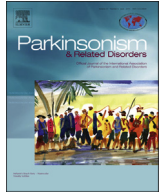




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## Testing for alcohol sensitivity of tremor amplitude in a large cohort with essential tremor

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## ABSTRACT

**Background:** Improvement of essential tremor (ET) amplitude after alcohol ingestion is usually based on patient reports but a quantitative test for large numbers of patients is lacking and the percentage of ET patients with a detectable alcohol effect is therefore unknown.

**Methods:** A validated and published alcohol home test was used in 104 ET patients. The Archimedes spiral was drawn before alcohol ingestion and at 4 time points after alcohol consumption and rated on a 10-point rating scale according to Bain and Findley. A second identical test without alcohol ingestion was performed by the same patients and evaluated by the same two raters to analyze the total variability of the spiral ratings.

**Results:** Alcohol reduces tremor in ET patients as a group and a rebound effect with an increase in tremor intensity was found the next morning. Sex, family history of ET, diagnosis (definite vs. probable) and medical history of alcohol responsiveness do not predict the alcohol response. The minimal detectable difference in the spiral score was 2 due to spontaneous tremor fluctuations and inter-rater differences. The test demonstrated alcohol sensitivity of the tremor in 46% of the patients. Responsivity to alcohol could only be seen in patients with spiral scores above 3.

**Conclusions:** Alcohol sensitivity is a feature of ET in at least 46% of the patients. We could not find predictors for alcohol sensitivity. The minimal detectable change is 2 scores and alcohol responsiveness was only detected in patients with baseline Archimedes spiral rating of  $\geq 3$ .

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## 1. Introduction

Essential tremor (ET) is the second most common movement disorder after restless legs syndrome and the most common type of tremor with an estimated prevalence of 0.4–3.9% [1]. The primary symptom is a symmetric postural and/or kinetic tremor in the upper extremities with or without cerebellar signs [2,3]. ET impedes voluntary movements such as eating and writing and, in some cases results in a substantial reduction of the quality of life [4]. Alcohol sensitivity of ET was first reported in 1949 and it is now widely accepted that alcohol alleviates ET in a sizeable proportion of patients [5,6]. About 50–70% of ET cases report alcohol sensitivity of tremor in their medical history [7–9]. However, studies

examining alcohol sensitivity studied below 20 ET patients only and the proportion of ET patients with a clinically detectable alcohol response is unknown [6,10–12]. For many studies a standardized procedure to test alcohol sensitivity is needed and alcohol sensitivity may be a biomarker of a subgroup of ET-patients [13]. Although, alcohol sensitivity is part of the secondary criteria for the diagnosis of ET, clinical effects of alcohol on ET have never been systematically analyzed using a standardized and validated test in a large number of ET patients. We have recently developed and validated a standardized home test assessing the effect of alcohol on tremor [14]. The aim of this study is the analysis of the effect of alcohol in a large number of patients with ET.

## 2. Methods

## 2.1. Patients and control individuals

The patient sample comprised 104 unrelated individuals

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recruited through the Department of Neurology of Kiel University hospital. All ET patients were diagnosed according to the TRIG consensus criteria of the Movement Disorder Society [2]. Of 104 ET patients (mean age 63.37 yrs, standard deviation:  $\pm 15.72$  yrs, 57% men) 63 fulfilled the criteria for “definitive ET” and 41 patients (mean age 64.11 yrs, standard deviation:  $\pm 15.14$  yrs, 61% men) the criteria for “probable ET”. The study was approved by the local ethics review board and written informed consent was obtained from all participants.

## 2.2. Test procedure

The alcohol home test was performed as described previously and is briefly summarized here [14]. Inclusion criteria were: age >18 yrs and the previously established diagnoses “definite ET” or “probable ET”, by a movement disorder specialist from the Department of Neurology of the University Hospital Kiel. Exclusion criteria were alcoholism in the patient history or other contraindications for alcohol intake. The patients were initially contacted and informed about the study by a letter asking for their participation. In a second stage, patients interested in the study underwent a telephone interview. The Widmark formula is a commonly used formula to estimate the amount of alcohol needed to reach a certain maximum blood alcohol concentration. Employing the Widmark formula we calculated the alcohol needed to reach a blood alcohol concentration of 0.6‰ as follows: amount of alcohol (gr) =  $0.6 (\text{‰}) / (\text{Body weight (kg)} \cdot r)$ , with  $r = 0.7$  for men and  $r = 0.6$  for women [15]. Patients were asked to perform the test in the evening before any food intake and drink the alcohol within 20 min. Before alcohol intake they were requested to complete a questionnaire containing baseline data, including the family history of ET or Parkinson disease and a self-judgment of the alcohol sensitivity of their tremor (yes/no). The source of alcohol, e.g. beer, wine etc. was not prescribed. Tremor severity was measured using a) two drawings with each hand of an Archimedes spiral from inside to outside and without supporting the arm at each of 5 time points, b) a global self-assessment of the proband for both hands together using the visual analog scale 1–100 (VAS 1–100) at each time point. Tremor severity was assessed before alcohol ingestion (t1) and 20 (t2), 40 (t3), 60 (t4) minutes after alcohol intake and the next morning (t5). The Archimedes spirals were rated semi quantitatively according to the Bain criteria on a 10-point scale (Archimedes spiral rating (ASR): 0 = no detectable tremor to 9 = severe tremor) [16]. These instruments were found to be valid measures of tremor severity in previous studies [14,17,18]. Two trained, independent and blinded examiners rated the Archimedes spiral (FH, TE). Training was performed by independently rating 50 unrelated Archimedes spirals by FH, TE, GK, SS and GD and a rating consensus discussion of these spirals afterward. Blinding was performed by riffing and assigning random numbers to the Archimedes spirals by a third person (GK). To determine the minimally detectable change of the ASR we needed to assess the total variability (inter-rater and intra-individual) variability of spiral scores of the same proband over time without the influence of alcohol. Therefore we asked the same probands to perform a second test under identical conditions but without alcohol ingestion, resulting in the same set of spiral drawings sketched over the same time period. All 104 ET patients were contacted via a letter and asked to repeat the test of whom 71 actually participated.

