had not been evaluated. We consecutively enrolled 1358 subjects aged >45 years from a general population attending a medical check-up. All subjects were submitted to medical examination and laboratory tests in addition to LSM, performed the same day by a single operator. Subjects with LSM values over 8 kPa were referred to a liver unit for further investigation. Subjects with missing data (n = 23), LSM failure (n = 51) or unreliable LSM values (n = 94) were not considered for the analysis. Among the 1190 remaining subjects, 80 (7.5%) had LSM over 8 kPa, including 9 patients with LSM above 13 kPa. Although normal liver tests were observed in 43% of them (38 of 89), a specific cause of chronic liver disease was found in all cases. NAFLD was the likely cause of chronic liver disease in 52 patients, alcoholic liver disease (ALD) in 20, both causes being associated in 7 additional patients. HCV and HBV chronic hepatitis were documented in five and four cases, respectively, and primary biliary cirrhosis in one. Liver biopsy was obtained for 27 patients, including the nine patients with LSM above 13 kPa. Among these nine patients, all showed liver cirrhosis due to ALD in five cases, chronic hepatitis C in three and chronic hepatitis B in one case. The 18 remaining biopsies showed liver fibrosis in all cases except one (isolated steatosis), with ALD and NAFLD being present in six and eight cases, respectively. In conclusion, LSM proved to be a useful and specific procedure to screen for cirrhosis in the general population and to detect undiagnosed chronic liver disease in apparently healthy subjects. Liver cirrhosis is an important public health problem involving 0.7% of the general population.

S14
IDENTIFICATION OF NEUROINFLAMMATION IN THE BRAIN IN VIVO AND IN VITRO AND THERAPEUTIC STRATEGIES TO COMBAT ITS PROGRESSION

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S14.1
INFLAMMATORY PROCESSES IN NEURODEGENERATIVE DISEASES
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Changes in morphology in specific brain regions are observed in various neurodegenerative diseases, e.g. Parkinson’s and Alzheimer’s diseases as well as in chronic alcohol abusers and adolescents involved in ‘binge drinking’. Such changes are known to be associated with alterations in motor function as well as in cognitive impairment. The exact triggers for each of these neurodegenerative processes are unknown, although alcohol and its metabolite acetaldhyde contribute to alcohol-induced brain damage. A common factor in all of these diseases is the occurrence of neuroinflammation, which occurs at an early stage of the disease process and drives the disease pathology. The signaling pathways that are involved in such neuroinflammation include various transition metals, iron and copper, mitochondrial dysfunction as well as activation of the innate immune system. Metals as well as alcohol metabolism can generate reactive oxygen species that can initiate lipid peroxidation by attacking polyunsaturated fatty acids in membrane phospholipids, generating a family of reactive aldehydes, which can undergo Michael-type additions to protein thiol, imidazole and amino groups. Together with other oxidative modifications, this generates protein carbonyls, causing protein denaturation and aggregation. In turn, this overwhelms the ubiquitin/proteasome system, which can no longer eliminate these defective, damaged proteins. Aggregates of these ubiquinated proteins are a prominent pathological feature found within intracellular inclusion bodies in specific brain regions in many ‘protein conformational’ neurodegenerative diseases, such as Alzheimer’s, Parkinson’s, ALS and Huntington’s disease.

