### DIFFERENCES IN BRAIN FUNCTION BETWEEN RELAPSING AND ABSTAINING ALCOHOL-DEPENDENT PATIENTS, EVALUATED BY EEG MAPPING

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Abstract — Aims: Early clinical electroencephalographers reported that low-voltage fast desynchronized patterns were frequently seen in chronic alcoholism, suggesting hyperarousal of the central nervous system (CNS). The aim of the present study was to investigate the brain function of drug-free, detoxified alcoholics, and compare this with that of normal controls, utilizing computerized quantitative EEG analysis and subsequent EEG mapping. Moreover, differences between patients relapsing or abstaining during 6 months of relapse prevention therapy, pharmacologically supported by either flupentixol decanoate 10 mg or placebo i.m. every 2 weeks, were determined. **Methods:** 22 drug-free, detoxified patients (15 men, seven women) aged between 27 and 58 (mean  $41.5 \pm$ 8.1) years, diagnosed as alcohol-dependent (ICD-10: F10.23) were included in the study. They were subdivided into abstainers (n = 11) and relapsers (n = 11), and matched with normal healthy controls according to age (mean 41.5 ± 8.4 years) and sex. A 3-min vigilancecontrolled EEG (V-EEG) was obtained and analysed off-line by multi-lead EEG power spectral analysis and subsequent mapping methods. Results: The drug-free, detoxified, alcohol-dependent patients showed, as compared with controls, aberrant brain function characterized by a decrease in delta and slow alpha and an increase in beta activity as well as an acceleration of the total centroid. These findings were more pronounced in relapsing than in abstaining patients. After 6 months of treatment, abstaining patients showed an increase in slow activity, a decrease in fast alpha, an acceleration of the delta/theta centroid and a deceleration of the alpha centroid, reflecting a normalization of brain function. Conclusion: EEG maps of alcohol-dependent patients differ significantly from those of normal controls and patients suffering from other mental disorders and thus EEG mapping may be used for diagnostic purposes. Moreover, the quantitative EEG may also be of prognostic value as relapsing patients differ from abstaining ones, since they show a significantly more pronounced hyperarousal of the CNS.

#### INTRODUCTION

The definition of relapse varies, ranging from the self-reported discontinuation of total abstinence to either temporary consumption of less than five standard drinks without loss of control (slip) or heavy consumption of alcohol with loss of control and return to the former habits of drinking (Scholz, 1996). As triggers of relapse, aetiopathogenetic models suggest biological changes due to a chronic intoxication with ethanol, methanol, aldehydes and their metabolites, resulting in symptoms of withdrawal, as well as psychosocial factors, psychiatric disorders and craving (Veltrup, 1994; Hertling et al., 2001). The phenomenon of craving has also been defined differently: The ICD-10 (Dilling et al., 1993) describes it as 'as a strong desire or sense of compulsion to take the substance', whereas the DSM-IV (American Psychiatric Association, 1994) refers to 'a persistent desire or unsuccessful efforts to cut down or control substance abuse'. Psychobiological models of craving (Verheul et al., 1999) imply the involvement of dopamine/opioids, GABA/glutamate or serotonin and/or reward seeking, relief seeking or obsessive personality styles. However, craving is not necessarily linked to increased risk of relapse (Rohsenow and Monti, 1999).

