with a major depressive disorder and in healthy control subjects during eyes-closed wakeful rest and quantified the long-range temporal correlations in the amplitude fluctuations of different frequency bands. We found that temporal correlations in the theta-frequency band (3-7 Hz) were almost absent in the 5-100 s time range in the patients but prominent in the control subjects. The magnitude of temporal correlations over the left temporocentral region predicted the severity of depression in the patients. These data indicate that long-range temporal correlations in theta oscillations are a salient characteristic of the healthy human brain and may have diagnostic potential in psychiatric disorders. We propose a link between the abnormal temporal structure of theta oscillations in the depressive patients and the systems-level impairments of limbic-cortical networks that have been identified in recent anatomical and functional studies of patients with major depressive disorder.

8. Mantere O, Suominen K, Melartin T, Valtonen H, Arvilommi P, Leppämäki S, Rytälä H, Isometsä E. Differences in patterns of axis I and II comorbidity of bipolar I vs. II vs. major depressive disorders. *Journal of Clinical Psychiatry* 2006;67:584-593.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

OBJECTIVE: To obtain a comprehensive view of differences in current comorbidity between bipolar I and II disorders (BD) and (unipolar) major depressive disorder (MDD), and Axis I and II comorbidity in BD in secondary-care psychiatric settings. **METHOD:** The psychiatric comorbidity of 90 bipolar I and 101 bipolar II patients from the Jorvi Bipolar Study and 269 MDD patients from the Vantaa Depression Study were compared. We used DSM-IV criteria assessed by semistructured interviews. Patients were inpatients and outpatients from secondary-care psychiatric units. Comparable information was collected on clinical history, index episode, symptom status, and patient characteristics. **RESULTS:** Bipolar disorder and MDD differed in prevalences of current comorbid disorders, MDD patients having significantly more Axis I comorbidity (69.1% vs. 57.1%), specifically anxiety disorders (56.5% vs. 44.5%) and cluster A (19.0% vs. 9.9%) and C (31.6% vs. 23.0%) personality disorders. In contrast, BD had more single cluster B personality disorders (30.9% vs. 24.6%). Bipolar I and bipolar II were similar in current overall comorbidity, but the prevalence of comorbidity was strongly associated with the current illness phase. **CONCLUSIONS:** Major depressive disorder and BD have somewhat different patterns in the prevalences of comorbid disorders at the time of an illness episode, with differences particularly in the prevalences of anxiety and personality disorders. Current illness phase explains differences in psychiatric comorbidity of BD patients better than type of disorder.

9. Vuorilehto M, Melartin T, Isometsa E. Suicidal behaviour among primary care patients with depressive disorders. *Psychological Medicine* 2006;36:203-210.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

BACKGROUND: Most national suicide prevention strategies set improved detection and management of depression in primary health care into a central position. However, suicidal behaviour among primary-care patients with depressive disorders has been seldom investigated. **METHOD:** In the Vantaa Primary Care Depression Study, a total of 1119 primary-care patients in the City of Vantaa, Finland, aged 20 to 69 years, were screened for depression with the Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire. Depressive disorders were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), and the 137 patients with depressive disorder were included in the study. Suicidal behaviour was investigated cross-sectionally and retrospectively in three time-frames: current, current depressive episode, and lifetime. Current suicidal ideation was measured with the Scale for Suicidal Ideation (SSI), and previous ideation and suicide attempts were evaluated based on interviews plus medical and psychiatric records. **RESULTS:** Within their lifetimes, 37% (51/137) of the patients had seriously considered suicide and 17% (23/137) attempted it. Lifetime suicidal behaviour was independently and strongly predicted by psychiatric treatment history and co-morbid personality disorder, and suicidal behaviour within the current episode was predicted most effectively by severity of depression. **CONCLUSIONS:** Based on these findings and their convergence with studies of completed suicides, prevention of suicidal behaviour in primary care should probably focus more on high-risk subgroups of depressed patients, including those with moderate to severe major depressive disorder, personality disorder or a history of psychiatric care. Recognition of suicidal behaviour should be improved. The complex psychopathology of these patients in primary care needs to be considered in targeting preventive efforts.

10. Leskelä U, Rytsälä H, Melartin T, Komulainen E, Sokero P, Lestelä-Mielonen P, Isometsä E. Is the influence of psychosocial factors on the outcome of major depressive disorder equal for all current levels of depressive symptoms? *Psychological Medicine* 2006; 36:779-788.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

BACKGROUND: Adverse life events and social support may influence the outcome of major depressive disorder (MDD). We hypothesized that outcome would depend on the level of depressive symptoms present at the outset, with those in partial remission being particularly vulnerable. **METHOD:** In the Vantaa Depression Study (VDS), patients with DSM-IV MDD were interviewed at baseline, and at 6 and 18 months. Life events were investigated with the Interview for Recent Life Events (IRLE) and social support with the Interview Measure of Social Relationships (IMSR) and the Perceived Social Support Scale - Revised (PSSS-R). The patients were divided into three subgroups at 6 months, those in full remission (n = 68), partial remission (n = 75) or major depressive episode (MDE) (n = 50). The influence of social support and negative life events during the next 12 months on the level of depressive symptoms, measured by the Hamilton Rating Scale for Depression (HAM-D), was investigated at endpoint. **RESULTS:** The severity of life events and perceived social support influenced the outcome of depression overall, even after adjusting for baseline level of depression and neuroticism. In the full remission subgroup, both severity of life events and subjective social support significantly predicted outcome. However, in the partial remission group, only the severity of events, and in the MDE group, the level of social support were significant predictors. **CONCLUSIONS:** Adverse life events and/or poor perceived social support influence the medium-term outcome of all psychiatric patients with MDD. These factors appear to have the strongest predictive value in the subgroup of patients currently in full remission.

11. Valtonen H, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä E. Prospective study of risk factors for attempted suicide among bipolar disorder patients. *Bipolar Disorders* 2006;8:576-585.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

OBJECTIVE: There are few prospective studies on risk factors for attempted suicide among representative samples of psychiatric patients with bipolar I and II disorders. We conducted a prospective study to investigate risk for suicide attempts among a secondary-level sample of psychiatric in- and outpatients with bipolar disorder (BD). **METHODS:** In the Jorvi Bipolar Study (JoBS), 1,630 psychiatric in- and outpatients from three Finnish cities were screened for BDs with the Mood Disorder Questionnaire (MDQ). Using the Structured Clinical Interview for DSM-IV Disorders (SCID)-I and -II, 191 patients were diagnosed with BDs (90 bipolar I and 101 bipolar II). Information on suicide attempts during the follow-up was obtained for 176 patients (92%) at the 6-month follow-up and for 160 patients (84%) at the 18-month follow-up. **RESULTS:** During the 18-month follow-up 20% of patients (35/176) attempted suicide. In a Cox regression model, baseline previous suicide attempts (OR 3.8, 95% CI 1.7-8.8; $p = 0.001$), hopelessness (OR 1.2, 95% CI 1.1-1.3; $p < 0.001$), depressive phase at index episode (OR 2.4, 95% CI 1.1-5.3; $p = 0.03$) and younger age at intake (OR 0.94, 95% CI 0.91-0.97; $p < 0.001$) were independent risk factors for suicide attempts during follow-up, whereas factors such as bipolar I or II, or comorbidity did not reach statistical significance. **CONCLUSIONS:** During a medium-term follow-up, as many as one-fifth of random psychiatric patients with BD attempted suicide, which highlights the public health importance of suicidal behavior in BD. Previous suicide attempts, hopelessness and depressive phase were the key indicators of risk.

12. Arvilommi P, Suominen K, Mantere O, Leppämäki S, Valtonen H, Isometsä ET. Adequacy of treatment received by diagnosed and undiagnosed patients with bipolar I and II disorder. *Journal of Clinical Psychiatry* 2007;68:102-110.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

OBJECTIVE: To investigate the adequacy of pharmacotherapy received by psychiatric inpatients and outpatients with a research diagnosis of bipolar I or II disorder, including patients both with and without a clinical diagnosis of bipolar disorder. **METHOD:** In the Jorvi Bipolar Study (JoBS), 1630 psychiatric inpatients and outpatients in 3 Finnish cities were systematically screened between January 1, 2002, and February 28, 2003, for bipolar I and II disorders using the Mood Disorder Questionnaire. By using SCID-I and -II interviews, 191 patients were diagnosed with bipolar disorder (90 bipolar I and 101 bipolar II). Information was collected on clinical history, diagnosis, and treatment. The adequacy of treatment received was evaluated. **RESULTS:** Of the 162 patients with previous bipolar disorder episodes, only 34 (20.9%) of all and 30 (55.5%) of those with a clinical diagnosis of bipolar disorder were using a mood stabilizer at onset of the index episode. Only 81 (42.4%) of all 191 patients and 76 (65.0%) of those diagnosed with bipolar disorder received adequate treatment for the acute index phase. The factor most strongly independently associated with adequate treatment was clinical diagnosis of bipolar disorder (OR = 25.34). In addition, rapid cycling (OR = 2.45), polyphasic index episode (OR = 2.41), or depressive index phase (OR = 3.36) independently predicted inadequate treatment. Outpatients received adequate treatment markedly less often than inpatients. **CONCLUSIONS:** Clinical diagnosis of bipolar disorder is by far the most important prerequisite for adequate treatment. Problems in treatment are associated mostly with outpatient settings, where adequacy of treatment of bipolar depression is a major concern. Lack of attention to the longitudinal course of illness is another major problem area.

13. Mantere O, Suominen K, Valtonen H, Leppämäki S, Arvilommi P, Melartin T, Isometsä E. Differences in outcome of DSM-IV bipolar I and II disorders. *Bipolar Disorders* 2007:(in press).

14. Honkonen TI, Aro T, Isometsä ET, Virtanen M, Katila H. Depression, quality of treatment and disability compensation: Comparison of two nationally representative samples during a 10-year period in Finland. *Journal of Clinical Psychiatry* 2007: (in press)
15. Holma M, Holma I, Melartin T, Rytsälä H, Isometsä E. Long-term outcome of major depressive disorder in psychiatric patients is variable. *Journal of Clinical Psychiatry* 2007 :(in press)

6.4. Mood and behavior

6.4.1. Research and public health significance of the area

The key areas of interest include the seasonal changes in mood and behavior, feelings of anxiety, symptoms of depression and insomnia at the general population level. On the other hand, anxiety, mood and sleep disorders are a focus of interest concerning clinical populations. The project aims at analyzing the genetic effect on the phenotypes by analyzing the behaviors of sleep, dietary intake and physical exercise and the parameters of electroencephalographic and hormone assessments.

The main goals of research are targeted by using a range of methods from data statistics and bioinformatics via interviews and interventions to systems biology and experiments in vitro. Data are derived from the nationwide register-based and individualized data on the reimbursed prescriptions (The Social Insurance Institution of Finland), hospital treatments (National Research and Development Centre for Welfare and Health), and causes of death (Statistics Finland). Using the unique personal identity code for each citizen (The Social Insurance Institution of Finland), the personal data on family relations (Population Register Centre) and the register-based population censuses (Statistics Finland), the samples of individuals, siblings including twins, nuclear families, pedigrees or reference populations can be identified and analyzed in subsequent studies.

Data are also collected as part of the general population surveys including Health 2000 Study and a series of the National FINRISK Studies (National Public Health Institute), and with the use of interventions on community-based and clinical populations for the project in particular. For the implementation of interventions with light therapy and physical exercise, the project when needed collaborates with the Lighting Laboratory at Helsinki University of Technology, and UKK Institute, respectively.

6.4.2. The main scientific achievements

Since the start the etiology of major depressive and bipolar disorders with the seasonal pattern, or seasonal affective disorder, have been a major focus of interest [1]. Interventions with light therapy and fitness training, together with measurements in the isolation unit or field conditions, have been applied for elucidation of the mechanisms of action underlying the pathogenesis. For the project, seasonal affective disorder has been taken as a representative of mood disorders in general. Moreover, seasonal changes in mood and behavior have been regarded as a proxy of abnormalities in the circadian clockwork which are responsive to interventions with the scheduled light exposure or physical exercise.

So far, the project has discovered the association of a mis-sense variant in the *Npas2* gene, showing a recessive effect of the leucine allele on disease susceptibility [2], and the association of a polymorphism in each of the three circadian clock genes, which form a functional unit, with the disease [3]. In an analysis of the combined effect of these three genes, the project demonstrated additive effects and identified a genetic risk profile for the disorder. Carriers of the risk genotype combination have a four-fold risk of having the disorder as compared with the remaining genotypes, and a ten-fold risk as compared with those carrying the protective genotype combination. These risk and protective genotype combinations need to be verified first and thereafter characterized further in terms of the phenotype. Having this goal in mind, we have started the analysis of a sample of approximately 6000 individuals being representative of the Finnish population aged over 30.

For the project, there is a hypothesis that abnormalities in the circadian clockwork are a key to the pathogenesis of seasonal affective disorder in particular and mood disorders in general. A rationale for the hypothesis is provided by two findings. First, earlier findings from the project showing that seasonal affective disorder was not associated with polymorphisms of functional relevance to the metabolism or transmission of serotonin gave support to the hypothesis. Second, transcriptional networks which include the circadian clock and have control of downstream pathways including the sleep-wake and seasonal cycles implicate further the potential impact of the circadian clock on the pathogenesis of seasonal affective disorder in particular or mood disorders in general.

Parallel to the recurrent major depressive disorder, bipolar disorder has been on the focus of interest. The project has demonstrated the high heritability of bipolar I disorder, with the estimate of .93, in a nationwide population-based twin sample [4] as well as the low lifetime prevalence for bipolar I disorder, with the estimate of .24, in a nationwide

random sample representative of the general population [5]. To elucidate the pathogenesis more in detail, the project has demonstrated that the left hemisphere white matter volumes link to the genetic factors predisposing to the disease [6], and carried out a population-based sample of families with bipolar I disorder yielding the high heritability estimates for psychomotor processing speed and executive functioning [7]. These cognitive test performances may be valid traits for subsequent genetic studies of bipolar I disorder, for instance those studies which have applied for a genome-wide scan and fine mapping strategies [8] and those which will use a genome-wide single-nucleotide polymorphism association and lymphocyte or cell line based expression arrays.

At the general population level, the project has found the association of sleep duration with health implications [9] and demonstrated the efficacy of dawn simulation for improvement in the quality of sleep in a community-based random sample [10]. The combination of light exposure with physical exercise was demonstrated to be of substantial benefit to those having marked seasonal changes in mood and behavior [11]. Because 38.9% of the general population aged 30 or over have seasonal changes in mood and behavior of a similar extent to winter blues, these interventions may be of benefit to as many as 1,266,531 citizens.

In a population-based trial on 29,133 men aged 50 to 69 years, the project has demonstrated that there is no association of low dietary intake of fatty acids and fish consumption [12], in contrast to low baseline serum total cholesterol concentration [13], with subsequent self-reports of depressed mood and a risk of hospital treatment due to a major depressive episode and of death from suicide during follow-up.

A population-based nationwide analysis of all the individuals who committed suicide demonstrated that suicide mortality does vary by season and needs attention to be applied for suicide prevention [14]. For the preventive measures, it is essential to focus on the high-risk group of individuals with a prior suicide attempt. Contacts with the health care system due to suicide attempts do occur most often in the late evening and around midnight. The finding challenges the adequacy of staff numbers for psychiatric consultations and of time to plan aftercare [15].

6.4.3. The main public health achievements

The project has been participating in dissemination of its research findings and expertise via media, including television, radio, newspapers, magazines, and Internet, to

the public in order to increase the awareness of health promotion against mood and sleep disorders. The project has been acting as a scientific expert for the Light Awareness Day in February, the Brain Awareness Week in March, the Vigilance Awareness Week in March, and the Sleep Awareness Week in October. The project has been the first one in Finland to provide light therapy, and to analyze its efficacy and effectiveness in a series of trials starting from 1988.

As part of these tasks, the project leader has acted as the supervisor for the EU-funded Enough Sleep consortium (of the FP6 STREP scheme) and taken actions in Finnish Medical Society Duodecim (Current Care guideline for the treatment of insomnia), both of which produce information to the laypersons as well. The project leader has in addition written three popular science books about mental health and participated in the editorial board of the textbook of psychiatry which has been used in the university level education.

The project leader has acted as a member of the Communication Unit at National Public Health Institute, and contributed to the Information Journal of National Public Health Institute, having a circulation of 8700 with a good coverage of policymakers, and to the Internet portal of the Finnish Government which is dedicated to the health affairs and targeted to the laypersons.

6.4.4. Funding for research and public health programs

Grants have been awarded to Timo Partonen from the Finnish Medical Foundation 66,000 EUR for Seasonal affective disorder: predisposing and protecting factors during 2002-2003, and from the Academy of Finland 150,000 EUR for Genetic etiology of bipolar disorder during 2003-2006 and 275,000 EUR for Molecular mechanisms of bipolar and recurrent depressive disorders with the seasonal pattern during 2004-2009.

In addition to these primary sources of funding, additional grants have been awarded from Finnish foundations to research associates working for the project.

6.4.5. Personnel

Timo Partonen, MD, is academy research fellow (Academy of Finland) and is currently working as the full-time project leader at the National Public Health Institute together with a number of research associates. Their current number is 22 of whom 5 are

post-doctoral scientists and 17 (5 biologists, 4 medical doctors, 4 graduate engineers, 2 psychologists, 2 masters of science) are PhD students.

6.4.6. Collaboration

The project will continue collaboration with National Public Health Institute, Department of Molecular Medicine (professor Leena Peltonen-Palotie), in Helsinki. The project is also part of a network of laboratories including Karolinska Institutet, Department of Molecular Medicine and Surgery (professor Martin Schalling), in Stockholm; King's College, Institute of Psychiatry, Section of Addiction Biology (professor Gunter Schumann), in London; and University of Helsinki, Department of Physiology (Dr Piia Aarnisalo) and Department of Medical Genetics (Dr Iris Hovatta), in Helsinki. In these studies the project will focus on the molecular genetics and systems biology of the circadian clock and their contribution to common and complex diseases, such as mood disorders, anxiety disorders, alcohol use disorders, metabolic syndrome, and non-insulin dependent diabetes mellitus. In addition, the regulation of the circadian clock genes will be analyzed *in vitro* and subsequently *in vivo* models.

The project links to University of Helsinki, Department of Psychiatry; Helsinki University of Technology, Lighting Laboratory (www.lightinglab.fi); Finnish Meteorological Institute; Finnish Cancer Registry; Finnish Institute of Occupational Health, Human Factors at Work. These joint projects will elucidate the mechanisms of action of light exposure using monochromatic spectra (Helsinki University of Technology), the spring peak in suicide mortality (Finnish Meteorological Institute), the risks of night-time shift work (Finnish Cancer Registry, and Finnish Institute of Occupational Health) and of jet lag for health, and the benefits and hazards of prescriptions for mental disorders.

The project links to National Research and Development Centre for Welfare and Health, Health Services Research; and The Social Insurance Institution of Finland, Health Research. These joint projects will analyze the impact of antidepressant medication on mortality including deaths from suicide or cardiovascular disease in a population-based cohort based on individualized prescriptions, and the effect of lithium medication, being specific to bipolar disorder and known to slow down the pace of the circadian clock in the suprachiasmatic nuclei of the anterior hypothalamus in the brain, on the incidence of dementia and diabetes.

6.4.7. Proposal for future work and expected benefits

Since the circadian clock genes are involved in the cell division cycle, metabolic cycles and reproductive actions in addition to their roles in the generation of the circadian rhythms and sleep-wake cycles, the strategy applying molecular systems biology for studies of common and complex diseases will be of interest in a range of fields in medicine.

The assessment of individual body time using the method of molecular timetable is relevant for mood disorders such as major depression, metabolic diseases such as metabolic syndrome, and malignant processes sensitive to the circadian clockwork abnormalities such as non-Hodgkin lymphoma or breast cancer. Such methods might be used later as a routine assessment in a range of patient populations.

Light exposure, physical exercise and sleep habits each are known to have influence and feed back on the circadian clock. Timed light exposure is taken a method to analyze the function and regulation of the circadian clock in specific. Applications of designed light exposures at home or working place conditions will be tested in collaboration with the Lighting Laboratory at Helsinki University of Technology.

Physical risk factors which contribute to the peak in suicide mortality during spring will be identified and the underlying mechanisms of action elucidated in collaborations with Finnish Meteorological Institute and the Department of Physiology at University of Helsinki, respectively.

For the future, in order to elucidate the circadian clockwork by applying for the principles of molecular systems chronobiology and to have a system-level understanding of transcriptional circuits underlying circadian clocks, the project will identify clock-controlled elements, including E/E' boxes, D boxes, RREs and NBREs, on clock and clock-controlled genes by using *in silico* analysis of mechanisms of action, real-time monitoring of circadian transcriptional dynamics, and *in vitro* circadian phenotype assay. Conditional and tissue-specific methods for animal models will be available to verify findings of interest *in vivo*. The project has made a move towards and negotiated about joint projects together with University of California Irvine, Department of Pharmacology (professor Paolo Sassone-Corsi) and of Psychiatry (professor William E. Bunney), in Irvine; University of Texas Southwestern Medical Center, Department of Biochemistry (professor Steven L. McKnight), in Dallas; University of Texas Health Science Center, Department of Biochemistry and Molecular Biology (professor Chen Chi Lee), in Houston; University of Lausanne, Center for Integrative Genomics (professor Mehdi Tafti), in Lausanne; University of Geneva, Department of Molecular Biology

(professor Ueli Schibler), in Geneva; and University of Tokyo, Department of Pharmacology (professor Hiroki R. Ueda), in Tokyo.

Ultimate goals for the project are to have answers to the following questions: What are the mechanisms of action by which the metabolic, circadian and sleep-wake cycles link and contribute to mood? To what extent does the interaction between light-dark and warm-cold transitions contribute to the spring peak in suicide mortality?

Subsequent aims on the basis of these data are to create measures for health promotion and suicide prevention.

6.4.8. Publications

[1] Partonen T, Lönqvist J. Seasonal affective disorder. *Lancet* 1998; 352: 1369-74

Seasonal affective disorder (SAD) is a form of recurrent depressive or bipolar disorder, with episodes that vary in severity. Seasonal patterns of depressive episodes are common, but SAD seems to be less common than such patterns suggest. SAD was at first believed to be related to abnormal melatonin metabolism, but later findings did not support this hypothesis. Studies of brain serotonin function support the hypothesis of disturbed activity. The short-allele polymorphism for serotonin transporter is more common in patients with SAD than in healthy people. Atypical depressive symptoms commonly precede impaired functioning, and somatic symptoms are frequently the presenting complaint at visits to family physicians. The best treatment regimens include 2500 lx of artificial light exposure in the morning. When patients seem to have no response or to prefer another treatment, antidepressants should be considered.

[2] Johansson C, Willeit M, Smedh C, Ekholm J, Paunio T, Kieseppä T, Lichtermann D, Praschak-Rieder N, Neumeister A, Nilsson LG, Kasper S, Peltonen L, Adolfsson R, Schalling M, Partonen T. Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* 2003; 28: 734-9

Disturbed circadian rhythms have been observed in seasonal affective disorder (SAD). The aim of this study was to further investigate this connection, and to test for potential association between polymorphisms in circadian clock-related genes and SAD, seasonality (seasonal variations in mood and behavior), or diurnal preference (morningness-eveningness tendencies). A total of 159 European SAD patients and 159 matched controls were included in the genetic analysis, and subsets were screened for seasonality (n=177) and diurnal preference (n=92). We found that diurnal preference was associated with both SAD and seasonality, supporting the hypothesis of a link between circadian rhythms and seasonal depression. The complete case-control material was genotyped for polymorphisms in the CLOCK, Period2, Period3, and NPAS2 genes. A significant difference between patients and controls was found for NPAS2 471 Leu/Ser ($\chi^2=9.90$, Bonferroni corrected $P=0.035$), indicating a recessive effect of the leucine allele on

disease susceptibility ($\chi^2=6.61$, Bonferroni corrected $P=0.050$). Period3 647 Val/Gly was associated with self-reported morningness-eveningness scores ($n=92$, one-way ANOVA: $F=4.99$, Bonferroni corrected $P=0.044$), with higher scores found in individuals with at least one glycine allele ($t=3.1$, Bonferroni corrected $P=0.013$). A second, population-based sample of individuals selected for high ($n=127$) or low ($n=98$) degrees of seasonality, was also genotyped for NPAS2 471 Leu/Ser. There was no significant difference between these seasonality extreme groups, and none of the polymorphisms studied were associated with seasonality in the SAD case-control material ($n=177$). In conclusion, our results suggest involvement of circadian clock-related polymorphisms both in susceptibility to SAD and diurnal preference.

[3] Partonen T, Treutlein J, Alpmann A, Frank J, Johansson C, Depner M, Aron L, Rietschel M, Wellek S, Soronen P, Paunio T, Koch A, Chen P, Lathrop M, Adolfsson R, Persson ML, Kasper S, Schalling M, Peltonen L, Schumann G. Three circadian clock genes *Per2*, *Arntl*, and *Npas2* contribute to winter depression. *Ann Med* 2007; 39: 229-38

BACKGROUND: Multiple lines of evidence suggest that the circadian clock contributes to the pathogenesis of winter depression or seasonal affective disorder (SAD). We hypothesized that sequence variations in three genes, including *Per2*, *Arntl*, and *Npas2*, which form a functional unit at the core of the circadian clock, predispose to winter depression. **METHODS:** In silico analysis of the biological effects of allelic differences suggested the target single-nucleotide polymorphisms (SNPs) to be analyzed in a sample of 189 patients and 189 matched controls. The most relevant SNP in each gene was identified for the interaction analysis and included in the multivariate assessment of the combined effects of all three SNPs on the disease risk. **RESULTS:** SAD was associated with variations in each of the three genes in gene-wise logistic regression analysis. In combination analysis of variations of *Per2*, *Arntl*, and *Npas2*, we found additive effects and identified a genetic risk profile for the disorder. Carriers of the risk genotype combination had the odds ratio of 4.43 of developing SAD as compared with the remaining genotypes, and of 10.67 as compared with the most protective genotype combination. **CONCLUSION:** Variations in the three circadian clock genes *Per2*, *Arntl*, and *Npas2* are associated with the disease, supporting the hypothesis that the circadian clock mechanisms contribute to winter depression.

[4] Kieseppä T, Partonen T, Haukka J, Kaprio J, Lönnqvist J. High concordance of bipolar I disorder in a nationwide sample of twins. *Am J Psychiatry* 2004; 161: 1814-21

OBJECTIVE: The few studies of bipolar I disorder in twins have consistently emphasized the genetic contribution to disease liability. The authors report what appears to be the first twin study of bipolar I disorder involving a population-based twin sample, in which the diagnoses were made by using structured, personal interviews. **METHOD:** All Finnish same-sex twins ($N=19,124$) born from 1940 to 1957 were screened for a diagnosis of bipolar I disorder as recorded in the National Hospital Discharge Register between 1969 and 1991 or self-reported in surveys of the Finnish Twin Cohort in 1975, 1981, and 1990. Thirty-eight pairs were thereby identified and invited to participate in the study; the participation rate was 68%. Lifetime diagnoses were made by using the Structured Clinical Interview for DSM-IV. The authors calculated probandwise and pairwise concordances and correlations in liability and applied biometrical model fitting. **RESULTS:** The probandwise concordance rates were 0.43 (95% CI=0.10 to 0.82) for monozygotic twins and 0.06 (95% CI=0.00 to 0.27) for dizygotic twins. The correlations in liability

were 0.85 and 0.41, respectively. The model with no familial transmission was rejected. The best-fitting model was the one in which genetic and specific environmental factors explained the variance in liability, with a heritability estimate of 0.93 (95% CI=0.69 to 1.00). CONCLUSIONS: The high heritability of bipolar disorder was demonstrated in a nationwide population-based twin sample assessed with structured personal interviews.

[5] Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S, Lönqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 2007; 64: 19-28

CONTEXT: Recent general population surveys of psychotic disorders have found low lifetime prevalences. However, this may be owing to methodological problems. Few studies have reported the prevalences of all specific psychotic disorders. OBJECTIVE: To provide reliable estimates of the lifetime prevalences of specific psychotic disorders. DESIGN: General population survey. SETTING AND PARTICIPANTS: A nationally representative sample of 8028 persons 30 years or older was screened for psychotic and bipolar I disorders using the Composite International Diagnostic Interview, self-reported diagnoses, medical examination, and national registers. Those selected by the screens were then re-interviewed with the Structured Clinical Interview for DSM-IV. Best-estimate DSM-IV diagnoses were formed by combining the interview and case note data. Register diagnoses were used to estimate the effect of the nonresponders. MAIN OUTCOME MEASURES: Diagnosis of any psychotic or bipolar I disorder according to the DSM-IV criteria. RESULTS: The lifetime prevalence of all psychotic disorders was 3.06% and rose to 3.48% when register diagnoses of the nonresponder group were included. Lifetime prevalences were as follows: 0.87% for schizophrenia, 0.32% for schizoaffective disorder, 0.07% for schizophreniform disorder, 0.18% for delusional disorder, 0.24% for bipolar I disorder, 0.35% for major depressive disorder with psychotic features, 0.42% for substance-induced psychotic disorders, and 0.21% for psychotic disorders due to a general medical condition. The National Hospital Discharge Register was the most reliable of the screens ($\kappa = 0.80$). Case notes supplementing the interviews were essential for specific diagnoses of psychotic disorders. CONCLUSIONS: Multiple sources of information are essential for accurate estimation of lifetime prevalences of psychotic disorders. The use of comprehensive methods reveals that their lifetime prevalence exceeds 3%.

[6] Kieseppä T, van Erp TG, Haukka J, Partonen T, Cannon TD, Poutanen VP, Kaprio J, Lönqvist J. Reduced left hemispheric white matter volume in twins with bipolar I disorder. *Biol Psychiatry* 2003; 54: 896-905

BACKGROUND: Although the heritability of bipolar I disorder (BPI) is high, few magnetic resonance imaging (MRI) studies of siblings of bipolar patients exist. We performed MRI brain scans on a nationwide sample of twins with BPI, as well as on their co-twins and a demographically balanced sample of control twin subjects, to detect any structural alterations related to the disorder and to the increased genetic risk. METHODS: The National Hospital Discharge Register, National Population Register, and Finnish Twin Cohorts were used to identify bipolar twins. Structured diagnostic interviews and MRI scans were obtained for 24 twins with BPI, 15 healthy co-twins, and 27 control twin subjects. RESULTS: Patients and co-twins showed a significant decrease in left hemispheric white matter volume. The disparity in patients was -16.1 cm^3 (95% confidence interval [CI] $-26.6, -5.6$) and in co-twins -11.3 cm^3

(95% CI -22.1, -0.4) compared with control twin subjects. No gray matter decrease was seen in patients or co-twins. CONCLUSIONS: The results of this first large-scale MRI study of twins with BPI, their co-twins, and appropriate control twin subjects, suggest that alterations of the left hemisphere white matter in BPI may reflect genetic factors predisposing to the disorder.

[7] Antila M, Tuulio-Henriksson A, Kiesepä T, Soronen P, Palo OM, Paunio T, Haukka J, Partonen T, Lönnqvist J. Heritability of cognitive functions in families with bipolar disorder. *Am J Med Genet* (published online 23 Apr 2007; doi: 10.1002/ajmg.b.30538)

Bipolar disorder is highly heritable. Cognitive dysfunctions often observed in bipolar patients and their unaffected relatives implicate that these impairments may be associated with genetic predisposition to bipolar disorder and thus fulfill the criteria of a valid endophenotype for the disorder. However, the most fundamental criterion, their heritability, has not been directly studied in any bipolar population. This population-based study estimated the heritability of cognitive functions in bipolar disorder. A comprehensive neuropsychological test battery and the Structured Clinical Interview for DSM-IV were administered to a population-based sample of 110 individuals from 52 families with bipolar disorder. Heritability of cognitive functions as assessed with neuropsychological test scores were estimated using the Solar package. Significant additive heritabilities were found in verbal ability, executive functioning, and psychomotor processing speed. Genetic contribution was low to verbal learning functions. High heritability, in executive functioning and psychomotor processing speed suggest that these may be valid endophenotypic traits for genetic studies of bipolar disorder.

[8] Ekholm JM, Kiesepä T, Hiekkalinna T, Partonen T, Paunio T, Perola M, Ekelund J, Lönnqvist J, Pekkarinen-Ijäs P, Peltonen L. Evidence of susceptibility loci on 4q32 and 16p12 for bipolar disorder. *Hum Mol Genet* 2003; 12: 1907-15

We performed a genome-wide scan for susceptibility loci in bipolar disorder in a study sample collected from the isolated Finnish population, consisting of 41 families with at least two affected siblings. We identified one distinct locus on 16p12 providing significant evidence for linkage in two-point analysis ($Z(\max)=3.4$). Furthermore, three loci with a two-point LOD score >2.0 were observed with markers on 4q32, 12q23 and Xq25, the latter locus having been earlier identified in one extended Finnish pedigree. In the second stage we fine mapped these chromosomal regions and also genotyped additional family members. In the fine mapping stage, 4q32 provided significant evidence of linkage for the three-point analyses ($Z(\max)=3.6$) and 16p12 produced a three-point LOD score of 2.7. Since the identified chromosomal regions replicate earlier linkage findings in either bipolar disorder or other mental disorders, they should be considered good targets for further genetic analyses.

[9] Fogelholm M, Kronholm E, Kukkonen-Harjula K, Partonen T, Partinen M, Härmä M. Sleep-related disturbances and physical inactivity are independently associated with obesity in adults. *Int J Obesity* (advance online publication 19 Jun 2007; doi: 10.1038/sj.ijo.0803663)

Objective: To study relationships between obesity, physical inactivity and sleep-related disturbances (obstructive sleep apnea (OSA), sleep duration, sleep disturbances concomitant with daytime tiredness) in adults (≥ 30 years). Design: Cross-sectional study with a random population sample. Participants: A total of 3377 men (mean age 52.3, s.d. 14.8, years) and 4264 women (56.4, s.d. 17.2, years). Main outcome measures: Dependent variables, measured: Waist circumference (WC) and body mass index (BMI). Independent variables, from a detailed interview/questionnaire: probable OSA, other sleep-related disturbances, sleep duration, type and frequency of leisure physical activity. Age, mental health, smoking and education were included in analyses as potential confounders. Results: In men, OSA and physical inactivity increased likelihood for abdominal obesity (WC ≥ 102 cm). Physical inactivity also increased, but long (≥ 9 h/day) sleep decreased likelihood for abdominal overweight (WC: 94-101 cm) in men. In women, abdominal obesity (WC ≥ 88 cm) was associated positively with OSA, moderate sleep-related disturbances, and physical inactivity. Education modulated the influence of age on abdominal obesity in both genders. Using BMI as the dependent variable did not change the general information obtained by the model. In addition, abdominal obesity was found to be an independent risk factor also in multivariable models predicting categories of a combined sleep duration and sleep disturbances. Conclusions: Sleep duration and sleep-related disturbances are associated with obesity, even after controlling for OSA and physical inactivity. The results support the hypothesis of vicious circle between sleep and obesity.

