

**POSTER SESSION 6**

Clinical studies on dependence and drug effects

Chair: Kaija Seppä

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**ALCOHOL DEPENDENCE - A COMPARISON BETWEEN GASTROENTEROLOGY AND PSYCHIATRY**Karl Wirnsberger, Walter Henriette, Lesch Otto Michael*Medical University of Vienna, Department of Psychiatry, Vienna, Austria*

Aims of the study: The liver-specific laboratory parameters of the first taking of a blood sample in the beginning of withdrawal of 233 patients addicted to alcohol (172 men, 61 women) have been compared at the Psychiatric University Hospital Vienna. 86 inpatient and 147 ambulant patients were involved. The patients had been classified according to the 4 course-types of the Lesch-typology (type I n=44; type II n=53; type III n= 92; type IV n=44). Hypothesis: 1. Addicted patients with first-grade relatives addicted to alcohol differ from patients without such genetic load as regards the severity code of the liver damage. 2. Women have higher liver-values than men. 3. There are differences between the degree of liver-load between 3 age groups (<35 ys, 35-50 ys, >50 ys). Results: 1. The hypothesis of different degrees of liver damage between alcohol-addicted patients with and without relatives addicted to alcohol could not be verified. 2. The analysis showed a higher degree of liver damage in all women (AST; ALT;  $p < 0.05$ ) compared to male patients. 3. The hypothesis of differences between the degree of liver damage between 3 age groups had been validated. The group of patients between 35-50 years had been more frequently out of the laboratory reference (parameter GGT;  $p < 0.05$ ). Discussion: Several studies are placing increasing emphasis on characteristics based on genetic origins compared to acquired behaviours. The latter seems to be more frequently postulated in association with alcohol dependency within first-degree relatives. So far, data ensure a diversity of genetic occurrence in the formation of the isoenzymes of alcohol dehydrogenase as well as alcohol dehydrogenase. Approaches of explanation regarding gender-related differences are to be found in the estrogen- and amino acid-metabolism which is involved in the alcohol-metabolism, and in the different proportion of total volume of body fluid. Alcohol employed as „medication" in combination with psychiatric disorders as characterised by the Lesch typology type II and III (anxiety, depression) causes varying drinking habits as well as differences related to onset of alcohol dependence. Nevertheless, it has to be pointed out that the mentioned criteria have to be replicated within bigger sample sizes.

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**ACUTE EFFECTS OF ALCOHOL ON ACQUISITION AND EXTINCTION OF AN APPETITIVE REWARD SEEKING RESPONSE IN SOCIAL DRINKERS**Sabine Loeber<sup>2</sup>, Theodora Duka<sup>1</sup><sup>1</sup>*Department of Psychology, University of Sussex, Brighton, United Kingdom,* <sup>2</sup>*Department of Addictive Behaviour and Addictin Medicine, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany*

Background: According to current knowledge, Pavlovian and instrumental conditioning play an important role in the development and maintenance of alcohol dependence: In phases of abstinence, the exposure to cues previously associated with drinking is hypothesized to contribute to the succumbing to craving and relapse. Thus, extinction of conditioned appetitive responses is an important aspect of current treatment approaches. However, although these conditioned drug associated responses are acquired under alcohol, it is not known how alcohol given acutely influences acquisition of an appetitive response. The present study had two aims. Firstly, we questioned whether alcohol given acutely would impair the acquisition of a reward seeking response (experiment 1). Secondly, we examined the effects of alcohol on extinction learning (experiment 2) to enhance current knowledge on mechanisms of extinction and conditions that might hamper it.

Methods: In experiment 1 alcohol (0.8g/kg) or placebo was administered to social drinkers (N=32) before they underwent an instrumental reward seeking procedure with abstract stimuli serving as S+ (always predicting a win of 10 pence) and S- (always predicting a loss of 10 pence). In experiment 2, thirty two social drinkers underwent the same procedure and, after administration of a dose of 0.8g/kg alcohol or placebo, extinction training was performed. Results: When alcohol was administered before performance of the reward seeking procedure (experiment 1) participants of the alcohol group performed the behavioural response to obtain the reward outcome more often than placebo subjects in trials associated with loss of money. This finding was observed although alcohol was not affecting explicit knowledge of stimulus-response outcome contingencies and acquisition of conditioned attentional and emotional responses. In contrast, when alcohol was administered before extinction training, our results did not show any impairment of learning of extinction after the administration of alcohol. Conclusions: These findings suggest that alcohol impairs in particular the stimulus-response translation process (i.e. performance of a response to obtain a reward outcome predicted by a stimulus rather than learning of the stimulus-reward contingencies per se. This is an important finding in light of the development of alcohol dependence.