Various attempts have been made to predict relapse and identify antecedents, focusing on variables like employment instability, residential or marital status, sex, age, ethnicity and family history (Polich *et al.*, 1981; Rounsaville *et al.*, 1987; Miller *et al.*, 1992), previous treatment history (Glenn and Parsons, 1991), stressful life events and negative mood states (Bromet and Moos, 1977; Finney et al., 1980; Marlatt and Gordon, 1985), depression and other coexistent psychiatric diagnoses (O'Leary et al., 1979; Rounsaville et al., 1987; Parsons et al., 1990; Glenn and Parsons, 1991), childhood attention deficit disorder symptomatology (Parsons et al., 1990, Glenn and Parsons, 1991), psychological trait disturbances and alcohol-related social difficulties (Jin et al., 1998), neuropsychological performance and psychosocial maladjustment (Glenn and Parsons, 1991), drug expectancies (Cummings et al., 1980; Brown, 1985), self-efficacy (Solomon and Annis, 1990), social support resources (Finney et al., 1980), reduced dopamine receptor function (Heinz et al., 1995), age of onset of alcoholism and cerebrospinal fluid serotonin metabolites (George et al., 1999) and subjective craving (Roelofs and Dikkenberg, 1987). Event-related potentials (ERP) were also applied to predict relapse, showing an overall prediction rate of 63%, and of 71% if depressive symptomatology and psychosocial maladjustment were considered (Glenn et al., 1993). Changes in rapid eye movement (REM) sleep revealed a prediction rate of 76-82% (Gillin et al., 1994). Miller et al. (1996) identified clients' coping resources (85% hit rate) and disease model beliefs as being most powerful in predicting relapse.

Prior EEG-mapping studies of detoxified alcohol-dependent patients, as compared with normal controls, showed an increase in absolute and relative beta power and a decrease in alpha and delta/theta power (Saletu, 1996, 1997), which is in agreement with earlier reports of low-voltage fast EEG patterns, as often encountered by visual EEG inspection (Kiloh *et al.*, 1981; Niedermeyer and Lopes da Silva, 1982). As slow activities are considered to be inhibitory, alpha activity an expression of normal brain functioning and fast beta activities excitatory, the low-voltage fast desynchronized patterns may be interpreted as hyperarousal of the CNS.

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Beta activity has also been used to predict relapse in dependent alcoholics. Bauer (1994, 2001) found high-frequency beta activity to significantly distinguish relapse-prone patients from abstinence-prone ones. Winterer *et al.* (1998) predicted relapse in chronic alcoholics by means of quantitative EEG (Q-EEG). He was able to correctly classify 83–85% of the patients, outperforming most earlier attempts at predicting the relapse rate on the basis of clinical evaluations.

The aim of this study, which was conducted within a larger investigation (Wiesbeck *et al.*, 2001), was to compare the EEG maps of drug-free, detoxified alcoholics with those of normal controls, and to describe differences between patients relapsing or abstaining during 6 months of relapse prevention therapy pharmacologically supported by either flupentixol decanoate 10 mg or placebo i.m. every 2 weeks. Furthermore, baseline differences between relapsing and abstaining alcoholics were obtained in order to evaluate the predictive properties of EEG mapping as described by Winterer *et al.* (1998) and Bauer (1994, 2001).

#### MATERIALS AND METHODS

#### Patients

Twenty-two drug-free, detoxified patients (15 men, seven women) aged between 27 and 58 (mean:  $41.5 \pm 8.1$ ) years were included in the study and matched with normal healthy controls according to age (mean:  $41.5 \pm 8.4$  years) and sex. Inclusion requirements were the fulfilment of at least six DSM-III-R criteria for moderate or severe alcohol dependence (303.90), a score of  $\geq 11$  in the Munich Alcoholism Test (Feuerlein et al., 1980), complete abstinence from alcohol and pharmacotherapy for a minimum of 14 and a maximum of 42 days after detoxification, the absence of withdrawal symptoms, that is a score of <2 on the Withdrawal Syndrome Scale for alcohol and related psychoactive drugs (Bech et al., 1989), absence of co-morbidity of depression (HAMD score <18) or anxiety (HAMA score <16) (Hamilton, 1959, 1960), absence of neurological or medical disorders and absence of psychiatric disorders requiring medication or hospitalization, a negative urine test for psychoactive drugs, and the intention to remain abstinent. Abstaining patients (n = 11; eight men, three women; age  $39.6 \pm 7.8$  years; seven on placebo, four on flupentixol decanoate) were matched with normal controls  $(n = 11; \text{ eight men, three women; mean age } 39.8 \pm 8.7 \text{ years}),$ as were relapsing patients (n = 11; seven men, four women; mean age  $43.4 \pm 8.2$  years; five on placebo, six on flupentixol decanoate; controls: n = 11; seven men, four women; mean age  $43.2 \pm 8.2$  years). Patients had been recruited in the course of a larger double-blind multi-centre study investigating the effect of flupentixol decanoate on the relapse rate of detoxified alcoholics (Wiesbeck et al., 2001). Patients were randomized to either flupentixol decanoate or placebo, which were both applied as i.m. injections in intervals of 2 weeks over a period of 6 months. Abstinence was defined as no alcohol consumption according to the patients' self-report and the results of alcohol breath analysis. Relapse was defined as selfreport of alcohol consumption or a  $\geq 40\%$  increase in GGT or  $a \ge 60\%$  increase in ALAT or ASAT compared with baseline.