[10] Leppämäki S, Meesters Y, Haukka J, Lönnqvist J, Partonen T. Effect of simulated dawn on quality of sleep - a community-based trial. *BMC Psychiatry* 2003; 3: 14

BACKGROUND: Morning light exposure administered as simulated dawn looks a promising method to treat Seasonal Affective Disorder, but it may moreover help with resetting the inaccurate organisation of body clock functions relative to sleep occurring in winter among people in general. Disturbances in sleep patterns are common and may compromise wellbeing even in the short term. Our hypothesis was that simulated dawn could improve the subjective quality of sleep during winter. **METHODS:** A community-based trial with 100 volunteer subjects provided with dawn simulators. Study period lasted for eight weeks, and subjects used the dawn simulators for two weeks at a time, each subject acting as his own control (ABAB-design). Main outcome measure was subjective quality of sleep recorded each morning with Groningen Sleep Quality Scale. **RESULTS:** 77 subjects completed the trial. Quality of sleep improved while subjects were using dawn simulator-devices ($p = 0.001$). The treatment became beneficial after six days' use of dawn simulator, but the effect did not last after the use was ceased. **CONCLUSION:** Dawn simulation may help to improve the subjective quality of sleep, but the benefits are modest. Further research is needed to verify these findings and to elucidate the mechanism by which dawn simulation acts on the sleep-wake pattern.

[11] Leppämäki SJ, Partonen TT, Hurme J, Haukka JK, Lönnqvist JK. Randomized trial of the efficacy of bright-light exposure and aerobic exercise on depressive symptoms and serum lipids. *J Clin Psychiatry* 2002; 63: 316-21

BACKGROUND: Season-related subsyndromal depressive symptoms during winter are common among populations at high latitudes. Both physical exercise and exposure to bright light can relieve the fatigue and downturn of mood associated with the shortening length of day. Serum cholesterol level may be re-

lated to changes in mood, but the evidence is contradictory. Our objective was to compare the effect of aerobic exercise with or without bright-light exposure on health-related quality of life, mood, and serum lipids in a sample of relatively healthy adult subjects. **METHOD:** A randomized controlled trial was conducted with subjects allocated to group aerobics training in a gym with bright light (2500-4000 lux) (N = 40) or normal illumination (N = 42) or to relaxation/stretching sessions in bright light as a control group (N = 42) twice a week for a period of 8 weeks. Changes in mood were recorded using questionnaires at the beginning of the study, at weeks 4 and 8, and at follow-up 4 months after the study. A blood sample was drawn before and after the 8-week intervention to measure the concentrations of serum lipids. **RESULTS:** Ninety-eight subjects completed the 8-week study. Both exercise and bright light effectively relieved depressive symptoms. Bright light reduced atypical depressive symptoms more than exercise ($p = .03$), based on the atypical symptoms subscore of the Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorders Version Self-Rating Format. There were no significant differences between the study groups in the changes in serum lipid levels. **CONCLUSION:** Bright light administered twice a week, alone or combined with physical exercise, seems to be a useful intervention for relieving seasonal mood slumps.

[12] Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lönnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry* 2004; 161: 567-9

OBJECTIVE: This study examined the association between the dietary intake of omega-3 fatty acids and low mood, major depression, and suicide. **METHOD:** A total of 29,133 men ages 50 to 69 years participated in a population-based trial in Finland. The intake of fatty acids and fish consumption were calculated from a diet history questionnaire. Self-reported depressed mood was recorded three times annually, data on hospital treatments due to a major depressive disorder were derived from the National Hospital Discharge Register, and suicides were identified from death certificates. **RESULTS:** There were no associations between the dietary intake of omega-3 fatty acids or fish consumption and depressed mood, major depressive episodes, or suicide. **CONCLUSIONS:** Dietary intake of omega-3 fatty acids showed no association with low mood level.

[13] Partonen T, Haukka J, Virtamo J, Taylor PR, Lönnqvist J. Association of low serum total cholesterol with major depression and suicide. *Br J Psychiatry* 1999; 175: 259-62

BACKGROUND: It has been suggested that low serum total cholesterol is associated with an increased risk of suicide. **AIMS:** To study the association between serum total cholesterol, depression and suicide using versatile, prospective data. **METHOD:** A total of 29,133 men aged 50-69 years were followed up for 5-8 years. Baseline blood samples were analysed for serum total and high-density lipoprotein cholesterol concentrations. Self-reported depression was recorded, data on hospital treatments due to depressive disorders were derived from the National Hospital Discharge Register and deaths from suicide were identified from death certificates. **RESULTS:** Low serum total cholesterol was associated with low mood and subsequently a heightened risk of hospital treatment due to major depressive disorder and of death from suicide. **CONCLUSIONS:** Our results suggest that low serum total cholesterol appears to be associated with low mood and thus to predict its serious consequences.

[14] Partonen T, Haukka J, Nevanlinna H, Lönnqvist J. Analysis of the seasonal pattern in suicide. *J Affect Disord* 2004; 81: 133-9

BACKGROUND: Suicide has been attributed to social and psychological factors but also to geophysical effects. Of the latter, changes in solar radiation and geomagnetic activities may contribute to the frequency and the seasonal pattern of suicides. **METHODS:** We studied with a population-based, nationwide analysis all the individuals who committed suicide (n=27,469) in Finland during the period of 1979 to 1999. The daily data on the number of suicides, and the mean and maximum levels of geomagnetic activity were compiled and modelled with Poisson regression using the number of inhabitants in each province as the denominator. Time series analysis of monthly numbers of suicides was carried out using a seasonal-trend decomposition procedure. **RESULTS:** There was a strong seasonal effect on suicide occurrence ($P < 0.00001$), the risk of suicide being greatest in spring. The seasonal effect was most pronounced when the number of suicides was relatively low. High levels of solar radiation activity were associated with the increased risk of suicide ($P = 0.00001$), but the effect of geomagnetic activity was weak. **LIMITATIONS:** No individual data on alcohol consumption or mental disorders were available. **CONCLUSIONS:** Suicide occurrence varies markedly by season and needs attention where prevention is concerned.

[15] Valtonen H, Suominen K, Partonen T, Ostamo A, Lönnqvist J. Time patterns of attempted suicide. *J Affect Disord* 2006; 90: 201-7

BACKGROUND: The association of mental disorders with time patterns of attempted suicide is poorly understood. **METHODS:** The study material consisted of all consecutive suicide attempts admitted to health care in Helsinki during a one-year period from 15 January 1997 to 14 January 1998. Clinical diagnosis was made according to ICD-10. **RESULTS:** Overall, the rate of suicide attempts varied markedly during the study period, peaking in autumn and being lowest during winter. Substance use disorders best explained suicide attempts occurring at weekends. There was considerable temporal variation among patients with mood disorders, compared to only slight variation among patients with schizophrenia spectrum disorders. Study subjects tended to contact health services in the late evening and around midnight. Those contacting health services outside normal hours received psychiatric consultation less frequently than others and were referred to aftercare less often. **LIMITATIONS:** Structured Clinical Interviews for DSM-IV Axis I and II Disorders were not used. **CONCLUSIONS:** There were marked time patterns of attempted suicide, especially among patients with mood disorders and substance use disorders. This contrasted with the limited fluctuation among patients with schizophrenia spectrum disorders. Contacts with the health care system occurred most often in the late evening and around midnight. The findings question the adequacy of staff numbers for psychiatric consultations and of time to plan aftercare.

6.5. Severe Mental Disorders

6.5.1. Research and public health significance of the area

Psychotic disorders are among the most severe and impairing medical diseases: active psychosis was ranked the most disabling condition after quadriplegia and dementia in a WHO study (Üstun et al 1999). They are also more common than has been assumed: the lifetime prevalence of all psychotic disorders in Finland is 3.48 per cent (Perälä et al, 2007). Thus, these disorders are a major public health concern.

The aetiology of psychotic disorders is multifactorial. Several genes of small effect combine with environmental effects to determine the outcome, although rare chromosomal abnormalities with major effect are also known (Blackwood et al 2001, Murphy et al 2001). The heritability of schizophrenia (Cannon et al 1998, Sullivan et al 2003) and bipolar I disorder (Kieseppä et al 2004) exceeds 80 per cent. Environmental factors probably account more of the liability than the remaining 20 per cent, since gene-environment interactions are typically attributed to genetic factors only in heritability calculations. Nevertheless, the high heritability of schizophrenia in Western countries suggests that genetic factors are currently more important than environmental factors in determining who develops schizophrenia or bipolar I disorder.

The Research Project on Severe Mental Disorders comprises a set of studies focusing on psychotic and other severe mental disorders. Our current scope is broad: we are investigating environmental and genetic risk factors and developmental precursors of psychotic disorders, prodromal phase of psychosis, epidemiology, comorbidity, and treatment of psychotic disorders, and neuropsychological impairments and brain structural and functional abnormalities related to psychotic disorders and liability to psychosis. The individual studies of the project are briefly described in the following.

The Genetic Epidemiology and Molecular Genetics of Schizophrenia

The research on the etiology and epidemiology of schizophrenia and other psychotic disorders was initiated at the Department of Mental Health and Alcohol Research at the end of 1980s, when the Genetic Epidemiology and Molecular Genetics of Severe Mental Disorders -study was started. In the 1990s, we formed, using nationwide health care registers, a representative cohort of 33731 persons with schizophrenia born in Finland from 1940 to 1976. The first-degree relatives of these individuals were identi-

fied from the Population Register Center, and information on relatives was linked back to the health care registers to obtain information on their treatments and diagnoses.

Two samples were collected for this population-based genetic study of schizophrenia. The first sample consisted of families with at least two siblings with schizophrenia from the whole geographical area of Finland. The second sample comprised patients and their parents and siblings from families with at least one member with schizophrenia from an isolated region in the northern part of the country with an exceptionally high lifetime risk (3.2%, Hovatta et al 1997) of schizophrenia.

About 3400 subjects from one thousand families have participated in the ongoing study and have given blood samples for DNA analysis. Approximately one third of them have been interviewed using the Structured Clinical Interview for DSM-IV (SCID), and administered a neuropsychological test battery. From the remaining affected individuals, we have obtained all case notes from psychiatric treatments, based on which we have rediagnosed the persons according to DSM-IV criteria and filled the OPCRIT checklist (McGuffin et al 1991).

The Psychoses in Finland -study

The Psychoses in Finland -study is a comprehensive study on the epidemiology of psychotic disorders based on the Health 2000 study, a health survey of a nationally representative two-stage cluster sample of 8028 persons aged 30 or over. We used both self-report data and information from nationwide health care registers to screen persons with possible psychotic disorder. All screen positives and a random sample of screen negatives were invited to participate in a reassessment that included the SCID-I interview and a neuropsychological test battery, and 543 participated in the interview. We obtained hospital and outpatient case notes from psychiatric and primary care units, except for the 6% who refused from the baseline Health 2000 survey. Final diagnostic assessment of psychotic disorders was based on DSM-IV-TR criteria and utilized both interview and case note data. In addition, comprehensive information on health and functional capacity is available from the health examination and interview of the Health 2000 study, and from several nationwide registers. We identified 249 persons with a lifetime diagnosis of psychotic disorder.

The Schizophrenia Twin Study

A representative sample of monozygotic and dizygotic twin pairs concordant and discordant for schizophrenia and demographically similar control pairs from Finnish

twins born 1940 through 1990 has been collected as a large collaborative project between National Public Health Institute and the University of California, Los Angeles. The twins have been evaluated using structured psychiatric interviews (SCID I-II, SANS, SAPS), neuropsychological testing, and magnetic resonance imaging (MRI), and blood samples have been collected for genetic analyses and for determining the zygosity. In addition, positron emission tomography (PET), functional MRI, magnetoencephalography (MEG), and electroencephalography (EEG) have been conducted for a number of twin pairs. Approximately 200 twin pairs have been evaluated, and the study is still ongoing.

The Helsinki High-Risk Study

The Helsinki High-Risk Study (HHR) is a follow-up study of offspring born to mothers with psychotic disorders, and its aim is to identify developmental precursors of psychotic disorders, and to investigate the outcome of children of mothers with psychotic disorder. Mothers (n=161) were identified from all female patients born between 1916 and 1948 who had been treated because of schizophrenia spectrum psychotic disorders in any of the mental hospitals of the city of Helsinki before 1975. The original study sample was limited to offspring born in Helsinki between 1960 and 1964, but we have now extended the study to all offspring of these mothers (n=337). Controls are previous same-sex births from the same maternity hospitals. Based on the National Hospital Discharge Register information, case notes from psychiatric hospital and outpatient treatments were collected for both parents and offspring and all were re-diagnosed according to DSM-IV-TR criteria. We filled the OPCRIT checklist (McGuffin et al 1991) and the Major Symptoms of Schizophrenia Scale (MSSS) (Kendler et al 1993), and collected additional information on the onset, course, and outcome of psychiatric disorders. Obstetric records, childhood developmental and school records, and criminal records were collected for both HR and control offspring. Information on those parents and offspring who had died and their causes of death have been obtained from the Statistics Finland.

The Prodromal Symptoms of Psychotic Disorders in Adolescent Psychiatric Patients -study

The ongoing Prodromal Symptoms of Psychotic Disorders in Adolescent Psychiatric Patients -study was started in 2003, and its objective is to find criteria for identifying young people with an emerging psychotic disorder that could be used outside prodromal clinics in adolescent psychiatric treatment settings. We screened all patients aged 15 to

18 years who sought treatment in adolescent psychiatric units in the Helsinki area using the Prodromal Questionnaire (Loewy et al 2005). After that, the screen positive and a random sample of screen negative adolescents were interviewed using the Structured Interview for Prodromal Symptoms (SIPS) and administered a neuropsychological test battery. A 12-month follow-up was made using the same methods. We have permission from the adolescents to follow up their inpatient and outpatient treatments for 10 years. Brain functional magnetic resonance imaging (fMRI) was conducted to 30 subjects with the most severe prodromal symptoms. Thus far, over 400 adolescent patients have been screened, and more than 100 have been selected for the interview and neuropsychological assessment. In addition, all the instruments have been tested in a pilot study of 80 adolescents in 2002. One branch of the prodromal study investigates predictors of psychotic disorders and other adverse outcomes in adolescents (n=53) residing in a reform school.

The Helsinki 1951-1960 Cohort Study

The Helsinki 1951-1960 cohort study is a cohort study of persons with schizophrenia born in Helsinki from 1951 to 1960 that analyses developmental factors that predict future development of schizophrenia (Cannon et al 1999), and the onset, course and outcome of schizophrenia as well as violent (Cannon et al 2002a) and suicidal behavior. The study population consists of all individuals who were born in Helsinki, Finland, between January 1, 1951 and December 31, 1960. Individuals with a diagnosis of core schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder and schizophreniform disorder, ICD-8 and ICD-9 diagnostic code 295) born during this 10-year period were ascertained from three health care registers. Based on hospital case notes, we have collected detailed information on symptoms, including the OPCRIT, from all subjects from the cohort (n=806) who had been treated because of schizophrenia spectrum psychosis (Pihlajamaa et al, in press).

The Finnish Conscript Study on Psychotic Disorders

The Finnish Conscript Study on Psychotic Disorders is based on a cohort of apparently healthy males conscripted into the Finnish Defense Forces since 1982. Linkage with the Finnish Hospital Discharge Register identified conscripts later diagnosed with bipolar disorder, schizophrenia, or other psychoses. We have published results on pre-morbid intellectual functioning in schizophrenia, bipolar disorder and other psychoses (Tiihonen et al 2005), and are currently investigating whether personality features, as measured by the MMPI, predict these disorders. We are extending the sample to include information on kinship (father, uncle, brother) in order to analyse whether genetic or

family-related factors modify the association between cognitive performance, personality features, and psychiatric disorders.

The Peijas Schizophrenia Study

Our study is a collaboration between the Peijas Outpatient Rehabilitation Unit, the Kellokoski Hospital, and the National Public Health Institute. We are creating a longitudinal, cumulative data set of patients with schizophrenia and other psychotic disorders that would be used both in clinical work and in research. The idea is similar to the Cumulative Needs for Care Register operating in South Limburg, the Netherlands (van Os et al 2006, Bak et al 2007). We will have a comprehensive baseline assessment, including neuropsychological examination, while follow-ups would be done using a smaller set of instruments. The data will be incorporated into the electronic hospital record system, and will be used to aid clinical work and in outcome studies. The project will also include validation of several rating scales and measures in Finnish. If successful, the method will be applied more widely at least within the Hospital District of Helsinki and Uusimaa.

We are currently choosing the assessment methods that will be used in the study. The brief Psychiatric Rating Scale (BPRS) and the Health of the Nation Outcomes Scale (HoNOS) have been piloted in the Peijas outpatient clinic since February. Both nurses and psychiatrists have found the instruments useful and are motivated to use them. We are currently selecting the neuropsychological test battery. Our aim is to start data collection in January 2008.

Other studies of the Severe Mental Disorders -project

The Mental Health in Early Adulthood -study (MEAF) is a follow-up study of the young adult sample of the Health 2000 study (N=1894). The study complements the PIF study; the two together provide reliable and comprehensive picture on the epidemiology of psychotic disorders in Finland. MEAF also provides interesting information on schizotypy in the general population.

Investigation on suicides and mortality in schizophrenia is one of the oldest research branches in the program; studies have been based on the National Suicide Prevention Project study sample (Heilä et al 1997, 1998, 1999a, and 1999b) and on nationwide registers (Heilä et al 2005).

The Viral Infections in the Aetiology of Severe Mental Disorders-study investigates whether viral infections, particularly CNS infections, predispose to later development of severe mental disorders. The study utilizes information on clinical samples

from 9,836 individuals analysed at the Department of Viral Diseases and Immunology during the 1960s and 1970s. Their data have been linked with information from the Hospital Discharge Register to identify persons treated for psychotic disorders.

In addition to these projects, the senior researchers from this project are collaborators in several projects conducted together with the University of Helsinki, the University of Kuopio, the National Research and Development Centre for Welfare and Health (Stakes), and the University of Southern California, Los Angeles.

6.5.2. The main scientific achievements

The Genetic Epidemiology and Molecular Genetics of Schizophrenia

We have been pioneers in using quantitative traits derived from neuropsychological tests as vulnerability markers (endophenotypes) in genetic studies. We have investigated neuropsychological functions and their heritability in patients and their family members (Tuulio-Henriksson et al 2002, Tuulio-Henriksson et al 2003, Tuulio-Henriksson et al 2004, Kuha et al 2007), and their clustering in families (Hoti et al 2004) and in individuals (Wessman et al, submitted). Using cognitive domains as quantitative phenotypes in a genomewide QTL analysis, the linkage signal enhanced in some previously identified chromosomal areas (Paunio et al 2004). Our findings related to DISC1 and reelin and cognitive functions further demonstrate the usefulness of the endophenotype approach (Hennah et al 2003, Hennah et al 2005, Wedenoja et al 2007). We have also investigated the prevalence and characterized the clinical phenotype of schizophrenia in the northeastern isolate (Arajärvi et al 2004, Arajärvi et al 2005), and studied growth patterns and risk of schizophrenia (Haukka et al, in press).

We have utilized the register-based cohort of persons with schizophrenia born in Finland from 1940 to 1969 in several studies. We have shown that the heritability of schizophrenia in Finland is over 80 per cent (Cannon et al 1998), but family-related environmental factors also contribute to the risk of schizophrenia (Haukka et al 2004). We found that the age at onset is lower and outcome poorer in highly familial than in sporadic schizophrenia (Suvisaari et al 1998). We found that fertility is lower in persons with schizophrenia, which is not compensated by higher fertility in their siblings (Haukka et al 2003).

Investigating the same cohort, we observed that the incidence of schizophrenia had declined in cohorts born in the 1960s, compared with cohorts born in the 1950s (Suvisaari et al 1999). We have also investigated regional variation in the incidence of

schizophrenia, finding strong regional variation but much less urban-rural differences in the incidence (Haukka et al 2001). In a set of studies investigating seasonal variation of births in schizophrenia (Suvisaari et al 2000, Suvisaari et al 2001, Suvisaari et al 2004) and its possible link to polioepidemics (Suvisaari et al 1999a), we found that seasonal variation of births in schizophrenia is diminishing, is partly explained by procreational habits of the parents, and is not related to genetic risk. We also investigated comorbidity between schizophrenia and type 1 diabetes, and found that the risk of schizophrenia is considerably lower in persons with type 1 diabetes than in the general population (Juvonen et al in press).

At the Department of Molecular Medicine, genomewide scans have been conducted at various phases of the study (Hovatta et al 1999, Ekelund et al 2000, Ekelund et al 2001, Paunio et al 2001, Ekelund et al 2004, Paunio et al 2004), and six areas of particular interest have been identified. Our most promising genetic findings thus far have been related to Disrupted in Schizophrenia Gene 1 (DISC1) (Blackwood et al 2001). We have found (Ekelund et al 2001) and replicated (Ekelund et al 2004) linkage to the DISC1 area in Finnish schizophrenia families, and identified an allelic haplotype (HEP3) that is associated with increased risk of schizophrenia and visual working memory function deficits, particularly among males (Hennah et al 2003, Hennah et al 2005). We reanalyzed our genome-wide data conditioning on the DISC1 HEP3 haplotype and identified a DISC1 interacting protein, NDE1, that also associates with schizophrenia and visual working memory functions (Hennah et al 2007). We are currently investigating the genes of the binding proteins of the DISC1 further, and also the cellular expression of the DISC1. Another chromosomal area of particular interest is 7q22 (Ekelund et al 2000). Within this area, we have observed an allelic variant in the reelin gene that is associated with lower function in tests measuring working memory, memory, and executive functioning (Wedenoja et al, in press).

Recently, a whole-genome association study was performed on 200 persons with schizophrenia, and 200 controls from our general population studies, revealing a novel genetic deletion associated with schizophrenia in the isolate families. The most promising findings from this study are currently being investigated in a larger association study sample.

The Psychosis in Finland study

The Psychosis in Finland study was the first study to report prevalences of all DSM-IV psychotic disorders from one country. The lifetime prevalence of psychotic disorders in the PIF study sample, 3.48%, is substantially higher than in other recent population surveys, possibly because we were able to use register data for case ascer-

tainment and had access to case notes. However, the lifetime prevalence of schizophrenia (1.0%) and non-affective psychotic disorders (2.29%) is so high that it may be these disorders genuinely are more prevalent in Finland than in most other countries. (Perälä et al 2007)

Investigating results from neuropsychological measurement, we found that persons with schizophrenia had a generalized cognitive impairment, persons with other non-affective psychoses showed memory and processing speed deficits, persons with major depressive disorders were impaired in processing speed, while persons with bipolar disorders showed no dysfunction as compared with a control group derived from the same study sample. (Tuulio-Henriksson et al, submitted)

The prevalence of type 2 diabetes in persons with schizophrenia (22.0%) and other nonaffective psychotic disorders (ONAP) (13.4%) was considerably higher than in the general population (6.1%) (Suvisaari, Perälä et al in press). Also the prevalence of metabolic syndrome was high in these groups (36.2% and 41.4% vs. 30.1% in the general population) (Suvisaari, Saarni et al in press), and persons with schizophrenia had high prevalence of coronary heart disease as well (14.8% vs. 10.8% in the general population). In contrast, persons with affective psychoses did not have increased prevalence of these disorders. Medical comorbidity in persons with schizophrenia and in some variables also in persons with other nonaffective psychotic disorder was even more striking when continuous variables rather than dichotomized diagnoses were examined. Compared with persons without any psychotic disorder, persons with schizophrenia had significantly higher fasting plasma glucose, insulin, and triglyceride levels, lower HDL cholesterol level, larger waist circumference and lower bone ultrasound attenuation value, suggesting lower bone mineral density. Persons with ONAP had larger waist circumference and higher body mass index, while persons with affective psychoses had larger waist circumference but also lower systolic blood pressure. When detailed body composition was investigated by bioimpedance, schizophrenia and other nonaffective psychotic disorders were associated with high fat percentage, and schizophrenia also with low fat free mass. Schizophrenia was strongly associated with abdominal obesity even after controlling for body mass index, suggesting a particular vulnerability to abdominal obesity in persons with schizophrenia.

Another important area in the Psychoses in Finland -study is the examination of functional disability. We found that after adjusting for age and sex, schizophrenia was associated with 5-fold odds of having visual impairment for distance, and 6-fold for impaired near vision, while other psychotic disorders were not (Viertiö et al, submitted). Schizophrenia is also associated with poor physical condition, and problems with mobility and activities of daily living.

The Schizophrenia Twin Study

We have investigated the inheritance of neuropsychological dysfunction in twins discordant for schizophrenia (Cannon et al 2000), the effect of genetic liability and illness on regional cortical gray-matter deficits (Cannon et al 2002), and more specifically, on hippocampus (van Erp et al 2004). We have also investigated how brain structure is influenced by individual genetic differences in general (Thompson et al 2001). We have shown that genetic liability to schizophrenia is associated with caudate D2 upregulation (Hirvonen et al 2005) and P50 and N100 decrease (Ahveninen et al 2006). When comparing cognitive functions in bipolar and schizophrenia twin, deficits in spatial working memory were related to genetic liability for schizophrenia but not bipolar I disorder, suggesting that they are specific to genetic liability to schizophrenia (Pirkola et al 2005). We also found in our schizophrenia twin sample two haplotypes within the DISC1 gene that were significantly overrepresented among individuals with schizophrenia and were associated with impairments in several memory functions and reduced gray matter density in the prefrontal cortex (Cannon et al 2005).

The Helsinki high-risk study

From the original sample consisting of 179 offspring, we have reported the cumulative incidences of mental disorders, relationship of maternal symptoms to offspring's risk of developing psychotic disorders, and childhood developmental factors that predict the development of psychotic disorders in the offspring (Niemi et al 2004a, Niemi et al 2004b, Niemi et al 2005a, Niemi et al 2005b). Among the HR offspring, social adjustment problems at pre-school age and severe neurological symptoms predicted future schizophrenia spectrum disorder, while school-age behavioral and emotional problems predict the development of non-psychotic disorders (Niemi et al 2005a). Within HR children, the combination of being in the lowest tertile for ponderal index at birth but having BMI in the highest tertile at seven years predicted future schizophrenia spectrum disorder (Niemi et al 2005). Of maternal symptoms, only positive symptoms predicted offspring's risk for schizophrenia spectrum disorders, being inversely related to offspring's risk (Niemi et al 2004b). More recently, we have investigated whether school achievement predicts later development of mental disorders.

From the extended sample, we have investigated findings on offspring's mortality, which was over two-fold higher in the high-risk offspring than in the general population. Within the high-risk group, having been diagnosed with a psychotic disorder was associated with higher mortality from unnatural causes, and maternal suicide attempts strongly predicted offspring's suicide. (Suvisaari et al, submitted)

The Helsinki 1951-1960 Cohort Study

In this cohort, poor performance in non-academic subjects at ages 7-10 years predicted later development of schizophrenia (Cannon et al 1999). Poor educational attainment, poor grades for attention at school, higher birth weight and larger head circumference were significantly associated with the risk of criminal offending in adulthood in persons with schizophrenia (Cannon M et al 2002). The validity of register-based schizophrenia spectrum diagnosis compared with case note -based OPCRIT diagnosis was found to be good in the largest validation study of hospital discharge register schizophrenia diagnosis ever conducted (Pihlajamaa et al, in press).

The Finnish Conscript Study on Psychotic Disorders

We found that poor performance on test assessing visuospatial reasoning was associated with increased risk of schizophrenia, other psychotic disorders, and bipolar I disorder. In contrast, good performance in the test measuring arithmetic reasoning predicted higher risk of bipolar I disorder. (Tiihonen et al 2005)

Other studies of the project

Hannele Heilä has investigated clinical characteristics and antecedents of suicide in persons with schizophrenia (Heilä et al 1997, 1998, 1999a, 1999b). She found that suicide was usually committed during an active phase of the illness, patients often had depressive symptoms, one-third of patients were receiving inpatient care, and over half of patients were not prescribed antipsychotic medication or they were not using it. Suicide risk is highest during the first five years after the onset of the illness (Heilä et al 2005).

In a previous study using a subset of the Viral Infections in the Aetiology of Severe Mental Disorders-study sample, we found no association between childhood viral CNS infection and later development of schizophrenia (Suvisaari et al 2003). In the future, we will be able to investigate the effect of different causative agents separately.

6.5.3. The main public health achievements

Our collaboration with clinicians in the Peijas area to develop systematic assessment and longitudinal follow-up of patients with schizophrenic psychoses has involved

training and supervision of clinicians. The project will involve validation of several psychiatric rating scales and measures in Finnish for clinical use. It may in the future be linked to a wider project aiming at specifying a core set of psychiatric instruments for clinical use throughout the country, and developing an internet-based training instrument for them.

Our prodromal study has introduced the prodromal concept and its assessment methods to adolescent psychiatric treatment settings in Helsinki. The clinicians have found both the assessment of prodromal features and neuropsychological testing very useful. Our researchers have taught and supervised clinical psychologists and psychiatrists in their use. The collaboration has benefited both parties.

The senior researchers of the project are active lecturers in universities and hospitals throughout Finland, and supervise doctoral theses in several Finnish universities. Jaana Suvisaari also organizes training concerning psychotic disorders of residents in psychiatry at the University of Helsinki.

6.5.4. Funding for research and public health programs

Jaana Suvisaari and Annamari Tuulio-Henriksson have positions from the Academy of Finland that include funding for their research projects as well. Three studies, The Genetic Epidemiology and Molecular Genetics of Schizophrenia, The Prodromal Symptoms of Psychotic Disorders in Adolescent Psychiatric Patients, and the Mental Health in Early Adolescence, receive currently funding from the Academy of Finland. The Academy has also funded the Psychoses in Finland -study from 2003 to 2006. The twin study is funded by the National Institute of Health. In addition, our PhD students have funding from several Finnish foundations.

6.5.5. Personnel

Docent Jaana Suvisaari, MD, PhD, psychiatrist, is the leader of the project and is involved in most of the individual studies, being the principal investigator of the PIF and MEAF studies. Other key senior scientists in several studies are docent Annamari Tuulio-Henriksson, PhD, psychologist, docent Jari Haukka, PhD, epidemiologist and statistician, and professor Jouko Lönnqvist, MD, PhD. Annamari Tuulio-Henriksson is the senior researcher leading and supervising neuropsychological investigations in most

of the studies in the Severe Mental Disorders -project and in other research projects conducted at the Department of Mental Health and Alcohol Research as well as the research on quantitative traits at the Department of Molecular Medicine. Jari Haukka supervises or conducts statistical analyses in many of these studies, besides leading a register-based epidemiological research branch at the department. Professor Jouko Lönnqvist launched the Genetic Epidemiology and Molecular Genetics of Schizophrenia -study and is its principal investigator. He is involved in all studies of the project, and is also the principal investigator of the twin study in Finland. Other senior scientists in the project are Laura Häkkinen (former Niemi), who is the principal investigator of the Helsinki High-Risk Study, and Matti Huttunen, who works as a senior scientist in the twin study, and is the principal investigator of the prodromal study. Other senior scientists of the department, particularly docent Timo Partonen, MD, PhD, docent Kimmo Kuoppasalmi, MD, PhD, docent Sami Pirkola, MD, PhD, Dr. Hannele Heilä, MD, PhD, and professor Erkki Isometsä, MD, PhD, collaborate with us in some of the studies.

Kirsi Niinistö, BA, is our research assistant, Tuula Mononen works in the Genetic Epidemiology and Molecular Genetics of Schizophrenia -study as research nurse, and Ulla Mustonen, BA, works as a clinical coordinator in the twin and prodromal studies.

PhD students

The Genetic Epidemiology and Molecular Genetics of Schizophrenia

Annamaria Kuha, MPsych, and Minna Torniainen, MPsych, are preparing their PhD theses on cognitive functioning in persons with schizophrenia and their unaffected relatives, and on the relationship between cognitive functions and other phenotypic features.

The Psychoses in Finland -study

There are five PhD students in the Psychoses in Finland -study: Jonna Perälä, MD, whose thesis focuses on the prevalence and comorbidity of different psychotic disorders and their regional and sociodemographic variation, Samuli Saarni, MD, MSocSc, whose thesis relates to health-related quality of life and its determinants, Annakajja Helén, MD, who investigates neuropsychological deficits and their role in determining the functional outcome of psychotic disorders, Satu Viertiö, MSc (Health), who investigates functional capacity among persons with psychotic disorders, and Krista Partti, BMed, who studies medical comorbidity in psychotic disorders.

The Helsinki High-Risk Study

Yrjö Lähteenlahti, MD, is preparing his thesis on the association between maternal and offspring's symptoms and on criminal behavior and its predictors in the offspring.

The Prodromal Symptoms of Psychotic Disorders in Adolescent Psychiatric Patients -study

Sebastian Therman, MPsych, is doing his PhD on the relationship between neuropsychological performance and prepsychotic symptoms, and their value in predicting who will develop psychosis in the follow-up, and on the structure of psychosis proneness. Marko Manninen, MPsych, is preparing his thesis based on the reform school study sample, investigating psychiatric morbidity and symptoms and neuropsychological functioning in reform school adolescents, and their association with outcome.

The Cohort Study of Persons with Schizophrenia Born in Helsinki During 1951-1960

Johanna Pihlajamaa is preparing her PhD thesis on total and suicide mortality and its predictors in schizophrenia spectrum psychoses.

Other studies of the project

Anu Castaneda, MPsych, is doing her PhD on the relationship between neuropsychological performance and anxiety and depressive disorders, and Antti Latvala, MPsych, on predictors and consequences cannabis use based on the Mental Health in Early Adulthood study sample. Sini Lähteenmäki, BMed, is preparing her PhD on eating disorders and disordered eating behavior based on the same study sample. Although these studies are focused on non-psychotic disorders, the senior researchers of the project (Suvisaari or Tuulio-Henriksson) supervise these theses.