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### **REDUCED ACTIVITY OF ANTICIPATORY REWARD SYSTEM IN PATHOLOGICAL GAMBLING: AN EVENT-RELATED FMRI STUDY**

Jung-Seok Choi<sup>1</sup>, Young-Chul Shin<sup>2</sup>, Wi Hoon Jung<sup>3</sup>, Myung Hun Jung<sup>1</sup>, Joon Hwan Jang<sup>1</sup>, Do-Hyung Kang<sup>1</sup>, Ji Yeon Han<sup>3</sup>, Ji-Young Park<sup>3</sup>, Chi-Hoon Choi<sup>4</sup>, Sam-Wook Choi<sup>5</sup>, Jun-Young Lee<sup>6</sup>, Jun Soo Kwon<sup>1,3</sup>

<sup>1</sup>Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea, <sup>2</sup>Department of Psychiatry, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, <sup>3</sup>Interdisciplinary Program in Cognitive Science and Brain Science, Seoul National University, Seoul, Republic of Korea, <sup>4</sup>Department of Radiology, National Medical Center, Seoul, Republic of Korea, <sup>5</sup>Department of Psychiatry, Ulsan University Hospital, Ulsan University School of Medicine, Ulsan, Republic of Korea, <sup>6</sup>Department of Psychiatry, Seoul National University Boramae Hospital, Seoul, Republic of Korea

To elucidate the functional brain activity specific to anticipation phase of reward in patients with pathological gambling (PG), we performed event-related functional magnetic resonance imaging (fMRI) study using a modified monetary incentive delay (MID) task. A total of 10 drug naive patients with PG and 14 age-, IQ-matched healthy controls were enrolled in this study. Subjects participated in a modified MID task, in which visual cues predicted that a rapid button response during brief target presentation would result either in monetary gain, loss, or no consequences, during fMRI scanning. Symptom severity was assessed by Yale-Brown Obsessive Compulsive Scale for pathological gambling and South Oaks Gambling Screen. Patients with PG have reduced activations in the ventromedial caudate nucleus and anterior cingulate cortex, and increased activations in the posterior cingulate cortex during anticipation of gain, with decreased activation in the anterior insula during anticipation of loss. No significant correlations were observed between brain activity and symptom severity in patients with PG. Our results provide that patients with PG may be less sensitive to positive and negative reward anticipation, and demonstrate functional abnormalities in the anticipatory reward system in PG.

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### **FAMILY HISTORY OF ALCOHOLISM AND THE SUBJECTIVE EFFECTS OF ALCOHOL**

Anna Söderpalm Gordh, Bo Söderpalm  
*of neuroscience and physiology, Gothenburg, Sweden*

Background: Alcohol has both stimulative and sedative properties that are thought to be related to both dopaminergic and GABAergic pathways in the brain. Acutely when alcohol is given, dopamine levels are increased in humans.

Research has shown that subjects with a family history of alcoholism (FHP) are at increased risk for alcoholism and that this group reacts different to alcohol than family history negative (FHN) subjects do. We tested the hypothesis that these subjects are more sensitive to the dopaminergic properties of alcohol and therefore show increased stimulative subjective responses to the effects following a single dose of alcohol compared to control subjects. Methods: 50 healthy men and women (17 FHP and 33 FHN) participated in two laboratory sessions, in which they consumed a beverage containing ethanol (0.6 g/kg in juice) or placebo (juice alone) in a randomized order. Primary dependent measures were self-report questionnaires of mood states. Results: Subjects with family history of alcoholism showed increased stimulative responses and an elevated positive mood state to ethanol compared to controls. Conclusions: At this moderate dose, ethanol increased stimulative subjective responses in individuals who were "family positive". This effect may paradoxically make the subjects drink more than people without a heritage, in order to experience the full spectrum and level of ethanol intoxication. In conclusion, the greater the reinforcing effects of the alcohol in FHP individuals the greater increase of risk for developing alcoholism.