#### EEG investigations

A 3-min vigilance-controlled EEG (V-EEG) and a 4-min resting EEG (R-EEG) were recorded at baseline and in a subsample (abstaining patients only) after 6 months of treatment by means of a 21-channel Nihon Kohden 4321-G polygraph (time constant: 0.3 s, high frequency response: 35 Hz; frequency range: 0.5-35 Hz; amplification: approximately 20 000 times; maximal noise level:  $2 \mu V$  peak to peak) with the subjects lying relaxed with eyes closed in an electrically shielded room. During V-EEG recordings, the technician kept the subjects alert. As soon as drowsiness patterns appeared in the record, the subjects were aroused by auditory stimuli (tapping). The present paper will discuss V-EEG data only. Electrodes were attached to the scalp according to the international 10/20 system. A vertical electro-oculogram (EOG) was recorded from an electrode at mid-forehead to the average of one electrode below the left eye and one electrode below the right eye. A horizontal EOG was recorded from the outer canthi. EEG recordings from 19 leads (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 to averaged mastoids) as well as two EOG recordings were digitized on-line by a 12-bit Burr Brown analogue-digital converter within a Hewlett-Packard Vebra system with a sampling frequency of 102.4 Hz. Spectral analysis was performed for 5-s epochs (512 sample points) with a frequency resolution of 0.2 Hz (Saletu et al., 1987; Anderer et al., 1987; Anderer et al., 1992), using the fast Fourier transform technique in floating-point arithmetic to maintain precision.

Artefact-free 5-s epochs were selected after minimizing ocular artefacts by means of an automatic artefact identification method as described by Anderer *et al.* (1987, 1992). The mean spectral curves contained data from 1.3 to 35 Hz quantified into 36 EEG variables: total power (TP); absolute and relative power (AP and RP, respectively) in 12 different frequency bands (1.3–3.5–7.5–10.5–13–16–20–25–30–35; 1.3–7.5–13–35 Hz); the dominant frequency (DF, in Hz), AP and RP of the DF; further the centre-of-gravity frequencies (centroids, C) and their standard deviations of the combined delta and theta, alpha and beta bands as well as of the total activity (T). Nineteen single values obtained from the 10/20 electrode set were mapped onto a numerical matrix,  $64 \times 64$ . Each interpolated value was based on the cubic distance from the values at the four nearest electrodes.

To display the difference in the distribution of the 36 EEG variables significance probability mapping (SPM) was used (Bartels and Subach, 1976; Duffy *et al.*, 1981; Saletu *et al.*, 1987).

#### Statistical analysis

Statistical analysis was based on the concept of descriptive data analysis as proposed by Abt (1988). All inter-group differences were tested descriptively. Normal distribution was tested by means of the Kolmogorov–Smirnov test. If in no cases the null hypothesis of normal distributions was rejected at alpha = 0.10, a two-sample *t*-test for inter-group comparison was used, if the assumption of normal distribution was violated, the non-parametric Wilcoxon Test and the Mann–Whitney *U*-test were used. To display inter-group differences in the distribution of the 36 EEG variables, significance probability mapping was used (Duffy *et al.*, 1981; Saletu *et al.*, 1987; Anderer *et al.*, 1992).