6.5.6. Collaboration

We have ongoing collaboration with the departments of Molecular Medicine (prof. Leena Peltonen-Palotie and her group), Health and Functional Capacity (prof. Antti Reunanen, docent Seppo Koskinen, docent Markku Heliövaara and their groups), and Viral Diseases and Immunology in our institute (prof. Tapani Hovi), with professor Ja-

akko Kaprio and his twin study group at the Department of Public Health at the University of Helsinki, with other Finnish universities, particularly with prof. Jari Tiihonen from the University of Kuopio and with prof. Jarmo Hietala and his group from the University of Turku, with prof. Tyrone Cannon and prof. Arthur Toga and their groups at the UCLA, and with Dr. Mary Cannon at the University of Dublin. Professor Leena Peltonen-Palotie is the other principal investigator of the Genetic Epidemiology and Molecular Genetics of Schizophrenia -study, and professor Tyrone Cannon is the principal investigator of the twin study.

6.5.7. Proposal for future work and expected benefits

Proposal for future work

In the Genetic Epidemiology and Molecular Genetics of Schizophrenia, we continue analysing our previously identified candidate genetic areas and the identified candidate genes and their association with clinical phenotypes and quantitative traits. Our particular interest is presently on the deletion detected in the genomewide association study. We will continue collecting families, focusing on families with identified risk alleles or chromosomal abnormalities. We are currently interviewing and testing a random control sample from the isolate. We continue investigating neuropsychological functioning in these families, and the association between cognitive and clinical features. We also investigate how psychotropic medication affects cognitive functions. The aim is to identify those cognitive features that are most tightly linked to genetic risk of schizophrenia.

In the PIF study, we will characterize the epidemiology and treatment of different psychotic disorders, e.g. delusional disorder and substance-induced psychotic disorders, further. We continue investigating medical comorbidity and functional disability in psychotic disorders. We will investigate mortality and its predictors in psychotic disorders. We will further examine the associations between cognitive functions and clinical symptomatology, functional disability, and comorbidity. We will also investigate psychotic-like symptoms and their correlates in the Health 2000 study sample. The sample will be used in genetic studies to investigate some candidate genes of psychotic disorders and also of the most comorbid medical conditions. We will participate in future follow-ups of the Health 2000 study sample, the first of which will be conducted in 2008-2009.

In the twin study, we will continue analysing candidate genes of interest in relation to the CNS phenotypes obtained on the sample, and will also integrate gene expression

data into this research. In addition, the proteomic and metabolomic profile of the twins will be analysed to search for relevant biomarkers for schizophrenia.

Clinical assessments in the prodromal symptoms of psychotic disorders in adolescent psychiatric patients -study will continue for 2.5 years. We aim to investigate whether prodromal criteria are able to identify adolescents at high risk for psychotic disorders, and if not, whether they could be modified to have better predictive value. We also investigate the significance of different neuropsychological deficits in predicting the clinical outcome of treatment-seeking adolescents.

In the Helsinki high-risk study, we will continue investigating predictors of adult psychiatric disorders, criminality, and mortality in offspring of mothers with psychotic disorder. Clinical and developmental predictors of suicide and other types of mortality is also the main focus currently in the Helsinki 1951-1960 cohort study.

The Peijas Schizophrenia Study will be started in 2008. The aim is to have longitudinal information on the course of schizophrenia and other psychotic disorders and factors affecting the outcome. Through this study in particular, the project will maintain its link to clinical work and to the development of treatment of psychotic disorders.

Expected benefits

Because of our large, epidemiologically representative, carefully assessed study samples, our studies may provide unique information on the etiology of psychotic disorders. We also provide information on the quality of life, comorbidity, and functional disability that persons with psychotic disorder living in the community have, and the treatment they receive. Such information is essential for developing health care for persons with psychotic disorders. Our results concerning premorbid developmental problems give information on which types of problems are particularly alarming in connection with genetic high-risk, which is useful when systems for supporting children who have parents with severe mental disorders are being developed. The prodromal study produces vital information on whether psychiatric symptoms and problems in neurocognitive domains can predict future development of psychotic disorders in treatment-seeking adolescents and thus enable the identification of ultra high-risk persons. In Finland, we provide information on the prevalence of psychotic disorders and the health, treatment, and needs of persons suffering from them. We educate clinical workers by distributing results from evidence based studies, and participate in the development of mental health care systems.

6.5.8. The most important publications of the project in years 1997-2007

Juvonen H, Reunanen A, Haukka J, Muhonen M, Suvisaari J, Arajärvi R, Partonen T, Lönnqvist J. Incidence of schizophrenia in a nationwide cohort of patients with type 1 diabetes mellitus. *Archives of General Psychiatry*; in press

Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland. hannu.juvonen@ktl.fi.

CONTEXT: Patients with schizophrenia have an increased risk of type 2 diabetes mellitus. However, very few studies have dealt with the association of type 1 diabetes and schizophrenia. Preliminary evidence points to a possible inverse association. **OBJECTIVE:** To investigate the incidence of schizophrenia in a nationwide cohort of patients with type 1 diabetes born in 1950 through 1959 in Finland. **DESIGN:** A cohort study of individuals born in 1950 through 1959 with a follow-up of 1969 through 1991. **SETTING:** Finland. Patients All individuals born in 1950 through 1959 with type 1 diabetes were identified through nationwide registers. The incidence of schizophrenia until 1992 among the total 1950-1959 cohort and in individuals with type 1 diabetes was calculated using information from 3 health care registers. **Main Outcome Measure** Incidence of schizophrenia. **RESULTS:** The incidence of schizophrenia was 0.21 per 10 000 person-years in the group with type 1 diabetes and 0.56 per 10 000 person-years in the group without type 1 diabetes ($P < .001$). **CONCLUSION:** The incidence of schizophrenia is decreased in patients with type 1 diabetes.

Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S, Lönnqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry* 2007;64:19-28.

Department of Mental Health and Alcohol Research, National Public Health Institute, University of Helsinki, Mannerheimintie 166, 0300 Helsinki, Finland. jonna.perala@ktl.fi

CONTEXT: Recent general population surveys of psychotic disorders have found low lifetime prevalences. However, this may be owing to methodological problems. Few studies have reported the prevalences of all specific psychotic disorders. **OBJECTIVE:** To provide reliable estimates of the lifetime prevalences of specific psychotic disorders. **DESIGN:** General population survey. **SETTING AND PARTICIPANTS:** A nationally representative sample of 8028 persons 30 years or older was screened for psychotic and bipolar I disorders using the Composite International Diagnostic Interview, self-reported diagnoses, medical examination, and national registers. Those selected by the screens were then re-interviewed with the Structured Clinical Interview for DSM-IV. Best-estimate DSM-IV diagnoses were formed by combining the interview and case note data. Register diagnoses were used to estimate the effect of the nonresponders. **MAIN OUTCOME MEASURES:** Diagnosis of any psychotic or bipolar I disorder according to the DSM-IV criteria. **RESULTS:** The lifetime prevalence of all psychotic disorders was 3.06% and rose to 3.48% when register diagnoses of the nonresponder group were included. Lifetime prevalences were as follows: 0.87% for schizophrenia, 0.32% for schizoaffective disorder, 0.07% for schizophreniform disorder, 0.18% for delusional disorder, 0.24% for bipolar I disorder, 0.35% for major depressive disorder with psychotic features, 0.42% for substance-induced psychotic disorders, and 0.21% for psychotic disorders due to a general medical condition. The National Hospital Discharge Register was the most reliable of the screens ($\kappa = 0.80$). Case notes supplementing the interviews were essential for specific diagnoses of psychotic disorders. **CONCLUSIONS:** Multiple sources of information are essential for accurate estimation of lifetime prevalences of psychotic disorders. The use of comprehensive methods reveals that their lifetime prevalence exceeds 3%.

Cannon TD, Hennen W, van Erp TG, Thompson PM, Lönnqvist J, Huttunen M, Gasperoni T, Tuulio-Henriksson A, Pirkola T, Toga AW, Kaprio J, Mazziotta J, Peltonen L. Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of General Psychiatry* 2005;62:1205-13

Department of Psychology, 1285 Franz Hall, University of California-Los Angeles, Los Angeles, CA 90095, USA. cannon@psych.ucla.edu

CONTEXT: Chromosome 1q42 is among several genomic regions showing replicated evidence of linkage with schizophrenia, but the specific susceptibility mechanisms underlying this relationship remain to be identified. **OBJECTIVE:** To examine a series of haplotype blocks of single-nucleotide polymorphic markers from a segment of 1q42 spanning the disrupted-in-schizophrenia 1 (DISC1) and translin-associated factor X (TRAX) genes for association with schizophrenia and several endophenotypic traits thought to be involved in disease pathogenesis. **DESIGN:** Population-based twin cohort study. **SETTING:** Finland. **PARTICIPANTS:** Two hundred thirty-six subjects, consisting of 7 twin pairs concordant for schizophrenia (6 monozygotic [MZ] and 1 dizygotic [DZ]), 52 pairs discordant for schizophrenia (20 MZ and 32 DZ), and 59 demographically balanced normal pairs (28 MZ and 31 DZ), were drawn from a twin cohort consisting of all of the same-sex twins born in Finland from 1940 through 1957. **MAIN OUTCOME MEASURES:** Psychiatric diagnosis, performance on neurocognitive tests of short- and long-term memory, and gray matter volume measurements taken from high-resolution magnetic resonance images. **RESULTS:** A common haplotype incorporating 3 single-nucleotide polymorphic markers near the translocation break point of DISC1 (odds ratio, 2.6 [P = .02]) and a rare haplotype incorporating 4 markers from the DISC1 and TRAX genes (odds ratio, 13.0 [P = .001]) were significantly overrepresented among individuals with schizophrenia. These haplotypes were also associated with several quantitative endophenotypic traits previously observed to covary with schizophrenia and genetic liability to schizophrenia, including impairments in short- and long-term memory functioning and reduced gray matter density in the prefrontal cortex, as demonstrated using a population-based brain atlas method, with a trend toward association with reduced hippocampal volume. **CONCLUSIONS:** Specific alleles of the DISC1 and TRAX genes on 1q42 appear to contribute to genetic risk for schizophrenia through disruptive effects on the structure and function of the prefrontal cortex, medial temporal lobe, and other brain regions. These effects are consistent with their production of proteins that play roles in neuritic outgrowth, neuronal migration, synaptogenesis, and glutamatergic neurotransmission.

Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T, Cannon TD, Lönnqvist J, Peltonen L. A haplotype within the DISC1 gene is associated with visual memory functions in families with a high density of schizophrenia. *Molecular Psychiatry* 2005;10:1097-1103.

Department of Molecular Medicine, National Public Health Institute, Helsinki, Finland.

We have previously reported evidence of linkage and association between markers on 1q42 and schizophrenia in a study sample of 498 multiply affected Finnish nuclear families, leading to the recent identification of four significantly associated haplotypes that specifically implicate the Translin-Associated Factor X (TRAX) and Disrupted in Schizophrenia 1 and 2 (DISC1 and DISC2) genes in the genetic etiology of schizophrenia. Previously, the DISC genes were found to be disrupted by a balanced translocation (1;11)(q42.1;q14.3) that cosegregated with schizophrenia and related disorders in a large Scottish pedigree. Interestingly, we also reported earlier suggestive linkage between endophenotypic quantitative traits of visual and verbal memory and microsatellite markers in close proximity to TRAX/DISC, on 1q41. Here, we tested if the identified allelic haplotypes of TRAX/DISC would be associated with visual and/or verbal memory function impairments that are known to aggregate with schizophrenia in families. One haplotype of DISC1, HEP3, displayed association with poorer performance on tests assessing short-term visual memory and attention. Analysis of affected and unaffected offspring separately revealed that both samples contribute to the observed association to visual working memory. These results provide genetic support to the view that the DISC1 gene contributes to sensitivity to schizophrenia and associated disturbances and affects short-term visual memory functions. This finding should stimulate studies aiming at the molecular characterization of how the specific alleles of DISC1 affect the visual memory functions and eventually participates in the development of schizophrenia.

Niemi LT, Suvisaari JM, Haukka JK, Wrede G, Lönnqvist JK. Cumulative incidence of mental disorders among offspring of mothers with psychotic disorder: Results from the Helsinki High-Risk Study. *British Journal of Psychiatry* 2004; 185:11-17

Department of Mental Health and Alcohol Research, KTL, National Public Health Institute, Helsinki, Finland. laura.niemi@ktl.fi

BACKGROUND: The Helsinki High-Risk Study follows up all women born between 1916 and 1948 and treated for schizophrenia-spectrum disorders in psychiatric hospitals in Helsinki, their offspring born between 1960 and 1964, and controls. **AIMS:** To determine the cumulative incidence of adulthood Axis I disorders among offspring. **METHOD:** Using all hospital and out-patient treatment records we re-diagnosed parents and offspring according to DSM-IV-TR criteria. Offspring were grouped by mother's diagnosis (schizophrenia $n=104$, schizoaffective disorder $n=20$, other schizophrenia-spectrum disorder $n=30$, and affective disorder $n=25$) and compared with a control group ($n=176$). The cumulative incidences of Axis I disorders among offspring were calculated. **RESULTS:** The cumulative incidences of any psychotic disorder were 13.5%, 10.0%, 10.0%, 4.0% and 1.1% among offspring of mothers with schizophrenia, schizo-affective disorder, other schizophrenia-spectrum disorders, affective disorders and controls, respectively. The corresponding figures for schizophrenia were 6.7%, 5.0%, 6.7%, 0% and 0.6%, and for any mental disorder 23.1%, 20.0%, 20.0%, 12.0% and 6.9%. **CONCLUSIONS:** Offspring of mothers with a psychotic disorder have heightened risk of developing a wide range of severe mental disorders.

Paunio T, Tuulio-Henriksson A, Hiekkalinna T, Perola M, Varilo T, Partonen T, Cannon TD, Lonnqvist J, Peltonen L. Search for cognitive trait components of schizophrenia reveals a locus for verbal learning and memory on 4q and for visual working memory on 2q. *Human Molecular Genetics* 2004;13:1693-702.

Department of Molecular Medicine, National Public Health Institute, Helsinki, Finland. tina.paunio@ktl.fi

Research to identify predisposing genes for complex diseases relying solely on clinical diagnosis is probably not ideal. Here, we analyzed genome-wide data for 168 schizophrenia families using neuropsychological variables associated with disease susceptibility, with the aid of SOLAR, a program for variance-component analysis. The linkage signal was greatly accentuated by application of the quantitative traits compared with diagnosis. We found evidence for a locus for verbal learning and memory on 4q21 ($Z=3.01$, $Z(mp)=3.84$ and empiric $P=0.031$ for delayed memory; $Z=2.96$, $Z(mp)=3.4$ and $P=0.026$ for verbal learning) and suggestive evidence for visual working memory on 2q36 ($Z=2.80$, $Z(mp)=2.08$ and $P=0.093$). In addition, some evidence emerged for a locus for recognition memory on 10p13, visual attention on 15q22 and executive function on 9p22 in the complete sample, as well as for delayed memory on 8q12, semantic clustering and intrusions on 1q42 and visual attention on 3p25 in the genealogically distinctive sample subsets. Of the loci linked to schizophrenia in diverse populations, in addition to the earlier mentioned regions, some evidence of linkage was observed for 2q, 6q, 7q, 11q, 13q, 14q, 18q and 22q. Our results reveal initial information on the effect of the loci associated with schizophrenia in multiple studies, and emphasize the value of trait components in the search for susceptibility loci for complex diseases.

Haukka J, Suvisaari J, Lonnqvist J. Fertility of patients with schizophrenia, their siblings, and the general population: a cohort study from 1950 to 1959 in Finland. *American Journal of Psychiatry* 2003;160:460-463.

Kansanterveyslaitos, National Public Health Institute, Helsinki, Finland. jari.haukka@ktl.fi

OBJECTIVE: Genetic factors are the most important risk factors for schizophrenia. However, despite the fact that patients with schizophrenia have significantly fewer offspring than the general population, schizophrenia persists. The authors investigated whether the siblings of patients with schizophrenia produce more offspring, thereby compensating for the low fertility of the affected individuals. **METHOD:** From all 870,093 individuals born in Finland from 1950 to 1959, the authors determined how many had schizophrenia or were siblings of schizophrenia patients and how many offspring they had. The population data were obtained from the Population Register Center of Finland, and the National Hospital Discharge Register was used to identify all persons who had been hospitalized because of schizophrenia. Appropriate regression models were used to model age at the birth of the first child, number of children, and proportion of males among offspring. **RESULTS:** Of the total population, 1.3% were patients with schizophrenia, and 2.8% were their siblings. The mean number of offspring among female siblings was slightly but significantly higher than among women in the general population (1.89 versus 1.83), while

the opposite was true for the male siblings (1.57 versus 1.65 among men in the general population). The mean number of offspring among patients with schizophrenia was 0.83 for women and 0.44 for men. **CONCLUSIONS:** Lower than average fertility among patients with schizophrenia is not compensated for by higher fertility among their siblings. Thus, the persistence of schizophrenia in the general population is not explained by this simple evolutionary mechanism.

Suvisaari J, Mautemps N, Haukka J, Hovi T, Lönnqvist J. Childhood central nervous system viral infections and adult schizophrenia. *American Journal of Psychiatry* 2003;160:1183-1185.

Department of Mental Health and Alcohol Research and the Department of Virology, National Public Health Institute, Helsinki, Finland. jaana.suvisaari@ktl.fi

OBJECTIVE: An earlier Finnish cohort study suggested that childhood viral CNS infections are associated with a fivefold increased odds of developing schizophrenia in adulthood. The authors sought to replicate this finding. **METHOD:** From the archives of the Department of Virology of the National Public Health Institute in Finland, 320 individuals born between 1960 and 1976 who had suffered virologically confirmed CNS infections before their 15th birthdays were identified. Of the infections, 202 had been caused by enteroviruses. The sample was followed up in the 1969-2000 records of the National Hospital Discharge Register of Finland to identify all cases of schizophrenia that emerged. **RESULTS:** The cumulative incidence of schizophrenia was 0.94% in the whole sample and 0.99% among individuals who had suffered enteroviral infections. These rates are comparable to that found in the general population. **CONCLUSIONS:** Childhood viral CNS infections were not associated with increased risk of schizophrenia.

Tuulio-Henriksson A, Arajärvi R, Partonen T, Haukka J, Varilo T, Schreck M, Cannon T, Lönnqvist J. Familial loading associates with impairment in visual span among healthy siblings of schizophrenia patients. *Biological Psychiatry* 2003;54:623-628.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.

BACKGROUND: The effect of familial loading on neurocognitive deficits in relatives of schizophrenia patients has been detected in family and twin studies. The present study examined this effect among healthy siblings of schizophrenia patients in a Finnish isolate with high prevalence of schizophrenia. **METHODS:** We assessed performance in verbal and visual span tasks, in tests measuring intelligence, and in declarative verbal memory and learning tasks in 31 and 67 healthy siblings from families with one schizophrenia patient, or with two or more patients, respectively. The differences between the groups were tested using linear mixed effects models. **RESULTS:** An effect of familial loading was detected in the backward visual span task, measuring immediate visual memory with requirements from the visual domain of working memory. In this task, the healthy siblings from multiply affected families performed worse than those from the singleton families. **CONCLUSIONS:** The finding that the multiplex vs. singleton differences were selective to the backward visual span task, strengthens the view that the visual domain of working memory may provide a valuable endophenotypic marker for genetic schizophrenia studies.

Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen V-P, Huttunen M, Lönnqvist J, Standertskjöld-Nordenstam C-G, Kaprio J, Khaledy M, Dail R, Zoumalan CI, Toga AW. Genetic influences on brain structure. *Nature Neuroscience* 2001;4:1253-1258.

Laboratory of Neuro Imaging and Brain Mapping Division, Department of Neurology, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, California 90095-1769, USA. thompson@loni.ucla.edu

Here we report on detailed three-dimensional maps revealing how brain structure is influenced by individual genetic differences. A genetic continuum was detected in which brain structure was increasingly similar in subjects with increasing genetic affinity. Genetic factors significantly influenced cortical structure in Broca's and Wernicke's language areas, as well as frontal brain regions ($r^2(MZ) > 0.8$, $p < 0.05$). Preliminary correlations were performed suggesting that frontal gray matter differences may be linked to Spearman's g , which measures successful test performance across multiple cognitive domains ($p < 0.05$).

These genetic brain maps reveal how genes determine individual differences, and may shed light on the heritability of cognitive and linguistic skills, as well as genetic liability for diseases that affect the human cortex.

Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, Finkelstein J, Hietaanen M, Kaprio J, Koskenvuo M. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *American Journal of Human Genetics* 2000;67:369-382.

Department of Psychology, UCLA, 90095, USA. cannon@psych.ucla.edu

While genetic influences in schizophrenia are substantial, the disorder's molecular genetic basis remains elusive. Progress has been hindered by lack of means to detect nonpenetrant carriers of the predisposing genes and by uncertainties concerning the extent of locus heterogeneity. One approach to solving this complexity is to examine the inheritance of pathophysiological processes mediating between genotype and disease phenotype. Here we evaluate whether deficits in neurocognitive functioning covary with degree of genetic relationship with a proband in the unaffected MZ and DZ co-twins of patients with schizophrenia. Twin pairs discordant for schizophrenia were recruited from a total population cohort and were compared with a demographically balanced sample of control twin pairs, on a comprehensive neuropsychological test battery. The following four neuropsychological functions contributed uniquely to the discrimination of degree of genetic loading for schizophrenia and, when combined, were more highly correlated within MZ pairs than within DZ pairs, in both discordant and control twins: spatial working memory (i.e., remembering a sequence of spatial locations over a brief delay), divided attention (i.e., simultaneous performance of a counting and visual-search task), intrusions during recall of a word list (i.e., "remembering" nonlist items), and choice reaction time to visual targets. Together with evidence from human and animal studies of mediation of these functions by partially distinct brain systems, our findings suggest that there are multiple independently inherited dimensions of neural deficit in schizophrenia and encourage a search for genes contributing to quantitative variation in discrete aspects of disease liability. On tests of verbal and visual episodic memory, but not on the liability-related measures, patients were more impaired than their own MZ co-twins, suggesting a preferential impact of nongenetic influences on long-term memory systems.

Suvisaari JM, Haukka JK, Tanskanen AJ, Lönqvist JK. Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. *Archives of General Psychiatry* 1999;56:733-740.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. jaana.suvisaari@ktl.fi

BACKGROUND: The declining incidence of schizophrenia observed in several countries is believed by many to merely reflect methodological problems in the studies performed. We report the first nationwide historical cohort study of changes in the incidence of schizophrenia, in which many of the previous methodological problems were overcome. **METHODS:** We used the Finnish Population Register to identify everyone born in Finland from 1954 to 1965. These persons were followed up from their 16th to their 26th birthdays, and all cases of schizophrenia (International Classification of Diseases, Eighth Revision and International Classification of Diseases, Ninth Revision code 295) that emerged were identified from the National Hospital Discharge Register, the Pension Register, and the Free Medicine Register. Persons for whom an age of onset could be defined were included in the analyses (n = 5645). We used the Poisson regression model to estimate the effects of age, sex, birth cohort, period of diagnosis, and season of birth on the incidence of schizophrenia. The relative importance of cohort and period were assessed using an age-period-cohort model. **RESULTS:** The incidence declined significantly in each successive cohort, from 0.79 to 0.53 per 1000 among males and from 0.58 to 0.41 per 1000 among females. The effects of cohort and period on the change were both significant. **CONCLUSIONS:** The incidence of schizophrenia has declined in Finland. This was partly caused by confounding factors, as reflected in the significant period effect. The significant birth cohort effect suggests that the intensity or frequency of one or more risk factors for schizophrenia has decreased.

Hovatta I, Varilo T, Suvisaari J, Terwilliger J, Ollikainen V, Arajärvi R, Juvonen H, Kokko-Sahin M-L, Väisänen L, Mannila H, Lönnqvist J, Peltonen L. A genomewide screen for schizophrenia genes in an isolated Finnish subpopulation, suggesting multiple susceptibility loci. *American Journal of Human Genetics* 1999;65:1114-1124

Department of Human Molecular Genetics, National Public Health Institute, Helsinki, Finland.

Schizophrenia is a severe mental disorder affecting approximately 1% of the world's population. Here, we report the results from a three-stage genomewide screen performed in a study sample from an internal isolate of Finland. An effort was made to identify genes predisposing for schizophrenia that are potentially enriched in this isolate, which has an exceptionally high lifetime risk for this trait. Ancestors of the local families with schizophrenia were traced back to the foundation of the population in the 17th century. This genealogical information was used as the basis for the study strategy, which involved screening for alleles shared among affected individuals originating from common ancestors. We found four chromosomal regions with markers revealing pairwise LOD scores >1.0: 1q32.2-q41 ($Z(\max)=3.82$, dominant affecteds-only model), 4q31 ($Z(\max)=2.74$, dominant 90%-penetrance model), 9q21 ($Z(\max)=1.95$, dominant 90%-penetrance model), and Xp11.4-p11.3 ($Z(\max)=2.01$, recessive 90%-penetrance model). This finding suggests that there are several putative loci predisposing to schizophrenia, even in this isolate.

7. DRUG RESEARCH UNIT

7.1. Drug research

7.1.1. Research and public health significance of the area

The project derives from the beginning of 1990s when the research topics included

- Drug and alcohol effects in drivers suspected to drive under the influence of drugs and alcohol.
- Clinical pharmacokinetic and -dynamic studies on opioids and other CNS active drugs in different patient groups,
- Perinatal exposure to drugs and tobacco during pregnancy,
- Development of assay methods for drugs of abuse,
- Epidemiologic studies on the use of drugs in traffic, drug use among conscripts, in prisons and psychiatric hospital,
- Health risks associated with the abuse of anabolic androgenic steroids and other anabolic agents, and
- Animal studies on addiction mechanisms.

Since then the research topics and resources have been restricted and include nowadays:

- Estimation of the prevalence of drug abusers in Finland by capture-recapture method, and
- Central pharmacology of addictive drugs in animals.

Prevalence of amphetamine and opiate abuse in Finland

Acknowledgment of the amount of drug abusers and the abuse pattern in the country is important to development of health and social affairs. Estimation of the prevalence of amphetamine and opiate abusers is made by capture-recapture method utilizing official data sources such as The Hospital Patient Discharge Register (maintained by STAKES), Criminal Report Register (maintained by the police), C-hepatitis Register and Register of Drivers Suspected to Drive Under the Influence of Drugs (maintained by KTL). The estimation is carried out regularly (repeated mostly every second year) and the results are utilized by national officials responsible for maintaining and development of health and social affairs.

Pharmacological modulation of addictive properties of psychomotor stimulants and morphine

Drug addiction is a disease that is characterized by compulsive drug use, augmentation of the drug dose due to tolerance, difficulties in withdrawal, and weakening of physical and mental health. Typically psychomotor stimulant drugs produce psychological dependence but cessation of their abuse does not necessarily induce physical withdrawal signs and symptoms unlike withdrawal from opiates. In order to understand the characteristics of addictive behavior and to be able to provide novel pharmacological treatment strategies for addiction diseases, it is essential to understand neurochemical mechanisms mediating the rewarding properties of drugs of abuse. Conditioning and sensitization are powerful modulators of addictive behavior. The involvement of brain dopaminergic system in the conditioning of the rewarding properties of drugs of abuse is generally recognized. Roles of other neuronal systems, however, are more incompletely understood, and even less is known about the mechanisms mediating sensitization of the rewarding properties of drugs of abuse.

Amphetamine-type designer drugs: Assessment of addiction potential

The expanding market for synthetic amphetamine-type stimulant drugs (ATSs) is currently believed to be one of the world's most severe drug problems. In addition to traditional drugs of abuse that are classified in Schedule I of Controlled Substances or its equivalent, there is an increasing variety of so-called designer's drugs in the illicit market. Designer drugs are compounds that often resemble traditional drugs in terms of efficacy and molecular structure. However, their distribution, possession, or use is often outside of existing legal controls. Since the advent of the Internet, designer drugs have been promoted world-wide in drug-culture related web sites. These commonly include presentations of both synthesis and use of these substances, together with users' descriptions of their subjective effects. Unfortunately, the users often consider the new synthetic drugs to be less harmful than traditional drugs, despite that the effects or health risks of their use are usually not known.

ATSs are believed to exert their central effects by increasing the synaptic concentrations of dopamine and 5-hydroxytryptamine (5-HT), as well as norepinephrine. Minor modifications in molecular and/or spatial structure results in a series of compounds whose subjective effects extend from stimulatory to hallucinogenic. A large body of evidence suggests that their ability to increase a strong elevation of extracellular dopamine levels in nucleus accumbens plays a crucial role in their stimulative and reinforcing effects, while hallucinogenic properties are thought to be associated with 5-HTergic activity. Although these compounds are abused by humans, their neurochemical effects, including addiction potential, remain largely unknown.

The abuse of anabolic steroids

Abuse of anabolic androgenic steroids became fairly commonplace in the 1970s and 1980s, particularly in the power sports. The uncontrolled use of anabolic agents is no longer localized to competitive athletes as they are nowadays being used widely by amateur power athletes, and also by non-athletic groups. The abuse of anabolic agents has become an important public health issue. Supraphysiological doses of anabolic steroids stimulate protein synthesis and increase muscle mass and power, especially when combined with weight training. However, this kind of abuse has many serious side effects, e.g. increasing athletes' risk of cardiovascular diseases and sudden cardiac death. Relatively little attention has been paid to abuse of anabolic agents.

The central effects of anabolic steroids and their interactions with other substances of abuse

Concomitant use of anabolic androgenic steroids (AASs) with more conventional drugs of abuse, such as amphetamine or cannabis, has increased among the young men. More than half of the population abusing anabolic steroids develops drug dependence that fulfills the criteria of ICD-10 classification. Anabolic steroids have been shown to induce aggressive and violent behavior and this is suggested to be enhanced by alcohol and other drugs of abuse. Understanding of the mechanisms behind harmful central effects of AASs is crucial for the development of preventive biochemical treatment methods for AAS and other type of drug abuse. Comparing underlying neurobiological changes caused by AAS and other type of addictive substances may open new insights to the addiction research and to develop treatment strategies towards AAS and other substance abuse. Addiction may reflect drug-induced adaptations in the central nervous system and common mechanisms behind different type of addiction may exist.

7.1.2. The main scientific achievements

Prevalence of amphetamine and opiate abuse in Finland

The number of heavy amphetamine and opioid users has increased significantly in Finland between 1995 and 2005. It has been estimated that the amount of heavy amphetamine and opiate users in Finland varies between 16,000 - 21,000 subjects. According to latest survey the number of the users is no longer increasing in the district of Helsinki but increases are still found in other parts of Finland.

Pharmacological modulation of addictive properties of psychomotor stimulants and morphine

The involvement of the GABA A and 5-HT₃ receptor mediated neurotransmission and their role mediating dopaminergic and 5-HT₃ (serotonergic) effects of cocaine, mazindol, amphetamine and methylphenidate in conditioning of the rewarding properties have been studied in several series of animal trials.

Both GABA A and 5-HT₃ receptor mediated neurotransmission are involved in regulatory action over conditioning of psychomotor stimulant reward. The GABA A receptor agonist diazepam, unlike another GABA A receptor agonist zolpidem with a distinct binding profile from that of diazepam, was able to prevent place preference in-

duced by cocaine and amphetamine. Hence, it appears that the GABA A receptor-mediated inhibitory control may involve "zolpidem-insensitive" receptors. 5-HT₃ receptors are involved in cocaine- and mazindol-induced neurochemical and behavioral effects, in particular the acquisition of conditioned reward. Instead, blockade of the 5-HT₃ receptors failed to modify the effects of methylphenidate, the drug with no significant effect on 5-HTergic system, thereby suggesting that the ability of a drug to increase 5-HTergic transmission would be a prerequisite for the drug to be susceptible to the 5-HT₃ antagonism.

Methylphenidate (MP) is a psychomotor stimulant drug widely used for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Although the abuse of MP is considered rare in controlled use for the treatment of ADHD among children and adolescents, its illicit use has been recognized by several reports indicating that methylphenidate possesses abuse potential. We have found that methylphenidate-induced place preference was enhanced by prior exposure to the drug, i.e. rewarding properties of methylphenidate appeared to be sensitized. This is not due to attenuation of withdrawal induced by prior exposure, or development of tolerance to methylphenidate's aversive properties. While dopamine DA 1 receptor antagonists unlike DA 2 receptor antagonists are able to directly prevent methylphenidate-induced place preference, both type of antagonists, when co-administered with methylphenidate during the prior exposure, prevents the enhancement of place preference. Thus, both DA 1 and DA2, the latter possibly more specifically, are involved in the sensitization processed of methylphenidate reward.

The role of potassium (K⁺) channel-related mechanisms in the conditioning of morphine's rewarding properties has been studied with two K⁺ channel blockers. Quinine, but not 4-aminopyridine attenuates morphine-induced place preference, whereas morphine-induced secondary hyperactivity is attenuated by both drugs. Our results imply that at least some K⁺ channel related effects of morphine are involved in conditioning of morphine induced reward.

Amphetamine-type designer drugs: Assessment of addiction potential

This series of studies have been carried out to assess the implication of changes in molecular structure on neurochemical and behavioral effects of design derivatives of amphetamine in the rat.

The finding that the hallucinogenic 4-methyl-2,5-dimethoxyamphetamine (DOM, "STP") does not elevate 5-HT-levels indicates that it acts directly by receptor activation

and not via reuptake inhibition. Similar to amphetamine, 3,4-methylenedioxyamphetamine (MDA) and its methyl derivative 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") act via dopaminergic and 5-HTergic mechanisms involving the inhibition of transmitter reuptake.

4-Methylaminorex is a stimulant drug of abuse that exists in four stereoisomers. Therefore it is an ideal compound for studying the impact of spatial structure on abuse potential and underlying neurochemical effects. The ability of the stereoisomers of 4-methylaminorex to elevate extracellular 5-HT and dopamine levels, as well as to induce motor activation, is strongly associated with the S-configuration of the molecule. The differences in the potencies between the 4-methylaminorex isomers are pharmacodynamic rather than pharmacokinetic in nature.

1-benzylpiperazine is a psychoactive compound increasingly encountered on the clandestine market. It induces place preference in the rat, indicating that the compound possesses rewarding properties, and thus abuse potential. Furthermore, as shown by experiments with dopamine and 5-HT receptor antagonists, both dopaminergic and 5-HTergic neuronal systems are involved in its action. It appears advisable to consider placing 1-benzylpiperazine under statutory control. Indeed, The Council of the European Union and the European Monitoring Center of Drugs and Drug Abuse (EMCDDA) are commencing risk assessment of 1-benzylpiperazine.

Abuse of anabolic steroids

Male power athletes were followed up for months or years during their self-regimen of substance abuse and during withdrawal periods. None of the volunteers were competitive sports athletes subject to doping regulations, and they abused the drugs, which they had obtained from the black market. Medical examinations were carried out in different hospitals and some comparisons were made to endurance athletes screened not to use any doping agents.