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### **STRESS AND THE SUBJECTIVE EFFECTS OF ALCOHOL BETWEEN MEN AND WOMEN**

Sejla Brkic, Anna Söderpalm Gordh  
*of neuroscience and physiology, Gothenburg, Sweden*

Alcohol is generally classified as a depressant drug, but it exerts both stimulant-like and sedative-like effects on many behavioural outcomes including subjective effects. Stimulant effects of alcohol are observed at low blood alcohol concentrations on the ascending limb of the blood alcohol curve whereas its sedative effects occurs at higher blood alcohol concentrations and on the descending limb of the blood alcohol curve. Stimulant and sedative properties of alcohol may contribute to alcohol consumption. The aim of this study was to investigate the hypothesis that the subjective effects of alcohol drinking differ between men and women after stress. 40 male and 40 female individuals participated in the study. They consumed alcohol (0, 0.2, 0.4, 0.6, 0.8 g/kg) after completing a standardized stress test (TSST). Subjective effects were obtained at baseline and then 20, 40 and 60 minutes after alcohol consumption using the Biphasic Alcohol Effects Scale (BAES). Breath samples were provided at the beginning of each session to verify a zero blood alcohol concentration (BAC) and then 20, 40, 60 and 90 minutes after alcohol consumption. The subjective stimulant- and sedative-like effects of alcohol revealed that the women scored higher on of the several items on the BAES scale (P The result shows that women experience alcohol more intense than men do. This effect is fascinating since there were no differences in alcohol blood concentrations between women and men.

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### **THE EFFECT OF A HIGH DOSE OF ALCOHOL ON PLASMA TESTOSTERONE AND CORTISOL IN PREMENOPAUSAL WOMEN**

E Sebastian Forsblom, Tuomas PS Saarenmaa, Taisto Sarkola, Tiina Etelälahti, Katri Pakarinen, Heikki Mäkisalo, CJ Peter Eriksson  
*National Institute for Health and Welfare (THL), Helsinki, Finland*

It is generally known that low doses of alcohol don't affect or moderately elevate, and that high doses usually lower testosterone levels in men. In women, especially during the use of oral contraceptives (OC) and during the midpoint of the normal menstrual cycle, low doses of alcohol are known to elevate testosterone levels. Little is known about the effects of high alcohol doses in women. The aim of the present study was to determine the effect of a high dose of alcohol on testosterone and cortisol levels in women with normal menstrual cycle or with the use of OC. Healthy nonalcoholic premenopausal women (n=19) participated in the study. The women were divided into two groups according to their use of oral contraceptives (OC+, n=8 and OC-, n=11). Each subject participated in a random order in two sessions, one including a control drink (lingonberry-blackcurrant juice) and one including alcohol (1.4 g/kg) mixed in the juice as a 10% solution. The drinks were consumed within 3 hours starting at 19.00.

Samples of venous blood were collected at 18.30, 20.00 and 23.00 in the evening and at 10.30, 12.00 and 13.00 the following day. An alcohol-induced elevation in plasma testosterone was determined in the evening (23.00) after the intake of alcohol for both OC+ (+168 %) and OC- (+93 %) women. The corresponding changes during the control situation were -25 % and -9 % for OC+ and OC-, respectively (overall significance for alcohol versus control groups: OC+,  $p=0,001$ ; OC-,  $p=0,004$ ). Significant alcohol-related testosterone effects were not observed next morning at 10.30, at which time alcohol already had been eliminated. No significant effects by alcohol on cortisol levels were detected. The present results support our earlier findings regarding the effect by alcohol on testosterone levels in women. The lack of hangover-stress related testosterone reductions, which typically is found in men, may be explained partly by remnants of the marked testosterone evening elevations and partly by the absence of major hangover-induced cortisol elevations.