#### RESULTS

### Baseline EEG mapping differences between drug-free alcohol-dependent patients and normal controls

In regard to absolute power (AP), 22 alcohol-dependent patients showed, as compared with 22 normal controls, a significant decrease in delta power over frontopolar regions and a significant increase in beta power over frontal, central, left parietal and right occipito-temporal regions (Fig. 1). Concerning relative power (RP), alpha power was significantly decreased over frontal and right parietal, temporo-occipital and occipital regions, and



Fig. 1. Maps of baseline EEG differences between detoxified alcoholics and normal controls in the vigilance-controlled EEG (V-EEG) ( $n = 2 \times 22$ ). Statistical probability maps (SPM; bird's eye view, nose at the top, white dots indicate electrode positions) depict inter-group differences in 13 absolute power (AP) measures (upper part of the figure), 12 relative power (RP) measures (middle part of the figure) and 11 dominant frequency and centroid measures (lower part of the figure). Red and purple represent significant (P < 0.05 and 0.01, respectively) increases; light blue and dark blue indicate significant (P < 0.05 and 0.01, respectively) decreases, as compared with normal controls. Alcoholics demonstrate reduced power in the delta and alpha bands, increased power in the beta bands and an accelerated centroid of the total power spectrum (CT), which reflects CNS hyperarousal.

beta power was significantly augmented almost ubiquitously. The dominant frequency (DF) was significantly decelerated over right frontal and left temporal regions, the total centroid (CT) was significantly accelerated over almost all brain regions.

### *EEG changes in abstaining alcoholics after 6-month treatment as compared with baseline*

After a 6-month treatment period abstinent alcoholics (two on placebo, four on flupentixol decanoate) demonstrated, as compared with baseline, increased absolute delta power over the right frontopolar region, while absolute alpha-2 power was significantly decreased over frontal, central, temporal and right parietal regions (Fig. 2). Absolute beta-1 power was significantly reduced over central, parietal and left frontal and temporal regions, absolute beta-2 power over left frontal and parietal regions. In RP delta/theta power was almost ubiquitously augmented, with the increase reaching the level of statistical significance over central, right frontopolar, frontal and



Fig. 2. Maps of EEG changes in abstinent alcoholics after 6-month treatment, as compared with baseline (n = 6). For description of the maps and the colour key, see Fig. 1. The increase in delta and theta and the decrease in beta power are opposite to the differences between patients and normals (described in Fig. 1) and indicate a normalization of brain function.

temporal and left parietal regions. Beta-1 power was significantly reduced over the right temporal region, beta-2 power over the right frontal and temporal and left parietal regions. The dominant frequency was significantly decelerated over frontal, right central and left frontopolar and temporal regions, the delta/theta centroid was significantly accelerated over frontopolar and left parietal and occipito-temporal regions, whereas the alpha centroid was significantly decelerated over temporal, right frontopolar and left frontal and parietal regions.

Patients on flupentixol decanoate 10 mg i.m./2 weeks showed, as compared with patients on placebo, a significant decrease in absolute beta-2 power over right central, parietal and occipitotemporal and left frontopolar regions (Fig. 3). In RP delta power was significantly increased over right central and left occipital regions, beta-1 power significantly decreased over the right temporal region, beta-2 power significantly decreased



Fig. 3. Maps of differences between EEG changes in abstaining patients after 6-month therapy with flupentixol decanoate (10 mg i.m./2 weeks) and placebo (n = 4, 2). For description of the maps and the colour key, see Fig. 1. Patients treated with flupentixol decanoate exhibit a greater increase in delta and theta and decrease in beta power than those treated with placebo. On the one hand this reflects the typical neuroleptic effect, on the other a more pronounced normalization of the abstaining alcoholics' brain function as compared with placebo.

over right temporal and parietal regions. The dominant frequency was significantly decelerated over frontal and right frontopolar regions, the alpha centroid was significantly decelerated over the right occipital region.

