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Predictability of alcohol relapse by hippocampal volumetry and psychometric variables

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ABSTRACT

We examined the relationship between relapse risk/duration of abstinence and hippocampal volume as well as the moderating role of various psychological factors in 34 patients who fulfilled the diagnostic criteria for alcohol dependence according to ICD-10 and DSM-IV and 16 healthy controls (9 females and 7 males). This study is part of a single-blind, placebo-controlled, parallel-group treatment trial with the anticraving substance acamprosate administered for 3 months. Patients underwent a psychometric evaluation and a measurement of the hippocampus with magnetic resonance imaging before beginning medication (*T0*). At 2, 4, 8, and 12 weeks after treatment, abstinence was evaluated by phone. Afterwards all patients switched to a long-term open label study with acamprosate. Hippocampal volume did not constitute a predictive factor for relapse probability in abstinent alcoholics. Furthermore, stress level, depressivity, gender, and treatment with the anticraving substance acamprosate did not show a significant correlation with relapse probability. The current investigation could not identify significant risk factors for relapses after successful alcohol withdrawal. Further studies are required to identify crucial factors which are responsible for successful or unsuccessful relapse prevention.

1. Introduction

Alcohol dependence is a major health problem in Western industrialized countries and one of the leading causes for years of life lived with significantly reduced health worldwide (Murray and Lopez, 1996). The disorder is typically chronic and characterized by a high rate of relapses after successful cessation therapy. However, risk factors for relapse are not fully understood despite their high relevance for the development of new treatment strategies for alcohol withdrawal.

We intended to examine a potential relationship between a few particular aspects of alcohol dependence in the context of establishing alcohol abstinence. Precisely, hippocampal volumes, certain psychological characteristics and anticraving medication were studied in the framework of an abstinence paradigm.

1.1. Hippocampal volumes and abstinence success

Some studies suggest that regional brain volumes are associated with therapeutic success in psychiatric disorders. For example, MacQueen et al. (2008) reported a positive correlation between hippocampal volume and remission rates in patients with recurrent major depressive disorder. In a work dealing with alcohol dependence, amygdala volumes were shown to be significantly associated with craving and abstinence, i.e., those individuals with smaller amygdala volumes had an increased craving for alcohol and increased alcohol intake during a follow-up period. Of note, no significant relationship between hippocampal volumes and treatment outcome was reported in the same investigation (Wrase. et al., 2008). Durazzo et al. (2011) succeeded in differentiating alcohol-abstainers and relapsers concerning cortical thickness, surface area, and volume of components of the brain reward system. Dealing with cocaine addiction, Ersche et al. (2011) reported a correlation between structural abnormities and behavioral characteristics of drug use; for example, greater compulsivity of drug use was associated with reduced volume in orbitofrontal cortex. However, an abstinence paradigm was not part of that study.

The role of craving as a learning phenomenon is currently the subject of intense research (Von der Goltz and Kiefer, 2009). It is obvious that damage to sensitive brain regions – for example, by instance by alcohol-induced atrophy – affects addiction memory itself (Robbins et al., 2008). We chose to take measurements of the hippocampus because this brain-region is decisively involved in contextual learning, which in turn plays a major role in drug-related memories (Floresco et al., 2001). Furthermore, it is well established that a volume loss in the hippocampal region can be detected in alcoholic patients (e.g., De Bellis et al., 2000; Mechtcheriakov et al.,

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2007; Sullivan et al., 1995). Both reduction of white matter (Badsberg-Jensen and Pakkenberg, 1993) and neuronal loss (Bengochea and Gonzalo, 1990) are held accountable. While earlier studies propose an unspecific effect of alcohol on the whole brain (Agartz et al., 1999), newer work suggests a specific vulnerability of the hippocampus (Beresford et al., 2006).

1.2. Psychological aspects of abstinence success

The traditional concept of the need for an alcoholic to "hit the bottom" before he or she can develop a stable abstinence (Orford, 1986) is increasingly replaced with the assumption of a complex interaction of psychological determinants including a variety of personal and contextual factors contributing to abstinence motivation (DiClemente et al., 2009). Prior to an elective alcohol detoxification not only identification of contextual psychological factors should be undertaken but also characteristics of craving itself should carefully be assessed. Individual stress levels appear to play an important role in the run-up to successful abstinence (Laudet and Stanick, 2010; Marlatt and Gordon, 1980) as well as negative affects like anger, irritability, depression, and boredom (Marlatt and Gordon, 1980).

1.3. Anticraving medication

Psychological parameters, more precisely a differentiation between reward craving and relief craving, also seem to prognosticate the effectiveness of anticraving medication to a certain degree: The opioid-receptor antagonist naltrexone (for review, see Garbutt, 2010) is apparently effective in reward cravers. By contrast, acamprosate appears to act centrally and more specifically to restore the normal activity of glutamatergic neurotransmission (Mann et al., 2008; Mason and Heyser, 2010). Using this drug to relieve craving and for later stabilization seems to be promising (Littleton, 2000; Verheul et al., 1999). Generally, correlations and dependencies between somatic phenomena and psychological predictors have not yet been thoroughly examined.

1.4. Aim of the study

The aim of the present study was to evaluate potential predictive factors for alcohol abstinence under acamprosate therapy, such as hippocampal volume, temperament and character issues, as well as individual stress levels. Furthermore, we aimed at replicating the well-known phenomenon of smaller than normal hippocampal volumes in those with alcohol dependence by including a healthy control group in the current investigation.