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### **THE FACTORS RELATED TO TOBACCO SMOKING AFFECTING ALCOHOL CRAVING IN ALCOHOL DEPENDENT INDIVIDUALS**

Kyeong-Sook Choi, Ho Jin Choi, Chang Hwa Lee, Bum Seok Jeong  
*Eulji University Hospital, Daejeon, Republic of Korea*

Objective: The aim of this study is to find out the factors related to tobacco smoking affecting alcohol craving in alcohol dependent individuals. Methods and Materials: Subjects of this study were 123 male smokers, 18 to 65 years of age, diagnosed with alcohol dependence. The study questionnaire consisted of demographical characteristics, alcohol drinking and smoking habits, Korean Obsessive Compulsive Drinking Scale (OCDS), 12-item Tobacco Craving Questionnaires (12-item TCQ), and Fagerström Test for Nicotine dependence (FTND). Subjects were divided into the group with high OCDS score and the group with low OCDS score according to their OCDS score. Results: The group with high OCDS score had higher frequency of alcohol drinking and more average amount of alcohol than the group with low OCDS score. Also the group with high OCDS score had higher average number of cigarettes per day, 12-item TCQ score and FTND score. In logistic regression analysis, the scores of 12-item TCQ and FTND were the most significant predicting variables for alcohol craving. Conclusions: This study presents that alcohol craving is significantly related to tobacco craving and nicotine dependence.

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### **GATEWAY AND REVERSE GATEWAY EFFECT'S HYPOTHESIS IN ADOLESCENT'S CANNABIS USE IN FRANCE IN 2005: TESTING A STRUCTURAL EQUATION MODEL**

Aurelie Mayet<sup>1</sup>, Stephane Legleye<sup>1,2</sup>, Marie Choquet<sup>1</sup>, Bruno Falissard<sup>1</sup>

<sup>1</sup>*Paris sud innovation group in adolescent mental health - INSERMU669, Paris, France,*

<sup>2</sup>*Observatoire français des drogues et toxicomanies, Saint Denis, France*

Background: Cannabis use among adolescents involves a complex set of factors. This phenomenon is also known, according to Gateway Theory, to progress by stages. For example, tobacco or alcohol use is known to lead to cannabis use. Aim of study was to verify, on a sample of French adolescents, a hypothetic sequential process which constitutes another application of gateway theory. Methods: Data came from a French nationwide cross-sectional survey carried out in 2005, involving 29,393 teenagers aged 17. Analysis used structural equation modelling, in which a same variable can be independent in an equation and dependent in another equation. This technique also permits to use latent variables, which can be deduced from a group of measured variables. Nature and way of links between variables were fixed after literature review and preliminary analysis on data. Results: The model was constructed, basing one's argument on the following stage process hypothesis: "outings with friends - tobacco and alcohol use - cannabis use - cannabis use disorders (abuse and dependence)". This model also took into account the reverse process "cannabis use - tobacco and alcohol use", also known in literature. Alternative paths were added for comparison. Coefficient associated with the stage process was effectively stronger than any coefficient associated to any alternative sequence. Moreover, a model in which alternative sequences has been deleted had a better likelihood than the complete model. Thus, cannabis use and misuse seemed to be mediated by licit substances use. Coefficient associated with the path "cannabis use - tobacco and alcohol use" was

weaker than coefficient associated with the reverse path, but was also significant. Conclusion: Despite cross sectional data collection, our results are statistically compatible with a stage process mediated by licit substance use and leading from outings to cannabis use. Thus, peer influence on substance use among adolescents is here underlined. However, model also shows that cannabis use could have a reverse influence on licit substances use. This confirms the complexity of substance use processes, which could be also explained by many confounding factors, like social or personal characteristics, not measured in this study.

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### **DORSOLATERAL PREFRONTAL CORTEX N-ACETYL ASPARTATE/TOTAL CREATINE (NAA/CR) LOSS IN MALE RECREATIONAL CANNABIS USERS**

Derik Hermann<sup>1</sup>, Alexander Sartorius<sup>1</sup>, Helga Welzel<sup>1</sup>, Sigird Walter<sup>1</sup>, Gisela Skopp<sup>2</sup>, Gabriele Ende<sup>1</sup>, Karl Mann<sup>1</sup>

<sup>1</sup>Central Institute of Mental Health, Mannheim, Germany, <sup>2</sup>Institute of Forensic and Traffic Medicine, Heidelberg, Germany