## Baseline EEG differences between relapsing and abstaining alcoholics as compared with normal controls

As compared with normal controls, relapsing patients (n = 11) demonstrated a significantly reduced absolute delta/theta power over both frontopolar regions as well as significantly increased absolute beta-3 power over right frontal and left temporal regions, absolute beta-4 power over right frontal and left toccipito-temporal and occipital regions, and absolute beta-5 power over frontal, right occipital and left parietal regions (Fig. 4). In RP alpha-1 power was significantly reduced over frontal and right occipital regions, beta power was significantly augmented over the high central, frontal, parietal, occipito-temporal and occipital, right frontopolar and left temporal regions. The beta centroid was significantly accelerated over the right occipital region, the total centroid over frontal, central,



Fig. 4. Maps of baseline EEG differences between relapsing alcoholics and normal controls ( $n = 2 \times 11$ ). For a description of the maps and the colour key, see Fig. 1. Relapsing patients show marked and highly significant differences as compared with normals, reflecting CNS hyperarousal.



Fig. 5. Maps of baseline EEG differences between abstaining alcoholics and normal controls ( $n = 2 \times 11$ ). For a description of the maps and the colour key, see Fig. 1. Abstaining patients show only minimal differences as compared with normals, which suggests only minor CNS hyperarousal.

parietal, occipito-temporal and occipital and right frontopolar regions.

In abstaining patients (n = 11) differences reached the level of significance only in absolute beta power over left frontal and central regions (Fig. 5).

The differences between relapsing and abstaining alcoholics were represented by a significant decrease in absolute alpha-1 power over both occipital regions, a significant increase in relative beta-3 power over temporal and right central regions, and a significant increase in relative beta-4 power over left temporal region (Fig. 6). Furthermore, in relapsing patients, the beta centroid was significantly accelerated over frontal and temporal and left central regions.

#### DISCUSSION

The present investigation showed a decrease in delta activity and alpha-1 activity, an increase in beta activity and an acceleration of the total centroid in the baseline V-EEG



Fig. 6. Maps of baseline EEG differences between relapsing and abstaining alcoholics ( $n = 2 \times 11$ ). For a description of the maps and the colour key, see Fig. 1. Relapsing patients show less alpha-1 power, more beta-3 and beta-4 power and a faster beta centroid than abstaining patients and thus exhibit a more pronounced CNS arousal, which is associated with a worse prognosis.

mappings of drug-free, detoxified, alcohol-dependent patients as compared with normal controls. These changes reflect a hyperarousal of the central nervous system and are in line with previous findings in abstaining alcohol-dependent patients (Bauer, 1994, 2001; Saletu, 1996, 1997; Costa and Bauer, 1997; Gunther *et al.*, 1997; Irwin *et al.*, 2002).

However, different views exist concerning the aetiology of these EEG changes in alcoholic patients. On the one hand, aberrations in brain function, especially in frontal regions, might contribute to the development of alcoholism (Gabrielli *et al.*, 1982; Propping, 1983; Deckel *et al.*, 1995; Harden, 1995; Saletu, 1996, 1997; Winterer *et al.*, 1998; Bauer, 2001). This is supported by various findings: beta activity was found to be related to the interaction of the two pre-morbid factors of childhood conduct disorder and paternal alcoholism (Bauer, 2001). Reduced absolute and relative alpha power over occipital and frontal regions and increased relative beta power were observed to characterize the EEG of subjects with a positive family history of alcoholism (Finn and Justus, 1999).

A paradoxical frontal cortical EEG response pattern to threat (more alpha suppression but less beta increase) (Finn et al., 2000) as well as excessive high-frequency beta activity (Bauer and Hesselbrock, 1993) were found in subjects with a positive family history of alcoholism and aggressive traits. A significantly higher cue-reactivity consisting of higher ERP amplitudes elicited by alcohol-related pictures than by those not related to alcohol was found in heavy social drinkers. This finding is in line with the results obtained in alcohol-dependent patients (Herrmann et al., 2001). Increased beta power was observed in the relatives of alcoholics (Pollock et al., 1995). Furthermore, rats drinking large amounts of alcohol showed decreased P300 and N1 ERP amplitudes in the amygdala and greater cortical EEG power and thus differed markedly from those drinking hardly any alcohol (Slawecki et al., 2000). The results obtained in this group were similar to those in alcoholpreferring rats, which may be related to the effect of neuropeptide Y (Ehlers et al., 1999). The hypothesis of a heightened central nervous arousal increasing the risk of relapse and reflected by an increase in beta activity was also substantiated by a corresponding elevation in cardiac output (Bauer, 1994).