Numerous adverse effects are associated with the abuse of anabolic agents. These include e.g. pathological remodelling of the myocardium, electrocardiographic changes such as severe QT dispersion, ventricular tachycardia, transient infertility, and atherogenic changes in lipoprotein profile. Many adverse effects are dose-related. Concomitant use of human growth hormone potentiates the effects of anabolic steroids on cardiac hypertrophy. Regardless of anabolic steroid-induced hypogonadotropic hypogonadism, human chorion gonadotrophic hormone maintains spermatogenesis but semen quality remains impaired.

The mortality of competitive powerlifters suspected to have used anabolic agents was compared with the mortality of population controls. The mortality during the 12-year follow-up was 12.9 % for the powerlifters compared to 3.1 % in the control population. Thus, the risk of death among the powerlifters was 4.6 times higher. These statistically highly significant results give evidence of an association between anabolic steroid abuse and premature death, and support the view that measures to decrease misuse of anabolic agents among both competitive and amateur athletes are justified.

The central effects of anabolic steroids and their interactions with other substances of abuse

The effects of the anabolic androgenic steroids, alone or with other substances of abuse, on dopaminergic and 5-HTergic activities in the brains of rat have been investigated by microdialysis.

Supraphysiological doses of anabolic-androgenic steroids lead to increased synthesis of dopamine and 5-HT in the brain areas that regulate motivation, emotions, reward-related associative learning as well as higher cognitive functions in rats. Sub-chronic treatment with high doses of nandrolone attenuates dose dependently the increase in extracellular dopamine concentration in nucleus accumbens evoked by amphetamine, cocaine or 3,4-methylenedioxymethamphetamine.

7.1.3. The main public health achievements

Knowledge of effects and risks of compounds which are suitable for abuse, and which are actively marketed on the Internet, is essential for educational and informational purposes and it is needed when considering their placing under statutory control.

Results from our studies with abusers of anabolic agents have been utilized when so called doping law was enforced in Finland in 2002, and further, when the law was applied into practice.

7.1.4. Funding for research and public health programs

These subprojects are supported by National Public Health Institute, and in part by the Yrjö Jahnsson Foundation, Helsinki, Finland, Finnish Foundation for Alcohol Stud-

ies, Helsinki, Finland, Ensio Hyvärinen Foundation, Helsinki, Finland, National Institute on Drug Abuse (NIDA), Bethesda, MD, USA, and medical companies.

7.1.5. Personnel

Timo Seppälä, MD, Docent

Esa Meririnne, MD

Aino Kankaanpää, PhD (Pharm)

Sanna Kurling, MSc

7.1.6. Collaboration

Professor Esa R. Korpi, Institute of Biomedicine/Pharmacology, University of Helsinki, Finland

Professor Eero Castren, Neuroscience Center, University of Helsinki, Finland

Professor Urho Kujala, Unit for Sports and Exercise Medicine, Institute of Biomedicine, University of Helsinki

Professor Per Rosenberg, Department of Anesthesia, Helsinki University Central Hospital, Finland

Dr. Tuomo Karila, Department of Orthopaedics and Traumatology, Helsinki University Central Hospital, Finland

Professor Liisa Ahtee, Department of Pharmacy, Division of Pharmacology and Toxicology, University of Helsinki, Finland

Professor Klaus T. Olkkola, Department of Anesthesia, Turku University Central Hospital, Finland

Professor Eija Kalso, Pain Relief Unit, Helsinki University Hospital, Finland

7.1.7. Proposal for future work and expected benefits

Because the recreational use of designer drugs, with changing variety of compounds emerging in the illegal market, continues to be a problem in most western countries, both acute and long-term effects of these drugs need to be studied further.

7.1.8 Main publications

Meririnne E, Kajos M, Kankaanpää A, Seppälä T: Rewarding properties of 1-benzylpiperazine, a new drug of abuse, in rats. *Basic Clin Pharmacol Toxicol.* (2006) Apr;98(4):346-50.

Drug Research Unit, Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki 30, Finland. esa.meririnne@ktl.fi

1-Benzylpiperazine (also known as 'Legal X', 'Legal E', or 'A2') is a psychoactive compound increasingly encountered on the clandestine market. Previous experimental data suggest that the compound possesses addictive properties. In the present study, we used the conditioned place preference method in the rat to test whether 1-benzylpiperazine possesses rewarding properties. Furthermore, the mechanisms of the 1-benzylpiperazine reward were investigated using selected dopamine and serotonin receptor antagonists. 1-Benzylpiperazine (1.25, 5, and 20 mg/kg) induced dose-dependently place preference. This place preference was attenuated by the antagonists SCH23390 (0.2 mg/kg; dopamine D1-like receptors) and MDL72222 (1.0 mg/kg; serotonin₃ receptors), but not by raclopride (0.8 mg/kg; dopamine D2-like receptors) or ketanserin (2 mg/kg; preferentially serotonin₂ receptors). Our results show that 1-benzylpiperazine possesses rewarding properties in the rat, which suggests the compound to be susceptible to human abuse. The brain dopaminergic and serotonergic systems appear to be involved in the 1-benzylpiperazine reward.

Meririnne E, Kajos M, Kankaanpää A, Koistinen M, Kiiänmaa K and Seppälä T Rewarding properties of the stereoisomers of 4-methylaminorex: involvement of the dopamine system. *Pharmacol Biochem Behav* (2005) 81: 715-724.

Drug Research Unit, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki 30, Finland. esa.meririnne@ktl.fi

4-Methylaminorex is a potential psychostimulant drug of abuse that exists as four stereoisomers: cis-4R,5S, cis-4S,5R, trans-4S,5S, and trans-4R,5R. The racemic mixture of the cis-isomers has been encountered in illicit samples, but previous animal studies suggest that also the trans-isomers could have similar stimulant-like properties. We tested whether the stereoisomers possess rewarding properties and compared their potency using the conditioned place preference method in rats. Furthermore, the involvement of the brain dopaminergic system in the 4-methylaminorex reward was tested with the dopamine D1- and D2-receptor antagonists SCH 23390 and raclopride administered systemically, or with the neurotoxin 6-hydroxydopamine injected into the nucleus accumbens. All the four isomers induced place preference, with no apparent differences in their potency. SCH 23390 and raclopride attenuated 4-methylaminorex-induced increase in place preference, and 6-hydroxydopamine also tended to be efficacious. These findings indicate that all the four stereoisomers of 4-methylaminorex possess rewarding properties and thus

abuse potential; the trans-isomers are at least as potent as the cis-isomers. Furthermore, the brain dopaminergic system appears to be involved in the 4-methylaminorex-reward.

Kurling S, Kankaanpää A, Ellermaa S, Karila T, Seppälä T The effect of sub-chronic nandrolone decanoate treatment on dopaminergic and serotonergic neuronal systems in the brains of rats. *Brain Res* (2005) 1044: 67-75.

Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland. sanna.kurling@ktl.fi

Anabolic-androgenic steroids (AASs) are widely abused by adolescents, although persistent AAS use can cause several adverse physical and mental effects, including drug dependence. The first aim of the present study was to study the action of nandrolone decanoate on dopaminergic and serotonergic activities in the brains of rats. In order to evaluate the anabolic or toxic effects of the dosing regimens used, selected peripheral effects were monitored as well. Male Wistar rats were treated for 2 weeks. Injections containing nandrolone (5 and 20 mg/kg, i.m.) or vehicle were given once daily, 5 days a week. The levels of dopamine (DA), 5-hydroxytryptamine (5-HT) and their metabolites were assayed from dissected brain regions 3 days after the last injection. Blood was collected for chemical assays before, after 1 week treatment and at decapitation. Both doses of nandrolone significantly increased the levels of 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of DA in the cerebral cortex, and the higher dose of nandrolone increased the concentrations of 5-HT in the cerebral cortex compared with the vehicle. In addition, after nandrolone treatment, the levels of hemoglobin and erythrocytes increased, and reticulocyte levels decreased. The results suggest that nandrolone at supraphysiological doses, high enough to induce erythropoiesis, induces changes in the dopaminergic and serotonergic neuronal system in the brains of rats. These phenomena may account to some of the observed central stimulatory properties that have been reported following AAS abuse.

Pokela M-L, Anttila E, Seppälä T, Olkkola K: Marked variation in oxycodone pharmacokinetics in infants. *Pediatric Anaesthesia* (2005) 15: 560-565

Department of Paediatrics, University of Oulu, Oulu, Finland.

BACKGROUND: The pharmacokinetics of oxycodone (13-hydroxy-7,8-dihydrocodeinone) has been studied in adults and in children who are older than 6 months but there is no information on the disposition of oxycodone in neonates and young infants. The aim of this study was to study the pharmacokinetics of oxycodone in infants varying in age from 0 to 6 months. **METHODS:** Twenty-two infants undergoing surgery were given postoperatively an intravenous bolus of 0.1 mg.kg(-1) of oxycodone hydrochloride. Ten of the patients were younger than 1 week (group 1), six from 1 week to 2 months (group 2) and six from 2 to 6 months (group 3). Plasma samples were collected for the analysis of oxycodone concentrations up to 24 h. Pharmacokinetics were characterized by noncompartmental methods. **RESULTS:** The median (range) values for the clearance (Cl) were 9.9 (2.3-17.2), 20.1 (3.7-40.4) and 15.4 (14.8-80.2) ml.min(-1).kg(-1) in the above three groups. The values for volume of distribution at steady-state were 3.3 (1.9-4.7), 5.6 (1.3-8.5) and 3.2 (1.8-6.0) l.kg(-1) and for elimination half-life ($t(1/2)$) 4.4 (2.4-14.1), 3.6 (1.6-11.6) and 2.0 (0.8-3.9) h, respectively. Both Cl ($r = 0.46$) and half-life ($r = -0.46$) were correlated to the age of the patient ($P < 0.05$). There were 13 patients who were on mechanical ventilation at the time of oxycodone administration. None of the spontaneously breathing infants had hypoventilation which required assistance during the study. **CONCLUSIONS:** The values for Cl and $t(1/2)$ varied greatly between the subjects. This variability was most pronounced in the two youngest groups. Routine dosing of oxycodone in young infants may be dangerous. The dose of oxycodone must be titrated individually.

Vekovischeva OY, Aitta-aho T, Echenko O, Kankaanpää A, Seppälä T, Honkanen A, Sprengel R, Korpi ER: Reduced aggression in AMPA-type glutamate receptor GluR-A subunit-deficient mice. *Genes, Brain and Behavior* (2004) 3: 253-265.

Institute of Biomedicine/Pharmacology, Biomedicum Helsinki, University of Helsinki, Finland.

The importance of AMPA-type glutamate receptors has been demonstrated in neuronal plasticity and in adaptation to drugs of abuse. We studied the involvement of AMPA receptors in social interaction and anxiety and found that in several paradigms of agonistic behavior naïve male mice deficient for the GluR-A subunit-containing AMPA receptors are less aggressive than wild-type littermates. GluR-A deficient mice and wild-type littermates exhibited similar basic behavior and reflexes as monitored by observational Irwin's test, but they tended to be less anxious in elevated plus-maze and light-dark tests. Maternal aggression or male-female encounters were not affected which suggests that male hormones are involved in the expression of suppressed aggressiveness. However, testosterone levels and brain monoamines can be excluded and found to be similar between GluR-A deficient and wild-type littermates. The reduced AMPA receptor levels caused by the lack of the GluR-A subunit, and measured by a 30% reduction in hippocampal [3H]-S-AMPA binding, seem to be the reason for suppressed male aggressiveness. When we analyzed mice with reduced number of functional AMPA receptors mediated by the genomic introduced GluR-A(Q582R) channel mutation, we observed again male-specific suppressed aggression, providing additional evidence for GluR-A subunit-containing AMPA receptor involvement in aggression.

Meririnne E, Ellermaa S, Kankaanpää A, Bardy A, Seppälä T (2004) Pharmacokinetics and tissue distribution of the stereoisomers of 4-methylaminorex in the rat. *J Pharmacol Exp Ther* 309: 1198-1205.

Drug Research Unit, Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland. esa.meririnne@ktl.fi

4-Methylaminorex, a potential psychostimulant drug of abuse, exists as four stereoisomers: cis-4R,5S, cis-4S,5R, trans-4S,5S, and trans-4R,5R, which were shown previously to possess stereospecific effects. This study characterized their pharmacokinetic and tissue distribution profiles, and metabolic turnover to norephedrine and norpseudoephedrine, in male Wistar rats. The rats received each isomer intravenously, intraperitoneally, or orally, followed by blood sample collection via cannula (pharmacokinetic study), or tissue sample collection at predetermined time points (tissue distribution study). The samples were analyzed for cis- and trans-isomers, and when appropriate for norephedrine and norpseudoephedrine, with gas chromatography/mass spectrometry. Trans-4S,5S-, cis-4R,5S-, and cis-4S,5R-isomers behaved comparably kinetically (volume of distribution 1.7-2.3 l/kg, distribution half-life 3.8-7.0 min, elimination half-life 35-42 min, and bioavailability 32-57% intraperitoneally or 4-16% orally), whereas trans-4R,5R-isomer differed from the others, with a longer elimination half-life (118-169 min) and higher bioavailability (100% intraperitoneally or 83% orally). The highest isomer concentrations were observed in the kidney followed most frequently by the liver, brain, muscle, and last by fat and blood. The elimination half-lives of the stereoisomers from the tissues were generally similar to those in blood. No pharmacologically significant amounts of norephedrine or norpseudoephedrine were detected in blood or the brain. In conclusion, differences between the stereoisomers of 4-methylaminorex in the pharmacokinetics and tissue distribution are described. However, these differences are not compatible with, and thus may not account for, the distinct behavioral and neurochemical effects of the stereoisomers demonstrated previously. Furthermore, metabolic turnover to norephedrine and norpseudoephedrine does not seem to contribute significantly to 4-methylaminorex pharmacology.

Karila TAM, Karjalainen JE, Mäntysaari MJ, ViitasaloMT, Seppälä TA: Anabolic androgenic steroids produce dose-dependent increase in left ventricular mass in power athletes, and this effect is potentiated by concomitant use of growth hormone. *Int J Sport Med* (2003) 24: 337-343

Pärssinen M, Seppälä T: Steroid use and long-term health risks in former athletes. *Sports Med* (2002) 32 (2) :83-94.

laboratory of Substance Abuse, National Public Health Institute, Helsinki, Finland. miia.parssinen@ktl.fi

This article focuses on anabolic steroid adverse effects on the cardiovascular system and mental health issues as well as the possible increase in the incidence of neoplasms in anabolic steroid users. On the basis of findings in the literature, the authors consider these three issues as the most significant concerning morbidity and mortality among anabolic steroid users. A study by Pärssinen et al. (2000) has shown an increased incidence of premature mortality among power lifters. Anabolic steroids and other concomi-

tantly used drugs are the probable cause of this increased mortality, as power training itself does not increase health risks and all types of physical activity promote health.

Kankaanpää A, Ellermaa S, Meririnne E, Hirsjärvi P, Seppälä T (2002) The acute neurochemical and behavioral effects of the stereoisomers of 4-methylaminorex in relation to brain drug concentrations. *J Pharmacol Exp Ther* 300: 450-459.

Drug Research Unit, Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. aino.kankaanpaa@ktl.fi

4-Methylaminorex is a stimulant drug of abuse that exists as four stereoisomers: cis-4R,5S, cis-4S,5R, trans-4S,5S, and trans-4R,5R. These isomers have previously been shown to differ markedly in various respects. In the present study we assessed the effects of the isomers of 4-methylaminorex (2.5, 5.0, and 10 mg/kg i.p.) on extracellular dopamine and 5-hydroxytryptamine (5-HT) levels in the nucleus accumbens, as well as behavior in the rats simultaneously. The relative concentrations of the isomers in the brain were also measured. The samples were collected by *in vivo* microdialysis and then analyzed for neurotransmitters with high-performance liquid chromatography/electrochemical detection and for cis- and trans-4-methylaminorex with gas chromatography/mass spectrometry. The behavioral effects of the isomers were assessed from videotapes recorded during the microdialysis experiments. All isomers elevated the extracellular levels of both dopamine and 5-HT, with the exception of trans-4R,5R. The rank order of potency for elevating dopamine was trans-4S,5S > cis-4S,5R approximately cis-4R,5S > trans-4R,5R, and for elevating 5-HT cis-4S,5R > trans-4S,5S approximately cis-4R,5S > trans-4R,5R. Analysis of the behavioral data, together with the neurochemical data, suggests that behavioral effects of the isomers of 4-methylaminorex are related to drug-induced dopamine release and, in the case of higher doses of the most efficacious isomers, to 5-HT as well. The brain concentrations of the isomers did not reflect their neurochemical efficacy, which implies that their differences are pharmacodynamic rather than pharmacokinetic.

Meririnne E, Kankaanpää A, Seppälä T (2001) Rewarding properties of methylphenidate: sensitization by prior exposure to the drug and effects of dopamine D1- and dopamine D2-receptor antagonists. *J Pharmacol Exp Ther* 298: 539-550.

National Public Health Institute, Department of Mental Health and Alcohol Research, Drug Research Unit, Helsinki, Finland. esa.meririnne@ktl.fi

In drug addiction, a sensitization phenomenon has been postulated to play a critical role. The aim of our study was to evaluate whether sensitization occurs to the rewarding properties of methylphenidate, a psychostimulant drug known to possess abuse potential, as assessed with the biased conditioned place preference method in rats. In addition, since the brain dopaminergic system is considered to be important in drug-reward, the involvement of dopamine D1- and D2-receptors both in the rewarding properties of methylphenidate and in sensitization to these properties was assessed. Conditioning with methylphenidate at doses of 1.25 to 20 mg/kg increased preference for the paired environment, whereas a dose of 0.31 mg/kg was ineffective. However, following the 7-day sensitization treatment with methylphenidate (0.62-20 mg/kg), conditioning with a dose of 0.31 mg/kg resulted in an increased preference for the paired environment, i.e., the rewarding properties of methylphenidate appeared to be sensitized. Control experiments indicated that the enhancement of preference was not due to attenuation of sensitization treatment-induced withdrawal nor to tolerance to aversive properties of methylphenidate. When conditioned with methylphenidate, D1-antagonist SCH 23390 but not D2-antagonist raclopride prevented place preference. However, when coadministered with methylphenidate during the sensitization treatment, both SCH 23390 and raclopride prevented the development of sensitization. These data indicate that the rewarding properties of methylphenidate are sensitized by prior exposure to the drug and that both D1- and D2-receptors, the latter of which possibly more specifically, appear to be involved in the development of this sensitization.

Kankaanpää A, Meririnne E, Ellermaa S, Ariniemi K, Seppälä T (2001) Detection and assay of the stereoisomers of 4-methylaminorex in urine, plasma and tissue samples. *Forensic Sci Int* 121: 57-64.

Research Unit on Substance Abuse, Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland. aino.kankaanpaa@ktl.fi

The 4-methylaminorex (4-MAX) is an amphetamine-related psychostimulant drug that has appeared on the clandestine market with a street name of "U4Euh". This compound exists as four stereoisomers, trans-4R,5R, trans-4S,5S, cis-4R,5S and cis-4S,5R, of which the cis forms have been classified as Schedule I substances in the US. The increasing variety of designer drugs has highlighted the importance of detection, identification, and quantitative measurement of these drugs, including 4-MAX, in biological samples. In the present study, the isomers of 4-MAX were detected in urine of rats treated with the drugs by some but not all of the on-site immunoassays tested, mainly as amphetamine or methamphetamine. To facilitate identification of 4-MAX by laboratories specialized in drug analysis, the electron-ionization mass spectrum and TLC data for underivatized 4-MAX using a routine laboratory drug-screening procedure is provided. In addition, a GC/MS method is described for the quantitative determination of cis- and trans-4-MAX as tert-butyl-dimethylsilyl-derivatives in plasma, urine and tissue.

Pärssinen M, Kujala U, Vartiainen E, Sarna S, Seppälä T: Increased premature mortality of competitive powerlifters suspected to have used anabolic agents. *Int J Sports Med* (2000);21:225-227

National Public Health Institute, Laboratory of Substance Abuse, Helsinki, Finland. miia.parssinen@ktl.fi

Misuse of supraphysiological doses of anabolic steroids is claimed to have serious side effects. The aim of the study was to determine the mortality, and the cause of premature deaths among a group of subjects who are strongly suspected to have used anabolic steroids for a non-medical purpose over several years. The mortality of 62 male powerlifters placed 1st-5th in weight series 82.5-125 kg in Finnish championships during 1977-1982 was compared with the mortality of population controls. The mortality during the 12-year follow-up was 12.9% for the powerlifters compared to 3.1% in the control population. By 1993 eight of 62 powerlifters and 34 of 1094 population controls had died, thus the risk of death among the powerlifters was 4.6 times higher (95% CI 2.04-10.45; $p = 0.0002$). The causes of premature death among the powerlifters were suicide (3), acute myocardial infarction (3), hepatic coma (1) and non-Hodgkin's lymphoma (1). These findings add to the growing amount of evidence of an association between anabolic steroid abuse and premature death, and support the view that measures to decrease AAS misuse among both competitive and amateur athletes are justified.

Korte T, Pykäläinen J, Seppälä T: Drug abuse of Finnish male prisoners in 1995. *For Sci Internat* (1998) 97: 171-183

National Public Health Institute, Helsinki, Finland.

The purpose of the present research was to estimate the extent and variety of abuse of illegal drugs, use and misuse of hypnotics and sedatives and anabolic steroids in the Finnish prison population. The study was undertaken during October-November 1995 at four prisons, three of which were closed institutions and one an open prison; one of the three closed institutions was a juvenile prison. There was a total of 707 inmates in the prisons selected for the study. Questionnaires were given personally to all prisoners in the open prison and in the young prisoners' division in the juvenile prison, but in two large central prisons only some divisions were selected for the study. The questionnaires were completed by 354 prisoners; 75 prisoners refused to respond. A total of 27.7% of subjects reported taking illegal drugs while in their current prison and 70.1% had sometimes used them. Of those who were drug-free before their first imprisonment, 21.7% began using drugs in prison. At present hypnotics and sedatives were reported as in use by 41.8% of subjects, one-third as prescribed drugs and about 10% illicitly. A total of 3.7% of subjects reported taking anabolic steroids in the current prison. Cannabis and amphetamine were the most common illegal drugs reported. Intravenous drug use was reported by 19.2% of the respondents at some point in their lives, and 10.7% of prisoners had injected drugs in their current prison. Use of illegal drugs and misuse of drugs were significantly higher among young prisoners (≤ 25 years of age).

Tallgren M, Olkkola K T, Seppälä T, Höckersted, Lindgren L: Pharmacokinetics and ventilatory effects of oxycodone before and after liver transplantation. *Clin Pharmacol Ther* (1997) 61:655-661.

Department of Anesthesia, Fourth Department of Surgery, Helsinki University Hospital, Finland.

The pharmacokinetics and ventilatory effects of oxycodone were studied in six volunteer patients with end-stage liver cirrhosis before and after orthotopic liver transplantation. Plasma samples and urine were collected for 24 hours after intravenous administration of 0.05 mg/kg oxycodone hydrochloride. Concentrations of oxycodone and its metabolites, noroxycodone and oxymorphone, were measured in plasma and urine. The median elimination half-life of oxycodone was 13.9 hours (range, 4.6 to 24.4 hours) in patients with cirrhosis before transplantation and 3.4 hours (range, 2.6 to 5.1 hours) after transplantation ($p < 0.05$). Correspondingly, oxycodone clearance increased from 0.26 L/min (range, 0.15 to 0.73 L/min) before transplantation to 1.13 L/min (range, 0.71 to 3.98 L/min) after transplantation ($p < 0.05$). Oxycodone depressed ventilation more strongly before transplantation than after transplantation ($p < 0.05$). Care should be exercised when oxycodone is used in patients with end-stage disease.

Kaukonen O, Kinnunen A, Partanen P, Seppälä T, Simpura J, Virtanen A: Estimating the number of amphetamine and opiate users in the greater Helsinki area. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Methodological pilot study of local level prevalence estimates. Lisbon: EMCDDA (1997): pp. 17-36

7.2. Drug dependence

7.2.1. Research and public health significance of the area

The research project started at the beginning of 2005 and includes several subprojects which are presented separately below.

Harm reduction and treatment of amphetamine dependence

Illicit drug use is currently a major national health problem also in Nordic countries. It has been estimated that the amount of problem users in Finland varies between 16,100 - 21,100 subjects. The most widely used illegal drug in Finland is cannabis. The use of hard drugs; e.g. amphetamine and opioids, has increased significantly between 1995 and 1999. Epidemiological studies have clarified the use of amphetamine, methamphetamine, and heroin in the district of Helsinki, and in the whole country. Compared with the situation 2 years earlier (year 1997), illicit drug use had increased by nearly 50% and the latest survey has shown that the number of drug users is no longer increasing in the district of Helsinki but increases are still found in other parts of Finland. Amphetamine use is a major health problem in Sweden, Australia and New Zealand as well. While methadone and buprenorphine have proven highly effective substitute medications for opioid dependence,

no pharmacological treatment has been found for amphetamine dependence. Partial dopamine agonists such as aripiprazole have been considered to be promising medications for addiction since they have been supposed to balance and restore normal function of the mesolimbic dopamine system. Some studies have suggested that oral dextroamphetamine may be used to replace illicit intravenous amphetamine use which proposes that oral methylphenidate might also be used to substitute for intravenous amphetamine use. Thus, the aim of the study was to compare the effectiveness of aripiprazole, methylphenidate and placebo in the treatment of amphetamine dependence using urinalysis as an objective measure of primary outcome.

Detoxification of buprenorphine dependence

Intravenous buprenorphine use in Finland is a major health problem. There have been reports of buprenorphine abuse in many other countries, such as Australia, Bangladesh, France, India and New Zealand. Elsewhere in the European Union the number of buprenorphine misusers is much lower; in the Czech Republic, Denmark, Germany and Sweden buprenorphine misuse is referred to only in informal sources; in the other countries misuse is reported to be extremely rare (close to zero). Majority of all opioid dependent subjects in Finland use i.v. buprenorphine as a primary drug (e.g., in 2004, 93% of opioid dependent patients seeking treatment in Helsinki Deaconess Institute used i.v. buprenorphine and only 6% i.v. heroin.) Although the advent of buprenorphine-naloxone combination (Suboxone) may have reduced this problem, it will not totally eradicate it, since buprenorphine is smuggled in large amounts from France and Baltic countries. The effectiveness of psychosocial treatments in opioid dependence has remained modest. Also pharmacological withdrawal or maintenance treatment of i.v. buprenorphine dependence is problematic, since there are no scientific data available on the efficacy or effectiveness of these treatments. Studies on heroin dependent patients indicate that buprenorphine (duration 1- 2 weeks) is superior to clonidine or methadone in the management of withdrawal, but it is not clear if longer treatment (lasting several weeks) is more efficient than the short one. The purpose of the 3-arm study is to compare the effectiveness of short (9 days) buprenorphine vs. long (25 days) buprenorphine vs. lofexidine treatment (21 days) in the management of i.v. buprenorphine withdrawal. The study will start in August 2007.

Comorbid drug use and other mental disorders

The treatment of mental disorders including the substance use disorders has developed significantly during the recent years. In addition to the randomized clinical trials

there are nowadays practice guidelines (e.g. published by APA), which are based on the scientific literature. Guidelines have been published at least for bipolar disorder, major depressive disorder, panic disorder, schizophrenia, substance use disorders and for borderline personality disorder. In addition, there are publications which include comprehensive treatment approaches for patients with comorbid mental and substance use disorder, but these approaches are mainly based on clinical experience and expert consensus, not so much on clinical efficacy and effectiveness trials. Therefore, there is urgent need to examine which treatments of mental disorders (e.g. mood, anxiety and psychotic disorders) are still effective in patients with comorbid disorders in spite of the presence of substance use disorder. Thus, randomized controlled trials to compare the efficacy and effectiveness between treatments are needed. In spite of the fact that antidepressant drugs are effective for major depression, the results of them cannot be generalized for example to the patient group with comorbid depression and opioid or amphetamine abuse or dependence. Only doxepin and imipramine seem to be effective in this comorbid patients group but for example SSRI drugs seem not to be effective in the treatment of depression in opioid dependent patients. There are to our knowledge only a few studies on the efficacy of the use of antipsychotic drugs to treat comorbid psychosis and substance use disorder. The purpose of the present study, therefore, is to evaluate the effectiveness of different drug treatments of mental disorders in patient group with comorbid mental and substance use disorder.

The prevalence of comorbid depression, anxiety disorders and psychosis in patients with substance use disorders is high. In addition, the prevalence of HIV in patients with intravenous substance use is increased. Therefore, potential harmful interaction between antidepressant, anxiolytics and antipsychotics with illicit drugs and HIV drugs are great. The aim is to study the pharmacokinetic and dynamic interactions of drugs to predict the possible harmful interaction between them. The first study has already been carried out (interaction between diazepam and efavirenz) and the manuscript is in progress.

Modern analytical approaches for drug determination in clinical and forensic toxicology

Abuse of illicit drugs and other psychoactive substances is a global problem. It has been estimated that 5 per cent of the world population (age 15-64) use illicit drugs at least once a year (UNODC 2006). In most of the countries, also in many developing ones, toxicological laboratories are increasingly performing drug analyses for a wide range of purposes ranging from work place drug testing, and drugs and driving cases to clinical purposes, such as therapeutic drug monitoring, emergency toxicology and compliance of patients for medication. Therefore, novel analytical techniques and applica-

tions for drug determination are valuable tools for toxicological laboratories and prerequisites for competent laboratory operation and performance.

Toxicological drug analyses have conventionally been based on chromatographic separation and mass spectrometric detection techniques after appropriate sample preparation in laboratory. Novel analytical strategies for analyte determination, such as fast gas chromatography combined with non-laborious micro-scale volume sample preparation, significantly improves cost-efficiency and rapidity of routinely applicable toxicological analyses. A lack of currently published research data and significant benefits from the fast techniques have opened a possibility to be on the frontline of research globally and improve not only our own laboratory performance, but of many other toxicological laboratories confronting the same challenges.

Another important trend emphasized at research focus, is the increasing role of so-called alternative matrices, such as oral fluid, in toxicological analyses. For example, oral fluid offer easy, supervised and non-invasive sampling with minimal opportunity for sample adulteration or substitution by the person tested. This is beneficial in various areas of drug testing, such as in roadside or workplace drug testing and in many areas of the health care sector.

Identification of club and designer drug use

The expanding market for synthetic amphetamine-type stimulant drugs (ATSs), including amphetamine, methamphetamine, and 3,4-methylenedioxyamphetamine (MDMA, "ecstasy") is currently believed to be one of the world's most severe drug problems. A particular challenge to laboratories performing drug tests is the fact that the ATS market is also changing, partly in response to the efforts of drug control authorities and partly as a result of the dynamics of abuse patterns. This trend is evidenced, for example, by the recent reports of fatalities related to the thus far less common ATSs such as 3,4-methylenedioxyethylamphetamine (MDEA), para-methoxyamphetamine (PMA) and 4-methylthioamphetamine (4-MTA).

Gamma-hydroxybutyrate (GHB) is an increasingly popular drug of abuse that causes stimulation, euphoria, anxiolysis and hypnosis depending on the dose used. Low doses of the drug are used recreationally, and also implicated in drug facilitated sexual assaults (DFSA). Because of the unusually steep dose-response curve, accidental GHB overdosing, leading to coma, seizures or death can occur. Being a controlled substance, GHB is often substituted with its non-scheduled precursors gamma-butyrolactone (GBL) and 1,4-butanediol (BD), which are rapidly metabolized into GHB in the body.

However, the presence of the precursors has also been demonstrated in urine and blood samples in cases of GBL and BD related deaths.

Given that chemical identification of club and designer drugs in biological samples is needed in hospital emergencies, post-mortem examinations, investigations of DFSAs, as well as drugs and driving cases, validated methods for their analyses are essential in every forensic laboratory.

Differentiation between therapeutic use of precursor drugs and abuse of amphetamines

Amphetamine and methamphetamine are widely abused substances that exist in two enantiomers, D- and L-(meth)amphetamine. Determination of enantiomeric composition of positive amphetamine findings may be needed in situations, such as differentiation between the use of prescribed pharmaceutical preparations consisting of one enantiomer only (e.g. Dexedrine (R)), and the use of clandestinely manufactured racemic amphetamine. In addition, there are drugs such as the anti-parkinsonian selegiline, which are metabolized to one enantiomer of amphetamine or methamphetamine, but may lead to false positive drug of abuse finding unless enantiomeric determination is used.

7.2.2. The main scientific achievements

Harm reduction and treatment of amphetamine dependence

The result showed that methylphenidate treatment was associated with statistically significant reduction in intravenous amphetamine use when compared with placebo. It is first controlled evidence of an effective pharmacological treatment for amphetamine dependence. It is likely that methylphenidate should be dispensed mostly on a daily basis under supervision because of its abuse potential. On the contrary, aripiprazole, a partial dopamine agonist, was associated with a higher proportion of amphetamine-positive urine samples than placebo. However, no conclusion can be made on the potential efficacy of aripiprazole in a relapse prevention among detoxified patients.

Modern analytical approaches for drug determination in clinical and forensic toxicology

Novel analytical strategies have been developed for screening, identification and quantification of wide-range of multiple illicit drugs (e.g. Δ^9 -tetrahydrocannabinol, cocaine, amphetamine-type stimulant drugs, opiates) and other psychoactive substances

(e.g. benzodiazepines, hypnotic agents, antidepressants, antipsychotics, antiepileptics) in biological specimens. The most recently published papers are based on unique approaches in toxicological analyses using fast capillary gas chromatography/mass spectrometry (GC/MS). The use of fast GC/MS decrease analyses costs and significantly improve sample throughput, speed and also in some cases reliability of analyses in a comparison to traditionally used conventional GC/MS, which has been considered a golden standard in toxicological analysis.

Scientific papers (Gunnar et al.) based on the applied research work and method development have been published in top-rated publications in the field of biomedical and organoanalytical chemistry. Possibilities of fast chromatographic separation and several applications have also been presented in scientific conferences and a doctoral thesis is under preparation. The method developed for simultaneous quantitative determination of 30 drugs of abuse in oral fluid was awarded as the best young scientist publication in the field of forensic toxicology by the International Association of Forensic Toxicologists (TIAFT) in Seoul, South-Korea 2005.