Background: Cannabinoids present neurotoxic and neuroprotective properties in in-vitro studies, inconsistent alterations in human neuroimaging studies, neuropsychological deficits, and an increased risk for psychotic episodes. Methods: <sup>1</sup>H-MR-spectroscopy, neuropsychological testing and hair analysis for cannabinoids was performed in 13 male non-treatment seeking recreational cannabis users and 13 male control subjects. Results: A significantly diminished N-acetyl-aspartate/total creatine (NAA/tCr) ratio in the dorsolateral prefrontal cortex (DLPFC) was observed in cannabis users ( $p = 0.0003$ ). NAA/tCr in the putamen/globus pallidum region correlated significantly with cannabidiol ( $R^2 = 0.66$ ,  $p = 0.004$ ). Results of the Wisconsin Card Sorting test, Trail making Test and D2 test for attention were influenced by cannabinoids. Discussion: Chronic recreational cannabis use is associated with an indication of diminished neuronal and axonal integrity in the DLPFC in this study. As chronic cannabis use is a risk factor for psychosis, these results are interesting because diminished NAA/tCr ratios in the DLPFC and neuropsychological deficits were also reported in schizophrenia. The strong positive correlation of NAA/tCr and cannabidiol in the putamen/globus pallidum is in line with neuroprotective properties of cannabidiol, which were also observed in in-vitro model studies of Parkinson's disease.

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### **EVENING TYPES SMOKE MORE AND ARE MORE NICOTINE DEPENDENT - A STUDY OF FINNISH ADULT TWINS**

Ulla Boms<sup>1,2</sup>, Jaakko Kaprio<sup>1,2</sup>, Christer Hublin<sup>3</sup>, Markku Partinen<sup>4</sup>, Pamela AF Madden<sup>5</sup>, Markku Koskenvuo<sup>1</sup>

<sup>1</sup>University of Helsinki, Department of Public Health, Helsinki, Finland, <sup>2</sup>National Institute for Health and Welfare, Helsinki, Finland, <sup>3</sup>Finnish Institute of Occupational Health, Helsinki, Finland, <sup>4</sup>RinneKoti Research Centre, Espoo, Finland, <sup>5</sup>Department of Psychiatry and Midwest Alcoholism Research Center, Washington University School of Medicine, St Louis, MO, USA

We studied the association of diurnal type, smoking behaviour and nicotine dependence using the Finnish Twin Cohort of same-sex adult twin individuals ( $n=23289$ ) unselected for smoking behaviour with surveys in 1975, 1981 and 1990 (Boms et al. 2004). Nicotine dependence was assessed later among smoking twins participating in the Nicotine Addiction Genetics Family Study ( $n=676$ ) (Loukola et al. 2008, Saccone et al. 2007). Answers to a question on diurnal type in 1981 were classified in four categories: Clearly a morning type, Some extent a morning type, Some extent an evening type, Clearly an evening type (Koskenvuo et al. 2007). Nicotine dependence was measured by DSM-IV and FTND. Regression analyses of all twin individuals examined the association between diurnal type and smoking behaviour and nicotine dependence. Evening types were more often ever and current smokers. Clearly evening types were almost twice as often (OR 1.9, 95%CI 1.7-2.1) current smokers compared to clearly morning types. Among ever smokers evening types had smoked 2.5 pack-years more than morning types (95%CI 1.8-3.2) and among current smokers they had smoked 2.1 pack-years more (95%CI 1.3-2.9). Among current smokers, there was no difference in average age of initiating smoking by diurnal type, but evening types smoked 2.7 cigarettes per day(95%CI 2.0-3.3) more than morning types.



Among current smokers in 1981, evening type did not predict smoking cessation by 1990 (OR 0.84, 95%CI 0.61-1.17). Evening types were more nicotine dependent. Adjusted for sex, age and age at initiation clearly evening type smokers were almost three times more often nicotine dependent (by DSM-IV) compared to clearly morning types (OR 2.9, 95%CI 1.6-5.3). Also nicotine dependence measured by FTND showed that clearly evening types were more dependent (scoring 0.59 points more, adjusted for age and sex, 95%CI 0.01-1.2), such that evening types had a mean, unadjusted FTND of 4.7 and morning types 4.0. Diurnal type is a novel risk factor for smoking and nicotine dependence. Evening types are more often current smokers, smoke more and are more dependent. Diurnal type however does not predict smoking cessation. The possible modulating effect of nicotine on diurnal type needs to be investigated.

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