2. Methods

2.1. Experimental schedule

This study is part of a single-blind, placebo-controlled, parallel-group treatment trial investigating the anticraving substance acamprosate administered for 3 months. Patients received either acamprosate capsules (333 mg) or identical placebo capsules. Acamprosate medication followed a weight-dependent dosage regime, i.e., above 60 kg body weight, patients received a daily dose of 1998 mg, and below 60 kg body weight, the daily dose was 1332 mg.

Subjects underwent a psychometric evaluation and magnetic resonance imaging (MRI) to measure the hippocampus before the beginning of medication (*T0*). At 2, 4, 8, and 12 weeks after treatment, abstinence was evaluated by phone. Afterwards all patients switched to a long-term open label study with acamprosate.

Recruitment, exposure, follow-up and data recruitment took place from July 2002 until June 2005. To access the full trial protocol, K. Spiegelhalder can be contacted via e-mail.

2.2. Participants

We studied 34 adult patients (10 females and 24 males) who fulfilled the diagnostic criteria for alcohol dependence according to ICD-10 (World Health Organization, 1993) and DSM-IV (American Psychiatric Association, 1994). All participants had to be abstinent for at least 4 days; other previous or current conflicting substance use or illicit drug abuse was excluded. Psychotropic medication was not allowed within 4 weeks before *T0*, except for benzodiazepines and clomethiazole which both had to be terminated for at least 7 days before *T0*. Patients with other psychiatric or neurological disorders or clinically significant hepatic impairment were not included. Breathalyzers were used to verify abstinence at *T0* and further visits or investigations. Additionally, 16 healthy controls (9 females and 7 males) were investigated. In the treatment trial, 18 patients received acamprosate, while 16 alcoholics were randomly assigned to a placebo group. The diagnostic procedure comprised a standard physical and psychiatric examination, excluding those with additional medical or psychiatric pathology. The study was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent before study participation. The study protocol was approved by the ethics committee of the University of Freiburg Medical Center.

2.3. Assessment

Prior to the beginning of the study, alcohol-dependent subjects underwent a psychometric evaluation, which took place at the Department of Psychiatry and Psychotherapy, University of Freiburg Medical Center. Possible withdrawal symptoms were evaluated by the Clinical Institute Withdrawal Assessment for Alcohol (CIWA, Stuppaeck et al., 1994), a 10-item scale (cumulative score, range 0–67), in which higher scores are attended by more serious withdrawal symptoms (e.g., a score >20 poses a strong risk of delirium tremens). The Alcohol Abstinence Self-Efficacy Scale (AASE, DiClemente et al., 1994), a 20-item self-report (mean overall score, range 1–20) designed to estimate self-efficacy applied to alcohol abstinence, was used to rate the individual ability to abstain from drinking. Higher scores suggest a greater degree of self-efficacy. Furthermore, lifetime drinking history including mean alcohol intake, number of previous withdrawals, and duration of abstinence, as well as family history of alcoholism, other substance dependencies and other psychiatric disorders were evaluated by clinical interview. Concomitant depressive symptoms were assessed using the Beck Depression Inventory (BDI, Beck et al., 1961). This 21-item questionnaire consists of questions about how the subject has been feeling in the last week. Scores of 19–29 indicate moderate depression; scores of 30 and higher suggest severe depression. The Perceived Stress Scale (PSS, Cohen et al., 1983), a 14-item instrument designed to measure the degree to which situations in one's life are appraised as stressful (mean overall score, range 0–56), was used to quantify individual stress levels. High scores indicate a high extent of perceived stress.

2.4. MRI acquisition

MR images were acquired at the Department of Diagnostic Radiology, Section of Medical Physics, University of Freiburg Medical Center, on a 1.5 T Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany). For volumetric assessment, a T1-weighted anatomical magnetization-prepared rapid gradient-echo sequence was recorded (160 sagittal slices with 256×256 voxels, $1.0 \times 1.0 \times 1.0$ mm^3, Mugler and Brookeman, 1990). First, anatomical scans were transformed to the stereotaxic coordinates of Talairach and Tournoux (1988). Subsequently, each hippocampus was outlined manually using the AFNI software (Cox, 1996; see Fig. 1). A combination of the sagittal and the coronal views was used for this purpose because this procedure allowed us to separate the hippocampus from the ventral and posterior border of the amygdala. For this differentiation, the alveus was used as internal landmark. The other anatomical boundaries were the lateral ventricle, the cisterna ambiens, and the white matter of the parahippocampal gyrus. White matter tracts (alveus, fimbria) were excluded from the hippocampus. The volume in each slice (the in-slice volume) was calculated by the number of voxels contained within each trace. Total volume of the hippocampus was the sum of all in-slice volumes. Images of patients and controls were presented to an independent rater in a random sequence without any cues to patient/control status. Accordingly, the rater was blinded to the identity and clinical status of the subject.

2.5. Statistics

The impact of alcohol dependence on hippocampal volumes was investigated with a regression analysis that included age and gender as covariates. In the patients group, similarly, regression analyses were used to analyze the impact of the duration of alcohol dependence, the mean weekly alcohol intake and the smoking status on hippocampal volumes with age and gender as covariates. The impact of acamprosate medication, hippocampal volume, BDI scores, AASE abstinence efficacy scores, AASE temptation scores, and PSS scores on the relapse risk in alcohol-dependent patients at 2, 4, 8, and 12 weeks after the inception of treatment was evaluated by logistic regression analyses with relapse as the dependent variable (2 = relapse, 1 = no-relapse)