Identification of club and designer drug use

In the field of applied analytical chemistry, the rapid pretreatment procedure with a single-step extraction-derivatization for analysis of ATSS by gas chromatography - mass spectrometry (GC-MS) is unique. It enables this method to be used, besides of quantitative determination of positive samples, also for preliminary screening of ATSS from a large number of whole blood, serum, oral fluid or urine samples. The use of GC-MS method for preliminary screening would markedly improve the qualitative accuracy of ATS screening by detecting a wider variety of substances and by complying better with the low cut-off values required for drug analyses in blood. The method has been published in a peer reviewed scientific journal (Kankaanpää et al., 2004).

The method developed for simultaneous, quantitative analysis of GHB, GBL and BD in blood and urine samples utilizes a salting-out approach, that has not been described for these compounds. This method was presented in the 44th international meeting of the International Association of Forensic Toxicologists (TIAFT) held in Ljubljana, Slovenia. Manuscript describing the method will be published in a peer reviewed scientific journal (Kankaanpää et al., in press).

7.2.3. The main public health achievements

Harm reduction and treatment of amphetamine dependence

Effective treatment can reduce the medical and social problems related to intravenous use of amphetamine.

Modern analytical approaches for drug determination in clinical and forensic toxicology

The analytical strategies published for determination of various illicit drugs and other psychoactive substances in biological specimens offer more comprehensive, sensitive, cost-efficient and faster analytical approaches for toxicological laboratories serving hospitals, rehabilitation clinics, law enforcement, and other research projects.

Identification of club and designer drug use

The method developed for analysis of ATSSs, as well as the GHB and precursor assay, has widened the selection of club and designer drugs analyzed by the analytical service of the Drug Research Unit. Since their accreditation, both methods have been used for routine analyses in the Drug Research Unit. Improved methods assure more versatile and reliable analysis services that both health care, including rehabilitation of drug addicts, and law enforcement benefit.

Differentiation between therapeutic use of precursor drugs and abuse of amphetamines

Ability to determine the enantiomeric composition of positive amphetamine findings has been essential in several forensic cases in which the patient has claimed to have used prescribed Dexedrine (R). After determination of enantiomeric composition of the positive amphetamine finding, the origin of the amphetamine causing the positive finding can be tracked to medicament vs. clandestinely manufactured amphetamine. Given that amphetamine is one of the most common drugs of abuse in Finland, and also use of prescribed D-amphetamine in treatment of ADHD is increasing, the significance of enantiomeric amphetamine analysis is still increasing.

7.2.4. Funding for research and public health programs

The subprojects Harm reduction and treatment of amphetamine dependence and detoxification of buprenorphine dependence has received funding from the program called *Addiktio* of the Academy of Finland. The funding of the rest of the subprojects is carried out by National Public Health Institute.

7.2.5. Personnel

Kimmo Kuoppasalmi, MD, PhD; Teemu Gunnar, MSc (Chem), BSc (Econ), Aino Kankaanpää, PhD (Pharm), Esa Meririnne, MD, PhD, Saija Turtiainen, MD, Jari Haukka, PhD

7.2.6. Collaboration

Professor Jari Tiihonen, MD, PhD, Department of Forensic Psychiatry, University of Kuopio, Niuvanniemi Hospital

Outi Kuikanmäki, MD, Pekka Tuomola, MD, Jaana Föhr, MD, Substance Abuse, Welfare Work and Mental Health Care, Helsinki Diaconess Institute

Helena Vormaa, MD, PhD, Heikki Katila MD, PhD, Department of Psychiatry, Institute of Clinical Medicine, Faculty of Medicine, University of Helsinki and Helsinki University Hospital, Department of Psychiatry

Matti Ristola, MD, PhD, Asko Järvinen, MD, PhD Department of Medicine, Division of Infectious Diseases, Helsinki University Hospital

Professor Erkki Vuori, MD, PhD, Department of Forensic Medicine, Faculty of Medicine, University of Helsinki

Professor Aarno Palotie, MD, PhD, Biomedicum Helsinki, Research Program in Molecular Medicine, University of Helsinki

Professor Raimo Salokangas, MD, PhD, Antti Mikkonen, MD, Mika Kallio MD, Turku University Hospital, Department of Psychiatry

7.2.7. Proposal for future work and expected benefits

Harm reduction and treatment of amphetamine dependence

The study needs to be continued as a comparison between methylphenidate and placebo to certify the effectiveness of methylphenidate in a larger patient population with higher statistical power.

Comorbid drug use and mental disorders

There is only scanty information on the treatment of comorbid depression and psychosis. The study will give new information to treatments of comorbid disorders.

Modern analytical approaches for drug determination in clinical and forensic toxicology

Rapid, cost-efficient and reliable multianalyte procedures for drug determination are vital for various toxicological laboratories confronting increasing amount of analysis requests, need for resource optimization and rising number of drugs to be tested. These challenges can be tackled by developing innovative analytical methodologies and applications, which finally serve the customers of laboratory services, e.g., in health care and law enforcement. Alternative biological specimens and especially oral fluid, has the potential to replace/supplement conventionally matrices (whole blood and urine) and ease drug testing procedure in many areas of clinical and forensic toxicology. Expertise from drug analysis in biological specimens are planned to be utilized in highly sensitive analysis of drugs of abuse in wastewater collected from sewage treatment plant. This will allow, e.g., epidemiological studies and a long-term approach to study drug use in general population in unique and representative manner.

Identification of club and designer drug use

In order to continue to be able to provide versatile and reliable analysis services in the future, it is essential to continuously monitor the changing abuse patterns, and to develop methods that are able to identify a wide range of novel drugs of abuse. This work will benefit both law enforcement and health care authorities.

7.2.8 Main publications

Gunnar T, Engblom C, Ariniemi K, Pressure-adjusted continual flow heart-cutting for the high throughput determination of amphetamine-type stimulant drugs in whole blood by fast multidimensional gas chromatography-mass spectrometry, *J. Chromatogr. A*; (2007), in press.

National Public Health Institute, Drug Research Unit, Mannerheimintie 166, 00300 Helsinki, Finland. teemu.gunnar@ktl.fi

Innovative features and technical improvements in modern bench-top quadrupole gas chromatograph-mass spectrometer (GC-MS) have prepared the way for faster and more cost-effective applications while still maintaining sufficient chromatographic resolution, speed of MS data acquisition and reliability of analytical methodology. In this paper, a short wide-bore capillary column with low film thickness (5 m x 0.32 mm i.d., 0.1 µm) was used as a pre-fractionating column and only chosen heart-cuts were transferred to the second chromatographic dimension (15 m x 0.25 mm i.d., 0.25 µm) by means of a pressure-adjusted continual flow type switching device for quantification of five common amphetamine-type stimulant drugs. The instrumental setting used, in combination with carefully optimized operational fast GC and MS parameters, markedly decreased the retention times of the targeted analytes, e.g. amphetamine 0.891 min and methamphetamine 1.037 min, and the total chromatographic runtime (1.700 min), as well as reducing the need for continuous cleaning of the MS ion source and increasing column life compared with conventional GC-MS approaches. The performance of the instrumental configuration and analytical method was evaluated in validation experiments and the method was also applied to authentic samples. The method demonstrates the potential of fast GC-MS in combination with a gas-phase microfluidic Deans switch device for analysing of (semi)volatile compounds, such as amphetamine-type stimulant (ATS) drugs. This should be particularly useful in modern laboratories aiming at cost-efficient analysis as well as the optimum use of available laboratory capacity and instrumentation.

Kankaanpää A, Liukkonen R, Ariniemi K (in press) Determination of gammahydroxybutyrate (GHB) and its precursors in blood and urine samples: a salting-out approach. *Forensic Sci Int*.

Drug Research Unit, Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, Helsinki, Finland. aino.kankaanpaa@ktl.fi <aino.kankaanpaa@ktl.fi>

Gamma-hydroxybutyrate (GHB) is an increasingly popular drug of abuse that causes stimulation, euphoria, anxiolysis or hypnosis, depending on the dose used. Low doses of the drug are used recreationally, and also implicated in drug-facilitated sexual assaults. Because of the unusually steep dose-response curves, accidental GHB overdosing, leading to coma, seizures or death can occur. Being a controlled substance, GHB is often substituted with its non-scheduled precursors gamma-butyrolactone (GBL) and 1,4-butanediol (BD), which are rapidly metabolized into GHB in the body. Here we describe an assay for GHB, GBL and BD in blood and/or urine samples. GHB and BD were extracted from diluted 200 µL aliquots of samples with t-butylmethylether (plus internal standard benzyl alcohol) in test tubes preloaded with NaCl. After acidification and centrifugation the solvent phase was transferred to a test tube preloaded with Na₂SO₄, incubated for 30 min, centrifuged again, and evaporated in vacuum. The residue was mixed with N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA) in acetonitrile, and injected into a GC-MS. When analyzing GBL, the salting-out step was omitted, and analysis was performed with a GC-FID apparatus. As revealed by the validation data this procedure is suitable for quantitative determination of GHB and its precursors in blood and/or urine samples.

Tiihonen J, Kuoppasalmi K, Föhr J, Tuomola P, Kuikanmäki O, Vormaa H, Sokero P, Haukka J, Merilinen E: A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry* 2007;164:160-2.

Department of Forensic Psychiatry, University of Kuopio, and the Department of Psychiatry, Helsinki University Hospital, Finland. jari.tiihonen@niuva.fi

OBJECTIVE: Problems related to illegal amphetamine use have become a major public health issue in many developed countries. To date, evidence on the effectiveness of psychosocial treatments has remained modest, and no pharmacotherapy has proven effective for amphetamine dependence. **METHOD:** Individuals meeting DSM-IV criteria for intravenous amphetamine dependence (N=53) were randomly assigned to receive aripiprazole (15 mg/day), slow-release methylphenidate (54 mg/day), or placebo for 20 weeks. The study was terminated prematurely due to unexpected results of interim analysis. An intention-to-treat analysis was used. The primary outcome measure was the proportion of amphetamine-positive urine samples. **RESULTS:** Patients allocated to aripiprazole had significantly more amphetamine-positive urine samples than patients in the placebo group (odds ratio=3.77, 95% CI=1.55-9.18), whereas patients who received methylphenidate had significantly fewer amphetamine-positive urine samples than patients who had received placebo (odds ratio=0.46, 95% CI=0.26-0.81). **CONCLUSIONS:** Methylphenidate is an effective treatment for reducing intravenous drug use in patients with severe amphetamine dependence.

Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Harkanen T, Koskinen S, Lönnqvist J: Lifetime prevalence, of psychotic and bipolar I disorder in a general population. *Arch Gen Psychiatry* 2007;64:19-28.

Department of Mental Health and Alcohol Research, National Public Health Institute, University of Helsinki, Mannerheimintie 166, 03000 Helsinki, Finland. jonna.perala@ktl.fi

CONTEXT: Recent general population surveys of psychotic disorders have found low lifetime prevalences. However, this may be owing to methodological problems. Few studies have reported the prevalences of all specific psychotic disorders. **OBJECTIVE:** To provide reliable estimates of the lifetime prevalences of specific psychotic disorders. **DESIGN:** General population survey. **SETTING AND PARTICIPANTS:** A nationally representative sample of 8028 persons 30 years or older was screened for psychotic and bipolar I disorders using the Composite International Diagnostic Interview, self-reported diagnoses, medical examination, and national registers. Those selected by the screens were then re-interviewed with the Structured Clinical Interview for DSM-IV. Best-estimate DSM-IV diagnoses were formed by combining the interview and case note data. Register diagnoses were used to estimate the effect of the nonresponders. **MAIN OUTCOME MEASURES:** Diagnosis of any psychotic or bipolar I disorder according to the DSM-IV criteria. **RESULTS:** The lifetime prevalence of all psychotic disorders was 3.06% and rose to 3.48% when register diagnoses of the nonresponder group were included. Lifetime prevalences were as follows: 0.87% for schizophrenia, 0.32% for schizoaffective disorder, 0.07% for schizophreniform disorder, 0.18% for delusional disorder, 0.24% for bipolar I disorder, 0.35% for major depressive disorder with psychotic features, 0.42% for substance-induced psychotic disorders, and 0.21% for psychotic disorders due to a general medical condition. The National Hospital Discharge Register was the most reliable of the screens ($\kappa = 0.80$). Case notes supplementing the interviews were essential for specific diagnoses of psychotic disorders. **CONCLUSIONS:** Multiple sources of information are essential for accurate estimation of lifetime prevalences of psychotic disorders. The use of comprehensive methods reveals that their lifetime prevalence exceeds 3%.

Gunnar T, Ariniemi K, Lillsunde P, Fast gas chromatography-negative-ion chemical ionization mass spectrometry with micro-scale volume sample preparation for the determination of benzodiazepines and β -hydroxy metabolites, zaleplon and zopiclone in whole blood, *J Mass Spectrom*, 2006; 41: 741-754.

National Public Health Institute, Drug Research Unit, Mannerheimintie 166, 00300 Helsinki, Finland. teemu.gunnar@ktl.fi

Fast gas chromatography/negative-ion chemical ionization mass spectrometric (GC/NICI-MS) assay combined with rapid and nonlaborious sample preparation is presented for the simultaneous determination of benzodiazepines and alpha-hydroxy metabolites, zaleplon and zopiclone in whole blood. The compounds were extracted from 100 microl of whole blood by simultaneous multitube, microscale liquid-liquid extraction (LLE) and derivatized by N-methyl-N-(tert-butyldimethylsilyl)trifluoroacetamide (MTBSTFA), without the need for the time-consuming concentration stage. In the analytical separation, various parameters of fast GC/NICI-MS were applied, e.g. the use of hydrogen as a GC carrier gas, a high carrier gas velocity, a small film thickness of the analytical column, fast MS data acquisition, fast temperature ramping, and high initial and final temperatures of GC column. Sensitive identification, screening and quantitation of 18 compounds of interest were achieved in chromatographic separation in only 4.40 min. Accurate and reproducible results were obtained by using five different and carefully selected deuterated analogues on the basis of the chemical properties of the target analytes. Nevertheless, for alpha-OH-midazolam, and for bromazepam and flunitrazepam at low concentrations, the results can be considered only semiquantitative on the basis of the validation data. The extraction efficiencies ranged from 74.3 to 105.7% and the limits of quantitation (LOQ) from 1 to 100 ng mL⁻¹. Rapid sample preparation and fast chromatographic separation allowed cost-efficient, reliable and high sample-throughput analyses with a low amount of manual work. The method was fully validated and accredited according to EN ISO/IEC 17025 standards and is applicable for sensitive, reliable and quantitative determination of benzodiazepines, zaleplon and zopiclone, e.g. in clinical and forensic toxicology. Copyright (c) 2006 John Wiley & Sons, Ltd.

Gunnar T, Eskola T, Lillsunde P, Fast Gas Chromatography-Mass Spectrometric Determination of Methadone and the Primary Metabolite EDDP in Whole Blood, *Rapid Commun Mass Sp*, 2006; 20: 673-9.

National Public Health Institute, Drug Research Unit, Mannerheimintie 166, 00300 Helsinki, Finland. teemu.gunnar@ktl.fi

A toxicological analysis was developed and validated for simultaneous screening and quantification of methadone (METH) and its primary metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). The method employs microscale liquid-liquid extraction (microLLE) and direct injection of a separated aliquot of the organic layer into a gas chromatography/mass spectrometric (GC/MS) system without any other pre-treatment stages. A fast GC/MS runtime (total 5.8 min; METH, Rt = 3.55 min; EDDP, Rt = 3.40 min) combined with rapid sample preparation allowed cost-efficient and routinely applicable performance with a low amount of manual work. The validated parameters included: linearity (25-1000 ng mL⁻¹) both; R(METH)² = 0.998 and R(EDDP)² = 0.997, accuracy (Bias(METH): from -0.05 to 11.3%, Bias(EDDP): from 1.11 to 4.37%); intra and inter-assay precision (RSD(METH): from 2.4 to 3.9%, from 4.89 to 10.3%; RSD(EDDP): from 4.50 to 6.20%, from 4.57 to 15.2%), extraction efficiency (METH = 95.5%; EDDP = 90.6%), LOQ(Meth,EDDP) = 25 ng mL⁻¹. Samples were stable for at least 25 h and no selectivity problems or baseline interference were observed. The method should be applicable for identifying and quantitative confirmation of possible misuse and/or illegal use of METH in toxicological cases. Copyright 2006 John Wiley & Sons, Ltd.

Gunnar T, Ariniemi K, Lillsunde P, Validated toxicological determination of 30 drugs of abuse as optimized derivatives in oral fluid by long column fast gas chromatography/electron impact mass spectrometry, *J Mass Spectrom* 2005; 40: 739-753.

National Public Health Institute, Drug Research Unit, Mannerheimintie 166, 00300 Helsinki, Finland. teemu.gunnar@ktl.fi

An analytical procedure was developed for the simultaneous sensitive identification, screening and quantitation of 30 drugs of abuse using 250 microl of human oral fluid. The method employs sequential mixed-mode solid-phase extraction (SPE), optimized derivative formation and long-column fast gas chromatography/electron impact mass spectrometry (GC/EI-MS). After sequential SPE elution, the most sensitive and stable derivatives were formed by taking careful account of the characteristics of the active functional groups and possible steric hindrances affecting derivatization chemistry. Amphetamine-type stimulant drugs were acylated with heptafluorobutyric anhydride, benzodiazepines and Delta(9)(tert-

butyldimethylsilyl)trifluoroacetamide and benzoylecgonine, codeine, ethylmorphine, 6-monoacetylmorphine, morphine, pholcodine, buprenorphine and norbuprenorphine with N-methyl-N-(trimethylsilyl)trifluoroacetamide. In addition, the following analytes were included: methadone, cocaine, alprazolam, midazolam, fentanyl and zolpidem. In GC separation, fast temperature ramping and high carrier gas flow-rate combined with long 30 m columns of i.d. 0.32 mm offered a reduction in analysis time and sharp peak shapes while still maintaining sufficient resolution and high sample capacity. Validated parameters including selectivity, linearity, accuracy, intra- and inter-day precision, extraction efficiency and limit of quantitation were all within required limits. In contrast to previously published methods, this single procedure is suitable for the simultaneous toxicological determination of the most common illicit drugs and benzodiazepines, and also zolpidem, in a small amount of oral fluid.

Kankaanpää A, Gunnar T, Ariniemi K, Lillsunde P, Mykkänen S, Seppälä T: A single-step procedure for gas-chromatography-mass spectrometry screening and quantitative determination of amphetamine-type stimulants and related drugs in blood, serum, oral fluid and urine samples. *J Chromatogr B* 2004;810: 57-68.

Drug Research Unit and Laboratory of Substance Abuse, Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland. aino.kankaanpaa@ktl.fi

We describe a rapid GC/MS assay for amphetamine-type stimulant drugs (ATs) and structurally related common medicaments in blood, serum, oral fluid and urine samples. The drugs were extracted from their matrices and derivatized with heptafluorobutyric anhydride (HFBA) in a single step, using the following procedure: 100 microl (oral fluid) or 200 microl (blood, serum, urine) of the sample were mixed with 50 microl of alkaline buffer and 500 microl of extraction-derivatization reagent (toluene + HFBA + internal standard), centrifuged, and injected into a GC/MS apparatus. As revealed by the validation data this procedure, with its limit of quantitation being set at 20 ng/ml for oral fluid, 25 ng/ml for blood or 200 ng/ml for urine, is suitable for screening, identification and quantitative determination of the ATs and related drugs in all the matrices examined. Thus, time-consuming and expensive multiple analyses are not needed, unless specifically required.

Vorma H, Naukkarinen H, Sarna S, Kuoppasalmi K: Long-term outcome after benzodiazepine withdrawal treatment in subjects with complicated dependence. *Drug Alcohol Depend* 2003; 70:309-14.

A-clinic Foundation, Helsinki, Finland. helena.vorma@hus.fi

BACKGROUND: The study aimed to monitor subjects with benzodiazepine (BZ) dependence after withdrawal treatment in order to evaluate long-term outcome and predictors of remaining BZ-free. Subjects with high-dose dependence or co-occurring alcohol problems were not excluded. **METHOD:** Seventy-six participants in an earlier, randomized, controlled trial of outpatient BZ discontinuation were interviewed, and documents from their treatment settings obtained, along with urine and serum samples for BZ use. Long-term outcomes for a cognitive-behavioral treatment group and a treatment-as-usual group were measured. **RESULTS:** BZ discontinuation treatment outcomes were maintained in both treatment groups. No between-group differences were found. At the end of the study 25% of the subjects were BZ-free, and the median dose decrease from pre-treatment levels was 16.1 mg in diazepam equivalents. Subjects with pre-treatment doses exceeding 40 mg were able to maintain their doses at therapeutic levels through the follow-up. Pre-treatment low BZ dose, no previous withdrawal attempts, and high life satisfaction predicted success in staying BZ-free. **CONCLUSIONS:** In subjects with complicated BZ dependence, the benefits of BZ discontinuation treatment may persist, but more studies are needed.

Vorma H, Naukkarinen H, Sarna S, Kuoppasalmi K: Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. *Addiction* 2002;97:851-9.

A-Clinic Foundation, Helsinki, Finland. helena.vorma@ktl.fi

AIMS: To evaluate whether gradual benzodiazepine taper combined with cognitive-behavioural treatment is more effective than standard treatment for patients with dependence in out-patient clinics. **DESIGN:** A randomized, controlled clinical trial, using standard questionnaires and serum and urine tests. **SETTINGS:** Four public-sector out-patient clinics for alcohol and drug abusers in Helsinki. **PARTICIPANTS:** Seventy-six patients with benzodiazepine dependence (DSM-III-R). Patients taking high doses of the drug or with alcohol use disorders were included to obtain a subject group representative of usual clinical practice. **INTERVENTION:** Subjects received gradual benzodiazepine taper combined with cognitive-behavioural therapy (experimental group) or standard withdrawal treatment not scheduled by the researchers (control group). **MEASUREMENTS:** The outcome was measured in terms of attaining a state of abstinence or by a decrease in the dosage during the study period of up to 12 months' duration. **FINDINGS:** No statistically significant differences in the outcomes were observed between the groups. A total of 13% of the experimental group and 27% of the control group were able to discontinue drug use. In addition 67% of the experimental group and 57% of the control group were able to decrease the dose. **CONCLUSIONS:** The search continues for improved methods of helping patients with complicated benzodiazepine dependence.

Heikman P, Kalska H, Katila H, Sarna S, Tuunainen A, Kuoppasalmi K: Right unilateral and bifrontal electroconvulsive therapy in the treatment of depression: a preliminary study. *J ECT* 2002; 18:26-30.

Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland. pertti.heikman@hus.fi

The short-term outcome of electroconvulsive therapy (ECT) was studied in 24 patients with a current major depressive episode (DSM-IV). Patients were randomized to high dose (400% above the seizure threshold) right unilateral (RUL) ECT, to moderate dose (150% above seizure threshold) RUL ECT, and to low dose (just above seizure threshold) bifrontal (BF) ECT. Primary outcome measures included number of treatments, Hamilton Depression Rating Scale score, and Mini-Mental State Examination score. High dose RUL ECT was associated with a significantly faster response to treatment than low dose BF ECT. Moreover, there was a tendency to a higher response rate with high dose RUL ECT compared with either moderate dose RUL ECT or BF ECT.

Heikman P, Katila H, Sarna S, Wahlbeck K, Kuoppasalmi K: Differential response to right unilateral ECT in depressed patients: impact of comorbidity and severity of illness. *BMC Psychiatry* 2002;2:2.

Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland. pertti.heikman@hus.fi

BACKGROUND: Recent electroconvulsive therapy (ECT) efficacy studies of right unilateral (RUL) ECT may not apply to real life clinics with a wide range of patients with major depressive episodes. **METHODS:** The study included two groups of patients. In addition to a homogeneous group of patients with major depression according to DSM-IV criteria with severity of the major depressive episode > 16 scores on 17-item Hamilton Rating Scale for Depression (HDRS) (Group 1, n = 16), we included a heterogeneous group of patients with less severe major depressive episodes or with a variety of comorbid conditions (Group 2, n = 24). We randomly assigned the patients to an RUL ECT treatment dosed at 5 or 2.5 times seizure threshold with an intent-to-treat design. The outcomes measured blindly were HDRS, number of treatments, and Mini-Mental State Examination (MMSE). The patients were considered to have responded to treatment if the improvement in HDRS score was at least 60% and they had a total score of less than ten. **RESULTS:** The Group 2 patients responded poorer (8% vs. 63%), and had more often simultaneous worsening in their MMSE scores than Group 1 patients. The differences in the outcomes between the two different doses of RUL ECT treatment were not statistically significant. **CONCLUSIONS:** ECT effectiveness seems to be lower in real-life heterogeneous patient groups than in homogeneous patient samples used in experimental efficacy trials.

Heikman P, Salmelin R, Mäkelä J, Hari R, Katila H, Kuoppasalmi K: Relation between frontal 3-7 Hz MEG activity and the efficacy of ECT in major depression. *J ECT* 2001;17:136-40.

Department of Psychiatry, Helsinki University Central Hospital, Finland. pertti.heikman@hus.fi

The efficacy of electroconvulsive therapy (ECT) in major depression has been linked to the accentuation of postconvulsive prefrontal electroencephalography slow-wave activity. We investigated the change in slow-wave activity (0.5-7 Hz) using whole-scalp magnetoencephalographic (MEG) recordings. The 3-7 Hz (theta) activity increased in the right frontal and occipital regions during the course of treatment. After four treatments, the increase of the theta activity in the left frontal cortex correlated with the efficacy of the ECT treatment. Moreover, the change of the ratio of left and right frontal theta activity to occipital theta activity had a positive correlation with the therapeutic effect. These findings suggest that an efficient ECT treatment increases MEG theta activity in the frontal cortex.

Heinäälä P, Alho H, Kiianmaa K, Lönnqvist J, Kuoppasalmi K, Sinclair JD: Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo controlled trial. *J Clin Psychopharmacol* 2001;21:287-92.

National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland.

Several studies have shown the opioid antagonist naltrexone to be effective when combined with psychosocial therapies for the treatment of patients who are dependent on alcohol with fixed medication and time (12 weeks). In this study, 121 nonabstinent outpatients with alcohol dependence (DSM-IV) were treated with sessions of cognitive coping skills (N = 67) or supportive therapy (N = 54) and either naltrexone 50 mg/day (N = 63) or placebo (N = 58) daily for the first 12 weeks and thereafter for 20 weeks only when craving alcohol (i.e., targeted medication) in a prospective one-center, dual, double-blind, randomized clinical trial. The dropout rate for all subjects was 16.5% during the first 12-week period and approximately twice that level by the end of the study. There were no significant group differences in study completion and therapy participation rates. After the continuous medication (12 weeks), the coping/naltrexone group had the best outcome, and coping/placebo had the worst. This difference remained during the targeted medication period (the following 20 weeks). Naltrexone was not better than placebo in the supportive groups, but it had a significant effect in the coping groups: 27% of the coping/naltrexone patients had no relapses to heavy drinking throughout the 32 weeks, compared with only 3% of the coping/placebo patients. The authors' data confirm the original finding of the efficacy of naltrexone in conjunction with coping skills therapy. In addition, their data show that detoxification is not required and that targeted medication taken only when craving occurs is effective in maintaining the reduction in heavy drinking.

Heikman P, Tuunainen A, Kuoppasalmi K: Value of the initial stimulus dose in right unilateral and bifrontal electroconvulsive therapy. *Psychol Med* 1999;29:1417-23.

Department of Psychiatry, Helsinki University Central Hospital and KTL, National Public Health Institute, Finland.

BACKGROUND: The outcome of electroconvulsive therapy (ECT) is affected by the placement and dose of the stimulus. In general, the ECT dose can be selected either by the dose-titration method (on which the measured seizure threshold level is based), or the method of predetermined dose (e.g. the age-based dosing and the fixed high dose method). **METHODS:** Seizure thresholds were measured in 50 patients with right unilateral (RUL) and in 30 patients with experimental bifrontal (BF) ECT stimulus. The ECT dose (mC) of the age-based dosing was calculated by multiplying the age (years) by 5.0 (age method) or 2.5 (half-age method). The fixed high dose was set to 378 mC. **RESULTS:** The seizure thresholds had only a moderate correlation with the age of the patients. The methods based on the predetermined dose would have led us to give patients with the lowest seizure thresholds in the RUL ECT group very high stimulus doses, up to 12 (age method) or 15 (fixed high dose method) times the individual seizure threshold. In contrast, the RUL ECT patients with the highest seizure thresholds would have received low stimulus doses down to 1.5 times (half-age method) the initial seizure threshold. In the BF ECT group the age based dose would have been similarly dependent on the initial seizure threshold level. **CONCLUSION:** The use of the dose-titration method is recommended, because it is the only method that allows for the individual selection of ECT stimulus dose relative to the seizure threshold.

7.3. Drugs and Driving

Alcohol, Drugs and Driving

The business idea of the Drugs and Driving Project is to study driving under the influence of alcohol and other psychoactive substances, to reinforce preventive work for reducing the number of traffic accidents, to develop testing methods for police use on the road and for the laboratory in order to recognize and identify drug use. Development of on-site methods and oral fluid testing may be useful e.g. in monitoring pain killers/opioid concentrations in cancer patients. Applicability of innovations will thus be tested in other areas, too. Former projects have benefited the Service Laboratory as well. Expertise has been given to the community e.g. in the mode of developing best practices in police work for recognizing external symptoms of drug use in order to take drug drivers off the roads (Training book: Huumeet ja Liikenne, 2003; instructions and orders of Ministry of Interiors: "Breath and saliva Testing on the road", "Drug dependence and driving permission", "Drug Use Control in road traffic / Field Sobriety Observation"), intervention practices for drunken drivers (Päihderiippuvuuden arviointi ja ajokelpoisuus, 1998, opas lääkäreille), legislation initiatives and work for law proposals for drugs and driving (Zero-tolerance law for illicit drugs and driving, 2003) (resulting Traffic Safety Award 2007) as well as best practices and work for legislation and decree for work place drug testing (Asetus huumausainetestien tekemisestä 218/2005; Huumausainetestaus työelämässä, 2006).

The Drugs and Driving project is lead by Dr. Pirjo Lillsunde. The project started in the beginning of 2007. The work leading to the start of this project is originating from a long and thorough expertise in the field as head of the former drug testing laboratory and as a ministerial expert in drug policy and in traffic policy. The objectives of the project are to provide information for drug- and traffic policy in order to prevent harm associated to drug and alcohol use, especially in road traffic.

The four on-going studies of the project funded by external funds are an EU-project Driving under the Influence of Alcohol, Drugs and Medicines (DRUID), The life course of DUI offenders (RATTI /Finnish Academy), Monitoring of opioid levels in plasma and oral fluid in cancer patients (HUS) and a developing project for opioid on-site tests (VTT/TEKES). The DRUID-project is a Integrated Project funded by the European Commission within the 6th framework programme. The DRUID- and (Life course of DUI offenders) Ratti-projects will last four years until 2010. The fifth important area is

work place drug testing, especially in establishing best practices in that area. Work Place testing practices (decree etc.) were prepared under Ministry of Social Affairs and Health and the Institute of collaboration

7.3.1. Research and public health significance of the area

One fourth of all fatal traffic accident victims were killed in drink driving accidents during the last few years in Finland. Driving under the influence of alcohol and/or drugs is often associated with alcohol, social, economical, medical, criminal and other problems. Mortality from accidents, suicides and homicides was found to be significantly higher among drunken drivers than in the general population. There is evidence that drug users are more prone to high risk behaviour than the general population. The zero tolerance law for drugs and driving has sharply increased the number of prosecuted drugs and driving cases. Between 1972-1994, approximately half of the Finnish drunken drivers were problem drinkers and 2/3 were recidivists.

Harmful effects of alcohol are one of the major health and social problems in Finland. They are intended to be reduced by means of different activities laid down in the Alcohol Program (Ministry of Social Affairs and Health 2004). One of the most efficient means in reducing harmful effects of alcohol is to prevent drunk driving. The traffic Safety Action Plan for the years 2006-2010 includes measures to be taken in order to prevent DUI. Its proposals are reducing legal limit from 0.5 o/oo to 0.2 o/oo and the use of alcolock as prevention (Ministry of Traffic and Communication, 2005). In addition, the growth of social exclusion is considered to be a major social problem and the greatest challenge to improving internal security (Ministry of the Interior 2004). The number of people living on the margin of society may increase and cause serious personal, health, social, and economic problems. Still today, people slide into a criminal way of life mainly because they feel excluded from society. Supporting young people by early intervention and encouraging their integration into society are important means in prevention of social exclusion. Driving license ownership is a marked symbol of independent and integrated citizenship, which impaired driving will jeopardize. The knowledge of the factors that lead to DUI is poor. Moreover, little is known about the past, present and future life course of the DUI offenders. New knowledge is needed in decision making for health policy and traffic policy actions e.g. planning and implementing prevention, intervention and treatment programs.

DRUID

DRUID deals with the scourge of drink-and-drug-driving and is intended to find answers to questions concerning the use of drugs or medicines that affect people's ability to drive safely. It will bring together the most experienced organisations and researchers throughout Europe, involving about 20 European countries. The aim is to gain new insights to the real degree of impairment caused by psychoactive drugs and their actual impact on road safety. All in all this Integrated Project will fill the gaps of knowledge and provide a solid base to generate harmonised, EU-wide regulations for driving under the influence of alcohol, drugs and medicine.

The main emphasis in KTL will be to assess the prevalence of alcohol and other psychoactive substances in drivers in general traffic and drivers involved in injury accidents, to calculate the accident risk for drug impaired drivers and to identify characteristics of drug impaired drivers. Equipment and skills to recognize drug users in traffic will be further developed. The work will serve as a basis to gain more knowledge in the field to aid the prevention and legislation actions.

The life course of DUI offenders

The main questions of this study are: 1) what are the factors that lead to driving under influence of alcohol and/or drugs? 2) what happens to the DUI offenders during their subsequent life span in terms of health and social position? 3) what kind of preventive conclusions can be drawn?

The study employs the register data of suspected driving under the influence of alcohol and/or drug cases. Data include all suspected DUI-drivers since 1988 in Finland, about 20.000 persons per year. The basic data will be complemented by linking data from other Finnish registers following privacy protection, data security and ethical rules. In this follow-up study the history of criminality, movement, employment periods, marital status, hospital inpatient treatment etc. before the indexed DUI can be investigated retrospectively, too. The site of the research is the Department of Mental Health and Alcohol Research in National Public Health Institute.

The results will improve the scientific understanding of DUI behavior, the impact of changes in laws and different policies on DUI behavior, and, the association of DUI episodes to the process of social exclusion, and to inequalities in health and mortality.