## 2.3. Calculations and statistics

Because the Bain ASR scale is an ordinal scale and ASR ratings are not normally distributed, we used non-parametric statistic tests. The Friedman-test (FT) for paired samples was used to

evaluate differences in ASR at all 5 time points together, the Wilcoxon rank test (WT) to assess differences between two paired samples, the Mann–Whitney-U (MWU) test to assess differences between two unpaired samples and the Spearman-Rho (SR) test to assess linear correlations. Fisher's exact test (FI) was used for cross-tabulated data.

## 3. Results

### 3.1. Variability of the ASR within subjects and between raters without alcohol over time

71 ET patients participated, drawing 2 spirals with each hand at each time point: t1 = 0, t2 = 20, t3 = 40, t4 = 60 min and t5 the next morning without drinking alcohol which adds up to 710 spirals. To exclude a systematic variation of the ASR over time we first compared the ASR over one hour between the time points (t1–t4) which did not show any statistically significant variation (data not shown). Inter-rater variability was assessed using the difference in the ASR between rater 1 (FH) and rater 2 (TE) for the same spiral. Inter-rater variability was negligible and nearly symmetrically distributed with a difference of +1 in 14 ratings, –1 in 9 ratings and complete concordance in 1397 ratings. To assess the total variability (inter-rater + intra-individual) of the ASR without alcohol over the test period of one hour (We excluded t5 which was only added to assess a possible rebound effect. In addition t5 was in the morning and it has been reported that tremor intensity is greater in the morning.) we decided to subtract in every patient, separately for both hands each ASR from t1 to t4 from all other ASR of the same individual in the same period. Since the patients drew 2 spirals this amounts to 8 spirals per hand for all four time points. These were rated by two persons resulting in 16 ASR per patient. 16 values amount to 120 differences between two values per patient and hand and 8520 differences for 71 patients per hand, hence 17,040 values in total for both hands. 184 values were missing leaving 16,616 values for the analysis. The differences were nearly symmetrically distributed around 0 (data not shown). The distribution of the absolute differences is shown in Fig. 1 demonstrate that 95.4% of all differences were  $\leq 2$  ASR and 99.4%  $\leq 3$  ASR. A difference of  $\geq 2$  ASR can therefore be detected with >95% certainty. Therefore we set the cutoff for the minimum detectable difference at  $\geq 2$  ASR. This value also corresponds well with the clinical experience in our

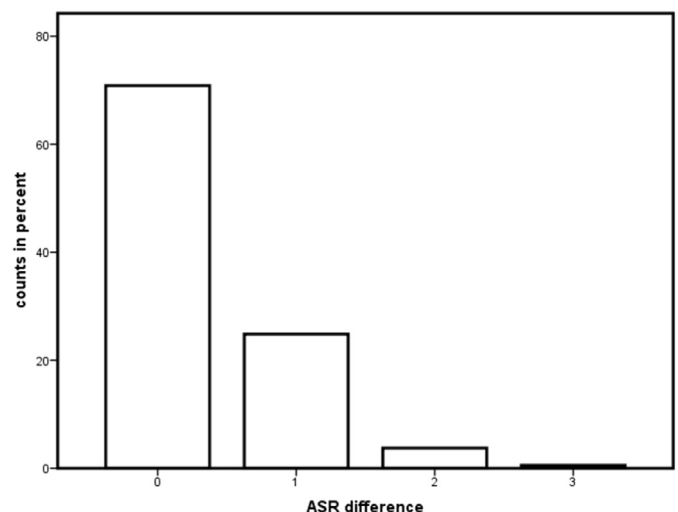


Fig. 1. Histogram of the percentage of the absolute differences between ASRs within one hour for both raters without alcohol. N = 16616 differences between ratings were taken into account.

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