S14.2
IMAGING NEUROINFLAMMATION IN ALCOHOLISM
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Cognitive deficits may impair the ability of patients’ engagement in behavior change programs. Alcohol-related brain damage (ARBAD) may present subclinically, and is a growing cause of cognitive impairment. While thiamine deficiency has been emphasized as a cause of ARBAD and parenteral thiamine is an important preventative strategy, the mechanisms are probably multifactorial. The role of neuroinflammation in the pathogenesis of a wide range of neurodegenerative processes following acute and chronic insults is receiving growing attention. Pre-clinical and post-mortem evidence suggest that neuroinflammation is important in the pathogenesis of ARBAD, but this has yet to be demonstrated in vivo in the human brain. The 18 kDa Translocator Protein (TSPO) is upregulated in activated microglia. PET ligands specific for the TSPO have been proposed to be useful for the quantification of neuroinflammation in human subjects in vivo. [14C]PK11195 has been used extensively for the past 20 years for this purpose, and hepatic encephalopathy, including cases precipitated by alcohol, is associated with increased [14C]PK11195 binding (Cagnin et al., 2006). The utility of [14C]PK11195 has been limited by uncertainties in its quantification, due to a low signal-to-noise ratio in the tissue and problematic plasma quantification. Novel TSPO ligands such as [14C]PBR28 address these problems (Imaizumi et al., 2008) and provide an exciting opportunity to probe the role of neuroinflammation in the pathogenesis of cognitive impairment related to chronic alcohol intake. Such a tracer could be used to investigate the relationship between microglial activation and indices of cognitive function. The time course of microglial activation has prognostic significance in other disorders (Rumackhansingh et al., 2011), and may be relevant in ARBD. The relationship between neuroinflammation and neurotransmitter perturbations in alcohol dependence and withdrawal may be detectable by imaging in vivo in the human brain (Umhaa et al., 2010). Finally, TSPO ligand PET studies provide the opportunity to quantify the change in neuroinflammation produced by novel prophylactic compounds.
expression. Post-mortem human alcoholic brain shows increased levels of neuroimmune genes consistent with ethanol-induced neuroinflammation. In brain slice cultures, exogenous IL-1beta, TNFalpha and MCP1 reduce neurogenesis. Neutralizing antibodies to IL-1beta added to slice cultures increased neurogenesis and completely reversed ethanol inhibition of neurogenesis. Exogenous IL-1 receptor antagonist, IL-1Ra, also blocked ethanol inhibition of neurogenesis, suggesting that IL-1beta mediates ethanol inhibition of neurogenesis. A number of drugs reverse ethanol inhibition of neurogenesis. Antidepressants that are effective treatments of human depression reverse ethanol induction of IL-1beta and stimulate neurogenesis. Drugs that blunt neuroimmune activation, block inflammasome formation or NFkappaB activation reverse ethanol inhibition of neurogenesis. These findings suggest that inflammasome induction and loss of neurogenesis contribute depression and negative affect. Antidepressants and anti-neuroinflammatory drugs reverse ethanol inhibition of neurogenesis through inhibition of IL-1beta. (This study was supported by NIH and NIAAA.)

S15
ESBRA/ISBRA JOINT SYMPOSIUM: IMAGING IN ALCOHOL RESEARCH
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S15.1
THE ROLE OF FUNCTIONAL NEUROIMAGING IN THE CHOICE OF TREATMENT FOR ALCOHOLICS
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In alcohol-dependent patients, alcohol-associated cues elicit brain activations in mesocorticollimbic networks related to the rewarding properties of the drug and were previously found to be associated with relapse behaviour. Functional magnetic resonance imaging (fMRI) was used to assess cue-reactivity during the presentation of alcohol-related pictures in 73 recently detoxified alcohol-dependent patients before and after randomized double-blind treatment with naltrexone, acamprosate or placebo. Using Cox-regression we examined the effect of fMRI cue-reactivity and treatment on the time to the first severe relapse. In early abstinence, the activated network consisted of the ventral striatum, cingulate gyrus and prefrontal areas. After 2 weeks of treatment with naltrexone, acamprosate or placebo cue-elicited brain activity in the striatum and the thalamus decreased in comparison with the first medication-free fMRI session. With increasing fMRI, cue-reactivity at the first fMRI session relapse risk was reduced in the Naltrexone compared with the Acamprosate group for the ventral striatum. Notably, remaining cue-induced brain activation in the ventral striatum during the second fMRI session was negatively associated with the time to first severe relapse. fMRI cue-reactivity can be used as a prognostic factor for relapse in alcohol-dependent patients. Alcohol-dependent patients with high fMRI cue-reactivity might especially benefit from Naltrexone treatment. [This work was supported by the DFG (He 2597/4-1&4-2; Sm 80/1-1) and the BMBF (01EB0110&01EB0410 km).]