The new knowledge is needed in decision making for health policy and traffic policy actions e.g. planning and implementing prevention, intervention and treatment programs. This study will identify entry points for relevant policies and interventions.

The project is funded by the the Finnish Academy. Dr Aini Ostamo is the responsible researcher and she is supervising two Ph.D. students in this project.

Monitoring of opioid levels in plasma and oral fluid

This study consists of two sub projects. The aim of the collaboration study with the Helsinki University Hospital Pain Clinic is to survey opioid concentrations in cancer patients' plasma and oral fluid. Absorption and the usability of different administration routes can be evaluated according to the plasma drug concentrations and to plan the drug administration/dosages to correspond the needs of the patient. Opioid levels in oral fluid and plasma are compared. The aim is to find out whether oral fluid could be used for monitoring opioid concentrations in cancer patients. It would open the possibility for on-site testing by cancer patient at home. Therefore this project is connected to another project with VTT Research center. VTT has developed a specific on-site test for detecting morphine (later other substances). The results of VTT on site test and laboratory GC/MS tests will be compared.

Although this is not a traffic project, this subproject gives added value to the traffic projects because of the technology used. The knowledge gained and methods developed in this sub project can be used in traffic projects as well as in drug testing generally.

Work Place Drug Testing

A follow-up study on work place drug testing will be done in 2007-2008 in collaboration with Institute of Occupational Health and with the Ministry of Social Affairs and Health. The aim is to investigate experiences and the extent that work place drug is done in the Finnish Society. Also the effect of the new legislation is studied.

7.3.2. The main scientific achievements

Success in seeking external funds has resulted in establishing the 'Päihteet ja liikenne' /Alcohol, Drugs and Driving Project in January 2007. Pirjo Lillsunde now has possibilities to concentrate more on alcohol, drugs and driving research since 2006. The project is at the very beginning. In addition to the earlier established international collaboration centers in EU-projects and good collaboration with the ministries (Traffic and Communication; Interior; Social Affairs and Health, Justice), new collaboration networks have been built with different KTL departments (Injury Prevention Unit etc),

with universities (Helsinki, Tampere and Turku), with Finnish Motor Investigation Insurers' centre / Traffic Safety Investigation Teams and with the Polytechnic Police Academy.

Drugs and driving research projects produced five publications in 2005-2007. During the previous Rosita project, laboratory methods were developed extensively and these methods were published and for example will be part of a doctoral thesis by Teemu Gunnar. One of those publications was awarded as a best young scientists' publication in 2005. Analyzing drugs in oral fluid opens new possibilities and oral fluid is used as important specimens also in the DRUID project. The analytical development work around the oral fluid is continuing.

Work place drug testing development work produced six publications in 2006-2007.

Publications in Drugs and Driving projects:

Engblom C, Gunnar T, Rantanen A, Lillsunde P. Driving Under the Influence of Drugs-Amphetamine Concentrations in Oral Fluid and Whole Blood Samples. *J Anal Toxicol.* 2007 31:276-80.

National Public Health Institute, Drug Research Unit, Mannerheimintie 166, FI-00300 Helsinki, Finland. charlotta.engblom

This study investigated amphetamine concentrations in both oral fluid and whole blood samples of persons suspected of driving under the influence of drugs. The data for the study were obtained from 153 cases. The mean volume of oral fluid collected with the Intercept oral fluid collection device was 224 microl. Because of the small sample volume of oral fluid, the results of the amphetamine concentrations in oral fluid were not used in the calculations for 39 cases. The total number of cases positive for amphetamine in oral fluid was 100 out of 114. In seven cases the oral fluid sample was positive (cutoff 25 microg/L), even though the whole blood sample was negative (cutoff 20 microg/L). All of the cases found positive in whole blood (n = 93) were also positive in oral fluid. Oral fluid would therefore be well suited as a testing matrix for amphetamine when driving under the influence is suspected. The results nevertheless indicated that the cutoff used for amphetamine in oral fluid (i.e., 25 microg/L) could be higher to correspond to the window of detection given by the level of 20 microg/L in whole blood.

Gunnar T, Ariniemi K, Lillsunde P. Validated toxicological determination of 30 drugs of abuse as optimized derivatives in oral fluid by long column fast gas chromatography/electron impact mass spectrometry. *J Mass Spectrom.* 2005 40(6):739-53.

National Public Health Institute, Drug Research Unit, Mannerheimintie 166, 00300 Helsinki, Finland. teemu.gunnar@ktl.fi

An analytical procedure was developed for the simultaneous sensitive identification, screening and quantitation of 30 drugs of abuse using 250 microl of human oral fluid. The method employs sequential mixed-mode solid-phase extraction (SPE), optimized derivative formation and long-column fast gas chromatography/electron impact mass spectrometry (GC/EI-MS). After sequential SPE elution, the most sensitive and stable derivatives were formed by taking careful account of the characteristics of the active functional groups and possible steric hindrances affecting derivatization chemistry. Amphetamine-type stimulant drugs were acylated with heptafluorobutyric anhydride, benzodiazepines and Delta(9)-tetrahydrocannabinol were silylated with N-methyl-N-(tert-butyl dimethylsilyl)trifluoroacetamide and

benzoylecgonine, codeine, ethylmorphine, 6-monoacetylmorphine, morphine, pholcodine, buprenorphine and norbuprenorphine with N-methyl-N-(trimethylsilyl)trifluoroacetamide. In addition, the following analytes were included: methadone, cocaine, alprazolam, midazolam, fentanyl and zolpidem. In GC separation, fast temperature ramping and high carrier gas flow-rate combined with long 30 m columns of i.d. 0.32 mm offered a reduction in analysis time and sharp peak shapes while still maintaining sufficient resolution and high sample capacity. Validated parameters including selectivity, linearity, accuracy, intra- and inter-day precision, extraction efficiency and limit of quantitation were all within required limits. In contrast to previously published methods, this single procedure is suitable for the simultaneous toxicological determination of the most common illicit drugs and benzodiazepines, and also zolpidem, in a small amount of oral fluid.

Gunnar T, Rantanen A, Engblom C, Seppä H, Lillsunde P. ROSITA 2 in Finland. Rosita-2 project, Final Report. 2006:55-95.

Lillsunde P, Gunnar T. Drugs and driving: The Finnish perspective. Bulletin on Narcotics 2007 in press.

Rantanen A, Gunnar T, Engblom C, Seppä H, Jama A, Lillsunde P. Roadside oral fluid testing : Comparison of the results of Drugwipe 5 and Drugwipe Benzodiazepines on-site tests with laboratory confirmation results of oral fluid and blood. Forensic Sci Int. 2007 Jul 17

National Public Health Institute, Drug Research Unit, Mannerheimintie 166, FI-00300 Helsinki, Finland.

Drugged drivers pose a serious threat to other people in traffic as well as to themselves. Reliable oral fluid screening devices for on-site screening of drugged drivers would be both a useful and convenient means for traffic control. In this study we evaluated the appropriateness of Drugwipe 5 and Drugwipe Benzodiazepines oral fluid on-site tests for roadside drug screening. Drivers suspected of driving under the influence of drugs were screened with the Drugwipe tests. Oral fluid and whole blood samples were collected from the drivers and tested for amphetamine-type stimulant drugs, cannabis, opiates, cocaine and benzodiazepines by immunological methods, GC and GC-MS. The performance evaluations of the tests were made by comparing the results of the Drugwipe tests with laboratory GC-MS confirmation results of oral fluid or whole blood. In addition to the performance evaluations of the Drugwipe tests based on laboratory results, a questionnaire on the practical aspects of the tests was written for the police officers who performed the tests. The aim of the questionnaire was to obtain user comments on the practicality of the tests as well as the advantages and weak points of the tests. The results of the performance evaluations were: for oral fluid (sensitivity; specificity; accuracy) amphetamines (95.5%; 92.9%; 95.3%), cannabis (52.2%; 91.2%; 85.1%), cocaine (50.0%; 99.3%; 98.6%), opiates (100%; 95.8%; 95.9%), benzodiazepines (74.4%; 84.2%; 79.2%) and for whole blood accordingly, amphetamines (97.7%; 86.7%; 95.9%), cannabis (68.3%; 87.9%; 84.9%), cocaine (50.0%; 98.5%; 97.7%), opiates (87.5%; 96.9%; 96.6%) and benzodiazepines (66.7%; 87.0%; 74.4%). Although the Drugwipe 5 successfully detected amphetamine-type stimulant drugs and the police officers were quite pleased with the current features of the Drugwipe tests, improvements must still be made regarding the detection of cannabis and benzodiazepines.

Publications in work place drug testing subproject

Lillsunde P, Haavanlammi K, Partinen R, Mukala K, Lamberg M. Finnish guidelines for workplace drug testing. Forensic Sci Int. 2007 May 11

National Public Health Institute, Helsinki, Finland.

The Finnish guidelines for workplace drug testing outlined here represent what is considered the best practice for workplace drug testing to be followed in Finland. The guidelines are based on the act on the protection of privacy in working life (759/2004), the occupational health care act (1383/2001) and the decree on workplace drug testing (218/2005). They start by defining situations in which workplace testing

is allowed and continue up to the point where the certificate is submitted to the employer. The role of the occupational health care system is crucial in the procedure. The guidelines include the best practice procedures to be followed by laboratories providing workplace drug testing services. The laboratory recommendations are based on general principles established internationally. In the Finnish guidelines, accreditation is an absolute prerequisite for a laboratory functioning as a workplace drug testing laboratory. The laboratory section of the guidelines includes specimen collection, laboratory organisation, analysis procedure, quality assurance and quality control measures. These largely conform to the European laboratory guidelines for legally defensible workplace drug testing published by the European workplace drug testing society (EWDTS), but there are differences. In addition to using urine as a specimen, the Finnish guidelines also encompass blood.

Lillsunde P, Mukala K, Partinen R, Lamberg M. Role of occupational health services in workplace drug testing. *Forensic Sci Int.* 2007 Apr 26.

National Public Health Institute, Helsinki, Finland.

In Finland, workplace drug testing is mainly performed in accordance with the Act on the Protection of Privacy in Working Life (759/2004), (<http://www.finlex.fi/en/laki/kaannokset/2004/20040759>) [1], the Occupational Health Care Act (1383/2001), (<http://www.finlex.fi/en/laki/kaannokset/2001/20011383>) [2] and the Decree on Workplace Drug Testing (218/2005) [3]. The role of occupational health services is stated in the Occupational Health Care Act. All workplace drug tests are carried out by health services according to good occupational health care practice. A referral for a drug test is given by a physician or a nurse working in health care services. When giving the referral, the physician or nurse should inform the person to be tested of the purpose and content of the test, record any medication they may be using, and make sure they are aware that they can later dispute the result of the test. The identity of the person should be checked before taking a sample. The analysis laboratory sends the result of the drug test to the health care service unit that has given the referral. If the test result is positive, the laboratory gives a detailed analysis of the test result. The health care service personnel provide the testee with the result. If it is negative, it may be given by a nurse. When the test result is positive, a Medical Review Officer (MRO) should interpret the answer and evaluate whether the positive result is due to medication, or another reasonable explanation offered by the person tested. The MRO informs the person of the options of rehabilitation treatment available to drug abusers stated in the written drug testing policy/programme of the employer/company. The testee takes the test result report to his/her employer personally.

Meririnne E, Henriksson M, Mykkänen S, Lillsunde P, Kuoppasalmi K, Lerssi R, Laksonen I, Lehtomäki K. Työpaikan huumetestaus puolustusvoimissa 2002-2005. *Suomen Lääkärilehti* 2007 14-15:1540-41b.

Meririnne E, Mykkänen S, Henriksson M, Lillsunde P, Lehtomäki K. Workplace drug testing in a military organization: results and experiences from the testing program in Finnish defence forces. *Forensic Sci Int.* 2007 Aug 6;170(2-3):171-4. Epub 2007 Jul 13.

Centre for Military Medicine, The Finnish Defence Forces, Lahti, Finland. esa.meririnne@mil.fi <esa.meririnne@mil.fi>

In the military environment drug abuse is a particular risk for occupational safety. In the Finnish Defence Forces a drug testing program was conducted in 2002-2005; soldiers, professional civilians, and military students were tested when applying for a work or right to study; furthermore, annually 5% of the personnel were subjected to random testing. In total, over 2000 urine samples were analyzed in an accredited laboratory for cannabis, opiates, amphetamines, or cocaine. In this article, the drug testing program as a part of the anti-drug strategy of the Finnish Defence Forces is described, and the findings including practical experiences and financial expenses are reported. Only one person applying for a civilian post tested positive for amphetamine and cannabis. In seven other samples codeine and morphine were detected; these were, however, due to prescribed medication, not drug abuse. In the execution of the program, no

particular difficulties were reported. In conclusion, it seems that the use of illicit drugs in the Finnish military is extremely rare, at least partly due to the successful anti-drug strategy. After an elaborate planning, even an extensive drug testing program can be executed without substantial setbacks. In the future, the effectiveness of drug testing programs as a means of improving occupational safety needs to be investigated in controlled studies using comparative design.

Lamberg ME, Kangasperko R, Partinen R, Lillsunde P, Mukala K, Haavanlammi K. The Finnish legislation on workplace drug testing. *Forensic Sci Int.* 2007 May 9.

Ministry of Social Affairs and Health, PB 33, FIN-00023 Government, Helsinki, Finland.

In Finland, the Act on the Protection of Privacy in Working Life (759/2004) that entered into force in 2004 incorporates provisions related to drug use testing, e.g. on the employers' right to process in certain situations information on job applicants' and employees' drug use. In the same context, provisions were added to the Occupational Health Care Act (1383/2001) on the employer's obligation to draw up, together with the staff, a written programme dealing with alcohol and drugs for the workplace. The programme defines the overall objectives for and the practices to be observed at the workplace in order to prevent substance abuse and to refer the problem users to treatment. The Occupational Health Care Act also includes provisions on drug tests and the drug test certificate as well as on reimbursement of the expenses of drug tests. Furthermore, the Act lays down a definition of drug tests. Every workplace shall have a plan/programme on drug-free workplace, where the jobs in which the workers have to present a drug test certificate to the employer must be defined. This plan/programme shall be discussed in cooperation on tripartite basis at the workplace. A Government decree on drug use testing (218/2005) has been issued in virtue of the Occupational Health Care Act. It lays down provisions on the practical performance of drug tests, i.e. taking and analysis of samples, and interpretation of the test results. The purpose of the Government decree is to ensure that workplace drug testing is carried out in a way presupposed by a good occupational health care practice and the laboratory quality standards, taking into account the integrity and protection of privacy of the persons tested as well as their other fundamental rights.

Lamberg ME, Lillsunde P, Mukala K, Partinen R. Huumausainetestaus työelämässä. Sosiaali- ja terveysministeriön julkaisuja 2006 2:54 s.

Several congress presentations are to be given by the team members in 2007, including two presentations as invited speakers: 1) Anna Pehrsson: Selection of Oral Fluid Collection Device for the DRUID-project (ICADTS2007, Seattle) and 2) Pirjo Lillsunde Drug Testing in Oral Fluid (International Congress of Therapeutic Drug Monitoring & Clinical Toxicology, Nice, 2007).

7.3.3. The main public health achievements

The traffic safety award was given by the minister of traffic and communication in June 2007 because of the previous work for developing best practices (police training - recognizing drugs from external symptoms, road side drug tests; instructions, orders and legislation changes, especially during the two EU-ROSITA projects 1998-2005). It has resulted in better means for the police to pick out drivers that are under influence of

drugs. The results can be seen also in the Drug Research Unit / Service Laboratory, where the number of samples has increased four fold in ten years. Police suspected 1010 drivers in 1996 for driving under influence of drugs and correspondingly 4025 drivers in 2006. In particular the Rosita project has benefited the Service Laboratory through blood screening method development which has prepared the Drug Research Unit's Service Laboratory for changes that were needed in analytical procedures for adjusting to the zero tolerance law.

The main achievement in drug policy in 2007 was that the UN resolution proposal made by Pirjo Lillsunde during the Finnish EU Presidency was presented as common EU resolution proposal in United Nations Commission for Narcotic Drugs. The resolution was accepted by all Nations in UN in March 2007 (Resolution 50/4 Improving quality and performance of drug analysis laboratories).

Work place testing practices were developed in collaboration with the Ministry of Social Affairs (Matti Lamberg and Riva Partonen) and Institute of Occupational Health (Kristiina Mukala) and a follow-up study in order to evaluate the legislative changes will start in 2007. As output a decree for workplace drug testing was accepted in 2005, the guide 'Best practices for work place drug testing' was published (Ministry of Social Affairs and Health) and three articles are in press in Forensic Science International. In work place drug testing research there was collaboration with the Finnish Defense Forces in the form of publications and congress presentations.

7.3.4. Funding for research and public health programs

Study	Contributor	Amount	Duration
DRUID	European commission	1 088 130.40	15.10.2006- 14.10.2010
RATTI	Academy of Finland	415 000	1.1.2007-31.12.2010
Opioids	Cancer Trust	7000	1.1.2007-31.12.2008
Opioids	VTT/TEKES	20 000	1.1.2007-31.12.2008

7.3.5. Personnel

Regular personnel

Head of Laboratory Pirjo Lillsunde, PhD docent (70 %) (30 % in the Service Laboratory)

RATTI

Senior researcher Aini Ostamo, PhD (50 %)

Project personnel

DRUID

Researcher Charlotta Engblom, M.Sc. (Tech).

Researcher Anna Pehrsson (née Rantanen), M.Sc. (Tech).

Researcher Kaarina Langel (50 %, starting October 2007), M.Sc (Tech).

Diploma work student Tom Blencowe, B.Sc.

RATTI

Senior researcher Aini Ostamo, PhD (50 %).

Researcher Antti Impinen, M.Sc. (50 %-80%).

Researcher Karoliina Ojaniemi, M.Sc.

7.3.6. Collaboration

DRUID

KTL is a partner in the consortium consisting of 36 partners from 18 European countries. The research colleagues in this consortium consist of experts and young scientists representing a multidisciplinary field.

The collaborators in Finland are:

Ministry of Interior / Police Department / Heikki Ihalainen; Mobile Police/ Pasi Kemppainen, Jari Pajunen, Jussi Pohjonen ja Emmi Virret.

Finnish Motor Insurers' Centre / Esa Rätty

Finnish Road Administration /Pekka Rätty

Helsinki University / prof. Erkki Vuori

RATTI

Jari Haukka, PhD, docent, senior researcher: National Public Health Institute (KTL), Department of Mental Health and Alcohol Research

Aarne Kinnunen, M.Sc, Ministerial Adviser: Department of Mental Health and Alcohol Research

Seppo Koskinen, MD, PhD, docent, chief physician: Department of Health and Functional Capacity

Tomi Lintonen, PhD, docent, senior researcher, Polytechnic Police Academy

Jouko Lönnqvist, MD, PhD, professor: Head of the Department Department of Mental Health and Alcohol Research, University of Helsinki, Department of Psychiatry

Tuija Martelin, PhD, senior researcher: Department of Health and Functional Capacity

Pia Mäkelä, PhD, docent, senior researcher: STAKES, The National Research and Development Centre for Welfare and Health

Mika Salminen, PhD, docent, Head of the Laboratory: KTL, Department of Infectious Disease Epidemiology

Heikki Seppä, Chief Superintendent: Ministry of the Interior

Heikki Summala, PhD, professor: University of Helsinki, Department of Psychology

Erkki Vuori, MD, PhD, professor: University of Helsinki, Department of Forensic Medicine

Monitoring of opioid levels in plasma and oral fluid

The main partner in this project is HUS/Pain clinic (prof. Eija Kalso and MD Tarja Heiskanen), VTT /PhD Timo Pulli and Helsinki University/Forensic Medicine Department, Forensic Medicine /Prof Erkki Vuori.

7.3.7. Proposal for future work and expected benefits

The project was just started in 2007. The aim is to strengthen and deepen this research field in KTL in collaboration with other partners. Results will be used in decision making for health policy, traffic policy and drug policy actions e.g. planning and implementing prevention, intervention and treatment programs. The aims are to reduce accidents caused by alcohol and drugs, reduce recidivism, prevent social exclusion and increase well being and health of the target groups and increase safety.

7.4. Paid Service Activity

7.4.1. Research and public health significance of the area

Driving under the influence of alcohol or drugs is a serious national problem. Blood samples or breath samples are annually taken from about 25 000 drivers on the request of the police. Paid service activity includes the analysis of alcohol and drugs in blood, and urine of suspected drunken and drugged drivers caught by police. In addition, drug analysis are also used for work place drug testing as well as drug testing in health care units, and in units of welfare for alcohol and drug abusers.

7.4.2. The main scientific achievements

Paid service activity has no scientific goals, but high level of customer-oriented services, customer satisfaction, quality assurance, fast response time and cost-effectiveness of the processes to produce the analysis results are needed.

7.4.3. The main public health achievements

Paid service activity must produce competent answer for police as a part of the preliminary investigation before the court proceedings. In addition, a lot of development work in co-operation with police has been carried out during the past few years (see in details Päihderiippuvuus and Päihteet ja liikenne -projects).

7.4.4. Funding for research and public health programs

The funding of paid service activity is based on a price list which has been agreed upon with the customers. No other funding for the paid service activity is available.

7.4.5. Personnel

The personnel includes altogether 22 persons, 10 of them with an academic degree. The rest of the workers are laboratory technicians or office workers. The equipment includes nine bench-top GC-MS instruments (which some of them are very modernly equipped) and a few GCs.

7.4.6. Collaboration

The contract with the police is a strategic one and thus also includes development work.

7.4.7. Proposal for future work and expected benefits

Continuous development work is needed to keep the paid service activity as competitive as possible.

8. ADOLESCENT MENTAL HEALTH UNIT

8.1. Mental health and psychiatric disorders in adolescence

8.1.1. Research and public health significance of the area

Most major psychiatric disorders have their onset in adolescence and the incidence and prevalence of psychiatric disorders in adolescence are high, so research on adolescent mental health and disorders may have a major public health impact.

"The Mental health in adolescence" project at the Dpt of Mental Health and Alcohol Research at the KTL started in 1998. It focuses on adolescent mental health and major psychiatric disorders. The main research areas are prevalence, risk factors, course and its predictors, and treatment of adolescent psychiatric disorders, particularly depressive disorders, and suicidal behaviour among youth. Health promotion and early identification of disorders among youth are other foci of the project.

The main databases for research consist of adolescent psychiatric patient cohorts and general adolescent and young adult population cohorts.

Adolescent psychiatric patient cohorts

The Adolescent Depression Study (ADS) is a naturalistic clinical research and development project on adolescent depressive disorders using a sample of 218 consecutive 13-19-year-old adolescent psychiatric outpatients (referred in 1998 - 2001) and a school-based control group of 200 age- and sex-matched controls. At baseline, the patients were screened for depressive symptoms and diagnosed using the K-SADS-PL interview. Several observer and self report measures were used at the baseline and at 12-month follow-up. Six-year follow-up interviews will be conducted in the autumn 2007 and spring 2008.

The follow-up study of youth with psychiatric disorders (FYPD) consists of over 500 subjects from two cohorts: unselected 13-22 year-old outpatients treated in 1984-1994 at a psychiatric outpatient secondary care clinic and 11 - 22-year old inpatients admitted to Kellokoski hospital in 1972-1975. Data were collected as part of routine clinical work and systematically coded in medical records using structured coding

sheets. Best estimate clinical diagnoses (DSM-III-R)] were assigned. A register follow-up of accidents in 302 outpatients was conducted in 2006.

The Kellokoski Adolescent Inpatient Follow-Up Study (KAIFUS) is a development and research project started in 2006. It aims at following up and finding clinical and biological predictors for outcome for 2 and 5 years in a patient cohort of 300 consecutive adolescent psychiatric inpatients and a school-based sample of 200 controls. At the moment, data collection is under way. Clinical interview and register follow-ups are to be conducted.

The Suicidality in Children and Adolescents (SCA) is a study aiming at developing the assessment and treatment of children and adolescents referred to the emergency department (ED) of the Hospital for Children and Adolescents of the HUCH. It consists of a retrospective pilot study and a prospective study. A retrospective hospital record pilot study sample of 100 children and adolescents referred due to intoxication at the ED of the Hospital for Children and Adolescents of the HUCH in 2003 has been collected and analyses are under way. Prospective structured data collection started in 2006 and is under way. The study aims at characterizing the intoxicated children and adolescents, at finding out what proportion of the intoxications are suicide attempts and at following up their outpatient treatment after discharge. Their outcome after two and five years after discharge will be studied in a register follow-up.

Adolescent general population cohorts

The Adolescent Mental Health Cohort Study (AMHC-Study) is an ongoing prospective cohort study of 3 278 15-year old subjects conducted in two Finnish cities Tampere and Vantaa. Data collection at baseline was conducted during the school term 2002 -2003 among ninth grade students of all the Finnish-speaking comprehensive schools in the two cities. The students completed a person-identifiable questionnaire during a school lesson. A two-year follow-up was conducted in 2004 - 2005 using postal questionnaires. The study examines epidemiology, comorbidity and risk and protective factors of non-psychotic disorders in adolescence.

Mental Health in Young Adults (MHYA) is a study of originally 1493 high-school students from Helsinki and Jyväskylä, with a 5-year follow-up of 709 students who volunteered for follow-up at the baseline. The study provides data on adolescent risk factors for major disorders in young adulthood, data on the epidemiology on current psychiatric disorders, particularly depression in young adulthood as well as data on help seeking and use of health care services.

Health promotion

In the health promotion projects several guides on early detection and depression, suicidal behavior, ADHD, conduct and substance use disorders for adolescents and their parents and professionals working with adolescents have been prepared and published in the internet (KTL homepage). The guides have been developed in a collaborative network of school nurses, counselors, social workers, and professional in the fields of treatment of youthful substance users and adolescent psychiatry in the city of Vantaa.

Other studies conducted in collaboration with the project

POLKU study is an ongoing study in Mikkeli focusing on psychiatric morbidity, particularly depressive, conduct and substance use disorders among 87 students in three correctional schools. Study 70 is a study of over 400 inpatients aged 12 - 17 years admitted at the ward 70 of the University Hospital of Oulu in 2001-2005. The Kuopio Adolescent Inpatient Study is a study of 63 adolescent inpatients treated at the adolescent psychiatric wards of the University Hospital of Kuopio in 1997-1999. The project collaborates also with the School Health Promotion Survey, conducted by STAKES and Tampere School of Public Health.

8.1.2. The main scientific achievements

Using the adolescent psychiatric patient cohorts, we have reported high rates of suicidality (42 - 49 %) among adolescent outpatients. Severe psychosocial impairment, psychiatric treatment history and mood disorders characterize suicidal adolescent patients in these cohorts. Particularly deliberate self-harm with no suicidal intent (mostly cutting) associated with anxiety symptoms. Our group is among the few reporting characteristics of adolescents with adjustment disorders, and suicidal behaviour among them, a little studied disorder in youth. Common risk factors for suicidality, like previous psychiatric treatment, poor psychosocial functioning, exposure to suicide of significant others, and depressed mood characterized suicidal patients with adjustment disorders. Improvement in adolescent outpatients' psychosocial functioning during treatment as usual was highly dependent on psychiatric diagnosis and comorbidity. Early dropping out from outpatient treatment associated with low parental socioeconomic status and substance abuse. Suicidal adolescent patients were as compliant as non-suicidal, a finding differing from many previous studies. During a 6-year follow-up of adolescent outpatients, total mortality (10.3 %) and suicide mortality (7.1 %) rates were high among

males. Severe impairment and suicidality associated with mortality. In a 20-year register-based follow-up of former adolescent inpatients, half of the subjects had not been long-term pensioned and better psychosocial functioning and capability for work in young adulthood associated with better outcome in terms of working capacity.

The rate of psychiatric comorbidity was high (78 %, particularly anxiety, substance use, eating and disruptive disorders) among adolescents with depressive disorders. Comorbidity with DSM-IV Axis II disorders was also high (41 %) which has not usually been elaborated in previous studies on adolescent depression. Only half of the depressed patients remitted during a 1-year follow-up, a considerably lower proportion than reported in most previous reports consisting of adolescents recruited to treatment trials indicating the need of studies in "real life" settings.

Our aims in analyzing the adolescent general population cohorts have been to report on the epidemiology of common psychiatric problems, their correlates and predictors, and use of services among adolescents and young adults. The prevalence of any psychiatric disorder among young adults was 24 %, the most prevalent being depressive (11 %), anxiety (7 %), substance use (6%) and personality disorders (6%). Current comorbidity was common (39%). Only one third of subjects with a current disorder, and less than half of those with depression reported a contact with psychiatric services indicating severe under-treatment. Comorbidity was related to impairment, treatment need, and treatment contacts among depressed young adults.

Depressive symptoms in adolescence predicted depressive disorders, but also comorbidity, psychosocial impairment, and problem drinking in early adulthood. Use of cannabis in young adulthood was related to male gender, absence of mother, frequent lack of interest and early age at first sexual intercourse. Relief smoking, relief drinking, and their interaction predicted higher average alcohol intake and heavy drinking in young adulthood. The level of somatic symptoms in early adulthood was predicted by the respective level in adolescence and by relief smoking among men. Among women, the level of somatic symptoms at follow-up was predicted by the respective level in adolescence, self esteem, and the number of negative life events at baseline. High trait anxiety and somatic symptoms among adolescent females and immature defence style among males predicted mental distress in young adulthood. After validating the Social Phobia Inventory for use in Finnish adolescents, the prevalence and correlates of social phobia have been studied and found to be prevalent among Finnish adolescents.

Using the School Health Promotion Survey database, we have reported an increased prevalence of depression and severe suicidal ideation among both those who were bullied and those who were bullies. Depression was most common among those students who were both bullied by others and who were also bullies themselves. When symptoms of depression were controlled for, suicidal ideation occurred most often

among adolescents who were bullies indicating need for psychiatric intervention both for victims of bullying and for bullies. Analyses of the same database showed early puberty to be associated with externalising symptoms among both genders, and also internalizing symptoms among girls.

8.1.3. The main public health achievements

The aims of all the clinical studies (ADS, KAIFUS, POLKU, SCA) are both to create databases for scientific purposes and to develop treatment practices. They all include education of clinical staff on psychiatric issues, different treatment approaches, and development of treatment and services for adolescents. The epidemiological and clinical data form a scientific basis for development.

The guides in the health promotion projects have been developed in a collaborative network of school nurses, councilors, social workers, and professionals in the fields of treatment of youthful substance users and adolescent psychiatry in the city of Vantaa. The guides base on analyses of the existing databases at the KTL and literature reviews. The guides cover early detection of depression, suicidal behavior, ADHD, conduct and substance use disorders. A guide on substance use and violence in adolescence is under preparation.

8.1.4. Funding for research and public health programs

In addition to departmental funds, the studies have been and are funded by the HUS EVO-funding, by the Health Promotion funds of the Ministry of Social Affairs and Health, and different Finnish foundations.

8.1.5. Personnel

Personnel currently paid by the KTL include Mauri Marttunen (20 %), Mirjami Pelkonen (20 %), and Tiia Pirkola (35 %). Other personnel, (one researcher (100 %), research assistant (20 %), research secretary (30 %) is currently paid by a fund from the Sigrid Juselius Foundation.

In all, eight post doc researchers and ten researchers preparing their theses participate in the studies.

8.1.6. Collaboration

All the patient cohort studies are conducted in collaboration between the Helsinki University Central Hospital and the Department of Mental Health and Alcohol Research of the KTL.

The AMHC-Study is carried out in collaboration between the cities of Tampere and Vantaa, the Tampere School of Public Health; Department of Mental Health, KTL, the Tampere University Hospital and the Helsinki University Central Hospital. The POLKU-study is a collaboration between KTL, University of Kuopio, two reform schools in Mikkeli, and with the Central Hospital of Mikkeli. The KAIFUS study is a collaboration between KTL and Kellokoski Hospital. The planned "Effectiveness of IPT-A in adolescent depression" study is to be conducted in collaboration with Laura Mufson at the Columbia University (USA), University of Tromso (Norway), and with 4-5 university sites in Finland.

8.1.7. Proposal for future work and expected benefits

The ADS study is in a phase of active analyses and reporting. Analyses on antidepressant treatment and its association with changes in suicidality in adolescent mood disorders are ongoing. Analyses of treatment emergent suicidality among subjects with and without antidepressant treatment are to be conducted. These analyses will shed light in the ongoing debate on the "suicidogenic" effect of antidepressants in adolescent mood disorders. In the autumn 2007, six-year follow-up of the patient cohort is to be conducted. Besides clinical follow-up and structured diagnostic interviews, a register based follow-up will be conducted. For selected 80 patients (20 subjects with only the index depressive episode, 20 who have a chronic depression, 20 who have "switched" to bipolar disorder, and 20 healthy controls) assessments including MRI scans and a neuropsychological test battery will also be made in order to find out the possible structural brain abnormalities and their association with neuropsychological impairment in different early onset mood disorders.

The KAIFUS study will provide data on the short- and long term outcome and both clinical and biological predictors of outcome of adolescent inpatients.

Further analyses of the AMHC database will be conducted in order to find out risk factors for the main outcomes (depression, conduct problems, aggression, alcohol and other substance abuse) during a 2-year follow-up. In the near future, 5-year follow-up of the subjects will be conducted.

In the ongoing health promotion project, a guide on substance use and violence in adolescence is under preparation.

Two trials are planned to start in 2007 / 2008. A study on the effectiveness of cognitive behavioral "Coping with stress (CWS) course" in the prevention of adolescent depression will be started in the autumn 2007 in collaboration between the KTL and three Finnish cities (Vantaa, Turku, Kuopio). The intervention has been piloted in Vantaa and found to be applicable. Subjects of the study will be 15-year-olds in schools with an R-BDI-score of 5-15 (300 students in intervention group and 200 students in comparison "treatment as usual" condition) followed up for 24 months.

Another trial will be "Effectiveness of IPT-A in adolescent depression" -study conducted in collaboration with Laura Mufson at the Columbia University, two university clinics in Norway, and 4 - 5 university clinics in Finland. It will be the first trial to test the effectiveness of IPT-A in Europe and it will consist of 180 13 - 18-year old depressed patients in the intervention condition and 180 patients in the control condition (treatment as usual).

8.1.8 The most important publications

Aalto-Setälä T, Haarasilta L, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Aro H. Major depressive episode among young adults: CIDI-SF versus SCAN consensus diagnoses. *Psychol Med* 2002;32:1309-1314.

National Public Health Institute, Department of Mental Health and Alcohol Research, Mannerheimintie, Finland.

