domestic animal species. Infection may course neurobehavioral disturbances and/or fatal neurologic diseases. Since BDV antibodies were detected in humans, neuropsychiatric diseases were considered to be potentially associated with human BDV infections. Further evidence that BDV may act as an etiopathogenic co-factor in these disorders derived from findings such as the isolation of human strains of BDV from patients with recurrent mood disorders. In addition, the antiviral drug amantadine appears to have antidepressive effects partly due to its antiviral efficacy on BDV.

This report stresses the role of BDV in patients with affective and obsessive–compulsive disorders (OCD). Furthermore, the use of amantadine in the treatment of BDV infected patients with major and bipolar depression as well as OCD will be shown with a special emphasis to clinical experiences and virological data: Amantadine reduced depressive symptoms in these disorders. In addition, clinical improvement was paralleled by a reduction of BDV infection parameters in the clinically responding patients.

# S21. Gene expression in addictive disorders

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## S21.1

Opioid genes in the actions of drugs of abuse: perspectives from human and experimental animal models

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Opioid neuropeptide genes are highly expressed in limbic-related brain regions that are considered important neuroanatomical substrates for drug addiction. It has been well documented that alterations in opioid neuropeptide gene expression occur not only after administration of opiate drugs, but also following the use of different types of psychoactive substances. The use of psychostimulant drugs such as cocaine whose primary pharmacological actions are at dopamine neurons have been shown in both humans and animal models to have strong effects on the mRNA expression of the dynorphin opioid peptide and its receptor, kappa. Recent studies have also demonstrated a tight interaction between the cannabinoid and opioid neuropeptide systems. The issues to be addressed relate to whether opioid neuropeptides might serve as common targets for "all" drugs of abuse, whether there is a limbic regional specificity of the opioid neuropeptide gene alterations following drug use, and what are the specific patterns of the opioid gene expression for different types of addictive substances.

## S21.2

Gene expession in addictive disorders

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Studies from several laboratories have shown that gene expression of many specific genes may be altered during administration of drugs of abuse. Of importance are the dramatic time-related changes which have been observed with respect to alterations in gene expression, specifically with the expression of some genes changed by acute exposure to a drug of abuse, and the expression of fewer and more selected genes altered during sub-acute and chronic exposure to a drug of abuse, and with yet a different profile possibly present in the abstinent state following withdrawal from chronic exposure. Gene expression changes may be large for some genes. However, for many genes, which may in fact be critical to the alterations observed in behaviors during and following exposure to a drug of abuse, the changes may be very small in magnitude and thus require sensitive techniques for the detection and measurement. Very different alterations have been observed following exposure to any specific drug of abuse (or potential therapeutic agent) depending not only on the duration and dose of exposure, but also on the precise mode and pattern of exposure. Thus, the development of novel animal models, which mimic either the human patterns of abuse or the exposures which pertain during pharmacotherapeutic interventions, are critical for elucidating the molecular changes and, thus, peptide, other neurochemical and behavioral effects which occur during such exposure.

## S21.3

Microarray analysis of brain gene expression in human alcoholism

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The goal of our work is to identify genes which are differentially expressed in the brains of human alcoholics as compared with non-alcoholics. We used cDNA microarrays to compare the relative levels of over 7000 gene transcripts from frontal and motor cortex. RNA samples were obtained from three independent case groups of alcoholics and compared to controls cases which were matched across a number of variables such as age, sex, and postmortem delay. We identified approximately 190 and 130 changes in gene expression in frontal and motor cortex, respectively. Of these changes, 56 were common to both frontal and motor cortex. The data were analyzed by hierarchical expression profiling of functionally related families of genes. The most striking and consistent changes in expression were in two functional clusters: genes coding for myelin-related proteins (50 named genes) and genes important for protein trafficking (45 named genes). There were also changes in mRNAs coding for proteins involved in neuroprotection and cell survival, calcium signaling, and regulators of the cell cycle. These results indicate an extensive reprogramming of gene expression in frontal and motor cortex by alcoholism.

## S21.4

From phenotype to genes and back: a functional genomics approach to alcohol dependence

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Animal paradigms can model important aspects of alcoholism, and have produced clinically effective treatment of this disorder, incl. naltrexone, acamprosate and ondansetrone. These compounds have been developed based on a priori knowledge of the role of opioid, amino acid and serotonergic transmission, respectively. Recently, functional genomics strategies have provided novel tools in the search for novel treatment targets. For this purpose, we have developed a model which allows us to study gene regulations underlying the transition from a low- to high-drinking state. Following repeated cycles of EtOH vapor intoxication and mild withdrawal, a persistent and acamprosate-sensitive high voluntary EtOH consumption is induced. In rats subjected to this procedure, the Affymetrix Rat Neurobiology GeneChip reveales long term differential gene expression of limited groups of genes in cingulate cortex and

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