S15.2
THE Dopamine D2/3 RECEPTOR AGONIST RADIOLIGAND \([11C](+)-PHNO AS A TOOL FOR STUDYING ALCOHOL DEPENDENCE IN HUMANS
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Dopamine plays a preeminent role in acquisition and maintenance of addictive behaviour. Animal studies have identified firing of brainstem dopamine neurons and release of dopamine into the ventral striatum as essential neurochemical components of reward-learning processes. Sensitization is a process in which repeated intermittent exposure to a substance causes increased behavioural and neurochemical response after re-exposure to the substance. Sensitization is believed to contribute to the persisting vulnerability to relapse in alcohol-dependent patients. On a neurochemical level, it is associated with increased striatal dopamine release. Brain imaging methods such as positron emission tomography (PET) have provided substantial insight into dopaminergic alterations in alcohol dependence. Imaging the competition between dopamine and a radioligand at postsynaptic dopamine D2/3 receptors allows for measuring changes in endogenous dopamine levels in the living human brain. So far, studies on the competition of a radioligand with dopamine in humans used D2/3 antagonist radioligands. Dopamine D2/3 receptor agonist radioligands are a recent development with the major advantage that they are more sensitive towards fluctuations in endogenous dopamine than their D2/3 antagonist counterparts. The full agonist radioligand \([11C](+)-PHNO is currently the most sensitive ligand for detecting changes in extracellular dopamine levels in the living human brain. Here we propose to use \([11C](+)-PHNO and PET as the current method of choice for studying dopaminergic alterations in patients with alcohol dependence. The method might help to build a rationale for dopamine agonist treatment in alcohol dependence. Moreover, \([11C](+)-PHNO may help to better understand sensitization and possibly even the dopaminergic response to alcohol-related environmental cues in relation to the risk of relapse. In summary, the dopamine D2/3 receptor agonist radioligand \([11C](+)-PHNO has the potential to substantially advance our knowledge on dopaminergic mechanisms in reward learning and sensitization in patients with alcohol dependence.

S15.3
MULTI-MODALITY IMAGING ASSESSMENT OF ALCOHOLISM’S DAMAGING EFFECT ON BRAIN SYSTEMS AND CIRCUITRY
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Alcoholism induces widespread yet selective damage of brain structure and disturbance of brain function that likely contributes to difficulty in sustaining sobriety and in achieving normal and efficient functioning. The multiple modalities of \textit{in vivo} magnetic resonance imaging (MRI) provide noninvasive methods to characterize alcoholism-related brain alterations. When coupled with neuropsychological evaluations, \textit{in vivo} brain structure and functional connectivity can reveal neural systems affected by alcoholism, and systems or loops invoked for compensation. Functional MRI (fMRI), structural MRI, diffusion tensor imaging and neuropsychological findings support central roles for frontocerebellar circuit alteration as underlying executive impairment related to alcoholism. We recently revealed the presence of a double-dissociation within frontocerebellar circuit characterized in alcoholics by some loops being structurally different from those of controls and others being similar. Functionally, preserved loops have been shown to compensate for damaged ones when alcoholics perform a challenging task. Specifically, through greater functional synchronization in the frontocerebellar motor loop, alcoholics were able to compensate for inefficient functioning of the parallel frontocerebellar executive loop. Another view of brain functioning derives from concepts of intrinsic functional networks, the most considered being the default-mode network (DMN). This large system becomes synchronously active when an individual is not stimulated by an external stimulus and thus is ‘at rest’. We found that the spontaneous slow fluctuations of fMRI signals in regions of the DMN were less synchronized in alcoholics than in controls, indicative of compromised functional connectivity even when the brain is ‘at rest’. Greater efficiency in several connections of this system correlated with longer sobriety in alcoholics. Thus, brain imaging tools have enabled \textit{in vivo} investigation of insult to specific brain circuits that form the basis for pathophysiological models of alcoholism as a disconnection syndrome accompanied by processing inefficiency of functional networks in alcoholism. (This study was supported by U.S. National Institute of Health grants AA010723, AA012388, AA017168, and AA017923.)

S16
ALCOHOLIC LIVER DISEASE AND LIVER TRANSPLANTATION
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S16.3
RELAPSE OF HARMFUL DRINKING IN LIVER-TRANSPLANTED ALCOHOLICS: RISK STRATIFICATION AND CHALLENGE TO THE 6-MONTH RULE
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Alcoholic liver disease (ALD) is still the most frequent and lethal complication in chronic alcoholism. Primary treatment modalities are abstinence,