BACKGROUND: We aimed to evaluate the diagnostic accuracy of a highly structured diagnostic interview in relation to a semi-structured diagnostic procedure. We compared the World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF) in diagnosing major depressive episode (MDE) to consensus diagnoses based on the SCAN interview (Schedules for Clinical Assessment in Neuropsychiatry). **METHOD:** Subjects comprised a follow-up sample of 239 20-24-year-old former high-school students who were administered the SCAN and immediately thereafter the CIDI-SF. Concordance was estimated for 12-month MDE, using different cut-points of the CIDI-SF and for any affective disorders. **RESULTS:** Correspondence between instruments was moderate for MDE (kappa = 0.43, sensitivity 0.71, specificity 0.82), but better for any affective disorder (kappa = 0.60, sensitivity 0.70, specific-

ity 0.90). Most false negatives suffered from their depression as much as those correctly identified by the CIDI-SF. False negativity was mainly due to not endorsing the stem questions of the CIDI-SF. Of the false positives almost half had an affective disorder other than MDE. CONCLUSIONS: The CIDI-SF seems to function best in identifying a broader category of affective disorders. It could be useful in large-scale community surveys where more extensive psychiatric interviews are not feasible.

Aalto-Setälä T, Marttunen M, Poikolainen K, Tuulio-Henriksson A, Lönnqvist J. One-month prevalence of depression and other DSM-IV disorders among young adults. *Psychol Med* 2001;31:791-801.

National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki.

BACKGROUND: We aimed to provide prevalence data on depression and other current mental disorders, impairment, need of psychiatric care and use of mental health services among young adults. **METHODS:** Based on a semi-structured clinical interview, current DSM-IV disorders, impairment, need of psychiatric care and use of mental health services were evaluated in a sample of 20-24-year-old young urban adults (N = 245), mean age 21.8, screened from a baseline population of 706. One-month prevalence estimates for disorders were calculated by the double sampling method, using various additional criteria to identify cases. **RESULTS:** One in four young adults (23.8%) suffered from a current mental disorder, the most prevalent being depressive (10.8%), anxiety (6.9%), substance use (6.2%) and personality disorders (6.0%). Prevalence estimates varied substantially according to the use of additional diagnostic criteria. Impairment (GAF < 61) together with DSM-IV symptom criteria produced an overall disorder prevalence of 10.3%, and 5.5% for depression. Prevalences were higher for females than males, except for alcohol abuse and personality disorders. Current co-morbidity was found in 39% of subjects with any disorder, and in more than half of those with depression. One-third of subjects with a current disorder reported an associated contact with psychiatric services and 16% had an ongoing contact. **CONCLUSIONS:** Our findings support the use of additional criteria to produce clinically relevant prevalence data. Co-morbidity should receive special attention due to its amplification of both need for psychiatric care and severity of impairment. Finally, our results show disturbed young adults to be severely undertreated.

Aalto-Setälä T, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Lönnqvist J. Psychiatric treatment seeking and psychosocial impairment among young adults with depression *J Affect Disord* 2002;70:35-47.

Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland. terhi.alto-setala@ktl.fi

BACKGROUND: We report data on 1-year prevalence and comorbidity of depression, related impairment, treatment need, and psychiatric treatment among young adults. **METHODS:** A sample of young urban adults (n=245) mean age 21.8 years was screened from a baseline population of 706 high-school students and given a semistructured clinical interview to evaluate 12-month prevalence of depression, psychosocial functioning according to DSM-IV GAF scale, need for psychiatric treatment, and use of mental health services. **RESULTS:** One in 10 young adults suffered from depression with associated psychosocial impairment, the female-to-male-ratio being approximately 2:1. Most depressive disorders were comorbid with other DSM-IV disorders, depression usually occurring secondary to other disorders. Comorbidity was related to impairment, treatment need, and treatment contacts. Less than half of the depressed young adults had ever contacted mental health services, and less than one-third reported treatment contacts during the index episode. Males were less likely than females to report previous treatment contacts or intention to refer to mental health services for their problems, but treatment contacts during the index episode were reported equally often by both sexes. **CONCLUSIONS:** A minority of the severely depressed young adults with associated impairment had sought treatment. Except for subjects with dysthymia, no gender difference emerged in treatment contact rates during the 12-month depression episode. Comorbidity showed important clinical implications by its relation to severity of depression and treatment contacts.

Aalto-Setälä T, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Lönnqvist J. Depressive symptoms in adolescence predict early adulthood depressive disorders and maladjustment *Am J Psychiatry* 2002;159:1235-1237.

Department of Mental Health and Alcohol Research, National Public Health Institute, Iirislahdenranta 30, FIN-02230 Espoo, Finland.

OBJECTIVE: The authors examined the association between self-reported depressive symptoms in adolescence and mental well-being in early adulthood. **METHOD:** A questionnaire assessing psychosocial well-being was given to a group of subjects (N=651) in their last 3 years of high school (mean age=16.8 years) and again when these subjects reached early adulthood (mean age=21.8 years). Diagnostic interview data were obtained from a subgroup of the young adults (N=245). Adolescents' depressive symptoms were analyzed in relation to their early adulthood mental health outcome data. **RESULTS:** Depressive symptoms in adolescence predicted early adulthood depressive disorders (major depression and dysthymia), comorbidity, psychosocial impairment, and problem drinking. **CONCLUSIONS:** Depressive symptoms in adolescence deserve attention as a potential risk for early adulthood mental disorders.

Haapasalo-Pesu K-M, Vuola T, Lahdelma L, Marttunen M. Mirtazapine in the treatment of adolescents with major depression. An open-label, multicenter pilot study. *J Child Adolesc Psychopharmacol* 2004;14:175-184.

Adolescent Psychiatry Clinic, Hansakatu 5, FIN-28100 Pori, Finland. kirsi-maria.haapasalo-pesu@satshp.fi

This multicenter, open-label study with a duration of 85 days was performed to evaluate the antidepressant efficacy and safety of mirtazapine (dose range, 30-45 mg) in 12-18-year-old adolescents diagnosed with major depression. Twenty-four (24) patients (15 female patients and 9 male patients) meeting the DSM-IV criteria for major depression and the Hamilton Rating Scale for Depression (HAM-D-17) score of 18 at baseline were enrolled in the study. The primary outcome measures were HAM-D-17, Beck Depression Inventory (BDI), and Clinical Global Impression (CGI) scales. Any changes in symptoms of anxiety were measured using the Hamilton Anxiety Rating Scale (HAM-A). The average age of the 23 subjects, who were eligible for analysis, was 16.3 years (standard deviation (SD) 6.11, median 17.3). The mean daily dose of mirtazapine was 32.9 mg. Mirtazapine showed a marked efficacy on all rating scales and was well tolerated. Mirtazapine had a beneficial effect on sleep. A rapid onset of sleep and pattern of action was seen. No dropouts due to adverse events were recorded. The most common treatment-emergent adverse events were tiredness, increased appetite, and dizziness. The results of this study suggest that mirtazapine may be an effective treatment for major depression in adolescents.

Holi MM, Eronen M, Toivonen K, Toivonen P, Marttunen M, Naukkarinen H. Left prefrontal rTMS in Schizophrenia. *Schizophr Bull.* 2004;30(2):429-34.

Helsinki University Central Hospital, Department of Psychiatry, Helsinki, Finland.

In a double-blind, controlled study, we examined the therapeutic effects of high-frequency left prefrontal repetitive transcranial magnetic stimulation (rTMS) on schizophrenia symptoms. A total of 22 chronic hospitalized schizophrenia patients were randomly assigned to 2 weeks (10 sessions) of real or sham rTMS. rTMS was given with the following parameters: 20 trains of 5-second 10-Hz stimulation at 100 percent motor threshold, 30 seconds apart. Effects on positive and negative symptoms, self-reported symptoms, rough neuropsychological functioning, and hormones were assessed. Although there was a significant improvement in both groups in most of the symptom measures, no real differences were found between the groups. A decrease of more than 20 percent in the total PANSS score was found in 7 control subjects but only 1 subject from the real rTMS group. There was no change in hormone levels or neuropsychological functioning, measured by the MMSE, in either group. Left prefrontal rTMS (with the used parameters) seems to produce a significant nonspecific effect of the treatment procedure but no therapeutic effect in the most chronic and severely ill schizophrenia patients.

Kaltiala-Heino R, Marttunen M, Rantanen P, Rimpelä M. Early puberty associates with mental health problems in middle adolescents. *Soc Sci Med* 2003;57:1055-1064.

Tampere School of Public Health, 33014 University of Tampere, Box 607, 33101 Tampere, Finland. merihe@uta.fi

This study set out to assess the relationship between pubertal timing and emotional and behavioural problems in middle adolescence. The study involved a school based survey of health, health behaviour and behaviour in school as well as questions about emotional and behavioural problems (the School Health Promotion Study). Secondary schools in four regions and 13 towns in Finland participated in the study in 1998. The respondents were 36,549 adolescents aged 14-16. The study included questions on depression, bulimia nervosa, psychosomatic symptoms, anxiety, drinking, substance use, smoking, bullying and truancy. Among girls, both internalising and externalising symptoms were more common the earlier puberty occurred. Among boys, externalising symptoms only were associated with early puberty. It is concluded that early pubertal timing is associated with increased mental health problems. Professionals working with adolescents should consider the mental health needs of early maturing adolescents.

Kaltiala-Heino R, Rimpelä M, Marttunen M, Rantanen P, Rimpelä A. Bullying, depressive symptoms and severe suicidal ideation. *BMJ*. 1999;319:348-351.

University of Tampere, Tampere School of Public Health, Box 607, 33101 Tampere, Finland. merihe@uta.fi

OBJECTIVE: To assess the relation between being bullied or being a bully at school, depression, and severe suicidal ideation. **DESIGN:** A school based survey of health, health behaviour, and behaviour in school which included questions about bullying and the Beck depression inventory, which includes items asking about suicidal ideation. **SETTING:** Secondary schools in two regions of Finland. **PARTICIPANTS:** 16 410 adolescents aged 14-16. **RESULTS:** There was an increased prevalence of depression and severe suicidal ideation among both those who were bullied and those who were bullies. Depression was equally likely to occur among those who were bullied and those who were bullies. It was most common among those students who were both bullied by others and who were also bullies themselves. When symptoms of depression were controlled for, suicidal ideation occurred most often among adolescents who were bullies. **CONCLUSION:** Adolescents who are being bullied and those who are bullies are at an increased risk of depression and suicide. The need for psychiatric intervention should be considered not only for victims of bullying but also for bullies.

Karlsson L, Pelkonen M, Heilä H, Holi M, Kiviruusu O, Tuisku V, Ruutu T, Marttunen M. Differences in the clinical characteristics of adolescent depressive disorders. *Depress Anxiety* 2006 Oct 18; Epub ahead of print

The National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland.

Our objective was to analyze differences in clinical characteristics and comorbidity between different types of adolescent depressive disorders. A sample of 218 consecutive adolescent (ages 13-19 years) psychiatric outpatients with depressive disorders was interviewed for DSM-IV Axis I and Axis II diagnoses. We obtained data by interviewing the adolescents themselves and collecting additional background information from the clinical records. Lifetime age of onset for depression, current episode duration, frequency of suicidal behavior, psychosocial impairment, and the number of current comorbid psychiatric disorders varied between adolescent depressive disorder categories. The type of co-occurring disorder was mainly consistent across depressive disorders. Minor depression and dysthymia (DY) presented as milder depressions, whereas bipolar depression (BPD) and double depression [DD; i.e., DY with superimposed major depressive disorder (MDD)] appeared as especially severe conditions. Only earlier lifetime onset distinguished recurrent MDD from first-episode MDD, and newly emergent MDD appeared to be as impairing as recurrent MDD. Adolescent depressive disorder categories differ in many clinically

relevant aspects, with most differences reflecting a continuum of depression severity. Identification of bipolarity and the subgroup with DD seems especially warranted. First episode MDD should be considered as severe a disorder as recurring MDD. *Depression and Anxiety* 0:1-12, 2006. (c) 2006 Wiley-Liss, Inc.

Karlsson L, Pelkonen M, Ruutu T, Kiviruusu O, Heilä H, Holi M, Kettunen K, Tuisku V, Tuulio-Henriksson A, Törrönen J, Marttunen M, Current comorbidity among consecutive adolescent psychiatric outpatients with DSM-IV mood disorders. *Eur Child Adolesc Psychiatry* 2006;15:220-31. Epub 2006 Feb 23.

The National Public Health Institute, Dept. of Mental Health and Alcohol Research, , Helsinki, Finland. linnea.karlsson@utu.fi

OBJECTIVE: To compare selected characteristics (age, sex, age of onset for depression, impairment, severity of depression, somatic comorbidity, and treatment status) of adolescents with currently comorbid and non-comorbid depression. **METHOD:** A sample of 218 consecutive adolescent (13-19 years) psychiatric outpatients with depressive disorders, and 200 age- and sex-matched school-attending controls were interviewed for DSM-IV Axis I and Axis II diagnoses. **RESULTS:** Current comorbidity, most commonly with anxiety disorders, was equally frequent (>70%) in outpatients and depressed controls. Younger age (OR 0.20; 95% CI 0.08, 0.51) and male gender (OR 0.02; 95% CI 0.09, 0.55) were associated with concurrent disruptive disorders. Current comorbidity with substance use disorders (SUD) was independent of age (OR 1.13; 95% CI 0.51, 2.49) and sex (OR 0.51; 95% CI 0.22, 1.17). Personality disorders associated with older age (OR 2.06; 95% CI 1.10, 3.86). In multivariable logistic regression analysis, impairment (GAF \leq 60) was associated with current comorbidity (OR 3.13; 95% CI 1.53, 6.45), while severity of depression and lifetime age of onset for depression were not. **CONCLUSIONS:** Adolescent depression presents with age- and sex-dependent patterns of multiple co-occurring problem areas. While many clinical characteristics of adolescent depression are not affected by comorbidity, comorbidity associates with increased impairment.

Pelkonen M, Marttunen M, Henriksson M, Lönnqvist J. Adjustment disorders among adolescent outpatients. *Eur Psychiatry* 2006, doi:10.1016/j.eurpsy.2006.04.010.

National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland; Department of Social Psychiatry, University of Tampere, Tampere School of Public Health, Tampere, Finland.

OBJECTIVE: Research on adolescent adjustment disorder (AD) is scarce. We characterized adolescent outpatients with AD in psychosocial background and treatment received compared with patients with other non-psychotic disorders (OND). Furthermore, we explored precipitant stressors, distress symptoms and behavioral problems among males and females with AD. **METHOD:** Data were collected prospectively on 290 consecutive psychiatric outpatients, aged 12-22 yrs, at a secondary care clinic in Finland. DSM-III-R diagnoses were assigned, based on all available information, at the end of treatment. **RESULTS:** AD was the second most common diagnosis among non-psychotic patients (31% of 290). Compared to OND-patients, those with AD were predominantly female and had less severe psychosocial impairment. In multivariate comparisons school-related stressors, problems with law and restlessness characterized males, and parental illness and internalizing symptoms females with AD. Intensity and duration of treatment of AD-patients varied widely. **CONCLUSIONS:** Adjustment disorder comprised a common clinical entity among adolescent outpatients. Psychiatric assessment and treatment should be individually targeted by taking into account gender-specific stressors and distress symptoms among young people with AD.

Pelkonen M, Marttunen M, Lönnqvist J, Laippala P. Factors associated with early drop out from adolescent outpatient treatment. *J Am Acad Child Adolesc Psychiatry* 2000;39:329-336.

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland. Mirjami.Pelkonen@ktl.fi

OBJECTIVE: To examine background factors, psychopathology, and psychosocial impairment among adolescents complying with or dropping out early from outpatient psychiatric treatment. **METHOD:** Family background, psychiatric history, and other data were collected prospectively on 143 male and 154 female outpatients aged 12 to 22 years. DSM-II-R psychiatric diagnoses were assessed at the end of treatment. **RESULTS:** Fifty-three adolescents (17.8%) attended 1 or 2 treatment appointments, and 33 of them (11.1% of 297) then dropped out; 50.5% of the total attended 3 to 13, and 31.6% attended 14 or more appointments. Low parental socioeconomic status was more common among the early dropouts than the other patient groups (88%, 69%, 63%, respectively). The early dropouts had had more problems with the law than the adolescents attending 14 or more appointments (18%, 6%), but less suicidal behavior (24%, 56%, respectively). Among the early dropouts, mood disorders were less common (21%, 49%), especially major depression (0%, 20%), and substance abuse was more common (9%, 0%) than among patients attending 14 or more appointments. **CONCLUSIONS:** Low parental socioeconomic status, not having mood disorder, not having psychotropic medication, and having substance abuse were associated with early dropout of adolescents from outpatient psychiatric treatment.

Pelkonen M, Marttunen M, Pulkkinen E, Koivisto A-M, Laippala P, Aro H. Excess mortality among former adolescent male outpatients. *Acta Psychiatr Scand* 1996; 94:60-66.

Tampere School of Public Health, University of Tampere, Finland.

Mortality among 156 males and 122 females referred to an out-patient adolescent psychiatric clinic in a Finnish town between 1984 and 1989 was examined. During the follow-up (mean duration 6 years; range 0-6.3 years for the deceased, 0.6-10.3 years for the survivors), 16 male subjects but no females had died. Among those who had died, the mode of death was suicide in 11 cases. The mortality for any cause for males was 10.3% and that for suicide was 7.1%. All male victims had similar high levels of individual and familial disturbances. Current suicidal ideation and suicide attempts, poor psychosocial functioning and a recommendation for psychiatric hospital treatment during the index treatment were associated with male mortality/suicidality. A high risk for mortality for several years after psychiatric treatment was found. It is concluded that, in clinical settings, perceived current suicidal tendencies should be assessed carefully.

Pelkonen M, Marttunen M, Pulkkinen E, Laippala P, Lönnqvist J, Aro H. Disability pensions in severely disturbed in-patient adolescents. Twenty-year prospective study. *Br J Psychiatry* 1998;172:159-163.

Tampere School of Public Health, University of Tampere, Finland.

BACKGROUND: Knowledge of working capacity from adolescence until adulthood among severely disturbed in-patients is scarce. **METHOD:** In a follow-up study of 61 adolescent in-patients, we studied associations between being on a disability pension 20 years after hospitalisation, and the patients' psychopathology and treatment-related factors during the hospitalisation and seven-year follow-up. **RESULTS:** Of the former in-patients, 27% had not been on a disability pension, 20% had short-term pension periods, and 53% were pensioned. Subjects whose overall psychosocial functioning had improved and who had not utilised in-patient services until the seven-year follow-up, had a better prognosis in terms of working capacity. Half of the subjects who had not been on pension during the follow-up had received a diagnosis of conduct disorder at discharge, and half of those pensioned had a psychotic disorder. **CONCLUSIONS:** The patients' level of psychosocial functioning and capability to work in young adulthood were associated with long-term prognosis in terms of working capacity. Adolescence seems to be the critical time for intensive psychiatric care combined with vocational rehabilitation programmes.

Poikolainen K, Tuulio-Henriksson A, Aalto-Setälä T, Marttunen M, Anttila T, Lönnqvist J. Correlates of initiation to cannabis use: a 5-year follow-up of 15-19-year old adolescents. *Drug Alcohol Depend* 2001;62:175-180.

Järvenpää Addiction Hospital, FIN-04480, Haarajoki, Finland. kari.poikolainen@a-klinikka.fi

Initiation to cannabis is often the first step in the use of illicit drugs. We studied the correlates of initiation in a 5-year follow-up study. A total of 21.4% of the subjects reported using cannabis at some time. Of the 139 users, 89.2% had tried cannabis not more than once or a few times. This initiation to cannabis was related to male gender, absence of mother, frequent lack of interest and early age at first sexual intercourse in logistic regression analysis. These factors seem to be useful in predicting initiation to cannabis.

Poikolainen K, Tuulio-Henriksson A, Aalto-Setälä T, Marttunen M, Lönnqvist J. Predictors of alcohol intake and frequent heavy drinking in early adulthood: a 5-year follow-up of 15-19-year old adolescents. *Alcohol Alcohol* 2001;36:85-88.

Finnish Foundation for Alcohol Studies, P.O. Box 220, FIN-00531 Helsinki, Finland.

Relative contributions of earlier drinking and smoking vs mental health risk factors in predicting alcohol intake and heavy drinking in young adulthood were assessed. Higher average alcohol intake and heavy drinking (13 or more drinks on one occasion) in 1995 were significantly related to male gender and earlier high scores in 1990 of relief smoking, relief drinking, and their interaction. Parental alcohol problems, social group, perceived degree of social support, trait anxiety, number of negative life events, self-esteem, grade-point average, somatic symptoms score, or immature, neurotic, or mature defence style measured in 1990 did not predict alcohol intake or heavy drinking 5 years later. The findings suggest that alcohol intake and heavy drinking in young adulthood can be predicted by earlier self-reports on relief smoking and alcohol intake in adolescence.

Ranta K, Kaltiala-Heino R, Koivisto A-M, Tuomisto M, Pelkonen M, Marttunen M. Age and gender differences in social anxiety symptoms during adolescence: the Social Phobia Inventory (SPIN) as a measure. *Psychiatr Res* (Accepted 12/2006)

School of Public Health, University of Tampere, Tampere, Finland; Department of Adolescent Psychiatry, Turku University Central Hospital, Turku, Finland.

The aim of the present study was to examine age and gender differences in social anxiety symptoms during adolescence, and to investigate the psychometrics of the Social Phobia Inventory (SPIN) among adolescents. The SPIN was administered to a large general population sample (n=5252) of Finnish adolescents aged 12-16 years. Age and gender trends in scores and internal consistency and factorial composition of the SPIN were examined in this sample. The test-retest reliability of the SPIN was examined in a smaller sample of adolescents (n=802). Results showed that girls scored higher than boys on the SPIN full scale and three subscales across the whole age range. Eighth graders (14- to 15-year-olds) scored higher than seventh and ninth graders on the full scale, for boys the differences were significant. Good test-retest reliability (r=0.81), and internal consistency (alpha=0.89) were found for the SPIN. An exploratory factor analysis (EFA) performed on a random half (n=2625) of the population sample yielded a one-factor model accounting for 38% of the variance between items. This one-factor model, plus an alternative three-factor model, were examined in the holdout half of the population sample (n=2627) by means of a confirmatory factor analysis (CFA). Some support was gained for both factor structures. Our results indicate that symptoms of social phobia may increase in mid-adolescence. The SPIN appears to be a reliable self-report instrument among adolescents.

Tuisku V, Pelkonen M, Karlsson L, Holi M, Kiviruusu O, Ruuttu T, Punamäki R-L, Marttunen M. Suicidal Ideation, Deliberate Self-harm Behavior and Suicide Attempts among Adolescent Outpatients with Depressive Mood Disorders and Comorbid Axis I Disorders. *Eur Child Adolesc Psychiatry* 2006;15:199-206. Epub 2006 Apr 8.

Dept. of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland. Virpi.Tuisku@ktl.fi

OBJECTIVE: We aimed to analyse and compare prevalence and associated clinical features of suicidal ideation, self-harm behaviour with no suicidal intent and suicide attempts among adolescent outpatients

with depressive mood disorders with or without comorbidity. **METHOD:** A sample of 218 consecutive adolescent outpatients aged 13-19 years with depressive mood disorders was interviewed using K-SADS-PL for DSM-IV Axis I diagnoses. They filled out self-report questionnaires assessing depressive and anxiety symptoms. Suicidal behaviour was assessed by K-SADS-PL suicidality items. **RESULTS:** Half of the subjects reported suicidal ideation or behaviour. There was no difference in prevalence of suicidal behaviour between non-comorbid and comorbid mood disorder groups. Multivariate logistic regression analyses produced the following associations: (1) suicidal ideation with self-reported depressive symptoms and poor psychosocial functioning, (2) deliberate self-harm behaviour with younger age and poor psychosocial functioning, and (3) suicide attempts with self-reported depressive symptoms and poor psychosocial functioning. **CONCLUSIONS:** Depressed mood disorders, whether comorbid or not, are associated with suicidal ideation and suicide attempts. Diagnostic assessment should be supplemented by self-report methods when assessing suicidal behaviour in depressed adolescents.

8.2 Finnish Twin Studies on Mental Health and Substance Use

8.2.1. Research and public health significance of the area

Genetic epidemiology of substance use and psychiatric morbidity using twins and families

8.2.2. The main scientific achievements

1. During the past six years, we have sought to establish a resource to identify loci and genes associated with nicotine dependence and alcohol use & abuse. We completed the data collection of our nicotine dependence families in mid-2006 (762 families recruited with 2412 family members). A joint analysis of this multicenter project of one quantitative phenotype, the maximum number of cigarettes ever smoked, was published in the American Journal of Human Genetics in May 2007, showing significant linkage to chromosome 22 in both Finnish and Australian families. A separate paper on only Finnish results for nine binary phenotypes replicated previous linkage findings on 10q (max LOD 3.12) for a smoker phenotype, and on 7q and 11p (max LOD 2.50, and 2.25, respectively) for the ND phenotype, and revealed a number of promising findings to follow-up on (Loukola et al, The Pharmacogenomics Journal, 2007). Analyses in the Australian data set did not show strong linkage and have not been reported. Ongoing analyses on nicotine withdrawal also indicate a stronger signal from Finnish than Australian families. Thus, for smoking, it is remarkable that the strongest linkage signals have come from the Finnish data set, despite the smaller number of families and lower

mean values of the phenotypes on average. This further indicates the value of relatively large but genetically isolated populations with homogeneous cultures and health care systems such as Finland and Iceland in searching for genes underlying complex traits.

2. Our second major study aim is to characterize risk across development connected to genes associated with substance dependence in adulthood. While some analyses are in progress or have been reported on our longitudinal studies of younger twins (the FinnTwin12 and Finntwin16) studies, we have started in the spring of 2006 a major data collection on the Finntwin12 sample, with a now fourth wave of data collection. This entails travel to Helsinki for a one day session, which starts with blood samples for serum and DNA, anthropometric measures, taste and smell assessments, neuropsychological tests and a structured psychiatric assessment of substance use, abuse and associated psychiatric conditions. The subjects are aged 22-24 years of age on assessment and thus our follow-up is more than 10 years as it started at age 11-12. The first year of assessments completed data collection for 250 subjects, and our goal is study 1000-1200 subjects by early 2009. This is a collaborative project with Professor Richard J Rose and co-workers, Department of psychology and cognitive science, Indiana University (joint NIH funding (AA-12502) for studies of alcohol-related behavior genetics in young Finnish twins); Finnish Funding comes from the Academy of Finland Centre of Excellence and other grants.

3. Our third research arm focuses on gene-environment interaction, by characterizing how the risk associated with susceptibility genes may be moderated by the presence/absence of environmental factors. A number of papers reporting such results have been published are under review or are in preparation. These analyses are based primarily on the FinnTwin12 and FinnTwin16 studies, and are done in close collaborations with Research Assistant Professor Danielle Dick, Washington University, St. Louis. Analysis of gene-environment interaction in the development of substance use, supported by NIH AA-15416.

4. We have extended our current research area to include other substance use than alcohol and smoking. The use of cannabis has increased in particular among younger Finns, though even the majority of ever-users only experiments a few times. Nonetheless this was felt to be an area worth including. Dr. Anja Huizink (University of Rotterdam) has received Dutch funding for the study of cannabis use in our younger twins (starting 1.11.06), and Jaakko Kaprio has received funding from the program called *Addiktio* of the Academy of Finland (starting 1.1.07) for studies on causes and consequences of alcohol and cannabis use, with collaboration of Academy researcher Jaana Suvisaari (KTL) and doc. Annamari Tuulio-Henriksson (KTL). As these are tightly associated with psychiatric morbidity, these tie into our broader research interests in neuropsychiatric genetics. Thus, we will examine the neuropsychological and neurophysi-

ological correlates of alcohol use in the presence and absence of cannabis use, based on the FinnTwin16 samples and the Health2000 sample of young adults with substance use and/or psychiatric problems and their controls.

5. In 2005, we have established collaboration with researchers in disability pension and sickness absence in Finland (Drs. Timo Klaukka and Antti Huunan Seppälä, from the The Social Insurance Institution of Finland and MSc Karoliina Harkonmäki, Local communities pensions fund). and with Professor Kristina Alexanderson (Karolinska Institute). The older twin cohort was linked to data on all pensions, with particular focus on disability pension. The data have been supplemented by information on diseases for which re-imbusement of medication expenses is provided and prescription drug information. This greatly expands the phenotypic database of the older twin cohort. Thus for the 24043 twins of known zygosity resident in Finland in 1975, there are 4894 records of disability pension with at least one diagnosis by the end of 2004; in addition with 10878 records of a right to reimbursed medication based on a medical certificate.

The most common diagnostic categories are hypertension, diabetes, psychotic conditions and CHD-related, including hyperlipidemia. We have classified for example all diabetes cases into those with T1DM (162 cases), T2DM (2077), and other kinds (igt, gestational diabetes and secondary, 97 cases). Currently analyses are underway, with a focus on depression, and low back pain (a subproject led by Annina Ropponen, PhD, University of Kuopio).

8.2.3. The main public health achievements

Knowledge about nicotine dependence has been very limited in Finland until now. Our family data has yielded information about the utility of different measures of nicotine dependence, and confirmed that nicotine dependence is very common, probably the most common form of substance dependence in Finland.

Our studies on the development of substance use and mental health in the younger twin cohorts have provided information about the importance of family and peer effects, particularly in the initiation of substance use, and that the genetic variance in substance use is moderated strongly by parenting practices, and by broad socio-economic indicators.

8.2.4. Funding for research and public health programs

In addition to departmental funds, the twin studies at KTL are funded by the the Academy of Finland Centre of Excellence and the Addiction programme of the Academy of Finland.

8.2.5. Personnel

Current personnel paid by KTL include Jaakko Kaprio (35%), Ulla Broms, Antti Latvala, Ulla Kulmala-Gråhn and Kristiina Saanakorpi. Ulla Broms is completing her PhD thesis on nicotine dependence, while Antti Latvala is starting his PhD projects on neuropsychological correlates of alcohol and cannabis use.

8.2.6. Collaboration

In addition, the Finnish twin cohorts have been used for many other non-psychiatric conditions, as evident from our publication list. These are primarily conducted at the Department of Public Health, University of Helsinki. A major project in this context has been the large European collaboration, Genomeutwin, but also other EU-projects such as Euroclot, Eurohead, Diogenes; likewise we have active collaboration with many Finnish scientists and research units.

8.2.7. Proposal for future work and expected benefits

We have planned for further follow-up of the twin cohorts with questionnaire studies of the older twin cohort, the FinnTwin12 and Finntwin16 cohorts. These would probably be undertaken in the next 2-3 years depending on funding. Register-follow-up will also continue. These continued longitudinal analyses will provide further information on the evolving development of substance use and mental health from early adolescence onwards into adulthood.

8.2.8. Main publications

1. Ahveninen J, Jaaskelainen IP, Osipova D, Huttunen MO, Ilmoniemi RJ, Kaprio J, Lonnqvist J, Manninen M, Pakarinen S, Therman S, Naatanen R, Cannon TD. Inherited auditory-cortical dysfunction in twin pairs discordant for schizophrenia. *Biol Psychiatry*. 2006 Sep 15;60(6):612-20. Epub 2006 Jul 28.

Department of Radiology, Harvard Medical School-Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts 02129, USA. jyrki@nmr.mgh.harvard.edu

BACKGROUND: Information on the inheritance of neurophysiological abnormalities might help elucidate the molecular genetic basis of schizophrenia. We used magnetoencephalography (MEG) and electroencephalography (EEG) to investigate the inheritance of auditory-cortical deficiencies in twin pairs discordant for schizophrenia. **METHODS:** Auditory EEG/MEG responses to frequent standard and occasional deviant tones were measured in mono- and dizygotic (MZ and DZ) twin pairs discordant for schizophrenia and demographically matched healthy twin pairs, recruited from a total population cohort. The MEG/EEG results were regressed against the genetic resemblance to patients with schizophrenia across the patients' unaffected MZ/DZ co-twins and control subjects (with genetic correlations of 1, .5, and 0 to schizophrenia patients, respectively). **RESULTS:** The EEG responses P50, N100, and mismatch negativity (MMN), as well as the MEG response P50m, were reduced in the schizophrenic patients. P50 and N100 were significantly decreased also in their unaffected co-twins, as compared with the control subjects. Importantly, the P50 and N100 decrease correlated with the unaffected subjects' genetic resemblance to schizophrenia patients. **CONCLUSIONS:** Our results suggest inherited abnormalities in cortical auditory processing in schizophrenia, reflected by the decreased P50/P50m and N100 amplitudes, whereas the MMN abnormalities might reflect predominantly state-dependent neurodegeneration.

Publication Types:

Comparative Study

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, Non-P.H.S.

2. Keski-Rahkonen A, Sihvola E, Raevuori A, Kaukoranta J, Bulik CM, Hoek HW, Rissanen A, Kaprio J. Reliability of self-reported eating disorders: Optimizing population screening. *Int J Eat Disord*. 2006 Dec;39(8):754-62.

Department of Epidemiology, Columbia University, New York, New York 10032, USA. anna.keski-rahkonen@helsinki.fi

OBJECTIVE: The objective of this study was to assess whether short self-report eating disorder screening questions are useful population screening methods. **METHOD:** We screened the female participants (N = 2881) from the 1975-1079 birth cohorts of Finnish twins for eating disorders, using several short screening questions and three Eating Disorder Inventory (EDI) subscales. Comparing these measures with clinician-conducted semi-structured diagnostic interviews (N = 549) of Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) anorexia and bulimia, we calculated their sensitivities and specificities and drew receiver operating characteristic curves to further compare these items. **RESULTS:** For current and lifetime bulimia, best tradeoffs between sensitivity and specificity were reached by addressing purging behaviors. For current and lifetime anorexia, the questions "Have you ever had anorexia" and "Has anybody ever suspected that you might have an eating disorder?" optimized tradeoffs

between sensitivity and specificity. These questions generally outperformed EDI subscales. **CONCLUSION:** Simple screening questions, although less than ideal, are at least as good as other available instruments for community screenings.

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Publication Types:

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Twin Study

3. Hirvonen J, van Erp TG, Huttunen J, Aalto S, Nagren K, Huttunen M, Lonnqvist J, Kaprio J, Cannon TD, Hietala J. Brain dopamine d1 receptors in twins discordant for schizophrenia. *Am J Psychiatry*. 2006 Oct;163(10):1747-53.

Department of Psychiatry, University of Turku, Kunnallissairaalantie 20, Bldg. 9, 20700 Turku, Finland.