On the other hand, the literature also implies that the EEG changes occurring under conditions of abstinence might indicate either a normalization of the EEG as well as of neuropathological, neurophysiological and neuropsychological measures (Bennett *et al.*, 1956; Page and Linden, 1974; Carlen *et al.*, 1978; Fleming and Guthrie, 1980; Muuronen *et al.*, 1989) or withdrawal (Coger *et al.*, 1978). In our study, after 6 months of treatment abstaining patients showed an increase in slow activity, a decrease in fast alpha and slow beta, an acceleration of the delta/theta centroid and a deceleration of the alpha centroid as compared with baseline. These changes are opposite to the differences between patients and normals and represent a normalization of brain function.

Also, other mechanisms of an altered EEG in alcoholic patients have been described. Persistent changes might reflect chronic intoxication. Pollock *et al.* (1992) found an increased uniformity of theta amplitudes in bilateral anterior and posterior brain regions. Neuroradiological and neuropsychological findings support the hypothesis of a higher susceptibility of the anterior brain to alcohol-related brain damage (Ratti *et al.*, 1999). Also the effects of ALDH2 genetic variations were observed and subjects expressing the ALDH2\*2 allele showed less slow alpha response and periods of decreased slow alpha activity after the ingestion of alcohol, which was explained directly by the higher blood acetaldehyde levels and indirectly by changes of peripheral parameters as heart rate and facial skin temperature (Wall *et al.*, 1993; Nishimura *et al.*, 2001).

The normalization of brain function was more pronounced in patients on flupentixol decanoate than on placebo, which reflects the typical neuroleptic effect. However, flupentixol decanoate was shown to have adverse effects on both relapse rates and the 'cumulative abstinence duration', contradicting the original hypothesis of the larger study and leading to the question whether flupentixol might even be able to induce craving for alcohol. It has been suggested that different types of alcohol-dependent patients might show different degrees of susceptibility to the adverse effects of flupentixol (Lesch and Walter, 1996; Wiesbeck *et al.*, 2001; Walter *et al.*, 2001).

Nevertheless, investigations of the predictive properties of the quantitative EEG regarding therapeutic outcome revealed that the baseline EEG of relapsing patients differed highly significantly from that of normal controls, reflecting CNS hyperarousal, whereas in abstaining patients the baseline differences to normal controls were minimal, suggesting only minor hyperarousal. Furthermore, the differences between abstaining and relapsing patients reached the level of significance regardless of the treatment (with the number of patients receiving placebo or flupentixol not being significantly different). These findings confirm the investigations by Bauer (1994, 2001) and Winterer et al. (1998) and show a worse prognosis for the patient group with a more pronounced frontal CNS hyperarousal. It may be hypothesized that these hyperaroused relapsing patients require more CNS sedation than abstaining ones, which indeed was seen in the group treated with flupentixol decanoate. However, as our post-drug EEG sample was very small and comprised only abstainers, as the results of the large clinical study (Wiesbeck et al., 2001) showed opposite findings (more relapsers in the group treated with flupentixol decanoate than with placebo), and last but not least as different subtypes of alcoholics have to be taken into account, further neurophysiological studies in larger subgroups seem to be necessary.

Our findings imply that future investigations of EEG measures in alcoholics concerning aetiopathological explanations as well as therapeutic strategies will have to adopt a more differentiated view of alcohol dependence. EEG maps of alcoholdependent patients differ significantly from those of normal controls and patients suffering from other mental disorders and thus EEG mapping may be used for diagnostic purposes (Saletu *et al.*, 2002b). Thus, EEG mapping may also be utilized as an objective measure for predicting relapse in chronic alcoholism, and for choosing the optimal drug for a certain patient, as according to a key–lock principle the drug of choice should induce changes opposite to those produced by the disease, thereby normalizing brain function (Saletu *et al.*, 2002a,b).

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