OBJECTIVE: It has been suggested that deficits in higher-order cognitive functions serve as

intermediate phenotypic indicators of genetic vulnerability to schizophrenia. The dopamine hypothesis of schizophrenia postulates that insufficiency of dopamine transmission in the prefrontal cortex contributes to the cognitive deficits observed in patients with the disease, and there is robust empirical evidence for a central role of prefrontal cortex dopamine D(1) receptors in working memory functions. **METHOD:** The authors examined the genetic and nongenetic effects on D(1) receptor binding in schizophrenia by studying monozygotic and dizygotic twin pairs discordant for schizophrenia as well as healthy comparison twins using positron emission tomography (PET) and the D(1) receptor antagonist ligand [(11)C]SCH 23390. Performance on neuropsychological tests sensitive to frontal lobe functioning was evaluated. **RESULTS:** High D(1) receptor density in the medial prefrontal cortex, superior temporal gyrus, and heteromodal association cortex (angular gyrus) was associated with increasing genetic risk for schizophrenia (comparison twins < unaffected dizygotic co-twins < unaffected monozygotic co-twins). Medicated schizophrenia patients demonstrated a widespread reduction in D(1) receptor binding when compared with the unaffected co-twin, and higher doses of antipsychotics were associated with lower D(1) receptor binding in the frontotemporal regions. **CONCLUSIONS:** This study demonstrated an association between genetic risk for schizophrenia and alterations in cortical D(1) receptor binding, an observation that has implications for future studies of the molecular genetics of schizophrenia. In addition, the data indicate a widespread reduction of D(1) receptor binding in medicated schizophrenia patients, supporting a link between antipsychotic drug action and dopamine D(1) receptor down-regulation.

Publication Types:

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Twin Study

4. Broms U, Madden PA, Heath AC, Pergadia ML, Shiffman S, Kaprio J. The Nicotine Dependence Syndrome Scale in Finnish smokers. *Drug Alcohol Depend*. 2007 Jun 15;89(1):42-51. Epub 2006 Dec 13.

Department of Public Health, University of Helsinki, Mannerheimintie 172, P.O. Box 41, 00014 Helsinki, Finland. ulla.broms@helsinki.fi

The Nicotine Dependence Syndrome Scale (NDSS) is a new multidimensional measure of nicotine dependence. The study aim was to examine the structure and heritability of the NDSS and its associations with nicotine dependence defined by FTND and DSM-IV criteria among Finnish smokers participating in an ongoing twin-family study. Adult twin pairs concordant for smoking from the Finnish Twin Cohort Study, and their siblings and parents were interviewed. Among 1370 smokers, the sum score of the NDSS (a summary measure of dependence) correlated moderately highly with FTND score ($r=0.62$). Subjects in the highest NDSS sum score groups were more likely to be nicotine dependent according to DSM-IV criteria compared with those in the lowest quintile (odds ratio=36.7, 95% confidence interval 13.0-103). In exploratory factor analysis, we derived three factors, named drive/priority, stereotypy/continuity and tolerance. The drive/priority factor correlated best with FTND ($r=0.54$). Genetic modeling showed no differences in the genetic architecture of NDSS or FTND by gender; the overall heritability estimate for NDSS was 0.30 (95% CI 0.06-0.47), and for FTND 0.40 (95% CI 0.23-0.55). The sum score of the NDSS is moderately highly associated with DSM-IV nicotine dependence as well as FTND. These analyses indicate that the NDSS functions well in a Finnish family-based sample and provide additional validation of a new scale developed to capture complex behavioural features of nicotine dependence.

Publication Types:

Comparative Study

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Twin Study

5. Korhonen T, Broms U, Varjonen J, Romanov K, Koskenvuo M, Kinnunen T, Kaprio J. Smoking behaviour as a predictor of depression among Finnish men and women: a prospective cohort study of adult twins. *Psychol Med.* 2007 May;37(5):705-15. Epub 2006 Dec 21.

Department of Public Health, University of Helsinki, Finland. tellervo.korhonen@helsinki.fi

BACKGROUND: Depression is associated with smoking, but the causality of the relationship is debated. The authors examine smoking behaviour as a predictor of depression among the Finnish adult twin population. **METHOD:** Based on responses to surveys in 1975 and 1981, the authors characterized the subjects as never smokers, persistent former smokers, quitters, recurrent smokers and persistent smokers. The Beck Depression Inventory (BDI) was applied in 1990 to measure depression (BDI score >9). Although the population consisted of twins, the authors first considered the subjects as individuals. Logistic regression models were computed for 4164 men and 4934 women. In order to control for family and genetic background, conditional logistic regression analyses were conducted among twin pairs discordant for depression. Bivariate genetic modelling was used to examine genetic and environmental components of the correlation between smoking and depression. **RESULTS:** Among the men, persistent smoking (OR 1 x 42, 95% CI 1 x 07-1 x 89) and smoking in 1975 but quitting by 1981 (OR 1 x 68, 95% CI 1 x 17-2 x 42) was associated with a higher risk of depression, while among the women only the quitters had an elevated risk (OR 1 x 38, 96% CI 1 x 01-1 x 87). The gender x smoking interaction showed persistent smoking to be a stronger risk for men. When family and genetic background were controlled, smoking remained a predictor of depression. Genetic modelling among the men suggested a modest correlation ($r_g=0.25$) between genetic components of smoking and depression. **CONCLUSIONS:** Smoking behaviour may be a gender-sensitive predictor of depression, the stronger association in men being partly accounted for by having underlying genes in common.

Publication Types:

Research Support, Non-U.S. Gov't

Twin Study

6. Pietilainen KH, Sysi-Aho M, Rissanen A, Seppanen-Laakso T, Yki-Jarvinen H, Kaprio J, Oresic M. Acquired obesity is associated with changes in the serum lipidomic profile independent of genetic effects - a monozygotic twin study. *PLoS ONE*. 2007 Feb 14;2:e218.

Obesity Research Unit, Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland.

Both genetic and environmental factors are involved in the etiology of obesity and the associated lipid disturbances. We determined whether acquired obesity is associated with changes in global serum lipid profiles independent of genetic factors in young adult monozygotic (MZ) twins. 14 healthy MZ pairs discordant for obesity (10 to 25 kg weight difference) and ten weight concordant control pairs aged 24-27 years were identified from a large population-based study. Insulin sensitivity was assessed by the euglycemic clamp technique, and body composition by DEXA (% body fat) and by MRI (subcutaneous and intra-abdominal fat). Global characterization of lipid molecular species in serum was performed by a lipidomics strategy using liquid chromatography coupled to mass spectrometry. Obesity, independent of genetic influences, was primarily related to increases in lysophosphatidylcholines, lipids found in proinflammatory and proatherogenic conditions and to decreases in ether phospholipids, which are known to have antioxidant properties. These lipid changes were associated with insulin resistance, a pathogenic characteristic of acquired obesity in these young adult twins. Our results show that obesity, already in its early stages and independent of genetic influences, is associated with deleterious alterations in the lipid metabolism known to facilitate atherogenesis, inflammation and insulin resistance.

7. Dick DM, Viken R, Purcell S, Kaprio J, Pulkkinen L, Rose RJ. Parental monitoring moderates the importance of genetic and environmental influences on adolescent smoking. *J Abnorm Psychol*. 2007 Feb;116(1):213-8.

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA. dickd@psychiatry.wustl.edu

Although there is a substantial literature on the role of parenting in adolescent substance use, most parenting effects have been small in magnitude and studied outside the context of genetically informative designs, raising debate and controversy about the influence that parents have on their children (D. C. Rowe, 1994). Using a genetically informative twin-family design, the authors studied the role of parental monitoring on adolescent smoking at age 14. Although monitoring had only small main effects, consistent with the literature, there were dramatic moderation effects associated with parental monitoring: At high levels of parental monitoring, environmental influences were predominant in the etiology of adolescent smoking, but at low levels of parental monitoring, genetic influences assumed far greater importance. These analyses demonstrate that the etiology of adolescent smoking varies dramatically as a function of parenting. (c) 2007 APA, all rights reserved.

Publication Types:

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Twin Study

8. Saccone SF, Pergadia ML, Loukola A, Broms U, Montgomery GW, Wang JC, Agrawal A, Dick DM, Heath AC, Todorov AA, Maunu H, Heikkila K, Morley KI, Rice JP, Todd RD, Kaprio J, Peltonen L, Martin NG, Goate AM, Madden PA. Genetic linkage to chromosome 22q12 for a heavy-smoking quantitative trait in two independent samples. *Am J Hum Genet*. 2007 May;80(5):856-66. Epub 2007 Mar 26.

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA.
saccones@msnotes.wustl.edu

We conducted a genomewide linkage screen of a simple heavy-smoking quantitative trait, the maximum number of cigarettes smoked in a 24-h period, using two independent samples: 289 Australian and 155 Finnish nuclear multiplex families, all of which were of European ancestry and were targeted for DNA analysis by use of probands with a heavy-smoking phenotype. We analyzed the trait, using a regression of identity-by-descent allele sharing on the sum and difference of the trait values for relative pairs. Suggestive linkage was detected on chromosome 22 at 27-29 cM in each sample, with a LOD score of 5.98 at 26.96 cM in the combined sample. After additional markers were used to localize the signal, the LOD score was 5.21 at 25.46 cM. To assess the statistical significance of the LOD score in the combined sample, 1,000 simulated genomewide screens were conducted, resulting in an empirical P value of .006 for the LOD score of 5.21. This linkage signal is driven mainly by the microsatellite marker D22S315 (22.59 cM), which had a single-point LOD score of 5.41 in the combined sample and an empirical P value <.001 from 1,000 simulated genomewide screens. This marker is located within an intron of the gene *ADRBK2*, encoding the beta-adrenergic receptor kinase 2. Fine mapping of this linkage region may reveal variants contributing to heaviness of smoking, which will lead to a better understanding of the genetic mechanisms underlying nicotine dependence.

Publication Types:

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

9. Viken RJ, Kaprio J, Rose RJ. Personality at ages 16 and 17 and drinking problems at ages 18 and 25: genetic analyses of data from Finn Twin16-25. *Twin Res Hum Genet.* 2007 Feb;10(1):25-32.

Department of Psychological and Brain Sciences, Indiana University, Bloomington 47405, USA.

We enrolled more than 3500 same-sex twins from 5 consecutive Finnish birth cohorts into a longitudinal study as each cohort reached age 16. Twins completed the Psychopathic Deviate (Pd) Scale of the Minnesota Multiphasic Personality Inventory at baseline, Sensation Seeking Scale items as each cohort reached age 17, and later, at average ages 18.5 and 25, the Rutgers Alcohol Problem Index (RAPI). Using raw maximum likelihood estimation, we fit a Cholesky model to the 4 variables assessed at 4 ages across the 4 twin types; we estimated genetic and environmental influences on the stability of alcohol problems across development and the genetic and environmental contributions to predictive correlations between adolescent personality and later alcohol-related behavior problems. With one exception, the phenotypic, genetic, and environmental correlations were very similar for males and females. The exception was that the lagged associations of Pd and RAPI reflect a higher genetic correlation among males than females and a higher environmental correlation among females than males. Our analyses suggest that developmental changes underlying variation in alcohol problems from late adolescence to early adulthood differ for males and females. In males, the main change is decreased variation due to shared environmental effects; the magnitude of genetic effects is stable over time, and the high genetic correlation, .95, suggests that the same genetic influences are important at both ages. Among females, in contrast, genetic influences decline in magnitude from age 18 to 25, and at least part of the genetic effect evident at age 25 differs from the genetic effect evident at age 18.

Publication Types:

Comparative Study

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Twin Study

10. Loukola A, Broms U, Maunu H, Widen E, Heikkila K, Siivola M, Salo A, Pergadia ML, Nyman E, Sammalisto S, Perola M, Agrawal A, Heath AC, Martin NG, Madden PA, Peltonen L, Kaprio J. Linkage of nicotine dependence and smoking behavior on 10q, 7q and 11p in twins with homogeneous genetic background. *Pharmacogenomics J.* 2007 Jun 5; [Epub ahead of print]

[1] Department of Molecular Medicine, National Public Health Institute, Helsinki, Finland [2] Finnish Genome Center, University of Helsinki, Helsinki, Finland.

The significant worldwide health burden introduced by tobacco smoking highlights the importance of studying the genetic determinants of smoking behavior and the key factor sustaining compulsive smoking, that is, nicotine dependence (ND). We have here addressed the genetic background of smoking in a special study sample of twins, harmonized for early life events and specifically ascertained for smoking from the nationwide twin cohort of the genetically unique population of Finland. The twins and their families were carefully examined for extensive phenotype profiles and a genome-wide scan was performed to identify loci behind the smoking status, ND and the comorbid phenotype of ND and alcohol use in 505 individuals from 153 families. We replicated previous linkage findings on 10q (max logarithm of the odds (LOD) 3.12) for a smoker phenotype, and on 7q and 11p (max LOD 2.50, and 2.25, respectively) for the ND phenotype. The loci linked for ND also showed evidence for linkage for the comorbid phenotype. Our study provides confirmatory evidence for the involvement of these genome regions in the genetic etiology of smoking behavior and ND and for the first time associates drinking and smoking to a shared locus on 10q. *The Pharmacogenomics Journal* advance online publication, 5 June 2007; doi:10.1038/sj.tpj.6500464.

11. Keski-Rahkonen A, Hoek HW, Susser ES, Linna MS, Sihvola E, Raevuori A, Bulik CM, Kaprio J, Rissanen A. Epidemiology and course of anorexia nervosa in the community. *Am J Psychiatry.* 2007 Aug;164(8):1259-65.

Department of Public Health, PO Box 41, 00014 University of Helsinki, Finland. anna.keski-rahkonen@helsinki.fi.

OBJECTIVE: Most previous studies of the prevalence, incidence, and outcome of anorexia nervosa have been limited to cases detected through the health care system, which may bias our understanding of the disorder's incidence and natural course. The authors sought to describe the onset and outcomes of anorexia nervosa in the general population. **METHOD:** Lifetime prevalences, incidence rates, and 5-year recovery rates of anorexia nervosa were calculated on the basis of data from 2,881 women from the 1975-1979 birth cohorts of Finnish twins. Women who screened positive for eating disorder symptoms (N=292), their screen-negative female co-twins (N=134), and 210 randomly selected screen-negative women were assessed for lifetime eating disorders by telephone by experienced clinicians. To assess outcomes after clinical recovery and to detect residua of illness, women who had recovered were compared with their unaffected co-twins and healthy unrelated women on multiple outcome measures. **RESULTS:** The lifetime prevalence of DSM-IV anorexia nervosa was 2.2%, and half of the cases had not been detected in the health care system. The incidence of anorexia nervosa in women between 15 and 19 years of age was 270 per 100,000 person-years. The 5-year clinical recovery rate was 66.8%. Outcomes did not differ between detected and undetected cases. After clinical recovery, the residua of illness steadily receded. By 5 years after clinical recovery, most probands had reached complete or nearly complete psychological recovery and closely resembled their unaffected co-twins and healthy women in weight and most psychological and social measures. **CONCLUSIONS:** The authors found a substantially higher lifetime prevalence and incidence of anorexia nervosa than reported in previous studies, most of which were based on treated cases. Most women recovered clinically within 5 years, and thereafter usually progressed toward full recovery.

9. ADDICTION PREVENTION AND TREATMENT UNIT

9.1. Background and goals

Addiction Prevention and Treatment Unit (RHY) was established in 2006 and is a continuation of the clinical team of Alcohol Research Center at KTL-MAO. Currently this growing unit has five full time members. Our mandate is not only to protect, maintain and improve the health of the Finnish people but also to prevent addiction related health problems and to evaluate and implement new treatments on substance abuse. As a clinical research unit, RHY plays an important role in this process in the areas of alcoholism, drug dependence and mental health. The strength of RHY comes largely from the unique ability to take a new treatments all the way from its beginnings in theory, through animal testing, to world-class double-blind placebo-controlled clinical trials, and then on to practical application. RHY has this unique ability because of its history, its affiliations, associations, and networking.

9.2. The Research, a far reaching impact and networking

The research at RHY is widespread, from primary to tertiary prevention in many fields of substance abuse. The research is polarized in three dimensions, i) epidemiological and preventive studies of hazardous alcohol drinking, ii) studies and implementation on new treatments on alcohol and opiate dependence, and iii) providing expert services in the field of substance abuse. The unit plays an active role in consulting Helsinki University Hospital and hospitals in Finland and elsewhere, including strong network with the Finnish Society of Addiction Medicine (president), the International Society for Addiction Medicine (vice president, ISAM) and providing expert consultations in preparation national and international Current Care Guidelines with Duodecim (team member) and the World Health Organization (advisor, WHO). Some of the organizations closely cooperating with RHY include:

Järvenpää Social Hospital
Unit on Substance Abuse Medicine, HY
Department of General Medicine, TaY
Helsinki University Student Health Service
A-clinics and A-clinic Foundation

Duodecim
 Neurobehavioral Health Service (Sarasota)
 New Era Assisted Recovery (Miami)
 University of Kentucky College of Medicine
 National Anxiety Foundation (USA)
 WHO
 ISAM, ESBRA, ISBRA

9.3. The research, achievements

Hazardous Alcohol Consumption, detection, prevention and implementation

Brief alcohol intervention has been proven to be effective in reducing heavy drinking among primary health care patients. In recent years RHY and National Public Health Institute have been increasingly more active in promoting the use of brief intervention in Finnish health care. This implementation activity has been based on high quality research leading to international publication and collaboration with national and international doers in action projects aiming at implementation of brief intervention. As an example of high quality research RHY-National Public Health Institute has been involved with international collaboration leading to the first review article in the field (Nilsen et al. 2006). As part of practical implementation activity RHY has been involved in National Brief Intervention Project (www.stm.fi/Resource.phx/hankk/hankt/vamp/index.htm) as well with Primary Health Care European Project on Alcohol (www.gencat.cat/salut/phepa/units/phepa/html/en/Du9/index.html), funded by the European Commission. Both of these projects aim at wide-spread implementation of brief intervention activity. The wide-spread implementation of this activity will lead significant public health improvement. The most important publications in this field of our research are:

1. Aalto M, Pekuri P, Seppä K. Use of laboratory markers and the AUDIT questionnaire by primary care physicians to detect alcohol abuse by patients. *Alcohol Alcohol* 2005; 40: 520-523.
2. Aalto M, Pekuri P, Seppä K. Implementation of brief alcohol intervention in primary health care: do nurses' and general practitioners' attitudes, skills and knowledge change? *Drug Alcohol Rev* 2005; 24: 555-558.

Department of Mental Health and Alcohol Research, National Public Health Institute, P.O. Box 33, FIN-00251 Helsinki, Finland. mauri.aalto@ktl.fi

Brief alcohol intervention reduces heavy drinking, but its implementation has been challenging. The purpose was to evaluate self-reported changes in attitudes, skills and knowledge regarding brief intervention among nurses and general practitioners (GPs) during an implementation project. A questionnaire

survey was used before and after the implementation to all nurses and GPs working at the time in the seven primary health-care centres of the city of Tampere, Finland. Several positive changes indicate an increased amount of knowledge regarding brief intervention among the professionals during the implementation. **CONCLUSIONS:** Brief intervention activity was found especially among the nurses. The success in increasing the knowledge can also be seen in a decrease of training needs. Instead, attitudes and skills among the professionals did not seem to develop positively. Increasing motivational skills especially seems to be the future challenge.

3. Aalto M, Hyvönen S, Seppä K. Do primary care physicians' own AUDIT scores predict their use of brief alcohol intervention? A cross-sectional survey. *Drug Alcohol Depend* 2006; 83:169-173.

Department of Mental Health and Alcohol Research, National Public Health Institute, P.O. Box 33, FIN-00251 Helsinki, Finland. mauri.aalto@ktl.fi

To define whether the Alcohol Use Disorders Identification Test (AUDIT) scores of primary care physicians themselves predict their willingness to use brief alcohol intervention. Cross-sectional self-administered questionnaire survey to all 3193 physicians providing primary health care in Finland. The response rate was 1909 (59.8%). Odds ratios from multinomial regression analysis were calculated for self-reported frequency (never, occasionally or regularly) of conducting brief interventions by physicians with AUDIT scores of 0-1, 2, 3, 4, 5-7 or ≥ 8 . The prevalence of heavy drinkers based on AUDIT score (≥ 8) was 14.5% among all physicians, 7.0% among females and 27.0% among males. Of the respondents 9.4% reported doing brief intervention regularly and 50.0% occasionally. AUDIT scores did not significantly predict either regular or occasional use of brief intervention. Instead, some other independent predictors for more frequent use of brief intervention were found. These included having a specialist licence in general practice or occupational health care and the location of the practice, but not gender or age. **CONCLUSIONS:** The present results indicate that in general heavy drinking among primary care physicians do not explain the low frequency with which brief intervention is used in primary health care.

4. Sillanaukee P., Massot N., Jousilahti P., Vartiainen E., Poikolainen K., Olsson U. and Alho H.: Enhanced clinical utility of gamma-CDT in a general population. *Alcohol Clin Exp Res.* 24(8)1202-1206, 2000.

Former employee of Department of Mental Health and Alcohol Research, National Public Health Institute, P.O. Box 33, FIN-00251 Helsinki, Finland.

The use of a combination of markers to detect excessive alcohol consumption has been reported to provide better sensitivity in the diagnosis of alcohol abuse than single markers. However, the optimal combination of markers for the diagnosis of alcohol abuse has not yet been found. The aim of this study was to compare the diagnostic value of carbohydrate-deficient transferrin (CDT) and gamma-glutamyltransferase (GGT) to discriminate among heavy drinkers (>280 g/week), moderate drinkers (105-280 g/week), and light drinkers (<105 g/week). Their mathematical combination, named gamma-CDT, which has been found to be a strong marker of alcohol abuse in a former study, was also evaluated. The study was conducted in a group of 6962 subjects (3974 males and 2988 females), between the ages of 25 and 74 years, who participated in a large cross-sectional risk factor survey carried out in five geographic areas in Finland. In each study area, an age- and gender-stratified random sample was drawn from the general population. Sensitivity, specificity, positive and negative predictive values, and receiver operating characteristic curves were used to evaluate the performance of CDT, GGT, and gamma-CDT. For both sexes, the combined marker had the highest specificity (95%) and sensitivity in detecting heavy drinkers. In all cases, gamma-CDT had the highest area under ROC plots. Our results also showed that GGT and CDT have similar, and rather low, sensitivity but high specificity in a general population.

CONCLUSIONS: Compared with single markers, a significant improvement of sensitivity was obtained when the combination of both markers was used, especially in females.

5. Sillanaukee P., Massot N., Jousilahti P., Vartiainen E., Sundvall J., Olsson U., Poikolainen K., Pönniö M., Allen J. P. and Alho H.: Dose response of laboratory markers to alcohol consumption in a general population. *Am J Epidemiol.* 152(8):747-751, 2000.

Former employee of Department of Mental Health and Alcohol Research, National Public Health Institute, P.O. Box 33, FIN-00251 Helsinki, Finland.

The dose response to alcohol use of carbohydrate-deficient transferrin (CDT), gamma-glutamyltransferase (GGT), and their combination (gamma-CDT) was studied in an age- and gender-stratified, random sample from Finland in 1997. A linear association with a threshold between alcohol consumption and the three markers was observed. Body mass index was negatively associated with CDT and positively with GGT. Age was positively associated with GGT and gamma-CDT. In conclusion, CDT appears to be an early phase marker of alcohol consumption. CONCLUSIONS: The combined marker, gamma-CDT, was less associated with factors such as body mass index but more strongly correlated with alcohol consumption than were the two markers separately.

6. Sillanaukee P., Strid N., Jousilahti P., Vartiainen E., Poikolainen K., Nikkari S., Allen J.P. and Alho H.: Association of self-reported diseases and health care use with commonly used laboratory markers for alcohol consumption. *Alcohol Alcohol.* 36(4):339-45, 2001.

Former employee of Department of Mental Health and Alcohol Research, National Public Health Institute, P.O. Box 33, FIN-00251 Helsinki, Finland.

The relationships of carbohydrate-deficient transferrin (CDT), gamma-glutamyltransferase (GGT) and their mathematical combination (gamma-CDT) with self-reported diseases were evaluated in a large cross-sectional risk factor survey. Significant gender effects were observed in associations of the markers with several medical conditions as well as with general health care utilization. In men, CDT was associated with rheumatoid arthritis. In both genders, GGT was positively associated with hypertension and diabetes. gamma-CDT was positively associated with hypertension in males and with asthma in females. CONCLUSIONS: This general population study demonstrates that these markers, although most commonly used to assess alcohol misuse, might also serve as health risk indicators.

Treatment of alcohol and opiate addiction, from bench to practice

An example of how RHY functions can be seen in the development, testing, and application of the treatment of alcohol dependence with the use of naltrexone and other opioid antagonists. The basis for the treatment came from basic research showing first that alcohol drinking is a reinforced learned behavior (Sinclair, *Nature*, 1973, 1974) with the reinforcement involving the same neural system as morphine. This was followed by a series of animal experiments showing that naltrexone, naloxone, and nalme-fene could be used safely, without prior detoxification, to extinguish alcohol drinking and acquisition. This resulted patents for the use of opiate antagonists in treatment of alcoholism (Sinclair, US, 1989; EU, 1995).

RHY put together a team and conducted a major double-blind placebo-controlled trial of naltrexone for treatment of alcohol dependence. Following the lead from theory and animal studies, the RHY trial was the first to show that naltrexone was safe and effective without detoxification. This is a major improvement for the cost and patient acceptability of naltrexone treatment and has now been widely incorporated in protocols around the world. The trial also proved the conclusion from theory and animal studies (Fig. 1), that naltrexone is effective only when drinking accompanied the medication rather than abstinence, also applies to the treatment of human alcoholics (Fig. 2). A database maintained by RHY, currently covering 68 clinical trials, clearly confirms those conclusions.

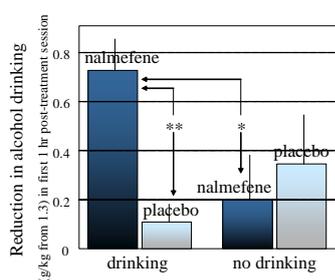


Figure 1. In rats, the opioid antagonist naltrexone produced significant benefits over placebo when paired with drinking but not when given when no drinking was possible. Shown is drinking on the 5th day (no medication) after 4 days of treatment.

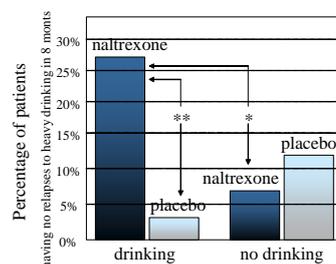


Figure 2. In human alcoholics, the opioid antagonist naltrexone produced significant benefits over placebo when paired with drinking but not when given when no drinking was possible. Shown here are the percentages of patients never relapsing to heavy drinking (<4 drinks/day or <4 drinking days/week).

The findings were put into practice in clinics in Finland and abroad, with a manual written describing the protocol for maximizing the benefits from this treatment. The procedures are constantly being improved on the basis of clinical experience in the field. Many treatments, especially in the field of addiction medicine, are in clinical practice without proven efficacy and thus ethically and economically questionable. Other areas of major achievements in our research include the detection of ineffectiveness of nitrous oxide in the treatment of alcohol dependence and withdrawal symptoms, the superiority of disulfiram pharmacotherapy and safety of buprenorphine-naloxone combination in the treatment of opiate dependence.

The most important publications in this field of our research are:

7. Heinälä P., Alho H., Kiianmaa K., Lönnqvist J., Kuoppasalmi K. and Sinclair D.: Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind placebo-controlled trial. *J Clin Psychopharm.* 21(3): 287-292, 2001.

National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland, pekka.heinala@ktl.fi.

Several studies have shown the opioid antagonist naltrexone to be effective when combined with psychosocial therapies for the treatment of patients who are dependent on alcohol with fixed medication and time (12 weeks). In this study, 121 nonabstinent outpatients with alcohol dependence (DSM-IV) were

treated with sessions of cognitive coping skills (N = 67) or supportive therapy (N = 54) and either naltrexone 50 mg/day (N = 63) or placebo (N = 58) daily for the first 12 weeks and thereafter for 20 weeks only when craving alcohol (i.e., targeted medication) in a prospective one-center, dual, double-blind, randomized clinical trial. The dropout rate for all subjects was 16.5% during the first 12-week period and approximately twice that level by the end of the study. There were no significant group differences in study completion and therapy participation rates. After the continuous medication (12 weeks), the coping/naltrexone group had the best outcome, and coping/placebo had the worst. This difference remained during the targeted medication period (the following 20 weeks). Naltrexone was not better than placebo in the supportive groups, but it had a significant effect in the coping groups: 27% of the coping/naltrexone patients had no relapses to heavy drinking throughout the 32 weeks, compared with only 3% of the coping/placebo patients. The authors' data confirm the original finding of the efficacy of naltrexone in conjunction with coping skills therapy. In addition, their data show that detoxification is not required and that targeted medication taken only when craving occurs is effective in maintaining the reduction in heavy drinking.

8. Alho H., Methuen T., Paloheimo M., Seppä K., Strid N., Apter-Kaseva N., Tiainen J., Salaspuro M. and Roine R.: Nitrous oxide has no effect in the treatment of alcohol withdrawal syndrome: a double-blind placebo-controlled randomized trial. *J Clin Psychopharm.* 23(2):211-4, 2003.

9. Alho H., Sinclair D., Vuori E., Holopainen A.: Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend* 17;88(1):75-8. 2007.

National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland. hannu.alho@ktl.fi

Buprenorphine (Subutex) is widely abused in Finland. A combination of buprenorphine plus naloxone (Suboxone) has been available since late 2004, permitting a comparison of the abuse of the two products among untreated intravenous (IV) users. A survey was distributed to attendees at a Helsinki needle exchange program over 2-weeks in April, 2005, At least 30% were returned anonymously. Survey variables included: years of prior IV opioid abuse, years of buprenorphine abuse, frequency, dosage, route of administration and reasons for use, concomitant IV abuse of other substances and amount paid on the street for both buprenorphine and buprenorphine+naloxone. Buprenorphine was the most frequently used IV drug for 73% of the respondents. More than 75% said they used IV buprenorphine to self-treat addiction or withdrawal. Most (68%) had tried the buprenorphine+naloxone combination IV, but 80% said they had a "bad" experience. Its street price was less than half that of buprenorphine alone. CONCLUSIONS: Buprenorphine seems to be the most frequently used IV drug in metropolitan Helsinki area. The buprenorphine+naloxone combination appears to be a feasible tool, along with easier access to addiction treatment, for decreasing IV abuse of buprenorphine.

10. E. Laaksonen; A. Koski-Jännes; M. Salaspuro; H Ahtinen and H. Alho. A randomized, multi-centre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. *Alc Alcohol*, in press 2007.

National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland. esti.laaksonen@ktl.fi

Acamprosate, naltrexone and disulfiram have been shown to reduce drinking and/or improve abstinence, but there are no randomized comparative studies on the effects of these three medication. This study compared the effect of brief manual-based cognitive behavioral intervention in conjunction with these three different pharmacotherapies. A randomized, open label, multicenter study in two phases; first,

12-week continuous supervised medication, followed by targeted medication up to 52 weeks in addition to a 67-week follow up period. 243 voluntary treatment-seeking alcohol-dependent adult outpatient were randomized to receive supervised naltrexone, acamprosate or disulfiram and brief manual-based cognitive behavioral intervention. The primary outcome measures were the time (days) to first heavy drinking day (HDD) and time during the first 3 months to the first drinking day after medication started. Secondary variables were abstinent days/week (0 drinks/day), average weekly alcohol intake, AUDIT (Alcohol Use Disorder Identification Test), SADD (Severity of Alcohol Dependence Data) and quality of life measures. All three study groups showed marked reduction in drinking from baseline to the end of the study. Disulfiram was twice more effective in reducing HDD and time to first drink, and more effective in reducing abstinence days and average weekly alcohol consumption, during the continuous and targeted medication periods. Disulfiram patients had a quarter of the alcohol intake during first 12 weeks compared with the others. There were no differences between the naltrexone and acamprosate groups in either phase of the study of drinking outcomes. However, naltrexone was better than acamprosate in reducing the severity of alcohol dependence indicator SADD scores. **Conclusions:** This randomized study indicates that acamprosate, naltrexone and disulfiram combined with brief manual-based cognitive behavioral intervention significantly reduces alcohol consumption and improves the quality of life. Supervised disulfiram was superior, especially during the continuous medication period, to naltrexone and acamprosate.

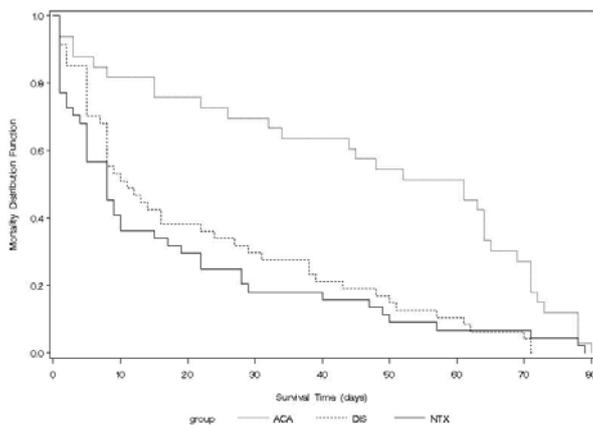


Fig 3. Time to first heavy drink (days) during the continuous medication period (1-12 weeks). Significant difference between DIS ($p = 0.001$) and others.

9.4. Funding for research and public health programs

The external funding for the research at RHY has been creditable. Approximately 40-50 % of the research budget has been funded by external sources; those are Y. Jahns-son Foundation, Alkoholitutkimussäätiö, Ahokaan Säätiö, Kordelinin Säätiö and HUS-EVO from Finland. The unit has been taking part Finrisk 1997, 2002 and 2007 national public health surveys and Terveys 2000 studies with several external funding sources. RHY has been taking part to National Brief Intervention Project funded by Social and Health Ministry of Finland, and to Primary Health Care European Project on Alcohol funded by the European Commission.

9.5. Future Challenges

Because the growing uptrend and demands of RHY it has many challenges in the field of maintaining top class experts in the team and marketing the research for external funding. So far the external funding has assured funding for five full time postgraduate students and is growing. Because Finland has limited resources in experts working in the addiction field, the personnel challenges may be more difficult to archive. However, we believe that the interesting and academic-type challenging research also attracts experts into our team in the future.

In the field of research much effort at RHY will be placed on the dissemination of the information about how to use brief intervention and effective medications on alcohol related problems effectively, with presentations at scientific conferences, interviews and websites, lectures, and publications. The development at RHY of a potential new treatment of alcohol comorbid depression and panic disorders is following a similar path.